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Società Italiana di Radiobiologia

Farmaci innovativi e ipofrazionamento

PALACONGRESSI DI RIMINI
30 settembre, 1-2 ottobre 2016

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Presidente: Elvio G. Russi

XXX CONGRESSO NAZIONALE AIRB
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INDICE

Programme

BIOLOGICAL EFFECTS OF TARGETED AGENTS ON BRAIN METASTASES

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Approximately 8–10% of adults with cancer develop brain metastases (BM). Among the drugs routinely delivered for metastatic cancer, many agents have pharmacokinetic limitations, mainly an unsatisfactory penetrability through the blood brain barrier (BBB). This limit continues to pose a challenge in the management of this stage of disease. The development of novel systemic approaches in patients (pts) with BM from primary breast, lung and melanoma cancer will be discussed in this dissertation.

Breast. Lapatinib has been developed for patients with breast cancer resistance to trastuzumab. Even though lapatinib can cross the BBB, the penetrability and distribution remain modest. Only modest activity has been found in phase II and III studies testing lapatinib as a single agent in pts with BM. Recently initiated phase II clinical trials are now testing the outcome of two PARP inhibitors: iniparib in combination with irinotecan in triple negative breast cancer and ABT-888 with WBRT.

Lung. The EGFR inhibitors gefitinib and erlotinib have been tested in patients with NSCLC and BM. Response rate vary between 10 and 40%. Similar to primary tumors, the response of BM to EGFR inhibitors is better in patients with activating EGFR mutations.

Melanoma. Treatment with the BRAF inhibitor vemurafenib showed complete or partial tumor regression and improved OS and PFS in patients with BRAF V600E mutation. Treatment with a different inhibitor of BRAF, GSK2118436, resulted in tumor regression in 9 patients and even showed some complete responses in a phase I/II clinical study. In a phase I trial, the BRAF inhibitor dabrafenib was shown to be safe and efficiently blocked BRAF in patients with melanoma BM. Two large phase II studies have been initiated to study the impact of the BRAF inhibitors vemurafenib and GSK2118436 in patients with melanoma BM. Ipilimumab is a new agent that targets CTL4 and promising antitumor efficacy has been revealed in phase III clinical trials conducted in patients with metastatic melanoma. In a phase III trial, treatment with ipilimumab led to improved OS in conventional treatment-refractory pts with melanoma BM. In a recent open-label, single-arm phase II trial, 86 pts, including 20 with asymptomatic BM at baseline, were treated with ipilimumab plus fotemustine. In a similar recent phase II clinical study, Margolin et al. showed that ipilimumab has promising activity in some patients with a melanoma BM, especially in patients with small, asymptomatic lesions while no unexpected toxic effects were observed. More phase III studies are needed to test whether ipilimumab can offer dura- ble responses in this disease.

BRAIN METASTASES RADIOTHERAPY: DOSES AND FRACTIONATION

M. Buglione, P. Borghetti, D. Tomasini, S. Pedretti, L. Triggiani, S.M. Magrini

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To date, the possible therapeutic approaches to BM are surgery, whole brain radiotherapy (WB) and stereotactic radiosurgery (SRS) alone or in combination. Median overall survival after WBRT is related to RPA classes. More aggressive treatments as SUR or SRS alone or combined to WBRT can double OS rates. In the RTOG 9508[1] trial 333 patients (1-3 metastases) were allocated to either WBRT or SRS-WB: SRS-WB improved functional autonomy for all patients and survival for patients with a single metastasis. Ten years later 252 patients were reclassified according to the GPA scale; survival advantage was found only in patients with high GPA score regardless to number of metastases.[2]

It is debated if the linear quadratic (LQ) model is able

to predict the biological effects of high fractional doses in BM. Different authors argue that TCP after a single stereotactic fraction is higher than expected according to the quadratic linear model. Others argue that the LQ model is experimentally validated up to a single fraction dose of 10 Gy.[3-4] A revision of 11 studies on SRS in BM has shown a good correlation between 12 months local control rate (LCR) and the biological equivalent dose (alfa/beta 12 Gy), calculated with the LQC model, for fractional doses ranging between 6 and 25 Gy; the analysis suggested excellent 12 months LCR after single-fraction doses higher than 20 Gy as opposed to clearly insufficient results for doses lower than 15 Gy.[5]

This approach does not allow to use the potential benefits of fractionation in terms of redistribution and reoxygenation and fractionated stereotactic treatments could be more effective. Tumour cell repopulation and repair of sub-lethal damage may occur when a significant interval between WBRT and SRS is provided. SRS treatments may require very long treatment sessions, possibly forcing to split them in multiple sessions.[6]

The possibility of use the contribution of the boost in larger volumes treated with lower doses is a definite advantage of the simultaneous integrated boost (SIB) compared to SRS. Volumetric modulated arc therapy (VMAT) and helical IMRT are able to deliver SIB. The first experience, in 2007[7] analysed fourteen patients submitted to radiotherapy, 60 Gy on the lesions (equivalent to 18 Gy in single fraction within the LQC) and 30 Gy on WB. Others experiences were reported with different fractionations: 30 Gy and 40 Gy on whole brain and on metastatic lesions, respectively; 60 Gy in 10 fr on metastases after a dose-escalation study from 35 to 60 Gy in 10 fr; 40 Gy in 20 franctions and during the last week of treatment a simultaneous boost on brain metastases of 20 Gy in 5 fr.[8-10]

Different doses and fractionation in SIB (SRS+WB) in SRS alone and in SRS+WB are going to be analysed and compared in terms of possible biological effects, results and dosimetric problems, in order to possibly identify the better one for the different patients.

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COMBINATION OF STEREOTACTIC RADIOTHERAPY WITH NEW AGENTS IN BRAIN METASTASES: DOES IT LEAD TO A THERAPEUTICAL ADVANTAGE OR JUST TO AN INCREASED TOXICITY?

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Aim: The aim of this review is reporting the existing and ongoing clinical trials to assess the efficacy and the safety profile of targeted therapy (TT) during stereotactic radiotherapy (SRT) (radiosurgery or hypofractionated stereotactic radiotherapy) for brain metastases (BM). A secondary objective is giving some practical recommendations to use in the daily clinical practice when often patients need to be treated with SRT treatment for BM while they are already receiving TT.

Introduction: TT, by targeting an aberrant cellular process and, consequently, by modulating signal transduction, cellular apoptosis, angiogenesis or the immune system, have radically changed cancer therapy. These agents have already been used in association with radiotherapy in several phase III trials but their specific role in the treatment of patients with BM is not well defined. Clinical evidence for combining SRT with TT is even less clear.

Methods: The Pubmed database was searched for case reports and clinical studies published between 2010 and 2016 that evaluated efficacy and toxicity of combining TT with SRT in patients with BM.

Results: Evidence for the association of SRT with TT is based mostly on retrospective studies with small sample sizes and short follow-up, although several prospective studies are on going (NCT0981890, NCT01276210, NCT01721603, NCT01703507). The majority of the existing series are in patients with BM from melanoma, breast cancer (BC) and renal carcinoma (RCC). The agents used were Vemurafenib[2] and Ipilimumab[3,4] for melanoma, Lapatinib and Trastuzumab[5,6] for BC and Sunitinib, Sorafenib[7] and Temsirolimus[7,8] for RCC. The efficacy was good in terms of neurologic symptoms control and/or intracranial control and/or survival. The severe toxicity rate is very low in most of the series (only in a single series G3/G4 toxicity was >5%). From a practical perspective, beyond the case of the above mentioned agents (for which data are available) and outside of a clin-

ical trial, using a therapeutic window in the order of at least 5 half-lives between TT and SRT should be recommended.[9]

Conclusions: Currently, data regarding the combination of SRT and TT are not robust but they are encouraging in terms of toxicity profile and efficacy.

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CETUXIMAB AND RADIOTHERAPY VERSUS CISPLATIN AND RADIOTHERAPY: RESULTS OF A MULTICENTRIC RANDOMIZED PHASE II TRIAL

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Aim: No published prospective randomized trials have compared Radiotherapy (RT) with concomitant Cisplatin (CDDP) versus concomitant Cetuximab (CTX) as first-line treatment of head-and-neck cancer. This randomized trial compares these two treatment regimens in terms of compliance, tolerability and survival.

Methods: Eligible patients were randomized to receive either CDDP 40 mg/m^2 weekly or CTX 400 mg/sqm as loading dose followed by CTX 250 mg/m2 weekly concomitant to radical RT.

Results: The study was discontinued early due to slow accrual, with a sample size half of that hypotesized. Seventy patients were recruited, 35 for each treatment arm. Randomization was effective, with no differences in terms of age, ECOG score, smoke habit, cancer location, stage and grading; patients treated with Cetuximab reported a significantly higher alcohol consumption. The number of patients who had a long break (more than 10 days) during the radiotherapy course was significantly higher in Cetuximab-arm (p=0.05). Hematologic, renal and gastrointestinal toxicities were more frequent in Cisplatin-arm, as opposed to more common cutaneous toxicity and need of nutritional support in Cetuximab-arm. Cutaneous toxicity and mucositis took longer to recover in the Cetuximab-arm, while median weight loss during the first four visits of follow-up was greater in patients treated with Cisplatin. High rates of infusion reactions (9%) and early death (13%) were observed in Cetuximab-arm. Survival, locoregional control and metastatic progression were similar between the two treatment arms.

Conclusions: Compliance to treatment was lower in the CTX arm. Cetuximab toxicity was relevant and should be further studied. In the analysis of the whole population the two treatment arms obtained similar survival results. Subgroup analysis on cancer location and HPV status are ongoing to identify patients who can take advantage from the CTX combination with radiotherapy.

THE PHASE III STUDY INTERCEPTOR IN LOCALLY ADVANCED HEAD AND NECK CANCER (LA-HNC). PRELIMINARY SAFETY REPORT

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Background: Concomitant CTRT and Cetuximab-RT have been considered a standard treatment in LA-SCCHN. Currently it is not known whether the addition of induction CT followed by bioradio could improve the outcome as compared to CTRT. On January 2010 we started a randomized multicentre phase III study comparing concomitant CT-RT vs induction CT, followed by RT and Cetuximab . The main objective is overall survival and secondary end points are response rate, progression

free survival, role of Bio-molecular prognostic factors (EGFR, HPV) and toxicities. The study is ongoing and enrolment of pts will close on December 2016. Hereby we present the preliminary safety report of the study.

Methods. Naïve patients with LA-HNC histological proven, adequate bone marrow, renal and hepatic function and age > 18 yr old are eligible. Treatment consisted of : Arm A docetaxel = 75 mg/mq, cisplatin = 75 mg/mq day 1, FU c.i. = 750mg/mq 96h, every 3 weeks for 3 times and cetuximab loading dose 400 mg/mq followed by weekly 250mg/mq with a standard Radiotherapy (RT) program equivalent daily dose 2Gy up to 70 Gy. Arm B cisplatin = 100 mg/mq day 1,22,43 concurrent with standard RT as in arm A. Statistic: We hypothesized to treat 278 pts to have a statistical power of 0.80 with a two tail design, α error < 0.05. The study will close on December 2016. Hereby we report the safety analysis of the first 170 pts.

Results: INTERCEPTOR accrued 273pts at June 30, 2016. The first 170 are considered in the present analysis (85 and 85 on Arm A and B). M/F were 70/15 and 66/19 in Arm A and B respectively. Toxicities are reported as the worst grade observed during the treatment. Haematological toxicities G1-2-3-4 in Arm A and B were: leukopenia 10/13/4/4 and 16/17/5/1; neutropenia: 6/9/8/10 and 7/16/5/2; anaemia: 40/21/2/0 and 37/17/3/0; thrombocytopenia were 17/3/0/0 and 8/4/1/0 respectively in arm A and arm B. Stomatitis G1/2/3/4 were 9/32/28/4 and 14/26/23/1. Weight loss was classified using CTA-CAE 3.0. In arm A and in Arm B 25/10/2 and 25/12/2 had G1/2/3 loss of weight despite nutritional support. Radiodermatitis G1/2/3/4 was 11/34/14/1 and 17/30/3/0 in Arm A and B. Dysphagia G1/2/3 was reported in 9/16/11 and 10/10/15 patients at first post treatment clinical evaluation. 2 patients (1 in Arm A and 1 in Arm B) developed Renal Failure.

Conclusions: Safety analysis allows study progression. Overall the only significant difference between the two arms was G 3 – 4 neutropenia (p = 0.017).

CETUXIMAB AND RADIOTHERAPY: THE INTERNATIONAL STUDIES

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Aims: In 2006, the landmark IMCL 9815 trial[1] demonstrated that the combination of Radiotherapy (RT) with Cetuximab (CTX), a chimeric mouse IgG1 monoclonal anti-EGFR antibody, led to better median overall survival compared with RT alone in locally advanced squamous cell carcinoma of the head and neck (SSCHN). Despite the fact that the concurrent CTX-RT regimen has since then been established as a standard treatment, its definitive place in the current armamentarium of SCCHN has yet to be defined. In order to provide further insights on CTX-RT combination, we rewiewed the latest international data presented in 2016.

Methods: Head and neck cancer symposium and ASCO meeting proceedings were analyzed.

Results: Gortec 2007-02 randomized phase 3 trial aimed to assess whether a sequential regimen consisting of induction TPF followed by CTX-RT was superior to concurrent chemo radiotherapy (CTRT) in patients with ≥N2b, N3 SCCHN. In the standard arm, 70 Gy at conventional fractionation were delivered together with 3 cycles of carboplatin 70 mg/mq/d + 5FU 600 mg/mq/ d D1-4, according to the Gortec regimen[2]. At a median follow-up of 31.2 months, no difference in PFS was observed between the two arms (370 patients randomized). TTCC 2007-01 was a randomized phase 3 trial aimed to compare the impact on overall survival of CTRT vs CTX-RT after induction TPF with a non-inferiority design. Strikingly, of 519 patients undergoing TPF, 20.2% (105 patients) were not further randomized to the concurrent regimen, mainly due to toxicity. At a median follow-up of 54 months, results were inconclusive due to a low number of events. Focusing on a different paradigm of treatment intensification, Gortec 2007-01 randomized 406 patients with limited nodal spread (N0-N2a) to RTCT ("Gortec" regimen, arm A) or RTCT + CTX (arm B). At a median follow-up of 4.4 years, 3-year PFS was 52.3% in arm B vs 40.5% in arm A (HR = 0.73; 95%CI 0.57-0.94; p = 0.015). At present, several de-escalation trials restricted to HPV- positive patients including CTX in treatment strategy are ongoing[3] or their data are not mature yet: ECOG 1308, RTOG 1016, TROG 12.01 and De-Escalate will be due in the near future.

Conclusions: The backbone of combined CTX-RT may still hold promise both in the context of

intensification strategies for HPV negative SCCHN and as a potential de-escalation component for the HPV positive population. Clinical research in next 5 years will provide further evidence to clarify the role of CTX-RT in SCCHN.

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NEW DRUGS IN LUNG CANCER

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Improving the outcome in lung cancer is arguably one of the biggest challenges in cancer therapy in the word today. Recent years have witnessed accelerated progress in the pre-clinical and clinical development of targeted agents for NSCLC that potentially could be of interest to combine wih radiotherapy and with systemic treatment .[1] The scientific rationale to combine radiotherapy (RT) with targeted (or cytotoxic) agents has been eloquently summarised by Bentzen *et al.*[2] Five exploitable mechanisms describe the radiobiological basis by which a specific

drug may interact with RT to improve a clinical outcome. Briefly, spatial cooperation refers to the use of RT for local disease and systemic therapy for micrometastatic or occult disease. The treatments are not envisaged to interact at the cellular level and therefore not required to be given concurrently. In contrast, the following three mechanisms require the drug to be present at the same time as the irradiation. Cytotoxic enhancement describes the enhancement of cell killing by modulating the induction or repair of cellular DNA damage. Biological cooperation refers to simultaneous targeting of different cell populations in a heterogeneous tumour such as a drug targeting hypoxic (relatively radioresistant cells) while irradiation targets less hypoxic cell populations. Temporal modulation refers to the effect of a drug on biological processes occurring in response to radiation and between fractions (DNA damage repair, cellular repopulation or proliferation, reoxygenation and redistribution). The fifth mechanism is normal tissue protection in which the drug reduces acute and/or late toxicity to enable either an increased RT dose to be delivered or reduce toxicity. There is a strong pre-clinical rationale to combine RT with epidermal growth factor receptor (EGFR) inhibitors, as the EGFR pathway is related to cell proliferation and DNA repair and a survival pathway that is upregulated by radiation itself. The scientific rationale to combine an EGFR inhibitor with RT is therefore principally to exploit the mechanism of temporal modulation and consequently not restricted to patients with sensitising mutations in the EGFR gene that are known to confer enhanced sensitivity to EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib. However, there is suggestion that tumours with an EGFR mutation, such as in exon 21 may be more sen.[3] (3). Transient ''normalisation'' of the abnormal structure and function of tumour blood vessels has been proposed as a mechanism of action by which antiangiogenic agents may alleviate hypoxia within tumour cells, thus improving radiosensitivity through the exploitable mechanism of biological cooperation. The majority of agents available for clinical testing of this strategy target the vascular endothelial cell growth factor (VEGF) receptor signaling pathway. Despite the activity of bevacizumab combined with chemotherapy in advanced NSCLC strategies to combine this antiangiogenic with RT have proved disappointing due to toxicity.[4]

Many of the targets being exploited for interaction with RT are also expressed on normal cells in a quiescent state or in the process of inflammation and wound healing. However, a net gain in the therapeutic ratio is expected when biomarkers can be identified that permit the selection of individuals with mutated or over-expressed targets, preferentially only in tumours.

A major step has been the identification of oncogenic driver mutations in subsets of NSCLC patients and the demonstration of clinical activity in drugs selectively targeting these mutations. The EGFR TKIs were the first class of drug recognised to have enhanced efficacy in patients with NSCLC harbouring sensitising mutations in the EGFR gene.[5,6] The second clinically validated drug target in NSCLC is the EML4-ALK gene rearrangement which confers sensitivity to the first in class ALK TKI crizotinib.[7] Lung cancer is one of the major cancer types for which new immune-based cancer treatments are currently in development. The effects of ionizing radiation on the immune system are under active preclinical and clinical investigation. In the United States, approximately 50 clinical trials are currently testing the addition of radiation therapy to various immunotherapeutic strategies. With such an exponential growth of interest, it might be useful to pause and reflect on the challenges associated with the promise of this new area of research. The discovery that blocking signaling through the T-cell surface immune checkpoint protein PD-1 can produce a very significant impact on clinical outcomes of patients with lung cancer not only gives us effective drugs that work as single agents, but perhaps more importantly has given us the proof-of-principle that lung cancer is certainly an immunotherapeutically responsive disease. With the discovery of the many ways that tumors can evade rejection by the immune system and the development of strategies to thwart these comes real hope that we will be able to significantly improve on results obtained with anti–PD-1/PD-L1 blocking antibody monotherapy. It is clear that there is considerable heterogeneity among patients with lung cancer with respect to which of the numerous potential immunoevasive mechanisms is operational. This means that in all likelihood we must interfere with several immunoevasive mechanisms for individual patients and that we must develop good biomarkers to identify which of these mechanisms is operational among individual patients to choose the proper combination of immunotherapeutics for each individual patient.

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STANDARD TREATMENT OF LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER: CONCOMITANT RADIO-CHEMOTHERAPY

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For unresectable locally advanced non–small cell lung cancer, concurrent chemotherapy and radiation therapy (CCRT) represents an established strategy with significant benefit on survival compared with exclusive RT and sequential integration (SCRT).[1] The benefit is mainly due to an improvement in local control and this observation correlates with biological rationale of concomitant association. Conversely, this approach is hampered by excessive acute toxicity, limiting CCRT to "fit" patients.

Since an overall outcome still unsatisfying, several efforts have spent to improve optimization of CCRT strategy. Looking at CT, multiple drugs have been employed, with different schedules; Cisplatin is the drug of choice, but its use is far to be standardized. So far, few phase III studies have been published, to directly compare different regimens with concurrent RT and standard protocols do not exists. Single-agent low-dose CT performs better than RT alone,[2] but only using Cisplatin rather than Carboplatin;[3] compared with SCRT, single-agent low-dose CCRT does not seem to show further benefit.[4] Thus, the most successful regimens for CCRT still are those using full-dose, Cisplatin-based, old-generation combinations with Etoposide, Vinorelbine, Vindesine and Mitomycin.[1,5] Combinations with third-generation drugs like Paclitaxel and Docetaxel have not shown any benefit, maybe because these agents can hardly be used at full doses in CCRT.[3,6]

So far, predictive and prognostic markers based on molecular characteristics of NSCLC, have opened the doors to a personalized approach of treatments. Newer drugs like Pemetrexed have been validated in selected hystologies and their use in combination with RT is under investigation.[7] Similar, the use of target therapies in CCRT strategies is unclear. Promising results resulted from phase I-II trials investigating Epidermal Grow Factor Receptor-Tyrosine kinase inhibitors. However, several of these trials suffer from selection bias, thus limiting definitive conclusions [8]. Moving to Cetuximab, a well-know phase III trial failed to confirm its benefit on survival.[9]

The influence of age on the outcome of CCRT is controversial. A pooled analysis from RTOG did not reported significant advantages in patients aged more than 70 [10]. Conversely in other subgroups analysis, healthy elderly seem to benefit from CCRT similar to younger patients. However, few data explain how to classify elderly patient as "fit" for CCRT. Similarly, little evidence exists concerning CCRT in patients with Performance Status higher than 1.

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HYPOFRACTIONATED RADIATION THERAPY IN LOCALLY ADVANCED NSCLC. EVIDENCES AND PERSPECTIVE

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Non-small cell lung cancer (NSCLC) is one of the most common and deadly forms of cancer in the United States. Approximately 25% to 40% of patients will present with locally advanced nonmetastatic cancer, and definitive thoracic radiation therapy (RT) plus chemotherapy is recommended if the disease is not resectable.[1] Current RT doses were established by Radiation Therapy Oncology Group (RTOG) study 73-01, a landmark randomized trial published by Perez *et al*.[2] in the early 1980s. Since then, many efforts were undertaken to investigate whether higher radiation doses could be safely delivered in order to improve the outcome. RTOG study 0617 was a randomized trial that compared high dose (74 Gy) versus standard dose (60 Gy) with concurrent and consolidation chemotherapy with or without cetuximab in patients with stage IIIA/IIIB NSCLC.[3] At the first planned interim analysis in June 2011, the high-dose arm (74 Gy) was

closed because it would not result in an overall survival (OS) benefit.

An analysis of a number of trials demonstrated overall treatment time (OTT) to be significantly associated with poorer survival.[4] OTT can be reduced through hypofractionation.

In the present review we will discuss the published data available on hypofractionated radiation therapy in locally advanced NSCLC. Hypofractioanted schedules may be employed as a mean to increase the total radiation doses with approaches: 1) "dose-per fraction" escalation; 2) "Equivalent dose" escalation. The first approach refers to the increase of the dose per fraction, while maintaining the "equivalent dose". Thus the biological advantage is essentially due to the reduction of the overall treatment time. The National Institute for Health and Care Excellence approved the 55 Gy in 20 fractions schedule in the UK.[5] The second approach refers to schedules delivering a higher dose of radiation than 60 Gy, with dose/fraction > 2 Gy. Thirion et al. have published their experience of 72 Gy in 24 fractions (3 Gy/fractions) with surprising outcomes.[6]

In 2010 the QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) review of the literature on normal tissue effects was published, summarizing tolerance data on an organ-by-organ basis.[7] However, this review is primarily focused on conventional fractionation and the lack of established constraints for hypofractionated treatment of NSCLC remains. A summary of dose-volume constraints for hypofractionated regimens in locally-advanced NSCLC will be presented and discussed.

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RATIONALE FOR HYPOFRACTIONATED RADIOTHERAPY AND TARGETED THERAPY IN GASTROINTESTINAL CANCER

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The biggest change in radiation over the past 5 years has been the delivery of very high doses of radiation (with a potential improvement of local disease control) in fewer fractions with precise targeting using IMRT-IGRT.[1]

Among the most prominent advances in oncology, in the recent years, has been the development of molecular targeted therapeutics agents able to modify specific molecular and cellular functions, critical for the tumor cell progression, rather than to the generic processes of cell division.[2]

Targeted agents may cause a toxicity profile independent from those caused by radiotherapy and may therefore facilitate cooperative effects without undue toxicity. Through combined modality treatment, these agents, could improve the therapeutic gain.[2]

Molecular targeted agents may interfere with the processes of DNA damage repair, repopulation, reoxygenation and cell cycle redistribution; therefore, in the range of doses of 2.25–8 Gy per fraction (hypofractionated regimen), when the cells still have a great capacity to repair, may affect the relationship between tumor cell killing and dose fractionation.[3]

Because the endothelial cell plays a central role as a primary target responsible for several clinical consequences of RT (especially for fraction dose > 2 Gy),[4] antiangiogenic/vascular targeting agents are the most studied drugs in association with radiation therapy in particular in gastrointestinal cancer.

The endothelial cell effects are important also for normal tissue responses and side effects; particularly, several studies showed a similar pattern of tissue response in the gastrointestinal tract and in the tumor where, the association between hypofractionated radiotherapy and targeted therapy should be carefully evaluated [4]. Prognostic biomarkers for gastrointestinal cancer, like the chromosome arm 18q deletion, microsatellite instability, *TP53* inactivation and EGFR/KRAS mutations, could be helpful to monitor therapy response and to predict outcome.[5]Quality assured radiotherapy is critical to the success of combination of targeted therapies and hypofractionated radiotherapy; target volume definition and minimization of irradiation to surrounding normal tissues must be the main goals of treatment.[6]

The development of molecular targeted agents represents a renewed opportunity to exploit the beneficial cooperative effects of combined modality treatment also in gastrointestinal cancer.

Today, the optimum scheduling of the two modality (timing and dosing of the drug relative to the total radiation dose and dose/fraction) is not sufficiently known.[7]

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HYPOFRACTIONATED RADIOTHERAPY: STANDARD APPROACH AND NEW CLINICAL PERSPECTIVES

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Current clinical trials and studies showed that hypofractionated radiotherapy (RT) should be a viable treatment option when compared with current fractionation regimens in gastrointestinal (GI) cancer.

Currently, short course (SC) RT is increasingly adopted as a standard of care for cT3 rectal cancer (RC) supported by randomized trials where SCRT followed by surgery reduced the risk of local recurrence also when combined with the total mesorectal excision[1,2] and no differences in terms of outcomes and toxicity were detected when SCRT was compared with long course RT.[3]

Recent trials of phase I and II about concomitant boost with Simultaneous Integrated Boost/ Intensity Modulated Radiation Therapy (SIB/IMRT) show the feasibility of a hypofractionated boost in RC.[4] Dosimetric studies support SIB-IMRT role to allow higher doses to target volumes without a significant increase of dose to the organs at risk, in esophagus cancer (EC) and pancreatic cancer (PC).[5,6]

The impact of stereotactic body radiotherapy (SBRT) in GI cancers remains to be established, but preliminary results look promising for PC and hepatocellular carcinoma (HCC). SBRT has recently been proposed as a new therapeutic option for PC, both in the neoadjuvant and in the definitive setting.[7] The role of preoperative RT is still controversy and the early systematic tumor spread is the principal reason. The adoption of SCRT schedules might allow the administration of a systematic chemotherapy, reducing the overall treatment time. Furthermore, SBRT allows dose escalation which has an important role in PC as indirectly confirmed by clinical trials in term of local control (LC).[8] PC SBRT shows promising outcomes as compared to conventional CRT with acceptable tolerance in terms of acute and late toxicities.[7] Promising rates of LC and low toxicities support also the role of SBRT for hepatic metastases and HCC.[9] Data on cholangiocarcinoma treated with SBRT is poor and the results are comparable to the fractionated CRT.

High dose brachytherapy (BT) excludes adjacent normal tissues from the high dose zone so effectively that it is used as boost in multimodality treatment for EC, extrahepatic biliary duct and PC but the available results are somewhat contradictory about the possible use of BT in a curative setting. Intraluminal BT is still an important part of palliative procedures especially in patients with EC, to reduce dysphagia, pain and bleeding and to improve the patient's well-being.[10]

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NEW DRUGS AND HYPOFRACTIONATION: CLINICAL RESULTS IN RECTAL, PANCREATIC AND HEPATOCELLULAR CARCINOMA

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Current efforts to deliver ablative doses to tumors with acceptable toxicity and to specifically target cellular com-

pounds to improve the efficacy of radiotherapy (RT) in rectal and pancreatic cancer and hepatocellular carcinoma (HCC) are discussed.

Rectal cancer: Two phase III studies, the Polish Colorectal (1) and the Trans-Tasman Radiation Oncology Study (2) compared short-course RT (five 5Gy fraction-SCRT) versus long course chemoradiation (50.4Gy+5FU) followed by surgery. Authors concluded that short SCRT can be applied for operable rectal cancer with an high pelvic control rates and acceptable toxicity. SCRT seems to be best used for "low risk" tumors i.e., those that are >5 cm from the anal margin, with-out circumferential margin involvement, and involvement of fewer than 4 lymph nodes. Moreover, SCRT may represent a safe and effective alternative treatment option in patients with obstructing rectal cancer not eligible for curative treatment (3). Four molecular targeted agents (cetuximab, panitumumab, bevacizumab and aflibercept) have been integrated into chemotherapy regimens to improve response and extend progression free (PFS) and overall survival (OS) with varying success (4-5). No clinical data on combination with hypofractionation regimens are available.

Ref.	Patients no. /disease stage	Study type	Drugs	OS	PFS	Benefit
Burtness *et al*[28], 2014	87/metastatic	II RCT	Docetaxel + Irinotecan ± Cetuximab	6.3 vs 5.4	3.9 vs 4.3	Negative
Fenstermaker *et al*[29], 2014	73/resected	II	GEM + Cetuximab	22.4	NA	Negative
Philip *et al*[30], 2010	743/locally advanced or metastatic	II RCT	GEM ± Cetuximab	5.9 vs 6.3	3 vs 3.5	Negative
Moreno *et al*[31], 2008	66/locally advanced	II RCT	RT + GEM ± Cetuximab	15	-	Negative
Lim *et al*[32], 2014	127/locally advanced	Retrospective	GEM + Capecitabine vs GEM + Erlotinib vs GEM	21 vs 12 vs 15	8.9 vs 5.2 vs 3.9	Negative for Erlotinib
Philip *et al*[33], 2014	10/metastatic	I RCT	GEM + Erlotinib + Cixutumumab vs GEM + Erlotinib	7 vs 6.7	3.6 vs 3.6	Negative
Watkins *et al*[34], 2014	44/advanced	II	GEM + Capecitabine + Erlotinib + Bevacizumab	12.6	8.4	
Herman *et al*[35], 2013	48/metastatic	II	Capecitabine + Erlotinib + RT followed by GEM + Erlotinib	24.4	15.6	
Palm *et al*[36], 2011	42/advanced	II RCT	GEM + Erlotinib	8	5	Negative
Moore *et al*[37], 2007	569/advanced	III RCT	Gem + Erlotinib vs GEM	6.2 vs 5.9	3.7 vs 3.5	Positive
Harder *et al*[38], 2012	17/metastatic HER2+	II	Capecitabine + Trastuzumab	6.9	12.5	Negative
Safran *et al*[39], 2004	34/metastatic	II	Gemcitabine + Trastuzumab	7		Negative
Bodoky *et al*[40], 2012	70/advanced	II	Capecitabine vs Selumetinib	5 vs 3.4	88% vs 84%	Negative
Infante *et al*[41], 2014	160/metastatic	II RCT	GEM + Trametinib vs GEM	8.4 vs 6.7	-	Negative
Fiedler *et al*[42], 2015	522/metastatic	II RCT	GEM +Ganitumab vs GEM	7.2 vs 7	3.7 vs 3.6	Negative
McCaffery *et al*[43], 2013	94/metastatic	I RCT	GEM+Ganitumab vs GEM	10 vs 3.9		Positive
Kindler *et al*[44], 2012	125/metastatic	II RCT	GEM + Ganitumab vs GEM + Conatumumab vs GEM	8.7 vs 7.5 vs 5.9	5.1 vs 4 vs 2	Positive
Bramhall *et al*[45], 2002	239/advanced	RCT	GEM + Marimastat vs GEM	165.5 d	92.5 d	Negative
De Jesus-Acosta *et al*[46], 2014	17/metastatic second line therapy	I	GEM+ inhibitor γ secretase	4	1.5	Positive
Goldstein *et al*[47], 2015	861/metastatic	II RCT	GEM + Nab-paclitaxel vs GEM	8.7 vs 6.6	-	Positive
Hosein *et al*[48], 2013	19/advanced second line therapy	II	GEM + Nab-paclitaxel	7.3	-	Positive
Paut *et al*[49], 2014	30/advanced locally	II	GEM + Capecitabine Bevacizumab	10.4		Negative
Kindler *et al*[50], 2010	535/advanced	II RCT	GEM + Bevacizumab vs GEM	5.8 vs 5.9	3.8 vs 2.9	Negative
Crane *et al*[51], 2009	82/advanced	II	RT + capecitabine+bevacizumab, followed by GEM + bevacizumab	11.9		Negative
Ko *et al*[52], 2010	36/metastatic GEM refractory	II	Bevacizumab + Erlotinib	102 d		Negative
Van Cutsem *et al*[53], 2009	607/metastatic	II RCT	GEM + erlotinib + bevacizumab vs GEM + erlotinib	7.1 vs 6	4.6 vs 3.6	Negative
Sohal *et al*[54], 2015	632/advanced	II RCT	GEM + axitinib vs GEM	5.1 vs 5.4	-	Negative
Spano *et al*[55], 2008	105/advanced and metastatic	II RCT	GEM + axitinib vs GEM	6.9 vs 5.6	-	Negative
Kindler *et al*[56], 2011	632/advanced or metastatic	II RCT	GEM + axitinib vs GEM	8.5 vs 8.3	-	Negative
Reni *et al*[57], 2013	427/metastatic	II RCT	GEM + Aflibercept vs GEM	6.3 vs 7.8	3.7 vs 3.7	Negative
Chiorean *et al*[58], 2014	27/advanced		GEM + Sorafenib followed by RT + GEM	12.6	10.6	Negative
Cascinu *et al*[59], 2014	144/advanced	II RCT	GEM + Cisplatin + Sorafenib vs GEM + Cisplatin	7.5 vs 8.3	4.3 vs 4.3	Negative
Gonçalves *et al*[60], 2012	104/advanced or metastatic	II RCT	GEM + Sorafenib vs GEM	3.7 vs 3.8	9.2 vs 8	Negative

OS: Overall survival; PFS: Progression free survival; RCT: Randomized control trial; Advanced diseases: Locally advanced and metastatic; RT: Radiotherapy; GEM: Gemcitabine.

Table 1. Targeted therapies in pancreatic cancer: studies overview (modifyed from Seicean A, 2015)

Pancreatic cancer (PC): Early metastatization supports the adoption of short RT schedules to avoid a chemotherapy delay. Stereotactic body RT (SBRT) permit the dose escalation, with safe local therapy delivering and minimal interruption of chemotherapy. Most experiences concern the *locally advanced PC* (LAPC) where 1-year and 2-year SBRT local control (LC) ranged from 59 to 95% and 50–92%, with severe late toxicity ranging between 0–22.3% (6). However, no established standard for the SBRT dose and fractionation schedule is reported. Also for borderline/resectable PC, although the studies are even more limited, SBRT plus neoadjuvant treatment was associated with improved OS and PFS (7). New targeted therapies, such as passive immunotherapy, may have a role in combination with radiochemotherapy by targeting various protein kinases, as well as specific immunotherapies, such as vaccines, and immunotherapy targeting tumor stem cells (Table 1). No clinical data on combination with hypofractionation regimens are available.

HCC: The majority of SBRT HCC series include patients unsuitable for standard treatments, but promising outcomes have been reported, with LC of 64% to 95% and OS 43% to 87% at 2 years. Given the risk of HCC recurrence outside the irradiated volume, there is rationale to combine RT with systemic therapies, but currently with limited evidence. Preliminary works combining sorafenib or sunitinib with RT have shown potential for long-term HCC control, but with increased toxicity (8-9-10).

In conclusion, the integration of targeted agents into hypofractionation RT regimens remains the next challenge.

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NEW DRUGS IN PROSTATE CANCER: MECHANISMS OF ACTIONS, INTERACTIONS IN THE TREATMENT AND SIDE EFFECTS

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Androgen receptor (AR) signaling is a crucial survival pathway for whole clinical evolution of prostate cancer and androgen-deprivation therapy (ADT) remains the principal treatment in metastatic disease. Although a majority of patients initially respond to ADT, most of them will develop castrate resistance. Metastatic castrate resistant prostate cancer (mCRPC) is a fatal phenotype of disease and remains strongly dependent of AR. The recent discovery that AR signaling persists during systemic castration led to the development of novel hormone therapies including Abiraterone acetate, Enzalutamide and others new hormone-drugs now under investigation. In recent years, also chemotherapy with docetaxel is dramatically changed. Results from the CHAARTED study (but also preliminary data from STAMPEDE trial) of docetaxel plus ADT for treatment of hormone-sensitive metastatic PC, show an great improve in disease free survival and in overall survival. The emergence of several effective therapies is encouraging, but now is extremely important identify factors (biomarkers) that influence the optimal timing of specific therapies. Considering where to place these agents in the treatment schedule of mCRPC, or whether these agents should be sequenced or combined to obtain the optimal benefit for the patient, is not yet clear. Furthermore, cross-resistance unfortunately may exist between these new agents, which may ultimately influence treatment decisions and sequence choices.

PROSTATE HYPOFRACTIONATION: WHERE WE ARE AND HOW MUCH WE ARE COMPETITIVE

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Radiation Oncology (RT) is radically changed: the available technology allows us to also deliver ablative doses, focused on prostate gland shape with rapid fall off dose to surrounding healthy tissues. Furthermore, Image Guided RT (IGRT) and RT on board tracking systems are able to minimize real time positioning errors or uncertainties of pelvic organ anatomy, including prostate-rectum-bladder daily relationships, before and during radiation delivery.[1]

Nevertheless, the real background for hypofractionation remains its intrinsic radiobiology behavior. Starting from the assumption that, with an increasing RT dose per fraction to prostate gland a radiobiological gain is expected, if α/β is really low probably lower than rectum, the therapeutic window can be enlarged in favor of significant tumor control probability (TCP) improvement and dramatic normal tissue complication probability (NTCP) reduction.[1-3]

Various schemes of hypofractionation have been proposed for prostate cancer RT: from moderate (19-30 fractions) to extreme(4-5 fractions).[4] In regard to Moderate hypofractionation, "superiority designed" randomized trials failed to demonstrate that hypofractionation is superior than conventional RT schemes. However, data of these and other randomized trials (including those designed for "non inferiority") showed that clinical outcomes and side effects are quite similar. More specifically, although in several cases genito-urinary (GU) and intestinal late toxicities (GI) seemed to be higher in hypo arms,[5] long-term freedom from biochemical failure (FFBF) rates were roughly equivalent between conventional and hypofractionation with IMRT (evidence level 1B), with 10-year FFBF rates of: 45-90%(low-risk), 40-60%(intermediate-risk), 20-50% (high-risk).[4] Also Quality of life seems to be comparable in the two arms as recently published by CHHiP trial with 2100 partecipants.[6]

Thus, while moderate hypofractionation, especially when IMRT, IGRT are utilized, represents a viable RT option to offer in clinical practice for prostate cancer patients, as confirmed by various international guidelines,[7] extreme hypofractionation deserves specific considerations.[3,4,7]

The assumed specific low α/β ratio of prostate cancer certainly could justify to further reduce the number of fractions to increase the therapeutic ratio. A potential technology gain from the use of upgraded IGRT, IMRT SBRT, provides sharper dose fall-offs and better dose conformity. Moreover, a dramatic reduction of RT duration from 6-8 to 1-2 weeks seems to be convenient for patients logistics, RT departments waiting lists and globally for Health system costs.[1-4]

In absence of randomized trials, for extreme hypofractionation only Phase I-II studies and retrospective experiences are available in this setting.[1-4,7] Although the shorter follow-up, SBRT and similar approaches to deliver extreme schedules of doses are showing promising rates of biochemical control (5-year FFBF of >90% for low-risk patients).[4] Nevertheless, SBRT can have more contraindications than conventional RT, and patients with certain contraindication (*e.g.* inflammatory bowel disease, large transurethral removal of prostate defect, low urinary flow, greater prostate gland dimensions) are usually excluded on clinical trials and protocols.[3]

Thus, extreme hypofractionation is strictly related on clinical expertise and technology assessment and could cautiously represent an option where patient selection is done, inside rigid protocols.[8] In the next future another possibility will be faced by clinicians: is the single fraction feasible in strictly selected prostate cancer patients? To date, only theoretical speculations are available and this approach remains at first step of investigational procedure.[9]

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COMBINATION OF ABLATIVE RADIOTHERAPY AND NOVEL DRUGS IN OLIGOMETASTATIC AND OLIGORECURRENT PROSTATE CANCER

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Patients with metastatic prostate cancer (mPC) represent a heterogeneous group, for whom hormonal therapy, +/- docetaxel-based chemotherapy is considered a cornerstone treatment.[1] In the era of individualized medicine, however, maximizing treatment options using systemic therapy and radiation therapy is being increasingly explored - especially in long-term survivors with limited disease burden - and some interest in the oncologic benefit of treating the prostate in a oligorecurrent setting (mPC with primary tumor uncontrolled) has also raised. As in other solid tumours, a growing evidence indicates that patients diagnosed with a limited number of metastases - the so-called oligometastases - have a better prognosis compared with patients with extensive metastatic disease.[2,3] Along with the introduction of novel imaging modalities, which has certainly increased the detection of mPC, the use of a lesion-directed approach such as stereotactic body radiotherapy (SBRT) may be effective and have the potential to spare or to delay the toxicity associated with the use of systemic therapies.[4] Additionally, when a oligometastatic disease become castration resistant, the ability to target the resistant clones by means of SBRT in conjunction with the opportunity to maintain the active drug on those still exhibiting sensitivity, might delay the progression to an overwhelming polymetastatic state, with the potential to extend overall survival.[5,6] On the other hand, emerging data, mainly generated from retrospective surgical series, show survival benefits in mPC patients following definitive therapy for the prostate.[7] Whether the irradiation of primary tumor in mPC (+/- associated with systemic treatments) might improve the therapeutic ratio like in metastatic renal cell carcinoma, remains investigational. In this framework, radiation therapy administered in the form of SBRT has the potential to play an important role owing to its intrinsic capability to act as a more general immune response modifier, as well as to the potentially better toxicity profile compared to surgery [8]. Clinical experience and challenges in the combination of ablative radiotherapy and novel drugs in oligometastatic/oligorecurrent prostate cancer are reviewed and discussed.

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BONE-TARGETED DRUGS: BIOLOGICAL BASIS AND RATIONAL USE

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Bone is the most common site for metastases in patients with breast and prostate cancers. Increased bone resorption is the hallmark of metastatic bone disease leading to skeletal-related events (SREs), wich include bone pain, pathological fracture, spinal cord compression and hypercalcemia. These SREs are really frequent without treatment to reduce bone resorption using bone targeted therapy (BTT).

The goals of BTT, bisphosphonates (Bs) and denosumab (D), are in fact the reduction of incidence and the delay in occurrence of SREs with improvement in quality of life, pain control and in some cases increased survival.

Few data are available on the optimal use of BTT, but several studies showed that to maximize their benefit they should be initiated as soon as bone metastases (BM) are diagnosed even if asymptomatic.

Since the risk of SREs is going to continue BTT should be prolonged beyond 2 years to prevent further skeletal events, and specifically it should not be interrupted once

skeletal events occur.

Bs accumulate in the mineralized bone matrix and are released during bone resorption. Second generation nitrogen-conteining Bs (pamidronate, zoledronic acid) act affecting osteoclast activity and survival by inhibiting a key enzyme of the mevalonate pathway (farnesyl pyrophosphate synthetase), preventing prenylation and activation of small signalling proteins such as Ras.

Recent meta-analytic data show that all Bs confer a significant advantage in terms of prevention of SREs, but phase III comparative studies demonstrated that zoledronic acid seems to be better than pamidronate and ibandronate. D is a human monoclonal antibody with high affinity and specificity for RANKL, ables to neutralize it as OPG, with theoretical immunosuppressive action on T and B lymphocytes development. Hence RANKL play an important role in migration of cancer cells, D may delay the development of BM and be used in the prevention of SREs. Recent studies showed that D, compared with zoledronic acid, is superior as inhibitor of RANKL and in prevention and delay of SREs, improving quality of life, also for sc administration and for good toxicity profile. Recently a new treatment opportunity for patients with prostate cancer and BM is represented by radium-223. It is an alfa-emitter and showed not only efficacy in preventing symptomatic skeletal events, but it is the first BTT associated with a significant OS improvement.

More recently several new drugs have been tested specifically in prostate cancer patients, such as cabozantinid, dasatinib, anti-endothelin drugs, and cathepsin K inhibitors, for bone disease control. Some of them documented efficacy in delaying SREs and improving bone pain, but at now all these drugs did not show any improvement of survival benefit in phase III studies.

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CLINICAL SCENARIOS OF BONE METASTATIC DISEASE

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Introduction: Survival rates for many primary cancers continue to improve, and prevalence of bone metastases (BM) will increase. The highest incidence of bone metastases is found in individuals 40–65 years of age. Males are slightly more prone to the development of bone metastases, probably reflecting the slightly higher prevalence of lung cancer in men, and of prostate cancer over breast cancer. This disparity may vanish, however, as new available treatment for breast cancer increase the overall survival of patients with this disease, thus increasing the period during which lesions in the bone and spine may arise. Extremities, pelvis and spine are the region more often affected by BM.

Clinical Presentation and Diagnostic Workup: The morbidity associated with BM, often referred to as skeletal-related events (SREs), includes bone pain (50-90%) that may require analgesics or the need for radiotherapy (29%) or surgery (3%), spinal cord/nerve root compression (7%), hypercalcemia (10%), and pathologic fractures (22%).

Bone pain. The most common complaint in patients with BM are pain and/or impaired mobility. Bone pain may be nociceptive or neuropathic. Nociceptive pain is caused by stimulation of nociceptors in the endosteum by chemical mediators, including prostaglandins, leukotrienes, substance P, bradykinin, interleukins-1 and -6, endothelins and tumor necrosis factor-alfa (TNF-alfa). Nociceptive pain may also result from direct infiltration or chemical irritation of nerves by tumors

Pain can be either a well localized focus of pain or a diffuse ache. Pain from extremity lesions tend to be well defined, in contrast with areas of spinal or pelvic involvement, which may produce vague, diffuse symptoms. If the lesion is in a weight-bearing area, eventually the pain tends to worsen with weight-bearing activity. Spinal metastases may also present as back pain in isolation, typically due to mechanical instability, or be accompanied by neurological symptoms (e.g., numbness, tingling, weakness, incontinence). Functional pain is caused by the mechanical weakness of the bone that can no longer support the normal stresses of common daily activities. The development of functional pain may be a marker for bone at risk of fracture. Mechanical pain is more typically associated with the focal bone loss within lytic lesions; however, it is important to note that radiographically, osteoblastic lesions may also weaken the bone through associated areas of osteolysis. This increases osteoclastic activity in osteoblastic lesions and therefore also compromises structural integrity.

Therefore, in patients with known cancer, the presence of pain and/or the other aforesaid symptoms cannot be under evaluated, because they can be suggestive of BM until proven otherwise. Bone scintigraphy is used for the diagnostic workup, allowing a total skeletal assessment, which is helpful for confirming the doubt of BM and the extent of the metastatic spread. Traditional X-ray imaging is used for the evaluation of suspiciously enhancing lesions. It permits a differentiation between lytic, blastic or mixed lytic-blastic BM. Computed tomography (CT) also shows smaller osteolysis, allows diagnosis of tumor extension into adjacent soft tissues and permits the evaluation of bone stability better than traditional X-rays. When a myelo-radicular compression is suspected or already diagnosed by CT, magnetic resonance imaging (MRI) has an important role in studying the local extension and the disease diffusion along all the spine. Nuclear imaging include bone scintigraphy (BS) and PET. Almost 50% of BS results are false-negative for bone metastases, and BS does not accurately distinguish between pathologic and non-pathologic fractures. PET is

now more commonly used for whole body metastatic surveys and as a staging technique in patients with known systemic cancer. A recent comparison of BS and PET found that PET was more accurate. However, PET is not part of the standard evaluation for its poor spatial resolution which necessitates concomitant use of CT or MRI and because of limited availability and resources,.

Spinal cord compression (SCC). SCC is considered a neurological emergency situation and suspected cases require urgent evaluation and prompt treatment. If left untreated for more than 24-48 hours, this may result in permanent paraplegia or quadriplegia in affected patients. Symptomatic SCC occurs in about 20% of patients with BM to the spine. Of these, 80% will experience muscular weakness or paralysis. Sensory changes include numbness and anaesthesia distal to the level of involvement. Approximately 17-35% of patients will have multiple sites of metastases within the spine. Urinary retention, incontinence and impotence are usually late manifestation of cord compression. However, patients with lesions at level of the conus medullaris can present with early autonomic dysfunction of the bladder, rectum and genitalia. Back pain occurs in the majority of cases, often localized to the area overlying the tumor and generally increases with activities such as coughing, sneezing or staining that increases intradural pressure There may also be radicular pain, radiating down a limb or around the chest or upper abdomen. Pain can be unilateral or bilateral depending on the level of spinal involvement. SCC to the cervical or lumbosacral region frequently results in unilateral pain, while involvement in the thoracic spine frequently results in bilateral pain. Local pain typically precedes radicular pain and can precede the appearance of other neurological signs by weeks or months. The most important predictor of survival was the ability to walk before and after treatment. These results suggest that early diagnosis and intervention may improve both outcome and survival. Early detection is imperative in the management of SCC. Early indications are often nonspecific, and a high index of suspicion on the part of clinicians is necessary. Definitive diagnosis of SCC is usually made by an MRI of the entire spine. In patients with previously diagnosed cancer, the presence of back pain alone is enough to warrant a full-spine MRI which allows the diagnosis of SCC, the numbers of interested sites and a correct differential diagnosis between benign and malignant causes of vertebral body compression fracture

Hypercalcemia. Hypercalcemia is the most common metabolic complication of BM. In breast cancer hypercalcemia traditionally occurs in about 10-20% of cases, and also commonly occurs in patients with lung and kidney cancers and certain hematological malignancies such as myeloma and lymphoma. In most cases, hypercalcemia is a result of metastatic bone destructions, with osteolytic lesions present in 80% of cases. However, the incidence of hypercalcemia has fallen markedly over the past two decades through the increasingly widespread use of bisphosphonates and chemotherapy. Hypercalcemia is mediated by up 2 principal mechanisms in metastatic bone disease, First, an increased osteoclastic activity, especially in patients with advanced metastatic disease and severe bone destruction at multiple sites. Second, a mobilization of skeletal calcium into the blood circulation and stimulation of the kidney to inappropriately reabsorb calcium by parathyroid hormone-related protein (PTHrP) secreted by certain tumors, particularly squamous cell histology. With mild degrees of hypercalcemia, patients are often asymptomatic but, as the level of calcium rises, patients become progressively dehydrated and may develop symptoms such as lethargy, nausea, vomiting, anorexia, and disorientation. Rehydration and initiation of bisphosphonate therapy will usually restore calcium levels to normal .

Pathologic fractures (PF). PF may be the first sign of metastatic bone disease, and are most commonly seen in osteolytic metastases involving the cortex. A fracture of the weight-bearing long bones can be a devastating event even in a healthy person. Patients with breast, lung, renal, and thyroid cancer are most like to have a PF due to bone metastases. Even in castrate-resistant prostate cancer, where osteoblastic metastases are typical, annual fracture rates in excess of 20% may be seen. As the development of a long bone fracture can have such detrimental effects in quality of life (QoL), efforts have been made to predict sites of fracture and to prophylactically manage the impending fracture through surgery. PF are associated with reduced overall survival in patients with bone metastases. Prophylactic orthopaedic fixation is often advised to avoid the trauma of PF, as it is less traumatic for patient and easier for surgeon. Radiotherapy generally follows surgery to inhibit further tumor growth and avoid further bone destruction. When a PF has occurred, the primary goal is to provide pain relief. Secondary intentions are to achieve stability and restore function using surgery (where there are no medical contraindications) and radiotherapy. Radiographic criteria for operative management of lytic metastases to bone are largely based on the femur. A fracture can be at risk of fracture due to the size (i.e., affecting >50% of the cortex or > 5 cm) and location of lesion (i.e., in a weigh bearing area). For these reasons patients should be referred to the orthopaedic surgeon.

Conclusions: In cancer patients a referred bone pain cannot be under evaluated in radiation oncology clinical practice. An accurate clinical assessment is mandatory during follow up. Radiological exams -that are often the only tools that allow a correct diagnosis- should be prescribed without hesitation to give a correct diagnosis and an appropriate therapy. This approach can improve QoL and sometimes survival of BM patients.

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LOCAL AND SYSTEMIC RADIOTHERAPY IN THE TREATMENT OF BONE METASTASES

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Radiation therapy is an effective treatment for bone metastases and can provide significant benefit to patients.[1] The aim of radiotherapy for metastatic bone disease is not only relief of bone pain but also prevention of pathological fractures, improved mobility and quality of life.[2,3] In addition the notion of oligometastases and oligo-recurrence has recently been proposed,[4-8] with the suggestion that local therapy to a small number of gross metastatic sites and recurrences may result in prolonged survival or even cure.[4-7] The most favorable prognostic factor is the control of primary lesion.[8,9] The oligo-recurrence overcomes this problem, these are cancer patients with one to several metastases or recurrences but have controlled primary lesions.[6] Lastly, the concept of sync-oligometastasis was proposed as the state that cancer patients have ≤5 metastatic or recur-rent lesions with active primary lesions.[10] In this scenario you can customize radiotherapy approach and different doses fractionation including 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, and a single 8 Gy fraction have shown pain relief equivalency. Fractionated treatment courses are associated with an 8% re-treatment and 20% after a single fraction.[10] About 40% of patients treated with radiotherapy fail to obtain pain relief[10] and the increase of life expectancy requires to repeat radiotherapy (retreatment),[3] 8 Gy in a single faction seems to be non-inferior and less toxic with an overall pain response of 28% versus 31% of the multiple fractions.[11]

Spinal metastases often cause pain and SBRT is an alternative treatment to palliative surgery, it is a non-invasive modality and improves a quality of life in patients with isolated spinal metastasis.[12] Stereotactic body radiotherapy may be useful for patients with newly discovered or recurrent tumor in the spinal column or paraspinal areas. It is necessary to treat this patients in centers with sufficient training and experience.

Radiotherapy remains the main treatment option for local symptoms, alternatively in patients with diffuse persistent bone pain Systemic Therapy (Radionuclide and bisphosphonates) offers a valuable treatment options for metastatic bone pain. Bisphosphonates do not obviate the need for external beam radiotherapy for painful sites of metastases and may indeed act effectively in combination with EBRT. Radionuclides are used up in osteoblastic metastases. They are systemic agents that act locally at sites of metastatic bone disease delivering the dose to a depth of 0.2 to 3.0 mm from their sites of deposition. Though the surrounding normal tissues are relatively spared, these agents can cause myelosuppression.[13] The incidence of myelosuppression is low, but may increase in patients at highest risk with tumor infiltration of bone marrow and/or toxicities after chemotherapy. ^{89}Strontium and ^{153}Samarium have a pain relief onset of 2- 3 weeks, partial response rates of 55-95%, complete response rates of 5-20%, and a mean duration of pain relief of 3-6 months. [14] Data does suggest that hemi-body EBRT may be used with equal success in patients with multiple sites of painful bone metastases in geographic areas where access to radionuclides is limited or in cases where their use is contraindicated.[15] ^{223}Ra dichloride is approved for intravenous radiotherapy for patients with osseous metastases from castration-resistant prostate cancer. It is an alpha-particle emitting radioisotope that mimics calcium and forms complexes with hydroxyapatite at areas of increased bone turnover, such as osseous metastases.[16] In conclusion the external beam radiotherapy has been and continues to be the mainstay for the treatment of painful, uncomplicated bone metastases.

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MELANOMA: CLINICAL DATA ABOUT ASSOCIATION OF RADIOTHERAPY AND DRUGS FOR BRAIN AND EXTRACRANIAL TARGETS

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The landscape of treatments in metastatic melanoma drastically changed after the introduction of targeted therapies and immunotherapy. Several preclinical findings support the rationale for the combination of immune checkpoints inhibitors and radiation. Retrospective observational series and few prospective trials showed the potential synergistic effect for metastatic melanoma. Some case studies have reported that BRAF inhibitors Vemurafenib and dabrafenib have radiosensitizing effects. A retrospective analysis by Hecht and colleagues found that 57% of 70 patients receiving concomitant therapy experienced acute or late toxicities. Case reports indicate that radiosensitization reactions can also occur in patients treated with RT and subsequent BRAF inhibition. Several analyses found that concurrent or proximity of RT and systemic therapy treatment improved response rates and OS, although results are inconsistent regarding the optimal order of administration. Radiodermatitis was the most common of these toxicities, with acute events (grade ≥2) occurring in 36% of patients treated with concomitant radiotherapy plus BRAF inhibitors. Severe dermatitis has also been reported in patients treated with WBRT and BRAF inhibitor therapy (either concurrent or sequential). In the retrospective study by Hecht and colleagues, BRAF inhibitor therapy increased the risk of acute dermatitis among patients treated with WBRT (44% vs. 8%; P = .07). In contrast, a retrospective study by Gaudy-Marqueste and colleagues found no evidence of radiodermatitis in 30 patients who received SRS and BRAF inhibitor therapy. On the other side, the association of radiation and immune checkpoint inhibitors is safer. Results from retrospective studies suggest that for patients with metastatic melanoma (including brain metastases), combining checkpoint immunotherapy (ipilimumab or nivolumab) with radiation of CNS or non-CNS metastases does not significantly increase the risk of toxicity. However, multiple retrospective studies on ipilimumab and one on nivolumab failed to show that adding checkpoint immunotherapy provided additional clinical benefit in patients receiving radiotherapy for brain metastases, at least regarding response rates and OS. Another important mechanism yearns for the association between radiation and immune checkpoint inhibitors are the abscopal effect. Observed responses in non-irradiated tumors are defined abscopal. Prospective trials are needed to confirm these results because the delayed kinetics of ipilimumab response complicate interpretation of retrospective data. Several prospective trials are ongoing with the aim of further exploring this combination in the clinical setting, hopefully confirming initial observations and opening a new therapeutic window for advanced melanoma patients.

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BRACHYTHERAPY IN THE TREATMENT OF SKIN-CANCERS

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Skin cancers are classified according to the nature of the cells from which they originate. They are classified in: Basal Cell Carcinomas (BCC), Squamous Cell Carcinomas (SCC), Melanomas and other rare histologies. The non-melanoma skin cancers are the most frequent tumors. 80% of these is represented by the BCC and the remaining 20% by SCC.[1] Melanoma accounts for 3% of all skin cancers but causes 75% of skin cancer related deaths.[2] The available therapies vary according to the histology and clinical presentation of the disease, and it is often enough to perform only local treatments, especially for non-melanoma skin cancers. The most common local therapies are surgical excision and radiation therapy (external beam or brachytherapy).[2] The choice between these two alternatives depends on the characteristics of the disease, its location and the possible cosmetic results.[3]

Radiation therapy has advantages in treating large lesions infiltrating deep tissues, as adjuvant therapy in case of non-radical surgery[4] and recurrence.[5] Radiation therapy is generally recommended for primary tumors and inoperable relapses of the face (especially if located on the eyelid, nasal wing or lip) and large lesions ear, forehead and scalp.[6] Other local therapies are represented by thermal coagulation, cryotherapy, local chemotherapy with 5-FU, electrochemotherapy and photodynamic therapy.[7] The choice between External Beam Radiotherapy and Brachytherapy takes into account many factors: size, location, infiltration depth and team expertise. Regarding brachytherapy, two different techniques can be used: superficial or interstitial brachytherapy.

Superficial brachytherapy con be performed using specific surface contact applicators or custom made mats or

moulds. This last technique is used especially in curved surfaces as in the face, arranging the plastic tubes in parallel for adequate coverage of the tumor area plus margins.[8] Interstitial brachytherapy is indicated when other techniques are not suitable for an optimal dose coverage of the tumor in particular when the thickness is more than 0,5 cm.[9] Even if LDR, HDR, and HDR techniques are all used in published experiences: the use of Intensity Modulated Brachytherapy (IMBT) procedures is preferable, especially when a regular implant configuration is difficult due to anatomical reasons. IMBT enables to optimize and individualize the dose distribution. The prescription dose needs to encompass the complete clinical target volume (CTV) plus margins and spare as much as possible the surrounding healthy structures. The results of brachytherapy are similar to those obtained with external beam radiotherapy. The range of local control using brachytherapy varies from 99% to 87%. The outcomes are better when the disease is represented by a primary tumor more than by a recurrence.[8]

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LOCAL CONTROL AND TOXICITY RESULTS IN BREAST CANCER TREATED WITH IORT BOOST AND EXTERNAL BEAM RADIOTHERAPY, WITH PARTICULAR ATTENTION TO THE ASSOCIATION WITH SYSTEMIC THERAPIES

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Aims: Radiation treatment after conservative surgery for breast cancer is the standard of care; in fact it reduces the risk of local recurrence even if it doesn't seem to have any impact on survival. EORTC study has finally documented the significant impact of a boost dose on the tumour bed in the local control particularly in young women.

Intraoperative radiation therapy (IORT) is a technique for delivery a single dose directly on the surgical bed, with the aim of administering a high dose to the target volume while respecting adjacent critical structures. There are limited data on the use of IORT in breast cancer, in particular as anticipated boost, however with excellent results in terms of local control and cosmetics, with acceptable toxicity. Recently some experiences have been reported about the IORT stimulatory effect n the wound fluid of operated breast cancer and that any radiotherapy delay may reduce local control. Furthermore IORT seems to change the cytokine pattern into a less-stimulating microenvironment. A persistent effect on the tumour bed can be expected owing to the micro vascular damage of high single dose used as boost.

Methods and Results: The experiences currently in progress on the use of IORT as a boost in breast cancer are presented, followed by standard fractionated radiotherapy (IRMA study) or hypofractionated radiotherapy (HIOB study), in terms of local control, aesthetic outcomes and toxicity, with particular reference to the integration with new drugs used in the treatment of breast tumors.

Conclusion: IORT used as boost during BCS has several theoretical advantages: radiation is delivered in the earliest time, eliminating any tumour cell proliferation before the start of external beam radiotherapy; geographic miss after oncoplastic surgery can be avoided; skin dose is lowered, thus reducing the risk of cutaneous side effects. Intraoperative treatment as anticipated boost could change the microenvironment, so enhancing the role of systemic drugs, in particular monoclonal antibodies.

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OUTCOME OF RE-IRRADIATION WITH IORT OR AFTER IORT IN BREAST CANCER

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Introduction and aim: To evaluate the outcome after partial breast re-irradiation with IORT for in-breast tumor recurrence (IBTR) following second breast conserving surgery or in case of recurrence after IORT. For patients suffering of recurrent breast cancer within the irradiated breast, generally mastectomy is recommended. The normal tissue tolerance does not permit a second full dose course of radiotherapy to the entire breast after a second breast-conserving surgery (BCS). A novel option is to treat these patients with partial breast irradiation (PBI). This approach is based on the hypothesis that re-irradiation of a limited volume will be effective and result in an acceptable frequency of side effects.

Methods: We performed a survey between all italian centers using IORT for partial breast irradiation. The list of centres was obtained from the Associazione Italiana di Radioterapia Oncologica (AIRO) website. We collected data on the outcome of patients who had a recurrence after IORT or received IORT for a recurrence after conventional radiotherapy. Outcome were collected both in terms of oncologic result and of therapy induced toxicity/cosmetic outcome. We compared our data with the corresponding evidence present in literature. Published evidence is scarce, reporting few hundreds of patients overall. The vast majority treated by brachytherapy.

Discussione and Conclusions: In a highly selected group of patients with IBTR, partial breast irradiation after second BCS could be a viable alternative to mastectomy, yielding high breast preservation rates without compromising oncologic safety. Whereas the evidence for brachytherapy is more solid, there is still little information about the effectiveness of PBI via IORT, which therefore should be investigated. There is no consensus on the optimal local treatment of a patients who present a IBTR after BCT and IORT. One potential treatment option for more favorable recurrences is a second attempt at BCT possibly completed by a PBI because of a more limited volume of initially irradiated breast tissue. Limited data are now available on oncologic and cosmetic outcome in this subset of patients.

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THE ROLE OF RADIOTHERAPY IN THE MODULATION OF ANTITUMOR IMMUNE RESPONSE

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Radiotherapy has an established role in the treatment of cancer, and its biological effect has traditionally been attributed to the direct tumoricidal properties of radiations. Recently, several studies, supported by an increasing number of clinical observations, have suggested that radiotherapy may exert different immunomodulatory effects on tumor cell and its microenvironment contributing to its therapeutic efficacy (Table 1).

Table 1. Immunogenic effects of radiation therapy.

Biological effect on tumor cell	Immunologic consequences
Cell surface translocation of calreticulin (Dendritic Cell - DC "eat-me" signal)*	Increased tumor cell phagocytosis through CD91
Release of High Mobility Group Box 1 (HMGB1)*	Immune cells chemotaxis, TLR4-mediated DC activation and antigen cross-presentation
Release of ATP (activator of the P2XR7 purinergic receptor of DC)*	DC inflammasome activation, secretion of IL-1 beta, and consequent priming of IFN-gamma producing CD8+ T cells
Cell surface translocation of heat-shock proteins (HSP)	Immunostimulatory effect on antigen-presenting cell (APC)
Reduction of CD47 expression (DC "do not-eat-me" signal)	Increased tumor cell phagocytosis
Release of tumor-derived DNA	Activation of the DNA-sensing pathways (STING) on DC resulting in cell activation and secretion of type I IFNs
Smac release from mitochondria	Increased sensibility of tumor cells to Granzyme-induced apoptosis
MHC molecules upregulation	Improved antigen presentation (i.e. tumor recognition by immune cells)
Increased expression of NKG2D ligands, co-stimulatory molecules, adhesion molecules (e.g. ICAM-1)	Improved recognition of tumor cells by cytotoxic lymphocytes
Generation of new peptides and increase of the pool of presented peptides	Improved anti-tumor response
Release of pro-inflammatory cytokines	Improved anti-tumor response
Upregulation of death receptors (e.g. FAS)	Increased cytotoxicity of T cells
Release of chemokines (e.g. CXCL16, CXCL10), normalization of tumor vasculature and changes in vascular endothelium	Increased recruitment and migration of immune cells at the tumor site
* These processes constitute the "immunogenic cell death" of tumor cells	

The immunogenic effects of radiotherapy raised the concept that radiations can act as an *in situ* vaccine thus providing an explanation for the ability of radiotherapy to induce regression of metastases outside of the irradiation field (the so-called abscopal effect). Nevertheless, in advanced tumors, antitumor immunity elicited by radiotherapy alone is generally insufficient to induce complete responses, and immune escape mechanisms eventually prevail. In recent years, the great advances in cancer immunotherapy have contributed to establish its role as the fourth pillar of cancer treatment, but, also in this case, the efficacy of immunotherapy is hampered by the immune evasion mechanisms of tumor cells. These considerations provided the rationale for combining radiotherapy with immunotherapy and paved the way for novel anticancer treatments based on the synergistic and complementary potentials from both treatments. In preclinical studies and clinical trials, radiotherapy has been associated with different immunotherapies, but the most interesting results have been observed in concomitance with immune checkpoint inhibitors targeting "Cytotoxic T-Lymphocyte Antigen 4" (CTLA-4) or "Programmed-Death-1" (PD-1) pathways. At this time, robust preclinical data and early clinical observations, report safety and efficacy from treatment regimens combining immunotherapy with radiation, nevertheless, many

important questions still need to be addressed and elucidated. For example, the timing of radiotherapy with respect to immunotherapy, the target site of irradiation, the radiation dose and fractionation needed for inducing the optimal immune response are still unclear. This presentation aims to summarize the recent literature on the complex immunogenic effects induced by radiotherapy including preliminary results emerged from current clinical trials combining radio-immunotherapy.

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HYPOFRACTIONATED RADIOTHERAPY: WHY NOT?

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Radiotherapy (RT) after lumpectomy in early breast cancer patients is an established treatment modality which conventionally takes 6-7 weeks to complete. The lower the ratio of alpha/beta (in Gy), the greater is the effect on normal and malignant tissues of changes in fraction size. Healthy tissues of breast and rib cage are sensitive to fraction size with alpha/beta values 5 Gy or less, so small changes in fraction size can produce relatively large changes in effects of RT on these tissues.[1] Shorter RT schedules have been tested in large multicenter randomized trials and have shown equivalent results to that of standard RT. Four randomized clinical trials have investigated hypofractionated whole breast radiation schedule (39-42.9 Gy in single fractionations di 2.6-3.3 Gy) compared to standard 50 Gy in single fractions di 2 Gy.[2-5] The 10 year follow-up data from START trials [6] are consistent with the 10-year results of the Canadian trials [5] which reported that local tumor control and breast cosmesis were similar with a regimen of 42.5 Gy in 16 fractions over 3.2 weeks compared with 50 Gy in 25 fractions over 5 weeks. The START trials reported radiation-related effects to normal breast tissue such as breast shrinkage, teleangiectasia, and breast edema as less common with the hypofractionated fraction regimen.[6] Data on lung and cardiac morbidity and survival rates is yet emerge for the current hypofractionation schedules. Even 10 years is insufficient to estimate the relative risk of heart disease, but the issue of fractionation is irrelevant for this organ.[7] An excess risk of ischaemic heart disease is apparent after cardiac doses >10 Gy, so the heart must excluded from the treatment volume whatever fractionation regimen is used.[8] Fractionation is also irrelevant where the lung is concerned, since lung tolerance, viz. 20 Gy in 2.0 Gy fractions, is exceded whatever fractionation is used. Hypofractionation in breast cancer is an issue that can have widespread implications in breast cancer throughout the world. If found to have equivalent cosmesis, locoregional control, and survival to standard doses and schedules; it would be a revolutionary breakthrough for the future for breast cancer. Unfortunately, the demonstration of all of these would need follow-up data nearing 15 years. For now, the general acceptance of hypofractionation in breast cancer hangs in the balance. If hypofractionation works, it will be a major breakthrough as it will reduce the number of hospital visits and also the waiting list in several cancer centers in developing countries where patients burden is an alarming problem.[9]

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THE ASSOCIATION BETWEEN TARGET THERAPY AND HYPOFRACTIONATED RADIOTHERAPY: LIGHTS AND SHADOWS

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Aims: To evaluate toxicity and outcome in breast cancer patients treated with target therapy and whole breast hypofractionated radiotherapy (HF-WBI).

Materials and Methods: Three randomized trials[1-3] in the last years have compared hypofractionated with con-

ventional radiotherapy for whole breast irradiation, showing the same results in terms of local control, survival and toxicity. The impact of the modern anthracycline- and taxane-based regimens in patients treated with HF-WBI is not well-known. For this reason, the use of hypofractionated regimens has been cautiously implemented in patients also receiving chemotherapy. The integration between target therapy and HF-WBI has been even less studied. This association is supposed to increase the risk of acute toxicity and poor cosmetic outcome.

Results: In the START A and B Trials 22% and 35% of patients, respectively, received adjuvant chemotherapy. In a retrospective study, Hijal *et al.*[4] reviewed prospectively collected effects of HF-WBI (42.4 Gy in 16 fractions) in 162 patients. Forty-eight patients (30%) received chemotherapy. Rates of acute and late skin toxicity were not significantly different with or without the use of chemotherapy. Kouloulias *et al.*[5] evaluated a unique hypofractionated radiotherapy schedule with 51.3 Gy in 18 fractions three times per week for early breast cancer resulting in a good tolerance; 76% of patients underwent hormonotherapy with tamoxifen. A recently study conducted at National Cancer Institut of Milan[6] showed that chemotherapy (22% of patients) and hormonotherapy with aromatase inhibitors (82% of patients) didn't impact on acute and late toxicity. 11% of patients received also [7] showed the same results. In this study 8% of patients underwent trastuzumab and 80% hormonotherapy.

In the metastatic setting, in last years, they have been published few works on the association between HF-WBI and target therapy. Targeting of the PI3K signaling pathway combined with PARP inhibition maybe a feasible approach to enhance effects of radiation in BRCA-proficient TNBC.[8] Meattini *et al*.[9] evaluated the safety of eribulin in metastatic breast cancer patients concomitantly treated with radiotherapy, showing the feasibility.

Conclusions: Recently-updated results from the Canadian and START trials also indicate that hypofractionated regimens represent a good treatment choice for many appropriately-selected women. Chemotherapy, trastuzumab and hormonotherapy with tamoxifen or aromatase inhibitors didn't impact on acute and late toxicity. However, the applicability of the results of these trials, in patients undergoing more recently target therapies, needs additional investigations.

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HYPOFRACTIONATED RADIATION THERAPY IN HEAD AND NECK CANCER: HOW DO THE DOSE CONSTRAINTS CHANGE?

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Approximately 70% to 75% of patients with Head and Neck (H&N) squamous cell cancers arising from the oropharynx, hypopharynx or supraglottic larynx have stage III or IV disease at presentation with 5-year survival rates of 30% to 40%. Radiation therapy (RT) and chemotherapy (CHT) strategies have evolved over the past several decades to improve these results, including split-course RT, alterated fractionation RT, concomitant CHT-RT, induction CHT, targeted therapies and various combined strategies. For many years a fraction size of about 2 Gy was assumed as the gold standard in RT and even a modest increase in fraction size (e.g. ≥2.5 Gy fractions) was considered hypofractionation. Unlike other tumoral sites, few studies regarding hypofractionated RT (HFRT) in H&N tumors have been conducted.

Several retrospective studies and prospective single-arm trials have evaluated various regimens of RT for patients with locally advanced, metastatic or recurrent H&N, including several experiences evaluating split-course regimen of accelerated HFRT (≥2.5 Gy per fraction). Differences in patients and tumors characteristics, RT volumes and techniques, and methods of toxicity assessment used in these studies do not allow a comparison between these treatments and a clear conclusion about the safety of hypofractionated regimens in H&N cancer is difficult to achieve. Despite these limitations, HFRT seems easy to deliver without substantial morbidity, particularly with the more recent implementation of intensity modulated RT (IMRT).

Stereotactic radiotherapy (SRT) imply the use of technologies which improve targeting accuracy and allows for moderate HFRT (≥5Gy per fraction). Many experi-

ences were reported about primary and secondary brain tumors, while for H&N cancer SRT was often reserved for the treatment of locally recurrent squamous cell carcinoma or second primary arising in previously irradiated area. After early-phase studies demonstrated the safety of schedules as 40-50 Gy in five fractions delivered to a limited volume, a significant amount of published data has arised, including hundreds of patients treated with this approach. While some articles described a 15-20% risk of severe, life-threatening complications, most demonstrate surprisingly favorable toxicity profiles and fairly promising control rates. Significant limitations, similar to those already described for HFRT studies (mainly regarding the toxicity reports), hinder the interpretation and preclude definitive conclusions.

Dose tolerance guidelines for HFRT or SRT in H&N cancer are extremely rare and, despite the availability of many recent dose-tolerance limits reports, these tends to be discordant, and ever changing. Until now a quantitative estimates of dose levels and related incidence of complications is lacking. Besides, human dose tolerance to radiation depends on many factors, radiation treatment-related (as dose, fractionation, volume, endpoint, follow-up time, estimated risk of the endpoint occurring within the follow up time) or non radiation-related (smoking, alcohol consumption, concomitant CHT or target therapy), as well as intrinsic radiosensitivity ("repair gene expression"). In 2010 QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) review of the literature on normal tissue effects was published, summarizing tolerance data on an organ-by-organ basis[1]. However, it is primarily focused on conventional fractionation and established constraints for HFRT in H&N cancer were lacking. Since RT-induced normal tissue responses are fraction size dependent, adjustments for fraction size based on linear quadratic (LQ) model should be taken into account when the dose per fraction significantly differs from the standard.

A general rule in radiation oncology is that with increased fractions size there is a higher risk of late normal tissue complications. Although classic linear-quadratic model can be used to predict the isoeffectiveness of different dose schedules, its utility is compromised at high dose per fraction, since the effect is probably due to different biologic mechanisms following HFRT. In the past three decades, macroscopic radiobiological models have been developed that incorporate the extensive knowledge of the dependence of cell killing on total dose, fraction size, interfraction interval, dose rate, cell cycle, hypoxic status and other factors, in regard to both tumor control probability (TCP) and normal tissue complication probability (NTCP)[2]. But the most important question is: what is the dose per fraction range for which the LQ model should be used? Based both on experimental and theoretical considerations, LQ seems to be a reliable mechanistically model for designing protocols using 2 to 10 Gy per fraction. Above 10 Gy, the model is expected to become progressively less accurate but, according to animal data, still acceptable for the design of clinical trials based on doses per fraction of 15 to 18 Gy[3]. However, the effects of very high dose per fraction or single high doses may be difficult to predict with the LQ model. Recently, beginning with simplistic graphs of dose-tolerance limits as a function of the number of fractions, and using published data on SRT, a dose-volume histogram (DVH) Risk Map was created, providing a comparison of radiation tolerance limits as a function of dose, fractionation, volume and risk level[4].

Table 1.

Reference	1 fraction	3 fractions	5 fractions
QUANTEC	Maximum dose 13 Gy for low risk of damage (< 1%)	Maximum dose 20 Gy for low risk of damage (< 1%)	
TG 101	Treshold dose 10 Gy to <0.35 cc; Treshold dose 7 Gy to < 1.2 cc; Max point dose (<0.035 cc): 14 Gy	Treshold dose 18 Gy (6Gy/fx) to <0.35 cc; Treshold dose 12.3 Gy (4.1 Gy/fx) to < 1.2 cc; Max point dose (<0.035 cc): 21.9 Gy (7.3 Gy/fx)	Treshold dose 23 Gy (4.6 Gy/fx) to <0.35 cc: Treshold dose 14.5 Gy (.9 Gy/fx) to < 1.2 cc; Max point dose (<0.035 cc): 30 Gy (6 Gy/fx)
Timmerman	10 Gy to < 0.25 ml; 7 Gy to <1.2 ml, Max point dose 14 Gy	18 Gy (6 Gy/fx) to < 0.25 ml; 11.1 Gy (3.7 Gy/fx) to <1.2 ml, Max point dose 22 Gy (7.33 Gy/fx)	22.5 Gy (4.5 Gy/fx) to < 0.25 ml; 13.5 Gy (2.7 Gy/fx) to <1.2 ml, Max point dose 30 Gy (6 Gy/fx)

Table 2.

Low risk					
Fractions	D50% (Gy)	D10% (Gy)	D1cc (Gy)	D0.1cc (Gy)	Dmax (Gy)
3	5.4	11.1	11.1 0.1%	16.3 0.2%	20.0 0.7%
4	7.2	12.8	13.6 0.2%	18.3 0.2%	21.0 0.5%
1	1.8	7.0	7.0 0.1%	8.5 0.1%	13.0 0.9%
2	3.6	9.1	9.5 0.1%	12.7 0.1%	16.5 0.6%
5	9.0	13.5	13.5 0.1%	20.0 0.2%	22.0 0.4%
High risk					
1	7	10.0	8.0 0.2%	10.0 0.2%	14.0 1.6%
2	11	14.0	12 0.4%	14.5 0.3%	18 1.1%
3	15	18.0	16 0.9%	18.0 0.4%	22.0 1.3%
4	18.5	20.5	20.0 2.2%	20.5 0.4%	26.0 1.8%
5	21.0	23.0	21.5 2%	22.5 0.4%	30.0 2.6%

Classical radiobiology teaches us that late effects are due to a high α/β value, similar to the generic 10 Gy ascribed to (aerobic) tumor clonogens. Consequently, HFRT should be less problematic for acute than for late complications. However, treatment duration can play an important role in H&N cancer: a too rapid treatment course may allow insufficient time for the repopulation of the cells of the mucosal lining killed by RT. A simple strategy may be to convert the dose received by the mucosal cells to 2 Gy equivalent dose value, using α/β =10 Gy and then to test if this dose lies within the safe

limit for the overall treatment duration considered using Fenwick model[5]. For the other OARs, the major concern of HFRT or SRT of H&N cancer is the late toxicity. For H&N RT, critical normal tissues/structures (OAR, Organ At Risk) include: cochlea, spinal cord, cranial nerves, oral cavity, mandible, carotid, larynx and pharynx, parotid glands and other salivary glands, apparatus of mastication.

Cochlea: the QUANTEC recommends a maximum dose of 21-30 Gy in 3-7 fractions [6]. Benedict et al reported a maximum tolerated dose of 17.1 Gy in 3 fractions and 25 Gy in 5 fractions [7]. Recently, data published in 2015 in Seminars Radiation Oncology identified two categories of cochlear damage risk[8]:

Low risk: maximum dose of 20 Gy in 3 fractions and 25 Gy in 5 fractions, corresponding to a risk of 13,2% and 13,8% of auditory loss respectively;

High risk: maximum dose of 22,5 Gy in 3 fractions and 27,5 Gy in 5 fractions, corresponding to a risk of 17,7% and 17,4% of auditory loss respectively.

Spinal cord: QUANTEC authors suggest limiting the spinal cord dose to 13 Gy in a single fraction, or 20 Gy in 3 fractions, with an expected <1% risk of spinal cord injury. Table 1 summarized the dose limit recommended by QUANTEC, TG 101 and Timmerman[9].

Recently, Grimm identified two categories of spinal damage risk, low (<1%) and high risk (<3%) dose tolerance limits in 1-5 fractions, including limits for specified volumes (D50%, D10%, D1CC, D0.1 CC) and maximum dose (Table 2)[10].

Optic Nerves and chiasm: radiation-related optic nerve and chiasm toxicity was identify with RION acronym (radiation-induced optic neuropathy) and results in diminished visual acuity or visual loss. Table 3 summarizes the dose limit for low, intermediate and high risk of RION.

Mandible: Data regarding the risk of radiation-induced necrosis are currently unavailable. HFRT could increase the risk of late effects, as radionecrosis. Major risk factors include high dose per fraction, bone infiltration and volume of the horizontal branch of the jaw irradiated at high doses.

Table 3.

Fraction N°	Dmax_low risk (<1%) (Gy)	Dmax intermediate risk (3%) (Gy)	Dmax high risk (5%) (Gy)
1	12.7	15.9	17.5
2	17.5	21.9	24.2
3	20.9	26.3	29.1
4	23.7	29.9	33.1
5	26.1	32.9	36.6

Parotid gland: QUANTEC reports dose constraints for xerostomia with conventional RT. Late salivary dysfunction has been correlated to the mean parotid gland dose, usually recovering after some time, and is usually prevented if at least one parotid gland is spared to a mean dose of less than 20 Gy or if both glands are spared to less than 25 Gy (mean dose). It might be that acute effects on parotid gland are characterized by a high α/β ratio and late damage (dependent on stem cell recovery) by a low α/β ratio. Detailed studies addressing fractionation are limited, with conflicting results. Submandibular gland sparing also significantly decreases the risk of xerostomia. Currently available predictive models are inaccurate, and additional study is required to identify more accurate models of xerostomia risk.

Larynx and pharynx: The dose–volume outcome data for RT-associated laryngeal edema, laryngeal dysfunction and dysphagia have only recently been assessed in conventional fractionated RT, and data regarding HFRT are still lacking.

For re-treatment cases a literature review showed that much less dose-volume data are available. Recent experiences showed that SRT with concomitant cetuximab is an effective treatment option for previously irradiated, locally recurrent squamous cell carcinoma of the H&N. With a total dose, as recommended by University of Pittsburgh, of 40-44 Gy delivered in 5 fractions or every other day over 1-2 weeks, grade 2 o 3 toxicities are not uncommon (10-20%). Most frequently reported toxicities include mucositis, dysphagia and dermatitis. Occasional grade 4 toxicity can be expected, depending on previous RT dose, time interval from initial RT to SRT, tumor volume, SRT dose, number of fractions and treatment duration. NTCP dose-response model may be used to estimate the probability of toxicities. Assuming an α/β ratio of 3Gy for normal organ effects, the fitted logistic model parameters using composite DVH for oral mucosa was TD50= 190.8 Gy. To keep the risk of grade 2-3 mucositis below 25%, 30%, 33% and 50%, the median composite EQD2 dose to oral mucosa should be kept below 55.6 Gy, 86.5 Gy, 105.5 Gy and 190.8 Gy, respectively. For spinal cord, in five fractions, the estimated risk levels of the typical 10 and 14 Gy maximum cord dose limits were 0.4% and 0.6%, respectively. Another commonly reported complication of re-irradiation (with SRT) of H&N cancer was a carotid blowout. In a study by Cengiz et al. tumor embracement of the carotid artery ≥180° and delivery of the whole prescribed dose to carotid artery were found to be predicting for an increased risk of carotid blowout.

To date, there is no evidence of problems when the LQ model has been applied in the clinic for moderate hypofractionation. For SRT many publications provided preliminary insight at least sufficient to prove its clinical feasibility, but much work is still needed to determine statistically reliable limits for optimal clinical use. The recent DVH Risk Map development with division of dose-volume effects in high-risk and low-risk categories could be useful for clinicians to evaluate alternative treatment plans based on acceptable risk levels appropriate for each unique clinical situation to better optimize radiation treatment.

Furthermore, many questions have to be answered. The variability in normal tissue response can be explained by stochastic effects, dosimetric factors (ie. dose heterogeneity), patient-specific habits (eg. smoking, alcohol consumption) or normal tissue-intrinsic radiosensitivity (repair gene expression). Until these issues are solved and more data are analyzed, new treatment schedules should be tested using state-of-the-art models.

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THORAX AND ABDOMEN HYPOFRACTIONATED RADIOTHERAPY: HOW DO DOSE CONSTRAINTS CHANGE?

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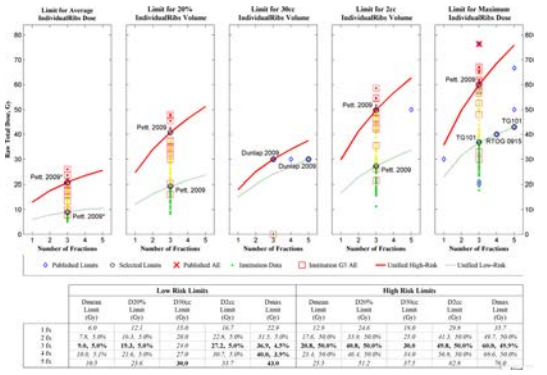
High dose per fraction techniques have now been in clinical use for more than 20 years but most institutions waited some time to publish long-term statistical outcomes data for normal tissue tolerance. Dose-tolerance guidelines for hypofractionated radiotherapy are extremely rare, and only simple spreadsheet of the sparsely published data was available up to now [1] In 2008 Timmerman presented an extensive collection of stereotactic ablative body radiotherapy (SABR) and stereotactic body radiation therapy (SBRT) dose-tolerance limits, but estimates of risk were not available yet [2]. An estimation of the risk continues to evolve as the literature matures. A recent issue of Seminars in Radiation Oncology [3] introduced the concept of Dose-Volume Histogram (DVH) Risk Map, with the aim to provide a comparison of radiation tolerance limits as a function of dose, fractionation, volume, and risk level. The graphical portion of the DVH Risk Map helps clinicians to easily visualize the trends of risk, while, a tabular part provides single parameters for clinical use allowing physicians to make a clinical decision for each critical structure in the treatment plan. The used Dx notation means that volume x of the anatomical structure exceeds dose D. Volume x can be a percentage of the total volume, such as 50% or 10%, or it can be absolute volume like1cc or 0.1cc. Small absolute volumes (2cc ,1cc or 0.1 cc) are frequently used, in place of percentage of OAR volume, as they are generally expected to be more important for SBRT. In the DVH Risk Map graphs, the dose is on the y-axis ,each subplot is for a specific volume, and the number of fractions is on the x-axis of each subplot. .

The DVH Risk Map for rib tolerance (Figure 1) from SABR and SBRT can be used as an example : the 5% and 50% risk levels for 1-5 fractions for 5 different volumes are given. For example for D2cc =49.8 Gy in 3 fractions, the estimated risk level was 50% and this was placed in the table for a 3- fraction high-risk limit. Similarly, the 5% risk level for D2cc= 27.2Gy in 3 fractions was interpolated and placed as the low - risk limit.

Figure 1. DVH Risk Map of the individual rib



Low risk limits related to dose, fractionation, volume, and risk level for esophagus, chest wall, aorta and major vessels, duodenum and small bowel[3-6,8] are collected in Table 1.

At bronchial level, high grades of side effects, such as occlusion and atelectasis were only seen in the upper, middle, and lower bronchi and the segmental bronchi. When 0.5 cc of a segmental bronchi is irradiated to 50 Gy in 5 fractions, it is about 50% likely to be occluded radiographically. Symptomatic toxicity could still be avoided as long as some segmental bronchi in each branch of the lung were outside the high-dose region. For grade1 radiographically evident side effects, the 50% risk level for a 5-fraction Dmax was 55Gy for mid-bronchi and 65Gy for main stem bronchi [7].

To assure the relationship between clinical toxicity and side effects to normal tissue, further investigations are needed.

Table 1. Low risk limits related to dose, fractionation, volume, and risk level for esophagus, chest wall, aorta and major vessels, duodenum and small bowel [3-6,8]

Low risk limits								
		1 fx	2 fx	3 fx	4 fx	5 fx	6 fx	7 fx
Esophagus	EUD limit Gy (% risk)	--	--	18,5 (5%)	20,8 (5%)	22,6 (5%)	24,2 (5%)	25,6 (5%)
	D10% Gy (% risk)	--	--	17,5 (5%)	19,6 (5%)	21,3 (5%)	22,7 (5%)	24,0 (5%)
	D 5cc Gy (% risk)	--	--	17,7 (19,7%)	18,8 (15,5%)	19,5 (12,5%)	20,2 (10,9%)	20,9 (10%)
	D 1cc Gy (% risk)	--	--	21,0 (6,9%)	23, 0 (5,2%)	25,0 (5%)	26,8 (5%)	28,4 (5%)
	D max Gy (% risk)	--	--	27,0 (6,3%)	30,0 (5,3%)	35,0 (9,8%)	38,5 (11,9%)	42,0 (15%)
Chest wall	D 50% Gy (% risk)	6	7,8	9,0	10,0	10,5	--	--
	D20% Gy (% risk)	12,1	16,3	19,3	21,6	23,6	--	--
	D 70cc Gy (% risk)	9,3 (10%)	12,4 (10%)	14,6 (10%)	16,2 (10%)	17,6 (10%)	--	--
	D 2cc Gy (% risk)	22,9 (10%)	31,5 (10%)	37,8 (10%)	43,0 (10%)	50,0 (11,2%)	--	--
	D max Gy (% risk)	24,2 (10%)	33,4 (10%)	36,9 (8,4%)	40,0 (7,6%)	43,0 (7,3%)	--	--
Aorta – major vessels	V 25 Gy cc (% risk)	1	3	5	7	9 (0,5%)	--	--
	D 4cc Gy (% risk)	16,1 (1 %)	21,9 (1 %)	26,2 (1 %)	29,5 (1 %)	32,4 (1 %)	--	--
	D 1cc Gy (% risk)	20,8 (1 %)	28,6 (1 %)	34,3 (1 %)	40,0 (1,2 %)	42,8 (1%)	--	--
	D 0,5cc Gy (% risk)	22,2 (1 %)	30,6 (1 %)	36,8 (1 %)	41,7 (1 %)	46,0 (1 %)	--	--
	D max Gy (% risk)	36 (33,8%)	40 (4,2%)	44,0 (1,9%)	49,0 (1,5%)	51,5 (1%)	--	--
Duodenum	D 50% (% risk)	12,5 (32,3 %)	14,0 (19,3 %)	15,0 (15,2%)	15,5 (12,7 %)	16,0 (11,4 %)	--	--
	D 30cc Gy (% risk)	9,0 (6,1 %)	12,5 (6,3 %)	15,0 (6,5 %)	17,5 (6,8 %)	20,0 (7,3 %)	--	--
	D 5cc Gy (% risk)	11,2 (0,6 %)	16,1 (0,9 %)	21,0 (1,8 %)	23,4 (1,7 %)	25,8 (1,8%)	--	--
	D 1 cc Gy (% risk)	17,0 (6,4 %)	21,5 (4,9 %)	25,3 (4,7 %)	27,0 (3,9 %)	28,0 (3,4 %)	--	--
	D 0,035cc Gy (% risk)	16 (5,3%)	25 (6,2%)	30 (6,2%)	31 (5,6%)	32 (5,2%)	--	--
Small bowel	D 50% (% risk)	3	6	9	11	12	--	--
	D 10% Gy (% risk)	4	8,5	13	16	18	--	--
	D 5cc Gy (% risk)	9,8 (2,1 %)	13,5 (2,3%)	16,2 (2,5 %)	17,9 (2,4 %)	19,5 (2,4%)	--	--
	D 2 cc Gy (% risk)	11 (2,3 %)	16 (3 %)	20 (3,7%)	23 (4 %)	25 (3,9%)	--	--
	D max Gy (% risk)	12 (1,4%)	18,6 (2,3%)	25,2 (3,6%)	28,5 (3,7%)	29,0 (2,8%)	--	--

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HYPOFRACTIONATED RADIOTHERAPY AND NEW DRUGS: NEW TOXICITY?

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The greatest potential to increase the effectiveness of radiotherapy lies in combining it with drugs that render tumours more sensitive to radiation, either by molecularly targeting tumour cells directly, by activating immune response or by modifying the tumour microenviroment in order to 'open' the therapeutic window.[1] In this regard, it seems that hypofractionated protocols might be superior.[2]

Many of targeted agents have been demonstrated in the preclinical setting to enhance the radiation effect, but the majority have not been investigated in phase I clinical trials for safety in the context of RT. One recent analysis evidenced that of the over 400 phase I trials published yearly, only 30 include RT.[3] More less data are available on combination of novel drugs and purposely hypofractionated RT. Moreover the literature shows many single institutional case series or case report that have provided mixed data, with some suggesting safety and others suggesting unexpected toxicities. Well note are the reported toxicities of erlotinib during abdominal hypofractionated RT for metastatic spinal cord compression who experienced fatal acute diarrhea,[4] or toxicities arising from the combination of SBRT and angiogenesis-targeting agents, particularly of late luminal gastrointestinal toxicities.[5]

Cancer immunotherapy is becoming one of the pillars, along with chemotherapy and radiotherapy, for the treatment of patients with cancer. Combination therapies, preferably with stereotactic ablative radiotherapy, are also being investigated.[6]

There are limited clinical results on the combination of stereotactic ablative body radiotherapy with immunotherapy, mainly used in palliative setting. How to minimize overlapping toxic effects of radiation and immunotherapy is an open questions. However early results of this approach are promising and warrant further investigation with a cautious eye on safety and toxicity.

An increasing number of patients are receiving hypofractionated RT and new agents, some of which carry potential for increased survival but also side effects. Some authors note that the dichotomy between curative and palliative therapies is also being progressively outdated. The question of how sequencing the radiotherapy with novel therapies and the evaluation of "new toxicities" associated is therefore relevant not only in metastatic situations, where quality of life is an end-point, but in curative too.

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THE MANAGEMENT OF TOXICITY INDUCED BY INNOVATIVE DRUGS ASSOCIATED WITH RADIOTHERAPY

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Considering innovative drugs, the concept of therapeutic advance is the only one that concerns professionals: it means that a new treatment benefits patients when compared with existing options. When judging whether a new product is a therapeutic advance, it is crucial to consider efficacy, safety, and convenience New drugs are generally approved on the basis of efficacy studies; safety outcomes are considered a secondary issue.[1]

Safety concerns include frequent as well as rare and serious adverse effects. Rare adverse effects can be recognized only after a large population has been exposed to the drug.[2]

New cytotoxic agents, targeted therapies, immunomodulatory therapies, new hormonal therapies entered into clinical practice in the last years. The safety data are currently very limited, in particular in combination with radiotherapy.

The therapeutic index of targeted therapies is not necessarily better than conventional cytotoxics as the target of these therapies can be found in normal tissues and therefore affect multiple organs.[3]

For immunologic drugs safety data are even more limited and toxicity of association with radiotherapy can only be assumed by the mechanism of action and the data from the Phase II Trials.

The main scenarios are 1) RT given to symptomatic lesions in metastatic patients treated with innovative drugs, 2) RT used as immunogenic boost in immune therapies, 3) RT as the main treatment associated with new drugs. For associations described in point 3, we now have enough data in head and neck cancer, lymphomas and breast cancer (Cetuximab, Herceptin, Rituximab) and in fact these drugs can't be viewed as an innovative since their entry into clinical practice for several years.[4-8]

As for the point 2, the doses necessary to determine a "vaccination in situ" are sufficiently low and the volumes limited as not to provide added toxicity. It remains to be evaluated if the choice of the lesion to irradiate can lead to a different toxicity according to the location (e.*g.* fibrosis in the lung) depending on the drug or drugs association.[9] Point 1 is the one that most interests currently in clinical practice, the most relevant data concerning the irradiation of brain metastases in combination with targeted therapies.[10-12]

Multidisciplinary management of new toxicity related to new drugs, especially in combination with radiotherapy is needed.[13-16]

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IMAGE GUIDED RADIOTHERAPY: CLINICAL INDICATIONS

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Aims: AIRO Regional Group Piedmont, Liguria and Aosta Valley elaborated a practical document on the use of IGRT (e.g. modality and timing of image acquisition for different kinds of treatments or for different organs, and radioprotection aspects). This document may be useful mainly for the institutions beginning their activity with IGRT.

Methods: The Group firstly proceeded analysing literature about this subject and successively brainstorming between Group members and other colleagues with particular expertise in this field (Physicians, Physicists, and Radiographers).

Results: Components of an IGRT System are: an imaging acquisition system, a reference imaging set, a software to match reference imaging and CT planning imaging, and a correction method protocol.[1-5]

Strategies of correction may be on-line and off-line.

In general, on-line strategies allow larger reduction of geometric uncertainty than off-line strategies do, but with more work, treatment time and received dose. Nevertheless off-line procedure seems likewise effective to reduce systematic error.

Table 1.

District/Organ	Verification modality	Verification timing
Brain	Off-line	First 3 fractions, then weekly
Head and neck	Off-line	First 5 fractions, then weekly
	On-line	Daily (if margins reduction)
Prostate	Off-line	First 5 fractions then weekly (standard margins)
	On-line	Daily (if margins reduction or hypofractionation)
	Planar imaging (planted markers) or US	Daily
Pelvis, Rectum, Anus, Uterus	Off-line	First 5 fractions, then weekly (3DCRT standard margins)
	On-line	Daily (IMRT)
Pancreas	On-line	Daily (IMRT)
Thorax	Off-line (e-NAL protocol)	First 5 fractions, then weekly
	On-line	Daily (IMRT, OAR near to target, hypofractionation)
Paravertebral region	Off-line	First 5 fractions, then weekly
	On-line	Daily (IMRT, stereotactic RT or hypofractionated IMRT)
Retreatments	On-line	Daily
Pediatric neoplasms	Personalized protocols	

In literature, two different procedures for off-line correction are reported: NAL (no action level) and SAL (shrinking action level). NAL is the most utilized method and in a study of de Boer *et al.*[6] a direct comparison between two procedures in 600 prostate cancer patients shows that NAL is more effective in terms of number of images necessary to reduce systematic error.

In Table 1 the suggested modality and timing of 3D verifications on the basis of literature indications are summarized.

Conclusions: In daily utilization of IGRT the evaluation of several clinical and dosimetric aspects is required. 3D imaging verification is indicated in particular for moving targets or for targets situated in critical areas near OAR, in case of retreatment or in case of treatment planning by IMRT or VMAT or SRS-SBRT. It's important to establish the frequency of each acquisition, the definition of parameters (Kv, mA, ms), the matching algorithms and the intervention protocols. Evaluation of exposition dose for each verification imaging, and optimization of protocols to reduce this dose are necessary.[7] Introduction of IGRT can increment treatments' duration and work for the Physicians at linear accelerator and for the Physicists in case of Adaptive Radiotherapy.

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CLINICAL INVESTIGATIONS ON MEDICAL DEVICES – FOCUS ON ONCOLOGIC RADIOTHERAPY (ACCELERATORS) – CURRENT SITUATION AND SCENARIOS

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Aims: In 2017 the new EU Medical Device Regulation will enter in force. It will take over current national regulations descending from Directive 93/42/CE. Clinicians are requested to know and to apply new rules oriented by an approach that requires an increased attention to clinical evaluation and to post market follow up. Clinical investigations have been deeply renewed by the incoming Regulation and a overview on this issue may be helpful .

Methods: Clinical investigations on medical devices follow different procedures whether they are pre-market (i.e. before CE marking) or post-market (i.e. on devices

placed on the EU market). The new Regulation has strenghtened the role of Competent Authorities: pre-market investigations shall be authorized, post-market investigations shall be notified. The new Regulation ensures, among other things, that data generated in clinical investigations is reliable and that the safety of the subjects participating in a clinical investigation is protected by the involvement of Ethic Committees.

Results: Clinical investigations on radiotherapic devices are not frequent in Italy, despite the availability of competencies and opportunities. Number of investigations regarding radiotherapy may be increased, and special attention must be paid to clinical investigations promoted by Health Institutions, because evaluation of the Competent Authority is focused on medical devices rather than on clinical procedures: law provisions assume that applications are submitted by manufacturers or on behalf of them and therefore design, manufacturing process and device managing procedures should be well known to the notifying entity.

Conclusions: Procedures regarding clinical investigations that involve medical devices may be improved by integrating different approaches of regulators, clinicians and manufacturers, in order to develop more efficient paths for conceiving and conducting clinical investigations.

COMBINING RADIOTHERAPY AND IMMUNOTHERAPY: NEW THERAPEUTIC HORIZONS FOR THE CURE OF CANCER?

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The immune system is important in preventing and controlling cancer. T-cells are a major component of the immune response, and the process is regulated by a series of costimulatory and inhibitory signals that serve as checkpoints.[1] Checkpoint blockade immunotherapy has recently received mainstream attention as a result of striking and durable clinical responses in some patients with metastatic disease and a reasonable response rate in many tumour types.[2-4] Immunotherapy and Radiotherapy (RT) could act together for a further improvement of the efficacy of both treatments. In rare cases, RT elicited distant and persistent anti-tumour effects (called "abscopal effect"), which are probably immune mediated.[5] However, the number of cases of abscopal effect observed in the clinical practice is small. The combination of immunotherapy and RT could enhance distant or systemic disease control via abscopal effect as shown in many preclinical experiences.

Furthermore, immunotherapy can increase the local effect of RT. Indeed, it is well known that an intact immune system is relevant for the therapeutic effect of RT.[6] Thus, combining RT with immunotherapy could increase the efficacy of both treatments, eliciting a systemic antitumor response.

Lastly, RT can increase tumor immunogenicity and facilitate T-cell killing of tumor cells, therefore enhancing the response rates to immunotherapy.[7,8]

For all these reasons, there is a strong rationale for exploring the combination RT immunotherapy.

Moreover, preclinical and some clinical data seem to confirm the synergism between the two treatments. However, these data, although promising, are unavoidably limited by the preclinical setting or by their retrospective nature. Moreover, from the analysis of published data, often contradictory results emerge, generating a lot of open questions, like the right dose and fractionation of RT or the exact timing of the combination. To explore these and other open issues, prospective trial are ongoing.

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NEW DRUGS AND RADIOTHERAPY WITH ALTERNATIVE FRACTIONATION SCHEDULES IN OLIGO-RECURRENT AND OLIGOMETASTATIC PATIENTS

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The oligometastic cancer could been considered as an intermediate state between localized lesions and those widely metastatic. In this state the disease is amenable to a curative therapeutic strategy and to a localized therapy [1] It possible to define oligometastic a cancer patient with 1–5 metastatic or recurrent lesions that could be treated by local therapy and achieve long-term survival or cure. The difference between oligometastasis and oligorecurrence is that in the first state is present an active primary lesion, in the second one the patients has no relapse of the primary lesions.[2]

Several authors reported that the benefit of local therapy increased as systemic therapy improved.[3,4]

Stereotactic radiotherapy permit to deliver a high dose of radiation very precisely to a target within the body (cranial and/or extracranial), as a single dose or a small number of fractions. Several dose' regimens were employed. In literature we are found studies showing that better results are obtained when biologically effective dose larger than 100 Gy (α/β=10 Gy) are delivered, in fractionated stereotactic treatments [5]. When using single fraction sessions, dose larger of 24 Gy are better than smaller ones.[6]

An important effect of high doses of radiotherapy is the activation of the innate and adaptive immune responses (IFN-γ, IL-4, CD 8+ cell activation). These effects were not observed with conventional fractionated radiotherapy or with chemotherapy.

The abscopal effect of high dose radiotherapy suggests that combining SRS or SBRT with immunotherapy in oligometastatic patients could give rise to new therapeutic strategies.[7]

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Selected Oral Communications

B001

IPILIMUMAB AND RADIOSURGERY/STEREOTACTIC RADIOTHERAPY WITH CYBERKNIFE® SYSTEM IN MELANOMA BRAIN METASTASES: MONOISTITUTIONAL EXPERIENCE

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Aims: Ipilimumab (Ipi), an anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) monoclonal antibody, has been shown to improve survival in patients (pts) with advanced melanoma. However, there is a lack of data about the efficacy of Ipi in pts with brain metastases (BM), as well as about its combination with radiotherapy (RT) and the right sequence of both treatments. The purpose of this study was to evaluate overall survival(OS), local control(LC) of the lesion treated, and whole brain control(WBC) in pts with melanoma BM treated with Stereotactic Radiotherapy (SRT)/Radiosurgery (SRS) with Cyberknife® system and Ipilimumab.

Methods: From November 2012 to march 2016 we treated 59 pts (30 M and 29 F) with melanoma BM. The median age was 61 years (28-81y). 48 pts received Ipi: 22 pts prior-RT (IPI PRE-RT), 6 pts concomitant-RT and 20 pts post-RT (IPI POST-RT). 10 pts not received Ipi (NO IPI) and 1 patient was not evaluable. Ipi was administered intravenously at a dose of 3 mg/kg over 90 min every 3 weeks for 4 doses. We treated 116 lesions of average size 12 mm (2-37), 92 with SRS (10-24Gy) and 24 with SRT (18-24Gy/2-3-5 fractions). We evaluated the local response according to RECIST criteria (complete response CR: disappearance of the lesion; partial response PR: at least a 30% decrease in the diameter of lesion; progression disease PD:increase in the diameter of the lesion >20%;stable disease SD: everyone else). We assessed LC as the sum of CR, PR and SD, WBC, and median OS from the date of the SRS/SRT procedure.

Results: 51 pts were evaluable for follow-up (FU). Median FU was 6 months (2-23). The one year-LC rate was 33%, 84%, 34% and one year-WBC was 55%, 42%, 29% for the group NO IPI, IPI PRE-RT, IPI POST-RT, respectively. Median OS was 10 months (95% c.i. 0-23), 8 months (95% c.i. 5-11) and 11 months (95% c.i. 7-15) for the group NO IPI, IPI PRE-RT, IPI POST-RT, respectively.

Conclusions: The results showed a better LC and WBC in the pts group IPI PRE-RT, instead the median OS seems to be higher in the pts group IPI POST-RT. The results in terms of median OS, compared with literature data, would seem to demonstrate a potential impact of Ipilimumab in the treatment of melanoma pts with BM. The recruitment of a greater number of pts, a longer follow-up and new prospective studies of combination SRS/SRT and Ipilimumab are needed to demonstrate the role of Ipilimumab also in the treatment of melanoma pts with BM and the better sequence with RT.

B002

CARDIOTOXICITY OF DIFFERENT HYPOFRACTIONATED RADIOTHERAPY CONCURRENTLY ASSOCIATED WITH TRASTUZUMAB IN EARLY BREAST CANCER

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Aims: To evaluate acute cardiotoxicity in patients (pts) with HER2-positive disease treated with different adjuvant whole breast Hypofractionated Radiotherapy (HRT), after breast conservative surgery, concurrently associated with the humanized anti-HER2 monoclonal antibody trastuzumab (TSZ).

Methods: From February 2008 to June 2016, 52 pts underwent adjuvant chemotherapy followed by TSZ and HRT with different schedules. Only pts <pT2 and <pN1a were enrolled in this analysis, sub-divided by breast's side, presence of cardiac risk factors (arterial hypertension, smoking, hypercholesterolemia, atrial fibrillation) and schedules. All pts received three-dimensional conformal RT to whole breast in supine position with three different HRT schemes based on age of pts: 46 Gy in 20 fractions(fx) (<40 years old)15pts, 39 Gy in 13 fx (<46 y.o) 16pts, 35 Gy in 10 fx (>46 y.o) 21pts, 4 fractions at week. A concomitant weekly boost on tumor's bed was delivered according to individual risk factors. Asymptomatic decrease in left ventricular ejection fraction(LVEF) was evaluated by echocardiogram at start and at the end of TSZ. All acute cardiotoxicities were assessed according to CTCAE-v3 criteria.

Results: At a median follow-up of 5 years (range 6-96 months) 49(94%)pts are alive; 1(2%) developed locoregional relapse and 2(4%) distant metastases. 21 pts (40%) had basal cardiac risk factors. Our overall results about cardiotoxicity are summarized in Table 1. According to breast side, left-sided radiotherapy was performed in 29 pts: 1/29 pts (3%) showed G2, 9/29 pts (31%) G1 and 19/29 pts (66%) G0. Right-sided radiotherapy was performed in 23pts: 2/23 pts (8%) showed G2, 4/23 pts (18%) G1 and 17/23 pts (74%) G0.

Conclusions: Differences in LVEF did not seem to be important despite HRT schemes. No G3 occurred, G1-G2 rates are similar to literature. Heart and left coronary artery's contouring has been focused only in the last years; currently this new contouring may reduce the cases of cardiac strokes, but probably doesn't affect LVEF. Further more follow up is needed to evaluate the new cardiotoxicity rate after new accurate Organs-At Risk of cardiotoxicity delineations.

Table 1.

	46 Gy/20 fx		39 Gy/13 fx		35 Gy/10 fx	
	pts	%	pts	%	pts	%
Grade 2 LVEF 50%-40%	2/15	13%	0/16	0%	1/21	5%
Grade 1 LVEF 60%50%	3/15	20%	5/16	31%	5/21	24%
Grade 0 LVEF >60%	10/15	67%	11/16	69%	15/21	71%

B003

EXPERIENCE USING ABIRATERONE AND ENZALUTAMIDE IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

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Aims: The therapeutic management of men with metastatic castration-resistant prostate cancer (mCRPC) has been transformed in recent years. The introduction of the newer androgen receptor (AR) pathway inhibitors, Abiraterone Acetate (AA) and Enzalutamide (ENZA), has shown to prolong overall survival in both the pre- and post-docetaxel states. We report herein the efficacy and safety in patients treated at Radiation Oncology of Campus Bio-Medico University.

Methods: Patients with mCRPC were evaluated and treated in pre- and post-chemotherapy setting with AA or ENZA. Toxicity, according to CTCAE vers. 4.02, with discontinuation due to adverse events, and time to treatment failure have been recorded. All patients were eligible to treatment without any major contraindication. Progression was assessed by means of radiographic, clinical and biochemical exams. Those with oligo-progression were treated by means of focal RT in order to continue the drug. Finally, some patients progressed with AA, than received ENZA, mainly after a wash out with docetaxel before ENZA starting.

Results: From September 2013 to June 2015 a total of 25 men with metastatic CRPC received therapy with AA or ENZA. Median age was 69 years. Metastatic sites at treatment beginning were recorded as follows: nodal (16%, n=3), bone (40%, n=10), visceral (8%, n=2), combined (36%, n=9). Eleven of these patients were metastatic at diagnosis while the remaining became metastatic after local therapy (prostatectomy 11 pts; and radiotherapy 3 pts). In 7/23 patients undergone to AA a cardiovascular comorbidity (major events) was registered. Treatment was discontinued for toxicity in 3 cases (all with AA): 1 patient for grade 3 diarrhea. 1 patient for increasing in transaminases (G2) and the last one discontinued therapy recording both toxicities (diarrhea G3 and increase in transaminases G2). Time to treatment failure for the entire cohort was: 11.8 months. During therapy with AA and ENZA 9 patients underwent to radiotherapy, 6 for bone pain and 3 for oligo-metastatic progression. Time to treatment failure after RT in these patients was: 8.1 months. Seven patients received ENZA after disease progression to AA. Time to treatment failure in these patients was: 6.5 months.

Conclusions: Few patients discontinued treatment due to toxicity; oligo-progression is, however, a rare condition, while RT can be administered safely with these drugs.

B004

EVALUATION OF THE SAFETY AND LONG-TERM PSA CONTROL OF THE ASSOCIATION ABIRATERONE ACETATE AND RADIOTHERAPY IN OLIGOMETASTATIC CRPC PATIENTS: A MULTICENTER RETROSPECTIVE OBSERVATIONAL COHORT STUDY

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Aims: Prostate cancer is one of the most common malignancies and main causes of cancer death in Western countries. The introduction of highly sensitive imaging techniques, a new clinical 'entity' of metastatic patients with a limited number of lesions has been defined: oligometastatic patients. In this patient group, the use of radiotherapy could achieve sufficient prostate-specific antigen (PSA) control. This study describes our experience with treating a castration-resistant PCa patients with Abiraterone Acetate and RT.

Methods: From January 2010 to September 2015, 54 patients from seven centers were included in this observational study. The average age was between 66 and 72 years. The patients had bone or lymph node recurrence of disease associated with biochemical progression. All patients had received primary treatment for the disease and the inclusion of the study showed a disease resistant to castration that might have already received treatment with chemotherapy. All patients received abiraterone acetate 1,000 mg / day associated with RT on metastatic lesions. The primary objective of the study was to determine the safety of the association; secondary objective was long-term PSA control.

Results: All patients included in the study had a reduction in PSA> 50% maintained for more than 8 months. The 80% of patients included in the study presented instrumental RC disease. The association of RT and abiraterone acetate was safe and easy to handle. Only one patient experienced a major cardiovascular event.

Conclusions: The RT and abiraterone acetate association showed excellent handling and safety. It is also detected a good efficacy of the combination.

B005

SBRT FOR OLIGOMETASTATIC PROSTATE CANCER RECURRENCES: PRELIMINARY DATA FROM A MULTI-INSTITUTIONAL EXPERIENCE

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Purpose: The aim of this study is to define the efficacy of stereotactic body radiation therapy (SBRT) for oligorecurrent prostate cancer (PCa) in terms of progression free survival (PFS).

Matherials and Methods: In 5 Radiation Oncology departments from Northern Italy, patients with oligorecurrent PCa (≤3 metastatic sites including lymph nodes and/or bones identified with PET choline or CT plus Bone Scan at the time of recurrence) were treated with SBRT (defined as a radiotherapy dose of at least 4 Gy per fraction). Data from primary treatment for PCa and from follow up after SBRT are reported. Statistical analysis to better define the pattern of relapse, the time to palliative androgen deprivation therapy, the time to castration-resistance and to second line hormonal therapies in patients undergoing SBRT for oligorecurrent hormone-sensitive prostate cancer (mHSPC) and castration resistant prostate cancer (mCRPC) will be presented after further updating. Toxicity data according to CTCAE 4.0 were also collected.

Results: 83 metastases (71/83 pelvic lymph nodes and 12/83 bones) were treated in 61 patients (37/61 HSPC and 24/61 CRPC). At the time of the primary treatment 47/61 patients had high-risk disease, 11/61 patients underwent radical radiotherapy and 38/61 postoperative (salvage or adjuvant) radiotherapy. Among the mHSPC patients, 10/37 assumed adjuvant ADT at the time of SBRT. Median follow up from SBRT was 9 months (range 1-115). 4/61 patients underwent SBRT for further oligorecurrence. Median PFS was 13 months in the mHSPC group and 14 months in the mCRPC group. At the time of writing (June 2016), 27/61 patients had a relapse. Late grade 1 and 2 toxicity was registered in 2/61 patients. No severe acute or late toxicity was observed.

Conclusions: SBRT for oligorecurrent PCa is a safe treatment. Further analysis is in progress.

B006

THE ROLE OF MELANOCORTIN RECEPTOR-4 GENE POLYMORPHISMS IN GLIOBLASTOMA PATIENTS TREATED WITH CONCOMITANT RADIO-CHEMOTHERAPY

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Aims: Melanocortins are peptides with well-recognized anti-inflammatory and neuroprotective activity. Melanocortin receptor-4 (MC4R) is present in astrocytes and it is expressed in the brain. Given the association of MC4R with antiinflammatory activity, induction of neural stem/progenitor cell proliferation in brain hypoxia, and prevention of astrocyte apoptosis, the aim of this study was to evaluate the possible prognostic, predictive and therapeutic role of the MC4R SNPs on GBM patients.

Methods: Sixty-one patients with a proven diagnosis of GBM, ECOG PS 0-2, age>18 years, and treated with radiotherapy and temozolomide according to Stupp protocol were enrolled. Genomic DNA was extracted and MC4R gene SNPs were analyzed; the allelic discrimination was performed using an ABI PRISM 7900 SDS (Applied Biosystems, Carlsbad, CA, USA) and with validated TaqMan® SNP genotyping assays (Applied Biosystems). Kaplan Meier curves were performed for statistical association with genotypes. The study has been approved by the Comitato Etico di Area Vasta Nord Ovest prot. n. 17013.

Results: Fifty-six patients were clinically evaluated. The median progression-free survival (PFS) and median overall survival (OS) of these patients were 10.8 months and 23 months, respectively. A relevant finding of our study was the identification of a MC4R genotype that was significantly associated with PFS: patients harbouring the rs489693 AA genotype had a median PFS of 3 months whereas patients with AC/CC genotypes had a median PFS of 13.7 months (P=0.0088). No significant differences in PFS and OS for the other genotypes of the investigated MC4R polymorphisms were found.

Conclusions: The rs489693 AA genotype is significantly associated with a shorter PFS in GBM patients treated with radiotherapy and temozolomide schedule.

The present, pilot study may represent the stimulus to prospectively investigate the role of MC4R polymorphisms as a predictive pharmacogenetic marker or as a target for new drug therapies for GBM patients.

Oral Communications

C001

EVALUATION BY SURVEY (INSTITUTIONAL AND PERSONAL) OF PALLIATIVE TREATMENTS IN CLINICAL PRACTICE IN THE ITALIAN NATIONAL CONTEXT. PROJECT OF THE AIRO STUDY GROUP "PALLIATIVE CARE AND SUPPORT THERAPIES"

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Aims: Evaluate characteristics of both institutional and personal approach of radiation oncologists operating in the field of palliative treatments to guide the activities promoted by the Study Group AIRO ""Palliative Care and Support Therapies.

Methods: Two questionnaires of 29 questions, respectively, aimed to explore the clinical practice and clinical staff 's personal orientation in different areas of palliation, namely: bone metastases, lung, brain, liver, lymph node and urgencies / emergencies in clinical radiotherapy. The questions were selected to study the spread of the data, the complexity of the treatments delivered; the attitude towards different treatment techniques used, the most commonly prescribed doses, and the influence of the use of prognostic score. Moreover, the assessment of integration with other disciplines and the supportive care management mode was pursued. In particular, questions have investigated some aspects: -20 questions on outlay data of the individual Radiotherapy Centre; -9 questions on general aspects concerning the clinical and organizational management; -20 questions on personal perception of palliative radiotherapy; -9 questions on personal orientation general aspects of clinical and organizational management. The questionnaire was proposed by representatives of the Study Group ""Palliative Care and supportive therapies "" to the heads of the Italyn radiotherapy centers, and distributed through ""Survey Monkey"" to the members of the Society.

Results: Currently 30 Radiotherapy Centres responded to the Survey providing data on their structure. At the moment about 210 members attended the AIRO Survey staff.

Conclusions: The overview of the results will be detailed in the Congress venue. The data collected will allow to assess the complexity of everyday clinical practice in the current national scene scenarios, in order to guide the future activities of the Study Group.

C002

PATIENT-REPORTED LATE DYSPHAGIA FOLLOWING IMRT PLUS CHEMOTHERAPY IN OROPHARYNGEAL CANCER: A CROSS SECTIONAL MULTICENTER STUDY

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Aims: The assessment of swallowing-related Quality of life is increasingly emerging among oropharyngeal cancer (OPC) patients (pts) with limited data about clinical and molecular predictive factors. First aim of this study is to search factor associated to patient-reported long term dysphagia using M.D. Anderson Dysphagia Inventory (MDADI) questionnaire in a OPC pts population receiving curative Intensity Modulated Radiation Therapy (IMRT) and chemotherapy (CHT).

Methods: A cross-sectional study was performed on 148 patients with OPC treated in 3 Italyn tertiary cancer centers. Patients with OPC staged III-IV receiving conventional IMRT with 70 Gy/2-2.12 Gy per fraction and concomitant platinum based CHT, with or without induction (I)-CHT, who have concluded their treatment at least 6 months earlier and in complete remission were included in this study. All pts completed the MDADI questionnaire, immediately before their follow-up visit. We analyzed the MDADI total scores (MDADI TS) according to the following variables: pts gender, p16 status, risk class, T stage, N stage, late xerostomia and dysphagia recorded according to CTCAE v4.0, enteral nutrition duration, time from treatment end and I-CHT yes or not.

Table 1. Patients characteristics.

Age, Sex	Mean 59 yrs (43-78), M=76% F=24%
Stage	T3-T4= 51%; N2-3= 84%
I-CHT	Yes=36%, No=64%
p16	Pos = 66%, Neg=23%, not available=10%
Risk group	High=24%, Intermediate=42%, Low=34%
Late xerostomia	G0=22%, G1=72%, G2= 6%
Late dysphagia	G0=31.7%, G1=43.2%, G2=20.3%, G3=4.2%
Time from treatment end	Mean: 35 months (range 6-79);<25 months = 43%;>25 months = 57%

Results: Patients characteristics are shown in Table 1. Mean MDADI TS was 73 (range, 40-100). MDADI TS distributions were significantly better in male compared to female pts (p= 0.0001) and in p16 positive pts compared to p16 negative pts (p=0.01). MDADI TS was significantly different in high, intermediate and low risk (IR, IR and LR) pts (p=0.01). Pts with late G0-1 xerostomia showed significantly better MDADI TS compared with pts with G2 xerostomia (p<0.0001) as well as pts with late G0-1 dysphagia compared to pts with G2 dyspagia (p=0.01). According to time from treatment, pts with an interval time (IT)<25 months had significantly worse MDADI TS compared to pts with this IT ≥ 25 months (p=0.03). No significant difference in MDADI TS was found analyzing pts according to T stage, N stage, enteral nutrition duration, I-CHT with or without. A multivariable analysis showed that LR group, late G0-1 xerostomia were significant independent predictors for better MDADI TS.

Conclusions: Globally, treatment with IMRT and concurrent CHT was able to maintain a good level of patient-reported dysphagia, with further improvements after 25 months of follow up. P16 status and late xerostomia are the main predictors of late dysphagia.

C003

TEXTURE ANALYSIS OF PAROTID GLAND AS PREDICTIVE OF RADIATION (RT)- INDUCED XEROSTOMIA: BEYOND THE NORMAL TISSUE CONSTRAINTS

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Aims. Normal tissue constraints for parotid gland in head and neck cancer patients represent a difficult challenge and in some cases cannot be satisfied. Aim of this study is the evaluation of parotid gland texture analysis (TA) as a predictive factor of xerostomia.

Methods. We performed a retrospective analysis of patients treated with IMRT to the head and neck from January 2010 till December 2015 and whose normal dose constraints for the parotid gland (Mean Dose<26 Gy for bilateral gland) could not be satisfied. Xerostomia was defined according to the common toxicity criteria. CT simulation DICOM images and RT structures (i.e. all the contours of the structures in the RT plan) were collected and the parotid gland treated at a higher dose was contoured on simulation CT and analysed with LifeX Software ©. TA parameters, achieved before RT, included features of gray level co-occurrence matrix (GLCM), neighborhood gray-level dependencematrix (NGLDM), gray-level run length matrix (GLRLM), gray-level zone length matrix (GLZLM), sphericity and indices from the grey-level histogram. We performed a univariate analysis and a multivariate analysis between all these parameters, the volume of the gland and the usual dose parameters (V30 and Mean Dose) and the development of acute and chronic xerostomia.

Results: Sixty-eight patients were included. Thirty-six (52.9%) developed acute xerostomia and twenty-eight (38.2%) developed chronic xerostomia. TA parameters significantly correlated (p<0,05) with acute xerostomia included V30, Mean Dose, Histogram Entropy, GLCM homogeneity, GLCM contrast, GLCM entropy, GLCM dissimilarity, GLRLM SRE, GLRLM RLNU, Contrast, Busyness, GLZLM GLNU, GLZLM ZLNU, GLZLM ZP. TA parameters significantly correlated (p<0,05) with

chronic xerostomia included V30, Mean Dose, Volume in voxels, Skewness, Kurtosis, GLCM Correlation, GLRLM SRE, GLZLM RLNU, Coarseness, Contrast, Busyness, GLZLM GLNU, GLZLM ZLNU. Logistic regression underlined a significant correlation between V30 (p:0.004), Entropy (p: 0.026), Contrast (p:0.010) and acute xerostomia (p<0.001, R2: 0.592), and between V30 (0.007), GLCM Correlation (p:0.029), GLZLM RLNU (p:0.013) and chronic xerostomia (p<0.001, R2:0.681).

CONCLUSIONS Our results appear to be promising since texture analysis, together with the normal dose constraints, seems to improve the prediction of xerostomia. Further studies on a large patient series are needed for an optimal estimate of these preliminary data.

C004

DOSE TO THE HIPPOCAMPUS IN RADIOSURGERY FOR MULTIPLE BRAIN METASTASES. NEED FOR A HIPPOCAMPAL SPARING APPROACH

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Aims: Neural stem cells in the hippocampusmay be implicated as the main site of treatment-related cognitive deficits. Clinical reports suggest that learning and memory impairment may be proportional to the volume and amount of irradiated tissue in this location. Some authors have suggested very low dose constraints for the bilateral hippocampi (BHp), when treated in conventional fractionation (7.3 Gy <40% of the BHp volume, Gondi et al, IJROBP 2013). The aim of this study was to evaluate the dose received by the hippocampus during Gammaknife Radiosurgery (GKRS) treatment for multiple brain metastases (BM) to understand if hippocampus receives significant dose during a radiosurgical treatment.

Methods: Among the patients with brain metastases treated from November 2012 to July 2015 using GKRSat the University of Florence, 20 plans of patients with ≥ 5 brain metastases were selected. In the "real" plans of those patients no attempt was made to spare the hippocampus. The "real" plans were reviewed and, after contouring of the bilateral hippocampi (BHp) according to the RTOG contouring atlas, dose/volume histograms were generated for BHp. Data regarding maximum dose, mean dose and dose to 40% of BHp were collected. In addition, brain volume receiving 12 Gy (V12brain) was registered. All the plans were replanned to minimize dose to the hippocampus volume ("theoretical plans").

Results: A total of 20 plans were reviewed. Median BHp volume was 3,95 cc. Median maximum dose to BHp was 2,35 Gy (range 0,9-10,9 Gy), while median average dose to BHp was 1,05 (range 0,5-3,2 Gy). Median dose to 40% of BHp volume was 1,05 (range 0,6-5,1 Gy). V12brain was <1% in all patients. In the" theoretical" plans of patients who had para-hippocampal lesions, the dose to BHpmay be significantly reduced.

Conclusions: Dose to BHp volume may be quite high during radiosurgery for brain metastases, especially in those cases where parahippocampal lesions occur. Since the hippocampus has been shown to be very radiosensitive also during a conventionally fractionated treatment, it is highly reasonable thinking that high single dose to this structure during a radiosurgical treatment should be avoided. Hippocampus needs to be included among the organs at riskduring the planning process of radiosurgery in order to be spared and to further minimize the risk of treatment-related neurocognitive impairment.

C005

30 GY SINGLE DOSE STEREOTACTIC BODY RADIATION THERAPY TO LUNG LESIONS: OUTCOME IN A LARGE SERIES OF PATIENTS

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Aims: We conducted a prospective study to evaluate the effectiveness, safety and toxicity of a Stereotactic Body Radiation Therapy (SBRT) in 30 Gy single dose, in the treatment of lung lesions.

Methods: From December 2008 to December 2015 a total of 201 lung lesions in 160 patients affected by lung oligometastatic disease or primary lung cancer were treated at our Institution. All lesions were treated with a 30 Gy single dose SBRT with a stereotactic body frame and a 3-D conformal technique. One-hundred sixty-six (82.5%) lesions were metastases, the remainder were primary tumors; main primary tumor sites were lung and colon-rectum (45.2% and 28.8%, respectively). Primary endpoints were local progression-free survival (LPFS) and toxicity, secondary endpoint were disease-free survival (DFS), metastases-free survival (MFS), overall survival (OS) and cancer specific survival (CSS).

Results: Median LPFS was not reached; 1- and 2-year LPFS were 88.2% and 77.5%, respectively. Overall response rate was 99.5%, complete response (CR) was achieved in 134 (66.6%) lesions, good or partial response in 43 cases (21.3%), stable disease in 23 (11.4%) cases and progression in one case. Local progression occurred in 34 (16.9%) lesions after a median time of 17 months. Volume <20 cc correlated with survival. Median survival time was 40 months (range 28-51 months) and 1- and 2-years OS were 84.7% and 63.9%, respectively. Median CSS was 48 months (range 38-57 months) and 1- and 2-years CSS were 87.1% and 67.6%, respectively. Median DFS and MFS were 16 and 22 months, respectively, while 1- and 2-years DFS and MFS were 64.4% and

43.1% and 67% and 48.5%, respectively. On the multivariate analysis CR was the most important factor significantly associated with improvement and survival. Acute toxicity occurred in 43 (21.3%) cases, with 10 (4.9%) cases of Grade ≥3 toxicity. Late toxicity occurred in 80 (39.8%) lesions and the rate of Grade ≥3 toxicity was 5.9% (12 lesions).

Conclusions: Our study represents, at our knowledge, the largest series in the literature on the use of SBRT 30 Gy single dose for lung lesions. Our results confirm the effectiveness of this schedule, both in primary or metastases, and can be safely administered in selected patients. Single dose SBRT is characterized by high patients' compliance and it can be easily interfaced with systemic therapies.

C006

NIVOLUMAB IN SQUAMOUS AND NON-SQUAMOUS NSCLC: THE EXPERIENCE OF RADIATION ONCOLOGY UNIT AT THE CAREGGI HOSPITAL

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Aims: Immunotherapy is one of the most important innovation in the treatment of advanced non-small-cell lung cancer (NSCLC). Nivolumab (N) is an anti PD-1 inhibitor, recently approved for the treatment of advanced squamous NSCLC after a line of therapy based on platinum. We reported our experience with N in compassionate use (Expanded Access Program – EAP) before and according to AIFA criteria in previous treated NSCLC.

Methods: 24 patients with stage IIIB - IV NSCLC were treated with N (3 mg/kg q14 ev) in our unit. Clinicopathological characteristics are described in Table 1. Tumor response was assessed by RECIST (version 1.1). Patients with progression of disease but with clinical benefit from N were treated beyond first progression and evaluated with a new CT scan after 6 weeks. Treatment was continued until clinicoradiological progression or unacceptable toxicities. Toxicities were evaluated with CTCAE (version 4.0).

Results: At the time of present analysis 15 patients are currently on N. Best response was progression of disease in 4 patients, pseudoprogression in 2 patients, while 7 patients have benefited from therapy with stable disease in 2 patients and partial response in 5 patients; 8 patients have not been evaluated yet for response. The average TTF was 154 days (range 8 to 301 days), corresponding to 5.09 months (range 0.27 to 10.30 months). Differences between squamous and non-squamous NSCLC are shown in Table 2. The treatment was well tolerated, with generally grade 1-2 toxicity. 3 patients performed palliative radiotherapy during N: no different toxicity profile was shown compared to N alone.

Conclusions: Nivolumab monotherapy is well tolerated, with a good response profile and encouraging data on survival. Radiotherapy during treatment doesn't show an increased toxicity. It will be necessary to continue the analysis to obtain more information about survival and response rate.

Table 1. Baseline charateristics of all treated patients with Nivolumab.

		All Treated Patients (N = 24)	
		No.	%
Age			
	Median	65,875	
	Range	43-81	
Sex			
	Male	12	50
	Female	12	50
Tumor Cell Histology			
	Non Squamous	14	58
	Squamous	10	42
Stage			
	IIIB	12	50
	IV	12	50
No. line of N treatment			
	II	14	58
	III	7	29
	IV	2	9
	V	1	4
EGFR Mutation Status (Adenok only)			
	Wild Type	12	100
	Mutant	0	0
KRAS Mutation Status (Adenok only)			
	Wild Type	11	91
	Mutant	1	9
ALK Rearrangement (Adenok only)			
	Not Rearranged	9	90
	Rearranged	1	10

Table 2. Differences Between Non-Squamous and Squamous NSCL in treatment with Nivolumab.

		Non-Squamous			Squamous		
		No.	% Non Squamous	% Total	No.	% Squamous	% Total
Best Response							
	PD	3	21	13	1	10	4
	pPD	0	0	0	2	20	8
	SD	0	0	0	2	20	8
	PR	5	36	21	0	0	0
	No first evaluation	4	29	17	4	40	17
	Not assessed	2	14	8	1	10	4
TTF, days							
	Median		138,4			175,67	
	Range		8 - 301			46 - 287	
TTF, months							
	Median		4,61			5,85	
	Range		0.27 - 10.3			1.53 - 9.57	
Failure Therapy							
	Palliative Care	3	75	37,5	3	37,5	75
	Other Chemotherapy	0	0	0	1	12,5	13
	Palliative Radiotherapy	1	13	12,5	0	0	0
Actual Status							
	LWD	6	43	25	6	60	25
	LWMD	4	29	17	2	20	8
	DFD	3	21	13	2	20	8
	DOC	1	7	4	4	0	0
Therapy with Nivolumab							
	Ongoing	9	64	37	6	60	25
	Interrupted	5	36	21	4	40	17
Progression							
	Local	0	0	0	1	50	17
	Systemic	4	100	66	1	50	17

Abbreviations: PD, progression disease; pPD, Pseudiprogression of disease; SD, stable disease; PR, partial response. TTF, time to failure. LWD, live with disease; LWMD, live with metastatic disease; DFD, dead for disease; DOC, dead for other cause.

C007

SHORT-COURSE PALLIATIVE RADIATION THERAPY FOR ADVANCED THORACIC TUMORS: FINAL RESULTS OF A PHASE II STUDY

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Aims: To assess the effectiveness of a SHort-course Accelerated RadiatiON therapy (SHARON) in the palliative treatment of patients with primary or secondary thoracic neoplasms, symptomatic, and not susceptible of surgery or radical radiotherapy.

Methods: A phase II clinical trial was planned based on optimal two-stage Simon's design. Eligibility criteria included patients with an Eastern Cooperative Oncology Group (ECOG) performance status of ≤3 and an expected survival>3 months. Twenty-five patients were treated with radiotherapy (total dose: 20 Gy, 5 Gy per fraction) in 2 days with twice daily fractionation. The primary endpoint was to evaluate symptoms response rate.

Results: Characteristics of the 25 enrolled patients were: male/female: 18/7; median age: 73 years (range: 46-93). ECOG performance status was <3 in 24 patients (96%). Two G1 skin (8%), 7 G1 haematological (28%) and 4 G1 pulmonary (16%) toxicities were recorded. No patient experienced G≥2 acute toxicities. With a median follow-up time of 6 months (range, 1 to 16 months), of the 25 symptomatic patients, 24 showed an improvement or resolution of baseline symptoms (overall palliative response rate: 96%). Three months overall survival was 87.5% (median survival time: 6 months; 95% CI 5.3-6.6 mo). Median survival without symptoms progression was 3 months (95% CI:2.2-3.7mo). In 24 patients with pain, a significant reduction of this symptom was recorded in terms of VAS (5.0 vs 2.9, p=0.02).

Conclusions: Short-course accelerated thorax radiotherapy (20 Gy in twice daily fractions, 2 consecutive days) is tolerated and effective in terms of symptom relief. A phase III comparison against a standard palliative regimen (30 Gy in 10 fractions) has been planned in this patient population.

C008

BALANCE BETWEEN SEVERAL FACTORS DETERMINES THE TYPE AND INTENSITY OF RADIATION-INDUCED ABSCOPAL EFFECT

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Purpose: The influence of several biological, biochemical and physical factors on type and intensity of radiation-induced abscopal effect (RIAE) was explored. Also, the radio-sensitizing potential of abscopal signals (AS) and the status of RIAE under hypoxia (H) were examined.

Methods: To explore the eventual influence of tumor histology and differentiation grade on RIAE, 4 tumor cell lines of different differentiation grade were used: lung cancer A549 and H460, and prostate cancer DU145 and PC3. The cells were incubated in H or normoxia (N) and then irradiated with wide range of doses (15cGy-3000cGy in 1 fraction) to obtain H or N-radiation-conditioned medium (H/N-RCM) for subsequent experiments. 2 identical sets of unirradiated N cells and H-resistant (HR) clones were then exposed to H/N-RCM and only 1 set was irradiated (2Gy) to evaluate also the radio-sensitizing potential of AS. Cell growth was monitored using real time cell electronic sensing system. Cell survival was assessed by colony forming assay. Levels of 15 different cytokines were assessed in obtained H/N-RCM to define the eventual RIAE-messenger.

Results: Both lung and prostate cancer ware able to induce RIAE. The type and intensity of RIAE depended on dose, tumor histotype, tumor differentiation grade and notably changed if AS were transmitted by N or H tumor cells (Figure 1). Under certain conditions RIAE induced even the radio-resistance, a phenomenon similar to adaptive response, but in this case acquired via AS by tumor cells that have never been irradiated. The effects of RIAE depended also on the respiratory ambient of cell-receivers of AS and changed significantly in N vs. H. The comparative analysis of growth factor´s levels with cell proliferation and survival showed a correlation between anti-proliferative Soluble fms-like tyrosine kinase, Interleukine-6 and almost all conditioned media types for these cell lines.

Conclusions: Our results proved that irradiation of H and N tumor cells lead to significant RIAE which is able to affect cell proliferation and radiosensibility. This phenomenon depends on several factors whose manipulation is possible and leads to induction of clinically applicable RIAE. The eventual definition of a perfect balance between these factors could lead to development of innovative approaches in modern radiotherapy treatment of prostate cancer, especially for those patients

with hormone-refractory ADC in which radiotherapy might have a limited role.

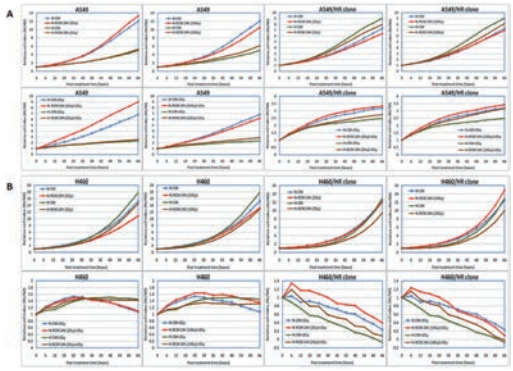

Figure 1 A. A549 cells were grown in either normoxia or hypoxia for 3 days. Once about 80% confluent, media was changed and cells were either left untreated or irradiated (2Gy or 10Gy). Cells were again incubated for 24h in the respective microenvironment after which media was collected. Two thousand A549 or A549/HR cells per well were plated in E-16 plates and exposed to N-CM / N-RCM / H-CM / H-RCM. 24h after, cells were exposed to direct irradiation of 2Gy. Growth of the cells was then followed dynamically using RT-CES. Cell number at each time was normalized to the cell number at the time of treatment. Standard error was less than ±10% for the duplicate values and since the results are shown as the ratio, error bars are not shown. B. H460 cells were grown in either normoxia or hypoxia for 3 days. Once about 80% confluent, media was changed and cells were either left untreated or irradiated (2Gy or 10Gy). Cells were again incubated for 24h in the respective microenvironment after which media was collected. Two thousand H460 or H460/HR cells per well were plated in E-16 plates and exposed to N-CM / N-RCM / H-CM / H-RCM. 24h after, cells were exposed to direct irradiation of 2Gy. Growth of the cells was then followed dynamically using RT-CES. Cell number at each time was normalized to the cell number at the time of treatment. Standard error was less than ±10% for the duplicate values and since the results are shown as the ratio, error bars are not shown. C. H460 cells were plated in two different cell concentrations in quadruplet sets (total 4 replicates). After overnight plating, cells were treated by incubating in N-CM, H-CM (obtained at 3 days pre-irradiation+24h post-irradiation in H), N-RCM (2Gy), N-RCM (10Gy), H-RCM (2Gy), H-RCM (10Gy) and left for colony formation. After incubation for 8-10 days, colonies were stained with crystal violet and the colonies containing more than 50 cells were counted. The surviving fraction (SF) was calculated as a ratio between the number of colonies formed and the product of the number of cells plated and the plating efficiency. Error bars represent standard error.

C009

ACCELERATED PARTIAL BREAST IRRADIATION (APBI) WITH 3D-CRT VS STANDARD RADIOTHERAPY (WBI) AFTER CONSERVING SURGERY (IRMA TRIAL): INTERIM COSMETIC AND TOXICITY RESULTS

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Purpose: To report interim cosmetic and toxicity results in patients (pts) enrolled from 5 italyn centers in the randomized IRMA trial

Materials and Methods: Women age ≥ 49 years with invasive breast cancer<3 cm, pN0-1, were randomly assigned after breast-conserving surgery to 3D-CRT APBI (38.5 Gy in 10 fractions twice daily) or WBI (50 Gy in 25 daily fractions ± boost). Pts received adjuvant systemic therapy according to institutional guidelines. Cosmesis was assessed according to IRMA protocol parameters. Toxicity was scored according to RTOG tables.

Results: From March 2007 to December 2013, 983 pts were enrolled in IRMA from 5 italyn centers (425 Bologna Bellaria, 240 Modena, 163 Reggio Emilia, 101 Bologna S. Orsola, 54 S.Giovanni Rotondo). Median follow-up was 5 years. No difference was observed in adverse cosmesis (fair and poor) among pts treated with APBI compared with WBI as assessed by physicians (20% vs 21.8% 1 year, 20% vs 19% 3 years) and by patients (14% vs 16% 1 year, 14% vs 14% 3 years). G3 acute skin toxicity was rare in both treatment arms (0% PBI vs 1.4% WBI), no further G3-4 acute toxicities were observed. G3-4 late skin toxicity was 0.42% (APBI) vs 0.79% (WBI) (p=0.4); G3-4 late subcutaneous tissue toxicity was 1.5% (APBI) vs 1.2% (WBI) (p=0.7); 2 rib fractures were observed in PBI patients; no further G3-4 late toxicities were observed. Axillary dissection (vs sentinel node) correlated with G3-4 late subcutaneous tissue toxicity (3.7% vs 0.9%, p<0.01); no correlation of toxicity with adjuvant chemotherapy was observed.

Conclusions: APBI with 3D-CRT resulted in similar acute and late toxicity and good/excellent cosmetic results compared with standard WBI. Additional follow-up is needed to confirm these results.

C010

A RANDOMIZED STUDY OF HYPOFRACTIONATED AND CONVENTIONAL BREAST IRRADIATION IN EARLY-STAGE BREAST CANCER: TOXICITY AND LONG-TERM OUTCOME

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Aims: To report acute/intermediate toxicity and long-term outcome of a randomized study testing hypofractionated scheme compared to the standard regimen in early breast cancer patients.

Materials and Methods: Between 4/2007 and 3/2010, 257 women with early breast cancer (pT1-3 pN0-1 M0) were randomly assigned after breast conserving surgery to receive 50 Gy in 25 fractions to whole breast (WB) + 10 Gy to tumor bed (TB) (2.0 Gy/fraction) versus 45 Gy to WB (2.25 Gy/die) + 5 Gy concomitant boost to tumor bed, once a week (1.25 Gy/week, using electrons) over 4 weeks. WB was irradiated with 3D conformal technique using tangential fields and 6 MV photons, while external electron beam was delivered to TB. Randomisation method was computer generated and was not blinded. The primary outcome was acute toxicity. Secondary outcomes included intermediate toxicity and cosmetic outcome, locoregional relapse and survival. For primary and secondary endpoints, analysis was by intention to treat. This study was approved by CE, number IEO S324.

Findings: 122 and 127 patients were assigned to short-term and long-term arm, respectively. No difference between acute and intermediate toxicity was observed. The short term-arm presented less acute toxicity than the long-term arm: the corresponding RTOG >2 toxicity was 39.3%% and 73.2% in the short-term and long- term arm, respectively (absolute difference = –7.1%, 95% CI = –12.4% to-1.8%). At 1 year, intermediate toxicity ≥ G2 was the same between the two arms (11.6% versus 11.3 %, p=0.94). For the assessment of secondary outcomes, median follow-up was 82 months (17-110 months). Five-year disease-free survival was 96.6% and 93.7% in the short-term and long-term arm, respectively (p=0.07). 5-year overall survival was 98.4% and 91.1% in the short-term and long-term arm, respectively. Non difference was observed in local, regional and distant recurrence rates between the two study arms.

Conclusions: The 4-week scheme is as tolerable and effective as the 6-week schedule, confirming that hypofractionation is a valid alternative in early breast cancer patients.

C011

HYPOFRACTIONATION WITH SIMULTANEOUS INTEGRATED BOOST FOR EARLY BREAST CANCER USING VMAT: ACUTE TOXICITY AND COSMESIS IN 1025 PATIENTS

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Aims: To evaluate acute toxicity and early clinical outcomes of hypofractionated simultaneous integrated boost (SIB) approach with Volumetric Modulated Arc Therapy (VMAT) as adjuvant treatment after breast-conserving surgery.

Materials and Methods: Patients presenting early-stage breast cancer were enrolled in a phase II trial. Eligibility criteria were as follow: age >18 years, invasive cancer or DCIS, Stage I to II (T <3 cm and N ≤ 3), breast-conserving surgery, any systemic therapy was allowed in neoadjuvant or adjuvant setting. All patients underwent VMAT-SIB technique to irradiate the whole breast with concomitant boost irradiation of the tumor bed. Doses to whole breast and surgical bed were 40.5 Gy and 48 Gy respectively, delivered in 15 fractions over 3 weeks Acute skin toxicities were recorded according to RTOG scoring criteria, and late skin toxicities according to CTCAE v4.0. Cosmetic outcomes were assessed as excellent/good or fair/poor according to the Harvard scale.

Results: Between August 2010 and June 2015, 1025 consecutive patients were treated. Median age was 60 year (range 19-89 years). The median follow up was 20 months (range 6-55). At the end of RT treatment skin toxicity profile was G1 in 50% of the patients, G2 in 15%, and one patient presented G3 toxicity. At six months of follow up skin toxicity was G1 in 28% of patients, G2 in 3%, no G3 cases; cosmetic outcome was good/excellent in 94% of patients. At one year skin toxicity was G1 in 13% of patients, 2 patients G2, 1 patient G3; cosmetic outcome was good/excellent in 93% of patients. After an early evaluation of clinical outcomes we have found 12 cases of progression disease, only one patient had an In-Breast-Recurrence.

Conclusions: The 3-week course of postoperative radiation using VMAT with SIB was well tolerated in acute and early late settings. Long-term follow-up data are needed to assess late toxicity and clinical outcomes.

C012

HYPOFRACTIONATION WITH NO BOOST IN PATIENTS WITH EARLY STAGE BREAST CANCER AFTER BREAST CONSERVATION: MONO-INSTITUTIONAL ANALYSIS OF 493 CONSECUTIVE CASES

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Aims: To evaluate local control, survival and toxicity profile in a mono-institutional cohort of early breast-cancer patients treated with adjuvant radiotherapy employing hypofractionated schedules.

Methods: Between 2005 and 2015, 493 women affected with early stage breast cancer were treated with adjuvant hypofractionated radiation (46 Gy/20 fractions or 40.05 Gy/15 fractions) without boost to tumor bed, because of age and/or favorable tumor characteristics. The primary endpoint was local control; secondary endpoints were contralateral breast recurrence, regional nodal recurrence, distance metastases, disease-free (DFS), cancer-specific (CFS) and overall survival (OS). Acute and late skin toxicity and cosmesis outcomes were also reported.

Results: Median follow-up was 47 months (range 3-124), median age 64. A total of 10 patients (2%) developed recurrence at any site for a total of 19 events. Seven local (in-breast), 1 in contralateral breast, 4 regional and 7 distant recurrences (lung, liver and bone) were seen. Up to 12 patients died during observation time; 3 deaths were related to breast and 9 to other causes. Actuarial 5-year OS, CSS, DFS and local control were 96%, 99%, 98% and 98%, respectively. Age, as linear variable, was associated with OS (HR 1.1, 95%CI:1-1.23: p=0.045) with a trend for triple negative subtype (HR: 18.73; 95%CI: 0.78-449; p value=0.071). On multivariate analysis tumor stage (T1 vs T2) and hormonal status (ER+ vs ER -) was seen as statistically significant with respect to LC; univariate analysis showed that Ki-67 (cut-off at 14) statistically affected LC (not confirmed on multivariate analyses). No acute skin toxicity>G3 was seen. Concerning late toxicity, 11 patients developed late fibrosis, 5 telangiectasia, 12 hyperpigmentation. One case of G2 pulmonary fibrosis and no cardiac toxicities was reported. Only 5% had fair or poor cosmetic outcomes, the others had excellent-good aesthetic results. Adjuvant chemotherapy was significantly correlated to>G2 skin toxicity and fair-poor cosmesis.

Conclusions: Low local recurrence rates and acceptable low toxicity profile were achieved with adjuvant hypofractionated radiotherapy and no boost to the tumor bed, comparably to results achieved in large randomized trials. Hypofractionation is a valid option with reliable overall clinical results. In selected patients with risk factors (T2 stage, ER -, Ki-67>14%) a boost dose to the surgical bed may potentially improve local control.

Table 1.

Characteristic	n (%)
No. of patients	493
No. of breasts treated	503
Age (years)	
Mean	64
Median	64
Range	41-86
Laterality	
Right	229 (46)
Left	254 (52)
Bilateral	10(2)
T size	
T1a	35 (7)
T1b	158 (32)
T1c	258 (51)
T2	52 (10)
Histology	
Ductal	350 (70)
Lobular	63 (12)
Other	90 (18)
Nodal status	
Nx	22 (4)
N0	397 (79)
N1	84 (17)
Grade	
1	224 (45)
2	232 (46)
3	47 (9)
Estrogen receptor status	
Positive	475(94)
Negative	28 (6)
Progesteron receptor status	
Positive	383 (76)
Negative	120 (24)
Her-2 status	
Positive	32(6)
Negative	471(94)
Ki67	
≤ 20	402(80)
> 20	101 (20)
≤ 14	309 (61)
> 14	194 (39)
Pattern	
Luminal A	369 (73)
Luminal B	83(17)
HER2 Like	32(6)
Triple Negative	19(4)
Radiotherapy	
46 Gy/20 fr	378(75)
40,05 Gy /15 fr	125(25)
Chemotherapy	
Yes	75(15)
No	418(85)
Hormone therapy	
Yes	466 (95)
No	27(5)
Trastuzumab	
Yes	27(5)
No	466(95)

C013

PARTIAL BREAST RE-IRRADIATION USING EXTERNAL BEAM RADIOTHERAPY FOR LOCAL RECURRENCE AFTER PREVIOUS WHOLE BREAST RADIOTHERAPY: EXPERIENCE OF EUROPEAN INSTITUTE OF ONCOLOGY

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Aims: Although the standard treatment of local recurrence after breast conservative surgery and whole breast (WB) radiotherapy (RT) is still represented by mastectomy, over the last decade there has been an increasing attitude towards performing a second conservative surgery followed by further radiotherapy with different techniques (intraoperative RT, brachytherapy, external beam RT). The aim of the study is to evaluate acute toxicity and clinical outcome of partial breast re-irradiation (re-PBI) with intensity modulated radiotherapy (IMRT), using an hypofractionated scheme.

Methods: Eligibility criteria included patients (pts) previously treated with WBRT who experienced in-breast tumour recurrence and were operated on with second conservative surgery. Re-irradiation was limited to the tumor bed. Re-treatment was performed using TomoTherapy IMRT with helical modality and BrainLab-VERO IMRT step-and-shoot with 5 fields.Planning Target Volume (PTV) was generated by Clinical Treatment Volume (CTV) with a margin of 5 mm. Daily Image Guided RT was applied (MegaVoltage Fan Beam Computerized Tomography (CT) for TomoTherapy and kiloVoltage Cone Beam CT for VERO). For target volume, planning objectives were: PTV: V100%≥95%, V95%≥98%, D0,03cc≤110%. Toxicity was evaluated using RTOG/EORTC criteria.

Results: Between 6/2012 and 11/2015, 52 consecutive pts were treated with re-PBI. Prescription dose was 37.05 Gy in 13 fractions. 12 pts were treated with TomoTherapy and 40 pts with VERO. Median age was 61 years. 40 pts received concomitant systemic therapy (chemotherapy: 7 pts, endocrine therapy: 31 pts, both: 2 pts). Acute toxicity was moderate: no >G2 acute toxicity was observed at the end of the treatment (erythema G1 in 48% of pts; desquamation G1 in 2% of pts; edema G2 in 8% of pts). At 1 month-follow-up, maximum acute skin toxicity (data available for 33 patients) was G2 (erythema G1 in 24% of pts; desquamation G1 in 15% of pts; edema G2 in 15% of pts). Overall, median follow-up was 9.7 months. 41 pts are alive without disease, 4 pts showed out-re-irradiation field recurrence, while 1 pts had in-field progression. 6 pts cannot be assessed for clinical outcome at the time of writing.

Conclusions: Re-PBI after second conservative surgery represents a feasible alternative to mastectomy, showing good toxicity profile. Longer follow-up and higher number of pts are needed to evaluate late toxicity and to establish the role of this treatment modality in local control.

C014

ACUTE TOXICITY IN PATIENTS WITH BREAST CANCER SUBMITTED TO HYPOFRACTIONATED RT ON WHOLE BREAST

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Aims: To evaluate retrospectively acute skin and lung toxicities in patients submitted to hypofractionated whole breast Radiotherapy after conservative surgery.

Methods: We retrospectively evaluated breast cancer patients, conservatively treated, in our Centres from March 2014 to January 2016. Among these we selected only patients submitted to hypofractionated radiation therapy. We recorded clinical skin toxicity report using RTOG scale and both breast and lung dosimetric studies including breast volumes, isodoses distribution, and lung constraints evaluation: precisely we considered V5, V12 and V20 as constraints for lung.

Results: 161 patients affected by breast cancer, previously submitted to breast conservative surgery, have been recruited. In 26 patients we could not evaluate toxicity because they lost the follow up controls. The characteristics of the patients were: T1/ N0 M0, RF +, dose disomogeneity<10%. None of them underwent to chemotherapy. In our study we used several Hypofractionated schemes: the daily dose fraction was between 2,65-2,75 Gy, the number of fractions was 15 or 16. Boost range was 1,2 Gy-3 Gy per fraction and the dose was delivered in a variable number of fractions (2, 3, 5). The predominant scheme used was: 2.75 Gy x 16 fractions. All patients completed the radiotherapy program. We evaluated acute toxicity in 135 patients: G0 toxicity was observed in 102 patients; G1toxicity in 31 and G2-3 toxicity in 2 patients The median value of CTV volumes was 693,6cc, the V5, V12 and V20 median values were 15,74%- 9,92%- 8,34% respectively. In our report there was not a correlation between toxicity and total volume irradiated.

Conclusion: Hypofractioned RT on whole breast was well tolerated with low acute toxicity and it can be considered a valid therapeutic option in this subgroup of patients. However, further analysis on a larger group of patients is necessary to assess frequency and grade of acute toxicity.

C015

EFFICACY AND SAFETY OF WEEKLY NAB-PACLITAXEL FOR METASTATIC BREAST CANCER PATIENTS: THE EXPERIENCE OF THE UNIVERSITY OF FLORENCE

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Introduction: Nab-paclitaxel is an albumin-bound formulation of paclitaxel designed to enhance the drug's clinical activity and improve its safety profile compared with taxanes formulated in chemical solvents. The safety and efficacy of nab-paclitaxel have been characterized in patients with metastatic breast cancer (MBC) in several clinical trials. This observational single-center study evaluated the efficacy and safety of weekly nab-paclitaxel (Abraxane®) as monotherapy for MBC treatment.

Patients and Methods: Twenty-three MBC patients treated at the Department of Radiation Oncology of the University of Florence were retrospectively evaluated. All patients received weekly nab-paclitaxel (150 mg/m2). We analyzed the median time to progression (TTP), median overall survival (OS), and best response to treatment according to RECIST criteria (progression of disease, stable disease, partial response, complete response). Main toxicities were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE 4.0) criteria.

Results: The median number of previous chemotherapy regimens was four (range 1-9); 30.4% of patients underwent palliative radiotherapy during nab-paclitaxel treatment, with a median of 19.7 days of chemotherapy suspension. At a median follow-up of 48 months (range 3-62), the ORR was 26%; three patients had a partial response (PR), three patients experienced stable disease (SD), and seventeen patients had a progression disease (PD). The median duration of response was 7 months. The median PFS was 5 months. The most commonly observed adverse events were neutropenia (26%: G1-2; 21.7%: G3-4), anemia (G1-2: 30.4%), sensory neuropathy (8.7%), nausea (13%). Six patients (26%) required dose reduction (125 mg/m2). Three patients (13%) discontinued treatment due to adverse events.

Conclusions: Our findings confirmed the effectiveness of weekly nab-paclitaxel and a favorable safety profile.

C016

SAFETY OF ERIBULIN MESYLATE AND CONCOMITANT RADIOTHERAPY FOR METASTATIC BREAST CANCER: THE EXPERIENCE OF THE UNIVERSITY OF FLORENCE

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Aims: Eribulin mesylate is a new non-taxane agent approved for the treatment of metastatic breast cancer (MBC). It is a structurally simplified synthetic analogue of halichondrin B, a natural product that was originally isolated from western Pacific sponge Halichondria okadai. This study evaluates the safety of eribulin in MBC patients concomitantly treated with palliative radiotherapy (RT).

Methods: A total of 17 patients affected by MBC undergoing palliative RT for a total of 25 lesions and concomitant eribulin were included in our analysis. Patients were treated between February 2012 and October 2014 at the Radiation Oncology Unit of the University of Florence (Florence, Italy). All patients signed informed consent. Patients with pulmonary or liver lesions underwent 4DCT simulation with abdominal compression, to account for breathing-related tumor motion. For all other lesions – for which breathingrelated motion was not considered feasible – gross tumor volume was contoured from conventional CT simulation images. Stereotactic body RT was planned and delivered using dynamic conformal arcs or multiple coplanar static beams. Patients received eribulin mesylate (1.4 mg/m^2 intravenously, on days 1 and 8, of a 21-day cycle). Dose reductions were permitted, and patients remained on prescribed treatment until they had no clinical benefit, or experienced disease progression, unacceptable toxicity or toxicity requiring three permanent dose reductions or a cycle delay ≥6 weeks. The following criteria were adopted for dose reduction: permanent reduction to 0.97 mg/m^2 in case of absolute neutrophil count 7 days, absolute neutrophil count 40 mg, but 100 mg morphine or equivalent, daily.

Results: The most frequent grade 3 hematologic adverse events were neutropenia (56%) and anemia (20%). Mean pain score decreased from 2 (baseline) to 0.7 (end of observation). Analgesic score remained stable (1.8 vs 1.6). Bone pain scores dropped within a few weeks and remained below baseline values throughout the analysis. The overall response rate was 29%, and the clinical benefit rate was 59%.

Conclusions: Eribulin is characterized by a manageable safety profile also when combined with palliative RT to bone metastases or ablative RT to visceral lesions.

C017

HYPOFRACTIONED ORTHOVOLTAGE RADIOTHERAPY FOR NON MELANOMA SKIN CANCER: A RETROSPECTIVE CASE SERIES

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Aims: The incidence of non – melanoma skin cancer (NMSC) continues to arise annually. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the two most common subtypes of NMSC. Although surgical excision remains the primary treatment for localized BCC and SCC, radiation therapy (RT) offers an effective alternative, especially in elderly patients with comorbidities, low performance status and critical location of lesion such as nose, eyes and facial skin. In consideration of cosmetic outcome, patient preference and compliance, radiation therapy (RT) as Roentgen therapy is the treatment of choice in order to achieve optimal overall results. The aim of this study was to estimate tumour control and toxicity in patients treated with hypofractioned orthovoltage radiotherapy.

Methods: From 2010 to 2013, 476 lesions in 407 patients were treated. 248 patients were male (61.0%) and 159 female (38.0%) , the median age of the patients treated was 84 years with a wide range from 52 to 101 years. Most of lesions (71.8%) histologically were basal cell carcinoma (BCC) , 28.2% were squamous cell carcinoma (SCC). Most of lesions were located on head and neck region, other anywhere on the body. Using orthovoltage radiotherapy, the treatment dose prescription was 2800 cGy in 4 fractions (700 cGy/fraction weekly) and 3500 cGy in 5 fractions (700 cGy/fraction weekly) with kVp energy between 50 - 150.

Results: The treatment was well tolerated in all cases, the most common early side effects were erythema, pruritus and rash dermatitis. Follow up was from 6 to 48 months. The highest skin acute toxicity was Grade 2, according to CTCAE v.4.02 and occurred respectively in 16% of the lesions. Late toxicity G3 was observed in 4 % of the lesions, most located in arms or legs. Complete regression occurred in 93.6 % of the lesions with a good cosmetic outcome. Partial remissions were 6.4% of the lesions.

Conclusions: Hypofractioned orthovoltage radiotherapy provides excellent results for local control and cosmetic results. Moreover the shorter, hypofractioned regimen facilities compliance especially in elderly patients and appears to be safe and effective.

C018

PRELIMINAR RESULTS OF FRACTIONATED CYBERKNIFE RADIOSURGERY FOR UVEAL MELANOMA

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Aims: We report our clinical experience of a hypofractionated Cyberknife Radiosurgery schedule for uveal melanoma treatment.

Methods: Between April 2014 and October 2015 12 patients (pts), mean age 65 years (range 36 – 82 years) suffering from uveal melanoma (11 choroidal melanoma and 1 ciliary body melanoma) were treated at Cyberknife Center, Centro Diagnostico Italyno, Milan. All of the pts had received a diagnosis and referral from an ophthalmologist. Cyberknife robot-controlled LINAC radiosurgery was performed delivering a total dose of 54 - 60 Gy (mean 60 Gy) given in 3 or 4 fractions (mean 3) of 15 - 20 Gy (mean 20 Gy) prescribed to the 79-82% (mean 80%) isodose surface. All pts underwent orbit MRI with gadolinium for coregistration with the planning CT scans. The planning target volume (PTV) included the contrast-enhancing lesion on MRI plus a 2.5 mm margins in all directions. All pts were irradiated eyelids closed, without peribulbar anesthesia, using a contention with a thermoplastic mask. At presentation the mean PTV volume was 2148 mm (range 701.82 – 5792 mm), mean tumor base measured ultrasonographically 11.75 mm (range 7-15 mm), mean thickness 4.6 mm (range 2.5 – 7.1 mm), with a mean distance of 5.7 mm (range 0 – 15 mm) from fovea and 6.1 mm (range 0 – 13 mm) from optic nerve.

Results: After a mean follow-up of 11.5 months (range 3 – 24) local control was achieved in 100% of pts. No patient underwent enucleation and none developed distant metastases (all pts underwent abdomen ultrasound and liver blood examination once every six months and chest CT once a year). We observed a reduction of 17% in median base and of 40% in median thickness that were respectively 10 mm (range 4.8 – 13 mm) and 2.75 mm (range 0.5 – 5 mm) at last follow-up. Visual acuity was reduced in 58% of pts, while in the others no change was found. Three pts suffered of radiation maculopathy, associated in one case with atrophy and in two cases with cystoids macular edema. Moreover radiation-induced optic neuropathy and radiation vasculopathy occurred respectively in 2 and 4 cases. 5 pts developed choroidal ischemia and 3 retinal detachment. At the last follow-up none had corneal anomalies and only one cilia loss.

Conclusions: These initial results of our Cyberknife schedule are consistent with data in literature and show a safe, minimally invasive and well tolerated method for treating uveal melanoma. Further follow-up is necessary.

C019

STAGED RADIOSURGERY FOR PETROCLIVAL MENINGIOMAS. PRELIMINARY RESULTS

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Aims: Despite total resection beeing the treatment of choice for meningiomas, the complete removal of petroclival meningiomas can be difficult because of their proximity to cranial nerves. The radiosurgery (SRS) is a well-established treatment for many patients with intracranial meningiomas, either in the exclusive or adjuvant setting. However, SRS of large meningiomas might be associated with significant morbidity. Staged SRS (s-SRS) has the potential to deliver sharply focused high doses per fraction without increasing the risk of toxicity The aim of this study is to prospectively evaluate the feasibility of s-SRS for petroclival meningiomas, including large volume lesions.

Methods: Between September 2011 and October 2013 at our Institute, s-SRS using the CyberKnife was prospectively performed on 30 patients (24 women and 6 men with a mean age of 57 years) with petroclival meningiomas. Patients with atypical or malignant meningiomas and those who had received prior radiotherapy were excluded. The average tumour volume was 11,86 cm3 (range 2,2–126,3 cm3); the average tumour prescription dose was 24,4 Gy, the number of fraction was 4 or 5.

Results: After a median follow-up of 30 months (range 13-36 months) the overall tumour control rate was 100% (25 patients with stable disease, 3 patients with partial response and 2 patients with complete response). Tumour control rates at 2 and 3 years was 100%. Among 28 patients who were symptomatic before staged radiosurgery, neurological follow-up showed an improvement in 43% of the patients, stable clinical course in 43% and a persistent deterioration of clinical symptoms in 14%. A transient neurological deterioration was observed in 11% of patients within the first year after treatment.

Conclusions: Our findings show that s-SRS using the CyberKnife is a safe and effective option in the treatment of large-volume petroclival meningiomas. A good tumour control and a low morbidity rate was achieved in our series, either as a primary or adjuvant approach. Long-term follow-up is necessary to confirm these results.

C020

WHAT IS THE IMPACT OF HIGH DOSE RADIOTHERAPY ON SURVIVAL AND NEUROCOGNITIVE FUNCTIONS IN NAÏVE GLIOBLASTOMA? A LONG TERM RESULTS OF A PROSPECTIVE PHASE II STUDY

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Aims: The aim of this analysis is to evaluate the outcomes and the neurocognitive functions (NCF) in long-term survivor glioblastoma patients (pts) treated with radio-chemotherapy plus Fractionated Stereotactic Conformal Radiotherapy (FSCRT).

Methods: Patients affected by Glioblastoma over 18 years old were enrolled in a prospective Phase II trial. According to CTV diameter they received a total dose of 50.4Gy or 59.4Gy with 3D-CRT plus two different FSCRT schedules: concomitant (9 Gy) plus sequential (10 Gy in 4 fractions) or only sequential boost (10Gy in 4 fractions). Concomitant and adjuvant Temozolomide at standard dose was administered. To evaluate the impact of intensification dose on NCF, pts with a survival more or equal to that observed by the EORTC/NCIC trial (14.6 months) were evaluated according to Mini-Mental-State-Examination (MMSE), considering space-time orientation, short-term memory, attention and ability to calculate, memory, language and construction skills .

Results: Thirty-eight pts were analysed (Table 1); no difference were significant between the two treatment groups in terms of sex, extent of surgery and RPA class.

With a median follow up of 77 months (range 25-87), median progression free survival (PFS) and overall survival (OS) were 10 and 23 months respectively; the 2-year and 5-year PFS and OS were 21% and 4.9%, 47% and 14%, respectively. The extent of surgery, RPA class and the RT schedules did not impact significantly the OS (p=0.15, p=0.89, p=0.52, respectively) and also the Cox' logistic regression revealed that the absence of residual tumor and sequential FSCRT boost schedule did not improved significantly OS (p=0.4, p=0.2, respectively).

At the start of this analysis, 11 pts were evaluable for NCF, which were preserved, except for 2 pts (MMSE score was 23 and 20). A complete preservation of memory and language functions was observed (mean MMSE score: 27.9); while the attention and the ability to calculate was the most damaged.

Conclusions: In our analysis a better outcome is showed in glioblastoma pts when high dose of radiotherapy is used. Despite the limitations of our analysis no detrimental in NCF were observed. A more accurate neurocognitive evaluation with specific scores is ongoing.

Table 1. Patients' characteristics.

Patients' characteristics	Total N= 38	Group A N=22 (57.9%)	Group B N=16 (42.1%)	Fisher test (p)
Age (years) Median (Range)	56 (25-72)	54 (34-72)	56 (25-65)	-
Sex n (%)				
Male	23 (60.5%)	13(59.1%)	10 (62.5%)	0.9
Female	15 (39.5%)	9 (40.9%)	6 (37.5%)	
Type of surgery n (%)				
Subtotal resection	26 (68.4%)	16 (72.73%)	10 (62.5%)	0.68
Complete resection	12 (31.6%)	6 (27.27%)	6 (37.5%)	
RPA class n (%)				
III	7 (18.4%)	5 (22.72%)	4 (25%)	0.8
IV	29 (76.3%)	16 (72.73%)	11 (68.75%)	
V	2 (5.3%)	1 (4.55%)	1 (6.25%)	

C021

ROLE OF 11C-CHOLINE PET-CT (CHO-PET) IN RADIATION THERAPY PLANNING OF PROSTATE CANCER PATIENTS

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Aims: In the era of image-guided radiotherapy (IGRT), PET has become an important tool, for tumour delineation in several types of cancer. Limited evidence is available on the use of Cho-PET in prostate cancer. Aim of this study was to verify the impact of this imaging modality in treatment planning of patients eligible for radiotherapy (RT).

Materials and Methods: From September, 2011 to 135 consecutive patients (median age 69 years, range 53-89) were referred to our Department for radiation therapy with radical intent (n=28), for postoperative adjuvant (n=13) or salvage therapy (n=50), for re-irradiation (n=19) or for radiotherapy on distant metastases (n=25). Before planning the radiotherapy course patients were submitted to staging or restaging Cho-PET, in order to confirm the indication to radiotherapy and the irradiation volumes. In the cases who subsequently underwent radiation treatment, GTV, CTV, PTV and OAR were outlined on CT images using Eclipse Varian Medical System software, whereas GTV-PET was defined as areas with pathologic uptake and contoured with dedicated software on Advantage GE workstation.

Results: Among the 135 patients submitted to Cho-PET, the indication to radiotherapy was modified in a total of 66 cases (48.8%) on the basis of the Cho-PET result. In particular, of the 28 patients evaluated with Cho-PET before radical radiation treatment, 11 (39.3%) showed evidence of positive nodes and a boost RT was planned. One patients (3.5%) was not submitted to the programmed RT because of the evidence of metastatic disease, the remaining 16 pts (57.2%) received the planned treatment. Of the 63 patients candidate to adjuvant/salvage RT, 30 (47.6%) had a Cho-PET negative or positive on prostatic bed only, were therefore irradiated on prostatic lodge as planned. On the basis of Cho-PET result, 22 pts (34.9%) received a boost on positive nodes; 5 patients (7.9 %) received radiotherapy on a distant metastatic site, 6 pts (9.5%) with evidence of multiple metastases received systemic therapy. Of the 19 patients studied with Cho-PET before re-irradiation, 10 (52.6%) had their indication confirmed, 4 (21.1%) were upstaged for distant metastases and excluded, 5 (26.3%) pts were excluded because of a negative Cho-PET. The indication of radiotherapy was also changed in 12 (48.0%) of the 25 patients submitted to Cho-PET before radiotherapy to metastatic lesions. Overall Cho-PET helped us to better define the radiotherapy programme in 42.8% of patients candidate to primary RT, 52.4% of pts undergoing adjuvant/salvage RT, 47.7% of patients with relapsed/metastatic disease.

Conclusions: In our series, Cho-PET had a significant impact on RT planning of patients affected from prostate cancer, determining a change in the management 48.8% of cases, considering all therapeutic indications.

C022

STEREOTACTIC BODY RADIATION THERAPY (SBRT) FOR LOW-RISK PROSTATE CANCER: RESULTS OF A MULTICENTER PHASE II STUDY

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The radiobiology of prostate cancer favors a hypofractionated dose regimen. Stereotactic body radiation therapy (SBRT) delivers fewer high-dose fractions of radiation which may be radio biologically favorable to conventional low-dose fractions commonly used for prostate cancer radiotherapy. We report the preliminary results of a prospective phase II clinical trial of radiotherapy SBRT of localized prostate cancer. 28 patients low-risk (pre-biopsy PSA ≤ 10 ng/mL, Gleason Grade3+3,clinical T-stage T1c or T2a/b, ≤ 3 positive biopsy) with 7 months' minimum follow-up received 36,25 Gy (BED 211 / ratio 1.5 Gy) in five fractions of 7,25 Gy with IGRT using Helical Tomotherapy (HT) and Elekta Axesse . The early and late urinary and rectal toxicities (GU,GI) were assessed using RTOG and CTCAE 4 (Common Terminology Criteria for Adverse Events) scoring system. After 6 and 12 months, urinary and rectal toxicities were assessed using validated quality of life (QoL) questionnaires Expanded Prostate Cancer Index Composite(EPIC).Patterns of prostate-specific antigen response was analyzed. The median age was 72 years (range 55-80) with the median follow-up of 23 months(range 7-36).The median pre RT detectable PSA was 5,84 ng/L (2,3-10,96). There were no CTCAE/RTOG grade 3 and 4 acute and grade 2-3-4 late rectal/ urinary complications. There were 2/28 (7,1%) patients with CTCAE/RTOG acute grade 2 urinary toxicity and 1/28 (3,5%) with CTCAE/RTOG acute grade 2 rectal. Late grade 1 toxicity was 14,3% (GI) and 21,4% (GU). The median PSA nadir was 0,43 ng/ml (0,12-2,27). At last follow-up no patient has had a PSA failure regardless of biochemical failure definition. Global health status/QoL was good and improved during the observational period. The early and late toxicity profile and PSA response after SBRT radiotherapy are very promising. Continued follow-up will be necessary to confirm durable biochemical control rates and low toxicity.

C023

MODERATELY HYPOFRACTIONATED RADICAL TOMOTHERAPY IN PROSTATE CANCER: OUTCOMES WITH 75-MONTHS FOLLOW UP

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Aims: To report 75-months clinical outcomes in prostate cancer patients (pts) treated with moderately hypofractionated radical tomotherapy (Hi Art II, Accuray, USA), with Simultaneous integrated boost (SIB), in a phase I-II study.

Methods: Patients with a follow-up ≥ 60 months were considered for this analysis. The 128 pts identified were: 55 low- risk[LR], 33 intermediate- risk [IR] and 40high-risk[HR]. IR and HR pts received 51,8 Gy on pelvic lymph-nodes (LN) and concomitant SIB to prostate up to 74,2Gy in 28 fr; LR pts were treated to the seminal vesicles to 61.6 Gy and to prostate to 71,4Gy in 28fr. Androgen deprivation (AD) was delivered to 27% LR/57% IR/87% HR pts for a median time of 12.5, 13.7 and 15,5 months (m) respectively. Biochemical relapse free (bRFS) survival (Phoenix definition), cancer-specific (CCS) and overall survival (OS) actuarial curves were assessed. Selected clinical/dosimetry variables were tested as potential predictors of GI /GU toxicity and of BCR/CCS/OS (Cox test) .

Results: Median follow and median age were 75 m (range: 60-99) and 74 y (57-84) respectively, while median Gleason score(GS) was 6 (3-10):GS<7: 75; GS=7: 39; GS>7: 13 ; missing:2. 73 pts were staged as T1, 46 as T2: 6 as T3; and for 3 pts the stage was unclear (Tx). The median initial Psa (iPsa) was 7.8 (1.2-826). The 75-m bRFS was 92.5% (LR: 94.2%; IR: 96.9%; HR: 84.5%); OS was 94.6% (LR:95.9%; IR: 95.8%; HR: 91.1%) and CSS was 97.4% (LR: 100%;IR:94.5%;HR: 97.1%). AD and class risk were not correlated with bRFS/OS/CSS. The incidence of G3 toxicity was around of 6% with drastically reduction of the prevalence at the last follow-up for both ≥G2 and ≥G3 toxicities indicating that symptoms were recovered in most patients.

Conclusions: The combination of pelvic LN irradiation and high dose to the prostate, (EQD2=88Gy) delivered with daily image-guided, intensity-modulated, moderate hypofractionation resulted in an excellent 75-m outcome, even in IR/HR patients. This encouraging result seems to be without correlation with AD considering the long time elapsed between the end of the AD and the last follow up of pts. The toxicity profile was acceptable

C024

RANDOMIZED STUDY OF HYPOFRACTIONATED RADIOTHERAPY VS ULTRABOOST ON DOMINANT INTRAPROSTATIC LESION FOR PROSTATE CANCER

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Aims: to show our experience of Dominant Intra-prostatic Lesions (DIL) radiotherapy (RT) up to EQD2 of 93,2 Gy, by Tomotherapy, in a randomized study comparing hypofractionated whole gland RT versus ultraboost.

Methods: Between March 2012 and May 2016, 38 patients with intermediate/high risk prostate cancer were enrolled in our randomized study of DIL dose escalation. All patients were submitted to multiparametric MRI to visualize DIL. Considering a mean α/β ratio of 3 for prostate cancer doses were: 83.2 Gy in 32 fractions of 2.6 per fraction (EQD2 = 93.2 Gy) on the DILs (only for patients included in the DIL arm), 75.2 Gy in 32 fractions of 2.35 Gy per fraction (EQD2 = 80.5 Gy) on the prostate gland and 67.2 Gy in 32 fraction of 2.1 (EQD2 = 68.5 Gy) on the seminal vesicles. The median age of patients was 71 years (range 56-80). The median iPSA was 7,05 ng/mL (range 4.12-18.5; mean 8.45) in the DIL-arm (D) and 7,09 ng/ml (range 3,7-15; mean 7,4) in No-DIL (ND) arm. The GS was in ND arm: 6 in 10 patients, 7 in 8 patients and 8 in 1 patient; in the D arm: 5 in 1 patient, 6 in 9 patients and 7 in 8 patients. Androgen deprivation therapy (ADT) was planned for overall 6 months in intermediate risk and for 2 years for high risk patients. Helical IMRT with Simultaneous Integrated Boost (SIB) technique was delivered using Tomotherapy (®Accuray, Madison, Wi, USA). Daily Image-Guided RadioTherapy was performed by integrated megavoltage CT. Acute and late toxicities were evaluated according to RTOG-EORTC scale. Outcome was evaluated as biochemical control (defined according to Phoenix criteria).

Results: Mean follow-up (FU) was 21 months (range 6-36). In D arm: overall severe acute gastrointestinal (GI) and genitourinary (GU) toxicities>G3 were 0%; G2 acute GI toxicity was 6% and G2 acute GU toxicity was 12%. Late toxicities>G2 were 0%. In the ND arm: acute toxicities>G3 was for GU 5% and for GI 0%; G2 acute GI toxicity was 5% and GU was 5%. Late toxicities>G2 were 0%. At last FU overall bDFS was 100%. Only 1 patient in each group was again in ADT.

Conclusions: Our results show ultraboost on the DIL, up to an EQD2 of 93,2 Gy, is feasible and safe by Tomotherapy, without increasing acute or late toxicities. However, in order to assess the biochemical response, a longer follow-up is necessary.

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C025

SHORT-TERM HIGH PRECISION RADIOTHERAPY FOR EARLY PROSTATE CANCER WITH CONCOMITANT BOOST TO THE DOMINANT LESION: AD INTERIM ANALYSIS AND PRELIMINARY RESULTS OF A PHASE II TRIAL (AIRC GRANT N° IG 13218)

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Aims: To report prelminary results of a cutting edge hypofractionated treatment with concomitant boost to the dominant lesion for patients with early stage prostate cancer (PCa).

Methods: This is a prospective phase II trial AIRC-Grant N° IG 13218 started in June 2015. Patients with low and intermediate risk PCa who met the inclusion criteria underwent hypofractionated radiotherapy (RT) to the prostate (36.25 Gy in 5 fractions) and a simultaneous integrated boost (SIB) to the dominant intraprostatic lesion (DIL) to 37.5 Gy in 5 fractions. The DIL was identified by a multiparamentric magnetic resonance imaging (mpMRI) co-registered with planning CT. Toxicity was assessed according to CTCAE v4.0 and RTOG/EORTC criteria. The preliminary evaluation of the first 13 patients was required to confirm the treatment's feasibility before completing the enrollment of 65 patients.

Results: The first 13 patients completed the treatment between June 2015 and February 2016. With a minimum clinical follow-up ranging from 1 to 6 months, no Grade 3 or 4 acute toxicity was reported. At the end of RT, only one patient experienced Grade 2 gastrointestinal (GI) toxicity, and 4 had Grade 1 genitourinary (GU) events. After one month Grade 1 GI toxicity was reported in 2 patients and Grade 1 GU in 4 patients; no ≥ Grade 2 toxicity has been recorded. At 6 months from the end of treatment, 8 patients have been evaluated, and no ≥ Grade 2 events have been e dxperienced: 1 patient had Grade 1 GI toxicity and 3 had Grade 1 GU toxicity.

Conclusions: Our preliminary data show the feasibility of an "extremely" hypofractionated schedule with concomitant boost on the DIL.

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C026

MODERATELY HYPOFRACTIONATED RADIOTHERAPY USING TOMOTHERAPY• FOR INTERMEDIATE/ HIGH RISK PROSTATE CANCER (PCA): OUTCOME AND TOXICITIES ANALYSIS IN 123 CONSECUTIVE PATIENTS TREATED AT THE RADIOTHERAPY (RT) UNIT OF MODENA

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Aims: Dose escalated RT has an important role in improving clinical outcome for PCa patients (pts). Hypofractionation shortens treatment time and may be biologically more effective but if it actually broadens the therapeutic window is unclear. Aim of the study is to investigate tolerability and clinical outcomes of a dose escalated RT regimen using simoultaneous integrated boost (SIB) hypofractionation for intermediate, high and very high risk PCa.

Materials and Methods: From 2008 to September 2015,123 pts with PCa underwent radical RT using a moderately hypofractionated regimen.Median age was 73 years.Forty-three pts had intermediate risk PCa (34.9%), 35 high (28.5%) and 45 very high risk (36.6%), according to 2016 NCCN Guidelines Class Risk Stratification. Gleason Pattern Score was <7 in 32 pts,equal to 7 in 50 and superior in 41;median GPS was 7.At diagnosis all pts had an elevated PSA: fifty-eight (47,1%) had initial PSA value (iPSA) <10 ng/mL, while in 41 (33,3%) it was between 10.1-20 ng/mL and in 24 (19.6%) >20 ng/mL. Upon clinical staging (based on TNM stadiation - AJCC 2010) 16.2% of pts had cT1, 39.1% cT2, 23.6% had cT3a and 21.1% had cT3b. After complete radiological staging pathological pelvic nodes were found in 11/123 pts (8.9 %). Eighty-eight of 123 pts received RT in association to neoadjuvant, concomitant and adjuvant androgen deprivation therapy (ADT)

Results: All pts were treated with hypofractionated RT regimen (2.3-3.82 Gy/day,17-32 total fractions) with or without ADT using Image Guided IMRT with Tomotherapy®. Median RT dose was 70 Gy. Target volume encompassed prostate in 9 pts (7,3%) and prostate and seminal vescicles in 38/123 (30.9%); pelvic abdominal RT was performed in 76/123 pts (61.8%) with prophylactic intent due to high risk of pelvic nodal involvement (based on Roach algorithm). Three- and 5-year actuarial OS were 91.4%(ES±3.0%) and 83%(ES±5.10%), respectively. Actuarial Biochemical Relapse Free Survival was 89.2%(ES±3.2) and 81.8% (ES±5.1) while Metastasis Free Survival was 93.3% (ES±2.7%) and 88.1% (ES±4.5%). Seven pts had >Grade 2 acute toxicity: 3 pts had gastrointestinal discomfort and 4 pts had urinary symptoms.

Conclusions: Our results of hypofractionated RT using Tomotherapy® show a good profile in terms of both oncological outcome and toxicity. Three and 5-year bRFS and correspondingly OS is excellent and confirms for the clinical routine recently published results of randomized controlled trials.

C027

RETROSPECTIVE ANALYSIS OF MODERATE HYPOFRACTIONATED SCHEDULE OF POSTOPERATIVE RADIOTHERAPY FOR PROSTATE CANCER

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Aims: To evaluate efficacy and safety of moderate hypofractionation using volumetric modulation arc therapy (VMAT) in patients submitted to radical prostatectomy.

Methods: From April 2011 to January 2016, 225 patients (pts) who underwent radical prostatectomy were treated with postoperative RT at Pisa University Hospital. Median age was 68y (range 48-83). D'amico class risk groups stratification was as follow: low 1(0.4%), intermediate 55(24.4%), high 106(47.2%) and very high 63(28.0%). Hundred and five (46.7%) pts with pT3-T4 pathological stage and/or positive margins were treated with adjuvant RT; 120(53.3%) pts with persistent PSA value (>0.2 ng/mL) or biochemical/clinical relapse were submitted to salvage RT. A schedule of 28 fractions was applied in all pts with dose per fraction of 225cGy, 230cGy or 235cGy, according to the treatment objective. Planning Target Volume included prostatic bed alone in 165 pts with no bad prognosis factors (PSA<1 ng/mL, adequate lymphoadenectomy, GS≤7); pelvic nodes in 60 pts with high PSA, positive nodes, inadequate lymphoadenectomy or GS>7 (50.4Gy were delivered using Simultaneous Integrated Boost). In 12 pts with persistent PSA, choline PET/CT documented active lesions outside the prostate bed (2 pts single pelvic bone lesions and 10 pts 1-3 positive nodes); the detected lesions were included in the postoperative RT volume. Radiotherapy was performed in association with ADT in 64 pts (28.4%). All treatments were planned using Varian Eclypse and performed with VMAT and 6 MeV photons.

Results: At time of data analysis, only 200 pts (91 treated with adjuvant RT and 109 with salvage RT) had an adeguate follow-up (6 months). Overall acute toxicity was the following: 10 pts (4.4%) reported genitourinary G3 toxicity; 2 pts (0.9%) gastrointestinal G3 toxicity; no G4 toxicity were recorded. In the adjuvant group biochemical 2 and 4-year PFS were 89% and 73%, respectively, whereas in the salvage group were 76% and 54%. PFS in adjuvant group was significantly better than PFS in salvage gorup (p=0.016). No difefrence in PFS between biochemical or clinical relapsed was observed (p=0.126).

Conclusions: In pts with prostate cancer, our preliminary results demonstrate the feasibility and safety of a moderate hypofractionation regimen +/-SIB using VMAT in the post operative setting. In selected cases (clinical recurrence) an increasing of prescription dose may improve PFS. However long term data are needed to confirm these results.

C028

MODERATELY HYPOFRACTIONATED SALVAGE RADIOTHERAPY (SRT) FOR A LOCAL RECURRENCE AFTER RADICAL PROSTATECTOMY (RP): ACUTE AND LATE TOXICITY RATES

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Aims: Clinical evidence supports the idea that higher doses of radiation lead to higher biochemical control rates also in patients treated with salvage radiotherapy (SRT). Moreover, by using Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) high doses can be delivered with a Simultaneous Integrated Boost (SIB). All patients had both a local recurrence shown by multiparametric magnetic resonance imaging (mpMRI) and a detectable PSA (> 0.20 ng/mL) after radical prostatectomy (RP). The aim of this study was to evaluate both acute and late toxicity rates in patients treated with IMRT/VMAT SRT to the total dose of 73.5 Gy in 30 fractions to the macroscopic disease and 69 Gy to the prostatic bed.

Table 1.

	Acute tox GU G1	Acute tox GU G2	Acute tox GI G1	Acute tox GI G2	Late tox GU G1	Late tox GU G2	Late tox GI G1	Late tox GI G2
No. pts	25	5	10	12	15	3	2	0
%	52	10	21	25	33	7	4	0

Methods: Between February 2014 and November 2015 48 consecutive patients were treated with SRT. Median age was 71 yrs (53-83). Median PSA level was 0.69 ng/mL (0.20-3.57). 16 patients were underwent ADT during SRT. Dose prescription was planned to administer an EQD2Gy (considering an a/b value of 1.5 Gy for prostate cancer) as SIB to the recurrences of 82.95 Gy and to the prostatic bed>70 Gy (range 69.77 -74.91 Gy), 29 pts (60%) were also simultaneously irradiated on the pelvic nodes (range 50.91 Gy – 69.77 Gy); three of these were pN+, 26 were pN0, 19 was pNx. CTCAE v. 4 criteria were used to respectively evaluate acute and late toxicity. The PSADT was <6 months in 15 (31%) of patients and >6 months in the remaining 33 (69%) patients.

Results: Median follow up was 8 mo (1-25). No grade 3+ acute or late genitourinary toxicity and gastrointestinal (CTCAE v.4) has developed. We reported the peak toxicity in the table. We observed (GR) grade 2 acute toxicity genitourinary (GU) in 10% of patients and GR2 gastrointestinal (GI) in 25% of patients; the late toxicity GR2 genitourinary (GI) was observed in 7% of patients. No patient experienced late GR2 GI toxicity.

Conclusions: Preliminary results show that moderately hypofractionated IMRT/VMAT SRT for a local recurren-

ce is well tolerated with acceptable acute and late toxicity rates. A longer follow-up is required to confirm the late toxicity profile and assess disease control.

C029

MODERATE HYPOFRACTIONATED POST-PROSTATECTOMY RADIOTHERAPY: A PRELIMINARY MONO-INSTITUTIONAL REPORT ON FEASIBILITY AND ACUTE TOXICITY

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Aims: to evaluate the acute toxicity profiles of a moderate hypofractionated regimen with volumetric modulated arcs therapy (VMAT) in prostate cancer (PC) patients underwent to radical prostatectomy (RP).

Materials and Methods: From December 2012 to February 2016, 125 patients, previously submitted to RP, received adjuvant (64 patients) or salvage (61 patients) radiotherapy (RT) inside an institutional protocol of moderate hypofractionation schedule using VMAT technique (Varian RapidArc, Palo Alto, CA, USA). Eligible patients were<85 years old, with an ECOG performance status of 0–2, histologically proven adenocarcinoma of the prostate without distant metastases, and pathological stage pT2–4 N0-1, with at least one of the following risk factors: capsular perforation, positive surgical margins, seminal vesicle invasion and/or postoperative PSA>0,2 ng/mL. Patients were stratified into low (1%), intermediate (9%), and high-risk (90%) groups. The median age was 68 years. The median doses were 66 Gy (range 65.5-71.4) to the prostatic bed and 52.5 Gy (range 50.4-54) to the pelvic lymph nodes, in 28 or 30 fractions. The acute genitourinary (GU) and gastrointestinal (GI) toxicities were scored according to the Common Terminology Criteria for Adverse Events CTCAE v4.

Results: All the 125 patients completed the planned treatment, with good tolerance. After RT, the median follow-up was 15 months. Acute toxicities were record¬ed for the GU [G0=45/125 (36%), G1=63/125 (50.4%); G2=13/125 (10.4%); G3=4/125 (3.2%)], the GI [G0=42/125 (33.6%); G1=72/125 (57.6%); G2=11/125 (8.8%); no G3]. Analyzing data according to RT intent, a higher rate of GU toxicity ≥ 2 was found in the adjuvant setting (17.1%) respect to salvage group (9.8%); p=0.01 at Fisher's exact text. Furthermore, at statistical analysis no difference was found between the type of surgery (Robotic,Laparoscopic or Open) and incidence of urinary incontinence (p=0.8). The actuarial Kaplan-Meier for biochemical disease free survival (BDFS) were 94% and 77% for adjuvant and salvage RT, at 36 months.

Conclusions: moderate hypofractionated postoperative RT with VMAT was feasible and safe with acceptable acute GU and GI toxicities. Longer follow-up is needed to assess late toxicity and clinical outcome.

C030

SALVAGE IMAGE-GUIDED STEREOTACTIC SECOND RE-IRRADIATION OF LOCALLY RECURRENT PROSTATE CANCER: SOMETHING VENTURED, COULD SOMETHING BE GAINED?

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Aims: Up to one third of prostate cancer relapses are inside the gland only: our aim is to present technical feasibility and efficacy of a 2nd external beam re-irradiation (re-EBRT), delivered to the prostate for local recurrence, in a group of three patients treated at European Institute of Oncology (IEO), Milan.

Methods: Between 05/2013 and 09/2015 three patients received a 2nd re-EBRT (3rd RT course) using image-guided intensity modulated RT or stereotactic RT (Table1). Intraprostatic relapse was diagnosed by multiparametric magnetic-resonance (mpRMN) and/or choline positron emission-tomography (PET); any patient had distant metastasis. Mean PSA at relapse was 3.7 ng/ml. Mean biochemical and clinical progression-free intervals from 1st re-EBRT were 27.8 and 39.2 months, respectively. Mean age at 2nd re-EBRT was 76 years. No patient received concomitant hormonal treatment. Before treatment planning, all patients had been evaluated for late toxicity from previous irradiation according to RTOG/EORTC criteria. No genito-urinary (GU) or gastro-intestinal (GI) symptoms were reported. Biochemical control was assessed according to Phoenix definition. Results: We did not record any acute or late GU or GI event. Mean follow-up time from the 2nd re-EBRT was 28.9 months. Biochemical and clinical response was registered in all patients. At present one patient is free of disease. Two patients experienced relapse after 22 and 23 months from 2nd re-EBRT, respectively. In one case it is biochemical relapse and intraprostatic relapse in the another one (4th local irradiation is currently under evaluation).

Conclusions: Second re-EBRT (3rd RT course) with high-precision technology is a safe option for isolated prostate cancer recurrence. No acute or late toxicity was observed. Local control seems suboptimal. These findings suggest some room for dose escalation. Further studies and larger series of patients are needed to standardize this treatment and to fully evaluate its potential in the treatment of recurrent prostate cancer.

Acknowledgements: This study was partially supported by the research grants from Associazione Italyna per la Ricerca sul Cancro (AIRC): IG-14300 "Carbon ions boost followed by pelvic photon radiotherapy for high risk prostate cancer", and IG-13218 "Short-term high precision RT for early prostate cancer with concomitant

boost to the dominant lesion".

Table 1. Summary of radiation treatments sort by patient.

	Treated Volume	Technique	Total Dose; Dose/ fraction	BED ($\alpha/\beta = 1.5$)
Apr- May 2010 (59 ys)	Prostate	3D- CRT	30 Gy; 6 Gy/ fract.	150.0 Gy
Feb 2010 (72 ys)	Prostate	SBRT CyberKnife®	30 Gy, 6 Gy/ fract.	150.0 Gy
Feb- March 2003 (52 ys)	Prostate	3D- CRT + Brachytherapy	50 Gy; 2 Gy/ fract.+ 100 Gy I-125 seeds	N.E.
Jan- March 2005 (65 ys)	Prostate+ 1/3 Seminal Vescicles	3D- CRT	76 Gy; 2 Gy/ fract.	177.3 Gy
Jul 2012 (61 ys)	Peri- prostatic node	SBRT VERO®	24 Gy 8 Gy/ fract.	152.0 Gy
March 2012 (72 ys)	Prostate	SBRT CyberKnife®	25 Gy, 5 Gy/ fract.	108.3 Gy
Patient 1				
Patient 2				
Patient 3				
Sept 2015 (76 ys)	Intraprostatic lesion (left lobe)	SBRT CyberKnife®	30 Gy, 6 Gy/ fract.	150.0 Gy
Sept- Nov 2005 (67 ys)	Prostate+ 1/3 Seminal Vescicles	3D- CRT	76 Gy; 2 Gy/ fract.	177.3 Gy
Sept- Oct 2013 (75 ys)	Intraprostatic lesion (apex)	SBRT CyberKnife®	25 Gy, 5 Gy/ fract.	108.3 Gy

BED: Biologically Effective Dose; 3D- CRT: 3 Dimensional- Conformal Radiation Therapy; SBRT: Stereotactic Body Radiation Therapy; NE: Not Evaluable

C031

SAFETY AND EFFICACY OF ENZALUTAMIDE IN THE TREATMENT OF ADVANCED PROSTATE CANCER: EXPERIENCE OF THE UNIVERSITY OF FLORENCE

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Aims: A significative rate of patients progresses after an initial response to treatment with LHRH analogues, evidence exists that that progression after ADT remains hormone driven. Various drugs showed to benefit patients with metastatic castration resistant prostate cancer (mCRPC). Enzalutamide is a non steroidal androgen receptor (AR) inhibitor that does not promote translocation of AR to the cell nucleus, prevents binding of AR to DNA and AR coactivator recruitment, it showed to significantly prolong median Overall Survival (OS) of patients with mCRPC either in post or in pre chemotherapy setting. The aim of our abstract is to report the data of patients treated in our institute with Enzalutamide, focusing on the outcome and toxicities.

Methods. We report data about 20 patients with mCRPC treated at our institution with Enzalutamide, progressed after docetaxel chemotherapy. Enzalutamide was administered at the dose of 160 mg/day. Total Androgenic Deprivation (TAD) with LHRH analogue or LHRH antagonist was continued. Primary end points were Time to Radiological Progression (TTRP), Time to Biochemical Progression (TTBP), Time to fist Skeletal Related Events (TTSRE) and Overall Survival (OS). Other outcomes reported are adverse events (AE), and PSA response.

Results. With a median follow up of 6,8 months (range 0.9-36.3), 8 patients were died and 16 had progressive disease either biochemical or radiological. The median TTRP, TTBP, TTSRE were 13 months, 8 months and 8 months and at 2 years 55%, 45%, 50% respectively . Median OS was 11 months (0.9-36.3 months) and at 2yrs was 60%. Results showed that neither baseline PSA, PSA reduction >50% and Hb >10 were associated with better/worse TTRP, TTBP. Seventeen patients (85%) had a reduction of PSA, five of them had a reduction of PSA>50%. Treatment was well tolerated, the most AE were astenia in 12 patients (none G3, G4), anemia in 8 patients (none G3 or G4), cephalgy in 2 patients, and reduction of patelets of grade G2 in 1 patient, no one had diarrhea, reduction of leukocytes or seizure events. One patient had an acute ischemic cardiac event and another one increasing in blood pressure and transitory ischemic attack, both had to discontinue Enzalutamide.

Conclusions. Our data confirm that Enzalutamide is a valid option in the treatment of mCRPC with a good profile of tolerance.

C032

QUALITY OF LIFE AT TIME OF DIAGNOSIS OF PROSTATE CANCER: RESULTS FROM THE PROS-IT CNR STUDY

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Aims: Prostate cancer (PCa) functional outcomes related to quality of life (QoL) have become as important as oncologic outcomes. Aim of the study is to evaluate in a large cohort of consecutive patients the general health and the cancer-specific quality of life after PCa diagnosis.

Methods: Pros-IT CNR is a multicenter, observational, prospective cohort study on PCa. Naïve patients, with histologically confirmed PCa, were eligible for the study. Quality of life was assessed by the Italyn version of SF-12 (PCS=Physical Component Summary and MCS=Mental Component Summary) and UCLA-PCI (UF, UB= Urinary Function and Bother; SF, SB= Sexual Function and Bother; BF, BB=Bowel Function and Bother). The differences between subjects enrolled in urologic (URO), radiotherapy and a few medical oncology centres (RO) were evaluated through the Generalized Linear Models on the ranked data, adjusting for age at diagnosis. Spearman's rho non-parametric correlation coefficients between UF and UB, SF and SB, BF and BB, were calculated, stratifying the analysis by department of enrollment.

Results: 1711 patients were consecutively enrolled in 97 centres: 996 patients (58.2%) in URO and 715 (41.8%) in RO centres.

In the whole population, the average PCS was 51.7±7.5, average MCS was 49.4±9.6. The average UCLA-PCI scores at enrollment were: UF: 93.1±15.8, UB: 88.5±23.5, BF: 93.7±13.2, BB: 93.4±18.2, SF: 49.4±32.0, SB: 63.9±35.1. Age was the main determinant of general and prostate cancer specific health (PCS, MCS, UF, UB, SF, SB, BF, BB: all <0.01). After age-adjustment, we reported differences between URO vs. RO populations in mental (MCS: 48.9 vs. 50.1, p=0.04) but not in physical component (PCS: 52.2 vs. 51.1, p=0.75). Moreover, we identified significant age-adjusted differences favoring URO pts in comparison with RO pts regarding urinary symptoms (UF: 94.1 vs. 91.9, p=0.04; UB: 90.9 vs. 85.3, p<0.0001), sexual activity (SF: 56.8 vs. 39.9, p<0.0001, SB: 68.2 vs. 57.9, p=0.0001) and bowel function (BF: 94.9 vs. 92.2, p=0.0004). We reported a significant correlation between urinary and bowel function and bother (0.5≤rho≤0.64, Figure 1, a,b) and differences in sexual function and bother between RO and URO pts (c).

Conclusions: Pros-IT CNR is the largest study on quality of life in men with PCa performed in Italy. Data on quality of life at time of diagnosis underline the remarkable differences between men enrolled in URO vs. RO centres.

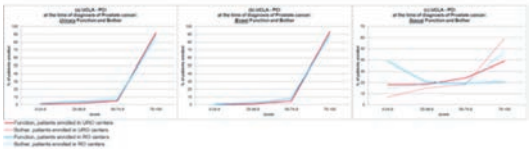

Figure 1.

C033

WEEKLY CISPLATIN AND ACCELERATED HYPO-FRACTIONATED VOLUMETRIC MODULATED ARC THERAPY WITH SIMULTANEOUS INTEGRATED BOOST FOR RADICAL TREATMENT OF ADVANCED CERVICAL CANCER IN ELDERLY PATIENTS

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Aims. To evaluate preliminary findings regarding local control (LC), overall survival (OS) and toxicity in a cohort of elderly-patients affected by locally advanced cervical carcinoma treated with radical intent by means of weekly-cisplatin and volumetric modulated arc therapy (VMAT) to the pelvis with simultaneous integrated boost (SIB) to macroscopic disease.

Materials and Methods. Eligible criteria of this prospective study were: age ≥ 70, Karnosky performance status 70-100, locally advanced histologically proven squamous cervical carcinoma, patients unable to undergo brachytherapy (BRT). A dose of 66/30 Gy to the macroscopic disease and 54/30 Gy to the pelvis with SIB-VMAT technique was prescribed. Clinical outcomes and toxicity data according to the Common Terminology Criteria for Adverse Events (CTCAE v4.0) were collected prospectively. LC and OS rates were estimated using the Kaplan-Meier method. LC was defined from the beginning of treatment to loco-regional relapse date. Local recurrence was defined as any relapse in field (pelvis or cervix). Time to progression (TTP) was considered from the beginning of treatment to the time of any recurrence or distant metastasis. OS was calculated from the date of diagnosis to the death or last follow-up date.

Results. Thirty patients were recruited. Median follow up was 30 months (range 6 - 48). Median age was 72 years (range 70 - 84). The 3-years OS and LC were 93% and 80%, respectively. The median time-to-progression was 24 months (range 6 - 30). The probabilities of 1-year, 2-years and 3-years local failure were 6.7%, 13.3% and 13.3% respectively. The probability of 2-years and 3-years distant progression was 13.3% and 16.7%, respectively. Analyzing clinical outcomes grouping based on stage of disease, II versus III, the 3-years OS was 100% and 85%, respectively. The 3-years LC was 91% for stage II, 67% for stage III. Acute and late toxicities were acceptable without severe event.

Conclusions. Weekly cisplatin and accelerated hypofractionated VMAT-SIB for radical treatment of advanced cervical cancer in the current cohort of elderly patients was feasible, especially for stage II disease. Long term results and prospective randomized trials with BRT are advocated.

C034

RADICAL CONCURRENT CHEMORADIOTHERAPY WITH IMAGE-GUIDED BRACHYTHERAPY (IGBT) IN ADVANCED CERVICAL CANCER: PROGNOSTIC FACTORS FOR LOCAL RECURRENCE (LR)

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Aims: to identify the predictive factors for LR after definitive chemoradiation (CT-RT) in advanced cervix cancer patients (pts).

Methods: From 2009 to 2014, 56 pts with cervix cancer, FIGO stage I-II 57.1%, III-IV 42.8% were treated with radical CT-RT in our Department. The median age was 56 yrs (range 36-85). The histology were squamous (squa) 78%, adenoca (adca) 16.1%, and others 5.4%. Concurrent CT was given to 73.3% of pts with external beam radiotherapy (EBRT) for a total dose of 45-50 Gy in 1.8-2 Gy/per fraction (fr). Parametrial dose was 5-10 Gy. 17.9% pts had neoadjuvant CT too. The IGBT median dose was 24 Gy (range 6-32.5 Gy) in 4 fr (range 1-5) once or twice a week for all pts. The mean total treatment time was 65 days (range 45-98). The median follow-up time was 37 months (range 5-90). The cumulative doses (EBRT + IGBT) were normalized to 2 Gy per fr (EQD2). D90 for the target and other DVH parameters such as D2cc, D1cc, D0.1 cc for OARs were calculated.

Results. During the median follow-up of 37 months, LR occurred in 8 (14,3%) pts, distant failure in 8 (14.3%) pts and both in 6 (10.7%) pts. The 3-yrs local control (LC) was 80% and the 3-yrs overall survival (OS), disease-free survival (DFS) and disease specific survival (DSS) rates were 71%, 59%, and 80% respectively. The median D90 dose was 63.7 Gy (47-99.8 Gy). Acute G2-G3 hematological toxicities were observed in 31 (55%) pts, G3 late toxicity for rectum and bladder were 1 (1.7%) and 2 (3.5%) respectively. Multivariate analysis indicated that tumor size>5 cm, non squa histology and D90>63.8 Gy were prognostically significant in terms of OS and DFS unlike age, FIGO stage, hemoglobin and positive nodes. On Kaplan Meier estimates, the median LC was 32 months: T size, D90, and histology were statistically significant. On univariate analysis for 3-yrs LC, we observed: T size $\leq$ 5 cm 90.8% vs>5 cm 63.8% (p=0.01); D90 $\geq$ 63.8 Gy 92.6% vs<63.8 Gy 60.7% (p =0.006); squa 83.6% vs adca 50% vs others 37% (p=0.004). On multivariate analysis T size (p=0.03) and D90 (p=0.02) were associated with better LC.

Conclusions: T size (>5 cm), D90<63.8 Gy and non squamous histology were risk factors for LR in our studies. These results emphasizing the need for modern IGBT methodologies (Intracavitary combined with interstitial, D90 dose at a curative level of 85-90 Gy). The definition of high-risk factors for LR is warranted to improve new strategies for treatment of locally advanced disease.

C035

HYPOFRACTIONATED INTENSITY-MODULATED RADIOTHERAPY AS A BOOST IN PATIENTS WITH LOCALLY ADVANCED CERVICAL CANCER TREATED WITH DEFINITIVE CHEMORADIOTHERAPY AND UNSUITABLE FOR BRACHYTHERAPY. THE EXPERIENCE OF THE EUROPEAN INSTITUTE OF ONCOLOGY

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Aims: We evaluated the safety and the efficacy of hypofractionated intensity-modulated radiotherapy (IMRT) boost after external beam radiation therapy (EBRT) in patients with locally advanced cervical cancer judged unsuitable for brachytherapy boost (BRT). Methods: Between June 2012 and April 2016, 24 patients were radically treated. Concomitant chemotherapy was performed in 21/24 pts, 2 pts received also neoadjuvant chemotherapy. Tumour characteristics, contraindications to brachytherapy, toxicity and tumor response were retrospectively collected. Median age was 56 yrs, 22/24 pts had squamous cell carcinoma. Clinical stage, according to the International Federation of Gynecology and Obstetrics, included 14 IVA-B Stage, 3 IIIB, 6 IIB, 1 IB2. EBRT was performed with IMRT including primary tumor, regional nodes and paraortic nodes if indicated, to a total dose of 43.2-50,4 Gy (1.8 Gy/fr in all cases) . Brachytherapy was excluded for anatomical (11 pts) and medical reasons (6 pts), patients'choice (5 pts), tumor characteristics (2 cases). The hypofractionated image-guided IMRT, including the cervix +/- parametrium, was given by 5 or 7 fields to a total dose of 20-25 Gy, with a median dose per fraction of 5 Gy (range: 2.5–8 Gy) and delivered every other day. Results: No patients developed gastrointestinal or genitourinary acute and late toxicity superior to Grade 2, defined according to the Common Terminology Criteria for Adverse Events. Only one stage IVB patient experienced a vescico-vaginal fistula during EBRT and received the boost after 3 months. Tumour control, evaluated in 20 patients, included complete or partial response, progression or stable disease in 13 (65%), 4 (20%), 1 (5%) and 2 (10%) patients, respectively. 2 pts (metastatic at the beginning) died early after treatments, 1 is lost at follow-up and 1 is still under investigation. At the last follow-up 11/20 pts (55%) are alive with no disease: 1 was IB2, 4 IIB, 2 IIIB, 5 IV. All stage IV were node positive but none had visceral mets at the beginning. 9/20 pts (45%) are alive with disease: 7 were stage IV, 1 IIIB , 1 IIB. 2 pts recurred in the cervix, 2 developed visceral mets and 5 had both sites.

Conclusions: Although BRT is the gold standard in the management of locally advanced cervical cancer, an hypofractionated IMRT boost is a good alternative in

unsuitable pts offering low toxicity profile and the results comparable to literature data in terms of local control.

C036

STEREOTACTIC BODY RADIOTHERAPY (SBRT) IN THE MANAGEMENT OF OLIGOMETASTATIC GYNECOLOGICAL CANCER

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Aims: The objective of this study was to assess the role of stereotactic body radiotherapy (SBRT) in the treatment of distantly recurrent, oligometastatic gynecological cancer.

Methods: The hospital records of 46 patients with18 F-fluorodeoxyglucose [18F-FDG] positron emission tomography [PET] positive, distantly recurrent, oligometastatic gynecological cancer were reviewed. All these patients had a number of target lesions<5, with largest diameter <6 cm . The treatment was delivered with a TrueBeam™ LINAC and RapidArc® technique, using 10 or 6 MV FFF beams. A total of 71 lesions were treated and lymph nodes represented the most common site of metastases, followed by lung, liver and soft tissues. Twenty lesions were treated with one- single fraction of 24 Gy and fiftyone lesions received 27 Gy delivered in three fractions, depending on the ability to fulfill adequate target coverage and safe dose/volume constraints for the organ at risk with either regimen.

Results: PET scan three months after SBRT showed a complete response [CR] in 46 lesions (64.8%), a partial response in 14 (19.7%), a stable disease in 5 (7.0%) and a progressive disease in 6 (8.5%). No lesions in CR following SBRT subsequently progressed. Overall acute toxicity occurred in 13 (28.9%) patients. The most common grade 1-2 adverse event was pain (n.9, 20.0%), followed by nausea and vomiting (n. 5, 11.1%). No grade 3-4 acute toxicities occurred, and no late toxicities were observed. Patients who failed to achieve a CR had a 2.375- fold higher risk of progression and a 3.602-fold higher risk of death compared with complete responders (p=0.04 and p=0.03, respectively).

Conclusions: SBRT offers an effective and safe approach for selected cases of oligometastatic gynecological cancer. Further clinical investigations are necessary to determine optimal dosing and fractionation schedules, and to properly select the subsets of patients who are likely to benefit from this therapeutic approach.

C037

STEREOTACTIC BODY RADIATION THERAPY FOR OLIGOMETASTATIC PATIENTS WITH OVARIAN CANCER

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Aims: Ovarian cancer is the gynecological malignancy characterized by the worst prognosis for its tendency to metastasize despite aggressive systemic therapies. Among recurrent ovarian cancer, patients with oligometastatic disease are supposed to have a better outcome since they could benefit from local approaches besides chemotherapy, considering also the limited alternative regimens of systemic therapy. The aim of our study is to evaluate the role of stereotactic body radiotherapy (SBRT) in terms of LC, DFS and toxicity in a setting of patients with oligometastatic recurrent ovarian cancer

Methods: Between January 2011 and November 2015, 19 patients (31 lesions) with recurrent oligometastatic ovarian carcinoma of any histology underwent SBRT. Toxicity and tumor response was scored using Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Scale. Tumor response was evaluated by CT/ PET, according to Response Evaluation Criteria in Solid Tumors.

Results: Median age at treatment was 64 years (range 40- 81 yrs) and median follow-up was 74 months (25-166 mo). The sites of disease were abdomino-pelvic lymphnodes (20 lesions), liver metastasis (8 lesions), lung metastasis (2 lesions) and para-vaginal mass (1 lesion). The SBRT doses were prescribed based on dimensions of target volumes and organs at risk constraints as follow: for lymphnodal lesions the dose prescription was 36-45 Gy in 6 fractions and only one case treated with 40 Gy in 4 fr; for hepatic lesions 61.89 -75 Gy in 3 fractions and also 45 Gy in 6 fractions, for the pulmonary lesions both cases received 48 Gy in 4 fractions meanwhile in the para vaginal recurrence dose prescription was 36 Gy in 6 fractions. None of the patients had grade 3/4 acute or late Gu or Gi toxicity. At a median follow-up of 27 months, when calculated at diagnosis of metastatic tumor, (range 6-65 mo) there were 3 local relapses of 31 treated lesions. The median LC was not reached. Both one year- and two year-LC were 92.9%. Median PFS was 14 months, with one year- PFS of 64.2% and 24.5% at two year. Complete radiologic response, partial response/stable disease and progressive disease were observed in 19 (61.3%), 9 (29%) and respectively 3 cases (9.7%).

Conclusions: In our experience SBRT is a feasible and well tolerated treatment approach in oligo-metastatic ovarian patients, with satisfactory results in terms of LC and DFS. Further studies are warranted to verify the real impact of SBRT on overall outcome of this setting of patients.

C038

CHEMORADIATION+SURGERY VS CHEMORADIATION+HDR-BRT IN ADVANCED CERVICAL CARCINOMA: A CASE-CONTROL STUDY

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Aims. To compare treatment outcomes in locally advanced cervical carcinoma (LACC) patients treated with neoadjuvant chemoradiation followed by radical surgery (surgery group: SG) versus radical chemoradiation plus brachytherapy boost (control group: CG). Results in terms of local control (LC), metastases-free survival (MFS), disease free survival (DFS) and overall survival (OS) were compared.

Methods. Seventy-six patients with LACC (SG) were matched to 76 patients (CG) with respect to age, histology and stage. Matching was performed without knowledge of outcomes. Patients characteristics are summarized in Table 1. The median FU was 35 months (range: 2-107) for SG and 29 months (range: 1-125) for CG, respectively.

Table 1. Patients' characteristics.

	Surgery group	Control group	TOTAL
AGE			
Median	54	55	54
Range	33-82	30-89	30-89
STAGE FIGO N (%)			
IIB	62 (81.6)	62 (81.6)	124 (81.6)
IIIA	1 (1.3)	1 (1.3)	2 (1.3)
IIIB	8 (10.5)	8 (10.5)	16 (10.5)
IVA	3 (3.9)	3 (3.9)	6 (3.9)
IVB	2 (2.6)	2 (2.6)	4 (2.6)
HISTOLOGY N (%)			
Squamous	67 (88.1)	67 (88.1)	134 (88.1)
Adenocarcinoma	5 (6.6)	5 (6.6)	10 (6.6)
Other	4 (5.3)	4 (5.3)	8 (5.3)

Results. At univariate analysis no significant differences between the two groups were recorded. Two-year and 5-year LC were 77.6% and 71.0% for SG and 76.1% and 70.3% for CG (p=0.8), respectively. Two-year and 5-year MFS were 79.3% and 70.8% for SG and 78.8% and 78.8% for CG (p=0.6), respectively. Two-year and 5-year DFS were 71.9% and 61.6% for SG and 66.1% and 61.0% for CG (p=0.8), respectively. Two-year and 5-year OS were 90.9% and 84.4% for SG and 90.3% and 69.9% for CG (p=0.4), respectively.

Conclusions. The two treatment approaches achieved comparable outcomes in patients with locally advanced cervical carcinoma. Further analyses are needed to compare the toxicity profile of these two treatment strategies.

C039

DEFINITIVE THREE DIMENSIONAL HIGH-DOSE RATE BRACHYTHERAPY (HDR-BRT) FOR INOPERABLE ENDOMETRIAL CANCER PATIENTS (PTS)

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Aims: To report our experience on HDR-BRT with or without external beam radiotherapy (EBRT) in pts with stage I-III endometrial cancer unfit to surgery.

Table 1. Dose schedules.

HDR-BRT	N° of patients (%)	EQD2 (α/β10)
2 x 7 Gy*	1 (6)	20 Gy
3 x 5 Gy*	1 (6)	19 Gy
3 x 6 Gy*	2 (12)	24 Gy
3 x 7 Gy	2 (12)	42 Gy
3 x 8 Gy	3 (18)	36 Gy
4 x 7 Gy	2 (12)	40 Gy
5 x 6 Gy	5 (28)	40 Gy
7 x 5 Gy	1 (6)	44 Gy
EBRT		
23 x 2 Gy*	1 (6)	46 Gy
25 x 2 Gy*	2 (12)	50 Gy

Legend: * patients submitted to external beam radiotherapy and brachytherapy
EQD2: Equivalent dose of 2 Gy per fraction calculated using the equation EQD2 = ([d+ α/β]/[2Gy+α/β]) derived from linear quadratic model.

Methods: From 2005 to 2016, 17 pts with endometrial cancer received definitive HDR-BRT and 3 of these

(18%) also EBRT. They were inoperable for comorbidities and/or old age. Median age was 79 years (range, 60-95), and median KPS 90% (range, 60-100). Histology was endometrial adenocarcinoma in 15 (88%) pts and non-endometrial in two (12%). In 15 (88%) pts FIGO clinical stage was I and in remaining two (12%) was III. All pts were evaluated with computed tomography (CT) and endometrial biopsy, 2 pts also with magnetic resonance imaging (MRI). Using a CT-based planning HDR-BRT was delivered using the Fletcher applicator. The clinical target volume (CTV) included uterus, cervix and upper vagina, prescription and optimization were performed on CTV. Follow-up was performed with physical examination, cervical cytology and CT or MRI wherever feasible. Local control (LC) was obtained when there was an interruption of vaginal bleeding. Local failure was defined by recurrent bleeding or imaging progression with confirmatory endometrial biopsy. Common Terminology Criteria for Adverse Events (CTAEC) version 4.03 was used to grade toxicities and Kaplan-Meier, and Log-rank test for statistical analysis.

Results: All pts completed treatment and had a clinical LC. Administered doses are shown in Table 1, median CTV was 80,6 cc (range, 50-270). After a median follow-up of 36 months (range, 6-131), 3 and 6 years LC rates were 86% and 69%, respectively. Cancer specific survival (CSS) at 1, 2 and 6 years was 100%, 91%, 72%, respectively. Age, histology, stage, dose and type of radiotherapy do not result significant prognostic factors for LC and CSS. Only stage seems to influence LC at 1 year: 50% for stage III and 91% for stage I (p=0.06). Toxicity was registered only in pts submitted to EBRT. Acute toxicity was: grade (G) 2 nausea in 1 (6%), G2 proctitis in 2 (12%), G2 diarrhea in 1 (6%), G2 anemia in 1 (6%) case. Two pts (12%) had G1 late rectal bleeding.

Conclusions: Our data show a good LC particularly in pts with stage I endometrial cancer. Definitive HDR-BRT could be an alternative treatment option for inoperable pts with good compliance and limited toxicity. EBRT does not seem to improve results but toxicity, though number of pts is limited.

C040

IN VIVO RECTAL WALL DOSIMETRY IN GYNAECOLOGICAL AND PROSTATE HDR BRACHYTHERAPY WITH MOSKIN DOSIMETERS

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Aims. Purpose of this study was to quantify the discrepancies between planned and measured doses to the rectal wall and to investigate the impact of the duration of the treatment planning procedure on these discrepancies during gynaecological and prostate image-guided high dose rate brachytherapy (HDR-BT).

Methods: MOSkins are a specific type of MOSFET dosimeters developed at the Centre for Medical Radiation Physics (University of Wollongong, Australia), optimized to measure the dose in steep dose gradients. In gynecological HDR-BT, three MOSkins were assembled over a semi-flexible rectal probe, which was placed in the rectum before CT imaging. A total of 51 *in vivo* dosimetry (IVD) measurements were performed. In prostate HDR-BT, two MOSkins were assembled on the trans-rectal ultrasound probe and 36 IVD measurements were performed. The absolute differences D between measured and calculated doses in the estimated dosimeter positions were quantified and a possible correlation between the observed discrepancies and treatment planning time was investigated.

Results. Grouping D according to the time elapsed between imaging and treatment (i.e., group 1: ≤90min; group 2: >90min), average D for groups 1 and 2 were 3.8±3.5% and 6.5±4.3% for gynecology and 5.1±3.0% and 8.3±6.2% for prostate HDR-BT, respectively. Average D and standard deviations were in both cases lower for group 1, demonstrating higher uncertainties of the calculated dose with higher treatment planning times.

Conclusions. Our study shows that the probability of morphological changes between imaging and treatment increases with time. Therefore, planning time should be kept as low as reasonably achievable to reduce uncertainties in calculated doses, both in gynecological and prostate HDR-BT.

C041

CETUXIMAB AND RT IN HEAD AND NECK CANCER: COMPLIANCE AND TOXICITY EVALUATION OF COMBINED TREATMENT

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Aims. In locally advanced head and neck cancer (LAHNC) RT+ Cetuximab (Ctx) allows to obtain better loco-regional control rate when compared to RT alone but Ctx could increase toxicities. On this basis we analyzed our experience in this setting of patients.

Materials and Methods: We evaluated all consecutive pts with histologically confirmed diagnosis of head and neck SCC and selected those that underwent to radical RT+Ctx; all these pts were considered unfit to receive CDDP based chemotherapy. We retrospectively revaluate pts using adult comorbidity evaluation-27 (ACE-27) to assess how comorbidities have been impact on compliance to treatment. A total dose of 70 Gy with conventional fractionation or doses

equivalent was prescribed, all RT techniques were considered. Ctx was administered at a loading dose of 400 mg/mq a week before RT start and once a week during RT at a dose of 250 mg/mq. Primary endpoints were compliance to treatment (days of breaks, need of hospitalization) and acute toxicity, assessed using CTCAe v4.

Table 1. Patients characteristics.

	N° patients (%)
Gender	
Male	24
Female	7
Age	
median	73
range	49-82
Cancer site	
Oropharynx	11
Oral cavity	4
Larynx	5
Hypopharynx	11
Stage	
III	5
IV	26
Smoking	
Yes	26
No	5
ACE-27	
0	4
1	7
2	16
3	4

Results. From January 2010 and December 2015 with a median follow up of 9 months (range: 1-75), we identified 31 pts (characteristics table 1).24/31 pts had age> 65 years. As regards RT, 25 pts were treated with conventional fractionation and 7 pts with accelerated RT (69.96Gy/33 fractions, 2.12 Gy/fx);13 pts received 3DCRT, 18 IMRT. 3 pts didn't completed radiotherapy course (ACE-27 =2): 1 died due to heart failure, 1 died due to worsening clinical conditions, 1 stopped on its own accord. Treatment breaks due to toxicity occurred in 8/31 pts (26%, median 3 days,range 1-9)- 6/8 presented ACE-27 ≥2. Median weight loss during RT was 6.5 kg (range: 0-14 Kg); 20/31 pts required nutritional support (3 PEG, 4 NGS, 10 liquid supplements and 3 parenteral nutritional)- 13/20 ACE-27≥2. 8 pts needed hospitalization, 6/8 ACE-27≥2. As regards acute toxicity, 20/31 pts presented grade 2-3 mucosites and 25/31 grade 2-3 dermatitis or acneiform rash. At last follow up 12/31 pts were alive (11 RC and 1 RP) with a median follow up of 42 months and 19/31 were dead (14 due to PD, 4 due to non- cancer related causes and 1 toxicity-pneumoniae), 6/19 died within 100 days from end of RT.Conclusions:We considered pts unfit to receive CDDP+RT nevertheless our data are in line with other experiences. Probably a better patient selection is advisable also for Ctx combined to RT to identify the subgroup of pts in which concomitant treatment gives major advantages vs RT alone.

C042

SHORT-COURSE PALLIATIVE RADIATION THERAPY FOR ADVANCED H&N TUMORS: FINAL RESULTS OF A PHASE II STUDY

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Aims: To assess the effectiveness of a SHort-course Accelerated RadiatiON therapy (SHARON) in the palliative treatment of patients with advanced primary or metastatic H&N tumors.

Methods: A phase II clinical trial was planned based on optimal two-stage Simon's design. Eligibility criteria included patients with an Eastern Cooperative Oncology Group performance status of ≤3. Twenty-three patients were treated with H&N radiotherapy at 20 Gy (5 Gy per fraction) in 2 days with a twice daily fractionation. The primary endpoint was the assessment of efficacy in terms of symptoms relief.

Results: Characteristics of the enrolled patients were: male/female: 9/14; median age: 83 years (range: 40-98). Eastern Cooperative Oncology Group performance status was <3 in 11 patients (47.8%). Grade 1-2 acute skin (60.9%) and mucositis (39.1%) toxicities were recorded. Only one patient (4.3%) experienced grade 3 acute mucositis. With a median follow-up time of 4 months (range, 1-32 months) 3 skin grade 1 and 2 skin grade 2 late toxicities have been observed. Of the 23 symptomatic patients, 21 showed an improvement or resolution of baseline symptoms (overall palliative response rate: 91.3%). Three-month overall survival was 89.7% (median survival time: N.R.). Median survival without symptoms progression was 5.0 months (95%CI: 1.8-8.1).

In 22 patients with pain, a significant reduction of this symptom was recorded in terms of VAS (mean baseline VAS vs mean VAS at follow-up: 4.6 versus 3.1, $p<0.001$).

Conclusions: Short-course accelerated H&N radiotherapy (20 Gy in twice daily fractions for 2 consecutive days) is tolerated and effective in terms of symptom relief. A phase III comparison against a standard palliative regimen (30 Gy in 10 fractions) has been planned in this patient population.

C043

STEREOTACTIC RE-IRRADIATION WITH CYBERKNIFE FOR RECURRENT HEAD AND NECK CANCER: SINGLE CENTER EXPERIENCE

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Aims: To report our experience in terms of clinical outcome and toxicity in patients treated with robotic stereotactic re-irradiation (SABR) for locally recurrent head and neck cancer (HNC).

Methods: Between February 2012 and December 2015, 40 patients were treated with Cyberknife for locally recurrent head and neck cancer. All patients have been deemed eligible for stereotactic re-irradiation with curative intent for a recurrent, previously irradiated, unresectable HNC. The GTV was defined on the basis of clinical and radiological findings and for delineation's purpose image fusion of MRI and/or FDG PET with planning CT was performed. The PTV was defined as the GTV plus a 1-mm margin. Planned dose was delivered in 5 fractions over a 2-week period. Clinical outcome was assessed according to RECIST criteria. Acute and late toxicities were evaluated according to NCI Common Terminology Criteria for Adverse Events (CTCAE version 4.0).

rapy, it warrants further prospective validation.

Table 1.

Site of re-irradiation	
Site	**No**
neck lymph nodes	9
paranasal sinuses	7
oropharynx	3
nasopharynx	6
larynx	4
oral cavity	6
nasal fossae	2
parotid gland	2
other site	1

Results: All patients were previously irradiated in an adjuvant or radical setting, with a median total dose of 66 Gy (range 50 – 70 Gy) delivered with standard fractionation. The median time interval between first treatment and SABR was 29 months (range 7 - 171 months). The median total dose delivered was 30 Gy (range 25 – 35 Gy) at 80% isodose in 5 fractions. Six patients (15%) underwent a concomitant treatment with Cetuximab. The median volume of recurrent GTV was 50 cc (range 9 - 211), sites of recurrent disease are listed in Table 1. At a median follow-up of 15 months, the 1-year local PFS rate was 60%, locoregional PFS was 37%, distant PFS was 71%, and PFS was 33%. The median overall survival was 10 months with a 1-year overall survival of 40%. At last follow-up, 69% died of disease, 4% died with disease, 15% died without progression, 10% were alive without progression, and 2% were alive with progression. Acute and late grade 3 toxicity was observed in 6% of patients respectively.

Conclusions: SABR with Cyberknife is a feasible and well tolerated treatment option for loco-regionally recurrent HNC, with clear potential for prolonged disease control in selected patients. As a non-surgical salvage therapy, it warrants further prospective validation.

C044

PREOPERATIVE RADIOTHERAPY WITH A SIMULTANEOUS INTEGRATED BOOST COMPARED TO CHEMORADIOTHERAPY FOR CT3-4 RECTAL CANCER: A MULTICENTRIC RANDOMIZED TRIAL

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Aims: Preoperative chemoradiotherapy (CRT) has been established as the standard treatment for T3-4 rectal cancers. In a previous phase II trial, limited toxicity and excellent local control using image-guided and intensity-modulated RT (IG-IMRT) with a simultaneous integrated boost (RTSIB) were reported instead of concomitant chemotherapy. The present multicentric randomized trial compares this strategy to CRT.

Methods: cT3-4 rectal cancer patients were randomly assigned to receive either preoperative IG-IMRT 46Gy/23 fractions plus capecitabine 825 mg/m^2 twice daily (CRT-arm) or IG-IMRT 46Gy/23 fractions with a SIB to the rectal tumor up to a total dose of 55.2 Gy (RTSIB- arm). Metabolic tumor activity reduction, by measuring the percentage of SUVmax difference (Response Index = RI) on sequential 18-fluorodeoxyglucose positron emission tomography (FDG-PET), was the primary endpoint. We assessed whether RTSIB was non-inferior to CRT with a non-inferiority margin of -10% for RI.

Results: A total of 174 patients were randomly assigned to the CRT-arm (n=89) or RTSIB- arm (n=85). Acute grade 3 toxicity was 6% and 4% in the CRT- and RTSIB-arm, respectively. There was no significant difference in

sphincter preservation (75% vs 68%, p=0.29). The R0 resection rate was 98% in the CRT-arm and 97% in the RTSIB-arm. The ypCR rate was 24% with CRT compared to 14% with RTSIB (p=0.13). The RI difference between RTSIB and CRT was -2.9% (95% CI, -10.1% to 4.3%).

Conclusions: Preoperative CRT is well tolerated when IG-IMRT is used. IG-IMRT SIB represents an attractive alternative to CRT for patients unfit for chemotherapy.

C045

PREOPERATIVE INTENSITY-MODULATED RADIOTHERAPY WITH A SIMULTANEOUS INTEGRATED BOOST IN LOCALLY ADVANCED RECTAL CANCER: AN ANALYSIS OF TOXICITY AND TUMOR DOWN-STAGING RELATED TO DIFFERENT INTENSIFICATION SCHEDULES

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Aims: Preoperative radiotherapy (RT) in combination with fluoropyrimidine-based chemotherapy (CT) is the standard of care for patients (pts) with locally advanced rectal cancer (LARC). The aim of the present study was to investigate the impact of different intensification doses of RT on the risk of acute gastrointestinal (GI) and genitourinary (GU) toxicities and on the tumor down-staging.

Methods: We retrospectively analyzed LARC pts treated with preop IMRT and different doses of simultaneous integrated boost (SIB) in 5 Italyn Centers between October 2013 and March 2016. Capecitabine (1650 mg/m2) was administered to all pts. Acute toxicity (CTCAE 4.0 scale) and efficacy (tumor down-staging) were correlated with different RT-doses used (Chi-square test). The equivalent dose at 2 Gy (EQD2) of intensification schedules was evaluated according to linear quadratic model (α/β=5.06 Gy for rectal cancer and α/β=3 Gy for small bowel-SB- and bladder).

Results: Overall, 76 patients stage IIA (12) and III (64) were evaluated. 45 Gy/25 frs were delivered to the mesorectum and lymph-nodes while a SIB was used to increase the rectal tumor and its mesorectum dose. SIB doses (EQD2 for rectal tumor) were: 52.5 Gy (53.9 Gy) 16 pts, 54 Gy (56.3 Gy) 24 pts, 55 Gy (57.9 Gy) 34 pts, 57.5 Gy (61.2 Gy) 2 pts. Dmax (EQD2) to SB and bladder were: 52.5 Gy (53.6 Gy), 54 Gy (55.8 Gy), 55 Gy (57.3 Gy) and 57.5 Gy (60.2 Gy). Dose constraints were bladder mean dose $\leq$ 21 Gy and V15 $\leq$ 150 cc for single loops SB. Overall, 74/76 (97.4%) pts completed the planned RT; G1-2 GI and GU toxicities were 38.2% and 30.3%, respectively. G3 GI toxicity in 5 pts (6.6%) and no G3 GU were reported. No differences resulted in incidence of any grade GU/GI toxicities between different SIB doses (p=0.28 and p=0.11, respectively). 57 pts underwent surgery. Overall tumor down-staging occurred in 38 (66.7%) pts including 14 (24.6%) pts with pT0. No differences between SIB doses and tumor down-staging (p=0.47) and pT0 (p=0.45) were observed.

Conclusions: The different IMRT-SIB doses (52.5 vs 54 vs 55 vs 57.5 Gy) + Capecitabine resulted in no different impact on tumor down-staging in these small and unbalanced available subsets of pts of the pooled analysis. Favorable treatment tolerance is remarkable with an optimal compliance to treatment (97.4%). No difference in GI/GU toxicity according to different intensified doses was reported. Only 6.6% of major GI toxicity was observed. No patients had G3 GU toxicity.

C046

PHASE II TRIAL ON SBRT FOR UNRESECTABLE LIVER METASTASES: LONG-TERM OUTCOMES AND PROGNOSTIC FACTORS OF SURVIVAL

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Aims: The aim of this study was to evaluate long-term efficacy and survival prognostic factors of SBRT for unresectable liver metastases.

Methods: 5 years local control (LC), overall survival (OS), progression free survival (PFS) and toxicity rates were analyzed in patients with unresectable liver metastases enrolled in a Phase II Trial on liver SBRT, with a prescription dose of 75 Gy on 3 consecutive fractions.

Results: Between February 2010 and September 2011, a total of 61 patients with 76 lesions were enrolled in this prospective trial, with a median follow-up time of 1.9 years. One-, three- and five- years LC rates were 94%, 78% and 78 %, respectively, with a median LC of 1.7 years. Median OS was 2.3 years and the survival rates were 83%, 30% and 21% at 1, 3 and 5 years, respectively. Univariate analysis showed two independent positive prognostic factors affecting survival: female sex (p=0.012) and primary tumour (p=0.001). Toxicity was moderate. One patient experienced G3 late chest wall pain, which resolved within 1 year from SBRT. No cases of RILD were detected.

Conclusions: Long-term results of this Phase II study suggest the efficacy and safety of SBRT for unresectable liver metastases also at 5 years of follow-up. Selection of cases with positive prognostic factors may improve long-term survival of these oligometastastic patients and may confirm the role of SBRT as an effective alternative local therapy for liver metastases.

C047

STEREOTACTIC BODY RADIOTHERAPY IN THE TREATMENT OF INOPERABLE HEPATOCELLULAR CARCINOMA

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Aims: To evaluate the feasibility and clinical results of stereotactic body radiation therapy (SBRT) in the treatment of hepatocellular carcinoma (HCC) in patients unsuitable for or failing to standard loco-regional therapies.

Methods: Patients with<3 inoperable HCC lesions sized<6 cm in total diameter were treated with SBRT . Prescription dose was adapted according to tumor size and liver function and comprised 36-48 Gy in 3 fractions or 40 Gy in 5 fractions (prescribed to 80 % isodose line). Primary endpoint included in-field (LC) local control and toxicity profile. Secondary endpoints were overall (OS), cancer-specific (CSS) and progression-free survival (PFS).

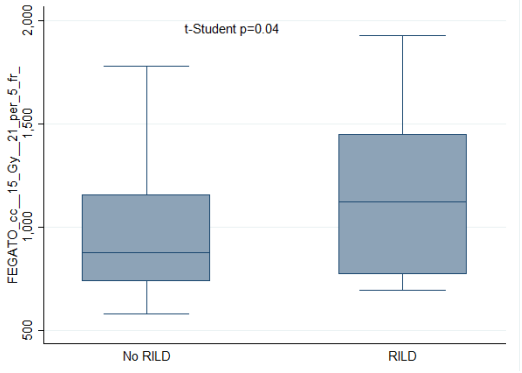

Figure 1.

Results: A total of 96 patients with 142 HCC lesions were treated. Median age was 68 (range 42-89).Most of the patients had Child-Pugh A5-A6 cirrhosis (78.1%), Barcelona Clinic Liver Cancer A (50%). Median lesion size was 25 mm (range 7-120 mm). Most lesions were in the right lobe (66.2%). In most patients SBRT was the first local treatment (56.3%). Up to 6.3% of patients had portal vein thrombosis.Median observation time was 16.6 months (range 1.3-38). Actuarial 1-year LC, PFS, CSS and OS were 92% (95% CI :0.84-0.96), 50% (95% CI: 0.38-0.61), 93.4% (95% CI : 84.7-97.2) and 81.5 % (95% CI: 71.5-88), respectively. Up to 20 patients (21%) experienced G3-G4 acute toxicity and one case of G5 toxicity was reported. Four cases (4.1%) of classic Radiation-induced liver disease (RILD) were observed; 22 patients (23%),experienced a modification of Child-Pugh classification (mainly 2-3 points).On multivariate analysis, no factors were predictive for LC while ≥2 points Child-Pugh classification modification predicted for OS (p=0.019). Moreover portal vein thrombosis predicted for CSS and lesion number predicted for PFS. The liver volume receiving less than 15 Gy in 3 fractions or less than 21 Gy in 5 fractions predicts for toxicity in term of both RILD (Graph 1) and impairment of liver function (increase of ≥2 points in Child-Pugh classification) (p = 0.028).

Conclusions: SBRT is a safe and effective treatment option for inoperable HCC, with acceptable LC rate and toxicity profile. Limiting treatment-related toxicity may have prognostic impact.

C048

STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR LOCALLY ADVANCED PANCREATIC CANCER (LAPC): A RETROSPECTIVE MULTI-INSTITUTIONAL EXPERIENCE

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Aims: Pancreatic carcinoma is projected to become the 2^ leading cause of cancer mortality by 2030. At diagnosis, 30% of patients (pts) present with LAPC involving adjacent structures such as blood vessels, not usually removed because of risk of postoperative complications. Patients with LAPC have an intermediate prognosis between resectable and metastatic pts (median OS ranging from 5 to 11 months). LAPC cause significant pain, obstruction,

and other morbidity due to direct extension of the primary tumor. Currently, a treatment option for LAPC is radiochemotherapy (RCT). SBRT is one emerging technique for treatment of LAPC, used by specialized centers to deliver a higher biologically effective dose of precisely targeted radiation in a short course of therapy. Conformity and rapid dose fall-off associated with SBRT offer the potential for dose escalation. We retrospectively review the experience of 5 different centers treating LAPC with SBRT.

Methods: We included 41 pts with LAPC, undergoing SBRT +/- chemotherapy (CT) with multiagent CT regimens. Exclusion criteria were metastatic disease and radical surgical treatment. Only palliative surgery was admitted. Median dose and median fractionation dose for SBRT were 25 Gy (range: 4-45) and 6 Gy (range: 4-22), respectively. Toxicity was evaluated by CTCAE.4 scale. Overall survival (OS) was estimated and compared by Kaplan-Meier and log-rank methods, respectively.

Results: We analyzed 41 pts (M/F: 21/20; median age: 71, range: 36-89). Median, 6 months, 1-year, and 2-year OS were: 15 months (range 13.5-16.4), 87.6%, 73.9%, 20.1%, respectively. At univariate analysis a better prognosis was recorded for pts with tumor located at the tail (p=0.046), with a histologic grade 2 tumor (p<0.001), treated with adjuvant CT (p=0.036). There was a trend for improved OS in pts with cT3 tumor stage (p=0.085), and in pts treated with biliary stent (p=0.066). Nodal stage was not significantly related to OS. Incidence of gastrointestinal (GI) G1-G2 acute toxicity was 40%. Only one case of G3 GI acute toxicity (4%) and only one of G3 GI late toxicity (4.5%) were registered.

Conclusions: Fractionated SBRT +/- CT results in tolerable acute and minimal late GI toxicity and warrants OS comparable to current standard treatment (RCT). Future studies should incorporate SBRT with more aggressive multiagent CT to optimize pts outcomes.

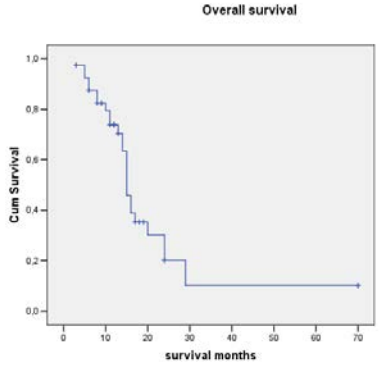

Figure 1.

C049

IMMUNOTHERAPY AND RADIOTHERAPY FOR MELANOMA BRAIN METASTASES: IS THERE A SYNERGISM?

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Aims: Melanoma has a high inclination to develop brain metastases. Prognosis of patients with melanoma brain metastases (MBM) is poor, with a median survival of 4-5 months. Immunotherapy (IT) demonstrated significant activity in metastatic melanoma. We conducted this retrospective study to investigate toxicity and outcomes of patients with MBM treated with radiation therapy (RT) and IT compared with historical data of patients with MBM treated with RT and other systemic therapies.

Methods: Patients with MBM treated in our institution with RT (whole brain RT or stereotactic radiosurgery) and IT between 2010 and 2015 were analyzed and identified as immunotherapy-group (IG). The same number of patients treated in the same period without IT was analyzed and identified as control-group (CG). The primary endpoint was local control (LC) and secondary endpoints were Overall Survival (OS), Intracranial Distant Disease Control (IDDC) and toxicity.

Results: Thirty-four MBM patients were identified for the analysis. All patients underwent RT. Fifty percent of patients (n=17) received IT, 17 received other kinds of systemic therapies (chemotherapy or BRAF inhibitors). In the IG, mean age was 53.3 years (range 30-81). In the CG, mean age was 54.8 years (range 32-80). Just three patients in the IG did not have also extra cranial disease at time of diagnosis, compared with 9 patients in the CG. In six cases IT was administered concomitantly to RT, in the remaining 11 patient IT was administered before (n=7) or after (n=4) RT. Fourteen patients in the IG received radiosurgery, compared with twelve patients in the CG. All the remaining received whole brain radiotherapy (WBRT). LC at 6 and 12 months in the IG group was 67.4%; LC at 6 and 12 months in the CG group was 87.5% and 58.3%, respectively (p=0.218). IDDC at 6 and 12 months in the IG was 64.7% and 35.3%,respectively, and in the CG 53.9% and 10.8%, respectively (p=0.009). OS at 6 months for IG and CG was 87.5% and 87.8%, respectively. At 12 months, OS was respectively 32.8% and 73.2% for IG and CG. Statistical significance was found in terms of OS (p=0.039). Concerning side effects, 4 patients developed seizures, 2 patients developed hemorrhage. Radionecrosis was observed during follow-up in 2 cases.

Conclusions: The combination of IT and RT for melanoma brain metastases did not result in a significant advantage in our experience. Further studies are recommended to better exploit this combined treatment.

C050

BRAF INHIBITORS THERAPY AND RADIOTHERAPY FOR MELANOMA BRAIN METASTASES (MBM): TOXICITY AND CLINICAL OUTCOME

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Aims: Both radiation therapy – whole brain radiotherapy (WBRT) / radiosurgery (RS) – and BRAF inhibitors (BRAF-I) have been shown to be useful in patients with brain metastases from melanoma (MBM). The possibility to combine these two treatments in order to amplify the effects of both is under investigation. The risk of an excess of radiosensitivity that can compromise the feasibility and safety of this combination is a major issue. We conducted a retrospective analysis, enrolling patients with MBM treated in our institution concomitantly with RT and BRAF-I.

Methods: 16 patients affected by metastatic melanoma were treated between 2012 and 2015. All these patients underwent radiation therapy for MBM in combination with BRAF-I. Primary endpoint of this study was toxicity, secondary endpoints were Local control (LC), intracranial distant disease control (IDDC) and overall survival (OS). Kaplan Meyer analysis was conducted.

Results: Median age was 53 (range 29-81). Fifty percent of the sample had also extracranial disease (n=8). Seven patients (43%) received treatment with Vemurafenib; other 9 (56%) patients received the combination of Dabrafenib and Trametinib. Radiosurgery was delivered in 63% of patients (n=10); remaining 6 patients (37%) received WBRT. In two patients of the RS group, radiation-induced necrosis was observed. In one patient radiation induced bleeding was detected. In all other cases no toxicity was recorded, including no events of scalp radiation dermatitis. Median survival was 10 months (range 5-18 months). LC at 6 and 12 months was 87.5%. IDDC at 6 months and 1 year was 61.9% and 27.1%, respectively. OS at 6 months and 1 year was 87% and 52.4%, respectively.

Conclusions: In our experience the combination of RT and BRAF inhibitors for melanoma brain metastases can be considered a safe and feasible combination. No serious concern about toxicity emerged in our series. Larger and prospective studies are recommended.

C051

STEREOTACTIC RADIOTHERAPY AND TARGET THERAPY FOR OLIGOMETASTATIC PATIENTS WITH RENAL CELL CARCINOMA

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Purpose: The aim of this study was the evaluation of local control (LC) and toxicity in oligometastatic patients with renal cell carcinoma (RCC) who had undergone stereotactic radiotherapy (SRT) with CyberKnife (Accuray, Sunnyvale, CA) or Vero™ (BrainLab) for cranial and extracranial metastases during the maximal response in systemic therapy.

Materials and Methods: Between January 2012 and September 2015, 23 patients (30 metastases) with metastases of RCC were treated with SRT alone to the new site of disease (if limited disease) or to residual disease during the maximal response in systemic therapy. Disease control was evaluated with serial imaging. Toxicity was recorder according to the Common Toxicity Criteria version 4.0.

Results: After a median follow-up of 9.4 months (range 1-36) 20 patients were alive. Ten patients received SRT alone and 13 patients received that during the maximal response of systemic therapy. The median equivalent of the dose (EQD2) was 50.6 Gy delivered with a median of 2.7 fractions (range 1-5) and the median biological equivalent dose (BED) was 51 Gy assuming / =10 for tumour. Six patients are lost in follow-up. Clinical and radiological response was thus evaluated in 17 patients and the their LC was 100% (57.1% of patients received SRT alone and the others patients are still undergoing systemic treatment. 27.7% of patients had more than 12 months follow-up and the LC was again 100%.). Progression of disease in the other sites was observed in all cases. No toxicity was observed.

Conclusions: SRT is a feasible approach that offer an excellent LC with low toxicity profile in the treatment management of oligometastatic patients with RCC with or without the association of systemic therapy. Further investigation is warranted to identify the patients who would probably benefit from this approach.

C052

STEREOTACTIC ABLATIVE RADIATION THERAPY FOR LUNG OLIGOMETASTASES: PREDICTIVE PARAMETERS OF EARLY RESPONSE BY 18FDG-PET/CT

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Aims: to investigate the role of 18FDG-PET/CT parameters as predictive of early response after Stereotactic Ablative Radiation Therapy (SABR) for oligometastases lung lesions.

Materials and Methods: SABR for lung oligometastases was performed when the following criteria were satisfied: a) controlled primary tumor, b) absence of progressive disease longer than 6 months, c) number of metastatic lesions ≤ 5. The prescribed total dose varied according to the risk-adapted dose prescription with a range of doses between 48-70 Gy in 3-10 fractions. Inclusion criteria of the current retrospective study were: a) lung oligometastases underwent to SABR, b) for each patient presence of 18-FDG-PET/CT pre- and post-SABR for at least two subsequent evaluations, c) Karnofsky performance status>80, d) life-expectancy>6 months. The following metabolic parameters were defined semi-quantitatively for each lung lesion: 1) SUV-max, 2) SUV-mean, 3) Metabolic Tumor Volume (MTV), 4) Total Lesional Glycolysis (TLG).

Results: From January 2012 to November 2015 fifty patients for a total of seventy lung metastatic lesions met the inclusion criteria of the present analysis. Pre-SABR, median SUV-max was 6.5 (range, 4 - 17), median SUV-mean was 3.7 (2.5 - 6.5), median MTV was 2.3 cc (0.2 - 31 cc). For patients with in-field disease progression median TLG was 17.4 (2 - 52.8), for the remaining the median value was 170.6 (0.5 - 171). For pre-SABR SUV-max ≥ 5 a progression/stable metastasis was noted in 88% of cases, while a complete response was observed in 94% of cases for pre-SABR SUV-max<5 (p<0.001, Sensitivity = 88%, Specificity = 94%). A pre-SABR SUV-mean<3.5 was related to complete response at 6 months after SABR (p 0.03, Sensitivity = 31%, Specificity = 34%, AUC = 0.32). In cases of in-field failure, a pre-SABR SUV-max>8 was related to a higher absolute value increase of SUV-max at 6 months of follow up comparing to pre-SABR SUV-max<8 (p 0.005). Delta SUV max 3-6 months was +126% for lesions with in-field progression versus -26% for the remaining (p-value 0.002). Delta SUV-mean 3-6 months was +15% for lesions with in-field progression versus for the remaining metastases (p-value 0.008). Finally, 86% of patients with local failure had distant progression versus only 19% in cases without local failure (p=0.004).

Conclusions: According to current findings, pre-SABR SUV max and mean seem to predict early response in lung SABR for oligometastases.

C053

STEREOTACTIC BODY RADIOTHERAPY FOR RECURRENT SINGLE PULMONARY METASTASES

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Aims. SABR (stereotactic ablative body radiotherapy) has been used to treat patients (p) with inoperable solitary pulmonary nodules and it was reported to achieve excellent rates of local control with limited toxicity in many cases of secondary pulmonary tumors. However, the PD after SABR in these p is usually reported. The present study analyzes the toxicity and the efficacy of the new SBRT in 6 p with secondary pulmonary relapse.

Methods: Between Jan 2014 and Mar 2015, six p, ECOG ≤2, underwent second course of SABR, for a new single localization of pulmonary metastatic cancer. These patients were previously treated for single metastatic lung nodule, to our institution with the interval between the previously stereotactic body radiation therapy of 27 months (range: 8-31). The p underwent to Simul-CT scan with institutional technique and are re-planned by using multiple non coplanar radiation beams. The maximum size of the nodules was<44 cm^3. The median planning target volume was 15.5 cm3 (2.4-61.2 cm^3). The total stereotactic body radiation therapy doses were: a) 45 Gy/3 fractions to the 80% isodose lines for parenchymal GTV (Pts. 4) , b) 50 Gy/5 fractions to the 95% for GTV close to critical structures (Pts 2). All fractions were scheduled three times per week. The biologically effective dose was calculated for each patient and the homogeneity index (HI) was calculated for each treatment plan. Dose constraints were set for the spinal cord , the rib, the superior vena cava, the lung, the heart and the carina.

Results: All p. are followed prospectively by serial CT scans and QoL measurements four time yearly. The minimum follow-up was 12 months (range, 9-15 months), and disease control was achieved for all p, None of these experienced toxicity of lung or rib ≥ grade 2. No p. required oxygen or had deterioration of the performance status during follow-up and no local progression of disease was recorded

Conclusions. Stereotactic body radiation therapy is associated with minimal morbidity and provides comparable local control when compared with surgical resection, so it is effective and safe in treating pulmonary metastasis, especially for those p who were medically unfit for a resection or who refused surgery.

C054

STEREOTACTIC RADIOTHERAPY IN OLIGOMETASTATIC OVARIAN CANCER PATIENTS TREATED WITH VERO™ AND CYBERKNIFE™ AT EUROPEAN INSTITUTE OF ONCOLOGY: PRELIMINARY RESULTS

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Aims: to retrospectively evaluate response and toxicity of stereotactic radiotherapy (SRT) for oligometastatic ovarian cancer patients (pts).

Methods: between 5/2012 and 9/2015 we enrolled 54 adult oligometastatic ovarian cancer pts to SRT at European Institute of Oncology. Indication criteria were: 1) low tumor burden (1–5 lesions); 2) contraindication to surgery; 3) localized persistent disease after chemotherapy (CT) or 4) no CT indication due to hematological toxicity (tox) or 5) CT lines not available or 6) patient refusal of CT. Toxicity and tumor response were evaluated using CTCAE and RECIST criteria. CT or PET was performed at 2-3 months (m.).

Results: 54 patients/86 lesions underwent SRT. We treated 57 nodal metastases (mets) and 29 visceral mets, 69 and 17 lesions were treated with VERO™ system and Cyberknife™, respectively. Median age was 60.4 years (range 45.7-81). All pts had previously received CT and/or hormonotherapy (HT). SRT consisted in re-irradiation for 6 lesions. Mean GTV was 13.2 cm^3 (range 0.5 - 90.05). Median dose was 24 Gy (range 16–45 Gy) in 3 fractions (range 2-5). Median follow-up (FU) was 9.1 m. (range 1.4-40.1). Radiological response at first FU (evaluable for 77 lesions) was: complete response, partial response, stabilization and progressive disease (PD) in 46 (60%), 17 (22%), 10 (13%) and 4 (5%) lesions, respectively. At last FU (available for 53 pts), 8 pts were alive with no evidence of disease, 42 alive with disease, 3 pts died of disease. Acute and late tox were low: 12 G1 (predominantly nausea) and 3 G1-events (2 constipation and 1 mild abdominal pain), respectively. Pattern of failure was mainly out-field (PD out-field, in-field, in- and out-field in 36, 3, and 2 cases respectively). Local control at last FU was observed in 68/77 evaluable lesions (88.3%). Median local progression free survival was 10.6 m. (range 6-21.3). Median progression free survival was 3.6 m. (range 1.5-25).

Conclusions: in our experience, SRT in oligometastatic ovarian cancer pts has shown excellent local control and toxicity profile. It might be a good alternative to other more invasive local therapies in order to delay systemic therapy especially in case of chemorefractory disease or intolerance to chemotherapy. The evaluation of site and volumes treated is ongoing.

C055

EXTRACRANIAL STEREOTACTIC RADIOTHERAPY IN THE TREATMENT OF LYMPH NODAL RECURRENCES: RESULTS FROM A DOSE ESCALATION TRIAL

F. Deodato[1], M. Ferro[1], G. Macchia[1], C. Annese[1], O. Zeuli[1], V. Picardi[1], M. Nuzzo[1], S. Cilla[2], A. Ianiro[2], S. Cammelli[3], G. Tolento[3], M. Marengo[4], A.L. Angelini[4], S. Picchi[3], G.P. Frezza[5], A. Farioli[6], V. Valentini[1,7], A.G. Morganti[3]

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Aims. To determine the maximum tolerated dose (MTD) of fractionated extracranial stereotactic radiotherapy (ESRT) to lymph nodal recurrences in different clinical settings.

Methods. Patients enrolled in a phase I clinical trial entered the analysis. Each enrolled subject was included in a different study arm, according to nodal site and previous treatment. Dose has been prescribed according to ICRU 62. A four no-coplanar beams class solution or a volumetric technique (VMAT) have been applied in all patients. The planning target volume (PTV) has been defined as gross tumour volume (GTV) plus 5-15 mm. According to different arms, patients received an ESRT dose ranging from 20 Gy up to the maximum planned dose of 50 Gy in 5 fractions. Dose-limiting toxicity (DLT) was any grade>3 acute toxicity or any grade>2 late toxicity. The MTD was exceeded if 2 of 6 or 4 of 12 patients in a cohort experienced DLT.

Results. 101 patients (M/F: 47/54; median age 67 years, range 43-87years) with 128 nodal lesions were treated. were treated. Of these, 48 (37.5%) were nodal recurrences in neck or chest, 34 (26.5%) were in abdomen and 46 (35.9%) were in pelvis. The primary tumour was most frequently gynaecologic cancer (44%), followed by genito-urinary cancer (22%), gastro-intestinal (13%), lung (13%) and other (9%). The median ESRT delivered dose was 35 Gy (20-50) in five fractions. With a median follow up of 19 months (4-104), the overall response rate was 88% (CI95: 80-93.6; Complete Response: 68%; Partial Response: 20%), with only 5% of patients developing disease progression. No DLT was recorded in this group of patients. Two- and 4-year local control were 81% and 70.2%, respectively. Two- and 4-year metastases free survival were 43.5% and 30.9%, respectively.

Conclusions. In quite varied setting of lymph nodal

recurrences an ESRT treatment in five fractions up to a dose of 50 Gy is safe and well tolerated.

C056

INTER-FRACTION MOTION IN STEREOTACTIC BODY RADIOTHERAPY WITH VOLUMETRIC MODULATED ARC THERAPY AND ON-LINE CORRECTION: SYSTEMATIC AND RANDOM SETUP ERRORS FROM ANALYSIS OF 125 IMAGE REGISTRATIONS FOR TORACIC AND ABDOMINAL OLIGOMETASTASES

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Aims: to analyse positioning error in 22 oligometastatic patients, consecutively treated with Stereotactic Body Radiotherapy (SBRT) using Volumetric Modulated Arc Therapy (VMAT) at the Radiotherapy Unit of San Donato Hospital - Arezzo.

Methods: Set-up errors for 23 courses of SBRT in 22 patients were assessed using cone-beam CT (CBCT). In 10 cases SBRT was delivered to abdominal metastases (5 bone, 5 lymph nodes), in the remanining 13 to thoracic metastases (3 bone, 9 lung, 1 lymph nodes). Positional error was online - corrected in x, y and z translational planes and rotational axes using a robotic couch, applying 2 mm and 2° action levels. Systematic and random setup errors were calculated for these anatomic sites.

Results: Ninety-five fractions were delivered with 125 image registrations. Across all fractions, the mean positional error for abdomen was greatest in the y translational plane (1.8 mm+/-5.9 mm) and y rotational axis (0.4°+/-1.5°), while for thorax in the z translational plane (-0.8 mm+/-5.2 mm) and x rotational axis (-0.3°+/-1.4°). The systematic translational setup errors were 0.1 mm+/-3.8 mm, 1.8 mm +/-3.9mm and 0.7 mm+/-3.6 mm for abdomen, and -0.9 mm+/-3.6 mm, 0.1 mm+/-4 mm and -1.4 mm+/-5.1 mm for thorax for x, y, z, respectively. The random translational setup errors were 0.3 mm, 0.7 mm, and 0.3 mm for abdomen, and 0.3 mm, 0.3 mm and 0.4 mm for thorax. The systematic rotational setup errors were 0.01°+/-1.5°, 0.5°+/-0.9°, and 0.2°+/-1° for abdomen, and -0.3°+/-1.1°, 0.2°+/-1.3° and 0.1°+/-1.8° for thorax. Random rotational setup errors were 1.2°, 0.9° and 0.9° for abdomen, and 0.8°, 0.9° and 1° for thorax.

Conclusions: With 4D planning CT and image-guidance, the current applied planning margins for abdominal and thoracic target volumes at our Institution appear safe.

C057

CONCOMITANT RADIOTHERAPY AND TKI IN EGFR-MUTANT OR ALK POSITIVE METASTATIC NON-SMALL CELL LUNG CANCER

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Purpose: To investigate the role of radiotherapy (RT) in the management of EGFR-mutant or ALK positive metastatic non-small cell lung cancer (NSCLC) treated with TKI at onset or after standard chemotherapy.

Table 1.

Variable	n.	%
Age	(median 62 years)	
< 65 years	22	53.7
≥ 65 years	19	46.3
TKI		
Gefitinib	25	61.0
Erlotinib	5	12.2
Crizotinib	9	22.0
2 TKI	2	4.8
N. previous CHT		
0	18	43.9
At least one	23	56.1
Site of RT		
Brain	27	65.8
Bone	10	24.4
Other sites	4	5.8
RT schedule		
S BRT	8	19.5
P alliative hypofractionation	33	80.5
Aim of RT		
Symptoms	20	48.8
Palliation	14	34.1
Oligoprogression	7	17.1

Materials and Methods: Clinical data of 41 patients (pts) treated with RT concomitant to TKI for EGFR-mutant or ALK positive NSCLC stage IV were revised. Time from start of TKI to death for any cause was the survival endpoint considered for analysis (TKIS). Kaplan-Meyer curve and log-rank test were elaborated for analysis of survival, while chi-square test was calculated to compare different variables.

Results: A description of the series is reported in Table 1. Median age of pts was 62 years. Biological target therapy for EGFR-mutant and ALK positive metastatic NSCLC was used in 73.3% and 22% of cases. Only 2 pts were submitted to 2 TKI. Stereotactic body radiotherapy (SBRT) was associated in 8 pts; 7 of them were treated for oligoprogressive disease and 1 for palliation (p 0.00). Median duration of biological target therapy was 10.9 months and median TKIS was 15 months. One and 2

years TKIS resulted 57.7% and 39.3%, respectively. TKIS was better in the SBRT group than in the hypofractionated RT one (80.0% vs 52.6% at 1 year, p 0.07) but the latter is negatively selected. Seven pts reported mild toxicity after radiotherapy (5 worsening of neurological symptoms, 1 emesis and 1 pain).

Conclusions: Biological target therapy with TKI is a recent opportunity to treat stage IV NSCLC with EGFR mutations or ALK translocation but scarce data are available on the effects of combined treatment. Our analysis shows that concomitant RT is feasible and safe, RT related toxicities were not higher than expected and pts with oligoprogression during TKI treatment might benefit of SBRT. These findings need to be confirmed in terms of progression free survival and overall survival.

C058

STEREOTACTIC BODY RADIATION THERAPY AND TARGET THERAPY FOR TREATMENT OF OLIGO-METASTATIC RENAL CELL CANCER

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Aims: Renal cell carcinoma (RCC) is generally poorly responsive to conventional radiotherapy, therefore patients (pts) have limited therapeutic options. We report our experience in the treatment of oligometastatic RCC using stereotactic body radiotherapy (SBRT) in patient treated with target therapy in terms of local control (LC), overall survival (OS) and compliance.

Methods: Between June 2011 and July 2015, 43 pts with oligometastatic RCC were treated with SBRT. Lesions irradiated were 124 (48 bone, 37 lung, 21 node, 18 epatic). Lung metastases with maximum diameter ≤ 3 cm were treated in single fraction (median dose 26 Gy, range 20-30 Gy, 80% isodose) while all others lesions were treated in hypofractionated regimens in 3-5 fractions (median dose 10 Gy/fx, range 8-12,5 Gy/fx, 70% isodose). The treatment was delivery by LINAC 6 MeV (Elekta Synergy-S) using dynamic beam modulator and VMAT optimization. Patients underwent to Computed Tomography and/or PET-CT scan 60 days after treatment and then every 4 months. 73% pts have been treated with target therapy drugs (sorafenib, sutinib), which was stopped 7 days before and 7 after SBRT.

Results: Median follow-up was 8 months (range 1-49). Overall LC was 59% at 8 months and 48% at 12 months. Despite the heterogeneity of patient cohorts, in our analysis there was no statistically significant difference in LC between lesions treated with single fraction and lesions treated with hypofractionated regimen but there is a positive trend for single fraction (p-value=0.087), considering a BED 10>100 Gy in both splits. On univariated analysis better local control was statistically related to target volume (LC for lesions ≤ 6 cc is 76% at 8 months vs 48.6 for lesions>6 cc). OS at 3, 5 and 10 years was 75%, 58% and 18% respectively. At time of analysis 20/43 (46,5%) pts were still alive (3 pts NED, 10 pts SD and 9 pts PD). No severe acute or late toxicity was observed, also in the subgroup of patients treated with target therapy.

Conclusions: Our results confirm that SBRT in the treatment of oligometastatic RCC is an effective and safe modality to control metastatic lesions with optimal compliance, even when associated with target therapy, reaching LC of 59% and 48 % at 1 and 2 years respectively. Although OS is not the primary end-point of this study, it shows interesting value (75% at 3 years, 58% at 5 years). A longer follow-up and clinical studies are needed to confirm our data.

C059

PEMETREXED WITH CONCURRENT GAMMAKNIFE RADIOSURGERY IN PATIENTS WITH BRAIN METASTASES OF LUNG ADENOCARCINOMA: A SINGLE CENTER EXPERIENCE

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Aims: To report the safety and the clinical outcome of patients with brain metastasis and primary non small cell lung cancer (NSCLC) treated with the combination of Pemetrexed and radiosurgery (RS).

Methods: From June 2013 to December 2015 we collected 16 patients affected by advanced NSCLC with brain metastases who had been treated with Pemetrexed following disease progression (DP) after first-line or futher-line chemotherapy and received RS such as the only treatment. Pemetrexed was administered at a dose of 500 mg/m^2 every 21 days. RS was delivered in a single session with a GammaKnife Perfexion; the radiochemotherapy treatment was considered associated when the administration of Pemetrexed was performed within 2 months before or after RS. Local relapse was defined as the radiological evidence of progression of the brain lesion treated with RS and distant brain progression as the development of new brain metastasis other than the lesion treated.

Results: RPA class was 2 in 62.5% patients and 1 in 37.5%, GPA class was between 0 and 3.0; 4 out of the 16 patients had extracranial metastases, at the time of RS all patients had extracranial disease and primary tumor controlled. The mean number of brain metastases treated was 4(range: 1-8). In the 68.7% an increased number of metastasis was detected at the stereotactic MRI respect to the baseline examination. Mean dose was 22 Gy (15-24 Gy) depending on the tumor size and the proximity with organs at risk. At the clinical follow up no patient developed new neurological symptoms, the MRI performed at 1 month from the treatment and at 3 months thereafter did not show radionecrosis signs in any patient. At a median follow up of 12 months 7(43.7%) patients were deceased, 1 patient for neurological causes, all other for systemic

progression; 4(25%) had a local recurrence and 5(31,2%) distant brain relapse. The mean time of systemic progression after the RS associated to Pemetrexed was 6 months (range: 2-15 months). The 1 year overall survival (OS) was 64,2%, the local DP free survival LDPFS was 71.5% and the distant brain progression free survival was 64.2%.

Conclusions: RS associated to Pemetrexed is a safe treatment for brain metastatic adenocarcinoma patients. The local treatment with RS in case of brain progression and extracranial disease controlled, could permit the continuation of the therapy with Pemetrexed delaying the chemotherapy change without compromising the clinical outcome.

C060

DEFORMABLE IMAGE REGISTRATION: PATTERNS OF FAILURE, TOXICITY AND DOSE MONITORING FOR RECURRENT HEAD AND NECK CANCER

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Aims: to present the applicability of a commercially available DIR tool in daily clinical setting

Methods: Image registration is a method of aligning two images into the same coordinate system and it could be rigid (RIR) or deformable (DIR). The algorithm for DIR used in our study, implemented in VelocityAI 3.1 [Varian Medical Systems, Palo Alto, CA] uses a multiresolution approach whereby metric is based on Mattes Mutual Information and the transform used is a cubic B-Spline. We retrospectively reviewed treatment planning of two patients treated, in our Department, for recurrent head and neck cancer, respectively: left retromolar trigone cancer relapsed in field (progression free survival, PFS: 11.73 months) and a tonsil cancer relapsed in field (PFS: 25.76 months). All patients were initially treated with conventionally fractionated regimen once daily, five times a week (SIB-VMAT,TPS: Eclipse). Mean dose delivered to high risk CTV was 62 Gy and to medium risk CTV 55 Gy. They received hyperfractionated stereotactic radiotherapy to the site of recurrence (1.2 Gy twice daily for 4 and 5 weeks, respectively. TPS: i-Plan). We compared the location of recurrences on second planning scans to the PTV from planning scans. In-PTV radiotherapy failures could mean resistant tumors, but recurrences near PTV borders may imply a geographic missing.

Results: We first rigidly aligned the previous treatment planning CT (CT1) on the new planning CT (CT2) and DIR between CT1 and CT2 was performed. The evaluation of registration quality is performed using DICE similarity coefficient; deformable warp map appears rigid around bones and spine and expansion was observed in the area of the new lesions, as expected from the recurrence. No recurrences were near the PTV borders. QUANTEC dose constraints of ipsilateral parotid and of pharyngeal constrictors were not respected. CTCAE 4.0 G2 dysgeusia was observed in tonsillar cancer, G3 dysphagia and G1 dysarthria in retro-molar trigon cancer.

Conclusions: Critical issue in re-irradiation is to avoid side effects in OARs without compromising the dose delivered to the target. DIR could improve quality and effectiveness of re-irradiation allowing safer treatments to patients. VelocityAI allowed us to sum plan from different treatment modality and, during treatment, it can let us to decide a different second treatment checking constraints on total dose or making a comparison between different treatment plans.

C061

APBI WITH INTERSTITIAL BRACHYTHERAPY FOR LOCAL RECURRENCES: ANALYSIS OF TREATMENT EFFICACY, COSMESIS, AND TOXICITY

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Aims: To review our institution's experience of treating ipsilateral breast tumor recurrence and chest wall locoregional recurrence using interstitial HDR brachytherapy

Methods: Between January 2009 and December 2014, 14 consecutive patients were enrolled. 5 patients initially treated with mastectomy with (2 patients) or without (3) adjuvant chest wall radiotherapy and 9 treated with breast-conserving surgery and postoperative irradiation (mean disease free survival: 130.8 months; median: 129.78; range: 12.3-237.3), developed a local recurrence (LR). The mean dose of previous radiation therapy was 55 Gy (range, 50–60 Gy).

In all patients the LR was resected, needles implantation was done post-operatively using a plastic template and then needles were replaced with flexible catheters. Plannification (Oncentra MasterPlan TPS) was made based on post-implant CT-scan. According to Paris system rules, implanted volume was adapted to tumor by varying the number of sources and active length and dose was prescribed at the 85% basal dose rate (median DHI 0.71, mean 0.70; range: 0.63-0.78). 5 patients was treated with single plane, 3 with two and 6 with three-plane implants. Intersource spacing varied from 1.2 to 1.4 cm and patients received HDR-BT using a total dose of 35 Gy (2 x 3.5 Gy/day, 3 patients), 34 Gy(2 x 3.4 Gy/day, 9 patients), 42 Gy (2x 3.5Gy/day, 1 patient).

Results: Treatment was well tolerated and no premature removal was required. After a mean follow-up of 29 months, no signs of LR were observed. RTOG/EORTC G1 acute toxicity was observed in 1 patients. No G2 or higher acute toxicity occurred. On the subject of late toxicities, there was 1 case of G2. Cosmetic results were evaluated at each follow-up visit on RTOG scale. 9 patients (64%) presented an excellent cosmetic results, 4 (28%) good (moderate teleangectasia and moderate aymptomatic fibrosis). Only 1 patient presented a fair cosmetic impact (skin retraction). No ulceration or necrosis was observed.

Conclusions: APBI with interstial brachytherapy for ipsilateral and chest wall locoregional recurrences appears to be a meaningful salvage treatment with acceptable toxicity.

C062

STEREOTACTIC BODY RADIOTHERAPY OR INTENSITY-MODULATED RADIATION THERAPY FOR OLIGOMETASTATIC TRANSITIONAL CELL CARCINOMA: A RETROSPECTIVE ANALYSIS OF 10 PATIENTS

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Objectives: The aim of our study was to retrospectively report on the image guided stereotactic body radiotherapy (SBRT) or intensity modulated radiotherapy (IMRT) employed, in our department, in 10 consecutive patients for bladder or prostatic urethra cancer with lymph node or bone recurrence, proposed as an alternative to systemic treatment.

Methods: Inclusion criteria for this retrospective study were as follows: adult oligometastatic transitional cell cancer (TCC) patients with lymph node or bone recurrence that underwent SBRT/IMRT but not other local therapy, written informed consent for treatment and use of anonymized data for research&training purposes. Previous radiotherapy, concomitant systemic therapy or surgery were allowed. Toxicity and tumor response were evaluated using Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scale and Response Evaluation Criteria In Solid Tumors.

Results: 10 patients/16 lesions underwent SBRT/IMRT (median 25 Gy/5 fractions) in our Institution between 6/2012 and 12/2015. Median age at SBRT/IMRT was 67.3 years (range 50.4-77.9). A re-irradiation was performed in one patient. Primary diagnosis included bladder and prostatic urethra cancer (9/1 pts). Previous systemic therapy or cystectomy was performed in all patients. Median follow-up was 14 months. Two grade 1 acute and none late toxicity events were registered. Complete radiological response, partial response, progressive disease and not evaluable were observed in 9 (60 %), 2 (13.3 %), 3 (20 %) and 1 (6.6 %) lesions, respectively. In-field and out-field clinical progression was reported in 4 patients. Out-field clinical progression was reported in 2 patients. Median progression-free survival was 6.2 months. Mean interval between TCC diagnosis and the first RT treatment was 2.8 years. At present, 3 pts are alive disease-free (at mean time of 16.6 months from RT), 3 alive with disease, 4 dead of disease.

Conclusions: SBRT/IMRT on lymph node or bone recurrence from TCC offers a good in-field tumor control with low toxicity profile. In small proportion of patients long disease control can be obtained. Patter of failure was predominatly out-field. Further studies on systemic treatment are needed to ensure better systemic control of disease.

Table 1.

Radiologic response to SBRT/IMRT	N° of lesions (16)
CR	10*
PR	2
NC(SD)	0
PD	3*
NA	1^

**One patient underwent re-irradiation with subsequent CR; ^dead patient*

C063

SECONDARY LUNG NODULES (SLN) TREATED WITH STEREOTACTIC BODY RADIOTHERAPY (SBRT): ANALYSIS OF A SINGLE INSTITUTION SERIES

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Purpose: To retrospectively evaluate efficacy of SBRT in secondary lung nodules (SLN) in order to define potential benefits in the management of stage IV disease.

Table 1.

Variable	Primary tumor				Total (45 pts)	
	Lung (31 pts)		Other sites (14 pts)			
	n.	%	n.	%	n.	%
Age (years)						
<65	6	19	5	36	11	24
≥ 65 e < 75	14	45	5	36	19	42
≥ 75	11	36	4	28	15	34
Performance Status						
0	4	13	5	36	9	20
1	25	81	8	57	33	73
2	2	6	1	7	3	7
Diagnosis						
Radiological diagnosis	6	19	2	14	8	18
Histological proven	25	81	12	86	37	82
Previous treatment						
No	1	3	3	21	4	9
Yes	30	97	11	79	41	91
SBRT schedule						
11 Gy x 5 fr	23	74	10	71	33	73
6.5 Gy x 8 fr	8	26	4	29	12	27
Technique						
3D Conformal arcs	2	6	1	7	3	7
VMAT	25	81	12	86	37	82
Helical IMRT	4	13	1	7	5	11

Materials and Methods: Data of all patients (pts) treated with SBRT for secondary lung nodules were reviewed. Local Control (LC), progression-free survival (PFS) and overall survival (OS) were considered as endpoints of the analysis. Kaplan-Meyer curves and log-rank

test were elaborated for analysis of survival, while chi-square test was calculated to compare different variables. P< 0.05 was considered significant.

Results: From 2012 to 2015 45 pts with SLN were treated with SBRT on 57 lesions and lung cancer was primary tumour for 31 of them (68.9%). Median age was 73 years. Clinical and therapeutic data of the total series and according to primary tumour have been reported in Table 1. Groups of pts with lung vs other primary tumours were homogeneous (p 2>0.05) for the characteristics shown in Table 1. After a median follow up of 13.1 months, 9 pts showed a progression disease on site of SBRT with a LC at 1 and 2 years of 89.1% and 63.9%. OS at 1 and 2 years was 91.4% and 67.3%, PFS at 1 and 2 years was 64.0% and 28.3% .

Conclusions: Lung cancer was the most frequent primary tumour in this series, but no significative differences with other primary sites were reported. SBRT for SLN was an effective treatment for pts with pulmonary metastasis with an high rate of LC and good OS and PFS considering the poor prognosis of stage IV disease.

C064

HYPOFRACTIONATED STEREOTACTIC BODY RADIATION THERAPY (SBRT) IN THE TREATMENT OF EARLY STAGE LUNG CANCER AND EXTRACRANIAL OLIGOMETASTASES FROM MULTIPLE PRIMARY CANCERS: A SINGLE INSTITUTION EXPERIENCE

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Aims: To retrospectively analyze the efficacy and the feasibility of Stereotactic Body Radiation Therapy (SBRT) in the treatment of early stage lung cancer and extracranial oligometastases from multiple primary cancers.

Methods: Between June 2006 and April 2016 we treated 97 patients (104 lesions) with SBRT. The patients included in the analysis had a median age of 71 years (range, 38-88) and presented with a Karnofsky performance status ≥ 70. All patients were assigned Charlson Comorbidity Index Scores (CCIS) according to the medical comorbidities they had. Treatment related toxicity was evaluated using the CTCAE version 4.0. The most used SBRT dose fractionation schemes were 40 Gy in 5 fractions and 35 Gy in 5 fractions. Disease progression was defined according to RECIST criteria from the end date of SBRT to the first clinical progression. Overall Survival (OS), Cancer-Specific Survival (CSS), Progression-Free Survival (PFS), and Local Control (LC) were calculated from the end date of SBRT to the last follow-up; in particular, for PFS the time interval was obtained from the end date of SBRT to the first clinical progression. Kaplan-Meier method was used to perform survival analysis, and log-rank test for correlations with dichotomized clinical variables based on the median value (age, KPS, CCIS). LC was correlated to the tumor primary site (lung vs prostate vs others).

Results: Median follow-up was 19 months (range, 0-99). One-year and 2-year OS were 97% and 92%, respectively. CSS at one year was 97%, and it was 93% at two years. PFS at one year was 91%, and it was 83% at two years. LC was 93.5% at one year and 92% at two years. At the univariate analysis, we found that KPS was the only statistically significant prognostic factor for OS, CSS (p=0.0001 for both) and PFS (p= 0.006). Finally, at univariate analysis we found that only lung and prostate as primary tumor sites are positively correlated with LC (p=0.03). 14 (14.2%) patients developed acute toxicity >2, while 7 (7.1%) patients developed late toxicity >2.

Conclusions: SBRT is an effective tool in the management of early stage lung cancer patients and patients with oligometastatic disease from multiple primitive cancers. Our results suggest that a careful patient selection would be desirable in order to more definitively determine the benefit of this treatment option.

Poster

P001

WHICH IS THE BEST TREATMENT FOR OLIGOMETASTATIC BRAIN PATIENTS? RESULTS OF FOUR DIFFERENT THERAPEUTIC APPROACH

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Aims: To verify whether brain oligometastases' treatment results in different outcomes when whole brain radiotherapy (WBRT) is combined with surgery or stereotactic radiotherapy (SBRT) boost or simultaneous integrated boost (WBRT + SIB) or stereotactic radiotherapy is administered alone (SBRT).

Methods: Files of oligometastatic patients affected by less 3 brain metastases were selected; according to the therapeutic approach were identified 4 groups: surgery plus WBRT (Group A), WBRT plus SBRT (Group B), WBRT-SIB (Group C) and SBRT alone (Group D). The four treatment groups were matched for the following potential prognostic factors: age, gender, performance status, tumor type, number of brain metastasis and recursive partitioning analysis class (RPA). The outcomes of patients in all groups were evaluated in terms of toxicity, local control and overall survival.

Results: From 538 patients submitted consecutively to radiotherapy for brain metastases, 147 patients were eligible (87 male; 60 female) for this analysis. 54 out of 147 patients (36.7%) had been undergone to surgery plus WBRT (Group A), 48 (32.7) to WBRT plus SBRT (Group B), 19 (12.9%) to WBRT plus SIB (Group C) and 26 patients (17.7%) to SBRT alone (Group D). The median number of brain metastases was 1 (range, 1-2) and median age of the patients was 59 years (range 37-87). Grade ≥ 3 acute toxicities, such as headache, hearing problems, nausea and vomiting did not occur in treated patients. Only 2 patients (1.3%) (group B) revealed radionecrosis, radiologically demonstrated and appeared 6 and 8 months after the completion of radiotherapy, respectively. Median follow-up was 121 months (range, 2 - 242 months). The median local control (LC) for the entire cohort was not reached. The 1 year local control was 85,3% in all patients. The median overall survival (OS) for the entire cohort was 20 months and the 1 year overall survival was 68% in all patients. Local control and overall survival data for each group are reported in table 1. Neither treatment proved to significantly impact OS (p=0.68).

Conclusions: Radiotherapy offers a good local control in asymptomatic patients. WBRT increases LC without to increase overall survival.

Table 1.

	Surgery +WBRT	WBRT + SBRT	WBRT + SIB	SBRT	p
Median LC	n.r	n.r	n.r	n.r	P=0.02
1 yr CL	84.5%	95.6%	83%	67.2%	
5 yrs CL	82%	90%	62%	58%	
Median OS	16 months	26 months	27 months	16 months	P=0.68
1 yr OS	62.3%	72.3%	75.2%	67.8%	
3 yrs OS	28.3%	31.9 %	25.1%	22.6%	
5 yrs OS	18.9%	16.1%	25.1%	22.6%	

P002

IMPLICATIONS AND TECHNICAL CONSIDERATIONS ON HIPPOCAMPUS AS ORGAN AT RISK IN STEREOTACTIC RADIATION TREATMENT FOR BRAIN METASTASES

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Aims: Hippocampal-dependent neurocognitive functions, including learning, memory and spatial informations processing, could be affected by brain radiotherapy. Aim of the present study is to evaluate the dose to omolateral and contralateral hippocampus (O-H, C-H, respectively) during Stereotactic Radiotherapy (SRT) or Radiosurgery (SRS) for brain metastases (BM).

Methods: Patients eligible for stereotactic treatment had a number of brain metastases<5, with a size ≤ 30 mm, Karnosky Performance Status (KPS) ≥ 80 and a life expectancy over 3 months. Gross Tumour Volume was delineated according to Magnetic Resonance Imaging (MRI) and Computed Tomography. A Planning Target Volume (PTV) was obtained from GTV adding a margin of 2 mm. The total dose, prescribed to PTV, ranged between 18-27Gy in 1 to 3 fractions. For each BM, a Volumetric modulated arc therapy (VMAT) was generated with one or two arcs and hippocampus sparing was not considered during optimizations phase. For the dosimetric evaluation of O-H and C-H, the Dmedian, Dmean, D0.1cc and the V1Gy, V2Gy, V5Gy and V10Gy were analyzed.

Results: From April 2014 to December 2015, 81 BM in 41 patients were treated with SRS or SRT and selected for the present analysis. The average values of PTV dimension was (5.8±9.5) cc. The average of hippocampus volumes was (1.1±0.3) cc. For the O-H, the average values of Dmedian, Dmean and D0.1cc were (1.5±3.6) Gy, (1.5±3.6) Gy, (2.2±4.7) Gy, respectively, while the V1Gy, V2Gy, V5Gy and V10Gy values were (25±40) %, (18.9±35) %, (8.9±25.3) % and (2.1±11.8) %, respectively. For the C-H, the average Dmedian, Dmean and D0.1cc were (0.7±1.5) Gy, (0.7±1.4) Gy, (0.9±1.8) Gy, respectively, while the average values of V1Gy, V2Gy, V5Gy and V10Gy were (18±35) %, (10.2±27.7) %, (2.8±15.4) % and (1.4±11.6) %, respectively. The differences between O-H and C-H, in terms of received dose, was statistically significant (p=0.03). Moreover, the evaluation of PTV dimension (>5cc or >6cc) was not correlated to increased dose of hippocampus (p= 0.06; 0.2, respectively).

Conclusions: During SRT or SRS treatments for BM, hippocampus received a very low dose and its clinical significance seems to be negligible, even if it is still under investigation. However, considering the increasing use of SRS for multiple brain metastases, also more than 10 BM for selected patient, the dose to hippocampus need to be seriously evaluated in the treatment planning.

P003

SURGERY FOLLOWED BY HYPOFRACTIONATED RADIATION THERAPY, WITH CONCURRENT AND ADJUVANT CHEMOTHERAPY IN NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME: A PHASE II STUDY

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Aims: To prospective evaluate outcome of newly diagnosed glioblastoma multiforme patients treated with maximal surgical resection, hypofractionated radiation-therapy (HRT), with concurrent and adjuvant Temozolomide.

Methods: Patients 18-70 years old, Karnofsky performance scale (KPS) ≥70, and tumor up to 10 cm were included. Surgery was performed in all patients with the aim to maximally remove the tumor. Extent of resection was defined as gross-total-resection(GTR) if >99%, near-total-resection(NTR) 90-99%, subtotal-resection(STR) ≤89%. HRT consisted in 60 Gy/4Gyfraction/15fractions. All patients received concurrent and adjuvant TMZ. Clinical outcome was assessed by neurological examination, neuropsicological evaluation and MRI, at 1 months after CHT-HRT and every 2 months thereafter. Response was recorded using the Response Assessment in Neuro-Oncology (RANO) working group

Results: We are showing an interim evaluation of the first 49 patients treated. GTR was performed in 16(32.65%) patients, NTR in 15(30.61%), STR in 9 (18.37%), and biopsy in 9 (18.37%). Following surgery, 47 (95.92%) patients received concurrent chemo-hypofractionated-radiotherapy and adjuvant TMZ for a median of 6 cycles. No severe peri-operative morbidity occurred and during RT neurological status remained stable. No Grade III-IV radionecrosis occurred. Hematologic toxicity was recorded in 6/48(12.5%) patients. The median follow up time was 16.9 months (range 12.4-25.6 months); the median and 1-year PFS was 12.2 months and 50.63%; the median and 1 year OS 15.4 months and 71.4%. KPS and the EOR were recorded as significantly conditioning survival.

Conclusions: Surgical resection followed by hypofractionated radiation therapy with concurrent and adjuvant Temozolomide is a safe and feasible treatment with promising perspectives.

P004

HYPOFRACTIONATED RADIOTHERAPY FOR GLIOBLASTOMA: PATTERNS OF CARE SURVEY FROM THE APULO-LUCANO AIRO INTERGROUP

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Aims: Hypofractionated radiation (HFRT) is emerging as a safe and equally effective treatment option for adult and elderly glioblastoma (GBM). To asses the routinary use of HFRT in the treatment of GBM the Apulo-Lucano AIRO (Italyn Association of Radiation Oncology) Intergroup collected data retrospectively from the Apulia' and Lucania' centres about patients treated from 2005 to 2010.

Methods: Questionnaires on patterns of care of GBM were sent to all the Radiation Oncology Centres of Puglia and Lucania. Data on age, PS, prognosis, fractionation, use of chemotherapy (CT), local control, toxicity and survival were requested.

Results: A total of 7 out of 8 regional centers answered to the questionnaire. Of the about 600 treated pts from 2005 to 2010 only 85 pts (14%) had HFRT with this distribution: Brindisi 20 pts, Lecce 20 pts; Bari 15 pts; Rionero in Vulture 10 pts; Barletta 9 pts; San Giovanni Rotondo 9 pts; Taranto 2 pts. Data are available for 75 out of 85 pts. Median age was 69 years (range 41-86); male/female ratio was 37/38; PS ECOG was>2 in 13 pts (18%). RPA class was IV in 57 pts (76%); V in 18 pts (24%). Histology of GBM was confirmed in 75 pts (87%) by surgery or biopsy (8 pts). Ten pts did not receive surgery. In all cases 3D conformal radiotherapy (RT) was applied using coplanar and no–coplanar MLC customized photons beams. The most used hypofractionated schedules were 266cGy x 15 (43%); 300cGy x 10-15 (47%); 250cGy x 15-20 (10%). Chemotherapy with Temozolomide (75 mg/m2/daily) was delivered concomitantly with RT to 57 pts (75%). Induction (1-3 cycles) or adjuvant CT (150-200 mg/m2 x 5 days montly) was given respectively before and after concomitant radiochemotherapy to 11 out of 56 pts and to 20 out of 56 pts. Radiation was suspended or finally interrupted in 11 pts out of 75 (14.5%); concomitant CT was suspended in 3 pts out of 57 (5%). Mean time between surgery or biopsy to start of RT was 57.5 days (range 20-183); mean treatment time was 20.9 days (range 10-35). No significant short term toxicity was observed for RT. Survival data are available only for 61 pts. Four pts are still alive after 8, 14, 26, 27 months after beginning RT. Mean survival is 10 months and 20 pts have been living longer than one year.

Conclusions: This survey confirms that HFRT for GBM is a pragmatic new treatment paradigm in poor-risk patients according to published results. HFRT has been given to 14% of GBM pts in Apulia and Lucania without significant toxicity.

P005

DO EGFR, KRAS AND ALK MUTATIONS IMPACT THE RESPONSE TO RADIOSURGERY IN PATIENTS WITH 1-3 BRAIN METASTASES FROM NON SMALL CELL LUNG CANCER (NSCLC)?

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Aims: Aim of the study was to evaluate outcomes and correlation to molecular status of exclusive radiosurgery (SRS) using Tomotherapy® with a non invasive approach in patients (pts) with brain oligometastases from NSCLC.

Materials and Methods: Between 2008 and 2015 68 pts with brain oligometastastases from NSCLC underwent SRS.Thirty-seven pts were male, while 31 female. Mean age was 64. Sixty-three pts were in RPA class 1-2,2 pts were in RPA class 3.Primary tumor was histologically-confirmed for all pts:57 had adenocarcinoma,6 pts SCC,3 pts Giant cell Carcinoma and 3 atypical neuroendocrine tumours.Molecular assessment (KRAS, EGFR,ALK status) was available in 43 pts. At time of SRS brain was the only site involved in 47pts, while 22 had also extracranial disease. Pre-SRS MRI showed supratentorial lesions in 55pts, 9 had subtentorial disease while 4 pts had both.Forty-nine pts had only 1 brain lesion,12 had 2 and 7 had three.All pts underwent single fraction SRS using Tomotherapy®, median dose delivered was 19 Gy (ICRU83).

Results: After a mean follow up of 14 months,15 pts were alive,whereas 53 pts had died.Complete response was demonstrated in 4 pts,partial response in 36,stable disease in 13 and progression of disease in 8 cases.In 2 pts imaging post-SRS was not performed due to rapid clinical deterioration. Overall response rate was 84%.One and two-years overall survival (OS) was 43%(±6,2%ES) and 27%(±5.8%ES), respectively.At univariate analysis class RPA 1 and 2, histology and response to SRS showed a statistically significant impact on OS with worse prognosis for pts in RPA class 3, with giant cell carcinoma and progression after SRS.At the same interval local control was 59.9%(ES±7.6) and 33.1%(ES±8.7) and progression-free survival was 24.6%(ES±5,5) and 11.7%(ES±4,7%). Thirty-four pts showed intracranial relapse (with 50% of "in field" failure); 79.4% pts experienced extracranial progression, whereas 32,3% experienced both. Better outcomes in terms of OS were observed for those pts with EGFR mutation, while KRAS wild-type pts seem to show a better 1 year LC compared to those expressing genetic mutation (56.4% Vs 23.7). Three pts developed symptomatic radionecrosis.

Conclusions: SRS using Tomotherapy® proved to be a feasible non invasive approach for pts with brain oligometastases from NSCLC and a good prognostic score.Molecular assessment may allow a better selection of pts who may benefit from treatment with targeted therapy even in a concurrent setting.

P006

ACCELERATED-HYPOFRACTIONATED INTENSITY-MODULATED RADIOTHERAPY PLUS TEMOZOLOMIDE IN PATIENTS WITH GLIOBLASTOMA: A PHASE I DOSE-ESCALATION STUDY (ISIDE-BT-3)

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Aims. We performed a dose-escalation trial to determine the maximum tolerated dose (MTD) of Volumetric Modulated Arc Therapy (VMAT) with standard concurrent and sequential-dose temozolomide (TMZ) in patients with resected glioblastoma multiforme.

Methods. Histological proven glioblastoma patients underwent VMAT dose escalation. VMAT was delivered over 5 weeks with the simultaneous integrated boost (SIB) technique to the two planning target volumes (PTVs) defined by adding 5-mm margin to the respective clinical target volumes (CTVs). CTV1 was defined by adding a 10-mm isotropic margin to the tumor bed plus any MR enhancing residual lesion; CTV2 was defined as the CTV1 plus 20-mm isotropic margin. Radiation dose was escalated to the PTV1 with the SIB-VMAT strategy. Two dose levels were planned: Level 1 (PTV2: 45/1.8Gy; PTV1: 72.5/2.9Gy) and Level 2 (PTV2: 45/1.8Gy; PTV1: 75/3Gy). All treatments were delivered in 25 fractions. Patients were treated in cohorts of between three and six per group using a Phase I study design. The recommended dose was exceeded if two of the six patients in a cohort experienced dose-limiting toxicity within 3 months from treatment. Concurrent and sequential TMZ chemotherapy was administered according to Stupp's protocol.

Results: Seventeen consecutive glioblastoma patients [male/female: 7/10; median age: 58 years) were treated. Six patients were treated at first dose level, with one of them experiencing a dose-limiting toxicity (DLT) (grade 3 neurological toxicity with seizures requiring hospitalization). Being the MTD not exceeded, the PTV1 dose was escalated to the highest planned dose level (75/3 Gy) and 11 patients were treated without any further DLT. After a median follow-up time of 7 months, no grade >2 late neurological toxicity was recorded.

Conclusions: The SIB-VMAT technique was found to be feasible and safe at the recommended doses of 45Gy to PTV2 and 75Gy (biological effective dose – BED - of 150 Gy, alpha/beta 3) to PTV1 in the postoperative treatment of patients with glioblastoma.

P007

TARGET THERAPIES (TTS) AND RADIOSURGERY (RS) OR FRACTIONATED STEREOTACTIC RADIOTHERAPY (FSRT) IN BRAIN METASTASES (BMS) FROM RENAL CELL CARCINOMA

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Aims: To retrospectively evaluate the effect of TTs on brain control (BC) and overall survival (OS) in patients (pts) with 1-4 BMs from renal cell carcinoma (RCC) submitted to RS or FSRT.

Methods: 46 pts with 74 BMs were treated. Male/female ratio was 31/15, median age was 62y (range, 29-76). Median KPS was 100% (range, 50-100), 14 (37%), 27 (59%) and 2 (4%) pts were in RPA class 1, 2 and 3, respectively, and 37 (80%) pts had extracranial metastases. Systemic disease was absent or controlled in 28 (61%) and in progression in 18 (39%) pts. In the majority of pts (41, 89%) neurologic functional score (NFS) was good (0-2). Median number of irradiated BMs per patient was 1 (range, 1-4). 37 (80%) pts with 63 BMs (85%) received RS at a median dose of 20Gy (range, 15-25). Remaining 9 (20%) with 11 lesions (15%) underwent FSRT at a dose of 5x6-7Gy. 23 (50%) pts received TTs (i.e., sunitinib, sorafenib, pazopanib, mTOR inibitors, and/or bevacizumab), 18 (78%) before and after RS or FSRT of BMs, remaining 5 (22%) only after. TTs were stopped 7-10 days before and started again 7-10 days after RS or FSRT.

Results: At a median follow-up of 19 months (range, 1-51), 41 (89%) pts with 66 (89%) BMs were evaluable. Local control was obtained in 96% of BMs: there were complete remission in 29 (44%), partial remission in 25 (38%), stable disease in 9 (14%), and progression in 3 (4%) BMs. During follow up, 21 (51%) pts had no brain progression, 4 (10%) had in-field relapse, 15 (37%) out-field relapse, and 1 (2%) in- and out-field relapse. Of 20 (49%) relapsing pts, 14 (70%) were retreated with RS, surgery, WBRT and FSRT (8, 3, 2 and 1, respectively). In-field and out-field relapse occurred after a median time of 21.5 and 8 months, respectively. At the time of analysis, 39/41 pts (95%) had died, 9 (22%) for brain progression, 30 (73%) for systemic progression. Median OS from irradiation was 61% (+/-7%) at 12 and 30% (+/-7) at 24 months, 15 versus 19 months in the no-TTs versus TTs pts, respectively (P=n.s.). Median duration of BC was 24 months (range, 3-51), without significant difference between no-TTs and TTs pts. No high grade iatrogenic

toxicity was registered.

Conclusions: RS and FSRT of BMs in RCC pts submitted also to TTs did not result associated to iatrogenic toxicity. Response and duration of BC was not conditioned by TTs. The 7-10 days of TTs interruption before and after irradiation could be omitted and RS or FSRT done concurrently with TTs.

P008

HYPOFRACTIONATED IMRT FOR BRAIN METASTASES WITH TRI-COBALT 60 VIEWRAY SYSTEM: DOSIMETRIC EVALUATIONS BY AN IN SILICO STUDY

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Aims: View Ray System is a new teletherapy system equipped with 3 rotating 60Co sources for IMRT and magnetic resonance imaging (MRI) for real-time vision of target volume (TV). To date, few dosimetric studies are available. The purpose of this in silico study was to evaluate the dosimetric impact of this equipment on hypofractionated IMRT in brain metastases (BM). In particular, we evaluated the impact of number of beams and PTV margins' decrease on TV, organ at risk (OAR) and normal brain.

Methods: Radiotherapy plans were structured with a mono-isocentric IMRT technique using 9, 15, 21, 42 and 63 beams. Margin to PTV was reduced from 3 to 0 millimeter for each arrangement of beams. The prescription of the dose followed ICRU 83 indication and it was fixed as 25.5 Gy in 3 fractions. Plans were considered acceptable when median absorbed dose of PTV, D50%, was equal to prescription dose, D98% was ≥ 95%, and D2% to optic chiasm and optic nerves, brainstem and normal brain were <19,5Gy, <23Gy and <21Gy, respectively. D50% of normal brain and to hippocampus were setted as low as possible. The plans were evaluated for TV coverage, dose conformity (CI), homogeneity (HI), dose to organ at risk (OAR) and to normal brain. Dosimetric comparisons between plans were performed using Wilcox test.

Results: In all, 16 brain metastases were evaluated and 320 plans were available. The median PTV was 2,3 cc (range 0.3-19.5cc). No difference was observed in HI. A higher CI was found with the reduction of the PTV margin (p: 0.001). Median volumes of 100%- and 50% isodoses were 1.2cc and 73.9cc respectively and both shrank with PTV margin (p=0.001). For the OAR, by lowering PTV margin from 3mm to 0mm there was a significant D2% reduction to the optic chiasm (0,62 Gy vs 0,44 Gy; p: 0.007), optic nerves (0,58 Gy vs 0,34 Gy; p: 0.003), brainstem (0,99 Gy vs 0,64 Gy; p: 0.004) and normal brain (17,73 Gy vs 15,13 Gy, p: 0.001). Moreover, PTV margins' change had an impact on D50% of normal brain and to hippocampus (Table 1). No significant statistical difference was observed for beams' number on TV and on sparing normal tissues. Time of exposure was not different between plans.

Conclusions: IMRT plans using the tri-60Co View Ray System are feasible according to ICRU 83. The benefit of real-time MRI-guided should allow the optimization of tumor targeting while reducing normal tissue irradiation. An ongoing study is comparing ViewRay versus LINAC-based plans in this subset of patients.

Table 1. Dosimetric Parameters according to PTV margins.

Dosimetric Parameters	PTV Margin GTV + 3mm	GTV + 2mm	GTV + 1mm	GTV	p-value
PTV (cc)	4 (1,7 - 19,5)	2,5 (1 - 15,8)	1,7 (0,6 - 12)	1,1 (0,3 - 8,9)	
Homogeneity Index	0,06 (0,04 - 0,09)	0,06 (0,03 - 0,07)	0,06 (0,02 - 0,08)	0,06 (0,01 - 0,07)	p: 0.099
Paddick Conformity Index	0,5 (0,1 - 2,1)	0,8 (0,1 - 2)	1,2 (0,1 - 5,7)	1,8 (0,2 - 6,6)	p: 0.001
Time exposure (sec)	6,2 (3,3 - 17,5)	6,74 (2,8 - 16)	6,8 (3,6 - 15,6)	6,45 (3,18 - 22,6)	p: 0.2
V100 (cc)	2 (0,8 - 10)	1,3 (0,5 - 8,3)	0,8 (0,3 - 6,8)	0,6 (0,2 - 5,1)	p: 0.001
V50 (cc)	90,5 (40,2 - 214,5)	73,4 (34,9 - 209,5)	65,7 (29 - 185,3)	54,4 (0,6 - 179)	p: 0.001
D2 % brainstem (Gy)	0,9 (0,3 - 20,3)	0,7 (0,3 - 17)	0,7 (0,2 - 16,1)	0,6 (0,1 - 16,6)	p: 0.004
D2 % optic chiasm (Gy)	0,6 (0,3 - 19,4)	0,6 (0,2 - 18,6)	0,5 (0,2 - 18,3)	0,4 (0,2 - 19)	p: 0.007
D2 % optic nerves (Gy)	0,5 (0,2 - 19,4)	0,5 (0,2 - 17,9)	0,4 (0,1 - 19,3)	0,3 (0,18 - 19,2)	p: 0.003
D2 % normal brain (Gy)	17,7 (12 - 21)	16,2 (11,9 - 21)	16,3 (10,5 - 20)	15,1 (9,8 - 19,9)	p: 0.001
D50% normal brain (Gy)	3,2 (1,6 - 4,8)	2,8 (1,3 - 4,6)	2,7 (1,3 - 4,3)	2,2 (0,8 - 4,3)	p: 0.001
D50 % hippocampus (Gy)	1,7 (0,3 - 15)	1,3 (0,3 - 15,9)	1,3 (0,2 - 10,1)	1,3 (0,2 - 12,1)	p: 0.044

Data are presented with median and range in brackets.

P009

OUTCOME EVALUATION OF OLIGOMETASTATIC PATIENTS TREATED WITH SURGICAL RESECTION FOLLOWED BY HYPOFRACTIONATED STEREOTACTIC RADIOSURGERY (HSRS) ON THE TUMOR BED, FOR SINGLE, LARGE BRAIN METASTASES

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Aims: The aim of this study was to evaluate the benefit of a combined treatment, surgery followed by adjuvant hypofractionated stereotactic radiosurgery (HSRS) on the tumor bed, in oligometastatic patients with single, large brain metastasis (BM).

Methods: Fom January 2011 to March 2015, 69 patients underwent complete surgical resection followed by HSRS with a total dose of 30Gy in 3 daily fractions. Clinical outcome was evaluated by neurological examination and MRI 2 months after radiotherapy and then every 3 months. Local progression was defined as radiographic increase of the enhancing abnormality in the irradiated volume, and brain distant progression as the presence of new brain metastases or leptomeningeal enhancement outside the irradiated volume. Surgical morbidity and radiation-therapy toxicity, local control (LC), brain distant progression (BDP), and overall survival (OS) were evaluated.

Results: The median preoperative volume and maxi-

mum diameter of BM was 18.5cm3 (range 4.1-64.2 cm^3) and 3.6cm (range 2.1-5-4 cm); the median CTV was 29.0cm3 (range 4.1-203.1 cm^3) and median PTV was 55.2cm3 (range 17.2-282.9 cm^3). The median follow-up time was 24 months (range 4-33 months). The 1-and 2-year LC in site of treatment was 100%; the median, 1-and 2-year BDP was 11.9 months, 19.6% and 33.0%; the median, 1-and 2-year OS was 24 months (range 4-33 months), 91.3% and 73.0%. No severe postoperative morbidity or radiation therapy toxicity occurred in our series.

Conclusions: Multimodal approach, surgery followed by HSRS, can be an effective treatment option for selected patients with single, large brain metastases from different solid tumors.

P010

HYPO-FRACTIONATED STEREOTACTIC RADIOTHERAPY ALONE USING VOLUMETRIC MODULATED ARC THERAPY (VMAT) FOR PATIENTS WITH SINGLE, LARGE BRAIN METASTASES UNSUITABLE FOR SURGICAL RESECTION

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Aim. Hypo-fractionated stereotactic radiotherapy (HSRT) is emerging as a valid treatment option for patients with single, large brain metastases (BMs). We analyzed a set of our patients treated with HSRT. The aim of this study was to evaluate local control (LC), brain distant progression (BDP), toxicity and overall survival (OS).

Methods. From July 2011 to May 2015, 102 patients underwent HSRT consisting of 27Gy/3fractions for lesions 2.1-3 cm and 32Gy/4 fractions for lesions 3.1- 5 cm. Local progression was defined as increase of the enhancing abnormality on MRI, and distant progression as new brain metastases outside the irradiated volume. Toxicity in terms of radio-necrosis was assessed using contrast enhanced T1MRI, T2 weighted-MRI and perfusion- MRI.

Results. The median maximum diameter of BM was 2.9 cm (range 2.1-5cm), the median gross target volume (GTV) was 16.3 cm^3 and the median planning target volume (PTV) was 33.7 cm^3. The median,1,2-year local control rate was 30 months, 96%, 96%; the median, 1-2-year rate of BDP was 24 months, 12%, 24%; the median, 1,2-year OS was14 months, 69%, 33%. KPS and controlled extracranial disease were associated with significant survival benefit ($p<0.01$). Brain radio-necrosis occurred in 6 patients (5.8%)

Conclusions. In patients with single, large BMs unsuitable for surgical resection, HSRT is a safe and feasible treatment, with good brain local control and limited toxicity.

P011

COMPARATIVE EVALUATION OF TWO DIFFERENT RADIOSURGERY MODALITIES IN BRAIN METASTATIC PATIENTS FROM SEVERAL SOLID TUMORS

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Aims: For limited brain disease the treatment choice is radiosurgery(RS) that obtain a local control in 90% of patients. Different technological modalities have been used:Gammaknife, Cybernife, Linac with comparable results and different incidence of symptomatic radionecrosis.To date no comparative randomized studies have been published in this matter. We draw this randomized study with the aim to evaluate incidence of symptomatic radionecrosis, local control (LC) rate and patients overall survival using two different modalities of RS, gammaknife vs linac.

Methods: The present prospective phase III study includes patients with limited BMs (up to 4) treated with RS. Inclusion criteria were a KPS ≥70, RPA class I-II, maximum diameter <3 cm and/or a total tumor volume <30 cc.The total dose delivered was 24 Gy at 50% isodose for BMs ≤ 20 mm or <4.2 cc, 20 Gy for BMs 21-30 mm or volume <14.1 cc for Gamma Knife RS and 24 Gy at mean dose to PTV for LINAC RS.Outcome evaluation consisted of physical examination and brain MRI performed every 3 months.Local progression was defined as radiographic increase of the enhancing abnormality in the irradiated volume on serial MR imaging, and distant failure by the presence of new brain metastases or leptomeningeal enhancement outside the irradiated volume. Suggestive of radionecrosis was considered the presence of central hypodensity and peripheral enhancement on T1-weighted post-contrast imaging, with edema on T2-weighted sequences and a clear lack of perfusion without any nodular highly vascularized area within the contrast enhanced lesion on perfusion MRI.

Results: This is a preliminary evaluation of the first 50 consecutives patients enrolled, for 77 BMs treated.The most common primary cancers was NSCLC (52%).BMs were present at diagnosis in 9 patients (18%), whereas they developed in 29 (58%) after primary tumor treatment. Radionecrosis was observed in 2 patients treated with gamma knife at a median time of 3 months. No symptomatic radionecrosis was recorded in Edge arm.At the last observation time 1 local progression in site of RS occurred.Four (8%) patients had new distant brain metastases, at a median time of 4 months (range 3-8 months), and 4 patients had extracranial progression.The 6 months and 1 year PFS were 100% and 95.2% and the 6 months and 1 year OS 86% and 80%.Comparable in both arms.

Conclusions: Gamma-knife and LINAC RS are comparable in terms of LC.The risk of radionecrosis is greater in GK arm.

P012

THE ROLE OF HYPOFRACTIONATED RADIOTHERAPY ASSOCIATED WITH BEVACIZUMAB IN PATIENTS WITH RECURRENT GBM: PRELIMINARY RESULTS

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Aims: Glioblastoma (GBM) is considered the most common malignancy of the Central Nervous System (CNS). Although surgical resection followed by radiotherapy (RT) with concomitant and sequential chemotherapy with Temozolomide represents standard upfront treatment, there is no consensus about the relapsed disease. Salvage surgery, chemotherapy (CT) and radiotherapy are often used as second-line treatments although no real clinical benefit has been confirmed yet. With this aim, we reported the results of a monoinstitutional experience studying the association of salvage radiotherapy and the antiangiogenic agent bevacizumab in patients with recurrent GBM.

Methods: from May 2010 to April 2016, we recruited 8 patients with recurrent GBM in our prospective study. After surgical resection, all patients have been given radiochemotherapy (RTCT) ± adjuvant TMZ according to the Stupp protocol. Hypofractionated RT (25 Gy in 5 fractions) was prescribed to active lesions without any clinical margins. Bevacizumab 7.5 mg/kg was administered the first day of radiotherapy and continued every 2 weeks until disease progression.

Results: Median age and KPS were 57 years (range 46-76) and 75 (range 70-90), respectively. Median follow-up was 18,5 months. After disease recurrence and before salvage RT, 7 patients have been given second-line CT and 3 patients underwent second surgery with histological confirmation of recurrent GBM. One patient was enrolled after the diagnosis of GBM recurrence. The median Kaplan Meier estimate survival after the diagnosis of disease recurrence was 16 months and the overall survival from the beginning of hypofractionated radiotherapic treatment was 4 months. Median Planning Target Volume (PTV) was 41.1 cm^3 (range 5.5-144.9). All patients showed an appreciable KPS improvement following treatment and reduced the corticosteroid dose. Three patients (37.5%), with a PTV greater than 25 cm^3, developed radionecrosis. No toxicities related to bevacizumab greater than grade 2 have been registered. At the analysis, 4 patients were still alive and undergoing maintenance therapy with Bevacizumab.

Conclusions: Hypofractionated RT associated with Bevacizumab in patients with recurrent GBM could represent a valid therapeutic choice with increased OS and improved KPS. Further studies a higher number of patients are required in order to confirm our findings.

P013

RADIOSURGERY (SRS) AND STEREOTACTIC RADIOTHERAPY (SRT) WITH CYBERKNIFE® SYSTEM FOR BRAIN METASTASES (BMS) ACCORDING A NEW PROGNOSTIC CLASSIFICATION SYSTEM DIAGNOSIS-SPECIFIC GPA (DS-GPA): MONOISTITUTIONAL EXPERIENCE

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Aims: Brain metastases (BMs) occur in approximately 20-40% of cancer patients (pts). Pts with BMs typically have a poor prognosis with a median survival of 3-6 months. For choosing the best treatment might be useful to select pts using the prognostic classification system. Sperduto et al reviewed the Graded Prognostic Assessment (GPA) (based on age, KPS, number of BMs, and presence or absence of extracranial metastases) in relation to primary tumor type creating a new index DS-GPA. The aim of our study is to evaluate retrospectively the median overall survival (OS) according to DS-GPA in BMs pts treated with SRS/SRT using Cyberknife® (CK) system.

Table 1.

	N patients	DS-GPA 0-1 Median OS (mo)	DS-GPA 1.5-2 Median OS (mo)	DS-GPA 2.5-3 Median OS (mo)	DS-GPA 3.5-4 Median OS (mo)	Median OS(mo)	Median OS (mo) Sperduto Trial
NSCLC	107/109 (2 pts not evaluable)	2 (11 pts)	5 (52 pts)	9 (36 pts)	8 (8 pts)	7	7
Melanoma	58/59 (1 pts not evaluable)	3 (1pts)	3 (6 pts)	7 (24 pts)	11 (27 pts)	8	6.7
Renal cell	11	2 (1pts)	3 (3 pts)	12.5 (4 pts)	6 (3 pts)	3	9.6
GI cancer	15	2 (1 pts)	7 (4 pts)	3 (4 pts)	12 (7 pts)	6	5.4
Breast cancer	52	/ (0 pts)	4 (7 pts)	9 (17 pts)	17 (12 pts)	8	13.8
SCLC	5					6	4.9
Total	248					7	7.2

Methods: From November 2012 to may 2016, we treated 284 pts (149 M, 135 F), median age 61.5 years (range 6-88). The primary tumors were: 109 Non small cell lung cancer (NSCLC); 5 small cell lung cancer (SCLC); 52 Breast cancer; 59 melanoma; 11 renal cell; 15 gastro intestinal cancer (GI); 4 head&neck (H&N); 14 gynecologic cancer; 7 bladder cancer; 7 other. We treated 551 BMs, average size 12,5 mm, 436 with a single fraction (fx) (10-24Gy), 7 with two fx (18-24Gy), 100 with three fx (18-30Gy), 8 with five fx (20-27.5Gy). The dose was prescri-

bed to 80% isodose line. We calculated the median OS stratifying the pts according to DS-GPA.

Results: The median Follow-up was 6 months (range 2-42). Median OS of all 284 pts was: 7 months (range 0-42). We calculated the median OS of 248 pts (NSCLC, SCLC, breast, melanoma, renal cell and GI cancer) stratify according to DS-GPA comparing our results with those of Sperduto trial. (Table 1). The median OS was 7 vs 7 months in NSCLC, 8 vs 6.7 months in Melanoma, 3 vs 9.6 months in renal cell carcinoma, 6 vs 5.4 months in GI cancer, 8 vs 13.8 months in breast cancer, 6 vs 4.9 months in SCLC in our experience and in Sperduto trial respectively.

Conclusions: our results in terms of median OS of all pts that the individual groups are similar or in some cases higher than those of Sperduto trial. Our study confirms the precious contribution of DS-GPA in correct selection of pts with BMs for the choice of the best treatment, and encourage the use of special technologies in properly selected pts.

P014

FRACTIONATED STEREOTACTIC RADIOTHERAPY IN THE TREATMENT OF MENINGIOMAS

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Aims: Over the past several years, the development of innovative radiotherapy techniques had afforted new opportunities in brains tumors. One of these innovations is fractionated stereotactic radiotherapy (FSRT) that is useful to treat tumor target with high precision and minimize radiation dose to normal tissues. We report our experience in the treatment of meningiomas with FSRT.

Methods: From March 2005 to November 2015, at the Radiotherapy Department of "Casa Sollievo della Sofferenza" General Hospital of San Giovanni Rotondo (Italy) 37 patients (22 female, 15 male) with 37 lesions underwent FSRT: 27 meningiomas, 2 meningiomatosis and 8 recurrences of meningioma. The median age was 63 years (range 23-79 years). Patients were immobilised by a BrainLab relocating stereotactic frame. Target volume definition was performed on MR images co-registered with the localisation CT. The treatment was delivered by a micro-multileaf collimator system and a 6 MV linear accelerator. Treatment plans included noncoplanar dynamic fields with uniform-intensity beams (1 isocenter, 4-9 arcs approximately 100° per arc). For each plan the dose-volume histogram was calculated for the planning target volume (PTV) and organs at risk (OR). The three-dimensional dose distribution was calculated using a computerized BrainLab system. The median treated volume was 13 cm (range 4-34 cm), the median EQD2 margin dose (80% isodose) was 43 Gy (range 11-64 Gy) in 3-28 fractions. The median dose per fraction was 3.5 Gy (range 1.6-6.5 Gy). The choice of treatment schedules depended on the position and on the conformation of the meningiomas.

Results: After a median follow-up of 53 months (range 130-2 months) the overall survival was 80% at five years and 55% at ten years. The disease-specific survival was 91% at five years and 78% at ten years. The univariate and multivariate analysis of survival revealed that male patients (p=0,018) and PTV volumes greater than 10cc (p=0,047) had the worst outcome.

Conclusions: A significant outcome improvement or stable disease was observed in patients treated with FSRT for meningiomas. We suggest this approach as a safe procedure for the management of meningiomas. The compliance was 100% and the treatment was well tolerated by all patients.

P015

CONCOMITANT RADIOCHEMOTHERAPY WITH TEMOZOLOMIDE (TMZ) IN EDERLY PATIENTS (EP) WITH GLIOBLASTOMA (GBM)

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Aims: The optimal strategy of EP with GBM remains debated. RT with TMZ for these patients is unclear and they are often managed with RT alone, TMZ alone or palliative modality. We report our experience of concurrent RT- Chemotherapy with TMZ in elderly GBM patients.

Methods: We analyzed data from medical records of patients>65 years old with pathological diagnosis of GBM in Veneto Institute of Oncology – Padua, and treated with concurrent radio-TMZ therapy. In concomitant setting TMZ dose was 75 mg /m2/die while the adjuvant dose was 150-200 mg/m2/die for 6 cycles. Kaplan- Meier method was used to establish progression – free survival (PFS) and overall survival (OS). Toxicity was assessed according to CTCAE 4.0

Results: We analyzed 60 patients (PTS), 34 males and 26 females; the average age was 70 (range 65-82).Performance status according to ECOG was 0-1 in 35 patients and 2 in 25 patients : a complete resection was performed in 35 pts, partial in 25 pts. Most patients (40) received RT within 6 weeks from surgery while 20 received>6 week (range 7-9). MGMT and IDH1 status when analyzed: MGMT was in 20 pts (46%) and all patients had wild-type IDH 1. A radiotherapy dose of 40 Gy in 15 fraction was administered in 34 pts, 60 Gy in 30 fraction in 26 pts without no significative difference in disease features between the two subgroups. Totally patients, PFS and OS were 9.5 and 12.7 months, respectively. In pts who received RT within 6 weeks from surgery os was 13.7 while 12.4 in those>6 week (p=0.9). 13% of pts had grad 3-4 haematological toxicity, 12% grade 3-4 fatigue,

3% nausea /vomiting. MGMT methylated and complete resection was associated with a longer survival. PFS was 9 vs 10 mont hs (p=0.4) and OS was 11.7 vs 13.7 months (p=0.1) in pts treated with 40 Gy and 60 Gy respectively. About toxicity, haematological 3-4 grade was 9 % vs 23% fatigue was 9% vs 15% nausea /vomiting was 3% vs. 4% in PTS treated with 40 and 60 Gy respectively.

Conclusions: Concurrent RT- TMZ therapy in elderly patients with GBM is an effective and safe strategy . There are no statistically differences in PFS and OS in 40 Gy and 60 Gy radiotherapy subgroups pts although we showed a slight trend for longer as in pts who received 60 Gy even if toxicity was higher in them. No difference in OS between pts receiving RT within 6 weeks or more from surgery.

P016

CLINICAL OUTCOME OF HYPO-FRACTIONATED RADIOTHERAPY IN PATIENTS WITH POOR-PROGNOSIS PRIMARY BRAIN TUMORS: 300 CGY VS 350 CGY PER TEN FRACTIONS. ANALYSIS OF TWO PHASE 2 STUDY

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Aims: To analyze the outcomes of patients with poor prognosis affected by high grade gliomas treated by hypofractionated radiotherapy plus concomitant and adjuvant Temozolomide.

Methods: Patients affected by high grade gliomas with poor-prognosis for poor performance status or gross residual tumor or underwent only to biopsy submitted to hypofractionated radiotherapy (30 Gy vs 35 Gy in ten fractions), were selected for this analyses For clinical Target volume (CTV), gross residual tumor plus surgical cavity and 30 millimeters were considered. Patients received concomitant TMZ (75 mg/mq/die) during the two weeks of radiotherapy. Adjuvant TMZ was administered according Stupp's study. The two treatment groups were matched for: age, gender, histological types (glioblastoma GBM, anaplastic astrocytoma AA, oligodendroglioma/ astrocytoma OA/OD) type of surgery and response to therapy (complete, partial, stable, progression). The outcomes of patients were evaluated in terms of toxicity, local control and overall survival.

Results: Fifty-six patients were selected (31 males; 25 female), the median age was 63 (range, 39-79). They underwent to radiation treatment with a total dose of 30 Gy (30 patients) or 35 Gy (25 patients) in 10 fractions. Twenty-six patients were treated after partial surgical excision (23 GBM, 2 AA, 1 OA) and 30 patients after only biopsy. With a median follow-up of 65 months (range, 3-116), the median local control (LC) was 6 months for the 30 Gy group and 10 months for the 35 Gy group; the 1-year LC rates were 16% and 40% respectively (p=0.12). The median overall survival (OS) was 10 months for the 30 Gy group and 11 months for the 35 Gy group. One-year survival was 39% and 43% respectively (p= 0.25). No significant difference was observed by comparing the LC and the OS with histological types (p=0.7 and p=0.06 respectively), with the response (p=0.3 and p=0.7 respectively), with type of surgery (p=0.3 and p=0.9). Brain edema toxicity G1-2 was observed in 5 patients and seizures toxicity G1 was observed in 2 patients (all in the 35 Gy groups).

Conclusions: Both the hypo-fractionated schedules, 300 cGy or 350 cGy per 10 fractions, are well tolerated and correlate with similar outcomes in this subset of patients; on the base of these date we are planning a new study with a larger sample to confirm and define the optimal fractionation modality.

P017

SAFETY AND EFFICACY OF BEVACIZUMAB CONCOMITANT TO STANDARD RADIOCHEMOTHERAPY IN CHILDHOOD HIGH GRADE GLIOMAS

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Aims: High grade gliomas (HGG) represent approximately 8–12% of all pediatric CNS tumors and are among the most vascularized cancers. The outcomes remain uniformly poor despite multimodality of treatments. Bevacizumab (BVZ) is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A (VEGF-A). Therefore VEGF could plays a important role in this subset of patientis. Poor studies analyzed the impact of BVZ-based therapy in children with HGG. Therefore we planned a study to assess the safety and the efficacy of BVZ concomitant to standard radio-chemotherapy (RT-CT) in childhood HGG.

Methods: Pediatric patients affected by HGG were treated according to standard schedule of Temozolomide (75 mg/mq) concomitant to radiotherapy. Bevacizumab 10 mg/kg was administered 14 days after the start of radiotherapy every two weeks. Radiation therapy included the tumor bulk with surgical cavity, plus a 30-mm margin. The total dose was 35-60 Gy (3.5 Gy/fr - 2 Gy/fr). All patients received sodium valproate during RT-CT. The primary endpoints as safety, toxicity and tolerability were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0. The secondary endpoints were the response, according to the RECIST Guidelines, the overall survival (OS) and the progression-free survival (PFS) calculated by the Kaplan-Mayer method.

Results: From October 2014 to March 2016, 8 patients (M/F: 6/2), with a median age at the time of diagnosis of

14 years (range 4-20), were enrolled. Seven out of eight patients underwent to gross tumor resection and one to biopsy. Three out of eight were anaplastic astrocytoma and 5 glioblastoma. All acute toxicities were reversible. One patients presented hematologic toxicity, grade 4 of thrombocytopenia during adiuvant chemotherapy, 5 months after the end of RT-CT. After RT-CT we observed a very good partial response in 4 patients, partial response in 2, one patient presented progressive disease (PD), one has not yet evaluated. One patient with very good partial response presented PD 5 months after the end of RT-CT. With a median FUP of 7.4 (range 4-15) months, 1 year PFS and OS were 55,6% and 53,3%respectively. Median PFS was not reached and median OS was 14 months.

Conclusions: Combinated treatment with Bevacizumab concomitant to RT-CT is safe and well tolerated. It may prolong the progression free survival of patients with HGG. Further investigation is ongoing.

P018

FRACTIONATED STEREOTACTIC SEQUENTIAL BOOST AFTER STANDARD CHEMORADIATION FOR GLIOBLASTOMA PATIENTS: FEASIBILITY, EFFICACY AND COMPARISON WITH AN HISTORICAL COHORT

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Aims. To assess the effectiveness and the toxicity of a sequential fractionated stereotactic boost in patients underwent concomitant chemo-radiotherapy for Glioblastoma (GBM) and to compare survival outcomes with an historical control group.

Methods. From 2007 to 2013 fifteen patients with GBM (WHO grade IV), 6 cm of maximum diameter, with a good performance: Karnofsky Performance Status (KPS) 80-100, were treated with a fractionated stereotactic radiotherapy (FSRT) boost with total dose of 20 Gy in four fractions following Stupp protocol (partial brain irradiation 60 Gy in 30 fractions with concomitant Temozolomide 75 mg/m^2). Toxicity was scored according to CTCAE 3.0 scale.

Results. At a median follow-up of 25.5 months (10-90), all patients recurred locally resulting in a median progression-free survival (PFS) of 15 months (6-24). Median overall survival (OS) for the experimental group was 28 months (19-36). Acute side effects included only grade 1 local alopecia and headache. One patient was re-operated for radiation necrosis (RN). Comparison with 15 patients matched historical control group showed a significantly better survival for patients treated with FSRT, as median PFS was 15 vs 8 months and median OS 28 vs 14 months. Sequential boost, surgery and O-6-methylguanine-DNA methyltransferase (MGMT) methylation resulted as significant prognostic factors.

Conclusions. A sequential FSRT boost after standard chemo-radiation, in selected GBM patients is well tolerated with poor toxicity. When compared to historical data both overall survival (OS) and progression free survival (PFS) resulted significantly improved in patients treated with a sequential boost.

P019

FEASIBILITY OF VMAT AND FLATTER FILTER FREE DELIVERY FOR BRAIN METASTASES PATIENTS TREATED BY STEREOTACTIC LINAC-BASED APPROACH

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Aims: Stereotactic radiosurgery (SRS) and Hypofractionated stereotactic radiotherapy (HSRT) are technical approaches able to guarantee high conformity and excellent results in terms of local control and tolerability in brain metastases (BM). Aim of the present preliminary study is to evaluate the feasibility and impact of Volumetric Modulated Arc Therapy (VMAT) and Flatter Filter Free (FFF) approach hypofractionated treatments in patients with a limited number of brain metastases.

Methods: From April 2014 to February 2016, 45 patients (23 male and 22 female) with 89 brain metastases (BM) were treated with SRS or HSRT and VMAT - FFF approach. VMAT was used by means of TrueBeamTM(Varian Medical Systems, Palo Alto, CA, USA). Patients eligible for stereotactic treatment showed a number of brain metastases<5, with a size $\leq$ 30 mm, Karnosky Performance Status (KPS) $\geq$ 80 and a life expectancy over 3 months. Median age was 67 (range 23-83), with a median KPS of 90 (80-100). Twenty-eight patients had a diagnosis of lung cancer, 11breast cancer histology, 1 ovarian cancer, 1 endometrioid cancer, 1 bladder cancer, 2 kidney cancer and 1 colon cancer. Magnetic Resonance Imaging (MRI) and Computed Tomography were requested to evaluate Central Nervous System status and Systemic Disease. All patients were stratified according to Graded Prognostic Assessment (GPA). Mean brain metastases number was 2 (range 1-8), median Gross Tumour Volume Brain metastases (GTVBM) and median Planning Target Volume (PTV) were 1.11 cc (range 0.01-57.2 cc) and and 2.96 cc (range 0.45-77.45 cc), respectively. Dose prescription was assessed according to brain metastases volume and anatomical position (i.e. eloquent area). Median dose prescription was 25 Gy in SRS (range 18-25 Gy) and 25 Gy in HSRT

(range 21-35 Gy) with a median number of 3 sessions (range 3-5 sessions).Mean PTV coverage (V95) of 98.5%±1.8 and V107 of 6.74%±18.1, while dose median to PTV was 24.1Gy±3.44. Dose constraint to brain minus PTV, defined as V12Gy<18.2 cc, was 14.5 cc. During treatment, to prevent neurological symptoms, a corticosteroid therapy was prescribed. Patients were evaluated with MRI after 45-60 days by the end of radiation treatment, then every 3 months.

Results: The median follow-up was 8 months (range 3-25 months). A good rate of acute toxicity profile was documented and all patients completed the treatment. We observed a complete radiological response in 15.3% of BM, a partial response in 36.5%, a stable disease in 28.2% and a BM progression in 5.9%; while in 14.1% of BM, radiological response was not evaluated due to patients' expire and 3 patients (with 4 brain metastases) were lost during follow up. A Central Nervous System (CNS) progression (defined as a new BM presentation) was reported in 17 patients. No cases of radionecrosis were found during follow up.

Conclusions: VMAT-FFF approach seemed to be well tolerated during preliminary evaluation. We also observed promising results with 80% of response rate and BM control after this radiosurgical and stereotactic hypofractionated linac based approach. Long follow-up is need to definitively establish the tolerability and the significant impact of stereotactic treatment using VMAT and FFF in brain metastases setting.

P020

HIPPOCAMPAL SPARING IN HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY FOR BRAIN METASTASES. TO CONTOUR OR NOT CONTOUR HIPPOCAMPUS? A DOSIMETRIC STUDY

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Aims: To evaluate hippocampal irradiation in patients treated with hypofractionated stereotactic brain radiotherapy (FSRT).

Methods: We performed a retrospective hippocampal dosimetric analysis on 20 patients with 1-4 brain metastases treated with 24 Gy/3 fractions or 20 Gy/4 fractions using volumetric intensity-modulated arc therapy (VMAT). Original plans did not include hippocampus as avoidance structure in optimization criteria, therefore hippocampus was retrospectively delineated on T1-weighted Magnetic Resonance (MRI) co-registered with planning CT and planning risk volume (PRV) for hippocampus avoidance was generated adding an isotropic 5 mm margin. Hippocampus was defined both as a single (Hu) and as pair organ (Hdx, Hsn). Delineation was performed using as reference RTOG atlas, than revised by neuroradiologist. Assuming an / ratio of 2 Gy, biologically equivalent dose in 2 Gy fractions (EQD2) was calculated. Constraints analyzed were: Dmax<16 Gy, D40%<7.3 Gy, D100%=Dmin<9 Gy. Neurological status (NS) was evaluated at baseline and during follow-up using CTACE 4.0 scale to define memory or other neurologic deficit.

Results: Among constraints analyzed Dmax and D40% have been exceeded in 9/20 cases (20 Gy in 5 cases, 24 Gy in 4). D100% was respected in all cases. Hu Dmax ranged between 17-58.9 Gy with a mean of 30.9 Gy; D40% ranged between 8-13.6 Gy and mean D40% was 13.1 Gy. PRV Hu showed a mean Dmax of 33.4 Gy (range 21-60.5 Gy) and a mean D40% of 10.6 Gy (7.7-13.6 Gy). When considered as pair organ, respectively Hdx and Hsn, mean Dmax was 42.8 Gy (range 29.8-58.9 Gy) and 18.9 Gy (range 16.2-20.2 Gy) while mean D40% was 17.7 Gy (7.6-43.7 Gy) and 9.9 Gy (range 7.4-14.4 Gy). PRV Hdx received a mean Dmax of 30.5 Gy (range 7.7-60.5 Gy) and mean D40% was 16.5 Gy (7.5-36.2 Gy); PRV Hsn received a mean Dmax of 23.5 Gy (range 16.1-28.8 Gy) and a mean D40% of 9.8 Gy (8.8-12.5 Gy). Constraints were not respected in more than 75% of cases both with and without PRV expansion margin. At 3-months follow-up, at least, 13/20 patients were clinically evaluable; NS was investigated in 8/13 patients while missed in 5/13. Neurological deficits occurred in 3/8 patients and 2 of these presented Dmax and D40% exceeding limit.

Conclusions: Hippocampus is often over-irradiated in brain FSRT. Its delineation should be performed especially in case of a certain life expectation where it might occur hippocampal damage and it could be reasonable to pursue the hippocampal saving.

P021

HYPOFRACTIONATED IRRADIATION FOR GRADE IV GLIOBLASTOMA MULTIFORME: A RETROSPECTIVE STUDY

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Aims: Outcomes for patients with glioblastoma multiforme (GBM) remain poor. Survival is further limited in elderly patients and those with poor performance status (PS). For these patients optimal treatment is controversial. The aim of the present retrospective study was to assess the outcomes and toxicity of hypofractionated radiotherapy (HRT) in this subset of patients.

Methods: We retrospectively reviewed 21 patients who received HRT with 3D-conformal technique (3DCRT) for the treatment of newly diagnosed grade IV GBM from july 2007 to april 2016 in our Department of Radiotherapy- Policlinico Umberto I, Rome. The median RT dose was 40 Gy (range 34-45 Gy) with a median fraction size of 266 cGy (range 250-340 cGy) in 15 fractions (range 10-18 fractions).

Results: Of the 21 patients reviewed, 14 (66.6 %) were males. At diagnosis, median age was 64 years (33-91 years). Tree patients underwent gross total resection (14.3%), 14 patients (66.7%) subtotal resection and 4

patients (19%) only biopsy. Five patients (24 %) had pre-RT PS (ECOG) equal to 2, 5 patients (24%) PS 1 and remaining patients PS 0. Eleven patients (52.3%) received concurrent temozolomide (TMZ). All patients completed the irradiation without interruptions due to toxicity. At the median follow-up of 5 months (range 1-10 months), 3 patients (14.3%) had evidence of tumor progression and 18 (85.7%) had died. Median Overall Survival was 5 months (range 1-10 months). The PS during RT and at follow-up was not significantly changed. No severe skin acute or late and CNS toxicity were noted.

Conclusions: With an acceptable toxicity profiles, suggested HRT schedules appear to be a feasible therapeutic option. Short-course radiotherapy with or without TMZ may be a reasonable alternative for patients with poor prognosis, unfit for six weeks of daily irradiation. Prospective studies are needed for further validation of these results, especially with the use of TMZ.

P022

RADIOSURGERY AND STEREOTACTIC RADIOTHERAPY WITH CYBERKNIFE• SYSTEM FOR MENINGIOMAS

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Aims: Aim of our work was to evaluate the impact of Radiosurgery (SRS)/Stereotactic radiotherapy (SRT) with Cyberknife® system in local control, clinical outcome and toxicity in patients with meningioma, according location, size and histological grade of lesion.

Methods: From January 2013 to January 2016, 33 patients (pts), 19 female and 14 male, median age 65 years, affected by intracranial meningiomas were treated with Cyberknife® system in our center. 14 pts (42%) had undergone prior surgery: 10 (30%) received gross total resection and 4 (12%) subtotal resection. 19 (58%) pts were treated for primary meningioma, 14 pts (42%) for recurrence. Clinical target volume (CTV) was the same volume of gross tumor volume (GTV); planning target volume (PTV) was the CTV plus a 2-mm margin in all directions. SRS was used to treat lesions<2 cm, SRT to treat lesions>2 cm or<2 cm near critical site such as optical chiasm, optic pathway, brainstem. Local Control (LC) and clinical outcome in terms of symptomatic resolution were analyzed. A correlation with progression disease (PD) and fractionation was made. Results: 33 pts were evaluated for follow up. Median follow-up was 17 months (range 2-35). Four pts died for progression disease, 2 pts after 5 and 8 months from radiotherapy (RT), and 1 patient after 27 months from RT was submitted to re-surgery and died at 31 months for post-surgical sepsis. 17 pts of 21 with follow-up of almost 12 months are in LC and 3 pts of 7 with follow-up of almost 24 months are in LC. The tumor volume decreased in 7 pts (21%) at median time of 19 months after end of treatment, was unchanged in 18 pts (55%) at median time of 12 months, and increased in 7 pts (21%) at median time of 17 months. We haven't any data imaging of patient who died at 8 months. PD not seems to be related to the fractionation. At baseline 30/33 pts (91%) were symptomatic with visual changes in 14/33 patients (42%), motor disorders in 12/33 pts (36%) and hearing disorders in 4/33 pts (12%). None acute neurological symptoms related to RT were reported. An improvement of visual functions was observed in 4 pts, complete resolution in 3 pts, improvement of motility in 3 pts, resolution in 3 pts, improvement of hearing disorders in 2 pts, resolution in 2 pts. (Tab.1)

Conclusions: Our experience confirm that SRS/FSRT with Cyberknife system allows a good disease control and improves, in a limited number of pts, visual, hearing and motor symptoms.

Table 1 Clinical outcome.

Symptoms	Pre-RT	Resolved	Improved	Unchanged	Worsened	New
visual function	14	3	4	4	2	1
headache	6	4	0	2	0	2
epilepsy	4	2	0	1	1	1
hearing disorders	4	2	2	0	0	2
motor disorders	12	5	3	3	1	3
memory	2	1	1	0	0	2
speaking disorders	1	1	0	0	0	0

P023

WHOLE BRAIN WITH HIPPOCAMPAL AVOIDANCE AND SIMULTANEOUS INTEGRATED BOOST FOR PATIENTS WITH ONE TO THREE BRAIN METASTASES: A PHASE I-II TRIAL

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Aims. Firstly, to evaluate the feasibility of using Tomotherapy to deliver whole brain radiotherapy with hippocampal avoidance (WBHA) and Simultaneous Integrated Boost (SIB) in terms of acute toxicity and then to assess the impact on quality of life (QOL) and neurocognitive functions (NCF). Secondly to evaluate intracranial tumor control and survival outcomes for patients (pts) with one to three brain metastases (BM).

Methods: Inclusion criteria where as follows: pts with radiological diagnosis of BM, KPS ≥ 70%, with 1 to 3 metastases, diameter ≤ 3 cm, absent or controlled extracranial disease. Pts.received 30Gy/10 fr to the WBHA

and 40Gy/10 fr as SIB to the BM. Toxicity was scored according to CTCAE 4.0. QOL and NCF were measured by SF 36 questionnaire and standardized neuro-cognitive tests as MMSE, Digit Span (forward and backward), Trail Making Test, Verbal Fluency Test by Novelli, The Auditory Verbal Learning Test (AVLT) by Rey, Rey complex Figure, Beck Depression Inventory, respectively. Radiological response was evaluated by contrast fMRI.

Results. From September 2014 to March 2016, 14 pts were enrolled. Pts characteristic were as follows: male/female 4/10; median age 62 yrs (50-72); median KPS 100% (70-100); median GPA class 2.5 (1.5-3.5); primary tumor was lung in 10 pts and breast in 4; BM total number: 29; site of BM: frontal 10, occipital 5, parietal, temporal and cerebellar 4 each, other sites 2. Eight pts received cisplatin-based chemotherapy and four TK or ALK inhibitors. Hippocampal dosimetric parameters were: right hippocampus: mean volume 1.28 cc (0.8-2.13), median Dmax 16.1 Gy (14.4-21.2), median D100% 10.2Gy (9-17); left hippocampus: mean volume 1.21 cc (0.8-2.15), median Dmax 15.9 Gy (13.8-20), median D100% 10.1Gy (9-15). All pts except one (93%) completed the scheduled treatment. No patient experienced severe acute toxicity; one pt discontinued radiotherapy due to sepsis that was unrelated to the treatment. Among eight pts who had at least a minimum of 3-months follow-up, so that evaluable for radiological response, only one experienced treatment failure (disease progression).

Conclusions. Preliminary results of this prospective study seem to show the feasibility of this treatment in terms of acute toxicity. Our purpose is to recruit a total of 25-30 pts to define the impact on neuro-cognitive sphere and its effectiveness in terms of brain disease control.

P024

RELATIONSHIP BETWEEN RECIST AND WHO CRITERIA IN RESPONSE EVALUATION FRACTIONATED STEREOTACTIC RADIOTHERAPY OF BRAIN METASTASIS

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Aims: To evaluate the agreement between WHO (World Health Organization) and RECIST (Response Evaluation Criteria In Solid Tumors) criteria for response evaluation in patients with brain metastases treated with fractionated stereotactic radiotherapy (FSRT).

Methods: We prospectively observed 26 patients with brain metastases from different primary tumors (breast, lung, colorectal), treated with FSRT from february 2015 to march 2016. Patients presenting 1-4 brain metastasis, aged<70 years and with a Karnofsky Performance Status (KPS) of 70-100 were included. Patients were treated with VMAT (Volumetric Modulated Arc Therapy) radiotherapy technique, using two different schedules, 20 Gy in 4 fractions (5 Gy/day) or 24 Gy in 3 fractions (8 Gy/day). For all patients a baseline MRI was performed before starting FSRT; to evaluate treatment response MRI was acquired 3 months after the end of FSRT, every 3 months during the first year of follow-up, then every 6 months. Response to treatment was evaluated considering changes both in larger tumor diameter according to RECIST criteria and 2 larger diameters according to WHO criteria, measured at each MRI control on T1 sequences.

Results: To date 13/26 patients were evaluable for tumor response at least at 3 months after the end of FSRT; 10/26 patients died (4 patients before first MRI evaluation, 6 patients before second MRI evaluation). For each patient treatment response on MRI was evaluated using both RECIST and WHO criteria at each MRI control. Of 13 patients evaluable for response at 3 months, 3 patients had an increase in lesion size, 2 patients a reduction and 8 patients stable disease. Evaluation of response to treatment showed an agreement between WHO and RECIST criteria for all patients evaluated at 3 months; this correlation appears to remain in subsequent MRI, where the number of patients evaluable is still too small.

Conclusions: Response evaluation in brain metastases treated with FSRT is a critical issue. In clinical practice 2 diameters are often difficult to obtain at MRI by the neuro-radiologist, in particular when assessing brain metastases (assuming that these have a sphere shape). In our study we found correlation and agreement between RECIST and WHO response criteria, therefore RECIST criteria could be used safely. A longer follow-up will confirm this trend.

P025

STEREOTACTIC RADIOTHERAPY IN ASSOCIATION WITH MONOCLONAL ANTIBODIES AND IMMUNOTHERAPY: ANALYSIS OF A MONOINSTITUTIONAL SERIES

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Aims: New perspectives in the management of brain metastasis (BM) include the increasing use of monoclonal antibodies and immunotherapy. The aim of this study was to analyse retrospectively our experience in the use of stereotactic radiotherapy (SRT) in association with these new agents.

Methods: We retrospectively analysed data of patients (pts) who received SRT in association with monoclonal antibodies or immunotherapy for BM. Inclusion criteria were: KPS>70, number of lesions<3, systemic therapy administrated within 1 months before or after the SRT. Gross tumor volume was delineated on MRI fused with planning CT. BM<2 cm were treated with a single dose of 24 Gy; BM>2 cm were treated with doses between 15-18 Gy. Dose was prescribed to 85% isodose. The treatment

was delivered by a linear accelerator using non-coplanar arcs with X 6 MV photons. We performed MRI follow-up (F/U) at 1 month after SRT, and then every 3 months according to RECIST criteria.

Results: Fourteen pts with BM were treated at our institution with SRT in combination with monoclonal antibodies/immunotherapy. Primary sites were: lung (5 pts), breast (4 pts), melanoma (4 pts), and kidney (1 pt). Drugs administered in association with SRT were: erlotinib (3 pts), crizotinib (2 pts), lapatinib (1), trastuzumab (3 pts), ipilimumab (3 pts), and sunitinib (1 pt). Ten pts were RPA II and 3 RPA I. Mean diameter of BM was 8.6 mm (range 6-17 mm). Two pts had 2 BM and the other 11 pts only 1 BM. At a median F/U of 9 months (range 1-48), 5/13 pts were alive. Local control (LC) rate at 3 months was 83.3% (10/12); 1 pts died 2 months after SRT, 1 pt developed a second BM. No symptomatic brain necrosis was observed. One pt with BM from primary melanoma at the MRI one month after SRT showed a slight increase in diameter (16 vs. 13 mm) and asymptomatic bleeding in the context of the BM treated with SRT.

Conclusions: In our experience, concurrent delivery of monoclonal antibodies/immunotherapy and SRT was associated with favorable loco-regional control and apparently no increase of toxicity. However, SRT combined with immunotherapy may cause a temporary increase of tumor size due to local inflammation or hemorrhage.

P026

POSTOPERATIVE STEREOTACTIC BRAIN IRRADIATION AFTER METASTASECTOMY

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Aims. To reduce the risk of brain metastases (BM) local recurrence, post-operative whole brain radiotherapy (WBRT) is generally done. However WBRT does not improve overall survival and carries the potential risk of neurocognitive decline. Fractionated stereotactic radiotherapy (FSRT) is an emerging treatment which permits to deliver high doses in few fractions minimizing radiation brain toxicity. Our experience on postoperative FSRT of BM surgical cavity is reported.

Methods. From August 2011 to February 2016, 13 surgical cavities in 13 consecutive patients (pts) were treated with FSRT. Male/female ratio was 7/6, median age 57 years (range, 44-71). The primary tumor site was: non-small cell lung cancer in 6 (47%) pts, breast cancer in 2 (15%) pts and other tumors in remaining 5 pts. Median Karnofsky performance status was 90 (range, 80-100). Before FSRT, brain recurrence was the only site of disease in 6 (47%) pts. Of remaining 7 pts with disease also outside the brain, 2 (15%) had a partial remission, 2 (15%) a stable disease, remaining 3 (23%) a progression. All pts were submitted to radical brain metastasectomy; the interval between surgical resection and adjuvant FSRT was<3 months. At follow-up magnetic resonance imaging was performed 3 months after FSRT, every 3 months for the first two years and then every 6 months.

Results. FSRT were administered using a 5-MV linear accelerator fitted with a commercial dynamic micro-multileaf collimator. All the lesions were treated to the planning target volume (PTV) enclosing at least 90% isodose. Median PTV was 29cc (range, 13-53). Nine (69%) pts received 5 x 6Gy, the remaining 4 (11%) pts 5 x 7Gy. No acute toxicity was registered. At a median follow-up of 18 months (range, 3-59), 8 (62%) pts remained free of brain disease, 3 (23%) had an out-field relapse, 1 (7.5%) an in-field relapse and another (7.5%) both in- and out-field relapse. These 5 pts with brain recurrence were treated with salvage RT (i.e., 2 pts with WBRT and the other 3 with radiosurgery). Median time to brain relapse and overall survival were 12 months (range, 3-30) and 15 months (range, 3-63), respectively.

Conclusions. Our data confirm that FSRT are safe and feasible. Hypofractionated regimen of FSRT showed satisfactory results in local brain control remaining radiosurgery or WBRT possible salvage treatments.

P027

SALVAGE FRACTIONATED STEREOTACTIC RADIOTHERAPY WITH OR WITHOUT CHEMOTHERAPY FOR RECURRENT GLIOBLASTOMA MULTIFORME: OUR EXPERIENCE

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Aims. Salvage treatments of glioblastoma multiforme (GBM) include resection and adjuvant chemoradiation for operable patients. In cases with inoperable disease, limited experience exists to suggest a particular treatment modality for improving survival for recurrent GBM. We report our experience with fractionated stereotactic radiotherapy (FSRT) with or without chemotherapy in patients affected by recurrent disease after standard chemoradiation or radiation therapy alone.

Methods: From 2007 to 2015, 44 patients (25 M and 19 F; men age 56.5±12.6 years) with recurrent GBM following resection and chemoradiation or radiation therapy alone for their initial tumor, received 15-30 Gy (mean 20.1 Gy) in one to five fractions via FSRT with a system equipped with robotic arm. Mean clinical target volume (CTV) was 20 ml. Twenty-nine patients received adjuvant systemic therapy with temozolomide (TMZ) and two received an association of TMZ and fotemustine and bevacizumab, respectively.

Results: Mean overall survival (OS) from date of recurrence was 19.1 months and 16.5 months from the end of FSRT. OS at 6 and 12 months was in 79 and 51.7%, respectively. 5/19 patients were alive at the time of the study at 6, 6, 12, 36 and 84 months from completion of FSRT. 2/44 (4.5%) of our patients experienced a 84-month survival from completion of FSRT. In 4/44 (9.1%) pts follow-up imaging revealed radionecrosis.

Conclusions: Radiation Therapy Oncology Group has recently established the role of re-irradiation for recurrent GBM. Our experience has demonstrated that FSRT delivered with linear accelerator equipped with robotic arm is safe and effective in patients affected by recurrent GBM disease after standard chemoradiation or radiation therapy alone, reaching a high OS, in some cases superior to three years, with limited toxicity.

P028

BRAIN SBRT AND SETUP ACCURACY: COULD IT BE AN IMPROVEMENT USING A 6-DEGREE OF FREEDOM (6-DOF) ROBOTIC COUCH?

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Aims: Brain Stereotactic Body Radiation Therapy (SBRT) is a consolidated technique; even if in a rigid system, brain SBRT constitutes a challenge, especially for margin reduction in a noble district. Rationale of a 6-DoF couch in brain region was studied.

Methods: Patients with metastatic brain lesions were enrolled. Uni-frame or trUpoint Arch (CIVCO support system) were used. Target's contouring was carried out MRI images fusion with the CT scans for planning. PTV was obtained adding 0.3 cm as margins to target (CTV). Treatment planning was performed by Eclipse™ Treatment Planning Systems (Varian Medical System®, Palo Alto, CA); Volumetric Modulated Arc Therapy was used for all plans. The total dose was: 25.5 Gy in three fractions or 25 Gy in five fractions. A daily KV-Cone Beam Computed Tomography (CBCT) was performed before each treatment day, comparing with CT scan images for planning (3D-3D match): translational and rotational shifts were identified and applied on the Protura TM Robotic couch 6-DoF. Using MIM 5.5.2 software, a CT was rigidly registered with CBCT. Then, translational shifts were applied, obtaining a translated CT(tCT), i.e. CT with only translational errors correction. Then, rotational errors were corrected too, obtaining roto-translated CT(rtCT). Initial treatment plan was copied to translated CT(tTP) and roto-translated CT(rtTP). Finally, dosimetric parameters were compared.

Results: From November 2015 to April 2016, 15 patients were enrolled, 58 CBCT and 116 treatment plans were performed. The mean (±SD) interfraction displacements in all DoF are reported in Table 1. No significant correlation was observed between the magnitude of translational and rotational shift. Dosimetric analysis showed no significant variations in PTV or CTV V95% coverage, even if there were some outliers mainly correlating with not spherical shape of target. Large variations (>2%) were found for OARs located nearby the targets.

Conclusions: A 6-DoF robotic couch could be useful to improve accuracy in IGRT era, especially in SBRT and also in brain region. The absence of correlations between rotational and translational shifts shows the importance to correct rotations independently of translations. The minimum variations on PTV and CTV coverage confirm the need to correct also small setup error when high dose is delivered. An ongoing analysis on setup systems and margin reductions was planned.

Table 1. Mean values, standard deviations, maximum and minimum shifts obtained with 3D-match between CBCT and kV. Percentage of shifts and rotations above three different cutoff are reported. Percentage variations of PTV, CTV and OARs constraints due to rotations are shown.

	Lat(x) (cm)	Vrt(y) (cm)	Lng(z) (cm)	Rol(x) (deg)	Pit(roll) (deg)	Rtn(y) (deg)	PTV V95%	CTV V95%	OPTIC PATHWAY R Dmax (Gy)	OPTIC PATHWAY L Dmax (Gy)	COCHLEA R Dmax (Gy)	COCHLEA L Dmax (Gy)	BRAINSTEM Dmax (Gy)	SPINAL CORD Dmax (Gy)
MEAN	-0.0	-0.1	-0.0	0.3	-0.3	1.0	0.2	-0.0	-0.0	0.1	-0.1	-0.2	0.2	0.0
SD	0.3	0.2	0.2	1.4	1.0	1.3	1.6	0.0	0.3	0.3	0.3	0.8	1.5	0.0
MAX	0.6	0.3	0.5	2.9	1.5	3.0	6.2	0.2	0.6	0.9	0.2	0.3	4.3	0.1
MIN	-0.6	-0.7	-0.5	-3.3	-2.5	-2.7	-0.9	-0.3	-1.3	-1.0	-0.6	-5.3	-3.4	0.0
1mm Trans	7%	2%	0%											
1mm Trans	22%	8%	7%											
1mm Trans	29%	20%	20%											
ROTAT >1				15%	8%	14%								
ROTAT >1				46%	31%	37%								
ROTAT >1				64%	36%	44%								

P029

HYPOFRACTIONATION IN BRAIN METASTASES RADIOTHERAPY: WHOLE BRAIN PLUS SIB WITH VOLUMETRIC MODULATED ARC THERAPY

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Aims: To evaluate a hypofractionated treatment for brain metastases, using whole brain radiation therapy(WBRT) –20 Gy/5 fr– and a simultaneous integrated boost(SIB), delivered to each lesions –40 Gy/5 fr– with VMAT-technique (Volumetric Modulated ArcTherapy/ RapidArc).The study also considers dosimetric coverage of the target and RT-related toxicity observed during the treatment and after 3 or more months of follow up.

Methods:17 patients with single or multiple brain metastases (max 5) were treated from 2012 to 2015.All patients had brain metastatic disease confirmed by neuroimaging techniques, and they had not previous intracranial radiotherapy.All patients were stratified by age and site of primary tumor; they received WBRT (DT–Total Dose: 20 Gy; Df-Dose per Fraction: 400 cGy) and a SIB to each brain metastasis up to DT 40 Gy, Df 800 cGy.The most important dosimetric parameters related to PTVwb and PTVmetastases were Conformation Number(CN) and Homogeneity Index(HI).To study brain disease response after 3 months, patients were revalued by neuroimaging and RECIST criteria.Acute toxicity was scored according to the RTOG 9508 scoring system.For longer-survival patients we studied late motor, sensory and cognitive toxic effects.

Results: The calculated CN95% related to PTVwb was satisfactory:0.79, but HI was less acceptable: 0.55.PTVboost had an acceptable HI:0.07,but CN95% was 0.63. Patients' median survival was 6 months;with regard to local control of brain disease,1 patient obtained CR (Complete Remission) of brain metastasis;3 patients

obtained PR(Partial Remission);4 patients had steady intracranial disease until they died;only 3 patients had a local progression after RT. RT-related acute toxicity affected only 4 patients with moderate ANS(Autonomyc Nervous System), CNS (Central NS) and hearing/visus disorders.Satisfactory neurocognition and quality of life were maintained by other patients.Low chronic toxicity (motor symptoms) was observed in two patients longer-term survivor.

Conclusions: VMAT represents a good conforming technique for brain volumes (CN value next to unity), affected by a low homogeneity of dose(HI high) due to concomitant treatment of metastases; homogeneity of dose to PTVboost is acceptable, like a typical stereotactic result.Our preliminary experience with this hypofractionated schedule suggests the advantages of WBRT+SIB: clinical results are comparable to the data in literature with shorter planning and delivering treatments' times.

P030

WHAT IS THE RESIDUAL ERROR AFTER 2D-ORTOGONAL KV? ANALYSES BY CBCT FOR CTV-PTV MARGIN DEFINITION IN INTRACRANIAL STEREOTACTIC RADIOTHERAPY

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Purpose: Kilo-voltage cone beam computed tomography (Kv-CBCT) is generally considered as the gold standard for stereotactic radiation treatment (SRS) verification. For intracranial SRS bony structures are generally considerd a good surrogates for target positioning and 2D projection or planar images might allow for similar repositioning accuracy in a faster manner. The primary aim of this report was to perform a preliminary analysis to quantify the residual error after two-dimensional (2D) orthogonal kV set-up correction using cone-beam CT (CBCT) for target localization in patients undergoing intracranial SRS.

Methods and Materials: All patients were immobilized with a thermoplastic face mask. After set-up using in-room lasers and marks placed at simulation, patients were imaged and repositioned according to orthogonal kV registration of bony landmarks to digitally reconstructed radiographs from the planning CT. A subsequent CBCT was registered to the planning CT using both soft tissue and bone information, and the resultant ''residual error'' was measured and corrected before treatment. Based on the discrepancies in x, y, and z directions, systematic and random differences were calculated and used to derive a CTV to PTV margin according to the van Herk formula.

Results: From 1rst June 2014 to 30th October 2015, 42 pairs of orthogonal kV images and 42 CBCT scans of 13 patients submitted to intracranial Linac-based stereotactic radiotherapy were analyzed. After repositioning according to orthogonal kV registration of bony landmarks a residual discrepancy >3 mm was observed with CBCT in 1 (2.3%), 5 (11.9%) and 4 (9.5%) scans on z, y and x direction respectively. A discrepancy >3 mm on at least one direction was observed in 8 CBCT scans (19%). Systematic and random differences were 0.38 and 0.93, 0.45 and 1.28, 0.61 and 1.63 mm on z, y and x direction respectively. Calculated CTV-PTV margins were 1.7, 2.1 and 2.8 mm on z, y and x direction respectively.

Conclusions: When using a thermoplastic face mask as immobilization device for intracranial stereotactic radiotherapy, translational residual errors after repositioning according to orthogonal kV registration of bony landmarks are of minimal entity but not negligible. These preliminary data suggest that a CTV-PTV margin of at least 3 mm is needed to ensure an adequate geometric accuracy when orthogonal KV images are used; this margin could be decreased when CBCT is added.

P031

DOSIMETRIC AND CLINICAL FEASIBILITY OF INTENSITY MODULATED HYPOFRACTIONATED RADIOTHERAPY WITH SIMULTANEOUS INTEGRATED BOOST (IMRT-SIB) FOR MALIGNANT GLIOMAS

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Aims: The aim of this study was to assess the dosimetric and clinical feasibility of hypofractionated IMRT/SIB with concomitant chemotherapy in malignant gliomas.

Materials and Methods: We evaluated retrospectively 16 patients (pts), (6 females, 10 males) with histologically confirmed gliomas (14 glioblastomas, 1 anaplastic astrocytoma, 1 anaplastic ologodendroglioma) postoperatively treated with SIB-IMRT and concurrent/adjuvant temozolomide according to the Stupp regimen between 2010 and 2016. Patients characteristic in table 1. High risk PTV (H-PTV) was surgical bed including residual gross tumor with 1/1,5 cm margin; Low risk PTV (L-PTV) was surgical bed with 2.5 cm margin. Total dose was 69 Gy, 2,3 Gy daily/fr to H-PTV, and 60 Gy, 2 Gy daily/fr to L-PTV. We valuate D95% and D1% for H-PTV and L-PTV, and V60, V50 and V45 for the brain, D1% or Dmax for optic chiasm, optic nerves and brainstem. Acute and late toxicity was assessed by clinical and MRI evaluation.

Results: We performed a dose-volume analysis for PTVs and OAR. Median D95% to H-PTV was 64,5 Gy (range 62-66), median D95% to L-PTV was 58,2 Gy (range 53,4-59,9). D1% was <107% in all pts. V50<66% and V45<100% brain dose-constraints were respected in all pts. The V60 <33% constraint was respected in 15/16 pts. Dose constraints for optic chiasm (Dmax<54 Gy), brainstem (D1%<59 Gy) and optical nerves (Dmax<54 Gy) were achieved in 15/16 cases.

Table 1.

Characteristics	N. of Patients	16
Age (yrs)	Range (34-79)	Median 58,3
Sex	Male	10
	Female	6
Pathology	Anaplasic Astrocytoma	1
	Oligodendroglioma	1
	Glioblastoma	14
Karnofsky PerformanceStatus	> 70	15
	< 70	1
Extent of Surgery	Grossly total resection (R0)	9
	Subtotal resection (R2)	6
	Partial resection (BIOPSY)	1
Tumor Site		
Frontal	4	Sin (3); Bilat.(1)
Parietal	1	Sin (1)
Occipital	1	Dx (1)
Temporal	2	Sin (2)
Parietooccipital	2	Sin (2)
Frontoparietal	3	Dx (2); Sin (1)
Temporoparietal	3	Dx (2); Sin (1)
Chemotherapy (STUPP)		
Temozolomide	Concomitant	16
Temozolomide	Adiuvant	10

Table 2.

PTV1 69 Gy
PTV2 60 Gy

CASE N.	D95% FOR PTV 1	V95% FOR PTV1	D1% FOR PTV1	D95% FOR PTV2	V95% FOR PTV2	D1% PRV TRONCO	ENC. V60	ENC. V50	ENC. V45
1	90,2	87,7	104,5	94	94	49	23,3	35,6	44,6
2	95,2	95,4	102	98,3	98	58,7	11,5	22,4	28,4
3									
4	93,3	91,9	105	99,7	98,5	53,6			
5	94,6	94,4	102	97,3	96,1	47,7	10,8	17,7	22,1
6			103,5	95,3	95,3	51,9	19,7	36,7	41,4
7	94,9	95,1	106	95,7	95,5	47,6	28,7	42	21
8	94,2	92,7	102	96,2	95,9	52	36,9	46	51,5
9	95,4	96,1	103	96,8	96,4	45,8	7,8	15,9	21,2
10	95,8	97,9	101	98,2	99,4	45,8	2,1	13,1	17,4
11	95	95	105	98	98,1	61,3	42	55,6	62,2
12	94,3	93,3	102	97,5	96,9	44,9	1,4	11,4	15,2
13									
14									
15									
16									

In one case total dose was reducted to 60 Gy because of dose to the optic chiasm >64 Gy. Concomitant chemoradiation treatment was completed in 15 pts (one pt interrupted treatment because of a thrombocytopenia G4). Two pts experienced thrombocytopenia G3. No apparent acute neurotoxicity was observed. Ten pts undergone adjuvant temozolomide (median cycles 3, range 3-12). We recorded radiological radionecrosis in 3 pts after 9-12-14 months (18,7%) and leukoencephalopathy in 1 pt after 3 months, in all but 1 case with concomitant recurrent glioblastoma. The median PFS was 8,3 m (range 2-20,97). The overall median survival was 10,6 (2-37+).

Conclusions: High conformity of dose distribution and homogeneity within the PTVs and good avoidance of organs at risk was achieved using IMRT. Hypofractionated SIB-IMRT in patients with malignant glioma is feasible and safe. The incidence of radiation necrosis observed not exceeds the risk registered in literature data.

P032

EFFICACY OF 4 GY X 5 FRZ HYPOFRACTIONATION IN THE RE-IRRADIATION OF BRAIN

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Aims: Metastatic process worst the prognosis of oncologic patient (pts). There is a rising incidence of brain metastasis (BM) due to increasing survival, a success of treatment progress in surgery, radiotherapy and chemotherapy. The improving in life expectancy, directly increase the risk of The delivery of total dose in fewer numbers of fraction than conventional (>3Gy/frz), is defined Hypofractionation. There are several schemes usually adopted in the palliative setting, but to date is not clearly what give a better compromise between efficacy and toxicities. For pts previous treated with whole brain radiation therapy (WB) for multiple BM, a second course of re-WB is an important palliative options. Aim of this retrospective study is to analyze the safety and efficacy of the re-WB with a 4 Gy x 5frz schedule.

Methods: A retrospective review was performed for 12 pts with BM who undergone re-WB. Data collected from our database, from March 2010 to May 2015, regarding demographic characteristics, primary tumor, metastasis, symptoms and fractionation radiotherapy were analyzed. The median dose for the first course of WB was 30 Gy (3 Gy x 10frz) and for the second was 20 Gy (4 Gy x 5frz). Radiation toxicity, LC and distant failure were described using respectively CTCAE v4.03 and RECIST criteria v1.1, for performance status the ECOG scale was used.

Results: The median performance status before re-WB was 2 (range, 1–3). The group consisted of 8 (66%) women and 4(33%) men with a median age of 58y. Histotypes were: 5 lung, 5 breast, 1 bladder and 1 melanoma. Between the first and second WB a median of 17,4 months intervened. At the time of re-WB 85% of all pts suffered from additional extra-cerebral metastases. At the start of the re-WB 9 pts (75%) had mild and 2 (16%) severe neurological symptoms, 1 patients (8%) was asymptomatic. Main side effects was fatigue. Five pts (41%) showed a clinical improvement of neurological symptoms after the therapy, 3 pts (25%) remained stable, 4 pts (33%) showed worse symptoms.

Conclusions: Re-WB with a hypofractionated schedule (4 Gy x 5 frz) represents an important therapeutic option with low rate of acute side effects for pts with recurrent BM. The treatment was also effective for symptomatic improve-

ment, but the limited survival of our cases don't give an answer on cognitive impairment and other late toxicities.

P033

ORGAN AT RISK SPARING WITH HELICAL TOMOTHERAPY IN SKULL BASE MENINGIOMAS

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Aims: Meningiomas close to the optic pathway represent a treatment challenge both for surgery and radiotherapy; our aim is to evaluate Helical Tomotherapy (HT) for the planning and treatment of complex-shaped meningiomas close critical structure as optic pathway.

Methods: In the 2015 2 patients with complex-shaped residual meningiomas were treated with HT at our Institution; both patients were Simpson IV grade and their histological profiles were atypical WHO grade II in one patient, and anaplastic WHO grade III in the other. The contouring of target and organs at risk was obtained with the aid of a magnetic resonance imaging-computed tomography fusion. Treatments included daily image guidance. The total prescribed dose was 55.2 Gy in 23 fractions of 2.4 Gy daily dose. When this radiation schedule was converted into the biological equivalent dose (BED) using an a/b ratio of 2.0 Gy, the BED dose was 121 Gy comparing to BED2 = 120 using standard fractionation of 60 Gy/30 fr. The gross tumor volume (GTV) was taken as the gross tumor shown on magnetic resonance imaging; The clinical target volume (CTV) was equal to the GTV while the planning target volume (PTV) was obtained with a 2–3 mm geometric expansion of the CTV. The PTVs volume was 38,98 cc and 45,1 cc. Minimum distance from optic pathway was 0 mm, and in both cases, there were an overlap region between PTV and optic pathway.

Results: All HT plans resulted in excellent target volume coverage with step dose-gradients. The conformity index was 1,08 and 1,06, V95%PTV was 99,5 % and V105%PTV was 0,5% for both plans. The maximal dose to the optic pathway was established according to QUANTEC and was 39,2 Gy and to 45,1 Gy. HT treatment was well tolerated in both cases; corticosteroids were administered at low dose just from last two weeks of treatment. Acute transient toxicity was grade 1 and included headache and ocular pain/dryness. At one year follow up no optical injury, temporal lobe injury or intracranial hypertension symptoms were detected and both patients have a radiological stabilization of the disease.

Conclusions: HT represents a safe and effective therapeutic chance for partially resected complex-shaped meningiomas close to the optic pathway. Optimal coverage and homogeneity indexes were achieved with appropriate values for optimization process reducing and minimizing maximal doses delivered to the eyes, lenses, and chiasm, despite the proximity of the target to these critical structures.

P034

AN UNUSUAL PRESENTATION OF METASTASIS FROM ENDOMETRIAL CARCINOMA: CASE REPORT

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Aims: Gynecological cancers are considered neurophobic. Intracranial metastases represent an uncommon complication of endometrial cancer with approximately 115 cases documented in literature.

Methods: We report a case of recurrent endometrial brain metastases (BM).

Results: A 55-year-old woman underwent hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy for endometrioid adenocarcinoma G3, FIGO IIIC. Whole-pelvis irradiation was applied (total dose: 48,6 Gy, fraction size:1.8 Gy, five fractions/week) with concurrent Cisplatin (50 mg/mq days 1 and 22 of radiotherapy), followed by HDR brachytherapy (10 Gy, two weekly fractions of 5 Gy each; TPS: Oncentra MasterPlan). The dose of 5 Gy was delivered with vaginal cylinders and specified to 0.5 cm from applicator surface. She underwent sequential chemotherapy with CBDCA AUC 5 and Paclitaxel (PTX) 175 mg/mq (1q21, total courses: 4). After a disease free survival (DFS) of 22,2 months, she presented dysmetria and homonymous hemianopsia. Brain magnetic resonance (MRI) described both bilateral frontal and a left occipital BM. Abdominal-CT showed a para-aortic lymph node metastasis. She was treated with local resection of BM and chemotherapy with CBDCA AUC 5 plus PTX 175 mg/mq (1q21, total courses: 6) with a complete node response. After 5 months from metastasectomy, MRI showed a regrowth of occipital BM that was treated with stereotactic radiosurgery SRS (9 multiple no-coplanar beams, 6-MV photons; BrainLab/Mitsubishi VERO). Total dose 25,5 Gy was prescribed to the 70% isodose and delivered in 3 consecutive fractions. Steroids and prophylactic anticonvulsant medications were administered during and after SRS. After 5.16 months, MRI showed a regrowth of the left frontal lesion and the development of massive edema around the occipital radio-treated lesion. She is still alive without acute/late toxicity (RTOG scale) and her neurological function improved after SRS. The survival from first diagnosis of BM is 15,8 months, from metastasectomy 15,3 months and after SRS 8.8 month; brain DFS after SRS is 5.16 months and overall survival (OS) 38 months.

Conclusions: To date, median survival after brain involvement is 5 months and the combination of surgery and radiotherapy yields higher survival rate. In our case SRS is well tolerated and no toxicity was observed. Further case reports may contribute to a better evaluation of treatment options.

P035

RADIOSURGERY FOR BRAIN METASTASES: DIFFERENT RESPONSES FOR DIFFERENT PRIMARY TUMOR

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Aims: Breast Cancer is the second type of neoplasm, after lung cancer, that most frequently causes brain metastases, with a chance to develop in 20-40% of patients. Aim of this study is to compare the response to stereotactic radiosurgery treatment (SRT) for breast cancer brain metastases with the response to SRT for metastases from different histological type and anatomical site cancer.

Methods: Between October 2013 and December 2014 a total of 8 patients (1 male ad 7 female) underwent SRT for 9 brain metastases (2 synchronous metastases), 2 from ovarian cancer, 1 from colon cancer, 1 from melanoma , 3 from breast cancer, 1 from NSLC, 1 from cervix cancer. All these kind of lesions was no larger than 25 mm and identified radiologically by performing MRI. Only one of the patients had been treated previously with a whole brain radiotherapy (more than a year from the current treatment). At the time of our pretreatment evaluation patients did not have other systemic metastases. The median KPS score was 85% (range 70-100%). In 20% of cases, the patients reported focal neurological deficits, the remaining percentage were not reported symptoms attributable to brain injury. The technique used was multiple non-coplanar dynamically shaped arcs. The median prescribed RS dose was 18 Gy (range, 10-21) and the median tumor volume was 1.3 ml (range, 0.02-30).

Results: We analyzed the control rate and early treatment response. Patients were evaluated at 3 months after radiosurgery. We considered response the response based on the primary tumor, as can be seen on the 8 patients in the study, the primary tumor mainly represented is breast cancer. On the basis of this finding, we have studied the positive response (partial or total), depending on the primary tumor. Based on the total response from the patients with breast cancer, the cancer most represented, we get a positive response value of 25% and a negative response of 75%; for other tumors these values are respectively 20% and 80%, compared to an average value of 22.22% for a positive response and negative response of 77.78%. Considering partial response, always based on the primary tumor (breast cancer), the positive response was 75%, compared with a negative response of 25%; for tumors classified as ""other"", the positive response was of 40.00%, with a negative response of 60.00%, while the average values (overall) are respectively 55.56% and 44.44%. In this case also, obtaining a $p<0.05$, the data assumes a value statistically significant.

Conclusions: The study gave results broadly in line with what has already been shown internationally, on the treatment of brain metastases by stereotactic radiotherapy that has proved successful in controlling brain metastases individual in a higher percentage and statistically significant in the case of secondary breast cancer lesions.

Table 1. Comparison of survival curves (Log rank test).

Chi-squared	6,6237
DF	1
Significance	P=0,0101

P036

INNOVATIVE SURGERY IN EARLY STAGE (T1-T2N0) OROPHARYNGEAL CANCER: IS IT SAFE TO OMIT RADIOTHERAPY AFTER TORS WITHOUT NECK DISSECTION?

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Aim: Trans-oral robot surgery (TORS) represents the newest mini-invasive surgical technology in the management of oropharyngeal squamous cell carcinoma (OPSCC). In our Institute, patients with early stage (I and II) OPSCC who refused curative radiotherapy (RT) were treated with TORS (using the Da Vinci Robot System) without planned lymph node dissection and/or adjuvant RT. Aim of this retrospective analysis was to evaluate oncologic results and cost-effectiveness of this approach.

Patients and methods: Between April 2008 and December 2015 21 pts (7 female and 14 male, median age 62 yrs, range 43-77 yrs) with clinical stage I and II OPSCC were treated with TORS. Tumor was located as follow: base of tongue in 3 pts, tonsillar fossa 11 pts, soft palate 5 pts and posterior pharyngeal wall 2 pts. HPV status was available for 10 pts (6 HPV+ and 4 HPV-). Neither elective neck dissection nor adjuvant RT were performed. For all patients a strict clinical and radiologic follow-up program for the early detection of pathologic neck lymph nodes was applied.

Results: Median follow up was 29 months (mean 39 months, range 3-97 months). Ten (47%) pts experienced a locoregional recurrence after a median time of 10 months (range 4-36 months): 8 pts (38%) had lymph node recurrence (5 pts retro-parapharyngeal nodes –RPN- and 3 pts in the neck), 2 (9.5%) pts primary site recurrence and 1 patient (4.7%) both lymph node and primary tumor recurrence. At the time of the assessment 18 (85%) pts were alive with no evidence of disease, 2 (10 %) pts were alive with disease and 1 (5%) patient died for non-cancer related disease. Salvage treatment was summarized in Table 1.

Table 1. Salvage treatments.

Site of recurrence	Fist salvage treatment	Local control	Second salvage treatment
Tumor recurrence	Surgery	No	RT-CT
Tumor recurrence	CT-RT	Yes	-
Neck lymph nodes	Surgery + Adj CT-RT	Yes	-
Neck lymph nodes	Surgery	Yes	-
Tumor and neck lymph nodes	CT-RT	Yes	-
RPN	Surgery	No	CT-RT
RPN	Surgery	No	CT-RT
RPN	Surgery	No	CT-RT
RPN	RT	Yes	-
RPN	CT-RT	Yes	-

RT =radiotherapy, CT-RT=concomitant chemoradiotherapy, RPN= retro-parapharyngeal nodes.

Conclusions: Results of this cohort suggested that TORS without neck dissection and/or adjuvant RT can be an efficacy alternative approach to curative RT for early stage OPSCC. Advantage of this approach is mainly represented by the avoidance of elective neck dissection and adjuvant treatments in about half patients but the cost-effectiveness of this strategy should be carefully evaluated in prospective trials. As expected about 38% of patients experienced a lymph node recurrence and most of them underwent salvage treatment with a curative intent. Moreover, our data suggested that RT (+/- chemotherapy) is probably more efficacy than surgery as salvage treatment.

P037

RE-IRRADIATION WITH CURATIVE INTENT IN PATIENTS AFFECTED BY SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK: A NATIONAL SURVEY OF THE HEAD AND NECK AND RE-IRRADIATION WORKING GROUPS ON BEHALF OF THE ITALIAN ASSOCIATION OF RADIATION ONCOLOGY (AIRO)

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Aims: To investigate the pattern of practice of re-irradiation (ReRT) with curative intent for squamous cell carcinoma of the head and neck (SSCHN) and to report on the RT techniques adopted for this purpose.

Methods: In March 2015, a 22 – item questionnaire consisting of 4 main sections was sent to all Italyn Radiation Oncology centers. Only one responder for center was allowed to take part to the survey.

Results: A total of 77 centers completed the survey. The majority (50/77, 64.9%) of participating radiation oncologists are experienced with>10 years of specialty. Of the responding centers, 63 (81.8%) perform curative ReRT for SCCHN, while 14 (18.1%) do not, most frequently (5/14, 35.7%) due to the avoidance of severe toxicity. Of the former group, more than half of centers (36, 57.1%) treat<5 patients annually with ReRT, while a higher number is reported in 24 (38.1%: between 5 and 10) and 3 (4.7%: between 10 and 20) centers, respectively. In section 2, the practice of adjuvant ReRT was investigated: 26/63 (41.2%) responders don't prescribe it in daily routine. If indicated, the most frequent RT schedule chosen is 60-66 Gy with conventional fractionation (16/36, 44.4%) to the tumor bed with 0,5 – 1 cm margin for 20/36 centers (55.5%). Most frequently, the RT technique adopted is rotational IMRT (16/36, 44.4%). The pattern of practice of ReRT for unresectable non-NP SCCHN was assessed in section 3, with 55/61 (90.1 %) participating radiation oncologists claiming to perform it. The commonest technique used is again rotational IMRT (19/55, 34.5%). Given the prespecified curative intent, the favored RT schedule used was 60-66 Gy at 2 Gy/fraction in 28/55 centers (50.9%) delivered to the GTV + 0,5 cm margin for 19/55 (34.5%) responders. The pattern of practice regarding ReRT for locally recurrent NP cancer was investigated in section 4: 47/61 (77%) centers claimed to perform it, preferentially (36/47, 76.5%) with IMRT, up to a total dose of 60-66 Gy delivered with conventional fractionation for 16/47 (34%) participating centers.

Conclusions: For the vast majority of italyn radiation oncology centers, curative Re-RT for SCCHN represents an unfrequent clinical indication, most commonly adopted via IMRT at standard fractionation. The results of the AIRO survey reflect the absence of strong evidence in support to this practice and the need of prospective data to better define its role in the context of modern RT technical availability.

P038

CLINICAL RELEVANCE OF BRACHIAL PLEXUS CONSTRAINT: A RETROSPECTIVE ANALYSIS IN LOCALLY ADVANCED H&N CANCER PATIENTS TREATED BY HYPOFRACTIONATED ACCELERATED SIB-VMAT RADIOTHERAPY

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Aims: to perform a dosimetric evaluation of the brachial plexus (BP) dose in locally advanced H&N cancer patients undergone moderate hypofractionated accelerated chemoradiation performed by a SIB-VMAT technique.

Methods: Patients with locally advanced H&N cancer receiving induction chemotherapy (ICT) and subsequent platinum based concurrent radiotherapy were included in this retrospective analysis. Toxicity and outcomes data were recorded during the routine follow-up. In all patients, right (RBP) and left (LBP) BP were delineated according to RTOG guidelines by the same radioncologist, RBP and LBP mean doses, V50, V55 and V60 were registered and correlated with late neurological toxicity.

Results: From July 2010 to January 2015, 50 patients [M/F: 40/10; median age: 57y, range 30-77; stage III: 11 (22%), stage IV: 39 (78%)] were treated and represent the object of the analysis. ORL subsites were as follows: oropharynx (22; 44%), epipharynx (8;16%), oral cavity (9; 18%), larynx (4; 8%) and hypopharinx (7; 14%). A cisplatin plus 5-fluorouracil chemotherapy schedule was administered as ICT in 72% of cases, while 22% of patients received a 3-drugs schema (cisplatin, 5-fluorouracil and docetaxel). A moderate accelerated hypofractionation was obtained by using a 2 arc SIB-VMAT technique. Doses to macroscopic disease (T and N) ranged from 67.5/2.25 Gy (8 patients; 16%) to 70.5/2.35 Gy (42 patients; 84%), while the high and low risk nodal areas received 60/2 Gy/die and 55.5/1.85 Gy/die in 30 fractions, respectively. As per DVH analysis, LBP and RBP mean dose were 48.4 Gy and 48 Gy, V50 were 68.5 cc and 68.9 cc, V55 were 56.1 cc and 58.9 cc, V60 were 28 cc and 32.6 cc, respectively. In 44% of cases part of the LBP was included within the high dose PTV (67.5Gy in 12% and 70.5 Gy in 32% of patients). Conversely, in 46% of cases part of the RBP was included within the high dose PTV (67.5Gy in 8% and 70.5 Gy in 38% of patients). With a median follow-up of 19 months (range 3-53) no symptoms of brachial plexopathy were reported, although in 87% of cases doses to BP exceeded the suggested literature constraint of 60 Gy.

Conclusions: A SIB-VMAT moderate accelerated hypofractionation at the doses reported in this analysis seems to be tolerable and safe, not correlating in our experience with neurological toxicity. Longer follow-up and further prospective studies in larger series are warranted to confirm these findings.

P039

A COMPARISON OF EARLY OUTCOMES IN MEDICALLY FIT PATIENTS WITH OROPHARYNGEAL CANCER RECEIVING INTENSITY MODULATED RADIOTHERAPY (IMRT) PLUS CETUXIMAB OR CISPLATIN

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Aims: to compare outcomes and acute toxicities of non-conventional fractionated intensity modulated radiotherapy (IMRT) plus cetuximab (cet-IMRT) with conventional fractionated IMRT plus cisplatin (cis-IMRT) for medically fit patients with locally advanced oropharyngeal cancer (OPC).

Table1.

Patient characteristics	TOTAL (35 pts)	SIBRT ERB (17 pts)	IMRT CDDP 18 (pts)
Age (Median)	60 (44-79)	62 (44-79)	59 (48-76)
Sex			
M	29	14	15
F	6	3	3
Histology	35	17	18
Squamous cell carcinoma			
Subsite			
Tonsil	24	10	14
Base of tongue	7	5	2
Soft palate	3	2	1
Posterior wall of pharynx	1	0	1
Stage			
III	7	4	3
IV	28	13	15
Grading			
Well differentiated	3	0	3
Moderately well-differentiated	7	4	3
Poorly differentiated	19	11	8
NOS	6	2	4

Methods: Consecutive patients with stage III/IV oropharynx's squamous cell cancer treated with IMRT plus Cisplatin or Cetuximab were selected from a prospectively collected database. In the Cet-IMRT group IMRT was delivered with a simultaneous integrated boost technique up to a total dose of 66 Gy in 2.2 Gy/fraction along 6 weeks to the macroscopic tumor (60 Gy/2 Gy and 54 Gy/1.8 Gy to the high and low risk areas respectively). In the Cis-IMRT group IMRT was delivered with conventional fractionation up to 70.2 Gy in 1.8 Gy/fraction to the gross tumor volume (59.4 Gy/1.8 Gy and 50.4 Gy/1.8 Gy to the high and low risk areas respectively). Acute toxi-

city were reported according to the CTCAE criteria v.4; local control and survival were calculated with the Kaplan Meyer method.

Results: Between March 2007 and December 2015, 35 patients with stage III-IV oropharyngeal cancer were treated:17 with Cet-IMRT and 18 with Cis-IMRT. Grade 3 skin toxicity occurred in 6 patients (17.1%, 29.4 and 5.5% with Cet-IMRT and Cis-IMRT respectively, p=0.08); grade 3 mucositis or dysphagia occurred in 14 patients (40, 58.8 and 22% with Cet-IMRT and Cis-IMRT respectively, p=0.04); 5 patients (all in the Cis-IMRT group, p=0.04). One treatment-related death was recorded with Cis-IMRT. The mean overall treatment time was 56 days (superior in Cis-IMRT p<0.01). Twelve patients (34%) had treatment breaks>10 days without difference between two groups. Median follow-up was 15 months (range 4-59 months). One-year actuarial overall survival, locoregional progression-free and distant-metastases-free rates were 79% vs. 71% (p=0.50), 71% vs. 66% (p=0.62), 85% vs. 93% (p=0.89) with Cet-IMRT and Cis-IMRT respectively.

Conclusions: Our date show that Progression free and survival outcomes did not significantly differ at short term between two schedule of treatment. The treatment-related death disadvantage strongly the Cis-IMRT group whereas acute mucosal and skin toxicity is more relevant in Cet-IMRT group.

P040

ACCELERATED HYPOFRACTIONATED VOLUMETRIC MODULATED ARC THERAPY WITH SIMULTANEOUS INTEGRATED BOOST FOR RADICAL TREATMENT OF ADVANCED HEAD AND NECK CANCER: THE IMPACT OF FLUORODEOXYGLUCOSE-PET/CT IN THE PLANNING STRATEGY

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Aims: To analyze the impact of Fluorodeoxyglucose-PET/CT (PET/CT) in the radiotherapy (RT) planning-strategy in HNC, focusing on neck-nodes treatment planning and correlating CT-scan and PET/CT performances.

Materials and Methods: Inclusion criteria of this retrospective analysis were: age>18 years old, histologically proven squamocellular HNC, patients candidate to curative RT ± chemotherapy, evaluation of stage of disease by means of PET/TC and CT-scan performed at our Institution.

Results: Sixty patients, treated between October 2011 and February 2016, were included in the analysis. Primary tumor site was represented as follow: Nasopharynx in 8 patients (13%), Oropharynx in 25 (42%), Oral Cavity in 19 (32%) and Larynx non-glottic in 8 (13%). Oral cavity tumors revealed to be at particular risk of nodal stage migration, occurring in 21% of cases (5/19). PET/CT findings caused changes in the management of RT volumes in 10% of patients. In one case of nasopharynx cancer, it was detected the primary tumor previously unknown at CT-scan, in 5 cases of oral cavity tumors neck-nodes PET/CT positive from one side and/or the other (not detected at CT-scan) were included in the high-risk volumes and in 2 cases of oropharyngeal cancer RT was avoided because of distant metastases detection.

Conclusions: Present findings showed that PET/CT images could be a guide in HNC in order to individualize the RT-curative strategy. Further investigations are advocated to evaluate if this strategy could impact on long-term outcomes in HNC.

P041

HYPOFRACTIONATED, PALLIATIVE RADIOTHERAPY FOR ADVANCED HEAD AND NECK CANCER: TREVIGLIO HOSPITAL EXPERIENCE

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Aims: Evaluate the feasibility, tolerance and efficacy of hypofractionated, palliative Radiotherapy for advanced Head and Neck cancer.

Materials and Methods: From January 2009 to December 2015 fifteen patients underwent radiation therapy for locally advanced Head and Neck cancer. Most patients were elderly with poor performance status and comorbidities that make them unfit for radical radiation therapy (see table 1 for patients features). The disease stage was: 27% stage III, 73% stage IVA-B. Hystologic tipe was epidermoid carcinoma in 95% of patients. For treatment planning was made a TC scan with 3 mm pitch; GTV T, GTV N and OAR were defined in each TC slices; GTV-CTV margin was 1,5 cm and PTV-CTV was 5 mm as usually in our institution. The total planned dose of Radiotherapy was 40 Gy in 16 fractions in 3 1/2 weeks, each fractions of 2.5 Gy per day. The treatment was performed with IMRT tecnique in 60% of cases and with 3D in 40% of patients; the set up was checked daily with CBCT in 47% of patients. All patients were reviewed at least once weekly or more frequently during Radiotherapy for assessing toxicity. Every 3 month after the completion of Radiotherapy the patient was evaluated; the toxicity and radiation efficacy was recorded; mostly it was investigated the palliation effects on dysphagia and local pain.

Results: The radiation therapy was well tollerated; G1-G2 toxicity was registered in 14 patients (93%); nobody stopped the treatment because of toxicity. The overall treatment time was 23 day. At the end of treatment 73% of patients reported improvement in symptoms (dysphagia and local pain). At first follow-up, three month after the end of treatment, complete response (RC) was achieved in 5 patients (33%), 5 (33%) patients had partial response >50%, 1 patient had partial response <50%

(7%) and 4 patients (27%) had stabile disease. The median follow-up time was 6 months; 60% of patients developed local relapse. The time to progression was 7,03 months.

Conclusions: The hypofractionated Radiotherapy regimen of 40 Gy in 16 fractions is effective for the large majority of patients for local control and symptom relief (endpoint of palliation for dysphagia and pain) with an acceptable toxicity.

Table 1.

Patients	
Sex	
Male	13
Female	2
Age	
<70	3
70-80	8
>80	4
IK	
60	5
70	10
>70	0
Comorbidity	
Yes	13
No	2

Reference

Jai Prakash Agarwal et al, Radiotherapy and Oncology 2008; 89: 51-56

P042

PREEMPTIVE TREATMENT WITH XONRID, A MEDICAL DEVICE TO REDUCE RADIATION INDUCED DERMATITIS IN HEAD AND NECK CANCER PATIENTS RECEIVING CURATIVE TREATMENT: A PILOT STUDY

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Aims: Acute radiation dermatitis is a common side effect of radiotherapy (RT) in head and neck cancer (HNC). Xonrid is a topical gel that prevents and treats skin symptoms. The aims of the study were: evaluate worst skin toxicity during RT and after 2 weeks (we), find mean and worst score of Patient Reported Outcome (PRO) according to Skindex-16 questionnaire and find median time to G2 radiation dermatitis development.

Methods: In this prospective pilot study we enrolled HNC patients (pts) with squamous cell carcinoma (SCC), treated with IMRT or VMAT, total dose >50-66 Gy in adjuvant setting and 66-70 Gy in radical setting, using 1.8-2.12 Gy/die. Concurrent platinum based chemotherapy was accepted, but not Cetuximab or cutaneous and connective diseases. Pts were preemptively treated with XONRID and standard of care (SOC). SOC consisted of washing with warm water and a mild pH-neutral soap. Pts were instructed to apply XONRID on the irradiated area two times daily, from the beginning until 2 we after the end of RT or resolution of symptoms. All pts have been evaluated at baseline, at weekly intervals during RT and 2 we after treatment completion by 2 different treating physicians, using the CTCAE v4.0 scale and the Skindex-16 questionnaire. Skin reflectance measurements were also acquired with a spectrophotometric imaging system (SpectroShade) at baseline and weekly.

Results: Between March 2015 and October 2015 41 pts were treated, definitive and postoperative treatment were performed in 34 and 7 pts respectively. The 78.1% of pts received platinum-based and the 36.69% TPF induction. The agreement in toxicity evaluation has been 100% between the two physicians. At the end of RT all pts experienced skin toxicities: 9 pts (22%) grade1 (G1), 31 (76%) G2 and 1 pt (2%) G3. G3 toxicity appeared after 5 we. Seven pts reached skin maximum toxicity (SMT) at 4 we and 20 pts after 7 we. Two pts reached their SMT at 9 we. The toxicity was higher in pts with radical setting ($p<0.05$). We observed a correlation among Skindex-16 scores, skin toxicity during treatment and an increasing trend of median spectrophotometry scores along with skin toxicity grades.

Conclusions: This study showed that Xonrid is safe and feasible, and reduces and delay the incidence of major toxicity. We observed a correlation between Skindex-16 scores and skin toxicity during treatment and an increasing trend of median spectrophotometry scores along with skin toxicity grades.

P043

CHONDROSARCOMA OF THE NASAL SEPTUM AND HARD PALATE: EXCELLENT FEASIBILITY AND CLINICAL COMPLIANCE WITH HYPOFRACTIONATED TREATMENT DELIVERED WITH HELICAL TOMOTHERAPY

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Aims: In our Institute we treat more than 80 Head&Neck patients yearly. The patient under study was an 86 years old man affected by a chondrosarcoma of nasal septum that underwent to R1 resection and was presented to our attention to evaluate adjuvant RadioTherapy (RT). The main challenge was to save the hard palate by acute toxicity and to avoid conjunctivitis.

Methods: Treatment volumes have been identified on pre surgery MRI and all Organs At Risk (OAR) were countered (including eyes, optic nerves, optic chiasm, lens, brain, brainstem, spinal cord, parotid glands, inner ear and oral cavity) and copied on a registered CT. The

Prescribed Dose (PD) of 62.5 Gy in 25 fractions was delivered with a full 360° 6 MV photon Helical TomoTherapy. The treatment plan was satisfactory due to the very high conformation of helical IMRT technique that allowes to spare critical OAR in proximity of PTV and to control the dose received by OAR within the PTV, such as oral cavity. The strategy was to divide the PTV in two regions: the upper PTV close to the eyes (PTV1) and the lower PTV overlapping with the oral cavity (PTV2). Our priority was to have optimal homogeneity and no hot spots on PTV2, while the coverage of PTV1 has been slightly sacrificed in favor of sparing the Eyes.

Results: The treatment beam-on time was 11.65 minutes, with a field width of 1.05 cm and a pitch of 0.287. Daily check shifts were assessed using Mega Voltage CT (MVCT) and expressed in terms of mean and standard deviation compared to the first fraction as LAT=(-0.4±2.5)mm, LONG=(-1.4±2.0)mm, VERT=(0.2±1.2)mm and ROLL=(1,1°±1.1°). The modified Homogeneity Index (mHI) written in figure and suggested by P. Pathak (J Med Phys 2013 38(2)) was kept as low as possible for both PTVs compatibly with an optimal coverage; in particular the resulting value of mHI was respectively 0,05 for PTV1 and 0,04 for the smallest PTV2. At the end of RT, the patient referred mild edema of the hard palate, slightly painful on palpation, erythema and pain in the anterior gingival region, few episodes of bleeding from the nose, absence of significant mucositis, no erosion hard palate. All these symptoms disappeared within 2 weeks by the end of RT.

Conclusions: Despite of the old patient age, the daily verifications made us sure that the patient repositioning was precise, as we appreciated from small shifts deviations. With a dose per fraction of 2.5 Gy, the patient had no severe acute toxicity on hard palate and on eyes.

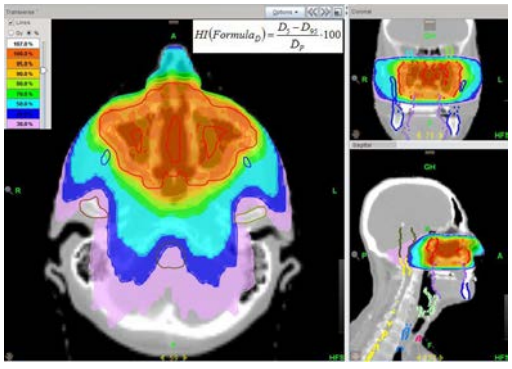

Figure 1.

P044

CHEMORADIATION FOR HEAD NECK CANCER: TOXICITY COMPARISON OF DIFFERENT FRACTIONATION SCHEMES OF IMAGE-GUIDED INTENSITY MODULATED RADIOTHERAPY (IG-IMRT, TOMOTHERAPY) AND SIMULTANEOUS-INTEGRATED BOOST (SIB)

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Aims: Concurrent chemoradiation (CRT) is a standard treatment for loco-regionally advanced head and neck squamous cell carcinoma (HNSCC). The aim of this retrospective study was to evaluate acute toxicity of different fractionation schedules of IG-IMRT and SIB with concomitant platinum based chemotherapy.

Methods: We retrospectively evaluated 44 patients with stage III/IV HNSCC of the larynx, oropharynx, nasopharynx and oral cavity who underwent definitive (n=25) or postoperative (n=19) SIB IG-IMRT between January 2013 and January 2016. All patients received concomitant chemotherapy with two different regimens: weekly (40 mg/m^2) or 3-weekly (100 mg/m^2) cisplatin based treatment. We delineated different clinical target volumes (CTVs) and planned different doses based on primary site of disease and RT intent. 27 patients were treated with hypofractionated schedule (2,12-2,20 Gy/fr SIB to primary tumor and/or positive resection margins; group A), while 17 patients received RT with standard fractionation schedule (1,8-2,0 Gy/fr; group B). Early toxicity was evaluated weekly according to the CTCAE scale 4.0.

Results: No severe life risking complications were observed during treatment. We reported G1/G2 mucositis in 67% of patients in Group A and in 65% in Group B. Severe painful mucositis, interfering with oral intake (G3) was observed only in 2 patients (7,4%) in Group A, both treated with concomitant weekly cisplatin, and in 2 patients (12%) in Group B treated with different chemotherapy regimens. Acute G1/G2 dysphagia occurred in 74% of patients in Group A and in 88% in Group B while severe dysphagia that needs tube feeding (G3) was observed in only one patient in Group B, treated with concomitant 3-weekly cisplatin based chemotherapy. 30% of Group A and B patients reported G1/G2 xerostomia, while no one presented grade 3 swallowing dysfunction. During treatment faint/moderate erythema (G1/G2) was observed in 44% of Group A and in 59% in Group B patients. Only 3 patients had reported grade 1 anemia, all treated with hypofractionated scheme (Group A), two of theme received weekly cisplatin based chemotherapy.

Conclusions: Concurrent chemoradiation with SIB IG-IMRT (Tomotherapy) is a safe treatment for stage III/IV HNSCC. In our small cohort of patients, we did not reported differences regarding acute toxicities between moderate hypofractionated and conventional schedule.

P045

CONVENTIONALLY FRACTIONATED IMRT AND ACCELERATED HYPOFRACTIONATED IMRT-SIB WITH CONCOMITANT PLATINUM BASED CHEMOTHERAPY FOR OPSCC: A SINGLE INSTITUTION EXPERIENCE

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Aims: To evaluate loco-regional response and acute toxicity in patients treated with conventional IMRT and hypofractionated IMRT-SIB for OPSCC in locally advanced stage.

Methods: Between February 2009 and February 2016, 48 consecutive patients with locally advanced OPSCC (IVa 87,5%, III 10,5% II 2%) received IMRT with or without SIB with concurred platinum based chemotherapy. Conventional RT was administered with a dose of 70 Gy in 35 fractions. IMRT-SIB was administered with a dose/fraction of 2,25 Gy per 30 fractions (67,5 Gy) to high dose PTV and simultaneously 54-60 Gy respectively to high risk and low risk PTVS in 30 fractions.

Results: 48 patients were retrospectively analyzed. 38 patients were treated with conventional IMRT and 10 patients with IMRT-SIB. 20 patients treated with conventional IMRT received TPF induction chemotherapy. All patients received concurrent Cisplatin 100 mg/m^2 chemotherapy for 2 cycles. Major acute toxicities were grade 3 mucositis: 40% in group treated with conventional IMRT (30% in patients who received induction chemotherapy) and 30% in group treated with IMRT-SIB; grade 3 odynophagia (5% in group received conventional IMRT and induction cht, 10% in group SIB-IMRT); grade 3 dysphagia only in 5% in group received conventional IMRT. Feeding tube occurred in 12 pts: 3 in group treated with IMRT-SIB and 9 pts in group treated with conventional RT (4 pts receiving induction chemotherapy). After a median follow up of 28,3 mounths (3-84 mounths), 14 patients died (11 for causes cancer related and 3 for other causes). At first imaging follow up (3 mouths after the end of radiotherapy), local control was: PARTIAL RESPONSE for 12 patients (38% in the group treated with conventional IMRT, 10% in the group treated with SIB and 20 % in the group receiving induction cht); STABILITY DISEASE for 1 patient (In the group treated with conventional IMRT) and COMPLETE RESPONSE for 35 pts (61% in the group treated with conventional IMRT, 90 % in group treated with SIB and 80 % in group receiving induction cht).

Conclusions: Despite the small sample, IMRT-SIB seems to be feasible with an acceptable acute toxicity rate and has a high grade of local response. A longer follow-up is needed to fully evaluate late effect.

P046

LONG-TERM RESULTS OF CONCURRENT CETUXIMAB AND RADIOTHERAPY IN LOCALLY ADVANCED HEAD AND NECK CARCINOMA

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Aims. Cetuximab showed a benefit in addition to radiotherapy (RT) in patients (pts) with LAHNC. Acute in-field toxicity is primarily skin and mucosal reaction. Retrospectively, we analyzed the response rate and long term toxicity in our pts submitted to this combination.

Methods. We selected 12 pts with LAHNC followed as an outpatients, that underwent radical treatment with cetuximab and RT between May 2007 and April 2012. Planned treatment consisted of cetuximab loading dose (400 mg/m^2) in 1 week prior and then weekly (250 mg/m^2) with 70-74Gy (1.8-2 Gy fraction) over 7-8 weeks. Acute and late toxicities were clinically graded according to the Common Terminology Criteria Adverse Events version 3. Median age was 55 years (range, 41-76), male/female ratio was 9/3. The primary sites of tumor were oropharynx, larynx, rinopharynx and hypopharynx, in 6, 4, 1 and 1 pts, respectively.

Results. Median follow-up was 83 months (range, 82-104). All pts received the planned dose of RT. Four (33%) pts required a prolonged treatment break (median 5 days, range 1-8) due to grade 3 acute dermatological toxicity (mucosal and skin reactions). In 3 (25%) pts the full 8 weeks of cetuximab were completed, in 3 (25%) pts the dose was reduced of 25% for skin toxicity, and in 4 (33%) pts cetuximab was discontinued after 6 infusion for cutaneous reaction. Overall acute grade 3 toxicity was observed in 4 (33%) pts: in one grade 3 in-field dermatitis at 50.4 Gy, in other three grade 3 mucosytis by 25.2, 25.2, and 32 Gy, respectively. All patients had at least one grade 1-2 late toxicity: subcutaneous toxicity in 12 (100%) pts, sticky saliva in 9 (75%), dry mouth in 9 (75%), dysphagia in 4 (33%) pts, respectively. We never registered grade 3-4 late toxicity. At instrumental control (MRI and/or PET-CT), given 3 months after treatment, 9 (75%) complete remission, 2 (17%) partial remission, and 1 (8%) progression were registered. The patient in progression died 2 months after the end of therapy. Median duration of response was 72 months (range, 6-104). Crude survival at 3 and 5 years were 67% and 58%, respectively.

Conclusions. Despite the relatively low number of examined pts, our data resulting from a very long follow up, confirm the efficacy of cetuximab and RT combination. The addition of cetuximab to RT is not associated to grade 3-4 late toxicity in long-term survivors.

P047

IMRT TECHNIQUE AND CONCOMITANT BOOST (SIB) WITH CONCURRENT CHEMOTHERAPY FOR THE TREATMENT OF THE HNC. A MULTICENTRIC EXPERIENCE.

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Aims: The intensity modulated radiation therapy (IMRT) for the treatment of head and neck cancer (HNC), is increasingly gaining ground in many radiotherapy centers. The primary benefit of using intensity modulated techniques is expressed in the limitation of radiation-induced damage, especially for preserving salivary function. There are still few experiences in the use of IMRT with simultaneous integrated boost (SIB-IMRT) in the treatment of head and neck cancers, in terms of disease's control and sparing of normal tissues. On the other hand, concurrent chemotherapy (CRT) in head and neck cancer is the treatment of choice for organ preservation or in unresectable disease. Our aim was to evaluate tumor response in HNC patients treated with SIB-IMRT and concurrent chemotherapy, and to rate tissue tolerance following different chemoradiotherapy schedules.

Table 1. Patients characteristics.

	N° Patients
Age<70 years	20
Age>70 years	10
Male	26
Female	4
PS 0-1	28
PS 2	2
Smoker	24
Non-smoker	6
Peg placement	8
Non peg placement	22
Tumor site	
Larynx	9
Oral cavity	9
Oropharynx	6
Nasopharynx	2
Hypopharynx	2
Paranasal sinus	2

Methods: Since January 2013 to April 2016, we selected 23 patients who undergone concurrent chemoradiotherapy in our Department and in the radiation oncology Unit of Papardo Hospital. All patients were treated using the IMRT technique with doses between 63 and 66 Gy and a daily fraction of 180-200 cGy, adding a SIB between 10 to 40 cGy/ die. Two different cytotoxic drugs were used: cetuximab (250 mg/m^2/ 7 days) and cisplatin (40 mg/m^2/7 days). All patients who undergone chemoradiotherapy using cetuximab, were subjected to induction therapy with platin based drugs and paclitaxel, before the concurrent treatment with chemo and radiotherapy.

Results: At the beginning of May 2016, 6 of the 23 patients had died after a median of 7 months of survival (range 2-19) for disease complication, 1 patients was lost at follow up and for the 16 patients still alive, the median of survival was 10 months (range 2-34). Among these, 14 patients did not have disease progression, all had got reduction in salivation and dysphagia during and after the treatment, these disorders had then improved over time, and currently only one of these patients has reduction in salivation and taste disorders. Only 2 patients had locoregional disease progression.

Conclusions: The use of IMRT associated with SIB and concurrent chemotherapy has shown to be a valid therapeutic approach both for disease control and limitation of side effects, for patients affected by cancer of the H&N region.

P048

PAIN AND DISCOMFORT IN RECURRENT/METASTATIC HEAD AND NECK CANCER PATIENTS: COULD CETUXIMAB TOGETHER WITH OTHER MEDICATIONS HELP TO IMPROVE THE PAIN AND DISCOMFORT CONTROL?

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Aims: To evaluate skin toxicity, impact on pain and nutritional status of Cetuximab treatment in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck

Methods: 30 patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck were treated from 2010 to 2015 at Radiotherapy Unit of San Donato Hospital with targeted anti-EGFR antibodies Cetuximab. Ten patients were ≥70 years, 20 <70 years, 26 were male and 4 female ad 24 were smokers. Eight patients had a percutaneous endoscopic gastrostomy (PEG). We evaluated acute toxicity according to CTCAe v 4.0, pain according Visual Rating Scale (VRS) and survival and the impact on outcome of age, site, gender, PS, smoking or non smoking patients and PEG placement.

Results: 23% of patients had nausea G1-G2, 13% vomiting G1-G2, 47% mucosites G1-G2 and 1 patient mucosites G3. 40% of patients had skin toxicity G1-G2 and 6,6% G3 and 17% had paronychia. Six (20%) patients had weight loss from 5-10% and 2 more than 10%. 40% reported hypomagnesemia. Neutropenia and anemia was reported in 2 and 3 patients respectively. One patient developed adverse reaction during the first infusion. One patient died for sepsis. Thirteen subject reported pain at recurrence, 12 of them showed a reduction of VRS mean score (from 2.5 to 1.6) during three months without increasing farmacological therapy. Median survi-

val from first diagnosis and from relapse were 20 (SD 2.8) and 10,5 (SD 1.5) months respectively. Prospectively 26,7 % and 60% of patients were alive at 1 year from relapse and from the first diagnosis. The survival rate was better in female (p=0.04). The correlation between survival and demografic and clinical characteristics were not significant, probably due to small sample size.

Conclusions: although patients with recurrent/metastatic head and neck squamous cell carcinoma have a poor prognosis, Cetuximab demonstrated an Overall Survival (OS) advantage in this clinical setting. Our experience confirmed literature data in term of median OS (10.5 months) and toxicity. A better pain relief was obtained above all during maintenance period. Moreover, as other studies, we hypothesized that a combinatory strategy (cetuximab toghether with other medications) can improve pain control.

P049

IMPACT OF VOLUMETRIC MODULATED ARC THERAPY WITH SIMULTANEOUS INTEGRATED BOOST (VMAT-SIB) FOR HEAD AND NECK CANCER PATIENTS: OUR EARLY EXPERIENCE

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Aims: Aim of our work was to observe the impact of VMAT-SIB for treatment, local control and acute toxicity of head and neck cancer Stage III-IV, and its impact on reduction of the waiting list. Methods: From January 2015 to May 2016 we evaluated eighteen patients (pts) 10 males and 8 women, with head and neck cancer, Stage III-IV. All patients received 3-weekly cisplatin 100 mg/m chemotherapy. For all patients was customized a thermoplastic head-neck-shoulders mask and acquired a thin-slice (2 mm) simul-CT. The identification and delineation of volumes (target and organs at risk-OARs) was performed on simul-CT scans fused with MR images. Treatment planning VMAT-SIB was performed with TPS Monaco 5.1 and Ray–station. We treated all pts in 28 fractions (fx), with 2.15 Gy - 2.2 Gy (total dose 60.2-61.6Gy) to the boost volume, with 2Gy or 1.9Gy (total dose 56-54Gy) to intermediate PTV volume, with 1.6 Gy or 1.8 Gy (total dose 45-50.4Gy) to the low PTV volume. In planning we have been focusing on dosimetric parameters of the oral cavity, parotid glands, superior constrictor. We evaluated the acute toxicity according to the RTOG criteria. Results: All patients with appropriate supportive therapy, have completed the treatment without interruption at prescribed dose. Skin toxicity G0 was reported in 8 pts, G1 in 9 pts, G2 in 1 pts; dysphagia G1 in 2 pts,G2 in 16 pts; taste, nausea and alopecia was reported in all pts. Higher toxicity was observed in oral cavity, with mucositis G1 reported in 5 pts, G2 in 11 pts, G3 in 2 pts We also analyzed the impact of hypofractionated treatment on local control, the shorter duration of treatment and consequent reduction of our waiting list that has ensured the start of treatment in 6 weeks for all patients enrolled. The use of hypofractionated treatment in our center has allowed a tolerable acute toxicity, in the curative treatment of patients ensuring a coverage of 95-98% of the PTV and the respect of costraints doses. The VMAT-SIB treatments allow an increase in local control, reduction of one week in the waiting list, acceptable treatment times for patients.

Conclusions: The VMAT-SIB is the optimal solutions in the radiation treatment of head and neck cancers, for a good toxicity profile, for patient's compliance derived from a shorter treatment, and for a better management of waiting lists.

P050

SAFETY ANALYSIS OF EGFR TYROSINE KINASE INHIBITORS (TKIS), ALONE OR IN COMBINATION WITH RADIOTHERAPY (RT), IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC NON-SMALL-CELL LUNG CANCER (NSCLC): A SINGLE INSTITUTION EXPERIENCE

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Aims: To assess the toxicity profile of single-agent EGFR-TKIs used in the treatment of patients with locally advanced or metastatic NSCLC, alone or in combination with RT.

Methods: We report data about 36 patients with locally advanced (25%) or metastatic (75%) NSCLC, receiving EGFR-TKIs. The exon 19 deletion was detected in 36 %, while L858R point mutation in exon 21 was observed in 22% of them; in 1 subject, both exon mutations were present. Sixteen patients were EGFR wild-type, all of them were treated with Erlotinib. Ten patients received Gefitinib, 19 received Erlotinib, and 7 received Afatinib; those were administrated at the standard dose of 250 mg/daily, 150 mg/daily and 40 mg/daily respectively, until disease progression or until adverse effects (AEs) became intolerable. EGFR-TKIs were used as I line treatment of locally advanced NSCLC in 33.3%, as I line of metastatic NSCLC in 38.8% and as II line of metastatic NSCLC in 27.9% of cases. Sixteen patients also received RT, mainly with 3 Gy/day, 5 days/week up to a total dose of 30 Gy; the median interval between EGFR-TKIs and RT was 5 days. Toxicity was documented according to the CTCAE V4.0, once a week during the first cycle of TKIs and during RT, then every month.

Results: After a median follow-up of 12 months, patients showed a G1-2 toxicities in 66% and G3 toxicities in 17.8 % of cases. In 16.2% was not reported toxicity. In G1–2, diarrhea was statistically worse for Afatinib and Gefitinib, whereas rash and fatigue were statistically worse for Erlotinib. Rash and diarrhea G3 were more fre-

quent with Afatinib than with Erlotinib or Gefitinib. The overall frequency of AEs leading to treatment withdrawal was 6%, occurring more often with Afatinib or Gefitinib. The reduction of dose was necessary in 35% of patients, in all of them we resumed TKIs standard dose when AEs improved to G1. The combination group with RT showed a similar toxicity, such as G3 in 20% versus 24% of EGFR-TKI alone; we noticed specific toxicity related to the RT such as alopecia G1 in 1 case, headache G2 in 1 case and Dysphagia in 1 case. We saw no cases of RT enhancing the TKI-related rash in the treatment area.

Conclusions: In our study we found a similar toxicity profile for EGFR-TKIs as those described in literature. A small percentage of patients were lead to treatment withdrawal but the standard dose was restored in almost all cases. Combination with RT caused negligible toxicities adding to those derived from EGFR-TKIs.

P051

EFFICACY OF HYPOFRACTIONATED IMAGE-GUIDED RADIATION THERAPY (3GY/FRACTION) IN PATIENTS AFFECTED BY INOPERABLE ADVANCED-STAGE NON-SMALL CELL LUNG CANCER AFTER LONG-TERM FOLLOW-UP

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Aims: To evaluate the long-term outcome of a hypofractionated radiotherapy (RT) in the treatment of patients affected by inoperable advanced-stage non-small cell lung cancer (NSCLC).

Methods: Seventhy-one patients with advanced-stage NSCLC (IIIA-IV) were treated at our Institution with hypofractionated radiotherapy (60Gy/20 fractions). Correct positioning was verified using an image-guided RT technique. Toxicities were graded according to the Common Toxicity Criteria for Adverse Effects v 4.0 scale.

Results: Overall, 8 patients achieved a complete response and 53 patients had a partial response (tumor response rate 86%). After a median follow-up of 32 months, locoregional progression occurred in 28 (39.4%) patients and distant progression occurred in 45 (63.3%). The 1-year and 2-years overall survival were 56% and 41%, respectively. The 1-year and 2-years progression-free survival (PFS) were 47.5% and 33.2%, respectively. The median duration of OS and PFS was 13 months and 12 months, respectively. The 2-year local PFS and metastases-free survival (MFS) were 53% and 40.3%, respectively. On univariate analysis, the T-size (≥5 cm), and type of response to RT (non-response/progressive disease) were significantly associated with worse OS. Type of response was identified as significant prognostic factors for PFS ($p<0.01$) local PFS ($p=0.015$) and MFS ($p<0.01$). Acute grade 3 esophagitis and pneumonitis occurred in 4 patients (5.6%) and 4 patients (5.6%), respectively. Late grade 3 esophagitis and pneumonitis occurred in 2% (one patient) and 4.2% (three patients), respectively. No patient experienced grade 4 acute or late RT-related toxicities.

Conclusions: Hypofractionated RT offers good disease control for patients with advanced-stage NSCLC with acceptable toxicity rates. Phase III randomized trials are necessary to compare hypofractionated RT with conventional RT.

P052

TEXTURE ANALYSIS AS A PREDICTIVE FACTOR IN EARLY STAGE LUNG CANCER TREATED WITH STEREOTACTIC ABLATIVE RADIOTHERAPY (SABR)

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Aims: Stereotactic ablative radiotherapy (SABR) is widely used in lung cancer primary treatment. The aim of present study is to evaluate the texture analysis (TA) as a predictive factor of treatment response.

Methods: This single center retrospective study included fifty-six consecutive patients (January 2011 – December 2014) with early stage lung cancer (T1-2a, N0) treated with SABR. The diagnostic CT DICOM images pre- and post- SABR were collected and analysed with an homemade ImageJ macro. TA parameters that were evaluated included mean (m), standard deviation (sd), skewness(sk), kurtosis (k), entropy (e) and uniformity (u). We analyzed progression free survival with modality of lung progression (PFS in-field and PFS out-field) after treatment and overall survival (OS), calculated with Kaplan-Meier method.

Results: During the observation period 15 patients (26,8%) showed evidence of recurrence, divided in recurrence "in-field" in 9 patients (16,1%), and "out of field" recurrence in 11 patients (19,6%). Five patients developed both "in field" and "out of field" recurrence; 14 patients (25%) died. Pre SABR parameters Entropy (e) and uniformity (u) were significantly associated with PFS "in field" (p:0,030), whereas kurtosis (k) was significantly associated with PFS "out of field" (p:0,031) and Mean (m) was significantly associated with OS ($p<0,001$). Post SABR parameters entropy (e) was associated with PFS "in field" (p:0,009), whereas mean (m) was associated with PFS "out of field" ($p<0,001$). A rise in mean ($p<0,001$), entropy (p:0,028) and a decrease in uniformity (p:0,028) resulted to be significantly associated with PFS "out of field".

Conclusions: Our results appear to be very promising

since the knowledge of the predictive factors of SABR could drive the selection of the best treatment in these patients (i.e. dose increasing in the patients at higher risk? Concurrent chemoradiation? Intensified follow up?). Further studies on large patient series are needed to best estimate the present preliminary data.

P053

CAN HYPOFRACTIONATED VMAT BE A SAFE AND EFFECTIVE TREATMENT FOR LOCALLY ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC) IN THE ELDERLY? RESULTS FROM AN OBSERVATIONAL STUDY

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Aims: To analyze feasibility and toxicity of radical hypofractionated RT schedules in elderly patients with NSCLC.

Materials and Methods: Elderly patients (≥70 years old) affected by stage III inoperable NSCLC were treated at our institution with radical IMRT (VMAT RA) according to moderately hypofractionated schedules: 55 Gy/20 fractions or 55 Gy/22 fractions or 50 Gy/20 fractions depending on dose constraints of adjacent organs at risk. Concomitant RT-CHT was not allowed. Patients underwent simulation CT in supine position, immobilized with a thermoplastic mask. PET CT was performed for simulation and coregistered with CT scan. Primary end point of this analysis were acute and late toxicities, secondary end points were local control and overall survival. Toxicities were scored according to Common Terminology Criteria for Adverse Events version 4.0.

Results: Between January 2013 and November 2015, 47 patients were treated at our Institution and included in this analysis. Mean age was 79 years (range 70-86). 25 patients were staged IIIA, 22 patients IIIB. All but one patients had pathological nodal involvement (N1:5, N2: 27, N3: 14). Most of patients were unsuitable for chemotherapy for comorbidities and poor general conditions. Eighteen patients received chemotherapy before RT. Acute G1-2 toxicity was recorded in 30 patients, mostly esophagitis, dyspnea and dry cough. Late toxicity was recorded in 14 patients, the most reported side effects were pneumonitis and dyspnea. No G3 or G4 acute or late toxicity were recorded. A complete response was obtained in four patients, 28 showed a partial response, while progressive disease was recorded in 2 cases. At the time of analysis, with a mean follow up of 11 months (range 1.08-25.43), 18 patients died for disease progression, one patient died for other causes, 10 patients were alive with distant metastases and 18 were alive without distant progression. Actuarial OS at 1 and 2 years were 52% and 35% respectively. Mean estimated OS was 15 months (range 12.02-18.22). Actuarial local control at 1 and 2 years were 72%. Twelve patients experienced local progression. Mean estimated LC was 12 months (range 9.6-15.1).

Conclusions: Radical hypofractionated IMRT (VMAT RA) is a valid treatment for locally advanced inoperable NSCLC in elderly frail patients . Our study shows that this approach is safe and effective also in a fragile elder population.

P054

MODERATELY HYPOFRACTIONATED TOMOTHERAPY IN MALIGNANT PLEURAL MESOTHELIOMA: OUTCOME PREDICTORS

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Aims: In a dose escalation study of moderate hypofractionated tomotherapy(HTT) we obtained statistically significant better local control adding a simultaneous integrated boost (SIB) on FDG-PET positive areas (BTV). Here we evaluate factors influencing outcome in MPM patients(pts) treated with HTT.

Methods: From May 2006 to April 2014 54 pts with MPM, progressive after previous treatments (surgery + chemotherapy) were treated with salvage HTT. Patient characteristics are presented in the scheme below.

Sex	Men: women = 44:10
Median age	69 years (39-82)
Median follow up	10.2 months (1.18-70)
Histology	Biphasic /sarcomatous: epithelial= 8:46
Location	Right pleura: Left pleura= 29:25
Initial Stage	I:II:III:IV= 10:15:22:7
Induction CT	Yes:no= 48:6
Surgery	Extrapleural pneumonectomy(EPP) vs Pleurectomy (P) vs Biopsy/Talc Pleurodhesis= 2 vs 19 vs 33
Boost on BTV	Yes:No= 40:14
Treated volumes	Median PTV: Median BTV= 3166.7 cc: 196.65 cc

Median survival was 10.2 (1.18-70) months, 4 patients, all treated with SIB, were alive at the last follow up. A univariate analysis was performed to identify which of these factors: BTV boost, volume of BTV, type of surgery, histology, stage, chemotherapy yes/no and volume of PTV influence Overall Survival(OS), Local Relapse(LR) and Distant and Local Relapse(R).

Results: Median survival for initial stage I vs II vs III vs IV was: 10.2: 22.07:9.97:5.72 (p=0.006). Only stage (I-II vs III-IV) was statistically significant in predicting OS: 13.11 vs 8.23 months(mts) (p=0.04) and only surgery yes(EPP/P) vs no (TP) for LR(p=0.009). SIB on BTV has an impact on survival for stage III-IV (p=0.05), but not for stage I-II (p=0.7). A BTV volume of 353.2 cc was

found to be the best cut-off having a statistically significant impact on OS (p= 0.0003). Median OS was 5.84 vs 7.8 vs 11.54 (p=0.04) for pts without SIB vs pts with SIB and BTV volume>cut off vs pts with BTV<cut-off. BTV volume< 353.2 cc significantly influences OS in stage III-IV (p=0.03). In stage III-IV SIB has a role in BTV< 353.2 cc, and pts with higher BTV treated with SIB have similar OS to pts without boost: 11.54 vs 6 vs 4.85 mts (p=0.04). In stages III-IV, type of surgery was significant for OS: EPP vs P vs TP= 1.61: 10.1:8.23 (p=0.001). For pts with TP BTV volume <353.2 cc is a significant predictor of survival (p=0.001) and these pts have a better OS than pts with larger BTV treated with SIB or without SIB: 13.11 vs 7.8 vs 7.74(p=0.04).

Conclusions: The BTV cut off volume <353.2 cc significantly influences OS in stage III-IV pts , even in those treated with palliative surgery, but irradiated with SIB and can help in patient selection for salvage SIB HTT.

P055

STEREOTACTIC BODY RADIOTHERAPY FOR MEDICALLY INOPERABLE EARLY STAGE NON SMALL CELL LUNG CANCER: A RETROSPECTIVE SINGLE-CENTER EXPERIENCE

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Aims: The aim of this study was to analyze the outcomes of patients (pts) with Stage I non-small-cell lung cancer (NSCLC), unfit for surgery, treated with stereotactic body radiotherapy (SBRT).

Methods: We retrospectively reviewed all pts with stage I NSCLC who underwent radical SBRT from April 2010 to August 2014. The total dose prescribed varied according to tumor site and maximum diameter. The median dose performed was of 56 Gy in 5 fractions (range, 54-60 Gy /3-10 fractions), prescribed to 80% isodose. All pts underwent image guided radiotherapy (daily Cone Beam computed tomography (CT)). Pts were assessed for toxicity once a week during the treatment and at each follow up (FU) visit after SBRT. Response rates were scored according to the RECIST guidelines versions 1.1 and for acute and late toxicity the CTCAE version 4.0 was used. Follow-up included physical examination and a chest CT scan +/- FDG PET/CT at 3, 6, 12 and 24 months, and thereafter annually after SBRT treatment. Response rates were scored according to the RECIST or PERCIST guidelines.

Results: 110 pts were included, 28 female and 82 male, median age was 78 years (range, 46-88). The median planning treatment volume (PTV) was 34,08 cc (range, 5.32-116,76). The median follow-up was 24 months (range, 2- 60). Two and 4 year local control rate, cancer specific survival, overall survival rate were 87.4% and 72.6%, 79.1% and 59.2%, 70.9 % and 31.3%, respectively. No statistically significant difference was found in the local control between sex (male vs female), Biological Effective Dose (BED) (>100 Gy vs ≤100 Gy), lung comorbidity (yes vs no) or PTV (≤ 34.08 cc vs>34.08 cc). No Grade 3 or greater acute and late toxicities were identified.

Conclusions: Lung SBRT for early-stage NSCLC unfit for surgery resulted in excellent local control with minimal toxicity.

P056

ONCOGENE-ADDICTED NON SMALL-CELL LUNG CANCER: RADIOTHERAPY AND TARGET THERAPY IN THE PARMA CENTRE EXPERIENCE

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Aims: The benefit and safety of radiotherapy (local therapy) in patients with oncogene-addicted non small-cell lung cancer (NSCLC) treated with target therapy are not clear. We investigated, retrospectively, the side effects and the role of radiotherapy in patients with oncogene-driven non small-cell lung cancer (EGFR mutated and ALK positive) treated with tyrosine kinase inhibitors (TKIs; EGFR-TKIs in EGFR-mutated and crizotinib in ALK positive).

Table 1. Sites of disease and treatment.

Sites of disease	No. of treatment	HypoRT	XRT
Brain	2	2	
Lung	7	5	2
Bone	14	14	
Lymph-nodes	1	1	

HyopRT: hypofractionation radiation therapy; XRT: external beam radiation therapy.

Table 2. Doses of radiotherapy.

Sites of disease	Mean Dose Gy (range)
Brain	30 Gy (3 Gy/fr.)
Lung	38,7 (30-60 Gy; 2-8 Gy/fr.)
Bone	20 (6-30 Gy; 3-8 Gy/fr.)
Lymph-nodes	25 Gy (5 Gy/fr.)

Methods: From March 2013 to December 2015 we identified 19 patients (8 males and 11 females) with adenocarcinoma: 2 of them received crizotinib for ALK posi-

tive and the other 17 received gefitinib for EGFR-mutated advanced NSCLC. All patients received radiotherapy on metastatic sites and/or on primary tumor. Treatment toxicity and median time to the new disease progression were recorded. Toxicity was assessed on the basis of RTOG-Criteria. Five patients received two cycles of radiotherapy in the same period.

Results: The average age was 64,5 years (range 46-81). Most patients (n=14) were treated for bone localization and as expected no toxicity was recorded. Any toxicity greater than G1 wasn't observed in patients treated for brain and lymph-nodes localizations. However we recorded G2 and G3 lung toxicity for two patients in treatment of gefitinib and thoracic radiotherapy. As for the median time to the new progression of the disease this proved to be 8 months (range 2-12 months).

Conclusions: Local therapy in patients with oncogene-addicted NSCLC is feasible with an acceptable toxicity profile and it is associated with more than 6 months of additional disease control.

P057

PRIMARY MALIGNANT LUNG NODULES (PMLN) TREATED WITH STEREOTACTIC BODY RADIOTHERAPY (SBRT): SURVIVAL AND TOXICITY ANALYSIS IN A SINGLE INSTITUTION SERIES

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Aim: To retrospectively evaluate efficacy and toxicity of SBRT in the management of PMLN.

Materials and Methods: Data of all patients (pts) treated with SBRT for primary lung cancer were reviewed. Local Control (LC), disease specific survival (DSS) and overall survival (OS), acute and late lung toxicity (ALT and LLT) and late radiological pulmonary effects (LRE), according to RTOG scale, were considered as endpoints of the analysis. Kaplan-Meyer curves and log-rank test were elaborated for survival analysis, while chi-square test was calculated to compare different variables. P< 0.05 was considered significant.

Results: From 2012 to 2015 46 pts with PMLN were treated with SBRT on 53 lesions. Clinical and therapeutic data of the series are reported in Table 1. Median follow up was 17.4 months. Progressive disease (PD) was reported in 4 cases (8.7%), while complete and partial response and stable disease was observed in 23 (50%), 11 (23.9%) and 8 (17.4%) pts, respectively. 2-year OS, DSS and LC resulted 76.5%, 94.3% and 86.7%, respectively. Patients never treated for lung cancer had a better DSS than those previously treated (p 0.009). No other variables significantly impacted on survival. ALT was observed in 17/46 pts (37%), including only 4 G3 cases. LLT was evident in 22 pts (47.8%), including 1 G3 and 2 G4 cases. LRE was observed in most pts (39/46, 84.7%, with 9 G3 cases, 19.5%) and was more frequent in older pts (p 0.035).

Conclusions: SBRT for PMLN allows to achieve good LC, OS and DSS rates independently by age, performance status, GOLD COPD stage, type of diagnosis. Both the schedules of SBRT seemed equivalent in efficacy and safety. LREs were common but only about half of the cases resulted clinically relevant with G3-G4 LLT in 3 pts (7%).

Table 1.

Variable	n.	%
Age	(median 75 years)	
< 75 years	21	45.7
≥ 75 years	25	54.3
Performance Status		
0	8	17.4
1	35	76.1
2	3	6.5
Diagnosis		
Radiological diagnosis	17	37.0
Histological proven	29	63.0
Staging		
TC	3	6.5
18fdg TC-PET	2	4.3
Both	41	89.2
GOLD COPD stage		
0	16	34.8
1-2	14	30.4
3-4	10	21.7
Unknown	6	13.1
Previous treatment		
No	36	78.3
Yes	10	21.7
SBRT schedule		
11 Gy x 5 fr	41	89.1
6.5 Gy x 8 fr	5	10.9
Technique		
3D Conformal arcs	4	8.7
VMAT	39	84.8
Helical IMRT	3	6.5

P058

STEREOTACTIC BODY RADIATION THERAPY (SBRT) REIRRADIATION FOR LOCOREGIONALLY RECURRENT LUNG CANCER

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Aims: To evaluate local control, overall survival (OS), efficacy and toxicity of re-irradiation with stereotactic body radiation therapy (SBRT) in patients with recurrent/progressive primary or secondary lung tumors after

previous radical radiation therapy or SBRT.

Methods: Between August 2011 and December 2015, 12 patients with locoregionally recurrent lung cancer were retreated with SBRT in single (23 Gy or 30 Gy) or multiple fractions (15 Gy x 3). The median interval between the initial irradiation and reirradiation was 18 mounths (range, 12-47). Previous treatment included radical radiation therapy (60 Gy) in 41.6% of lesions and single fraction SBRT (23 Gy or 30 Gy) in 58.4% of lesions.

Results: The median follow-up was 19 months (range 7-49 months). The median overall survival after the second course of SBRT was 35 months (range 22 - 66 months), and the one-year and two-year survival rate were 91.6% and 75%. The progression-free survival time ranged from 12 to 47 months (median, 18 months). 25% of patients reported acute grade 1 and 2 toxicity. No grade 3 or higher toxicity were reported. Complete response was observed in 2 patients (16.6%), and stable disease in 7 (58.3%). One patient died for progressive systemic disease.

Conclusions: Reirradiation using SBRT for locoregionally recurrent lung cancer is a feasible treatment can provide benefits without severe complications to the majority of selected patients and is associated with good local control and acceptable toxicity.

P059

ROLE OF THE STEREOTACTIC ABLATIVE BODY RADIOTHERAPY (SABR) IN THE TREATMENT OF PULMONARY OLIGOMETASTATIC/ OLIGORECURRENT NON-SMALL CELL LUNG CANCER PATIENTS: EFFICACY AND TOXICITY

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Aims: Stage IV non-small cell lung cancer (NSCLC) is a poor prognosis disease. Palliative chemotherapy and/or best supportive care are considered standard treatment. Nevertheless, for patients with oligometastatic disease (1-5 metastases), better prognosis has been observed. We evaluated response rate, survival, time to progression and toxicity in oligometastatic/oligorecurrent NSCLC patients treated with stereotactic ablative body radiotherapy (SABR) delivered to all active sites in the lung.

Methods: Fourthy lung metastases in 29 patients affected by oligometastatic/oligorecurrent NSCLC were treated with SABR to all active sites of disease. Inclusion criteria were: controlled primary tumor with complete response or stable disease after surgery/radiotherapy/ combined therapy; ≤4 synchronous or metachronous lung metastases at the time of treatment; no other active sites of distant metastases.

Results: We reported the following response to treatment: complete response in 25% of lesions, partial response in 65% of metastases, stable disease in 10%. Ninenty-two percent of patients had complete metabolic response, and 8% had a partial metabolic response. Median follow-up was 24 months. The 1-year and 2-year OS was 86.2% and 49.6%, respectively. The 1-year and 2-year PFS was 81% and 41.7%, respectively. Median time to progression and median OS were 18 months and 24 months, respectively. Local control was 92.8% at 1 year and 64.3% at 2 years. Overall, acute toxicity occurred in 20.6% (6/29) of patients; three patients experienced grade 2 pneumonitis. Grade ≤2 late toxicity occurred in 55.1% of patients. One patient experienced grade 3 toxicity.

Conclusions: Aggressive stereotactic radiotherapy is a feasible and well-tolerated treatment for oligometastatic/oligorrecurrent NSCLC patients with lung metastases offering longer survival. Ablative radio therapy has a potential role in the management of well-selected stage IV NSCLC patients while increasing their quality of life and survival.

P060

EVALUATE TREATMENT PATTERNS AND OUTCOMES OF STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR CENTRALLY LOCATED LESIONS

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Aims: The purpose of this study was to evaluate treatment patterns and outcomes of stereotactic body radiotherapy(SBRT)for centrally located lesions.

Methods: We selected 25 eligible patients who were treated at our Institutions with SBRT to centrally located lesions(<2 cm from main bronchial tree)between 2004 and 2014.We excluded patients with a follow-up shorter than 4 months. We evaluated Overall Survival(OS), Local Progression Free Survival(LPFS) and treatment related toxicity. OS and LPFS were determined using Kaplan-Meier method. Toxicity was reported using CTCAE version 4.0.

Results: Twenty five patients with a median age of 72,6 years (range 48-85), 14 male and 11 female were treated. The ECOG performance status (PS) was 0 for 8 patients, 1 for 11 patients and 2 for 6 patients. The majority of patients (24patients) were recurrences/secondary tumors, 1 patient had centrally located primary NSSLC. Twelve patients were treated with multiple static fields technique, 5 patients were treated with VMAT and 8 patients were treated with CyberKnife. In 18/25 patients the treated lesion was the only site of disease. Median size of lesions was 30,1 mm(range 10-45). Average PTV size was 46,3cc (range 16,1-118,7cc). Median number of fractions was 3 (range 1-8) and median total dose was 30Gy (range 8-56Gy). Average BED was 62 (range 14,4-112,5). Patients were followed with physical examination and CT imaging. After SBRT 5 patients had complete response, 11 patients had partial response, 4 patients had stable disease and 5 patients had progression disease. Six out of 20 patients who presented a response had local recurrence.

The Local Progression Free Survival(LPFS)for 6 months, 1 year and 2 years was 79.3, 70.3 and 60.1 respectively. Overall survival(OS) at 1 and 2 years was 90.6% and 63.2% respectively. Toxicity was low,with no Grade 3 or higher acute or late toxicity.Acute grade 1 toxicity was reported in 3 cases (grade 1 dyspnea in 2 patients and grade 1 fatigue in 1 patient; acute grade 2 toxicity was reported in 2 patients and (esophagitis, cough). No relevant late toxicity was reported.

Conclusions: Our experience showed that SBRT appears to be a safe and effective management strategy for centrally located lesions. The majority of patients in our series are treated with low doses compared to current doses. Nevertheless in our study we had 14 patients that had local control disease. The role of SBRT in the treatment of the central lung lesions requires further studies to establish the efficacy and safety.

P061

HYPOFRACTIONATED RADIOTHERAPY IN PATIENTS WITH INOPERABLE NON-SMALL-CELL LUNG CANCER: ROLE OF IGRT IN CLINICAL PRACTICE

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Purpose: to evaluate if image guided hypofractionated 3-Dimensional radiation therapy (IGRT) byCone-beam CT can favourable impact on acute and late toxicity of patients with inoperable non-small cell lung cancer (NSCLC) and treated by hypofractionated radiotherapy. Methods and Materials: this study includes 49 patients with unresectable stage I-IV NSCLC receiving image guided hypofractionated (IGRT group) from 2009 to 2014. This group of patients was retrospectively compared with a group of 53 patients treated from 2003 to 2006, matched for inclusion criteria and subjected to the same fractionation scheme without the use of Cone-beam CT during treatment (No-IGRT). HypoRT was delivered in 20 daily fractions of 3Gy per fraction witha total dose of 60 Gy. Toxicities were graded according to Radiation Therapy Oncology Group morbidity score.Results: at a median follow-up was 15 months (range, 4-56 months) all patients completed radiation therapy. Regardless of the stage of disease, the IGRT group experienced a significantreduced incidence of acute side effects (erythema 8%, esophagitis 37%, odynophagia 11%,pneumonitis 21%) with respect to the No-IGRT group (erythema 28%, esophagitis 75%,odynophagia 34%, pneumonitis 44%). Differently the incidence of late toxicity was comparablebetween the two groups. When patients were stratified for disease stage, the Stage I-II undergoingIGRT did not experience a significant improvement in the rate of acute toxicity with respect to theNo-IGRT group. Differently, the stage III-IV undergoing IGRT, experienced a significant advantagein terms of>G2 acute toxicity [esophagitis (IGRT 1% vs No-IGRT 24%) and odynophagia (IGRT0% vs No-IGRT 19%)]. The percentage of OS, CSS and DFS at 2 years were comparable betweenthe two groups [(IGRT group: OS at 2 years 50% in stage I-II and 35% in stage III-IV, CSS 60% instage I-II and 38% in stage III-IV, DFS 33% in stage I-II and 32% in stage III-IV) vs. No-IGRTgroup: OS at 2 years 53% in stage I-II and 29% in stage III-IV, CSS 54% in stage I-II and 36% instage III-IV, DFS 40% in stage I-II and 23% in stage III-IV). Conclusions: the hypofractionatedcurative radiation therapy is a feasible and well-tolerated treatment for patients with locallyadvanced NSCLC with a comparable tumor control. The use of IGRT impacts significantly on theincidence of acute toxicity related to esophagitis and odynophagia only in the Stage III-IV.

P062

ROLE OF SABR IN PATIENTS WITH CENTRALLY LOCATED NSCLC

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Aims: The aim of this study is to evaluate the effectiveness and the safety of hypofractionated ablative radiotherapy in patients with centrally located NSCLC in terms of local control, toxicities and overall survival (OS).

Methods: Between Jun 2011 and November 2015 45 patients (pts) were treated with Hypofractionated Image guided-Volumetric Modulated Arc Therapy (IGRT-VMAT) for centrally located NSCLC stage III-IV or centrally recurrent NSCLC biopsy-proven. Target was contoured using volumetric mdc enhanced CT and PET/CT scan and OAR according RTOG 0236 Trial criteria. Dose Constraints used were: Single lung V10<20%, Dmax bronchus 38 Gy, Dmax esophagus 35 Gy, Dmax Spinal cord 22.5 Gy, Dmax Heart and pericardium 38 Gy. The dose was prescribed to 80% isodose line. The VMAT treatment was delivered by 6MV beam modulator Linac with 4 mm MLC and in breath hold using ABC (Active Breathing Coordinator) device. Patient set-up ad isocenter position was controlled before each fraction by CBCT. Target volume ranged from 18 to 161 cm3 (median 52.1). Median delivered dose was 40 Gy/5fx (median BED 10 of 100 Gy). Toxicities were assessed by CTCAE 4.0 criteria and the results were evaluated 2 months after the end of SABR and every 4 month successively using CT and PET/CT.

Results: Median follow-up was 16 months (range 3-45). 26/46 (56.5%) of treated lesions show complete respons and 12 (26.2%) partial response. Local control was 89% at 12 months and 72% at 18 months. 7 pts showed recurrence margin-field and 2 both in field and margin field.OS was 84% and 73% at 12 and 18 months respectively. The most common Grade 2 toxicity was disphagia, that occurred in 7 pts. Late toxicity G3 was observed in 3 pts (esophageal stenosis in 1 case and bronco-esophageal fistula in 2 pts), but broncoscopy showed local recurrence in all cases.

Conclusions: In our experience hypofractionated treat-

ments with ablative dose for centrally located NSCLC is safe if dose constraints for Oar are respected. Treatments with BED 10 values of 100 Gy or more are effective leading to LC rate of 89% and 72% at 12 and 18 month respectlively. To reduce the incidence of recurrence in field and margin-field is mandatory an accurated definition of GTV. PET/CT can be a usefull instrument to define treatment volumes.

P063

SAFETY OF LUNG STEREOTACTIC BODY RADIOTHERAPY (SBRT): A SINGLE INSTITUTION PROSPECTIVE STUDY BASED ON RTOG 0915 PROTOCOL CONSTRAINTS

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Purpose: To evaluate toxicity in patients treated with lung SBRT (60 Gy in 5 fractions) based on of RTOG 0915 protocol constraints.

Methods and Materials: Between 2010 and 2015, 77 pts were treated with SBRT for single or multiple lung lesions, 43 pts. (55.8%) for a primary lung tumor and 34 pts. (44.2%) for metastatic lesions. A total of 80 lesions were treated. Patients were CT-scanned and treated in head-first supine position using an arm (QFixTM arm shuttle and Vac QfixTM Cushion or Wingstep) and knee support (CIVCO – Kneefix), the majority of pts. in free-breathing with no abdominal compression and 5 pts. with a breath-hold system in deep inspiration. Four-dimensional CT images were acquired. Maximum intensity CT reconstruction was used for ITV delineation and average CT reconstruction for OAR contouring and dosimetric calculation. The margin ITV-PTV was 10 mm and 6 mm for pts. treated without or with cone beam CT for on-line setup verification, respectively. We prescribed 60 Gy as the median dose and 57Gy to 95% of PTV volume and OAR constraints are reported in Table 1. Dose calculation was performed in 70% of the cases with a collapsed cone convolution algorithm (typically for a 7 field 3D technique) and the remaining 30% with a Monte Carlo algorithm (for dynamic MLC IMRT and VMAT). Treatments were delivered in 28% of the cases on an Elekta-Precise accelerator with electronic portal image on-line setup verifications and the remaining 72% on an Elekta Synergy accelerator (Agility Collimator) with cone beam CT. We evaluated pre-treatment respiratory function and we treated only pts. with %FEV1>40%. We report toxicity according to CTCAE v3.0.

Results: All dose/constraints were respected except for the chest wall dose that was higher than 30 Gy in 8 pts. (10.3%). Toxicity was evaluated in all patients except one that was lost in follow-up. Only lung or chest wall toxicity was observed: 11 pts. (14.2%) had G2 dyspnea, one patient had G3 dyspnea, 8 pts. reported G2 chest wall pain and 1 patient presented with a symptomatic rib fracture. Lung toxicity was more frequently observed in patients treated for primary tumors (18.1% vs 11.7%) because of more chronic lung disease present prior to the treatment.

Conclusions: The use of these RTOG 0915 constraints is safe in both metastatic and primary lung lesions for a 5 fraction approach with a total dose of 60 Gy when advanced dose calculation algorithms are used. Pretreatment respiratory function requires particular attention.

Table 1.

Serial constraints	Volume	Gy/fx	Maximum dose Gy
Cord	1cc	<2.72	26
Trachea and large bronchus	4cc	<3.12	34,8
Brachial plexus	3cc	<4.72	27,2
Heart	15cc	<5.6	34
Large vessels	10cc	<8.6	49
Chest wall	70cc		30
Esophagus	5cc	<3.76	30
Stomach	10cc	<3.52	27,2
Parallel constraints			
Lungs	V10		<30%
	V15		<30%
	V20		<15%
Ipsilatral lung	Mean dose		<10Gy

P064

HYPOFRACTIONATED RADIOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED NON-SMALL-CELL LUNG CANCER: RESULTS FROM OUR DEPARTMENT

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Aims: We retrospectively analyzed the clinical outcomes and the toxicity of three-dimensional (3D) hypofractionated radiotherapy (HFRT) in patients with locally advanced non-small-cell lung cancer (NSCLC).

Methods: Sixteen patients with locally advanced NSCLC received HFRT (60Gy/20 fractions), between January 2005 and December 2015. 9 patients were male and 7 female . The mean age was 60 years (range 45-80). 6 patients were classified as IIIA stage and 9 patients as IIIB, according to TNM classification. Histology evidenced squamous cell carcinoma in 5 patients and adenocarcinoma in 11 patients. Four patients presented with resectable stage IIIA underwent surgery: 2 patients received

neo-adjuvant chemotherapy and adjuvant radiotherapy, 2 received adjuvant RT. Two patients classified as unresectable stage IIIA received sequential radio-chemotherapy Stage IIIB patients received concurrent radio-chemotherapy. Toxicities were graded according to the Common Toxicity Criteria for Adverse Effects v 4.0 scale.

Results: The median follow up was 30 months (range 4-80 months). 5 of the patients showed a complete response, 3 achieved partial response, 4 had stable disease and 4 developed metastases. As side effects related to RT, we observed grade 2 lung toxicity in 6 patients, grade 2-3 esophagitis and gastrointestinal toxicity in 7 patients, grade 2-3 hematologic toxicity in 6 patients, grade 2 asthenia in 5 patients, acute postoperative mild pain in 4 patients. OS in patients who presented with resectable stage IIIA was 36 months [range 10.97-67.02] and 29,5 months [range 10.38-75.99] in unresectable stage IIIA patients. The median OS in stage IIIB patients was 34,7 months [range 6.96-73.69]. PFS was longer in stage IIIA patients (median 26,5 months range [6.64-54.04] for resectable stage IIIA NSCLC and 20 months [range 9.4-75.99] for unresectable stage IIIA NSCLC) than in stage IIIB patients (median 21,3 months [range 1.84-70.04]).

Conclusions: High dose accelerated HFRT with a dose of 60 Gy or greater with sequential chemiotherapy is feasible. HFRT offers good disease control for patients with advanced-stage NSCLC with acceptable toxicity rates. Phase III randomized trials are necessary to compare hypofractionated RT with conventional RT and also to obtain the maximum tolerated dose of accelerated HFRT.

P065

RETROSPECTIVE EVALUATION OF CYBERKNIFE® IN THE TREATMENT OF LUNG LESIONS: CLIINICAL OUTCOME AND TOXICITY PROFILE

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Aims: LOT (lung optimized treatment) is an evolution in Cyberknife® technology which allows treatment of lung cancer without invasive fiducial implantation procedures. The aim of this analysis was to evaluate the technical feasibility, toxicity profile and clinical outcome.

Methods: Between 1/2014 and 12/2015 53 patients (pts) (M/F 39/14) were treated with Cyberknife® using LOT at European Institute of Oncology (IEO). The median patient age was 72.6 years (range 31.8-90.3). Treated lesions were 57; 26 with histopathological confirmation (24 primitive pulmonary cancer, 2 pulmonary mets), 27 were untyped tumors. Forty-nine pts treated a single lesion, while 4 pts treated multiple target lesions. For 12 pts treatment using LOT was a re-irradiation for a recurrence in field. Concomitant systemic therapy was administered in 3 pts. Three tracking methods were used: 0-View tracking method (treats an ITV using Xsight Spine tracking for patient alignment) in 24 pts, 1-View tracking method (tracks targets that are visible in only one X-ray image) in 18 pts, 2-View tracking method (tracks targets that are visible in two X-ray images) in 14 pts. Median dose/fraction was 15 Gy (range 4-18). In most cases the isodose prescription was at 80%. The median PTV was 24.3 cm^3 (range 2.7-161.1). Toxicity was evaluated by RTOG/EORTC and CTCAE V4.1. Tumor response was evaluated with RECIST V1.1 criteria.

Results: The median follow-up was 5.1 months (range 1-15.4). Acute toxicity (within 6 m.) was observed in 21 of 44 pts with follow-up (47.7%): according to RTOG/EORTC criteria only G1 and G2 toxicity was registered (no G3 orG4); in CTCAE V4.1 two events of G3 toxicity were observed (cough, dyspnea). Late toxicity (after 6 m.) was observed in 10 of 19 pts with follow-up (52.6%): all events were G1 and G2 RTOG/EORTC events. (no G3 or G4); in CTCAE V4.1 one event of G3 toxicity was registered. According to RECIST V1.1 guideline complete response, partial response, stable disease and progressive disease was observed in 23.9%, 26%, 43.5% and 4.3% respectively.

Conclusions: This first analysis demonstrated high feasibility and minimal toxicity of LOT in lung cancers. Promising response rates have been registered. Further studies are necessary in order to confirm our results.

P066

RIB FRACTURE AND NEUROPATIC PAIN IN PATIENTS WITH PERIPHERAL LUNG LESIONS TREATED WITH FOUR FRACTIONS SCHEDULE LUNG STEREOTACTIC BODY RADIOTHERAPY

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Aims: The aim of this study was to evaluate the efficacy and tolerability of SBRT for the treatment of peripheral lung lesions near the rib and the chest wall in a cohort of patients treated between 2014 and 2015 at our institution.

Methods: Eligible patients included those with primary lung tumors clinically staged T1 N0 M0 NSCLC or lung metastases treated with SBRT. The treatment was performed with a stereotactic body frame and a volumetric arch treatment. A control with CBCT was perfomed before each fraction. All peripheral tumors received a dose of 61.6 Gy in 4 consecutive fractions. The dose was prescribed to isocenter with inhomogeneity of 65% to PTV. Clinical outcomes were evaluated by Computed Tomography (CT) and a Positron Emission Tomography (PET). The primary end point was rib fracture and/or neuropatic pain; secondary end point was local control.

Results: A total of 30 patients with 33 lesions (18 primary lung tumors clinically staged T1 N0 M0 NSCLC and 12 lung metastases) were included in the study. Biopsy was performed in 85 % of cases. Median age was

74 years (range 57-85). Median follow-up was 9.2 months (range, 1.8-21.5 months). Response, according to RECIST criteria, was as follow: 39.4 % complete response, 33.3% partial response, 15,2% stable disease, and 9.1% progressive disease. In one patient (3%) the response has not been evaluated. Treatment was well tolerated. Only one patient (3%) developed rib fracture and neuropatic pain six months after the end of therapy.

Conclusions: Stereotactic radiotherapy in four fractions for the treatment of lung lesions near the rib and the chest wall is safe and well tolerated with accetable toxicity.

P067

DOSE RECALCULATION ON TARGET VOLUMES USING A DEFORMED PLANNING COMPUTED TOMOGRAPHY IN LUNG CANCER PATIENTS TREATED WITH STEREOTACTIC RADIOTHERAPY (SBRT)

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Aims: To evaluate the dose delivered during the course of lung SBRT treatments, we have performed a dose recalculation on a deformed planning computed tomography (CTdef) generated by a deformable registration (DIR) using the planning computed tomography (pCT) and the pre-treatment cone beam computed tomography (CBCT).

Methods: Five patients treated with SBRT were retrospectively analyzed. Their planning CT was deformed using the daily CBCTs and creating a deformed planning computed tomography (CTdef) for each fraction . Using the DIR, the target structures have been propagated on the deformed planning CT and verified from physician. A study with anthropomorphic phantom has been performed to validate the procedure of recalculation on CTdef. The plan of the patient has been recalculated on each CTdef and the target coverage has been evaluated comparing the original plan and the sum dose on the CTdef (all parameters were normalized to each value from the original plan).

Results: The study with the phantom showed that there are not significant difference between the DVH calculated on pCT and on CTdef. Comparing target volumes on pCT and CTdef, the mean difference of HU has been within ±5% which is insignificant from a dosimetric point of view, as well as volumes themselves (PTV and ITV) were not significantly changed. The differences in terms of D95 in the PTV, D98 and min dose in the ITV between pCT and CTdef were not statistically significant.

Discussion: We have evaluated the recalculated dose to ITV and PTV in five patients treated with SBRT for lung tumors, using deformed CT generated with the anatomic information acquired with CBCTs. At least for target volumes it has proved a feasible procedure and able of minimizing the uncertainties because of less variations in HU compared to direct dose calculation on CBCT. Recalculated minimum dose to ITV and prescription dose (D95) to PTV was consistent with the original plans. The next development of this procedure involves the verification of the doses received by critical organs, even with the limitation of FOV in CBCT.

P068

USE OF SLOW ACQUISITION CONE BEAM CT AS RESPIRATORY GATING IN TREATMENT OF LUNG TUMORS IN FREE-BREATHING PATIENS

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Aims: Hypofractionated or stereotactic treaments for lung tumors, require particular caution due to target position correlating with breathing acts. We evaluated the possibility to prevent target missing using slow acquisition cone beam CT.

Methods: We evaluated 20 patients undergoing hyperfractionated (50 Gy in 10 fractions) or stereotactic fractionation (50 Gy in 5 fractions) for lung tumor treatments. All patients did a free breathing treatment. Each fraction was verified using a slow acquisition cone beam CT and evaluated with the Symmetry software by Elekta. In the verification images we reported the 95% isoline just to be sure that the target would be inside the 95% isoline during all the fraction.

Results: 150 fractions were verified and among these 20 (13,3%) showed a target movement beyond the 95% isoline and in 12 (8%) it was impossible to adjust the target coverage using manual corrections, suggesting the necessity to enlarge the margin to the target and to recalculate the dose distribution.

Conclusions: In our experience breath holding treatments for lung tumors, is not easy for patients and relatively time consuming. We prefer to delivery treatments in free breathing using a daily slow acquisition cone beam CT although in 8% of cases we need to change the target conformation.

P069

ASSESSMENT OF RESULTS AND OUTCOMES DERIVED FROM HYPOFRACTIONATED LUNG TUMORS IRRADIATION

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Aims: With the increase in life expectancy and advancing age, there is growing demand to consider definitive radiotherapy as a treatment option, specially for older patients, with lung cancer Our.group's experience in hypofractionated radiotherapy of lung tumours started since 2008. Our medium size center treats more than 1000 patients/year with 2 Elekta Linacs. We decided to analyze retrospectively the efficacy of the hypofractionated radiotherapy of lung tumours in 115 patients,with max. diameter 4 cm, and minimum 12 months of follow-up period.

Methods: Patient's were 26 - 97 years old (median 75);

all of them were unfit for surgery. CTVs were from 0.5 to 33.5 ccm, and corrispondent diameters were from 1 to 4 cm. CTV - PTV expansion were 5 mm in latero-lateral and 1 cm. in cranio - caudal dimension. We used 3D conformational tecnique based on irradiation with at least nine noncoplanar fiels, and prescription to PTV was 100% of dose. Dose fractionations were: 45-50 Gy/ 5 Fr. for peripheral and/or hylar lesions and 48 Gy/ 4 Fr or 39 Gy/ 3 Fr. for hylar and/or central lesions.

Results: Median follow-up period was 38 months (from 12 to 72), and local failures were very rare events, with complete control at 12 months, only 10 failures at 24 months, and 15 at 36 months. Most common failure was distant mets and 50% of patients are alive at 36 months. 30% died of concomitant other illnesses, due to age. Complications were: 3 coast fractures, no lung or heart tox. No dyspnea, but only CT-lung signs of pneumonitis.

Conclusions: The results support the benefit in choosing of hypofractionated of lung tumours is very useful in our experience in selected cases. Hypo fractionated radiotherapy is an effective and safe treatmen. The risk-benefit ratio is very favorable, with a very high local control and virtually no side effects, also in very older patients, with a low KS. The results are limited as this is a single-institution study. Nevertheless, a large majority of patients remained free of local recurrence and without significant clinical toxicity.

P070

STEREOTACTIC BODY RADIOTHERAPY WITH HELICAL TOMOTHERAPY FOR EARLY STAGE NSCLC AND LUNG METASTASIS

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Aims: To investigate the effectiveness of stereotactic body radiotherapy with helical TomoTherapy (HT-SBRT) in early stage primary or secondary lung cancer.

Methods: Between March 2014 and February 2016, 23 patients (pts), median age 66 years (range 26-91) underwent ablative SBRT by HT: 11 pts (47.8%) for primary malignancy and 12 pts (52.2%) for lung metastasis. Pts were staged using contrast-enhanced thoracic CT and positron emission tomography (PET)-CT scans. Pts were immobilized in breast board with an abdominal pressure mould mask. The planning target volume (PTV) included a margin of 10 mm in craniocaudal direction and 5 mm in all other directions around the internal target volume (ITV). The ITV was defined based on the volumetric sum of the clinical target volumes of a free breathing planning CT and pretreatment MVCT scan of pts in the treatment position. Different schedules of radiotherapy were used: 40 Gy, 50 Gy and 60 Gy in 10 daily fractions and 60-70 Gy in 8-10 alternate fractions . The median BED10 was 75 Gy (range 56-119). Treatment related toxicity was evaluated weekly during treatment and at each follow-up visit, using CTCAE v4.0 toxicity scale. For the first year after treatment, follow-up evaluation and chest CT were conducted every 2–3 months.

Results: Mean duration of RT was 18 days (range 11-30) and all patients were treated successfully with mild acute adverse events. With a median follow-up of 10 months (range 2-25) no $\geq$ G2 radiation pneumonitis or esophagitis was registered; only one patient (4.3%) showed G2 non-cardiac chest pain. Up until the most recent CT follow-up two local failure were registered. Two patients died, one as a result of distant recurrence and one from renal insufficiency.

Conclusions: Use of HT-SBRT in primary or metastatic lung tumors demonstrates low risk of normal tissue complications and high local control rates.

P071

SAFETY AND EFFICACY OF STEREOTACTIC ABLATIVE BODY (SABR) RADIOTHERAPY IN VERY ELDERLY PATIENTS WITH LUNG CANCER: A MONOISTITUTIONAL EXPERIENCE

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Aims: The therapeutic strategy for elderly patients is controversial, several retrospective studies have not reported benefits of CRT in elderly patients with lung cancer. SABRT, highly conformal radiation therapy, has achieved tumor control rates similar to historical results from surgery. We evaluated tumor control, DFS, RFS, compliance, acute and late toxicity treatment-related of SABR for lung tumors in very elderly patients.

Methods: We retrospectively examined the SABR in very elderly patients, “fit and frail” according to Charlson Comorbidities Index, treated for lung tumors. We determined tumor control, patients’ compliance, acute and late toxicity treatment-related, DFS and RFS. Between March 2011 and March 2015 we treated 25 patients, age between 75 and 85 (median 80), 18 men and 7 women with lung lesions primary, histologically compatible with adenocarcinoma or squamocarcinoma, or lung metastasis. Lesions’ diameter ranged between 10-50 mm. Lung cancer T1-T2 N0 (staged I-II) was recorded in 10 pts, the remaining 15 pts were stage IV for breast (5 pts), colon-rectal (6 pts) and lung (4 pts) primary tumors. (Figure 1). Spirometry’s values (FEV1-DLCO) we evaluated before and after SABR. Prescribed dose ranged 36-48 Gy in 3-4 daily fractions (BED range 79.20-105.60 Gy). Total doses were decided in consideration of site of disease (central versus peripheral), tolerability of organs at risk, PS and age. All patients were immobilized supine with arms above their head and target volume was delineated according ICRU 83 on CT/PET imaging. We used TPS “Elekta Monaco” to elaborate treatment planning and LINAC “Synergy Elekta” to deliver sessions of radiation therapy. Patients’ positioning was recorded and verified with kV Cone Beam CT, the organ motion was evaluated with

software Simmetry Elekta. Toxicities treatment-related were evaluated according to the RTOG/ EORTC scale.

Results: We obtained Complete Remission in 7 pts; Partial Remission in 15 pts , Stable Disease in 3 pts.

These last group showed progression disease 3 months after SABRT (BED <100). Neither hospitalitation or death within 30-60 days of completing treatment was recorded. We recorded dyspnoea G1-2 in 18 pts as acute toxicities, late toxicities with chest pain G1 and dyspnoea G1-2 in 8 pts. Median follow up was 20 months (3-36).

Conclusions: Our study showed that the treatment with SABR is well tolerated in very elderly patients unfit and frail to specific cancer therapies.

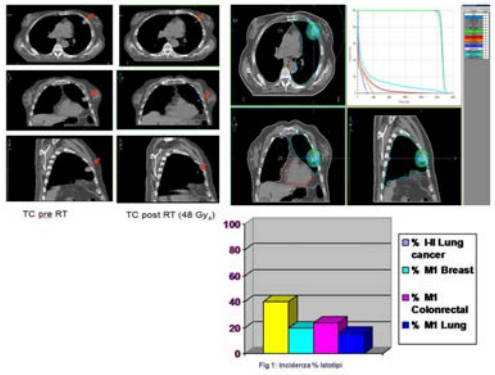

Figure 1.

P072

MORPHOLOGICAL AND METABOLIC CHANGES AFTER LUNG STEREOTACTIC BODY RADIOTHERAPY (SBRT)

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Purpose: To describe morphological and metabolic changes of lung lesions treated with stereotactic body radiation therapy (SBRT) on computer tomography (CT) and FDG-PET, respectively.

Materials and Methods: Between January 2013 and December 2015, 35 patients (40 lesions) received SBRT in our Institution. FDG-PET for planning was applied to 27 patients, and 13 of them (9 NSCLC, 2 metastatic lesions and 2 not histologically proven) underwent at least one FDG-PET restaging. Free-breathing slow-acquisition CT scan and FDG PET/CT scan in the treatment position were performed for simulation purposes and planning. Dose was gradually escalated over the time, starting at 30 Gy in 6 fractions (BED=45 Gy) and reaching 60 Gy in 3 fractions (BED=180 Gy). Follow-up (F/U) was performed with a CT-FDG-PET after at least 3 months. A "post-SBRT CTV" (CT1 and CT2) was contoured and measured on restaging CT (cc) and FDG-PET1 and 2 (SUVmax). The following criteria were adopted for response evaluation: CR=reduction of 100%, PR=reduction >30%, SD=reduction <30%, and PD=increase >20%.

Results: After median F/U of 6 months (range 3-11) from the end of SBRT, 13 patients underwent PET/CT restaging (CT1 and FDG-PET1). On CT1, 1 patient had CR, 9 PR (range 35-84%), 2 SD (range 9-35%), and 1 PD. On FDG-PET1, 2 patients had CR, 10 PR (range 34%-88%), and 1 SD. A second restaging was performed after median F/U of 13 months (range 7-20) in 7 patients (CT2 and FDG-PET2). On CT2, 1 patient had CR, 5 PR (range 51-89%), and 1 was not evaluable because of presence of radiation pneumonitis. On FDG-PET2, 1 patient had CR, 5 PR (range 34%-93%), and 1 SD. More detailed results are reported in Table 1.

Conclusions. In our experience, morphological and metabolic changes of lung lesions treated with SBRT occurred over time, accordingly. We plan to include more patients and to introduce a further diagnostic parameter (e.g. TLG) to better analyze volumetric and metabolic changes and to identify the optimal restaging modality after SBRT.

Table 1. CT and FDG-PET results.

Pts	cc CT-p	cc CT 1	CT Δ1	cc CT 2	CT Δ2	SUVmax p	SUVmax 1	SUVΔ 1	SUVmax 2	SUVΔ2
1	0.7	0	100%	0	100%	5	1.5	68%	2	58%
3	8.5	5.5	35%	2.8	67%	13.7	4	71%	4.1	69%
5	9.6	2.3	76%	1	89%	23.8	1.8	92%	1.6	93%
6	1.2	0.4	67%	0.4	67%	3.7	1.5	59%	2.7	27%
12	4.9	4	18%	RP	n.e.	8.2	5.4	34%	4.4	46%
13	3.3	1.3	51.5%	1.3	51.5%	7	2	72%	2	72%
8	3.5	3.2	9%	-	-	11.6	5	57%	-	-
9	1.9	0.3	84%	0.3	84%	10.8	1.3	88%	0	100%
2	13	4.2	67%	-	-	13.3	0	100%	-	-
4	4.1	0.8	80.5%	-	-	15	0	100%	-	-
10	26.7	12.2	54%	-	-	9.4	4	59%	-	-
11	1.2	1.2	0%	-	-	1.2	1.2	0%	-	-
7	9.6	3.1	67%	-	-	9.1	2.7	70%	-	-

CT-p: planning CT;
CT1: volume in cc on first restaging CT
CT2: volume in cc on second restaging CT
CT Δ1: % of cc reduction between CT-P and CT1
CT Δ2: % of cc reduction between CT-P and CT2
SUVmax1: SUVmax on first restaging PET
SUVmax2: SUVmax on second restaging PET
SUVΔ 1: % SUVmax reduction between SUVmax(planning) and SUVmax1
SUVΔ2: % SUVmax reduction between SUVmax(planning) and SUVmax2
n.e.: non-evaluable
RP= radiation pneumonitis

P073

STEREOTACTIC BODY RADIOTHERAPY FOR LUNG METASTASES: A TWO INSTITUTIONAL EXPERIENCE

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Aims. To evalute local control following stereotactic body radiotherapy (SBRT) for lung metastases in oligometastatic patients.

Methods: From February 2010 to November 2015 a total of 51 patients (pts) with a median age of 73 years (range 45-87 years) were treated at two institutions. SBRT was performed in case of controlled primary tumor, exclusion of surgery, and number of metastatic sites ≤ 5 in no more than 3 different organs . The primary involved organs were the lung (n = 18), gastroenteric tract (n = 15), head and neck (n = 4), urinary tract (n = 8), breast (n = 4) and the other origins (n = 2). The histology of the primary tumor was adenocarcinoma in 23, squamous cell carcinoma in 10 pts. At the time of SBRT 34 pts had single lung metastasis, 14 pts two or more metastases. Radiation doses were prescribed to the PTV encompassing 95% isodose and varied according to tumor site, maximum diameter, prior lung RT and dose limits OARs. The median SBRT dose was 36 Gy (range 10,5-50 Gy) in 1-6 fractions. The median GTV delineated on CT images was 4 cc (range 0,15-24 cc). SBRT was performed with a stereotactic body frame and a 3D-conformal technique. The primary endpoint was local control (LC) defined as a lack of any significant tumor regrowth on follow-up CT or PET on the base of Recist scale.

Results: At the last observation, the numbers of treated lesions with a complete, partial, stable and progressive response were 19, 3, 6, 23, respectively. Of these 51 pts 5 were NED, while 34 showed progression disease in other sides. After a median follow-up interval of 15 (range 3-103) months, the 1-year rates of LC, overall survival and progression-free survival were 57 %, 87% and 87 %. On univariate analysis, 1-year LC was 57% in pts with only one metastasis versus 39% in those with 2 or more metastases (p = 0,03). On multivariate analysis, multiple lung metastases and squamous histology were associated with worse LC. No correlation was found between LC and GTV or radiation doses (BED equivalent). No cases of acute or late toxicity were recorded . Only 2 patients experienced a late G3 esophageal toxicity according NCI CTCAE vs 3.0.

Conclusions. Despite the small number and heterogeneous characteristics of our patients, in terms of primary tumors, number and metastatic sites, therapy modalities and fractionation schedules, this analysis shows that SBRT for oligometastasis in the lung achieved an acceptable tumor control with minimal toxicity.

P074

ARE 6-DEGREE OF FREEDOM (6-DOF) USEFUL IN LUNG SBRT? ANALYSIS OF A PROSPECTIVE SUDY

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Aims: Stereotactic body radiation therapy (SBRT) is now widely employed as a definitive treatment for various tumours, including early stage lung tumour or lung metastases. It needs extreme setup accuracy to hit the target: utility of 6-DoF was analysed in this subset of patients when SBRT was performed.

Table 1. Mean values, standard deviations, maximum and minimum shifts obtained with 3D-match between CBCT and kV. Percentage of shifts and rotations above three different cutoff are reported. Percentage variations of PTV, CTV and OARs constraints due to rotations are shown.

	Lat(x) (cm)	Vrt(y) (cm)	Lng(z) (cm)	Rot(x) (deg)	Pitch(y) (deg)	Rtn(z) (deg)	PTV V95%	CTV V95%	Spinal Cord Dmax (Gy)	Spinal Cord V(Dth)=0.35cc	Heart Dmax (Gy)	Esophagus Dmax (Gy)	Total Lung V(Th) 20	Total Lung V(Th) 13,5	Total Lung V(Th)5
MEAN	0.1	-0.1	-0.0	0.2	0.3	-0.2	-0.3	-0.0	-0.0		0.0	0.0	0.0	-0.0	0.0
SD	0.4	0.4	0.6	1.3	1.3	1.3	1.2	0.0	0.3	0.0	0.8	0.2	0.0	0.0	0.2
MAX	1.0	1.1	1.6	3.0	3.0	2.6	2.6	0.2	0.8	0.2	4.2	0.5	0.1	0.1	0.4
MIN	-0.8	-0.9	-1.5	-3.7	-2.0	-3.4	-3.8	-0.2	-0.8	-0.1	-3.0	-0.3	-0.1	-0.1	-0.6
Shift>5mm	15%	13%	20%												
Shift>3mm	44%	32%	52%												
Shift>2mm	59%	72%	68%												
ROTA T>2				10%	13%	8%									
ROTA T>1				39%	44%	41%									
ROTA T>0.5				64%	62%	68%									

Methods: Primary or metastatic lung tumours with diameter until 5 cm, were considered. Breast board or Body Pro-Lok(CIVCO support system) were used. Eclipse™ Treatment Planning Systems (Varian Medical System®, Palo Alto, CA) was used performing Volumetric Modulated Arc treatment plans. The total dose was: 42 Gy in three fractions (lesions<3 cm), or 50 Gy in five fractions (lesions with diameter between 3 and 5 cm). Before dose delivery, a daily KV-Cone Beam Computed Tomography (CBCT) was performed, comparing with planning CT scan: translational and rotational shifts were identified (Varian 6D Online Review System) and applied on the Protura TM Robotic couch 6DOF. Mean translational and rotational shifts were calculated. Using MIM 5.5.2 software, a CT was rigidly registered with CBCT. Then, translational shifts were applied, obtaining a translated CT(tCT), i.e. CT with only translational errors correction. Then, rotational errors were corrected too, obtaining roto-translated CT(rtCT). Initial treatment plan was copied to translated CT(tTP) and roto-translated CT(rtTP). Finally, dosimetric parameters were compared.

Results: From July 2015 to April 2016, 17 patients were enrolled (10 with primary lung tumours and 7 with metastatic lung lesions) with a median age of 74 yrs. Sixty-six CBCT were performed 132 treatment plans were calculated (66 tTP and 66 rtTP). The mean (±SD) interfraction displacements in all DoF are reported in Table 1. No significative correlation was observed between the magnitude of translational and rotational shift, so rotations need to be identified regardless of translations magnitude. No significant differences were found on CTV V95% in roto-translated plans. Not negligible differences (>2%) due to rotations were found in Organs

at Risk(OAR) located nearby the targets as reported in Table 1.

Conclusions: This work confirms that a 6-DoF robotic couch could be useful to improve accuracy in IGRT era, especially in SBRT. Small influence on PTV and CTV coverage observed could derive from an optimal setup and by sufficient margins. The analysis on setup systems and margin reductions is ongoing.

P075

HELICAL TOMOTHERAPY HYPOFRACTIONATED RADIOTHERAPY FOR PRIMARY AND METASTATIC LUNG LESIONS: PRELIMINARY RESULTS

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Aims: We report our experience with Hypofractionated radiotherapy (RT) with Helical Tomotherapy (HT) in primary non-small cell lung cancer (NSCLC) and lung metastases.

Methods: Between March 2014 and February 2016, 30 patients were treated with HT hypofractionated RT, 18 for primary NSCLC and 12 for metastatic lung lesions. Patient immobilization was obtained with the aid of a breast board and an abdominal pressure mould mask. The Gross Tumour Volume (GTV) was defined merging the treatment planning CT with a MVCT scan. The planning target volume (PTV) was obtained by adding a 10mm margin in craniocaudal direction and a 5mm margin in all other directions. Treatment schedules differed according to extent of target volume: patients with early stage NSCLC or lung metastases were allocated to shorter fractionation schemes, i.e. 40, 50 and 60Gy in 10 daily fractions, 70 and 60Gy in 10 and 8 alternate fractions, respectively; patients with advanced NSCLC underwent more protracted hypofractionated schedules, with 25 to 28 fractions and a total dose of 50 to 62.5Gy for parenchymal lesions and 46 to 48.6Gy for lymph nodes . The median BED10 was 75Gy (range 56-119) for the shorter fractionation schedules and 72.2Gy (range 62.5-78.1) for the more protracted ones. Side effects were evaluated weekly during treatment and at each follow-up visit, using CTCAE v4.0 toxicity scale.

Results: All patients completed RT without interruptions, with mean duration of treatment of 18 days (range 11-30) for the shorter schedules and 34 days (range 28-45) for the more protracted hypofractionation. After a median follow-up of 11 months (range 3–27), we observed G1 radiation pneumonitis in 8 (27%) patients, G2 in 2 (7%) and no cases ≥ G3 radiation pneumonitis. One patient experienced G2 non-cardiac chest pain and one G1 esophagitis. No other side effects were reported. At 6 months two (7%) patients had progression at the irradiated site; no other local failures were observed in the subsequent visits. During the follow-up period, 3 (10%) patients died, 2 as a consequence of disease progression in other sites and one from renal insufficiency.

Conclusions: Our preliminary data support safety and efficacy of hypofractionated RT with HT for lung lesions.

P076

EFFICACY AND SAFETY OF STEREOTACTIC RADIATION THERAPY FOR THE TREATMENT OF REMNANT DISEASE IN PATIENTS AFFECTED BY PULMONARY CARCINOMA: A POTENTIAL ASSOCIATION AFTER 3D CONFORMAL RADIATION THERAPY

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Aims: Lung carcinomas (LCs) are typically treated with resection, chemotherapy (CHT) and/or radiation therapy (RT), on the basis of findings revealed by pretreatment imaging. We believe that stereotactic body radiation therapy (SBRT) performed after standard RT can be an useful approach in patients with residual disease from LC, which may achieve local control of disease with limited toxicity.

Methods: Six consecutive patients (5 M and 1 F, mean age of 62.17 years, ranging 43 to 70), affected by LCs (5 non-small cell lung carcinomas and 1 small cell lung carcinoma) localized in right lung (3 pts) and left lung (3 pts), received SBRT for residual disease after 3D conformal radiation therapy because of LCs from 2012 to 2016 at our University Hospital with a median delivered dose of 21 Gy in 3 fractions through linear accelerator equipped with robotic arm. Previous treatment consisted in 3D conformal radiation therapy delivered with a median dose of 60-66 Gy in 30 fractions. Four patients received CHT in association with RT, 1 started CHT but was not able to continue because of haematological toxicity and the remaining 1 received only RT. Patients underwent Computed Tomography (CT) every three months after SBRT. RECIST criteria 1.1 were used to assess response. Positron Emission Tomography/Computed Tomography (PET/CT) was used to evaluate response in cases of equivocal findings.

Results: At two-year follow-up, 5 patients were alive and 1 died because of extrapulmonary disease: 2/5 showed partial response (PR), 2/5 stable disease (SD) and 1/5 progression of disease (PD) due to brain metastases. These results were confirmed also at three-year follow-up, with the exception of 1 patient with SD which experienced PD. Only 1 female patient, alive after five years, developed pulmonary fibrosis. No other additional toxicities were observed in our series.

Conclusions: Our experience on SBRT for residual disease in patients treated with 3D conformal RT demonstrates that SBRT is well tolerated with good local control of disease (5/6 patients or 83.3%). SBRT should be considered in this setting of patients, and prospective studies are warranted.

P077

HYPOFRACTIONATED SCHEMES IN PATIENTS WITH INOPERABLE NON-SMALL CELL LUNG CANCER: A MULTICENTER PROSPECTIVE STUDY

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Aims: Local tumour control is fundamental for outcome of lung cancer therapy. Local tumor control can be negatively influenced by accelerated repopulation of tumour cells during radiotherapy and chemotherapy. Approaches which tend to reduce accelerated repopulation might improve local control. We wish to evaluated different hypofractionated radiation therapy schedules for therapy of lung cancer.

Methods: We are conducting a prospective study in which patients with inoperable Non-Small Cell Lung Cancer (NSCLC) receiving conformal radiation therapy using standard fractionation on lung plus a boost with stereotactic technique performed with linear accelerator equipped with robotic arm (group A) versus conformal standard fractionated irradiation plus a boost with stereotactic body radiation therapy performed with non-dedicated linear accelerator (group B). Group A patients were treated with a dose 60-66Gy on tumor area plus a boost of 21-24 Gy in three fractions on residual disease; Group B patients were treated with a dose of 45-50 Gy on tumor area plus a boost of 30 Gy in ten fractions on residual disease.

Purposes: The purposes of our study are to evaluate short and long term results: in particular, we aim to study differences in tumor response, survival and toxicity. Until now, no grade 3-4 toxicities have been observed.

Conclusions: Approaches for reducing the effects of cell repopulation using accelerated hypofractionated radiotherapy are feasible and safe for patients with NSCLC. Our reported low toxicity rates are encouraging.

P078

EIGHT FRACTIONS SCHEDULE STEREOTACTIC BODY RADIOTHERAPY FOR EARLY-STAGE NSCLC OR LUNG METASTASES: EVALUATION OF TOXICITY AND OUTCOME

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Aims: The purpose of this study was to evaluate toxicity and outcomes of multifractionated stereotactic body radiotherapy (SBRT) for primary non-small cell lung cancer (NSCLC) or lung metastases.

Methods: Eligible patients included those with primary lung tumors clinically staged T1-T2 N0 M0 or lung metastases treated with SBRT between 2011 and 2016. Descriptive analysis was used to report patient demographics and treatment patterns. Overall survival (OS) and local control (LC) were determined using Kaplan-Meier method. Toxicity was reported using the Common Terminology Criteria for Adverse Events version 4.02.

Results: In total, 49 patients with 55 lesions (24 T1-T2/N0/M0 NSCLC and 31 lung metastases) were treated with 8 fractions SBRT in our institution. Biopsy was performed in 93% of cases. Median age was 71 years (range 38-84), 72.5 years (range 51-84) for primary NSCLC patients and 68 years (range 38-82) for lung metastases patients respectively. Mean PTV volume was 18,56 cc. SBRT dose varied from 48-75.2 Gy (median 75.2) delivered in 8 fractions, with median BED10 105 Gy (range 76.8-105). Median follow-up was 10.93 months (range 1.53-51.43). Response, according to RECIST criteria, was as follow: 21 complete responses (38.2%), 26 partial responses (47.3%) and 8 stable disease (14.5%). Lung toxicity after treatment was low with 9 cases>Grade 2 (16.4%); the maximum toxicity collected was G3 in 2 patients (4,1 %). We didn't record any G4/G5 toxicity (CTCAE 4.02). One-year LC for primary NSCLC and lung metastases was 86.7% and 93.3%, respectively. Two-years LC for primary NSCLC was 74.3%. One-year OS for primary NSCLC and lung metastases was 64.5% and 70.8%, respectively. Two-years OS for primary NSCLC and lung metastases was 32.3% and 20.8%, respectively. At the time of our analysis, 44 patients were alive, in particular, 27 alive with disease and 17 with no evidence disease.

Conclusions: Stereotactic radiotherapy in eight fractions for early non-small cell lung cancer or lung metastases is a safe and feasible treatment, with good local control and acceptable toxicity.

P079

LATE TOXICITY OF CONCOMITANT BOOST IMRT AFTER BREAST CONSERVING SURGERY: FINAL RESULTS OF A PHASE II TRIAL

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Aims. To evaluate the results in terms of late toxicity using hypofractionated radiotherapy (MARA-1) in early stage breast carcinoma as compared to a control group (CG) treated with standard fractionation.

Methods. This trial is a prospective phase I-II study on accelerated IMRT (MARA-1). Primary endpoint was to evaluate late toxicity and secondary endpoints were acute toxicity, local control and survival. In the CG the whole breast received 50.4 Gy in 28 fractions (fx) with a sequential boost on the tumour bed of 10 Gy in 4 fx with 3D technique. In MARA-1 an IMRT technique was used and prescribed dose to the breast was 40 Gy in 16 fx with a concomitant boost of 4 Gy. Late toxicity was graded using Radiation Therapy Oncology Group / European Organization for Research and Treatment Cancer (RTOG/EORTC) criteria.

Results. Four hundred forty-seven patients were included in this analysis (MARA-1: 317; CG: 130). The median follow-up was 52 months (range: 3-115). Late skin and subcutaneous toxicity were acceptable: 5-year actuarial cumulative incidence of G3 late skin toxicity was 1.5% in control group while no G3 toxicity was observed in MARA-1. Five-year actuarial cumulative incidence of G3 late subcutaneous toxicity was 0.8% in control group and 0.3% in MARA-1. At multivariate analysis, tobacco smoking and larger PTV volume were associated with an increased risk of late G1 skin toxicity (HR: 2.15, CI95%: 1.38-3.34 and HR: 1.12, CI95%: 1.07-1.18, respectively), whereas patients with a larger PTV also showed an increased risk of G1 and G2 late subcutaneous toxicity (HR: 1.14, CI 95%: 1.08-1.20 and HR: 1.14, CI 95%: 1.01-1.28, respectively). Even the use of accelerated-hypofractionated regimen increased the risk of late G1 and G2 subcutaneous toxicity (HR: 2.35, CI 95%: 1.61-3.41 and HR: 3.07, CI 95%: 1.11-8.53, respectively).

Conclusions. Assessing late toxicity by clinical examination, a higher incidence of late subcutaneous side effects was recorded in patients undergoing hypofractionated-accelerated radiation therapy. However, this increase was limited to G1-G2 toxicity. Further trials with prolonged follow up are needed to better define patients' subgroups more prone to develop late toxicity when treated with hypofractionated regimens.

P080

TOXICITY COMPARISON BETWEEN TRASTUZUMAB AND/OR CHEMOTHERAPY/ HORMONAL THERAPY IN PATIENTS RECEIVING ADJUVANT HYPOFRACTIONATED RADIOTHERAPY FOR BREAST CANCER

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Aims: Comparing trastuzumab treated patients (pts) skin toxicity to the same toxicity in pts only receiving chemotherapy (CT) and/or hormonal therapy (OT), submitted to hypofractionated adjuvant radiotherapy (RT). Moreover estimate the heart toxicity in the same subset of pts.

Methods: From January 2013 to December 2015, 214 breast cancer pts, submitted to conservative surgery, received in our Institution hypofractionated adjuvant RT, fifteen of them concomitant with trastuzumab. RT started 3-4 weeks after CT completation and total dose was 39 Gy/13 fractions with 3 concomitant weekly boosts of 1Gy (4 in case of close margins). Only 1 pts was treated on sovraclavicular fossa. 88% received OT with tamoxifen or aromatase inhibitors combined or not wih LH-RH analogue, 16% chemotherapy (anthracyclines and/or taxans) and 7% (15pts) trastuzumab (started during chemothetapy and lasted for 1 year). Skin toxicity has been assessed for all pts by RTOG scale at the end of RT, after 1, 6 and 12 months. Heart toxicity was monitored among trastuzumab treated pts by electrocardiogram and echocardiogram before, during and after the end of RT and CT. Ten of them had cancer on left side. 14 received CT (1 athtrcyclines based CT, 4 taxans based CT and 9 both). Eleven received OT: 10 aromatase inhibitors and 1 tamoxifen plus LH-RH analogue.

Results: Among no trastuzumab subset, skin toxicity at the end of RT was G0 47.8%, G1 46% and G2 6.2%; 1 month after G0 66.2%, G1 31.8% and G2 2%; after 6 months G0 79.2%, G1 20.8, G2 0%; after 12 months G0 87.6%, G1 12.4%, G2 0%. Among trastuzumab group at the end of RT G0 7%, G1 86%, G2 5%; after 1 month G0 47%, G1 33%, G2 13%, not determined (n.d.) 7%; after 6 months G0 47%, G1 33%, G2 0%, n.d. 20%. No significant differences between the 2 groups are evident for G2 toxicity. A more relevant rate of G1 toxicity is presesent in trastuzumab group only at the end of RT and after 6 months . In the same group no patient developed significant and/or symptomatic hearth toxicity. In fact in no case was observed a LVEF decrease of 10 points of the starting value or LVEF<50%.

Conclusions: While considering the small number of trastuzumab pts, our data show that, after breast conservative surgery, adjuvant hypofractionated radiotherapy concomitant with trastuzumab is feasible and safe, without heart toxicity and relevant increase of skin toxicity.

P081

THE IMPACT ON BREAST VOLUME ON ACUTE AND LATE TOXICITY OF HYPOFRACTIONATED TRIDIMENSIONAL RADIATION TREATMENT

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Purpose: To evaluate the impact of CTV on acute and late toxicity in women undergoing whole breast hypofractionated 3D-radiation therapy.

Materials and Methods: In this retrospective study, 150 patients undergoing breast-conserving therapy between 2012 and 2016 were screened, and all consecutive patients were included in the study. Either neoadjuvant or adjuvant chemotherapy was considered as exclusion criterion. All patients were treated supine with hypofractionated 3D-radiation treatment to the whole breast (42.4 Gy in 16 fractions) followed by a boost dose (10 Gy in 4 fractions). Clinical toxicity data were collected and analyzed using the MEDCALC statistical package. Logistic regression with ROC curve analysis with the determination of Younden index was performed in order to individuate a CTV volume related with the occurrence of grade 2 or greater acute or late cutaneous and/or subcutaneous toxicity.

Results: Radiation Therapy Oncology Group grade 2 or greater toxicities was acutely noted in 11.3% of patients and at later follow up (> 3 months) in 10.8%, respectively. Grade 3 acute toxicity was observed in 3 patients. No grade 4 acute and late toxicity was observed. The logistic regression analysis indicated that there was a significant association between CTV and Acute (OR= 1.004; 95%CI: 1.002 to 1.006; p=0.0035) and late (OR= 1.04; 95%CI: 1.01 to 1.06; p=0.022) toxicity. The ROC curve analysis and the Younden Index indicated that for CTV volumes greater than 960 CC the incidence of grade 2 or greater acute and late toxicity was significantly higher than for CTV lower volumes.

Conclusions: Adjuvant hypofractionated 3D-RT is a feasible and well tolerated radiation regimen for the treatment of women with CTV volumes lower than 960 cc. Although increasing breast size leads to increased clinical toxicity, the incidence and the severity of overall toxicity was acceptable.

P082

EVEROLIMUS PLUS EXEMESTANE IN METASTATIC BREAST CANCER: THE UNIVERSITY OF FLORENCE EXPERIENCE

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Aims: Everolimus plus exemestane proved to be an efficient and feasible treatment for metastatic HER2-negative breast cancer in the pivotal phase 3 BOLERO-2 trial. We aimed to assess the results of our experience with everolimus plus exemestane in our center from April 2013 to May 2016.

Methods: We retrospectively analyzed 36 post-menopausal women with ER-positive HER2-negative metastatic breast cancer, after recurrence or progression following endocrine therapy with a non-steroidal aromatase inhibitor. We analyzed the median time to progression (TTP), median overall survival (OS), and best response to treatment according to RECIST criteria (progression of disease, stable disease, partial response, complete response). Main toxicities were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE 4.0) criteria.

Results: The median age at first diagnosis of breast cancer was 66 years (range 46-86), with a median disease free survival from the first diagnosis of 91 months (range 11-268). Median age at initiation of everolimus plus exemestane treatment was 65 years (range 46-86). Seven patients (19.4%) initiated everolimus plus exemestane as a first line of chemotherapy in the advanced setting, while 7 (19.4%) started treatment as a second line of treatment. At time of analysis, 21 patients were deceased. Median OS from initiation of everolimus was 12 months (range 1-88), while median TTP was 7 months (range 1-26). Out of 33 patients, best response to treatment was partial response in 7 cases (21%), stable disease in 18 (54%), and progression of disease in 8 (24%). Grade 1-2 hematologic toxicities were developed by 16 patients (44.4%), while no G3+ hematologic toxicities have been observed. Interstitial pneumonitis was observed in 4 patients (11%). Treatment was suspended due to toxicity in 21% patients, and the median number of days of interruption was 29.

Conclusions: Our results confirm that everolimus plus exemestane is a valuable option for patients with hormone receptor-positive HER2-negative metastatic breast cancer, with a good efficacy and safety profile. The observed outcome are in line with existing published literature.

P083

ONCE-WEEKLY HYPOFRACTIONATED RADIOTHERAPY IN ANCIENT PATIENTS WITH LUMINAL B HER-2 NEGATIVE PN0 BREAST CANCER: PRELIMINARY RESULTS OF A CASE SERIES

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Aims: The purpose of this study is to analyse the early results in term of Ipsilateral Breast Tumor Recurrence (IBTR) and skin toxicity of a consecutive case series of patients older than 70 years affected by Luminal B pN0 breast cancer treated with a once-weekly hypofractionated radiotherapy.

Methods: A total of 54 patients were treated with WBRT between April 2012 to April 2013. Patients were given 6 Gy in 5 weekly fractions (total dose 30 Gy) over 5 weeks. All the patients are clinically classified as Luminal B breast cancer Her-2 negative (i.e. ER positive, HER2 negative, and either Ki-67>14 % or PR low or G3). The PTV was represented by whole breast. Whole-breast radiation therapy was performed with the patients in the supine position using a simple forward-planned intensity-

modulated WBRT using a field-in-field technique. For left breast cancer for each case it was contoured the Left Anterior Descending Artery (LAD) with the dosimetric end-point to keep the mean dose to this structure lower than 4 Gy to minimize potential cardiac late effects. It was accepted a V107 %<3% on external body contour corresponding to breast gland. PTV coverage was considered acceptable when D95% was>95%.

Results : The minimal follow-up for all the patients was at least 36 months. Only two patients experienced a IBTR (2.7 % of case series). The common biological features of these 2 patients were a Ki-67>35 % and the presence of intraductal component as DCIS. Maximum detected acute skin toxicity was Grade (G) 0 in 65.5% of patients, G1 in 22.5%, G2 in 7 % G3 in 4%, and G4 in 1%. Late skin toxicity consisted of G1 fibrosis in 25% of patients, G2 in 4%, and G3 in 5 %. Grade 1 edema was observed in 10% of patients, G2 in 3%, and G3 in 5%. G1 telangiectasia occurred in 2% and G3 in 1%. G1 hyperpigmentation was found in 7% of patients, G2 in 3%. Pain was observed as G1 in 15 % of patients. Cosmetic results were good to excellent in 90 % and fair to poor in 10%

Conclusions: A Once-weekly hypofractionated regimen seems a feasibile approach also for patients beloging to the Luminal B, Her-2 negative, pN0 subgroup. Particular attention in this setting should be devolved for patients in wich an intraductal component is present and in wich proliferative rates are high. Cosmetic results with a minimum follow-up of 3 years seems to be promising. Longer follow-up time is necessary to get more solid conclusions.

P084

RADIOTHERAPY WITH VOLUNTARY DEEP-INSPIRATION BREATH-HOLD USING BRAINLABEXACTRAC IN LEFT-SIDED BREAST CANCER PATIENTS WITH PREEXISTING CARDIAC RISK FACTORS: ADVANTAGES AND REPRODUCIBILITY OF TECHNIQUE

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Aims: Voluntary deep breath hold technique (vDIBH) is judged as the key to achieve the greatest cardiac sparing in whole breast irradiation. The aim is to estimate the heart, lung and planning target volume (PTV) dosimetric constraints and the reproducibility of vDIBH using BrainLabExactrac monitoring system .

Methods: Women with left BC submitted to breast-conserving surgery (BCS) with cardiac risk factors (heart disease and/or cardiotoxic systemic therapy) underwent to whole breast RT comparing free-breathing (FB) with vDIBH. Target and organ-at-risk (OAR) volumes were delineated in both CT scans and for both of them a treatment planning was performed. We compared the dose distribution for the heart, left anterior descending coronary artery (LAD), ipsilateral lung and (PTV) . Paired t test has been used to compare dosimetric OAR and PTV parameters between FB_CT and vDIBH_CT treatment plans. The online monitoring during EPI acquisition and treatment were made by BrainLab Exactrac system. Moreover daily real time electronic portal imaging (EPI) in DURING modality (captured during the beam delivery) were acquired in order to check the reproducibility.

Results: 30 patients were included in the study. Dosimetric data are showed in Table 1. vDIBH plans provided better PTV coverage (p=<0.001). The percentage of reduction of mean dose to the heart was 24.17%, to the LAD 33.62%. An increase of 14.85% of the percentage of left lung volume receiving 20 Gy was recorded in vDIBH plans, however being always below the recommended dose constraint. The mean set-up error, in mm, was: 0.21 in medial-lateral direction (ML; with systematic and random errors of = 0.10, = 0.10), 0.16 in cranio-caudal direction (CC, with = 0.08, = 0.08), 0.27 in the dorso-ventral direction (DV, = 0.16, = 0.12); for field 2 was 0.20 in ML (= 0.09, = 0.11), 0.19 in CC (= 0.09, = 0.11), 0.24 in the DV (= 0.14, = 0.10). The mean residual intra-fraction motion recorded during field delivery for field 1 was 0.22 in ML (= 0.13, = 0.09), 0.27 in CC (= 0.13, = 0.13), 0.25 in the DV (= 0.14, = 0.10); for field 2 was 0.23 in ML (= 0.12, = 0.12), 0.29 in CC (= 0.16, = 0.15), 0.24 in the DV (= 0.13, = 0.11).

Conclusions: vDIBH plans provided better PTV coverage, reducing delivered dose to heart and LAD. vDIBH delivered with Brainlab Exatrac seems accurate for both set-up and intra-fraction motion.

Table 1. Dosimetric data comparison between FB and vDIBH.

	FB treatment plans	vDIBH treatment plans	p value
PTV V95% (%)			
Mean	96.526	97.813	<0.001
SD	1.977	1.977	
Ipsilateral V20Gy (%)			
Mean	7.217	8.305	0.023
SD	3.046	3.388	
LAD (Dmax, Gy)			
Mean	18.020	11.414	<0.001
SD	5.124	6.126	
Heart (Dmean, Gy)			
Mean	2.006	1.521	0.001
SD	1.099	0.489	

FB=free-breathing; vDIBH= voluntary deep inspiration breath hold; PTV V95%= volume of PTV receiving 95% of prescribed dose; LAD= left anterior descending artery

P085

INTRAOPERATIVE ELECTRON RADIOTHERAPY 21 GY IN EARLY BREAST CANCER: COULD KI67 REPRESENT A SELECTION CRITERIUM IN PREOPERATIVE SETTING?

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Aims: To evaluate the influence of Ki67 percentage among most important prognostic factors in selecting patients suitable for IORT in early breast cancer.

Methods: From 02/2006 to 01/2016, 758 patients underwent breast-conserving surgery and IORT at Papa Giovanni XXIII Hospital, Bergamo (Italy). Median age was 64 (range 42-84 years). IORT was delivered to the tumor bed by a dedicated linear accelerator NOVAC 7 HITESYS (NRT, Italy), using 9 MeV electron beam, a single dose of 21 Gy at 90%. Statistical analyses were performed with Kaplan-Meier method and differences among groups were made using Log-Rank test (p value<0.05). Prognostic relevance of characteristics considered for the outcomes was assessed with Cox proportional hazard regression analysis. Correlations among most statistically significant factors were evaluated with multivariate analysis and log linkehood ratio test.

Results: Median follow up was 5.2 years (range 0-9 years). Results from univariate analyses, showing that age>50 years, non lobular histology, tumour size ≤2 cm, pN0 or pNmic, ki67< 20%, non triple negative receptor status, lymphovascular invasion (LVI) and G1-G2, defined 2 groups of patients, "suitable" and "unsuitable" for IORT, evidencing statistically significant differences in all clinical outcomes, except for OS (p<0.231), with a higher rate of breast related events moving from "suitable" to "unsuitable" group. Focalizing on in-breast tumor recurrences (IBTR), multivariate analysis showed that only LVI remained a statistically significant prognostic factor (p<0.05), with value of Ki67 and patient age (p<0.10) close to statistical significance. Using the log linkelihood ratio test, adding age and LVI to Ki67 we obtained a model that described the data in terms of maximum likelihood (p=0.027). In this case both LVI and Ki67 still remained statistically significant (Ki67 p <0.001, age p=0.12, LVI p=0.03).

Conclusions: Preliminary results from our analysis showed the importance of Ki67 and LVI as prognostic factors to make patients eligible to IORT: LVI can be evaluable only in postoperative setting and Ki67 could represent a surrogate additional criterium in selecting patients suitable for IORT. Further analyses with higher patient sample and longer follow up are needed.

P086

EXTERNAL BEAM RADIOTHERAPY (EBRT) VS. INTRAOPERATIVE RADIOTHERAPY (IORT) FOR BREAST CONSERVING THERAPY: A LARGE MATURE SINGLE INSTITUTION MATCHED-PAIR EVALUATION

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Aims: Comparative outcome data after intraoperative radiotherapy(IORT) and external beam radiotherapy(EBRT) for breast cancer at >5ys median follow-up are rare. We present a large, mature single-institution matched-pair-comparison reporting survival and relapse-rates in patients treated with either modality.

Methods: Complete datasets for 258 IORT-pts treated between 2000 and 2010 were matched with 258pts postoperatively treated with EBRT by age/histology/tumor size, grading/lymph-node-status/hormone-receptors/type of adjuvant therapy/surgical margins/treatment-date. EBRT was performed with 2 tangential fields to whole breast (50Gy/25fractions) and with 9-12MeV direct-electron-field-boosts to tumor bed (10-16Gy/5-8 fractions). A non-dedicated Linac (green-line-setup) with direct 8-12MeV electron fields (21Gy prescribed to 90%-isodose) delivered IORT. Relapse at surgical intervention site was classified as true local recurrence(LR). All recurrences in the treated breast (any quadrant) were classified as Ipsilateral Recurrence(IR).

Results: Median follow-up was 79months (12-156) for both groups. IR were 11 after IORT and 6 after EBRT. LR for IORT and EBRT groups were 8 and 3, respectively. Cumulative incidence of IR at 5ys were 2.3%(IORT) and 1.4%(EBRT), (p=n.s., HR 1.8 CI 95% 0.69-5). Cumulative incidence of LR at 5ys was 1.5%(IORT) and 0.8%(EBRT), (p=n.s., HR 3.1 CI 95% 0.8-11.3) Overall survival(OS) at 3/5ys was 98.8%/96.1%(IORT) and 98.8%/95.3%(EBRT), (n.s.). Disease-free survival(DFS) at 3/5 ys was 97.2%/93.2%(IORT) and 98%/93.5%(EBRT) (n.s). Between IORT and EBRT, no differences in non-breast-cancer-related-deaths or second-cancer-incidence were recorded. When analyzed according to ASTRO-criteria for accelerated-partial-breast-irradiation(APBI), outcome was better in the APBI-suitable group than in the entire cohort and the APBI-unsuitable group. The IR at 5ys for APBI-suitable/cautionary/unsuitable were 0%/2,7%/8% respectively

Conclusions: In line with published randomized-trial-data, IR-rate was higher after IORT than after EBRT if no stringent patient selection was performed. Non-breast-cancer-mortality and second-cancer-incidence did not differ between IORT and EBRT. In patients suitable for

APBI according to ASTRO-criteria, similar IR-, LR- and OS-data indicate that IORT is a viable alternative to EBRT.

P087

IS CONCURRENT TRASTUZUMAB WITH ADJUVANT HYPOFRACTIONATED WHOLE BREAST RADIOTHERAPY SAFE AND FEASIBLE? TOXICITY ANALYSIS IN STAGE I-II BREAST CANCER AFTER BREAST CONSERVATIVE SURGERY AND ADJUVANT CHEMOTHERAPY

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Aims: To retrospectively assess acute toxicity and outcome related to the concurrent administration of Trastuzumab (T) with adjuvant hypofractionated whole breast radiotherapy (hWBRT) after breast conservative surgery and adjuvant chemotherapy (CT) in patients with stage I-II breast cancer.

Methods: From 2010 to 2015, 428 patients were referred to the Radiotherapy Unit of San Donato Hospital-Arezzo, and after completion of CT received adjuvant hWBRT (40 Gy/2.67 Gy daily fractions followed by a 10-15 Gy boost to surgical bed). Of them, 35 were treated with WBRT and concurrent manteinance T, delivered every 3 weeks (loading dose of 8 mg/kg, then 6 mg/kg for 1 year) (group 1) and a comparison was made with a control group of 35 women who underwent the same hWBRT without T (group 2). The two groups were homogeneous in terms of type of surgery, stage, ER/PgR receptors, breast size, type of adjuvant CT. Acute skin toxicity was assessed according to the RTOG Criteria. Statistical analysis was made using the Student's T-test and the outcome evaluated with Kaplan-Meier survival curves.

Results: All patients completed hWBRT. Acute skin toxicity occurred in 94.2% and 85.7%, respectively for group 1 and 2 (p=0.4, 95% CI -0.08 to 0.19). Although the incidence of G2 toxicity was lower in hWBRT+T group (14.2% vs 20%), the difference was not statistically significant (p=0.22, 95% CI -0.36 to 0.09). G3 toxicity was observed only in group 2 (2.9%). After a median follow-up of 40.9 months (4.4-67.2), for both groups 5-year OS and DFS were 100% and 97.1% respectively.

Conclusions: In this study, acute toxicity of concurrent T and hWBRT was accetable and did not differ significantly from toxicity observed for hWBRT only. Longer follow-up is warranted to confirm these results and compare long term toxicity.

P088

FHYPOFRACTIONATED-ACCELERATED CONCOMITANT BOOST IN MODERATE-HIGH RISK BREAST CARCINOMA: A PHASE I-II STUDY

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Aims: To evaluate the results in terms of local control and late toxicity using intensity modulated radiotherapy with a concomitant boost in breast cancer (BC). These results were compared with a control group (CG) of patients treated with standard 3-dimensional (3-D) radiotherapy plus sequential boost.

Methods. Primary endpoint was local control; secondary endpoints were late skin and subcutaneous toxicities. Patients with moderate-high risk BC were enrolled and treated with forward-planned IMRT technique. Prescribed dose to the breast was 50 Gy in 25 fractions (fx) with a concomitant boost to the tumor bed of 10 Gy. In CG group, whole breast received a total dose of 50.4 Gy in 28 daily fx with a sequential boost to the tumor bed of 10 Gy in 4 fx. Late skin and subcutaneous toxicity were evaluated using Radiation Therapy Oncology Group/ European Organization for Research and Treatment Cancer (RTOG/EORTC) scoring scale.

Results. Four hundred and fifty one patients were included in our analysis (MARA-2: 321; CG:130). Median follow up was 52 months (range: 3-115). Five-year local control was 96.7% and 97.6% in CG and MARA-2 groups, respectively (p=0.676). At univariate analysis, patients treated with IMRT showed a significant increase of late G1 and G2 subcutaneous toxicity (p<0.001). Five-year G1 subcutaneous late toxicity free-survival (LTFS) in CG and MARA-2, respectively; moreover, 5-year G2 subcutaneous LTFS were 96.5% and 80.0% in CG and MARA-2, respectively. Five-year actuarial cumulative incidence of G3 late subcutaneous toxicity was 0.9% in MARA-2. G1 and G2 late skin toxicities were similar in the two groups and no patients showed G3 ≥ late skin toxicity in MARA-2.

Conclusions. This study showed the feasibility of using IMRT technique in postoperative radiotherapy in patients with moderate-high risk BC with no significant differences in term of LC, with a reduction of the treatment duration and without significant increase of G>2 late effects.

P089

CLINICAL COMPARISON OF TWO DIFFERENT HYPOFRACTIONATED SCHEDULES OF RADIOTHERAPY IN ADJUVANT SETTING OF EARLY BREAST CANCER THERAPY

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Aims: The use of hypofractionated schedules is challenging the standard fractionation and has now been considered an advantageous option particularly among elderly women. The results of randomized controlled trials have shown that hypofractionated schemes are not inferior to standard fractionation in terms of local recurrence, disease-free survival, overall survival and acute and late toxicity. In this study is reported our experience with two different hypofractionated regimes.

Methods: From 2011 a schedule of 16 fractions (16-fx) (266 cGy 5 days/week) adjuvant radiotherapy was introduced in the treatment of elderly patients (>70 years) with early stage breast cancer. From 2015 we have adopted a 5 fractions (5-fx) schedule (570 cGy one day/week) in the adjuvant setting of over 80 women (or for younger women with important comorbidity) with early stage breast cancer, according with good results of FAST trial and in order to minimize discomfort related to frequency of radiotherapy. In this study we have compared acute toxicity valuated with RTOG scale between 10 women treated with 5-fx and 15 women treated with 16-fx selected with the same features of the first group. Acute toxicity was considered during treatment and within three months by the end of therapy. All patients received conservative surgery and systemic therapy according with pathological features. (Table 1)

Results: All patients have completed the treatment as planned without severe toxicity. No severe toxicity was reported among 5-fx group and only one patient reported G3 toxicity for erythema and moist desquamation among the patients treated with 16-fx. A clear correlation statistically significant between toxicity and CTV volume or hot spots presence was no reported due to too little number of patients considered and low events reported. On other hand the only patient with G1 toxicity in 5-fx had the higher Dmax (110%) and the bigger CTV volume (771,4ccm) among the 5-fx group. In the same way among 16-fx group the patient that reported G3 toxicity have a CTV of 607,2 ccm (on average) and Dmax 108,3 (the higher among 16 fx group).

Conclusions: In our experience hypo fractionated regimens seem to be safe and reliable in the elderly setting with early breast cancer although longer follow up and more patients are requested.

Table 1. Pathological features and results.

patological features				
hystological tipe				
	CDI	CLI	CDLI	CDI+DCIS
5 hypo	7	1	0	2
16 hypo	6	0	2	7
grading				
		G1	G2	G3
5 hypo		0	8	2
16 hypo		0	11	4
volume T				
		T1	T2	N1
5 hypo		10	0	0
16 hypo		11	4	3
systemic treatment				
		OT	CHT	IT
5 hypo		10	0	0
16 hypo		14	1	0
RT plan				
	mean CTV (cc)		mean D max (%)	
5 hypo	380,61		107,7	
16 hypo	638,76		107	
acute skin toxicities (RTOG)				
	G0	G1	G2	G3
5 hypo	9	1	0	0
16 hypo	4	1	6	1

P090

HYPOFRACTIONATED RADIOTHERAPY WITH CONCOMITANT BOOST FOR BREAST CANCER: A DOSE ESCALATION STUDY

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Aims: to test the maximum tolerated dose (MTD) of a concomitant boost to the tumor bed for patients at high risk of recurrence treated with whole breast radiotherapy (RT). The secondary endpoints are to evaluate the acute and late toxicity and the cosmetic result recorded by appropriate scales.

Materials and Methods: patients with breast cancer with pathological stage pT1-2 and at least one of the following risk factors for local recurrence were enrolled: N1 disease, lymphovascular invasion, extensive intraductal component, close margins, non hormone sensitive disease, grading G3. All patients were treated with hypofractionated RT to a dose of 40.05 Gy in 15 fractions. The dose escalation to the tumor bed was delivered through a daily concomitant boost at 3 levels of dose: 48 Gy (3.2 Gy/die), 50.25 Gy(3.35 Gy/die) and 52.5 Gy (3.5 Gy/die) respectively. We included 3 patients for each step (3 additional patients if a dose limiting toxicity (DLT) Grade ≥2 occurred); dose escalation to a higher step was allowed if all patients of the lower one had completed the treatment without DLT. A clinical evaluation of the patients was carried out before treatment, 2 times a week during RT, at

the end of the same, at 3, 6 and 12 months after the end of RT. A cosmetic evaluation was performed, too. Patients filled the EORTC QLQ - C30 / BR23 on quality of life at each evaluation.

Results: We enrolled a total of 9 patients (3 for each dose level) with a median age of 62 years (range 44-83). Patients' characteristics are reported in Table1. No dose limiting toxicity Grade ≥2 occurred. The maximum toxicity collected during RT was G2 skin toxicity in 7 (77%) patients. This toxicity resolved at the first follow up. At a median follow up of 18 months we didn't record any G2 toxicity. There was a worsening in the self perception of cosmetic outcome at the end of treatment in 6 cases (66%). However, at a median follow up of 18 months, we recorded an improvement of 16% (from the end of radiotherapy) in the mean cosmetic score for the whole patient population. The cosmetic score recorded at 18 months was not different from the basal evaluation (p=NS). The evaluation of QoL found an improvement of the medium score at the end of treatment of 8% compared to initial. Further improvement of 12% in the medium score was recorded at 18 months.

Conclusions: The 3-week course of postoperative RT with dose escalation to the tumor bed to 52,5 Gy has been achieved without dose limiting toxicities.

Table 1.

CHARACTERISTICS	NUMBER OF PTS	PERCENTAGE
Adjuvant chemotherapy	4	44%
ER +	9	100%
PgR+	8	88%
HER2 +	2	22%
Ki 67 >20%	4	44%
lymphovascular invasion	1	11%
N1 5	55%	
G1 1	11%	
G2 4	44%	
G3 4	44%	
extensive intraductal component	3	33%
Lobular Carcinoma	1	11%
Ductal carcinoma	8	88%

P091

EARLY BREAST CANCER PATIENTS TREATED WITH HYPOFRACTIONATED ADJUVANT RADIOTHERAPY AND CONCOMITANT TRASTUZUMAB: 5-YEAR OUTCOMES AND TOXICITY

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Aims: To report 5-year outcomes and toxicity in early breast cancer pts treated with whole breast hypofractionated adjuvant radiotherapy(HRT) and concomitant trastuzumab after breast conservation surgery(BCS).

Methods and Materials: From February 2009 to October2011, 442 pts with breast cancer pTis-T2 pN0-N1(up to 3 positive lymph nodes) underwent forward planned intensity modulated HRT to a TD=40 Gy/15 fr at out institution, and reached 5 year median follow up; 31/442 pts presented c-erb B2 overexpression and were treated with HRT and concomitant trastuzumab. Acute toxicity during HRT was evaluated using the RTOG scale, while late side effects were assessed using SOMALENT score.

Results: Patients' median age was 60,5(28-75)years; tumor breast side: 20 left and 11 right. Histology: DCI: 24 pts; DCI+DCIs: 6 pts; DCI+ LCIs:1 patient; apocrine carcinoma: 1 patient. With a median follow-up of 63,8 (42,5-79,2) mts 3/31 pts (9,7%) presented a local relapse, 2/31 pts (6,5%) a lymph nodal relapse and 4/31 pts (12,9%) a distant relapse, confirming the higher propensity for locoregional and distant relapse of c-erb B2 positive tumors. All pts were alive at the last follow up. Acute toxicity was G0 in 7 pts (22,6%), G1 in 20 pts(64,5%) and G2 in 4 pts(12,9%) with no G3 toxicity. Late G1 edema and hyperpigmentation persisting up to 18 mts after HRT was observed in 7 pts (22,6%). Two persistent late toxicities were registered only in pts treated with FEC chemotherapy before HRT: one G2 fibrosis, starting 36 months after the end of HRT, with breast volume of 1812 cc (cut-off observed in our series: 866 cc), and one G3 teleangiectasy with breast volume of 596 cc. Two cardiac toxicities were registered, both in left sided breast cancers, one in a patient treated with AC x3 cycles+TXT x 12 weeks+trastuzumab x 12 mts, another in a patient treated with FECx5 cycles+trastuzumab x 12 mts, which presented a mediastinal relapse, treated with salvage chemotherapy. The same patient presented BPCO exacerbations, again after the salvage chemotherapy. While chemotherapy and breast volume were important predictors for acute toxicity, the association of trastuzumab was not statistically significant for both acute and late toxicity at the multivariable analysis.

Conclusions: HRT after BCS demonstrated good outcomes and low toxicity. The association of hypofractionated radiotherapy with trastuzumab does not increase acute and late toxicity.

P092

INTRAOPERATIVE PARTIAL BREAST (IORT) WITH ELECTRONS: PRELIMINARY RESULTS OF THE MULTICENTER GROUP OF THE EMILIA ROMAGNA REGION ITALY

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Background: In the Region of Emilia Romagna Italy

there are four centers with dedicated accelerator for intraoperative radiation therapy to breast cancer treatment with electron: Radiotherapy of Bologna Bellaria, Radiotherapy Ferrara, Radiotherapy Rimini, Radiotherapy of Reggio Emilia. The purpose of this paper is to present the preliminary data of common experience in the intraoperative treatment of breast cancer.

Methods: From 2009 to May 2016 we were treated with intraoperative radiotherapy (IORT)as a radical treatment of 498 patients with breast carcinoma after conservative surgery. All centers are equipped with Electron Linear Accelerator LIAC (Sordina)with beams of different energy (6,8,10 Mev) and followed the same training program. Until December 2013, the enrollment of patients was done according to the protocol of the Emilia Romagna Region IRMA3 . From 2014 in accordance with the guidelines Italyn Association of Radiation Oncology (AIRO) for breast IORT : Age> 60 years and menopausal status ,unifocal disease invasive non lobular histology,T ≤ 2 cm, disease with favorable biological profile (low proliferation index, hormone receptor-positive, HER 2 negative or phenotypic group luminal A), the absence of lymph node metastases (N0),macroscopically negative surgical margins. All patients received a dose of 21 Gy isodose of 90% with energy as a function of the thickness of the breast volume.

Results: Three of the 498 patients (0.6%)had a local recurrence of the disease. One patient had an axillary lymph node recurrence, one patient had recurrence in the same quadrant and one patient in a different quadrant.

Conclusions: The results of our experience confirms the feasibility of intraoperative treatment in terms of local control in the subset of low-risk patients in line with the most recent trials. It is however necessary a longer follow-up and a more accurate analysis of the data.

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P093

ACUTE AND SUBACUTE CUTANEOUS TOXICITY OF CONCURRENT ASSOCIATION OF BREAST RADIOTHERAPY WITH TRASTUZUMAB

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Aims: To analyze acute and subacute skin toxicity in patients(pts) who underwent adjuvant chemotherapy(CT) plus/minus trastuzumab(TSZ) and different whole breast Hypofractioneted Radiotherapy(HRT) in order to state if the humanized anti-HER2 monoclonal antibody trastuzumab may have radiosensitising effects on skin tissues.

Methods: In our study we assess skin toxicity of 3 different HRT schedules and concomitant TSZ compared with HRT and CT alone, according to the CTCAE-v3 criteria. Only pts with ductal invasive carcinoma <pT2 and <pN1a were considered in this analysis, metastases or bilateral breast disease were excluded. Prescribed dose was: 46 Gy in 20 fractions(fx) (<40 years old), 39 Gy in 13 fx (<46 y.o), 35 Gy in 10 fx (>46 y.o), 4 times a week.

Results: We compared acute and subacute cutaneous toxicity of 104 pts divided into 2 groups: 52 treated with HRT-CT+TSZ (group1) and 52pts with only HRT+CT (group2). In each group: 15pts underwent 46Gy, 16pts 39Gy and 21pts 35Gy. According to individual risk factors a weekly concomitant boost was added on tumor bed. All results are summarized in Table 1. Although the skin toxicities rates were comparable in the 2 groups, G2-G3 acute skin toxicity was more evident in group 1(TSZ) with the intensified 35 Gy/10 fx schedule.

Conclusions: In our experience the association of TSZ with HRT and CT seems to be tolerated, regardless the radiotherapy schemes. However, an increased acute toxicity may be expected when an intensified HRT is associated with CT and TSZ.

Table 1.

	ACUTE TOXICITY				SUBACUTE TOXICITY			
	GROUP1 (TSZ)		GROUP2 (NO TSZ)		GROUP1 (TSZ)		GROUP2 (NO TSZ)	
46 Gy	G3 -	46 Gy	G3 6%	46 Gy	G3 -	46 Gy	G3 -
	G2 7%		G2 27%		G2 -		G2 -
	G1 53%		G1 20%		G1 20%		G1 13%
	G0 40%		G0 47%		G0 80%		G0 87%
39 Gy	G3 -	39 Gy	G3 -	39 Gy	G3 -	39 Gy	G3 -
	G2 6%		G2 6%		G2 -		G2 -
	G1 50%		G1 44%		G1 25%		G1 12%
	G0 44%		G0 50%		G0 75%		G0 88%
35 Gy	G3 4%	35 Gy	G3 -	35Gy	G3 -	35 Gy	G3 -
	G2 19%		G2 -		G2 10%		G2 10%
	G1 48%		G1 71%		G1 19%		G1 33%
	G0 29%		G0 29%		G0 71%		G0 57%

P094

INTRAOPERATIVE RADIOTHERAPY AS A BOOST DURING BREAST-CONSERVING SURGERY USING ELECTRONS: LATE TOXICITY ASSESSMENT AND IMPACT OF SYSTEMIC THERAPY

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Aims: To assess late breast toxicity after intraoperative boost followed by hypofractionated external beam radiotherapy (HEBRT) of the whole breast according to adjuvant systemic treatment with chemotherapy (CT) or hormonal therapy (HT).

Methods: Between June 2004 and December 2009, 388

breast cancer women were treated with breast-conserving surgery. Adjuvant radiotherapy consisted of electron intraoperative therapy boost of 12 Gy to the tumor bed followed by HEBRT, consisting of 13 daily fractions of 2.85 Gy to the whole breast to a total dose of 37.05 Gy. For the study purpose, patients receiving systemic therapy and having at least one clinical examination with a minimum follow-up period of 5 years. Late breast side effects were assessed using LENT-SOMA scale. Toxicity ≥ G2 was taken into account in the present analysis. Patients were divided according to the type of systemic therapy: chemotherapy+/-hormonal therapy group (CT group) and hormonal therapy alone group (HT group).

Results: One hundred sixty-four out of 388 patients were evaluable for analysis with a median follow-up of 73.7 months (range: 60-118). Median age was 41.5 (24.1-48). All but 11 patients (7%) had 0-II stage disease. Invasive ductal carcinoma was the most frequent histology (89%). Median interval between surgery and HEBRT was 22.5 days (16-43). Ninety-two patients received HT alone (56%) while 72 were treated with CT +/- HT (44%). CT was initiated with a median interval of 50.5 days after surgery (28-83); 28/72 (38%) patients started CT during HEBRT or within 7 days of its completion. At last follow up 81/164 patients (49%) reported breast toxicity ≥ G2: 39 in the HT group (24%), 42 in the CT group (26%). Sixty-four percent of patients who started CT during HEBRT or within 7 days of its completion had late skin reactions ≥ G2 vs 50% of women started CT later on. More frequent toxicities in the two groups are listed below (HT group vs CT group): 16 (41%) vs 17 (41%) breast volume retraction, 16 (41%) vs 22 (52%) breast asymmetry and 20 (51%) vs 27 (64%) tumor bed fibrosis with only 4 and 2 patients reporting pain respectively in HT and CT group.

Conclusions: Late breast side effects were similar between the groups, with most of the patients being asymptomatic, except for tumor bed fibrosis, where toxicity was worse in patients receiving CT than those receiving HT. In those cases in which CT started within 7 days of HEBRT completion, toxicity tended to increase.

P095

WHOLE BREAST HYPOFRACTIONATED RADIATION THERAPY IN BREAST CANCER: EVALUATION AND RESULTS IN 369 PTS

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Aims: adjuvant radiotherapy after breast conservative surgery is an important step in management of breast cancer, but fractionation and total dose are changing in latest years. We evaluated the efficacy of hypofractionation regimen with 42,4 Gy/16 fractions to the whole breast, followed by boost 10 Gy/ 4 fractions.

Methods: We selected 369 patients (range of age: 33-85 years), treated in our Institution from June 2008 to May 2014, after conservative surgery, with 42,4 Gy/16 fractions to the whole breast, followed by boost 10 Gy/ 4 fractions. The tumor stage was from pT1a to pT4b and the nodal stage was from pN0 to pN1a. Median follow-up was 38 months (range 24-92).

Results: At last follow-up 3 patients (0.81%) had local relapse, 1 patient (0.27%) had nodal relapse, 11 patients (2.98%) had metastases and 7 patients (1.89%) died for disease. On the base of these results we observed that five years overall survival (OS) was 92.8%, the cancer-specific-survival (CSS) was 96.1%, while disease free survival (DFS) was 93.6%. Five years local relapse free survival (LRFS) was 97.0%, loco-regional relapse free survival (LRRFS) was 97.0% and metastases free survival (MFS) was 96.5 %.

Conclusions: whole breast RT schedules using 16 daily treatments followed by 4 daily boost treatments after breast conserving surgery is safe and effective with a low profile of toxicity.

P096

HYPOFRACTIONATED RT WITH OR WITHOUT BOOST IN BREAST CANCER: AN INSTITUTIONAL ANALYSIS OF TOXICITY

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Aims: Whole breast irradiation (WBI) is the gold standard after breast conserving surgery (BCS), followed by an additional boost when negative prognostic factors are present. WBI can be administered with hypofractionated schedules, on the basis of the relatively low / ratio for breast cancer (BC). The aim of our study was to investigate the effects of an additional hypofractionated boost (HB) and Trastuzumab in terms of acute and short-term late skin and subcutaneous tissue toxicity.

Methods: Between January 2014 and April 2015 228 women, median age 62 years (range 34-88) with early BC (pT1-pT2, N0-N1) underwent hypofractionated RT (single dose of 2.65 Gy to 42.4 Gy in 16 fractions) ± HB (single dose 2.65 Gy to 10.6 Gy in 4 fractions) and Trastuzumab. We enrolled 112 patients (pts) without HB (49,12%) and 116 with HB (50,88%). HB was delivered if risk factors such as young age, positive nodes, negative hormonal receptors, high Ki67 or HER2/neu overexpression were present. According to the risk of relapse chemotherapy (CT) and/or Hormonal Therapy (HT) and/or Trastuzumab were administered. For the analysis of the acute and late toxicity CTCAE 4.03 scale was used. Pts had physical examination at 5th, 10th, 16th and 20th day of RT and then 1 and 6 months after the end of treatment. Statistical analysis was carried out by the Chi-square test and the Mann–Whitney's U-test was used to compare continuous variables.

Results: HB group characteristics were: younger age

(median 55 vs 67), longer time gap between surgery and RT (median time 19 weeks vs 16), more advance stage (21,9% stage II vs 6,6%), CT (47 pts vs 4), HT (98 pts vs 76). Hypofractionated RT was well tolerated with or without HB and no G3 overall toxicity was documented. HB and Trastuzumab (despite the number of patients is low) did not contribute to major skin toxicity at 5th, 10th, 16th and 20th day of RT and then 1 and 6 months after the end of treatment. At 5th, 10th day of RT and 1 month after RT, BMI ≥ 25 (p=0,002) and number of lymph nodes excised ≥ 10 (p=0,004) significantly impacted upon toxicity occurrence. CT emerged as a risk factor for hyperpigmentation 6 months after RT: 80% vs 20% (p=0.012). In the table were reported the toxicity events.

Conclusions: Administration of HB and Trastuzumab is feasible, safe and well tolerated in terms of acute and short-term late skin and subcutaneous toxicity. Long term follow up data and a larger sample size are needed to confirm these data, assess late toxicity and clinical outcomes.

Table 1.

		WITHOUT HB (112 pts)					WITH HB (116 pts)					
		5 days	10 days	16 days	1 month	6 months	5 days	10 days	16 days	20 days	1 month	6 months
G1	Dry Skyn	–	–	–	5	1	–	1	1	2	3	4
	Hyperpigmentation	–	–	2	60	12	–	4	6	6	62	21
	Induration/fibrosis	–	–	1	3	6	–	–	–	–	6	19
	Pruritus/itching	–	–	6	2	–	2	2	5	6	2	1
	Desquamation	–	1	6	9	1	1	–	6	14	4	1
	Rash: dermatitis	9	36	65	20	3	12	40	70	72	15	3
	Teleangiectasia	–	–	–	–	–	–	–	–	–	–	–
	Skin ulceration	–	–	1	–	1	–	–	–	1	–	–
	Burn	–	–	–	–	–	–	–	–	3	1	–
	Edema	5	3	7	3	14	11	15	13	18	17	15
G2	Dry Skyn	–	–	–	–	–	–	–	–	–	–	–
	Hyperpigmentation	–	–	–	1	–	–	–	–	1	2	–
	Induration/fibrosis	–	–	–	–	–	–	–	–	–	–	–
	Pruritus/itching	–	–	–	–	–	–	–	–	–	–	–
	Desquamation	–	–	–	–	–	–	–	–	1	–	–
	Rash: dermatitis	–	2	7	–	–	–	–	7	19	–	–
	Teleangiectasia	–	–	–	–	–	–	–	–	–	–	–
	Skin ulceration	–	–	–	–	–	–	–	–	–	–	–
	Burn	–	–	–	–	–	–	–	–	–	–	–
	Edema	1	1	–	1	2	–	–	–	–	1	–

P097

HYPOFRACTIONATED RADIOTHERAPY IN BREAST CANCER TREATMENT: 3-DIMENSIONAL CONFORMAL VERSUS INTENSITY MODULATED RADIOTHERAPY

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Aims: to compare 3-Dimensional Conformal Radio Therapy (3D-CRT) and 4-fields Intensity Modulated RadiationTherapy (IMRT) treatment plans, in terms of target dose coverage, integral dose and dose to Organs at risk (OARs) in early breast cancer (BC) hypofractionated RT.

Methods: Twenty consecutive patients with early BC, after lumpectomy, were selected for the present analysis. A total dose of 40.5Gy in 15 fractions was prescribed to Planning Target Volume (PTVbreast) of the whole breast, while a simultaneous total dose of 48Gy was prescribed to the PTV of the surgical bed (PTVboost). For each patient both a 3D-CRT plan with two couples of tangential-fields, and a 4-fields sliding-window IMRT plan were generated. Conformity and homogeneity indexes (CI, HI) were calculated for PTVs. For evaluation of OARs and normal tissue (NT), V5Gy, V10Gy and various organ specific VxGy values were analyzed.

Results: In terms of HI, IMRT (0.18±0.02) was superior to 3D-CRT (0.23±0.02) for the PTVbreast ($p<0.0001$). Both techniques achieved the required dose for the PTVboost coverage, but a significant difference for CI was observed in favour of IMRT (0.9±0.4) compared to 3D-CRT (3.7 ± 4.3) ($p<0.0001$). With regards to the heart, IMRT improved both mean and near-maximum doses. The inter-patients average of the heart Dmean was (1.9±1) Gy for 3D-CRT, and (1± .8) Gy for IMRT ($p< 0.0001$). For the analysis of left BC, the inter-patients average of the heart Dmean was (2.9 ± 0.8) Gy for 3D-CRT, and (1.7±0.6) Gy for IMRT ($p=0.0005$).

For the ipsilateral lung, the average of Dmean for overall patients was 6.3 ± 1.4 Gy with 3D-CRT, and 4.8 ± 1.3 Gy with IMRT ($p<0.0001$). The V25Gy value of the ipsilateral lung was also lower with the use of IMRT ($p<0.0001$). For the contralateral lung, the inter-patients median of Dmean to the contralateral lung was 0.4Gy for 3D-CRT and 0.08Gy for IMRT ($p<0.0001$). For the contralateral breast, both Dmean and D2% were improved by the use of an IMRT planning technique. The inter-patients average of Dmean was (0.3±0.3) Gy for IMRT, while (1±0.5) Gy for 3D-CRT ($p<0.0001$). For NT, all DVH parameters are in favor of IMRT, except the V5Gy for which the difference was not statistically significant. The mean value of Dmean was 2.2 ± 0.6 for 3D-CRT and 1.5 ± 0.4 for IMRT ($p<0.0001$).

Conclusions: IMRT technique significantly reduced the dose to OARs and NT, with a better target coverage compared to 3D-CRT. Clinical evaluations are advocated.

P098

INITIAL BREAST CANCER ADJUVANT RADIOTHERAPY WITH HYPOFRACTIONATED REGIMEN: A MONOISTITUTIONAL RESULTS OF SAFETY AND EFFICACY AFTER A FOLLOW-UP OF UP TO 13 YEARS

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Aims: Adjuvant treatment of breast cancer is one of the most common indications for radiotherapy (RT) in western countries due to the high incidence of breast cancer. In women with breast cancer who undergo breast-conserving surgery (BCS), whole breast irradiation reduce the risk of local recurrence and can prevent the need for mastectomy. At our center, we conducted a study with hypofractionated radiotherapy (HFRT), in order to shorten the overall treatment time, and we evaluated efficacy and toxicities.

Methods: Between april 2002 and december 2015 a

total of 263 patients (pts, age 40-82 years), with pT1 and pT2 N0/N+ M0 breast cancer and negative surgical margins, underwent accelerated adjuvant irradiation after conservative surgery for early breast cancer. Patients with local postoperative complications, those with large breasts (volume>1000 cm^3), or patients with implants for augmentation or reconstruction, were excluded from the study because of the increased risk for late fibrosis or cosmetic deterioration following RT. Patients were treated by means of an accelerated hypofractionated schedule of irradiation at a total dose of 42.4 Gy given in 16 fractions over a period of 22 days.

Results: Pts were evaluated every 6 months for 5 years and then yearly. At a median follow-up time of 7 years (range 0-13 years), a cumulative incidence of local recurrence was of 1% (3 pts), the probability of survival over time was 84,6%. Neither skin ulceration nor necrosis were observed, a grade I-III acute skin toxicity was reported in 47 pts (18%). A late development of skin grade I-II sclerosis or teleangectasia was seen in 26 pts (10%). No symptomatic late lung toxicity was reported, but only a grade I pneumonitis was seen in 8 pts (3%). To date, no late cardiac events were reported.

Conclusions: Moderately hypofractionated radiotherapy using schedules such as 42,4 Gy in 16 fractions administered within 3 weeks has been shown to be as efficient and safe as conventionally fractionated radiotherapy for most breast cancer patients who need adjuvant radiotherapy after BCS. The hypofractionated schedule shortened the overall treatment time with no increase of skin acute toxicity and late lung or cardiac effects. HFRT is a valid option for eligible patients and its use should be encouraged. This regimen, according to the mature data reported in literature, in our opinion should be considered the new standard following BCS for early stage breast cancer.

P099

HYPOFRACTIONATED WHOLE-BREAST RADIOTHERAPY: ASSOCIATION OF SYSTEMIC TREATMENTS AND DOSIMETRIC PARAMETERS WITH TOXICITY AND COSMETIC OUTCOME

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Aims: The aim of this study was to evaluate toxicity and cosmetic outcome in breast cancer patients treated with adjuvant hypofractionated radiotherapy (RT) to the whole breast, and to identify possible risk factors for toxicity.

Methods: Four hundred and seventy women with early breast cancer, who underwent conservative surgery, were enrolled in the study. The patients received 45 Gy in 20 daily fractions(2.25 Gy). The boost to the tumour bed was administered with a total dose of 9 Gy in 3 consecutive fractions. Acute and late toxicity according to RTOG scale, and cosmetic outcome were assessed during and after RT.

Results: In our population study the mean age was 75 years. Adjuvant chemotherapy and/or targeted therapy ware performed in 80/270 (17%) and 20/470 (4%) patients, respectively. At the and of the RT 426/470 patients (91%) developed acute skin toxicity, 281/426 G1 (66%), 133/426 G2 (31%), and 12/426 G3 (3%). The median follow-up was 47 months (range 12-100 months). Late skin and subcutaneous toxicity evaluation was available for all patients. Late skin toxicity was recorded in 34/470 patients (7%), and late subcutaneous toxicity in 133/470 patients (28%). At last follow up, a good or excellent cosmetic outcome was reported in 96% of the women. By chi-square test, we found a significant difference for the occurrence of acute toxicity between adjuvant treatments (chemotherapy/targeted therapy vs. hormone therapy) ($p= 0.04$), and also breast volume (>500 cc vs. <500 cc) ($p = 0.02$) and maximum RT dose (>47.2 Gy vs. <47.2 Gy) ($p = 0.02$). Regarding the late toxicity and cosmetic outcome, no differences with clinical and dosimetric parameters were found.

Conclusions: These results confirmed the feasibility and safety of the hypofractionated RT in patients with early breast cancer. In our population, we showed a higher risk of developing acute toxicity for patients who underwent chemotherapy and targeted therapy, and patients with higher breast volume (>500 cc) and dose inhomogeneity (maximum dose>47.2 Gy). These factors may be selection criteria for hypofractionated schedules.

P100

HYPOFRACTIONATED RADIOTHERAPY IN EARLY BREAST CANCER. A SINGLE- CENTER EXPERIENCE

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Aims: Adjuvant radiotherapy after breast-conserving surgery is indicated in the vast majority of breast cancer patients. Conventionally fractionated radiotherapy with 50 Gy in 25 fractions is considered standard of care for several decades. The long-term results of randomized studies on different schedules hypofractionated radiation therapy were recently published and they may change clinical practice. HIgh -quality evidence supports that hypofractionated radiation treatment (HFRT) is as effective and safe in early breast cancer as conventionally fractionated radiation treatment. The local recurrence rates and acute toxicity after HFRT was analyzed in our center at the Department of Radiotherapy, Policlinico Umberto I, "Sapienza" University of Rome.

Methods: In our study we enrolled 120 women undergoing conservative surgery for early breast cancer (stage IA, IB, IIA, IIB) and with breast residual volume of less

than 600 cc. Adjuvant radiotherapy was delivered in 16 daily fractions for a total dose 42.56 Gy, 2.66 Gy per fraction. Boost to the tumor bed was administered with a total dose of 10 Gy in 4 consecutive fractions in all women. Acute toxicities were scored using CTCAE version 4. Late toxicities were scored using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scale.

Results: Median follow-up was 28 month (2-43). None of 120 patients had local recurrence. The local recurrence-free survival was 100% at 3 years. 56 patients (74,2%) presented acute skin toxicity: grade 1 in 56 pts (63%), G2 in 28 pts (31%) and G3 in 5 pts (6%). Fatigue and breast pain acute toxicity was less than grade 3. Late skin toxicity evaluation was available for all 120 patients with a minimum follow up of 3 months. The distribution of toxicity was: 25 pts (23%) with grade 1 and 3 pts (2%) with grade 2. No worse late skin toxicity was observed. At last follow up, a good or excellent cosmetic outcome was reported in 106 of the women.

Conclusions: These results confirm the feasibility and safety of the hypofractionated radiotherapy in patients with early breast cancer. The absence of local recurrence rates and acceptably low acute toxicity were achieved in a local setting with HFRT. HFRT is a valid option for eligible patients and its use should be encouraged. Long-term follow up is need to confirm this finding.

P101

CLINICAL AND DOSIMETRICAL ISSUES IN WHOLE BREAST CANCER HYPOFRACTIONATED 3D CONFORMAL RADIOTHERAPY IN OUR CLINICAL PRACTICE

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AIM: To evaluate a role of dosimetric parameters according NTCP model to predict late toxicity and cosmesis in hypofractionated whole breast 3D conformal radiotherapy according the Ontario Canadian trial. METHODS: A retrospective analysis on 215 historical consecutive early breast cancer patients treated with breast conserving surgery and adjuvant hypofractionated whole breast radiotherapy from 2004 -2011 at 6 years mean follow-up was conducted. The prescribed dose (PD) was 42.56 Gy in 16 fractions (266c Gy/fr 5fr/week), without boost .The breast diameter (the breast width over 25 cm at the posterior border of the medial and lateral tangential beams) and chemotherapy were not an excluding matter for patients' accrual. To assess the impact of 10%-20% dose hot spots on different percent value of PTV breast volume we retrospectively fit the NTCP model by Lyman dose-volume plot for late normal tissue for each patient using the α/β= 3.4 Gy for late change of breast appearance. Cosmesis was graded according to EORTC cosmetic rating system; late skin and subcutaneous toxicity were evaluated with RTOG/EORTC scale version 2. At the baseline a surgical cosmesis score was obtained according scoring criteria by Taylor. The X-square and paired t-test for univariate while the Pearson covariance for multivariate analysis were applied. RESULTS: For late toxicity and cosmesis at 6 years mean follow up data from all the 215 patients were collected. Skin or subcutaneous late toxicity was recorded in 47/215 (22 %); G3 toxicity occurred in 11 pts (5 %). Cosmesis with excellent-good score resulted in 172 patients (80%) while fair-poor score in 43 pts (20%). In univariate analysis with X-square test the V110>10 % of the PTV breast related to toxicity significantly ($p<0.005$); a statistical significant relation of PTVbreast>1300 cc to toxicity ($p<0.003$), cosmesis to V110>10% and PTV breast volume over 1300cc ($p<0.0059$) were found. Univariate analysis with T-test again confirmed these results. Multivariate analysis with Pearson covariance correlation test again showed the significant relation for toxicity and cosmesis with PTV breast, V110, surgery while a weak correlation was found for breast diameter and cosmesis.

Conclusions: To use safely one of the most important whole breast 3D hypofractionated radiotherapy schedule we found some predictive parameters that may be useful in selection of eligible patients. A longer follow up time is necessary to validate our results.

P102

PILOT STUDY RESULTS OF AFTEREIGHT 1.0 STUDY: AN ANTICIPATED BOOST WITH INTRAOPERATIVE ELECTRONS FOLLOWED BY SHORT-COURSE HYPOFRACTIONATED WHOLE BREAST RADIOTHERAPY IN EARLY BREAST CANCER POSTMENOPAUSAL PATIENTS

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Introduction and rationale: Intraoperative electrons as a boost in the adjuvant settings after breast conserving surgery (BCS) represent a relatively novel approach which has been gathering a growing body of literature. For whole breast irradiation (WB RT), conventional fractionation is the most common regimen, but increasing interest on hypofractionation has gained significant strength In our Institution, along with the long-established hypofractionated regimen of 13 fractions delivered to WB after 12 Gy intraoperative boost, an even shorter hypofractionated scheme for WB RT has been adopted for postmenopausal women. A phase II study combining intraoperative boost and hypofractionated 8-fraction scheme WB RT, called AFTEREIGHT 1.0, was designed and approved by IEO CE. We report here a preliminary experience on the pilot study which preceded the phase II

trial.

Materials and Methods: During BCS, 12 Gy intraoperative boost with electrons prescribed at 90% isodose, was delivered to the tumor bed. If they fulfil the eligibility criteria (invasive cancer, postmenopausal status, tumor stage T1-T2 pN0-pN1a), patients received 32 Gy to the whole breast in 8 fractions over one week and a half using image-guided intensity-modulated radiation therapy (H-IG-IMRT). Treatment was delivered with TomoTherapy Hi-Art system (Accuray Inc., Sunnyvale, CA) in Direct modality. Patients did sign a generic consent for radiotherapy and all of them gave consent for use of anonymised data for research and training purposes.

Results: From May 2012 to October 2013, 16 patients were enrolled in the pilot study. All of them completed the whole planned treatment scheme. Median age was 61.2 years (range, 50.9-77.2). Median follow-up was 23.8 months, (range 12.4-35.1). Acute and intermediate toxicity was evaluated for 16 and 14 patients, respectively, while chronic toxicity evaluation was available for 8 patients. Breast and tumour bed underwent separate assessment. No severe acute toxicity (RTOG grade 3-4) was observed. No patients complained about symptoms of severe intensity (score 8-10 according to NRS scale). Regarding chronic toxicity, 2/8 patients showed asymptomatic oedema. Grade 3 fibrosis was observed in one patient, who suffered from an immediate postoperative complication (infection). Radiological fat necrosis was detected in three patients.

Conclusions: The acute/intermediate toxicity observed in the pilot study was mild/moderate and encouraged the development of the phase II trial, AFTEREIGHT 1.0, where 177 eligible patients will be enrolled.

P103

HYPOFRACTIONATED ADJUVANT RADIOTHERAPY IN BREAST CANCER: ANALYSIS OF OUTCOME AND ACUTE AND LATE SOFT TISSUES TOXICITY IN A MONO-INSTITUTIONAL COHORT

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Aims: to report the local control and soft tissues toxicity, in breast cancer patients (pts) treated with hypofractionated adjuvant radiotherapy (HRT), 40 Gy in 15 fractions (2,67 Gy/fraction), after breast conservative surgery (BCS), with a 5-years median follow-up.

Methods and Materials: from February 2009 and October 2011, 442 pts were treated with HRT after BCS. Local tumor relapse was defined as recurrence of cancer at irradiated breast. The acute toxicity was evaluated during RT treatment by RTOG scale. Late side effects as edema, fibrosis, hyperpigmentation and telangiectasia, were individually assessed, using SOMA-LENT score, at 6 months from the end of radiotherapy and then every year. The association between possible risk factors and development of early and late complications was identified using multivariate logistic regression analysis.

Results: after a median follow-up of 65,4 (12-84,8) mos the rate of local failure at 5 years was 2,25%. RTOG acute toxicity was: G0 in 164 pts (37%), G1 in 220 pts (49,8%), G2 in 53 pts (12%) and G3 in 5 pts (1,2%). In 9 pts a delayed toxicity≥G2 was detected at 1-3 weeks after the end of radiotherapy. We observed a strong correlation between acute toxicity≥G2 and breast volume (p=0,0001), with best cut-off 866 cc derived from ROC analysis. Another important correlation was found with chemotherapy (p=0,003), particularly if concomitant (p=0,017). 99 pts (22,5%) showed edema and/or hyperpigmentation at 6 mos after treatment and then the rate decreased over time until disappear, without new events. On the contrary, the rate of pts who presented fibrosis and telangiectasia was neglectable at 6 mos (0,68%) but increased over time to become 6.5% at 5 years. The use of build up bolus in more than 7 fractions (p=0,0003), breast volume (p=0,0006), age<56 years (p=0,021), and previous axillary dissection (p=0,0004) were the most important predictable factors for edema and hyperpigmentation, while the development of fibrosis and telangiectasia was correlated with acute toxicity (p=0,0115) and the presence of edema at 6 mos (p=0,0006).

Conclusions: in our experience HRT is a safe treatment with high rate of 5 year local control, as reported in literature, and low toxicity. The predicting factors of toxicity emerged from our analysis could help to better manage the breast HRT in terms of cosmetic result.

P104

HYPOFRACTIONATED RADIOTHERAPY FOR >50 YEARS OLD BREAST CANCER WOMEN AFTER CONSERVING SURGERY

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Aims: Radiation therapy (RT) is successfully used together with surgery and chemotherapy in the treatment of breast cancer. Although 50 Gy in 25 fractions of 2 Gy is the most commonly used schedule, many published reports have confirmed that shorter courses of RT are equally effective compared to longer RT schedules. The aim of this retrospective analysis is to evaluate efficacy and toxicity in a group of breast-cancer patients treated with a hypofractionated schedule.

Methods: Between June 2005 and December 2012, two-hundred breast cancer patients >50 years were treated at Radiotherapy Department in Taranto with adjuvant hypofractionated RT. The mean age was 70 years (range: 51-85 years). All patients underwent lumpectomy and axillary dissection was performed in 63.5% of patients, with a median number of 12 nodes removed (pN1 stage in 4% of patients). Sentinel node biopsy was performed in 38% of patients. Pathological stage was pTis in 1%, pT1 in 72% and pT2 in 27% of patients with a median tumor

size of 1.6 cm. Estrogen receptor status was positive in 86.4%, negative in 12.1%, not known in 1.5% of patients. Progesteron receptor status was positive in 70.5%, negative in 27.5%, not known in 2% of patients. Chemotherapy was recommended for 31% of patients (24.9%) while 65.5% received hormonal therapy alone. All patients received adjuvant RT with a hypofractionated regimen and a total dose of 42.56 Gy (2.66 Gy/die) and an electron boost of 10 Gy was added for women <70 years (10.5% of patients). Acute and late toxicity were evaluated according to the RTOG-EORTC scale. Local recurrence rate, distant metastases rate and overall survival was calculated.

Results: Mean follow-up was 56 months (range 6-130 months) and eight patients were lost to follow-up. Acute and late skin toxicities are shown in table 1. No acute lung toxicity was observed while 1.6% of patients had late lung fibrosis. At the time of analysis, most of patients (92%) were alive without disease, 1.5% were alive with local recurrence (but with no distant relapse), 2.5% died with distant metastases (including one with contralateral breast cancer) and 4% died due to cardiac disease (2% irradiated for left breast and 2% irradiated for right breast). Median time to local recurrence was 43 months while median time to distant metastases was 26 months.

Conclusions: Our results provide support for the use of hypofractionated RT with a total dose of 42.56 Gy (2.66 Gy per fraction) in selected woman especially >50 years, without positive nodes and with tumor size <2 cm. This hypofractionated schedule is safe with good local control and it allows a short course of treatment, allowing a larger number of patients to be treated, also with a reduction in cost to the health system.

Table 1.

Toxicity grade	Acute skin toxicity (%)	Late skin toxicity (%)
G0	14.5	81.3
G1	70	16.7
G>2	15.5	2

P105

HYPOFRACTIONATED RADIOTHERAPY AFTER IORT IN EARLY-STAGE BREAST CANCER: TOXICITY AND COSMETIC RESULT

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Aims: Reduction of treatment time and evaluation of the toxicity in senior women affected by early-stage breast cancer treated with single-dose intraoperative radiotherapy (IORT) and subsequently external re-irradiation (ERT) with hypofractionated whole breast radiotherapy (hRT) compared with conventional whole breast radiotherapy (cRT).

Methods: In our center, between March 2013 and May 2015, 29 patients, previously treated with quadrantectomy and IORT based on the age and the histological exam of biopsy, underwent to ERT for definitive histological features. On these 29 patients, 16 were treated with hRT that consisted of 42,4 Gy in 16 fractions with 2,65 Gy/fraction and the other 13 underwent to cRT of 50 Gy in 25 fractions. Toxicity was assessed at the end of ERT and at 3 and 6 months using RTOG/EORTC toxicity scale. Cosmetic results were assessed at 1 year in agreement with Harvard criteria.

TABLE 1. Patient, Tumor, and Treatment-Related Characteristics

	Hypofractionation (N=16)	Conventional Fractionation (N=13)
Age (years)	Median 69 (range 63-80)	Median 73 (range 61-80)
< 69	5	2
69-73	7	5
> 73	4	6
Breast		
Right	9	5
Left	7	8
Tumor pathology		
Ductal (+ in situ)	13 (6)	9 (3)
Lobular	3	4
Pathologic T stage		
T1	13	8
T2	3	5
Pathologic N stage		
N0	11	9
N1	5	4
Resection margins		
Negative	10	10
Close	6	3
Vascular invasion		
L0	13	10
L1	3	3
Histologic grade		
1	2	0
2	8	10
3	6	3
Molecular subtype		
Luminal A	3	1
Luminal B (HER2 +)	12 (2)	12 (1)
Triple negative	1	1
Chemotherapy		
Yes (+ trastuzumab)	3 (2)	3 (1)
No	13	10
Hormone therapy		
Yes	15	12
No	1	1

Results: At median follow-up of 18 month, all patients are alive and no one had recurrence of disease. The main characteristics of patients, tumor, and treatment-related are summarized in Table 1. One patient of 80 years with left breast cancer and cardiological comorbidity, during cRT, showed acute cardiac toxicity. Her ERT was stopped at 16 Gy in 8 fractions. Excluding this case, all other patients have completed their treatment as preview, with a total duration of 3 weeks for the hRT arm and 5 weeks for cRT arm. The acute skin toxicity at the end of ERT was of grade 1 in all cases for both treatment arms. At 3 and 6 months of follow-up, late skin and subcutaneous tissue toxicities were scored as grade 1 in 4 cases treated with hRT and 3 cases treated with cRT, and grade 0 in 11 cases of hRT arm and 8 cases in cRT arm. All these patients showed excellent or good cosmetic results at 1

year. Two patients, one treated with hRT and one with cRT, developed important late skin and subcutaneous toxicity as grade G4 and G3 with poor and fair cosmetic results at 1 year, respectively.

Conclusions: the hRT shows a reduction of 2 weeks of overall treatment time compared with cRT. Although the examined cases are few and the follow-up short, the observed toxicity data are consistent with the results published in the literature. Therefore, even in women previously undergone to IORT, it would seem to be recommendable a hRT compared to cRT providing benefits on the daily discomfort for patients and savings of health resource, with acceptable toxicity profile.

P106

HYPOFRACTIONATED ADJUVANT RADIOTHERAPY IN BREAST CANCER: EVALUATION OF TOXICITY AND ANALYSIS OF AESTHETICAL OUTCOMES

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Aims: The aim of our study was the evaluation of acute and late toxicity, the grade of aesthetic satisfaction and the incidence of locoregional recurrence (LRR) reganding a hypofractionated RT schedule for breast cancer patients.

Methods: From June 2008 to Dicember 2015, 125 women (median age 73) were treated for breast cancer (Stage 0-III) with a hypofractionated radiation schedule after breast-conserving surgery. Most patients received 40.05 Gy in 15 daily fractions, 2.67 Gy for fraction to the whole breast plus an additional sequential boost dose of 6 Gy in 2 fraction (3 Gy) to the tumor bed. 1/125 patients had neoadjuvant chemiotherapy, 1/125 patients had concomitant CMF during RT, 7/125 patients have had anthracyclines based chemotherapy before RT and 117/125 didn't receive chemotherapy but only hormonal therapy. Toxicity evaluation was performed according to the RTOG toxicity scales. Cosmetic questionnaire was used to evalue patients approval about aesthetic results.

Results: Median follow up was 42 months. Neither local recurrence was noted in any patients during this 7-year follow up. Grade 0 acute skin toxicity was observed in 30/125, Grade I acute skin toxicity was observed in 88/125 patients and grade II in 7/125 patients who had undergone to anthracyclines based chemotherapy. Regarding to skin late toxicity we detected Grade I hyperpigmentation in 43/125 which slowly decreased during the follow up; we noticed a long lasting grade I fibrosis in 22/125 women; 7/125 patients developed mild infiammatory telengectasia at 18 months. In response to the cosmetic questionaire, 108/125 of patients stated they were very satisfied with the overall appearance of the breast, 10/125 moderately satisfied, and 7/125 either slightly or not at all satisfied.

Conclusions: This hypofractionated schedule resulted an effective treatment in terms of local control. Patients treated with this type of approach showed lower toxicity and very good cosmesis.

P107

HYPOFRACTIONATED IMRT AFTER CONSERVATIVE SURGERY IN PATIENTS WITH EARLY STAGE BREAST CANCER TREATED WITH SYSTEMIC ADJUVANT THERAPY: REPORT OF ACUTE TOXICITY

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Aims: To assess acute toxicity after adjuvant hypofractionated IMRT to the whole breast, in patients receiving neoadjuvant/adjuvant chemotherapy and/or hormonal therapy.

Methods: This retrospective analysis included 95 patients with a diagnosis of early stage breast cancer treated with breast conserving surgery and neoadjuvant or adjuvant systemic therapy followed by hypofractionated external beam radiotherapy, delivered between May 2013 and November 2015. Patients were treated using intensity modulated hypofractionated radiotherapy (Tomo Therapy® Inc., Madison, WI). The schedule of treatment consisted of 40.05 Gy in 15 fractions (2.67 Gy/fraction) to the whole breast and 48 Gy in 15 fractions (3.2 Gy/fraction) to the tumor bed with simultaneous integrated boost. Patients were divided in two groups: 64 patients (67 %) received only adjuvant hormonal therapy and 31 (33 %) were treated with chemotherapy +/- hormonal therapy. Systemic medical treatment was given in in three modalities: neoadjuvant, adjuvant or concomitantly to radiotherapy). Acute toxicity defined as major grade of skin reactions observed into 6 months after the end of radiotherapy was assessed according to RTOG scale.

Results: In all patients the clinical evaluation of acute skin reactions was available. Median age was 54 years (range 34.1 - 76.5). The median follow- up was 6.5 months (range 1-31.7). In a global evaluation of both groups, toxicity grade 2 of any type was observed in 29 patients (30.5%) and toxicity grade 0-1 was present in 66 patients (69.5%). Toxicity grade 3 or 4 was not observed. Skin acute reactions were similar in the whole breast and in the boost area. In the group of patients treated with hormonal therapy, acute toxicity grade 2 was present in 22 patients (34.4%) and included only edema. Acute skin reactions grade 0-1 were observed in 42 patients (65.6%).

In patients that received chemotherapy, acute skin reactions grade 2 were present in 7 patients (22.06 %) , including edema and erythema. Skin acute toxicity grade 0-1 was assessed in 24 patients (24 patients).

Conclusions: Hypofractionated external beam radiotherapy is safe, well tolerated and feasibly in patients who received adjuvant hormonal therapy or neoadjuvant/adjuvant chemotherapy+/- hormonal therapy with an acceptable rate of skin acute reactions.

P108

THE DOSIMETRIC IMPACT OF HYPOFRACTIONATED WHOLE-BREAST RADIOTHERAPY ON TANGENTIAL IRRADIATION WITH FIELD-IN-FIELD AND IRREGULAR SURFACE COMPENSATOR TECHNIQUE

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Aims: The aim of this study was to evaluate the breast dose heterogeneity in hypofractioned whole breast irradiation comparing the dosimetric aspects between an irregular surface compensator (ISC) and a conventional tangential field technique (3D-CRT) using dynamic wedges and Field-in-Field (FiF).

Methods: Treatment plans were implemented in 71 patients with breast cancer. For each patient, treatment planning was designed using tangential fields for breast irradiation with two different techniques: 3D-CRT with FiF and ISC. Both techniques have been planned to deliver the optimized dose distribution. The Eclipse treatment planning system (Varian Medical Systems, Palo Alto, USA) with Anisotropic Analytical algorithm (AAA) was used for dose calculation. The tissue heterogeneity correction was used in all the treatment plans. The prescription dose was 40.05 Gy in 15 fractions. All the plans were treated with 6 MV or 15 MV photon energy from the Clinac iX with 120 MLCs (Varian Medical Systems, Palo Alto, USA). The two different treatment plans (3D and ISC) were compared objectively using the dose volume histograms (DVHs) for doses in PTV and the organ at risk (OAR). With regard to PTV, the following values were compared: the percent volumes receiving at least 95% and 105% of the prescribed dose (V95% and V105%), conformity index (CI) and dose homogeneity index (DHI). The t-test was used for comparing each dosimetric parameter. The significance level was set at $P<0.05$.

Results: Compared with the 3D-CRT with FiF technique, the ISC technique significantly improves conformity index ($P=0.33$). However, no significant difference for Homogeneity index was observed ($P< 0.01$). The impact on OAR dose constrains was equivalent in both techniques.

Conclusions: The present study aimed to compare two techniques of whole breast irradiation in terms of the homogeneity of dose distribution and the number of hot spot regions. Compared with 3D-CRT with FiF, ISC technique improves significantly ($P=0.33$) the conformity index, with a comparable homogeneity index. Furthernore, the ISC technique reduced the size of the hot spots. Because of these advantages, this recent technique has been applied for many patients with breast cancer at our institution.

P109

ESTIMATE OF PARAMETER A FOR GEUD IN LEFT-SIDED BREAST TANGENTIAL IRRADIATION CORRELATED TO LONG-TERM CARDIAC MORTALITY RISK

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Aims: To determine the biological parameter a in the generalized equivalent uniform dose (gEUD) concept for tangential left-sided breast irradiation, considering as endpoint the cardiac mortality probability. A method for determining the a values was investigated by using the total prescription dose (TPD) to the target volume and the (near-)maximum dose to the heart (ICRU 83).

Methods: Parameter a can be determined by imposing the equivalence between the equation of the relative seriality model (RS) in the case of homogeneous irradiation when using gEUD and in the case of heterogeneous irradiation. The equality was obtained by forcing parameter a with a spreadsheet.

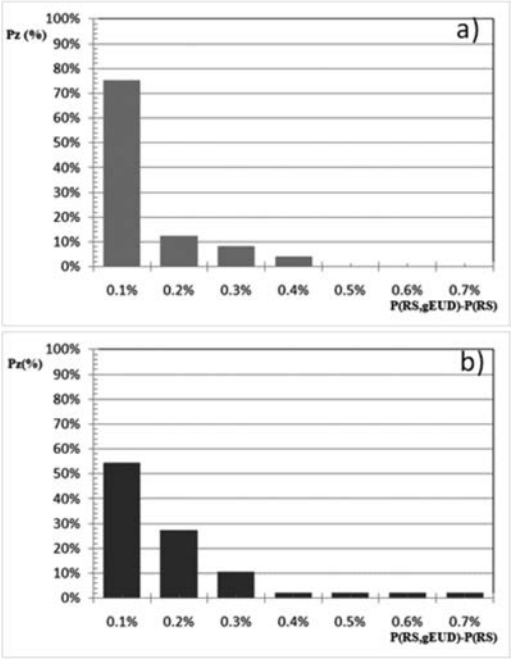

Figure 1.

Results: The method proposed here was developed prescribing four different doses to the left-sided breast for 12 patients' plans. Reporting the a values vs. TPD for every patient plan, a set of a values ranging from 5.09 to 7.23

were determined and fitted by second-order equations, and for every TPD the a values showed dependence on the near-maximum dose to the heart. To evaluate the accuracy of the method it was applied in 48 patients, for whom tangential left-sided breast radiotherapy plans were optimized; thus calculated, the parameters a were used to determine the gEUDs, and by using the RS model in homogeneous cases, to determine cardiac mortality probabilities. These calculations were compared to the cardiac mortality probabilities calculated with the RS model in the heterogeneous case, with an accuracy within 0.5% in terms of probability difference.

Conclusions: This method is a practical and simple way to determine parameter a, requiring only the TPD to the breast and the dose near-maximum to the heart, which can be determined from the physical dose volume histograms, available with every TPS. This dependence also shows a probable serial behavior of the heart.

P110

RESULTS OF A MONOINSTITUTIONAL EXPERIENCE OF HYPOFRACTIONATED RADIOTHERAPY IN STAGE 0 BREAST CANCER

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Aims: Adjuvant radiotherapy in breast conserving surgery is a standard option in infiltrating and "in situ" breast cancer. Hypofractionation can be raccomended as standard treatment in infiltrating breast cancer. The aim of our study is to evaluate the impact of moderate hypofractionation in patients affected by in situ breast cancer.

Methods: We selected 61 patients treated from August 2008 to May 2014, median age 57 years (range 38-82) with pT0 breast cancer. Radiotherapy was delivered in 16 fractions 2,65 Gy/die for a total dose of 42,4 Gy with high energy fotons (6-15 MV). No patient had a boost treatment. All patients under went to CT simulation with a dedicated CT scan in supine position on a breast board device. Median follow-up was 38 months (range 24-92).

Results: At last follow-up only 2 patients (3.28%) had local relapse. On the base of these results we observed that five years overall survival (OS) was 100%, the cancer-specific-survival (CSS) was 100%, while disease free survival (DFS) was 90.8%. Five years local relapse free survival (LRFS) was 92.6%, loco-regional relapse free survivals (LRRFS) was 92.6% and metastases free survival (MFS) was 100 %.

Conclusions: In conclusion, moderately hypofractionated radiotherapy 42.4 Gy/16 fractions in breast cancer after conservative surgery has been shown to be a valid therapeutic option in "in situ" disease as well as in infiltrating.

P111

EXCLUSIVE ELECTRON INTRAOPERATIVE RADIOTHERAPY IN EARLY-STAGE BREAST CANCER: A MONOINSTITUTIONAL EXPERIENCE

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To evaluate the effectiveness of intra-operative radiotherapy (IORT) in breast cancer in terms of local control, aesthetic results and disease-free survival.

Patients and Methods: From June 2007 to December 2014, 164 patients with early-stage breast cancer were submitted to quadrantectomy and IORT. A total dose of 21 Gy prescribed at 90-100% isodose was delivered in all cases. Patients were evaluated after surgery for early and late complications.

Results: Median Follow-up was 21.1 (range: 17-84) months. In 12 patients (7.3%), breast ultrasound showed liponecrosis. Eight patients (4.8%) developed grade 2 fibrosis. Disease-free survival rates at 2 and 3 years were 90% and 88%. Three patients (1.8%) developed local recurrence, two patients (1.2%) distant metastasis. Four patients died. The 2- and 3-year overall survival rates were 100% and 98%, respectively.

Conclusions: IORT could be an appropriate therapeutic alternative in selected patients although it remains investigational; longer follow-up to confirm these results is required.

P112

EVALUATION OF ACUTE AND LATE CARDIAC TOXICITY IN PATIENTS TREATED WITH HYPOFRACTIONATED RADIOTHERAPY FOR BREAST CANCER

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Aims: The aim of this study is the assessment of cardiotoxicity in patients receiving adjuvant radiation therapy in breast tumors. Therapeutic innovations allowed an improvement for overall survival, implying a greater interest in evaluation of late side effects, such as cardiotoxicity.

Methods: From March 2014 to April 2016, 42 patients were enrolled, one patient underwent neoadjuvant chemotherapy, 9 adjuvant chemotherapy and 25 hormonal treatment. Before radiation treatment all patients were subjected to a preliminary assessment: ECG, cardiological examination, and blood tests (blood count, ESR, BUN, creatinine, serum sodium, potassium, CT, LDL-C, HDL-C, blood glucose, troponin-A and BNP). Blood tests were made before radiotherapy, instead at fourth and at sixteenth fraction were tested troponin A and BNP. At follow up after one month were repeated all tests done at

baseline. One year and two years after the treatment were repeated ECG, Troponin-A and BNP.14 pts were treated on the right breast, 28 on the left breast.

Results: Median age was 56 years. 30 pts have completed cardiological follow-up one year after treatment, 11 of these had an evaluation after two years from the end of RT. We haven't observed changes statistically significant of ECG, troponin-A and BNP during radiotherapy as well at two years post treatment. We have not reported changes related at side, right and left breast.

Conclusions: Patients with breast cancer have a long survival, which implies an increased interest for the toxicity caused by radiotherapy. With our study we showed that with new technique of 3D conformal radiotherapy, CT multislice for delineation of target volume and dose planning, results in a better distribution of the dose in the breast, with the possibility of reducing the dose to healthy organs such as the heart resulting in reduction of acute and late toxicity. Are needed longer follow-up to better evaluation of a long term side effects.

P113

IN VIVO DOSIMETRY BY EBT3 GAFCHROMIC FILMS DURING IORT BREAST TREATMENT

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Introduction: The purpose of this work is to assess the dose prescribed and delivered with a EBT3 gafchromic to patients during IORT breast treatment.

Methods: Linear Electron Accelerator LIAC (Sordina) was used to treat, from 09/04/2014 to 06/05/2015, sixty-six patients affected by early-stage breast cancer. Thirty-nine patients underwent exclusive treatment (21 Gy) and other twenty seven patients only for boost (9 Gy) with electron beams of different energy (6,8,10 Mev). The choice of energy depended on target thickness while the size of applicator according on the dimension of the lesion. The prescription dose was the 90% of isodose curve: from 15 mm (6MeV) to 27mm (10Mev). The entrance dose was derived from the surface dose measured with a EBT3 gafchromic; another film was positioned upper the shielding disk, used to preserve lung, in order to obtain the dose maps through tissue. Films were analyzed 24-72hs after the irradiation using Epson Scanner.

Results: The mean values of entrance dose are: 19.75Gy and 9.35Gy measured on EBT3, while the theoretical values calculated from PDDs curve are 20.05Gy and 9.49Gy. Including all treatments (exclusive and boost), the comparison between expected dose from PDD curves and measured dose is less than 3% in 83% of all cases for entrance dose and in 80% for the dose measured under the bed surgery. No discrepancies greater than 7% were found.

Conclusions: *In vivo* dosimetry appeared both reliable and feasible. The use of gafchromic allows a verification of output LIAC during treatment and also an evaluation of real dose delivered to target. Agreement between measured and expected dose found, is quite good with average percentual difference less than 1.5%.

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P114

INTRAOPERATIVE RADIOTHERAPY FOR EARLY BREAST CANCER: A MONOCENTRIC EXPERIENCE

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Aims: Single-dose intraoperative radiotherapy (IORT) is an alternative treatment for selected cases of early stage breast cancer. The purpose of this study is to present preliminary results of patients treated with IORT at Bellaria Hospital, Bologna, Italy.

Methods: We analysed data of 108 women who underwent lumpectomy and IORT with primary intent. IORT treatment was performed with a dedicated mobile electron accelerator (21 Gy were prescribed at 90% isodose). Data collected were histopathology, adjuvant treatment, clinical tolerability, local recurrences and outcomes.

Results: From December 2011 to December 2015, 108 women (median age 72 years) were treated with IORT. 75% of patients were treated with adjuvant ormonotherapy and 11.1% with combined chemotherapy plus hormonotherapy. The median follow-up was 26 months (range 2-52). 82.4% of patients had disease that was <2 cm in size, 65.7% of patients had an infiltrative duct carcinoma. At the end of follow-up 89.9% had a G0-G2 grade of late parenchymal fibrosis and 69.4% of patients a good cosmetic result. One patient underwent a mastectomy after five months because of chronic fistula in the irradiated area. One patient had a local relapse in a different quadrant and one patient had an axillary lymph node recurrence. Only one patient developed systemic metastasis. One patient died from breast progressive disease.

Conclusions: IORT represents a safe and effective

alternative treatment option in selected patients with early breast cancer. Low complication rate with good clinical and cosmetic outcomes support IORT as a treatment option for selected women.

P115

ACUTE TOXICITY IN HYPOFRACTIONATED RADIOTHERAPY FOR BREAST CANCER: OUR EXPERIENCE

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Aims: The aim of this study is to evaluate the acute toxicity of hypofractionated radiotherapy for patients with diagnosis of breast cancer.

Methods: We evaluated the data of 205 patients (median age 69 years, range 41-86) treated in our institution from August 2012 to March 2016 for diagnosis of breast cancer. All patients underwent to conservative surgery. The histological type of cancer is summarized as follows: infiltrating duct carcinoma 138 pts (67.3%), tubular infiltrating carcinoma 13 pts (6.3%), undifferentiated carcinoma 14 pts (6.8%), intraductal carcinoma 13 pts (6.3%), other 27 pts (13.3%). Stage according to American Joint Committee on Cancer (AJCC) were stage 0: 13 pts (6.3%), stage I: 139 pts (67.8%), stage II: 51 pts (24.9%), stage IIIA: 2 pts (1%); 182 patients were N0, 23 patients were N1 but not candidates to treatment on supraclavear nodes. 178 pts (86.8%) had positive receptors for ER, PgR and they received hormonal therapy; 43 pts (20.9%) underwent to adjuvant chemotherapy before radiation treatment. All patients underwent to hypofractionated radiotherapy treatment delivered with LINAC 6MV 3D Conformational technique in 16 fractions of 2.66 Gy/die for a total dose of 42.56 Gy.

Results: The evaluation of the acute toxicity was made by visiting the patients every 5 sessions during treatment and then two weeks after the end of the same. According to RTOG SKIN TOXICITY, our results were ; G0 30 pts (14.6%), G1-G2 170 pts (82.9%), G3 5 pts (2.4%) and G4 0 pts (0%). Nobody stopped the radiotherapy course.

Conclusions: The treatment was well tolerated and the observed acute toxicity is comparable to that reported in other stuidies of literature; also acute toxicity in hypofractionated regimen does not appear to be higher than that seen with standard fractionation. The data thus show the feasibility and tolerability of radiation therapy in hypofractionated regimen in patients diagnosed with breast cancer.

P116

ACCELERATED HYPOFRACTIONATION IN WHOLE BREAST IRRADIATION: EVALUATION OF ACUTE/LATE SKIN TOXICITY AND CLINICAL OUTCOMES

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Aims: The aim of this paper is the retrospective evaluation of clinical outcomes and acute/late toxicity in accelerated hypofractionation for whole breast radiotherapy (WBRT) in patients >60 years.

Materials and Methods: From January 2012 to March 2016 we recruited 33 patients surgically treated with breast conservation: nodulectomy was performed in 33% of patients and quadrantectomy in the remaining 67%; axillary lymph nodes dissection was performed in 6% of cases. Median age was 73 years (61-86), the most frequent histological subtype was invasive ductal carcinoma in 84% of patients: stage 0 were 6%, stage IA were 78%, stage IB was 3%, stage IIA were 10%, stage IIB was 3% (according to American Joint Committee on Cancer, 7th Edition). Subsequent hypofractionated WBRT was managed with a median prescription dose of 42,5 Gy (range 40-42,8 Gy) delivered in 15-16 fractions. Acute and late skin toxicity assessment was performed using CTCAE v4.0 scales. We evaluated aesthetic outcomes following Harvard criteria.

Results: With a median follow-up of 21 months (range 2-50), all patients underwent weekly physical examination during treament, and, subsequently, at every follow-up visit reporting G0 acute skin toxicity in 52% of patients, G1 in 42% , and G2 in 6%, no G3-G4 skin toxicity was observed. In 12% of patients, during treatment, we observed breast pain probably correlated to surgery. Regarding late toxicity, we recorded only one case of breast hyperpigmentation (G1); according to Harvard criteria, cosmetic results were excellent in 82%, good in 15%, with only one case (3%) of fair cosmetic judgement. As far as clinical outcomes concerns, we observed no evidence of local or distant failure.

Conclusions: Accelerated hypofractionation for whole breast radiotherapy represents an efficient and well tolerated treatment option for elderly patients, allowing a shortening of overall treatment time, without increasing skin toxicity, and offering at the same time an excellent local and distant control.

P117

ASSESSMENT OF ACUTE SKIN TOXICITY AND QUALITY OF LIFE DERIVED FROM HYPOFRACTIONATED WHOLE-BREAST IRRADIATION AS COMPARED TO CONVENTIONAL WHOLE-BREAST IRRADIATION

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Aims: Many randomized trials demonstrated that hypofractionation is as effective as conventional fractionation for whole-breast irradiation (WBI) following breast conserving surgery (BCS), with similar late morbidity. A reduction in total dose provides an added benefit in order of less acute toxicity, which is more dependent on the total dose of radiation than the fraction size, compensating a potential increased late toxicity, due to the higher dose per fraction. The purpose of this study was to assess the acute skin toxicity (AST) and quality of life (QOL) of hypofractionated WBI as compared to conventional WBI.

Methods: In this study, performed at Oncological Radiotherapy Dept.of A.O.U. San Giovanni di Dio e Ruggi d'Aragona Salerno, women with invasive breast cancer who had undergone BCS with clear margins and negative axillary nodes were randomly assigned to receive conventional WBI (50 Gy in 25 fx over 35 days) or hypofractionated WBI (42.5 Gy in 16 fx over 22 days). AST was measured using the ECOG and WHO toxicity scales. Quality of life was assessed by a Questionnaire based on compliance to treatment, number of interruptions, treatment attractiveness in terms of time and economic effort, fatigue, skin and breast side effects. AST and QOL were measured at baseline and 2, 4 and 8 weeks from the start of treatment. QOL was also assessed at baseline and 4 weeks posttreatment. Mean change scores from baseline were compared between treatment groups.

Results: The observational study started in 2014. From then to now 177 patients participated: 93 were randomized to conventional WBI and 84 to hypofractionated WBI. Baseline characteristics were similar between groups. AST was initially similar between groups but was statistically significantly less with hypofractionation towards the end of the 8-week period for both scales. A statistically significant treatment-by-time interaction was also observed for overall QOL as well as QOL attributed to specifically medical domains as well as skin and breast side effects, fatigue. At 4 weeks posttreatment, hypofractionation resulted in improved overall QOL, as well as QOL attributed to specifically medical domains with a statistical significance.

Conclusions: The results support the benefit in choosing of hypofractionated WBI following BCS in selected cases.

P118

HYPOFRACTIONATED RADIOTHERAPY OF THE BREAST MAY REDUCE THE CARDIAC EXCESS MORTALITY RISK

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Aims: Today there is substantial equivalence between radiotherapy schemes for breast in terms of TCP, but we wondered if the long term effects on the heart were the same. This small experience compare some the hypofractionation radiotherapy schedules most used in literature, having as end-point the cardiac mortality risk at 15 years.

	Control Pcardiac(%)	Canadian Pcardiac(%)	START A1 Pcardiac(%)	START A2 Pcardiac(%)
pz 1	0.37%	0.28%	0.21%	0.32%
pz 2	0.31%	0.22%	0.16%	0.25%
pz 3	1.25%	0.89%	0.67%	1.04%
pz 4	0.69%	0.50%	0.38%	0.58%
pz 5	0.79%	0.57%	0.43%	0.66%
pz 6	4.74%	3.46%	2.89%	4.02%
pz 7	1.69%	1.42%	1.20%	1.67%
pz 8	0.87%	0.69%	0.56%	0.81%
pz 9	2.04%	1.59%	1.21%	1.87%
pz 10	0.25%	0.18%	0.14%	0.21%
P/P_{max} =	1.00	0.75	0.58	0.87

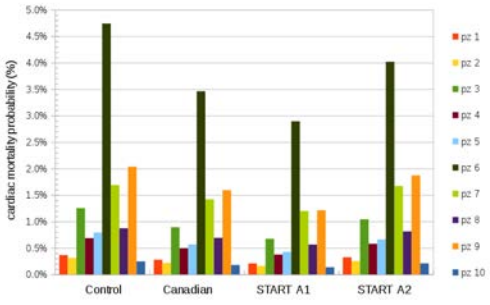

Figure 1.

Methods: Many radiation oncologists remain hesitant, bearing in mind the devastating experience from the past becoming apparent not sooner than 10 years after treatment, with cardiac toxicities after inappropriate irradiation schedules and techniques. Awaiting "answers in the coming years" we think that some prevision are now possible, thanks to some available probabilistic model. Field in Field irradiation with tangential beams technique either for whole left sided breast irradiation or for the sequential boost were used on 10 female patients, who showed a not negligible cardiac risk from DVH analisys. We compared the risk of cardiac death at 15 years applying the Relative Seriality Model (RS) [Gagliardi 1996]. For each patient,

4 treatment plans were optimized according to the following schedules: "Control" (50Gy/25fr and boost of 10Gy/5fr) [Owen 2006], "Canadian" (46.5Gy/16fr and boost of 10Gy/4fr [Whelan 2010]), "START A1" (39Gy/13fr and boost of 10Gy/4fr [Haviland 2013]) and "START A2" (41.6Gy/13fr and boost of 10Gy/4fr [Haviland 2013]). In RS model / =3, g=1.28, s=1 and a D50=52.5 Gy were assumed.

Results: Over the past two decades, evidence has been accumulated from well-conducted, large, prospective randomized trials, comparing shorter RT courses to 50 Gy in 25 daily fractions. These trials and institutional series have confirmed that shorter courses of RT are equally effective compared to longer RT schedules for women with invasive or in situ breast cancer, and have provided that the total dose of RT is appropriately reduced. If the STAR A1 schedule is adopted the excess cardiac mortality risk due the radiotherapy may decrease up to an half if compared with the Control schedule. Surprisingly the least favorable is the most widely used schedule (Figure 1).

Conclusions: Careful evaluation of the heart-absorbed dose has to be adopted in any Radiotherapy Center and although a risk of cardiac death <1% after breast RT is considered acceptable, V25Gy<10% is necessary but not sufficient to limit the excess cardiac mortality risk for each patient and for every RT schedule; otherwise a "bad experience" is always around the corner.

P119

HYPOFRACTIONATED RADIATION TREATMENT IN EARLY BREAST CANCER

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Aims: The purpose of the study was to evaluate the acute and late side effects of skin and local disease control in patients with breast cancer who received adjuvant radiotherapy hypofractionated.

Materials and Methods: From april 2014 to march 2016, in our center, were treated 31 women with breast cancer who had undergone conservative surgery. The median age was 67 (range 51-82). All the patients had a histological of invasive ductal carcinoma, 24 (77%) in stage T1 and 7 (23%) in stage T2. All women were treated with conformal 3D external beam radiotherapy for a total dose of 42.40 Gy, with 2.65 Gy fraction dose and for 5 days a week.

Results: All women completed radiotherapy. Twenty-eight patients (90%) presented acute toxicity of Skin of Grade 1 and three patients (10%) presented acute toxicity of Skin of Grade 2. In a 6.8 months average follow-up was not observed any late skin toxicity and none local or distant recurrence was noted in any patient.

Conclusions: In our study, with hypofractionated radiation therapy, we didn't find any significant side acute skin effects such to invalidate the therapeutic choice. Hypofractionated adjuvant radiotherapy has been proved to be an appropriate treatment choise for local control desease without late skin side effects. However a longer follow-up and a larger number of patients are needed to confirm these results.

P120

ADJUVANT HYPOFRACTIONATED RADIOTHERAPY IN EARLY STAGE BREAST CANCER

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Introduction: Five randomized trials have evaluated the efficacy of Hypofractionated Radiotherapy (HFRT) in comparison to conventional regimens, in patients undergoing breast-conserving therapy. Various single and multi-institutional studies have also evaluated the efficacy of following HFRT breast-conserving surgery. Most of them demonstrated high rates of local control, disease-free survival, and overall survival. Despite the potential benefits, widespread use of HFRT has been limited by concerns relating to toxicity and a lack of long-term data to establish efficacy and safety. The purpose of this retrospective study is to evaluate the acute and late toxicity as well as the cosmetic effect of postoperative whole breast HFRT.

Materials and Methods: Between 2010 and 2016, 40 females underwent HFRT after conservative surgery for early breast cancer. The median age was 62.5 years. According to the histology 5 patients (pts) had ductal in situ and 35 pts invasive ductal carcinoma. The pathological stage revealed pTis in 5 pts, pT1bN0 in 8 pts, pT1cN0 in 22 pts, pT2N0 in 3 pts, pT1bN1 in 1 pts and pT1cN1 in 1 pts. Axillary lymph node dissection received 9 pts and sentinel node biopsy 22 pts. Adjuvant chemotherapy was administered in 7 pts. The RT schedule consisted by an accelerated hypofractionated course delivering 42,56 Gy in 16 daily fractions (2.66 Gy/day) in the whole breast. 12 pts received 10 Gy boost dose at the surgery bed. 3D-conformal RT was delivered by two tangential opposed 6 MV photon beams. To improve the homogeneity of the dose distribution wedge compensation and a field-in-field technique were used.

Results: After a median follow-up of 33,5 months (17,25-54,25), all patients were alive/disease-free and tolerated their treatment well without any interruption. Acute skin toxicity Grade 1 presented 20 pts (faint erythema/dry desquamation), and 8 pts had Grade2 (mild erythema/moist desquamation). Late skin toxicity Grade1 presented 14 pts (mostly in pigmentation change). Late subcutaneous toxicity Grade1 presented 14 pts (barely palpable increased density). Mild fibrosis and teleangectasia limited mostly to the boost area observed 5 pts. The overall objective cosmetic outcome was generally good.

Conclusions: According to the retrospective data of literature our accelerated HFRT schedule was not associated with high radiation-induced acute and late skin toxicity and resulted to be more convenient and less costly than the standard fractionation.

P121

A PHASE I AND II TRIAL ON INFUSIONAL 5-FLUOROURACIL AND GEFITINIB IN COMBINATION WITH PREOPERATIVE RADIOTHERAPY IN RECTAL CANCER: 10-YEARS ANALYSIS

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Aims: To investigate long term outcomes of a Phase I and II study (1839IL/0092) of preoperative radio-chemotherapy (RT-CT) with an anti–epidermal growth factor receptor drug (Gefitinib) and 5-Fluorouracile (5-FU) in locally advanced rectal cancer (LARC).

Methods: Patients (pts) with LARC (Stage III), were enrolled to receive RT (total dose of 45 Gy to the posterior pelvis plus 5.4 Gy on the tumor and corresponding mesorectum as boost). Concurrent CT with 5-FU (225 mg/m^2) continuous intravenous infusion and dose escalation of Gefitinib (250-500 mg) orally was administred, followed by surgery (total mesorectal excision) after 7-8 weeks. An intra-operative RT boost of 10 Gy was allowed. Adjuvant CT was administrated in ypN1-2 pts. After a more of 10 years median follow-up (FUP) Local Control (LC), Metastasis Free Survival (MFS), Desease Free Survival (DFS), Desease Specific Survival (DSS) and Overall Survival (OS) were analyzed as primary endpoints and the late toxicity as secondary endpoint. Predictive endpoints of clinical outcome were tested by univariate and multivariate Cox analysis. At the Kaplan Meier plots, the investigated variables were: age, sex, Gefitinib's dose and interruptions, adjuvant CT, surgery type, ypT, ypN, TRG grade.

Results: At a median FUP of 133,5 months (mos) (range 25-158mos), 39 of the 41 initially enrolled pts were evaluable (28M, 11F). Five years LC, DFS, MFS, DSS and OS were 84%, 61%, 68%, 92% and 87%, respectively. The median LC, DFS, DSS and OS were not reached. Confirmed predictors of outcome were found for: -MFS: at univariate analysis: ypT, ypN, TRG grade; at multivariate analysis: ypT (p=0.007), TRG Grade (p=0.02); -DFS: at univariate analysis: ypT, ypN, TRG grade; at multivariate analysis: ypT (p=0.003); -DSS: at univariate analysis: ypT, ypN; at multivariate analysis: ypN (p=0.008); -OS: at univariate analysis: age, ypN; at multivariate analysis: age (p=0.01) and ypN (p=0.002). Grade 3-4 late toxicity occurred in 38% of pts: gastrointestinal (10,2%) and sexual toxicities (28,2%) were recorded.

Conclusions: Long term outcomes supported literature data. The addiction of Gefitinib did not improve outcomes in LARC. Therefore it should be evaluated in association to standard RT-CT in selected pts, after molecular analysis assessment.

P122

ADAPTIVE RADIOTHERAPY WITH TOMOTHERAPY CONCOMITANT WITH CHEMOTHERAPY IN PREOPERATIVE TREATMENT OF RECTAL CANCER. AN UPDATE

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Aims: To report the clinical results of seven years experience with Adaptive Radiotherapy concomitant with chemotherapy in the preoperative treatment of rectal cancer.

Materials and Methods: patients (pts) with T3/T4N0 or any TN+ rectal adenocarcinoma were enrolled in this observational trial. Chemotherapy consisted of Oxaliplatin 100 mg/m^2 on the days -14, 0, +14, and continuous infusion 5-FU 200 mg/m^2/day from day -14 to the end of radiotherapy. Concomitant Radiotherapy (RT) started on the day 0, was delivered with Tomotherapy, and consisted of 41.4 Gy in 18 fractions (frs) (2.3 Gy/fr) to the PTV defined as CTV, the tumor and regional lymph-nodes contoured on an initial simulation CT and MRI, with a margin of 0.5 cm. Simulation CT and MRI were repeated after 9 frs of RT for the planning of the adaptive phase: PTVadapt was generated by adding a margin of 5 mm to the residual tumour visible on the intermediate MRI images (GTVadapt). A simultaneous integrated boost of 3.0 Gy/fr was delivered to PTVadapt on the last 6 frs of RT (total dose: 45.6 Gy in 18 frs).

Results: From September 2009 to May 2016, 71 pts completed the preoperative treatment. Toxicity. One G4 (1.5%) and 9 G3 (12%) diarrhea, and 3 G3 proctitis (4%) occurred. Diarrhoea started before the adaptive RT phase in all cases. Treatment feasibility. Sixty-eight/71 pts (96%) received the full dose of RT. The median duration of RT was 25 days (22-36 days). 66/71 (93%) and 61/71 (86%) received the full dose of oxaliplatin and 5-FU, respectively. Responses. Two pts achieved clinical complete response (cCR) and refused surgery, 1 pt was lost, 1 pt had early distant progression, and 7 pts are waiting for surgery. Sixty pts were resected (57 R0, 3 R1). Median time to surgery was 11 weeks. Sixteen pts (27%) had pathological complete response (pCR), 16 pts (27%) had ≤5%, and 6 pts (10%) had 6-10% of residual viable cells, respectively. Regarding the two patients with cCR who refused surgery, 1 pt is still in cCR after 69 months, 1 pt had local relapse and underwent transanal resection 1 year after the preoperative treatment.

Conclusions: This study confirms that adaptive boost strategy is feasible with an acceptable G3 toxicity rate and a very encouraging tumour response rate. A further dose escalation to the PTVadapt could be feasible and could increase the pCR and/or cCR rates.

P123

STEREOTACTIC ABLATIVE RADIOTHERAPY IN THE TREATMENT OF HEPATOCELLULAR CARCINOMA>3 CM

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Aims: Stereotactic ablative radiotherapy (SABR) is a safe treatment approach for hepatocellular carcinoma (HCC) with comparable results to other local therapies. For lesions larger than 3 cm, no definitive standard treatment is present and several options are available. We retrospectively review local control (LC) and survival results of SABR in patients with HCC lesions>3 cm.

Methods: Between 2012 and 2015 we treated 29 patients (39 lesions) having histological or radiological diagnosis of HCC and at least 1 lesion sized>3 cm. (Table 1) Patients were prescribed 36-48 Gy in 3-5 fractions (mainly 16 Gy x 3 fractions or 8 Gy x 5 fractions), in 3-5 consecutive days according to clinical and dosimetric decision making. Radiological response was evaluated according to the modified Response Evaluation Criteria In Solid Tumors (mRECIST). Pathological response was assessed through the rate of tumor necrosis relative to the total tumor volume. Acute and late toxicities were scored using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (CTCAE v 4.0).

Results: A total of 15 lesions (52%) had complete, while 10 (34%) had partial remission; 3 (11%) a stable disease. Mean time for CR achievement CR was 5.8 months (range: 1-17). One- and two-year actuarial LC, progression-free (PFS), cancer-specific (CSS) and overall (OS) survival were 100%, 57.9% (standard error: 0.09; 95%CI: 36.9-74.2) and 41.2% (standard error: 0.12; 95%CI: 17.7-63.5), 80.7% (standard error: 0.08; 95%CI: 59.6-91.5) and 63.3% (standard error: 0.11; 95%CI: 38.4-80.3), 71.7% (standard error: 0.08; 95%CI: 51.2-84.7) and 56.2% (standard error: 0.10; 95%CI: 33.8-73.6). On multivariate analysis, achieving a CR within the target lesion had a borderline significance with respect to PFS (HR: 0.83; SE=0.014; z:-1.15; p=0.095;95%CI:0.71-7.45). Time between HCC diagnosis and SABR delivery (< vs>12 months) was significantly correlated to OS (HR:16.5; SE:21.5; z=2.14; p=0.032; 95%CI:1.27-213.3) as CLIP score (score: 0-1 vs 2) (HR:5.6; SE:4.6; z= 2.10; p=0.036; 95%CI:1.11-27.8). A total of 6 major toxicity events (G3-G4) were recorded (20%). In 2 patients (6%), a Radiation-induced liver disease (RILD) was seen.

Conclusions: In conclusion SABR provided LC and survival rates comparable to other local therapies for patients with HCC lesion sized>3 cm, with acceptable toxicity profile.

Table 1. Patient and tumor characteristics.

	VARIABLE	N.
Age	Mean (Range)	70 (55-88)
Sex	Female	6 (21%)
	Male	23 (79%)
ECOG PS	0	27 (93%)
	1	2 (7 %)
	2	0 (0%)
Underlying liver disease	PHCC	14 (48%)
	PHBC	5 (17%)
	PHBDC	2 (7%)
	ALCI	4 (14%)
	NASH	4 (14%)
CTP class	A5-A6	19 (66%)
	B7	7 (24%)
	B8	2 (7%)
	B9	1 (3%)
BCLC stage	A	11 (38%)
	B	14 (48%)
	C	4 (14%)
OKUDA score	1	15 (52%)
	2	10 (34%)
	NA	4 (14%)
CLIP score	0	7 (24%)
	1	13 (45%)
	2	9 (31%)
	3	0 (0%)
Prior treatments	None	16 (55%)
	RFA	6 (21%)
	TACE	4 (14%)
	RFA+TACE	2 (7%)
	RFA + Sorafenib	1 (3%)
Lesion size (mm)	Mean (Range)	47 (31-120)
Lesions per patient	1	20 (69%)
	2	8 (28%)
	3	1 (3%)
Location	Caudate lobe	1 (3%)
	Right lobe	17 (59%)
	Left lobe	11 (38%)
Portal vein thrombosis	Yes	4 (14%)
	No	25 (86%)

P124

PHASE II STUDY ON STEREOTACTIC BODY RADIATION THERAPY (SBRT) FOR UNRESECTABLE LOCALLY ADVANCED PANCREATIC CANCER

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Aims: To assess the efficacy of stereotactic body radiotherapy (SBRT) in patients with inoperable locally advanced pancreatic cancer (LAPC).

Methods: Patients with unresectable LAPC without

distant metastasis were treated with SBRT, after multidisciplinary board evaluation. Prescription dose was 45Gy in 6 fractions. Primary end-point was local control (LC). Secondary end-points were OS, PFS and toxicity. Local control was defined according to RECIST criteria. Acute and late toxicity was scored according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Results: Between 2011 and 2013, 45 patients with LAPC were enrolled in a Phase II trial. Median FUP was 13.5 months and 23.5 months for alive patients. FFLP was 90% at 1 and 2-years. On univariate ($p<0.03$) and multivariate analysis ($p<0.001$), lesion size was significant for LC. Median PFS was 8 months. Median OS was 13 months. On multivariate analysis, tumor size ($p<0.001$) and FFLP ($p<0.002$) were significantly correlated with OS. 32 patients (71%) with LAPC received chemotherapy before SBRT. Median OS from diagnosis (OSd) was 19 months. Multivariate analysis showed that LC ($p<0.035$), tumor diameter ($p<0.002$) and CT before SBRT ($p<0.001$) were significantly correlated with OSd. Ca19.9 value increased in 28 cases of LAPC (62%). Univariate analysis showed that Ca19.9<300U/ml was closely correlated ($p=0.05$) to a better OS.

Conclusions: SBRT is an efficacy and safe treatment of LAPC, with no G3 toxicity or greater. Our results suggest that SBRT may be a promising therapeutic option in the multi-modality treatment of these patients.

P125

3S (SUPER-STEREO-SIB) RADIOTHERAPY FOR PANCREATIC CARCINOMA: A FEASIBILITY PLANNING STUDY

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Aims: To perform a planning feasibility analysis of a modulated dose prescription within a pancreatic tumor treated by SRT, delivering a low dose to the duodenum (site of more common toxicity) and a high dose to the vessel invasion (more common reason of unresectability).

Methods: 15 patients with a pancreatic head adenocarcinoma with vascular involvement were included. Targets were defined as follows: 1) duodenal PTV (PTVd): the GTV overlapping the duodenal planning at risk volume (PRV) (from the pylorus to the duodenojejunal junction adding 5 mm in craniocaudal (CC) direction, 3 mm in the other directions); 2) vascular CTV (CTVv): the surface of contact or infiltration between tumor and vessel plus 5 mm margin around the vessel (including the vessel whole circumference). The vascular PTV (PTVv) was considered as the CTVv plus an anisotropic margin (5 mm CC direction, 3 mm in other directions). The tumor PTV (PTVt) was defined as the GTV plus an anisotropic margin (5 mm CC direction, 3 mm in other directions) including the PTVv and excluding the PTVd. The following doses were prescribed (in 5 daily fractions) to the PTVs: 30 Gy (6 Gy/fraction (fr) to the PTVd, 45 Gy (9 Gy/fr) to the PTVv, and 37.5 Gy (7.5 Gy/fr) to the PTVt, respectively. Constraints were based on AAPM TG101 recommendations: Dmax of PRVduodenum<32.0 Gy, Dmax of PRVspinal cord<30.0 Gy, Dmax of PRVstomach<32.0%, D700cc liver<21.0 Gy, D200cc kidneys<17.5 Gy. All plans were generated with Masterplan Oncentra TPS and the treatment was delivered with a step and shot IMRT technique. The primary end point was the rate of patients in whom the constraint Dmean>90% was achieved for the 3 different PTVs. Secondary end-points were the percentage of patients in whom a PTVv near minimum dose (D98%)>90%, a PTVv D95%>95%, and a median dose (D50%)>95% were achieved.

Results: PTVv Dmean>90%, PTVv D2%<115% and OARs Dmax constraints were achieved in all patients. Both PTVv D98%>90% and PTVv D95%>95% were achieved in 6 patients (40%).

Conclusions: Although the objective of PTVv D95%>95% was achieved only in 40% of patients, the study showed that in 100% of patients it was possible to administer a strongly differentiated mean and median dose, and in particular a low dose to the overlap region between the target and duodenum, a high dose to the site of vascular infiltration, and an intermediate dose to the remaining target volume.

P126

HYPOFRACTIONATED RADIOTHERAPY WITH CONCURRENT GEMCITABINE IN LOCALLY ADVANCED PANCREATIC CANCER: A SINGLE INSTITUTION EXPERIENCE

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Aims: The management of locally advanced pancreatic cancer (LAPC) remains a controversial issue. Induction chemotherapy (CT) followed by chemoradiotherapy (CRT) is an option in these group of unfavourable patients (pts). We analyzed the safety and feasibility of a moderate hypofractionated radiotherapy (Hypo-RT) associated with concurrent gemcitabine (GEM).

Methods: We retrospectively analyzed acute toxicity (according to CTCAE 4.0 scale) and compliance to treatment of unresectable pts, treated between March 2012 and December 2015, with Hypo-RT and concurrent GEM 40 mg/m^2 twice weekly after induction CT.

Results: data of 45 pts were available: median age was 63 yrs (range 45-79), 27 pts (60%) were males and 18 pts (40%) were females and median KPS 90 (range 70-100). 26 pts (58%) had T3, 17 pts (37,7%) T4, 2 pts(4.4%) T2 disease, respectively; 16 pts (35.5%) were N+, 27 pts (60%) N0. In 34 pts (75.5%) tumor involved the head of pancreas and in 11 pts (24.4%)involved the body or tail. 44 pts (97.7%) completed the Hypo-RT; 42 Gy/15 frs (280cGy/fr) to PTV1 (tumor and lymph-nodes) with a simultaneous integrated boost of 49.5 Gy/15 frs (330cGy/fr) to PTV2 (macroscopic disease). Hypo-RT was discontinued in 2 pts (4.5%) whereas GEM was interrupted in 39 pts (88%). The median number of cycles of GEM was 3 out of 6 planned cycles (range 1-6). Major G3 gastrointestinal (GI) toxicity occurred in 2 pts whereas 36 pts (80%) reported hematological or GI, G≤ 2 toxicity.

Conclusions: This moderate hypofractionated radiotherapy appears feasible with a compliance of 97.7%. However, only 50% of planned cycles of twice weekly concurrent gemcitabine was feasible after induction CT. These encouraging results on feasibility should be further evaluated on the impact of resectability, disease control and survival.

P127

STEREOTACTIC RADIOTHERAPY (SBRT) VS STANDARD CHEMORADIATION (CRT) IN LOCALLY ADVANCED PANCREATIC CANCER (LAPC): A CASE-CONTROL STUDY

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Aims: In the last decades a treatment option for LAPC has been represented by CRT, however SBRT is considered an emerging option for these patients (pts). Unfortunately, comparison between these two treatment techniques, in terms of toxicity and pts outcome, are lacking. Therefore, aim of this multicentric study is to compare toxicity and outcome between two cohorts of pts treated with SBRT or CRT.

Methods: A case-control study was performed. Forty-two patients were enrolled (M/F: 25/17; median age: 68.5; range: 36-89). Pts in the two groups were matched according to: age </≥ 65years, tumor diameter </≥ 3 cm, cT, cN, neoadjuvant chemotherapy, adjuvant chemotherapy. Median dose in pts treated with SBRT was 25 Gy (range: 12-30) and median dose in pts treated with CRT was 54 Gy (range: 30-63). Toxicity was evaluated by CTCAE v4.0 scale and survival curves were assessed by Kaplan-Meier method.

Results: The incidence of GI ≥ G2 acute toxicity was 31% in the SBRT-arm and 37.5% in the CRT-arm, while the incidence of hematological ≥ G2 acute toxicity was 6.3% in both groups. Late GI bleeding was recorded in 6.3% and 8.3% pts treated with SBRT or CRT, respectively. One-year, 2-year and median survival were 50.3%, 30.2% and 13 months (range: 7.3-18.7) in pts treated with SBRT, respectively. One-year, 2-year and median survival were 51.8%, 33.8% and 16 months (range: 7.5-24.5) in pts treated with CRT, respectively.

Conclusions: This analysis showed that SBRT compared to CRT, is correlated with a similar incidence of adverse effects and with a comparable survival.

P128

STEREOTACTIC ABLATIVE RADIATION THERAPY PRIOR TO LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA: A SINGLE-INSTITUTION EXPERIENCE

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Aims: Stereotactic ablative radiotherapy (SABR) is a safe treatment approach for hepatocellular carcinoma (HCC) with comparable effectiveness to other local the-

rapies. Only scant information is available concerning the role of SABR prior to liver transplantation (LT) for HCC. We present a consecutive case series investigating the role of SABR as a bridge or dowstaging option in HCC patients subsequently submitted to LT.

Methods: Between September 2012 and May 2014, 8 patients for a total of 13 lesions underwent SABR prior to LT. Inclusion criteria were a pathological or radiological diagnosis of HCC, lesion size ≤ 6 cm or lesion number ≤3 with a total diameter ≤ 6 cm, no extrahepatic metastases, Child-Pugh class A-B, ECOG Performance Status ≤ 1. Patients were prescribed 36-48 Gy in 3-5 fractions (8 Gy x 5 fractions or 16 Gy x 3 fractions), in 3-5 consecutive days according to clinical and dosimetric decision making. Radiological response was evaluated according to the modified Response Evaluation Criteria In Solid Tumors (mRECIST). Pathological response was assessed through the rate of tumor necrosis relative to the total tumor volume. Acute and late toxicities were scored using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (CTCAE v 4.0).

Results: Among the 13 pathologically evaluated lesions, 8 (61.5%) lesions had a complete response 2 (15.3%) had a minimal pathological response and other 2 (15.3%) showed stable disease. The remaining lesion had a significant pathological response. Maximum detected toxicity included a G2 GGT increase in 2 patients (at 1 and 3 months respectively). One patient developed a non-classic RILD with a 5-fold increase in transaminase enzymes level and a shift in Child-Pugh category from B7 to C10 due to bilirubin increase. Only 1 modification in the surgical strategy was needed during LT. (Table 1)

Conclusions: SABR proved to be a safe and effective local therapy prior to LT in HCC patients. Prospective controlled clinical trials are needed to evaluate its efficacy compared to other local therapies in this setting.

Table 1.

Patients	SABR toxicity (CTCAE v 4.02)	LT complication	Achild-Pugh points	AMELD score	Radiological response (mRECIST v4)	Pathological response	Status
1	G2 GGT elevation (3 months)	Sclerotic retraction of the retrohepatic region involving inferior vena cava	0	0	CR (CT) 2 months	CR	NED
2	Non-classic RILD (1 month)	None	7	+9	SD (MR) 1 month	Minimal pathological response (2 lesions)	NED
3	None	Sclerotic retraction of the retrohepatic region involving inferior vena cava	0	0	SD (CT) 3 months	CR (2 lesions)	NED
4	G1 bilirubin elevation (10 days)	None	1	+3	NA	Significant pathological response	NED
5	G1 asthenia (1-3 months), G1 bilirubin elevation (15 days)	Sclerotic retraction of the retrohepatic region involving inferior vena cava and hepatic hilar region with hepatic artery parietal fibrosis	1	+10	SD (CT) 2 months	CR	NED
6	G1 transaminase elevation	None	1	-1	NA	SD (2 lesions)	Died of multi organ failure 24 days after LT
7	G2 GGT elevation (1 month)	None	1	+2	CR (MR) 3 months	CR	NED
8	None	None	0	0	NA	CR (3 lesions)	NED

Legend: SABR: stereotactic ablative radiation therapy; CTCAE: Common Terminology Criteria for Adverse Events; LT: liver transplantation; MELD: Model for End-stage Liver Disease; mRECIST: Modified Response Evaluation Criteria In Solid Tumors; NED: alive with no evident disease; CR: complete response; CT: computed tomography; RILD: radiation-induced liver disease; SD: stable disease; MR: magnetic resonance; NA: not available

P129

STEREOTACTIC ABLATIVE RADIATION THERAPY (SABR) IN THE TREATMENT OF LUNG OLIGOMETASTATIC PATIENTS WITH COLORECTAL CANCER: EFFICACY AND TOXICITIES

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Aims: To evaluate efficacy and tolerability of SABR in the treatment of patients with colorectal cancer with exclusive oligometastasis to the lung.

Methods: We treated 65 lung metastases in 41 patients with oligometastatic colorectal cancer. Inclusion criteria were: primary tumor controlled, ≤ 5 lung metastases, no other active sites of disease at the time of the SABR. Dose prescription was: 23Gy/1 fr per central lesion <30 cc (18 lesions), 30Gy/1fr for peripheral metastases <30 cc (33 lesions), 45Gy/3fr for peripheral lesion >30cc (9 lesions). Twenty-three patients had 1 metastasis (56%), 14 patients had 2 metastases (34%)and 4 patients tree-to-four metastases (10%). Median BED was 120 Gy. OS, PFS, MFS, local control and toxicity were evaluated.

Results: Median follow-up was 28 months (ranged 3-76 mo). Median actuarial survival was 34 months (c.i. 20-47 months). Overall survival (OS) at 1-, 2- and 5-years was 82%, 51.5% and 27.1% respectively. Complete response (CR) was achieved in 25/65 lesions (38.4%). Median disease-free survival (DFS) was 24 months (ranged 13-34 months). DFS at 1-, 2- and 5-years was 79.6% and 41.2% and 22.8%, respectively. Complete response (CR) was the only prognostic factor significantly correlated with OS, PFS and metastasis-free survival (MFS) (p= 0.001 in each case). Patients with CR had 1-, 2- and 5-years OS of 100%, 90.8% and 67.5%, while patients with partial response (PR) and stable disease (SD) had respectively 69.8, 34.5% and 65%, 63.5% at 1 and 2-years and 15.2% at 5-years. Acute G1-2 lung toxicity, according to the CTCAE-V4.0, was 10.7%, G3 lung toxicity was 3%. Late G1-2 toxicity rate was 24.6%. No late G3 toxicity was found.

Conclusions: SABR have a high rate of local control in the lung metastasis from colorectal cancer and also affect survival. CR statistically correlated with OS, PFS and MFS, even at long-term. There is a need of prospective trials to confirm these data and to identify the right selection criteria and the best timing with systemic therapies.

P130

STEREOTACTIC BODY RADIOTHERAPY FOR UNRESECTABLE CHOLANGIOCARCINOMA: A SINGLE INSTITUTIONAL EXPERIENCE

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Aims: Cholangiocarcinoma is a rare, locally-aggressive malignancy of the biliary tree. Locoregional therapy is the preferred treatment approach for patients not amenable to surgery. The aim of this study is to report single institutional clinical experience in terms of efficacy and toxicities in patients treated with Sterotactic Radiation Therapy (SBRT) for primary tumor or for local recurrence.

Methods: From September 2011 to November 2015, 20 patients (pts) underwent abdominal SBRT for cholangiocarcinoma lesions (4 pts with uresectable primary and 16 pts for recurrent cholangiocarcinoma) for a total of 42 lesions treated. Sites treated included liver (32 lesions) and lymph node of hepatic hilum (10 lesions). SBRT was delivered in three consecutive daily fractions. The median prescribed dose was 37.5 Gy in 3/fx to 67% isodose line (BED10 >100 Gy). The Volumetric Modulated Arc Therapy (VMAT) treatment was delivered by 6MV beam modulator Linac with 4 mm MLC and in breath hold using ABC device. Patient set-up ad isocenter position was controlled before each fraction by CBCT. Gold fiducials, as surrogate target, were implanted in liver one week before simulation CT in 13 patients. For other patients, metallic stent in biliary duct was utilized. Toxicities were scored by CTCAE v 4.0 and treatment response was graded by RECIST and PERCIST.

Results: Median target volume was 11.47 cc (range 1.06-111.06 cc). Median dose delivered to isocenter was 45.21 Gy in 3 fractions. The median follow-up was 13 months (range 2-46 months). Local control was 85% but 9 patients experienced intrahepatic progression. 12 pts developed also extrahepatic progression (lymph nodes, lungs, bones and peritoneum). Median progression free survival was 5 months. Overall Survival was 80% at 1 year and 48% at 2 years. The most common Grade≥2 early toxicities were nausea (7 pts) and vomiting (3 pts). Late toxicities included 2 Grade 2 biliary stenosis. No liver failure was reported.

Conclusions: SBRT in patients with local recurrence or with unresectable cholangiocarcinoma is an effective therapy and appears to be a safe non invasive treatment option for selected pts. The toxicity profile was acceptable. Although colangiocarcinoma is a rare malignancy, more information is needed to stratify patients to the treatments from which they are most likely to benefit, In view of the development of other local therapies (transarterial chemoembolization and radiofrequency ablation).

P131

QUALITY OF LIFE (QOL) IN PATIENTS WITH ANAL CANCER TREATED WITH INTENSIFIED IG-IMRT

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Purpose: To investigate QoL in anal canal cancer patients treated with SIB-IG-IMRT(52.8– 55Gy and 43.2-45Gy/24-25fx toPTV1-2) and to evaluate the correlation with clinical compliance to treatment.

Materials and Methods: From March 2009 to December 2015 60 pts were treated with RT/CT.QoL was assessed in 30 pts by EORTC QLQ-C30 and CR29 questionnaires (qst).Late toxicity was scored according to CTCAE v3.0. Pts were divided in 4 groups according to timing qst compilation: I(qst at 6-18 months), II(19-30 months), III(31-42 months), IV(>43 months). Here, we report patient record outcome (PRO) and physician evaluation about pelvic late toxicity.

Table 1.

pts	TNM	Pain		Diarrhea		Fecal incontinence		Urinary symptoms	
		I Q	II Q	I Q	II Q	I Q	II Q	I Q	II Q
1	T3N0M0	1	1	1	1	1	1	2	2
2	T1N0M0	1	1	2	2	1	3	1	2
3	T3N0M0	1	1	1	1	1	1	1	1
4	T3N1M0	1	1	1	1	1	1	1	2
5	T2N0M0	1	1	1	1	1	1	1	1
6	T1N1M0	2	3	1	1	1	2	1	2
7	T2N1M0	1	1	1	1	1	1	2	1
8	T2N0M0	1	1	1	1	2	1	1	1
9	T3N1M0	3	2	4	3	3	3	2	1
10	T1N0M0	2	3	2	1	2	1	2	2

Q-questionannaire
1-none
2-a little
3-a lot
4-very much
Only 4/10 pts reported a worsening of pelvic symptoms

Results: In group I,17qst were completed:pain was reported "very much" in 2 and "a lot" in 1 qst respectively vs in clinical evaluation mild pain was reported only in 1 pt; diarrhea has been reported in 1 qst as "very much" vs 1 moderate diarrhea reported by physician. Fecal incontinence was reported in 2 qst like "a lot" vs clinical evaluation reported occasional use of pads in 3 pts and daily in 1 pt. In II group 10qst: pain was reported very much and a lot in 2 qst respectively, while in clinician evaluation no pain was reported;diarrhea hasn't been reported.Fecal incontinence was reported in 1 qst like "a lot" while clinical evaluation reported occasional use of pads. In III group 6 qst: "a lot" of pain has been reported in 1 qst, not reported in clinical evaluation; diarrhea has been reported in 1 qst as "very much" vs moderate in clinical evaluation. Fecal incontinence was reported in 1 qst "a lot" vs clinical evaluation was reported fecal continence. In the IV group 7 qst: "a lot" of pain has been reported in 1 qst, in clinical evaluation was reported no pain; diarrhea has been reported in 2 qst as "a lot", and clinical evaluation reported moderate diarrhea and increased stools for day. Fecal incontinence was reported in 1 qst like "a lot", clinical evaluation reported no use of pads.10/30 pts have

done 2 qst at 12 months and 29 months after RT(table 1). QoL(according to a number scale from 1-bad to 10-good)assessed by patients has been evaluated as grade 3,4,5,6 and 7 in 3.4%,23.3%,23.3%, 23.3% and 26.7% of pts, respectively.

Conclusions: As reported in literature also in our experience symptoms rates registered by clinicians were lower than PRO, despite the major of pts considered acceptable their QoL. Development and evaluation of PRO tools in clinical practice could be useful for physicians for a better assessment of late side effects.

P132

STEREOTACTIC BODY RADIOTHERAPY FOR LIVER METASTASES USING TOMOTHERAPY• : A RETROSPECTIVE ANALYSIS

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Aims: To evaluate efficacy and toxicity of stereotactic body radiotherapy (SBRT) using Tomotherapy® (TOMO) for liver metastases (mts).

Materials and Methods: From 2008 to date 11 patients (pts) with liver mts were treated with SBRT with TOMO®. Primary tumor was colorectal carcinoma in 55%(6/11) of pts whereas 45%(5/11) had mixed primaries (lung, anal and pancreatic cancer). None had liver dysfunction, 45% had diabetes and 55% had cardiovascular disease. A single lesion was treated in 55% (6/11) of pts, 2 lesions in 36%(4/11) and 4 lesions in 9%(1/11). Fifty-five percent of lesions were ≤3 cm, while the remaining 45%(5/11) were between 3 and 6 cm.In order to achieve appropriate target definition, SBRT planning was performed with computed tomography(CT) simulation scan with intravenous contrast in 55%(6/11) of pts. Four-D planning was performed in 82%(9/11) and both modalities were used in 36% of pts. The "liver volume - CTV" was ≥1000cc in 91% of pts. Two pts were treated with a total dose of 30 Gy in 3 fractions (fx), 1 pt with 37,25 Gy in 3 fx fractions, 2 pts with 40 Gy in 4 fx, 4 pts with 50,25 Gy in 3 fx and the last 2 pts with 60 Gy in 3 fx depending on lesions dimension and site. All pts were treated with IG-IMRT with TOMO®. BED10 was >117 in 55%(6/11). In 64%(7/11) of pts the dosimetric prescription was given according to International Commission on Radiation Units & Measurements (ICRU) 83. In 82%(9/11) of pts the treatment was performed every other day,while in 2 pts it was delivered every day. No interruptions were recorded in any of the pts.

Results: Median follow up was 5,3 months. After 3 and 6 months. Overall Response Rate was 82% and 43% respectively. One Year Overall and Progression free Survival were respectively 37.4% (SE±16.4%) and 12.1% (SE±11.1%). At univariate analysis clinical response was found to be statistically significative in terms of OS being after 1 year 76% (SE±15%) for pts with PR/SD and 45% (SE±19%) for those with PD (p<0,006). Better outcomes in terms of Local Control (LC) were also showed in pts submitted to SBRT with BED10 >117 Gy with 1 yr LC equal to 40%(SE±29.6) . No pts had acute toxicity >G3.

Conclusions: SBRT with Tomo® seems to achieve good oncological outcomes in terms of local control and survival being a "non invasive", feasible and well tolerated approach for pts with liver oligometastases.

P133

NEOADJUVANT DOSE ESCALATED RADIOTHERAPY WITH THREE-DIMENSIONAL INTEGRATED BOOST (3DCRT-IB) AND CONCOMITANT FLUOROPYRIMIDINE CHEMOTHERAPY FOR LOCALLY ADVANCED RECTAL CANCER (LARC). FEASIBILITY, EFFICACY AND PREDICTIVE VALUE OF PET-CT

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Aims: To investigate the feasibility and the efficacy of a moderate neoadjuvant hypofractionated radiation schedule with concomitant fluoropyrimidine chemotherapy in patients with locally advanced rectal cancer (LARC) and the predictive value of restaging PET-CT.

Methods: From 2008 to 2012, 24 LARC patients, stage IIA-IIIB (N1) underwent chemoradiation preoperatively. All patients were firstly staged and then, after neoadjuvant treatment, re-staged with digital examination, blood tests, colonoscopy, pelvic MRI and 18FDG PET-CT scan. A 5-fluorouracil (5-FU) chemotherapy was concomitantly administred in 9 patients whereas 15 patients received Capecitabine. Radiotherapy consisted in 50 Gy/25 fractions on pelvic CTV (rectum, mesorectum, iliac, obturator and presacral nodes) and 56 Gy/25 fractions on BTV boost defined as 60% of SUV max. PTV was CTV (for both pelvic and boost) plus 1 cm in all directions. Toxicity was graduated with CTCAE v 3.0 2006. At restaging PET-CT a method named "BOSS" (BTV overlapping simple solution) was used, then results (overlap volumes and percentage of overlap volumes between BTV boost and FDG uptake post chemoradiation) were matched up with pathologic classification system by Mandard (TRG).

Results: Median age was 60 years (77-49), median time to surgery was 9 weeks (8-12), 16 patients underwent rectal anterior resection (RAR), 5 abdominoperineal resection (Miles), one patient was not operated on. Median distance to anal verge was 5 cm (2-12) and median pretreatment CEA value was 1.65ng/ml. At median follow-up of 55 months (20-89) cumulative acute ≥ G3 toxicity was 12.3%, only 1 patient (4.1%) experienced chronic ≥ G3 toxicity. Pathologic complete response (pCR) and

major response (TRG 1-2) rates were 20.8% and 45.8% respectively. 18 patients were alive with no evidence of disease, 3 patients developed a recurrence (3 at distance and one also local), 2 patients died from disease and one developed a second malignancy. BOSS method permitted to correctly predict 11 non responders patients (TRG 3-5) and to identify 11 responders (TRG 1-2) otherwise classified as non responders with other PET-CT parameters.

Conclusions: Dose escalation with 3DCRT was well tolerated and led to an high rate of pCR. Boss method is highly sensitive to properly predict response to treatment. Further investigations in a larger cohort of patients and comparison with dose escalated IMRT-SIB boost are needed.

P134

INDUCTION CHEMOTHERAPY AND STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR LOCALLY ADVANCED INOPERABLE PANCREATIC CANCER (LAPC): PRELIMINARY RESULTS OF A PROSPECTIVE TRIAL

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Purpose: To evaluate safety and effectiveness of an induction chemotherapy (CHT) regimen followed by SBRT in LAPC

Methods: Patients (pts) with non-metastatic inoperable LAPC were enrolled on a prospective single-institution study. Four CHT cycles was administered. If no progression was observed after CHT, pts received 3 fractions of 8, 10 or 12 Gy (total dose 24-36 Gy) of SBRT based on tumor location in relation to stomach and duodenum. 4D-CT with oral and i.v. contrast was used for treatment planning and IGRT-IMRT for delivery. Seven weeks after SBRT tumour re-staging and evaluation for surgery was performed. Toxicity was scored according to CTCAE v4. Progression free survival (PFS), freedom from locoregional progression (FFLRP), freedom from distant metastasis (FFDM) and overall survival were calculated using the Kaplan-Meier method.

Results: Between February 2014 and January 2016 we enrolled 12 pts. Two pts developed distant metastasis after induction CHT, 10 received SBRT. Total SBRT dose was: 36 Gy (2 pts), 30 Gy (1 pt) and 24 Gy (7 pts). At present 3/8 pts (37%) underwent resection (1 pt with positive resection margin and 2 with negative resection margin); for 2 pts post-SBRT restaging and evaluation for surgery is pending. With an overall median follow-up of 12.4 months (range, 3–20), for all patients the locoregional control rate was 66%. Median PFS, FFLRP, FFDM and OS were 12.2, 17.3, 12.2, 17.9 months respectively; estimated 1-year PFS, FFLRP, FFDM and OS rate 52%, 76%, 52% and 70% respectively. Three pts developed acute G3 or greater hematologic toxicity (1 anemia and 2 neutropenia), no acute G3 or greater nonhematologic toxicity was observed. One pt developed ulcers (G2) that were medically managed. Late G3 or greater toxicities were not observed.

Conclusion: Induction CHT and SBRT in three fractions resulted in excellent local control of LAPC with a low rate of side effects. Further therapy optimization to reduce systemic progression is needed.

P135

6-DEGREE OF FREEDOM (6-DOF) COUCH AND ABDOMINAL STEREOTACTIC BODY RADIATION THERAPY (SBRT): IS IT USEFUL?

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Aims: The necessity of a precise setup and localization is extremely important in all treatments, especially for Stereotactic body radiation therapy (SBRT) in abdominal region, to face organ motion when high dose is delivered. A 6-Dof couch utility was analysed in abdominal SBRT.

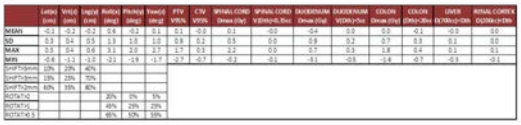
Methods: Primary pancreatic tumours or metastatic liver lesions, until 5 cm, were enrolled. Breast board or Body Pro-Lok (CIVCO support system) were used. Eclipse™ Treatment Planning Systems (Varian Medical System®, Palo Alto, CA) was used for Volumetric Modulated Arc Therapy (VMAT). The total dose was: 35 Gy or 30 Gy in five fractions, depending on respect of dosimetrical constraints, in particular duodenum Dmax. Every CBCT was rigidly registered with the simulation CT(sCT) by MIM Maestro software to obtain a new CT scan. Translational shift before and rotational shift after, detected during the manual or automatic 3D match, were applied to the new CT scan to obtain for each fraction the translational CT (tCT) and the roto-translational one (rtCT). The reference treatment plan (refTP) was copied on tCT and rtCT, obtaining translational (tTP) and roto-translational (rtTP) treatment plans. The daily dose volume histogram (DVH) was calculated for both the treatment plans. Finally dosimetric impact of 3 and 6 DOF correction on the targets and organs at risk was analyzed.

Results: Seven patients were enrolled (4 primary pancreatic tumours, three liver metastatic lesions), 25 CBCT were compared to CT images, 50 tTP and 50 rtTP were calculated. The mean (±SD) interfraction displacements are reported in Table 1. No significative correlation was observed between translational and rotational shifts. No significant differences were found on CTV and PTV V95% in roto-translated plans, except two outliers on PTV (abs(Δ)>1.5%) related to average rotations of 2° (Table 1). Variations >2% due to rotations were found in Organs at Risk(OAR) located nearby the targets. In general more than 50% of variations due to rotations correc-

tion resulted in improvement of accuracy on duodenum.

Conclusions: Protura TM Robotic couch could improve accuracy of setup especially in SBRT. Rotation shifts' correction is necessary independently from translational shifts. These correction allow to reduce variations on PTV's and CTV's coverage, and PTV margin. Organs at risk are more sensible to rotational shift, in particular when located nearby the targets. An ongoing analysis on setup systems and margin reductions was planned.

Table 1. Mean values, standard deviations, maximum and minimum shifts obtained with 3D-match between CBCT and kV. Percentage of shifts and rotations above three different cutoff are reported. Percentage variations of PTV, CTV and OARs constraints due to rotations are shown.



P136

FEASIBILITY AND EFFICACY OF MODERATE HYPOFRACTIONATED SIMULTANEOUS INTEGRATED BOOST WITH INTENSITY MODULATED RADIOTHERAPY IN NEOADJUVANT TREATMENT OF LOCALLY ADVANCED RECTAL CANCER

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Aims: To evaluate the toxicity and the efficacy in term of pathological complete response (pCR) of neoadjuvant radiotherapy with Intensity Modulated Radiation Therapy (IMRT) and Simultaneous Integrated Boost (SIB) technique and concomitant chemotherapy (CT) in locally advanced rectal cancer (LARC).

Methods: We treated patients (pts) with non–metastatic LARC (stage III according to TNM 7th classification). The prescribed dose to the total mesorectum and the related lymph nodes was 45 Gy at 1.8 Gy/fraction. The gross tumor disease and the corresponding mesorectum were treated with a moderate hypofractionated schedule with SIB-IMRT (55 Gy at 2.2 Gy/fraction). Concomitant CT with oral capecitabine or/plus weekly oxaliplatin was administered . Acute adverse events were recorded according to v.4.0 CTCAE scale. Surgery was planned at least 8 weeks after the end of chemo-radiotherapy (CRT). If there was no evidence of disease at the restaging, a wait and see strategy was considered. Adjuvant CT was planned if there was a significant risk of disease recurrence.

Results: From May 2015 to February 2016 we enrolled 39 pts (median age: 64 years [range 44-77years]; M:F=2.2). Mesorectal fascia was involved at the diagnosis in 18 pts (46%). All pts completed the radiation treatment however 8 pts (20%) received less than 4 cycles of concomitant CT because of hematological or gastrointestinal (GI) toxicity. No grade 3 or 4 hematological, genitourinary or skin toxicity were reported. GI toxicity was recorded in 31 pts (79%) with 3 cases of grade 3 toxicity (3 cases of diarrhea, one of them associated with severe proctitis). The 95% of pts received a TME surgery (69% Anterior Resection and 26% Abdominal-Perineal Resection). Based on the restaging, 2 pts did not undergo surgery. pCR was obtained in 10 pts (26%). The TRG1-2 rate was 54%. Adjuvant CT was administered to 18 pts. At a median follow-up of 18 weeks the local control (LC), the disease-free survival (DFS) and the overall survival (OS) rates were 100%, 92% and 97%, respectively.

Conclusions: This SIB-IMRT schedule is well tolerated in LARC. Even in pts with G3 toxicity, the prescribed dose is delivered, after adequate supportive care. Results in terms of efficacy were comparable with literature data. A longer follow-up is needed to evaluate outcomes as LC, DFS and OS.

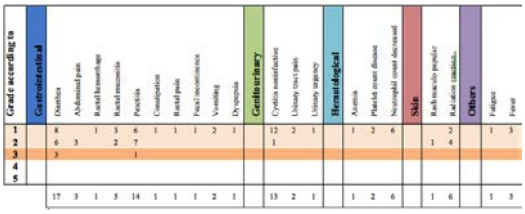

Figure 1.

P137

CLINICAL OUTCOME AFTER PREOPERATIVE HYPOFRACTIONATED SHORT-COURSE RADIOTHERAPY FOR RECTAL CANCER

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Aims: Current standard for locally advanced rectal cancer is preoperative chemoradiotherapy and eventually postoperative adjuvant chemotherapy according to tumour stage. The purpose was to evaluate clinical outcome for rectal cancer after preoperative short course radiotherapy (RT) with fractions of 5 Gy to a total dose of 25 Gy and standard total mesorectal excision (TME).

Methods: 110 patients with pathological proven rectal cancer were referred for preoperative RT at our institution. Fifty-four patients (median age 70 years; male : female = 1.7 : 1) were treated with short course RT (total dose 25 Gy, 5 Gy/die), according to the following criteria: elderly patients or unfit for preoperative chemotherapy due to severe co-morbidities. Surgery with TME was performed within the following three weeks.

Results: Surgery consisted in lower anterior rectal resection (72.2%), abdomino-perineal resection (25.9%) and hemicolectomy (1.9%). Histopathological reports showed stage 0 (1.9%), I (16.7%), II (40.7%), III (33.3%) and IV (7.4%). Perioperative mortality was 1.9% and perioperative complications were observed in 9.2% of the patients. Median follow-up was 24 month (6-149

months). Five-year overall survival rate was 50.2%, cancer specific survival rate was 74.5% and freedom from systemic progression was 68%. Eight-year overall survival rate was 40%, cancer specific survival rate was 51% and freedom from systemic progression was 50.4%. There was no difference in local control (95.3%) after 5 and 8 years follow-up. Late toxicity higher than grade II was observed in 7.4% of the patients.

Conclusions: Preoperative short-course RT followed by TME achieved favourable local control and cancer specific survival rates.

P138

ANAL CANCER TREATED WITH TOMOTHERAPY: ANALYSIS OF ACUTE TOXICITY AND RESPONSE IN OUR INSTITUTION EXPERIENCE

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Aims: The purpose of our study is to report on the acute toxicity and response to treatment in patients affected by squamous cell anal carcinoma (SCAC) that underwent helicoidal intensity-modulated radiation therapy (IMRT) with tomotherapy (TO) at our institution.

Materials and Methods: 19 patients affected by SCAC and treated with TO between December 2009 and July 2015 were retrospectively analyzed. Most of patients (63.1%) presented with locally-advanced disease (2 patients stage IIIA and 10 patients stage IIIB respectively). Concurrent chemotherapy (CT) was administered in 84% of patients; the most adopted schedule was with mitomycin and 5-FU (62% of patients). 79% of patients underwent a planning CT-PET. A sequential IMRT schedule was delivered in 1 patients (5%) while 18 (95%) underwent simultaneous integrated boost (IMRT-SIB). The dose/fractionation prescribed to PTV1 (high-risk volume), PTV2 (intermediate-risk volume) and PTV3 (low-risk volume) ranged between 59.4– 50 Gy, 50.4 – 45 Gy and 45 – 37.5 Gy, respectively, at a corresponding dose per fraction range of 2.2 – 1.8 Gy for PTV1, 2 – 1.68 Gy for PTV2, and 1.8 – 1.5 Gy for PTV3, delivered in a range of 25-33 daily fractions. Acute toxicity was scored according to NCI – CTCAE v.4. Response was assessed at 12 weeks after the end of treatment via digital rectal examination (DRE) and anoscope. Disease-free survival (DFS) and overall survival (OS) were calculated from the end of treatment respectively to the date of first event of disease recurrence and to the date of death from any cause or of last follow-up.

Results: The median follow-up of our study population was 13 months (range 6-45). In 11 patients treatment was interrupted for acute toxicity (median duration of treatment breaks was 8 days, range 1-16). In terms of acute toxicity, the only G3+ reported toxicities were diarrhea and dermatitis. Complete response was achieved in 14/18 patients (77.8%), partial response/stable disease in 2 (11.1%) and local disease progression in 2 (11.1%). All patients were alive at last follow-up. The median OS was 13 months (range 6-45), while the median DFS was 11 months (range 3-26). The 1-year DFS was 79%.

Conclusions: In our experience, concurrent chemoradiation with TO for SCAC was associated with a favorable acute toxicity profile. Considering the prevalence of very advanced loco-regional disease in our cohort, early response assessment is remarkable, although a longer follow-up is needed.

P139

ACUTE GASTROINTESTINAL TOXICITY AFTER HYPOFRACTIONATED RADIATION THERAPY IN PANCREATIC CANCER

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Aims: Pancreatic cancer represents an unresolved oncological problem. Due to the typical asymptomatic onset, the vast majority of patients presents unresectable disease at diagnosis. In these patients, the prognosis is poor with a 5-year survival rate of 5% and median survival is only 8 to 12 months. One of the major objectives of the radiotherapy in these patients is optimizing quality of life by symptom's control besides local control. Toxicity represents the major dose-limiting factor for the intimate connection between the pancreas and the gastrointestinal tract, stomach and duodenum. Aim of this study is to evaluate the acute toxicity profile, the feasibility and the safety of hypofractionated radiation therapy in locally advanced pancreatic cancer treated by IMRT technique in our Department of Radiotherapy- Pol.Umberto I- La Sapienza di Roma.

Methods: Between February and April 2016, six patients with diagnosis of unresectable pancreatic head adenocarcinoma cT4 cN1 M0 (sec. American Joint Committee On Cancer 2016) were included. The median age was 73 years (Range 60-80). All patients underwent hypofractionated RT after chemotherapy by Gemcitabine 1000 mg/mq. Delivered dose was 52 Gy in 13 fractions (400cG/die 5/W) to PTV which consisted of gross disease and positive nearby regional lymph nodes. Radiotherapy was delivered with IMRT technique. Follow-up occurred at 30 days from the end of RT. Primary end point included rates of gastrointestinal (GI) toxicity graded using the CTCAE (version 4.03) and as second endpoint the response analyzed by RECIST criteria

Results: All patients have completed the treatment without interruption for acute toxicity. Only one patient (17%) presented gastrointestinal toxicity: nausea G2, vomiting G2 and abdominal pain G1, with complete regression of symptoms after appropriate medical therapy. The other patients developed dyspepsia G1. No patient experienced a weight loss of more than 5% of initial body weight (G0). At present, all patients are alive: 1 patient in partial response; 5 patients in local stability and one of these has a peritoneal disease.

Conclusions: Hypofractionated radiotherapy by IMRT for unresectable pancreatic cancer is safe and effective.

The treatment was well tolerated. Acute side effects were mild, with no experiencing GI grade 3 or greater toxicity. This study is limited by the small number of patients and by the short time of follow up. It needs enrollementIt of new patients.

P140

PREOPERATIVE SCRT FOR LOCAL ADVANCED RECTAL CANCER. A CLINICAL EXPERIENCE

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Aims: Assess the outcome and side effects of preoperative short course radiotherapy (25 Gy tot / 5 Gy / fx) (SCRT) in a selected population of patients with locally advanced rectal cancer (LARC).

Methods: In our study were evaluated 47 patients (LARC) treated at our Centre from 19 January 2009 to 15 September 2015. These patients were selected based on the distance from the anal margin (> 4 cm), and / or inability to perform a Radio-chemotherapy treatment for age or comorbidities. All patients were treated according to the protocol short course radiotherapy on the posterior pelvis. Radical surgery has been scheduled with a minimum of 7 day interval after the last day of treatment. All patients were staged with MRI and treated with 3DCRT.

Results: The median age was 72.3 years (range 44-89), 9 patients were older than 80(80-89). M: 29, F: 18. Clinical stage: cT2 cN1: 3, cT3 cN0: 16, cT3 cN1: 20, cT3 cN2: 4, cT4 cN1: 3, cT4 cN2: 1. All patients completed the planned radiotherapy course, 1 refused surgery Acute toxicity was evaluated during treatment and 2 weeks after the end of RT, and only one event of a serious nature (proctitis G3) was observed. The average delay of surgery was 29 days (7-55 days). 33 RAR, 13 APR were performed. A patient refused surgery. In the whole we observed 29/46 downstaging. In 4 patients a complete pathologic remission was achieved, the delay to surgery was respectively: 32, 34, 35 and 55 days. In 2/9 older patients occurred a death within 30 days after surgery for failure of the stoma. In low rectal cancers (< 4 cm) 3/12 RAR were performed, due to downstaging. Perioperative complications were: 13/46

Conclusions: In our experience the SCRT is safe and effective. The rate of complete pathological responses (8.7%), are very close to those found in similar clinical trials, such as Stockholm III.

P141

CROSS REGIMEN FOR OESOPHAGEAL CANCER: SINGLE CENTER EXPERIENCE

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Objectives: Multimodality treatment is considered the standard approach for advanced oesophageal and junctional cancer (OJC). CROSS (Chemo-Radiotherapy for Oesophageal tumours followed by Surgery Study) is one of the referral regimens. This work aims to analyse our experience with CROSS

Methods: From January 2013 to December 2015 forty seven consecutive fit patients with resectable, (T3-4,N0,M0, anyT,N+,M0) OJC were enrolled to receive neoadjuvant concurrent radio - chemo therapy (radiotherapy 41,4 Gy in 23 fractions to tumour site and locoregional lymphnodes with concomitant 5 courses of carbo-taxol). Patients showing no progression at Ct and PET CT 6 weeks after neoadjuvant treatment were then evaluated for oesophagectomy. We recorded patients' characteristics, toxicity, response to therapy, postoperative and oncological outcomes. Statistical analysis was performed using SPSS Statistics.

Results: Forty-seven patients; M:F=39:8; median age 65 (40-81), ECOG-PS low (0-1). Adenocarcinoma was the most common histology (63,8%); 66% of tumours were located within the lower and junctional oesophagus. Toxicity was mild in 74,5% patients; 11 pts (23.4%) experienced severe toxicity and 8 (17%) did not complete neoadjuvant therapy. Ten patients (21,2%) didn't undergo surgery due to progression (5), unfitness (2), death (3), so 37 patients underwent radical surgical resection. Postoperative morbidity (according to Clavien Dindo classification) and mortality were 29.7% (11) and 8,1% (3). Complete pathological responses were 7 (18,9%). Actuarial overall and disease-free survivals at 30 months were 73.3% and 73.5% (median follow-up 11.5 months). Recurrence rate was 25% (9). Survival and recurrence rates were not associated to downstaging (p= 0,611 and p=0,68).

Conclusions: Preoperative concomitant radio - chemotherapy with CROSS regimen is considered safe and effective; our experience suggests a careful patients' selection to improve results.

P142

EXCLUSIVE HYPOFRACTIONATED RADIOTHERAPY IN ASSOCIATION WITH EPOETIN ALFA IN THE TREATMENT OF LOCALLY ADVANCED RECTAL CANCER PATIENTS PRESENTING IN EMERGENCY ROOM WITH ACUTE BLEEDING: A SINGLE CENTER EXPERIENCE

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Aims: To describe our center's experience in clinical management of a particularly challenging setting of patients presenting in emergency department with blee-

ding due to an histologically confirmed locally advanced cancer of medium and/or lower rectum.

Methods: Since September 2013 to May 2016 18 patients (12 men and 6 women, mean 64 years) presented to Emergency Room with acute transrectal bleeding whose origin was histologically demonstrated to derive by rectal cancer. Mean (± SD) admission haemoglobin (g/dL) was 9.1 (± 2.4). 3 patients with haemoglobin values below 7 g/dL received major blood transfusion. After the stabilization procedures performed at the General Surgery Department (5 patients underwent a colostomy procedure) the patients received 36 Gy/12 fractions (5 fractions 5 days a week) of irradiation with concomitant 40000 UI/week of epoetin alfa. Before starting radiation therapy all patients were staged by contrast enhanced CT scan and by a multiparametric MR imaging. Hypofractionated radiation therapy was delivered with an isocentric 3 field in field technique on a PTV whose cranial border was setted at bottom of sacro-iliac joints to minimize the small bowel doses. Clinical outcome measures were symptomatic response rate, toxicity, colostomy-free survival, and overall survival. Multiparametric MRI was imported in the treatment planning system (TPS) to quantify the GTV volume (T2w sequences contour) in cc.

Results: Eight weeks after treatment, all patients underwent a multiparametric MR imaging to assess locoregional response. A volumetric reduction of more than 30 % of GTV as lined on T2w images was observed in 41 %. Only 2 patients had a volumetric response less than 20 %. The rates of reduction or resolution of pain and bleeding were 90% and 100%, respectively. The 1-, 2-year colostomy-free survival rates were 100%, 65% respectively (median, 22 months). The 1-, 2- year cumulative overall survival rates were 90 %, 45 % respectively (median, 20 months). No patients stopped treatment because of gastrointestinal or genitourinary toxicities.

Conclusions: Hypofractionated radiation therapy may represent a safe and effective treatment in a critical subgroup of patients unfit to receive chemotherapy at the time of initial evaluation. The excellent reduction of tumor burden stimulate the intriguing hypothesis that hypofractionation is able to offset the radiosensibilization contribution of fluorpyrimidines.

P143

PREOPERATIVE SHORT COURSE RADIOTHERAPY IN ELDERLY PTS (≥75 YEARS) AFFECTED BY LOCALLY ADVANCED RECTAL CANCER

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Background: Short course radiotherapy (SCRT) is a consolidated option of preoperative treatment in patients (pts) with locally advanced rectal cancer (LARC). Particularly in elderly (≥75 years) pts, unfit for chemotherapy because of associated comorbidities, it could be a good option to reduce the rate of locoregional failure. In this retrospective analysis we evaluate the safety of SCRT in that subset of pts (≥75 years).

Methods: From March 2012 to February 2016, 28 pts (mean age 80.3 years, range 75-86), with LARC (clinical stage IIa, IIIa, IIIb in 17.8%, 3.6% and 78,6% of cases, respectively) were submitted to preoperative SCRT. Nine pts had cardiac disease, 7 pts circulatory disease, 9 pts diabetes, 1 patient kidney failure and 1 cirrhosis. All of them had karnofsky PS ≥70. The distance from anal verge was between 3 and 7 cm in ten pts (35,7%) and between 7 and 12 cm in eight pts (64,3%). 25Gy in 5 FF were administered with linac (6-15 MV) using 3DCRT or VMAT. CTV included GTV, mesorectal region and locoregional drainage nodes (obturator, internal and common iliac, presacral). The mean volume of small bowel that received 25Gy, 20Gy and 15Gy was 6.9cc, 88cc and 166cc, respectively. Nobody received chemotherapy.

Results: All pts completed planned RT and underwent surgery after a mean of 16 days (range 7-55 days). Seven out 10 pts with low rectal cancer had sphyncter preservation. Histopathological results: T downstaging was obtained in 11 pts (39.3%) and a SD in 17 pts (60.7%); five pts (18%) had R1 resection (four distal and one radial margin). Toxicities: Only one patient had severe acute toxicity (diarrhea G4; intestinal V20=220cc). Late toxicity occurred in seven pts (25%): two subocclusions treated with surgery, one perianal fistula and four fecal incontinences. Comorbidities did not seem to be correlated with toxicities. Outcomes: The mean follow-up was 21,4 months (range 5-44). Three pts died (2 pts for other reasons and 1 for distant disease), two pts were alive but with distant metastases and 23 pts were alive without disease. No local recurrences were observed.

Conclusions: In elderly pts (≥75 years) affected by LARC and unfit for chemotherapy, preoperative SCRT could be a safe treatment also in pts with significant comorbidities. In this analysis a T downstaging near to 40% was observed, probably due to an unexpected delay of surgery in some pts.

P144

CLINICAL BENEFIT OF ADDING OXALIPLATIN TO STANDARD NEOADJUVANT CHEMORADIOTHERAPY IN LOCALLY ADVANCED RECTAL CARCINOMA: A META-ANALYSIS

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Aims. Neoadjuvant fluoropirimidine (5FU)-based chemoradiotherapy (CRT) has been considered the standard of care for locally advanced rectal cancer (LARC). Whether addiction of oxaliplatin (OXP) will further improve clinical outcomes is still debated. We conducted a meta-analysis to evalua-

te the role of OXP in this patient population.

Methods. Literature searches were carried out in PubMed, Medline and Scopus databases. End points were overall survival (OS), disease free survival (DFS), local failure (LF) and distant failure (DF). Odd ratio (OR) with 95% confidence interval (CI) was calculated using random effects model.

Results. Four randomized trials were included. Patients treated with OXP-5FU CRT had significantly decreased DF (OR = 0.76; 95% CI, 0.60 to 0.97; p = 0.03) compared to standard CRT. OS, DFS and LF were not significantly different between groups.

Conclusions. OXP significantly decreased DF, but does not improve OS e DFS compared to 5FU CRT. Precise role of OXP in neoadjuvant setting of LARC remains to be determined.

P145

STEREOTACTIC BODY RADIOTHERAPY IN OLIGOMETASTATIC PTS WITH LUNG METASTASIS FROM COLON-RECTAL CANCER

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Background: the approach to pts with lung metastasis from primary colon-rectal cancer is based on systemic therapy and the role of stereotactic body radiotherapy (SBRT) is still to be investigated. The present work aims to study the impact of SBRT in oligometastatic patients (pts) with lung metastasis from colon-rectal cancer.

Methods: From May 2010 to March 2015, 33 consecutive pts (median age 66 years, range 31-88) with lung metastasis from colon-rectal cancer were treated with SBRT. All pts were treated using Image Guided Radiotherapy (IGRT) and stratified according to K-RAS and B-RAF genotype. The primary endpoint was local progression free survival and the secondary endpoint was the safety profile of SBRT.

Results: A total of 56 active lesions were treated. Nineteen out of 33 pts were affected by rectal cancer while 14 pts by colon cancer. The radiotherapy delivered dose and the adopted fractionations were 24-27 Gy as a single fraction for 40 lesions and 27-42 Gy delivered in 3 fractions (2-3 times a week) for 16 lesions. A single metastatic nodule was treated in 15 pts, 2 in 13 and 3 in 5 pts. Median Planning Target Volume value was 21.45 cc (range 6-156). The median follow-up was 22,8 months (range 1.3-45.7). Local relapses were recorded in 23 lesions (41.1%); six, 12 and 18 months treated lesions control rate were 87.8, 62.0 and 30.0%, respectively. Median time to progression within the irradiated sites was 13.4 months and median progression free survival outside the irradiated lesions was 6.8 months. No differences in local control were observed considering K-RAS and B-RAS genotype. Severe toxicity were not recorded.

Conlusions: SBRT could represent a safe and valid approach in pts with lung metastases from colon-rectal cancer. However, before considering a pts suitable for SBRT, the planned outcome and the impact on systemic disease have to be carefully investigated. Further studies are needed in order to select pts potentially suitable for SBRT.

P146

PROSTATE CHANGES AFTER 12 GY-INTRAOPERATIVE RADIOTHERAPY: HOW TUMOR CELLS RESPOND TO SINGLE HIGH DOSE? *IN VIVO* RADIOBIOLOGICAL ASPECTS

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Aims: Aim of this work is to evaluate apoptotic pathways involved in prostate cancer treated with intraoperative radiotherapy (IORT) with 12 Gy, studying the effects on cancer cells, prostatic intraepithelial neoplasia (PIN) and normal cells

Methods: We selected a sample of 10 patients, out of 111 IORT-prostate, for a preliminary feasibility study. Selection criteria were: no neoadjuvant hormone therapy, Gleason score>7. Proteins involved in the apoptotic cascade (Bax, Caspases -3 and -9) were studied before and after 12 Gy single shoot in neoplastic cells, high grade PIN areas and in normal prostate cells. Immunofluorescent detection of antigens (anti-Bax, anti-caspases-3 and -9), were performed on bioptic sample and on surgical specimens 5-mm slices. On surgical specimens there were also detected Bcl-2, and ki-67 with immunoistochimical analysis. A count of positive spots for immunofluorescence (Bax+, Caspases-3 and -9+/all nuclei, 40x magnification) was performed on tumor cells, PIN, healthy tissue areas. Bax and caspases immunofluorescent positivity was compared in different areas and in neoplastic areas before and after single shoot high dose

Results: A significant increase in Bax, Caspases-3 and -9 expression was detected in tumor and PIN areas comparing IORT treated and untreated samples ($p<0.05$). After 12 Gy-single dose, healthy areas expressed significantly lower level of Bax and caspases positive with respect to neoplastic cells ($p<0.0001$), while in PIN areas, Bax positive cells were significantly more present than in neoplastic areas ($p=0.0001$). Mean Bcl-2 in neoplastic cells is 17% (range: 1-23), mean ki-67 in neoplastic area is 4.5% (range: 1-17). With multivariate analysis, we find that cancer cells with Ki-67 $\geq$ 8% show a trend toward greater expression of Bax ($p=0.0641$)

Conclusions: After 12 Gy irradiation, Bax and caspases overexpressed in tumor and PIN cells, in particular in prostate cancer with higher proliferation index. PIN areas seem to be more radiosensitive than neoplastic areas and healthy cells do not activate apoptosis after single shoot, showing an intrinsic radioresistence. This preliminary study represents the basis for an extensive work in which

we would correlated clinical parameters with pathology and apoptotic factors. In fact, the comprehension of these relationships could allow to better understand the mechanisms of high dose per fraction and, radioresistence in order to personalize treatments.

P147

CAN WE DO BETTER FOR BONE METASTASES? BONE OLIGOMETASTATIC PROSTATE CANCER (BOPC) AND HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY: THE EUROPEAN INSTITUTE OF ONCOLOGY EXPERIENCE. A RETROSPECTIVE ANALYSIS OF 64 PATIENTS

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Aims: To evaluate clinical outcome of hypofractionated Stereotactic Body Radiotherapy (SBRT) for BOPC.

Methods: 64 BOPC patients(pts) [85 lesions(ls)] were treated in our Institution between 3/2012 and 12/2015. Median iPSA and GS were 9.78ng/ml and 7, respectively. Initial NCCN category was low in 1 pt, intermediate in 19pts, high in 32pts, not available in 3pts and 9pts were in stage IV at the diagnosis. Primary therapy included surgery ± Radiotherapy(RT) and/or androgen deprivation (AD) in 40pts, RT (± AD) in 20pts, and AD only in 4pts. 37(58%)pts presented single ls, 27(42%) had from 2 to 4ls. All pts gave written informed consent and received SBRT to all visible ls. Median dose delivered was 24 Gy in 3fractions. 12(19%)pts treated also non-bone lesions of whom 5(8%)pts, intraprostatic primary tumor. Median age at SBRT and KPS were 70 and 100, respectively. A re-irradiation was performed in 3(3.5%)ls. 37pts received AD and 1 chemotherapy. 39(61%)pts experienced their first recurrence, 25(39%) were already in stage IV since a median of 23months(mo) (range 4-131 mo). Pain was reported in 19(30%)pts (23ls). Median follow up was 14(range 4-40)mo.

Results: Biochemical response at 3mo was evaluable in 61 (95%) pts: complete response(CR), partial response (PR), stable disease(SD) and progression disease(PD) was observed in 14(23%), 20(33%), 5(8%) and 22(36%)pts respectively. In 45(70%)pts a radiological response was assessed after a median time of 6 (2-24)mo: CR, PR, SD and PD were observed in 29(49%), 6(10%), 11(19%) and 7(22%) ls, respectively. Pain response was complete, partial, indeterminate and unknown in 14(61%), 2(9%), 5(22%) and 2(16%) ls, respectively. No pain worsening was registered. Clinical progression was reported in 29(74%)pts after a median of 9mo (3-28). In 16(19%)ls in-field relapse occurred after a median of 10.5 (5-29) mo. Only in 1 case surgical stabilization was requested due to the in-field progression. Acute toxicities included G1 and G2 in 1 and 1 pts respectively, late G1 toxicity was reported in 2pts. At the time of analysis 10pts are alive disease-free, 49 alive with disease, 2 dead of disease and 3 lost at follow-up.

Conclusions: SBRT offers high-compliance approach to BOPC. Radiological response and pain control is obtained in at least 70% of pts. Toxicity profile is excellent. Further investigation is warranted to define the pts that benefit most from SBRT and the optimal combination with other treatment modalities.

P148

HYPOFRACTIONATED RADIOTHERAPY AFTER RADICAL PROSTATECTOMY: TOXICITY AND BIOCHEMICAL FAILURE

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According to / ratio for prostate(1,5) and for critical organs, IMRT allows simultaneous delivery of higher RT doses to CTV and lower doses to normal tissue in the attempt to reduce toxicity. Our purpose is to evaluate our experience in the treatment of prostate cancer after surgery,adjuvant or salvage,whit hypofractionated IMRT delivered by Helical Tomotherapy and Arc Therapy,with daily IGRT.This technique could result in a same or better outcome in term of tolerance and clinical results.Between 05/10 and 01/16 50 pts,median age 68yrs[48-81],stage pT2a[3pts],pT2b[3pts],pT2c[10pts],pT3a[10pts],pT3b[23pts],pT4[1pt],median PSA 0,29[0.003-5.48], underwent to EBRT after prostatectomy,27[54%]adjuvants and 23[46%]salvage,23[46%]already under hormone therapy:14[61%] in adjuvant group and 9[39%] in the salvage one. IMRT was delivered by Helical Tomotherapy(HT), 44[88%]pts, and Arc Therapy (Trilogy),6[12%]pts, with daily IGRT.The prescribed dose was 62.50Gy for prostate bed,56.25Gy for seminal vesicles bed to all patients and 50Gy for pelvis to 32pts[64%], 21 with N0 and 11 with N1,in 25 fx. During and at the end of the treatment pts were evaluated about GU and GI symptomatology according to RTOG criteria for acute and late toxicity. All pts received the prescribed dose. Acute toxicity has been evaluated at the end of the treatment for 50 pts; late toxicity has been evaluated after minimum 6 months (37/50[74%]pts). The median follow up is 16 months [1-70];3-years OS is 90,5%[I.C.95%] (2/50pts are dead, only one for prostate cancer progression); 3-years DFS is 92,8% [I.C.95%](3/50pts biochemi-

cal relapse). The most significant severe GU acute toxicity reported at the treatment end were grade 3 urethral stenosis [2%]; median of average dose to bladder was 31,36Gy, range 7,38-49.6Gy;median of V50 to bladder was 18%[0-50]. One pt had a break at 12th fraction due to his diverticulitis flare,but he finished the treatment; median of average dose to rectum was 29,44Gy, range 10,08-38,9 Gy; median of V50 to rectum was 12,5%[1-26].The most significant GU late toxicity, evaluated after minimum 6 months of follow up,were grade 3 persisting urethral stenosis for one pt;one pt suffers from chronic cystitis. For GI late toxicity only one pt has reported grade 3 subocclusion related with the diverticulitis flare during the EBRT. The hypofractionated radiotherapy after radical prostatectomy could be considerated safe for toxicity and biochemical failure.

Table 1.

Grade	Gu Acute Toxicity		Gi Acute Toxicity		Gu Late Toxicity		Gi Late Toxicity	
G0	36	72%	37	74%	25	67%	35	94%
G1	13	26%	12	24%	10	27%	1	3%
G2	0	0%	1	2%	1	3%	0	0%
G3	1	2%	0	0%	1	3%	1	3%
		50				37		

med on 29 patients, on the correlation between DVH and TPS data (OAR's dimensions/doses, target) and acute toxicities has been conducted.

Results: 68 pts with a median age of 74 yrs were treated in the defined period and received Hypo RT. 26 (38%) pts had high risk disease; 41 (60,3%) pts assumed ADT (androgen deprivation therapy), all of them for more than three months. RT volumes involved prostate only, prostate+seminal vesicles base and prostate+seminal vesicles respectively in 21, 23 and 24 pts. G2 urinary and rectal toxicity has ben observed in 20(29%) and 11(16%)pts. No acute G3-4 gastrointestinal toxicity has been observed. For two patients a TURP was planned (one had a catheter placed -G3-, the other a temporary sovrapubic cystostomy -G4-, respectively at 3 and 6 months after RT, for urethral stricture). No correlations are evident with different clinical and therapeutic variables. A dosimetric correlation between bladder V50>15% and urinary toxicity >=G2 is reported (p=0.026).

Conclusions: This report shows that acute toxicity of mild hypo-fractionated RT seems acceptable. Longer term follow up of a larger number of patients and the evaluation of late toxicity, along with clinical outcome (according to a complete set of dosimetric parameters) should be obtained to confirm these preliminary data and compare them with those obtained with conventionally fractionated RT.

P149

PRELIMINARY ANALYSIS OF ACUTE TOXICITY IN PATIENTS TREATED WITH MILD HYPO-FRACTIONATED RADICAL RADIOTHERAPY FOR PROSTATE CANCER

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Aims: To report acute toxicity of patients (pts) treated with mild hypo-fractionated (Hypo) radical radiotherapy (RT).

Materials and Methods: From August 2014 to March 2016 pts with histologically confirmed low-intermediate-high risk (T1b-T4 N0M0) prostate cancer and Karnofsky Performance Status 80-100 were considered eligible for Hypo radical RT (19-20 fractions of 3,2 Gy once daily). All pts were treated with VMAT-IGRT. Dose constraints for bladder and rectum were defined using the BED2 conversion from normo-fractionated regimen. Toxicity was considered "acute" if occurred during and/or within three months after the treatment. Acute urinary and gastrointestinal toxic effects were scored according to the CTCAE 4.0 with self-assessment questionnaires at baseline, once a week during RT, 1 month and 3 months after the end of the treatment. Distribution differences of toxicity in relation with clinical and therapeutic variables were analyzed with 2-test (SPSS®) and considered statistically significant if $p<0.05$. A preliminary dosimetric analysis, perfor-

P150

CYCLIN D1 SILENCING SUPPRESSES TUMORIGENICITY, IMPAIRS DNA DOUBLE STRAND BREAK REPAIR AND THUS RADIOSENSITIZES ANDROGEN-INDEPENDENT PROSTATE CANCER CELLS TO DNA DAMAGE

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Aims: Patients with hormone-resistant prostate cancer (PCa) have higher biochemical failure rates following radiation therapy (RT). Cyclin D1 deregulated expression in PCa is associated with a more aggressive disease: however its role in radioresistance has not been determined.

Methods: Cyclin D1 levels in the androgen-independent PC3 and 22Rv1 PCa cells were stably inhibited by infecting with cyclin D1-shRNA. Tumorigenicity and radiosensitivity were investigated using in vitro and in

vivo experimental assays.

Results: Cyclin D1 silencing interfered with PCa oncogenic phenotype by inducing growth arrest in the G1 phase of cell cycle and reducing soft agar colony formation, migration, invasion in vitro and tumor formation and neo-angiogenesis in vivo. Depletion of cyclin D1 significantly radiosensitizes PCa cells by increasing the RT-induced DNA damages by affecting the NHEJ and HR pathways responsible of the DNA double-strand break repair. Following treatment of cells with RT the abundance of a biomarker of DNA damage, γ-H2AX, was dramatically increased in sh-cyclin D1 treated cells compared to shRNA control. Concordant with these observations DNA-PKcs-activation and RAD51-accumulation, part of the DNA double-strand break repair machinery, were reduced in shRNA-cyclin D1 treated cells compared to shRNA control. We further demonstrate the physical interaction between CCND1 with activated-ATM, -DNA-PKcs and RAD51 is enhanced by RT. Finally, siRNA-mediated silencing experiments indicated DNA-PKcs and RAD51 are downstream targets of CCND1-mediated PCa cells radioresistance.

Conclusions: In summary, these observations suggest that CCND1 is a key mediator of PCa radioresistance and could represent a potential target for radioresistant hormone-resistant PCa.

P151

OUTCOMES IN INTERMEDIATE RISK PROSTATE CANCER PATIENTS TREATED WITH HYPOFRACTIONATED RADIOTHERAPY

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Aims: To evaluate the outcomes in intermediate risk prostate cancer treated with hypofractionated radiotherapy (HyRT).

Methods: Between March 2007 and December 2015, 156 patients affected by intermediate risk (T2b–T2c prostate cancer or Gleason Score equal to 7 or pre-treatment PSA value ranging from 10 to 20 ng/mL) prostate cancer were treated with HyRT. The median age at diagnosis was 74 years (range 53-88). MRI was used to better delineate the Clinical Target Volume (CTV) when available. The CTV1 included the prostate plus seminal vesicles and the CTV2 the prostate alone. A 5 mm expansion in all direction was used in the patients submitted to daily kv Cone Beam CT, to generate PTVs. A 3D-CRT and a 15 MV photons linear accelerator was used to deliver the treatment. The PTV1 received 43.8 Gy in 12 fractions and the PTV2 received 54.75 Gy in 15 fractions, three times a week. Neoadjuvant, concomitant and adjuvant ADT was administered for a total of 9 months and was started 3 months before RT.

Results: After a median follow-up of 60.2 months (range 7 to 108 months, 95% I.C.: 55,7-64,8), 13 patients (8.3%) died, of whom 11 for intercurrent disease and 2 (1.3%) for PCa. The 5 and 8-year OS were 90.6% and 84,6%, respectively. The 5 and 8-year CSS were both 98.1%. Fifteen patients (9.6%) developed biochemical recurrence after a median follow up of 29 months (range 10-80 months). Of these patients, 13 (8.3%) had also a clinical detectable disease. The 5 and 8y-bRFS was 89.3% and 83,3%, respectively. Among the 13 patients with clinical recurrence, 8 (51.3%) had local recurrence, 2 (15.4%) developed distant metastases, and 3 (23.1%) had both local recurrence and distant metastases. Acute genito-urinary (GU) toxicity of grade 1 occurred in 78 patients (50.0%), grade 2 in 12 patients (7.7%) and grade 3 in 3 patients (1.9%). Acute gastro-intestinal (GI) toxicity of grade 1 were observed in 26 patients (16.7%), grade 2 in 15 patients (9.6%). None developed acute GI toxicity of grade 3 or 4. Late GU toxicity occurred as follows: grade 1 in 49 patients (31.4%), grade 2 in 7 patients (4.5%), grade 3 in 2 patients (1.3%). Late GI toxicity of grade 1 was observed in 18 patients (11.5%), grade 2 in 4 patients (2.6%) and grade 3 in 1 patient (0.6%).

Conclusions: The hypofractionated schedule used is well tolerated with a low rate of acute and late grade ≥ 2 gastrointestinal and genitourinary toxicities and is useful to obtain high rate of tumor control.

P152

STEREOTACTIC BODY IRRADIATION (SBRT) OF PROSTATE AND SEMINAL VESICLES WITH HELICAL TOMOTHERAPY: FEASIBILITY AND DOSIMETRIC RESULTS

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Aims: We present preliminary data of a feasibility study for a (SBRT) protocol for low and intermediated risk prostate cancer that delivers 36,25 Gy to the prostate (P) and 31,6 Gy to the seminal vesicles (SV) in five fractions.

Methods: Ten consecutive patients previously treated with a moderate hypofractionated scheme were considered. The original prescription was 70.2Gy (2.7Gy/fr) to the prostate gland (PTV1.1) and 61.1Gy (2.35Gy/fr) to the SV (PTV1.2). Seven mm margins were posteriorly added to the CTV and 10 mm in all other directions to create PTV. Prior, patients were instructed to ingest a low fiber diet and a "ad-hoc" protocol for rectal and bladder filling. A knee-feet device immobilization was used during CT simulation and treatment deliver. For each patient new plans were created using the same CT images and contours with a prescription of 36.25 Gy to PTV1.1 and 31.6 Gy to PTV1.2 in five fractions. All plans were elaborated in helical tomotherapy platform. Technical settings used for standard plans was (pitch 0.215, field width 2.5 cm, modulation factor 2.5).

Results: Mean target coverage V95% and maximum dose (D2% were 97,4 (96.5-99.4%) and 103% (103%-106%) of the prescription dose. Maximum doses (D1cc) and V32.6 Gy for the rectum were 36.25 Gy and 10%

(6%-14%). V18Gy was on the average 46% and 47% for rectum and bladder respectively. Values of V18Gy greater than 45% for bladder were observed for patients with a bladder volume lower han 200 cc. V14.5 Gy for femoral heads was 1.8% and the average value of D50 for penile bulb was 29.7 Gy (12.3 Gy-36.5 Gy). The average treatment time was 12.3 minutes.

Conclusions: SBRT of prostate and SV with tomotherapy is feasible. The main dosimetric goals can be achieved with default technical settings in a reasonable delivery time. Better dose distributions to organs at risk are expected if a dedicated SBRT protocol is used in order to reduce CTV-PTV margins and different technical settings are considered to increase dose conformation.

P153

SALVAGE IMAGE-GUIDED EXTERNAL BEAM RE-IRRADIATION OF LOCAL RECURRENCE IN PROSTATE CANCER: CLINICAL OUTCOME AND DOSIMETRY

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Aims: To assess the potential clinical and dosimetric benefits of external beam re-irradiation delivered to either the prostate or prostatic bed for local recurrence after radical or adjuvant/salvage radiotherapy.

Table 1. Treatment characteristics

ORGAN	DOSIMETRY	
URINARY BLADDER	Mean total	Range
D30% (Gy)	3.03	(0.5 - 24.8)
RECTUM	Mean total	Range
D30% (Gy)	6.55	(0.8 - 15)
D60% (Gy)	2.95	(0.4 - 20.8)
PENILE BULB	Mean total	Range
V29Gy (%)	0.21	(0 – 1.5)
POSTERIOR RECTAL WALL	Mean total	Range
Dmax (%)	38.78	(14.6 - 64.3

Methods: Between November 2009 and January 2016, 60 patients with local recurrence of prostatic cancer after radical or adjuvant/salvage radiotherapy, were treated in the European Institute of Oncology. Median age was 63 years (range, 47.1-81.7) and median prostate-specific antigen (PSA) at the time of relapse was 21.7 ng/ml (range=3.5-228.5). This retrospective analysis included 37 patients that received with image-guided re-EBRT delivered with VERO® technology, of this, 18 patients were treated with a total dose of 30 Gy in 5 fractions (6 Gy/each) and in 19 patients were delivered 25 Gy in 5 fractions (5 Gy/each), we provide also dosimetric data (see table). Patients with distant metastasis at the time of re-EBRT were excluded. Acute and chronic toxicity was assessed according RTOG/EORTC criteria. A concomitant hormonal treatment was administered in 10 patients. Biochemical control was assessed according to Phoenix definition.

Results: The mean and median follow-up were 20.7 and 17.1 months, respectively (range, 2-65.5). Acute genitourinary (GU) toxicity included G1 and G3 events in 7 and one patient, respectively. Acute gastrointestinal (GI) toxicity included G1 event in 3 patients. Chronic GU toxicity included G1 and G2 events in 8 and 4 patients, respectively. Chronic G1 GI toxicity occurred in 2 patients. At the last follow-up 19 patients (51.4%) show no evidence of disease, 16 (43.2%) are alive with biochemical or clinical disease and 2 patients (5.4%) died: 1 due to disease progression and 1 due to second cancer.

Conclusions: Re-EBRT, using image guided approach, is a feasible option for local prostate cancer recurrence achieving tumour control at about 2 years in half of the patients (unselected series). No severe acute and chronic toxicity after re- EBRT was observed. Considering that currently there are no consistent data in literature regarding dosimetry in re-irradiation of recurrent prostate cancer, we suggest that our promising results provide a benchmark to estimate the toxicity profile.

P154

FLINAC-BASED EXTREME HYPOFRACTIONATION FOR LOCALIZED PROSTATE CANCER WITH VOLUMETRIC MODULATED RADIATION THERAPY: PRELIMINARY REPORT OF A PHASE II STUDY

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Aims: Extreme hypofractionation, also called stereotactic body radiation therapy (SBRT), in prostate cancer (PC) is a promising radiation treatment that delivers highly conformal dose in few fractions, typically 4 to 5 fractions. Aim of the present preliminary analysis of a phase-II prospective study is to evaluate the feasibility and preliminary side effects of SBRT in a cohort of localized PC patients.

Materials and Methods: The study, approved by the Ethical Committee, started on January 2014. Inclusion criteria were: age ≤80 years, World Health Organization performance status ≤2, histologically proven prostate adenocarcinoma, low-/intermediate-risk according to D'Amico criteria, no distant metastases, no previous sur-

gery other than transurethral resection of the prostate (TURP), no other malignant tumor in the previous 5 years, a pre-SBRT International Prostatic Symptoms Score (IPSS) ranging between 0 and 7. The SBRT schedule was 35Gy for low risk and 37.5Gy for intermediate-risk PC in 5 fractions, delivered in consecutive days. SBRT was delivered with volumetric-modulated radiation therapy (VMAT). Toxicity assessment was performed according to CTCAE v4.0 scale. Neoadjuvant/concomitant hormonal therapy was prescribed according to risk classification.

Results: At the time of analysis, forty-two patients were recruited in the protocol and treated. Median age was 74 years (63-80) and median follow-up was 16 months (range=4-24). According to risk-category, 31/42 patients were low risk and 11/42 were intermediate-risk. Median initial prostate-specific antigen (PSA) was 6.1 ng/mL (range=3.4-12.8 ng/ml). Median Gleason score was 6 (6-7). IPSS pre-SBRT was registered for all patients, with a median value of 4 (range=0-10). All patients completed the treatment as planned. Acute genitourinary (GU) toxicity was: G0 29/42, G1 7/42, G2 6/42. Acute gastrointestinal (GI) toxicity was: G0 36/42, G1 4/42, G2 2/42. No acute toxicities superior or equal to G3 were recorded. Late GU and GI toxicities were mild without severe events: GU-G0 39/42, GU-G1 2/42, GU-G2 1/42; GI-G0 40/42, GI-G1 2/42. At one-year of follow-up, IPSS was recorded in 25/42 patients with a median value of 4.5 (range= 0-18). At the time of analysis, biochemical control was 100%.

Conclusions: Preliminary analysis of this SBRT phase-II prospective study for low-/intermediate-risk PC proved to be feasible and tolerable. Longer follow-up is needed to assess late toxicity profiles and clinical outcomes.

P155

ACUTE GENITO-URINARY TOXICITY IN HYPOFRACTIONATED RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER: A PRELIMINARY EXPERIENCE

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Aims: To evaluate correlations between clinical and dosimetric parameters and acute genito-urinary (GU) toxicity in hypofractionated prostate cancer radiotherapy, and to test the International Prostate Symptoms Score (IPSS) questionnaire as a measurement tool of acute GU toxicity.

Methods: In 35 patients the IPSS questionnaire was prospectively collected before and at the end of hypofractionated radiotherapy (60 Gy, 3 Gy per fraction) for localized prostate cancer. All patients underwent intensity modulated radiation therapy (IMRT), and the treatment set-up was daily checked with an on board cone beam CT system. Acute GU was scored by the radiation oncologist, according to the RTOG/EORTC toxicity scale. We analyzed dose-volume-histograms (DVHs) parameters of bladder, bladder wall, and trigonal region. In particular, we correlated maximum doses and a set of appropriate Vx (percent of OAR volume receiving the x dose) to acute grade ≥ 2 GU toxicity. Correlation between dose volume parameters considered as continuous variables and grade ≥ 2 toxicity was assessed by Student's t-test for independent samples in case of normal distribution, otherwise by non-parametric Mann-Whitney test. Data were tested for normality with the Kolmogorov Smirnov test. Correlation between grade ≥ 2 toxicity and clinical parameters (previous abdominal surgery, chronic bowel disease, diabetes, smoking, antihypertensives, antiaggregants) was performed using the 2-test for categorical variables.

Results: 10 (28.5%) patients experienced acute grade 2 GU toxicity, no grade 3 toxicity was recorded. No DVH parameter (maximum dose, V58, V60) or clinical parameter was significantly correlated with acute GU toxicity. An IPSS score ≥ 10 before the start of radiotherapy was correlated to acute grade ≥ 2 GU toxicity ($p=0.05$), and a 7 or more points increase in the IPSS score at the end of radiotherapy respect to the baseline score was correlated to acute GU toxicity ($p=0.03$).

Conclusions: This preliminary experience shows that the IPSS questionnaire is a useful tool in monitoring patients undergoing hypofractionated radiotherapy for localized prostate cancer. The baseline IPSS score might be used to discriminate patients that will develop an acute GU toxicity.

P156

MODALITY OF PROGRESSION AFTER STEREOTACTIC RADIATION THERAPY FOR OLIGOMETASTATIC PROSTATE CANCER NODAL RECURRENCE

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Aims: SBRT have demonstrated high local control rate for treatment of nodal metastases in patients (pts) with oligometastatic prostate cancer (PCa) with low toxicity profile. The lymphatic modality of PCa dissemination opens the debate about the opportunity to treat the whole lymph nodal chain or only the nodal recurrence. The aim of this retrospective study is to evaluate the modality of nodal progression after SBRT for nodal recurrence

Methods: From March 2009 to November 2015, 35 pts underwent SBRT for oligometastatic Pca (38 lesions treated). Nodal recurrence was detected by 18F-Choline PET/CT. 25 pts relapsed in pelvic lymph nodes, 8 pts in lomboaortic nodes and 2 pts both pelvic and lomboaortic nodes. The median prescribed dose was 30 Gy in 3/fx to 70% isodose line (median total dose to isocenter 35.50 Gy BED10 >100 Gy). The Volumetric Modulated Arc Therapy (VMAT) treatment was delivered by 6MV beam modulator Linac with 4 mm MLC. Patient set-up ad isocenter position were controlled before each fx by CBCT. Toxicities were scored by CTCAE v 4.0. Treatment response was evaluated by PSA and 18F-Choline PET/CT.

Results: Median target volume was 6.6 cc (range 0.3–229.7 cc). No grade 3/4 toxicities were recorded. Median follow-up was 27 months (range 5-78 months). Local control was achieved in 97.4% (37/38) of treated lesion. Median DFS after SBRT was 6 months (range 2-46). 24/35 pts (68.6%) had a new lymph nodal progression after SBRT (10/24 pts showed also bone metastases). 5/35 pts (14.3%) had only bone recurrence. Nodal recurrences were located in pelvis (8 pts), in lomboaortic nodes (7 pts) and in distant nodal sites such mediastinum or sovraclavicular fossa (9). 7/24 pts showed relapse in the lymph node chain treated, 17/24 pts in distant nodal sites. Pts treated on lomboaortic nodes showed relapse both below or above the treated site (3/8 in pelvis, 3/8 in the same chain and 5/8 also in distant nodal site). 18 pts underwent to a new course of SBRT, 15 started a new course of ADT

Conclusions: SBRT for nodal metastasis in pts with oligometastatic PCa is a safe and effective treatment with high rate of local control (97.4%). Only 29.1% of nodal recurrence occurred in the same lymph node chain, while 70.8% occurred in distant nodal sites and 42.8% in bone, not included in a prophylactic treatment, therefore justifying the irradiation only of nodal recurrence . Due to the small sample size and short follow up, our results need to be confirmed in other series.

P157

SALVAGE SBRT IN ISOLATED NODAL OLIGORECURRENCE FROM PROSTATE CANCER: A MONOISTITUTIONAL EXPERIENCE

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Aims: a status of disease with a limited number of distant lesions and a controlled primitive tumor is recently defined as oligo-recurrence: this group of patients is more favorable than the others with a high number of metastases and, in prostate cancer, often is represented by a single node. The objective of this retrospective study was to evaluate the acute and late toxicity rates, in salvage stereotactic body radiation therapy (SBRT) as a treatment modality in nodes oligo-recurrence, from prostate cancer.

Methods: between February 2013 and May 2016, 25 patients, for a total of 38 isolated lymph nodes from prostate cancer, were treated with SBRT, delivered with Truebeam Stx(Varian®), at UPMC San Pietro FBF radiotherapy center of Rome. The median age at primitive diagnoses was 67 (range 50-78) years. For the primary treatment, radical prostatectomy and postoperative irradiation, exclusive radiotherapy or prostatectomy was performed in 12 (48%) patients, 10 patients (40%) and 3 patients (12%), respectively. Median previous RT dose was 72 Gy/35 fr. Median PSA at recurrence was 2.02 ng/ml. All patients with arising PSA underwent a [11C] PET-CT before SBRT, in order to exclude other sites of disease. The SBRT dose varied from 24 to 30 Gy, in 3-5 fractions, according to the RT treatment for the primitive lesion or a close organ at risk. A daily CBCT and X-ray (BRAINLAB ExacTrac®) scans were acquired before each treatment session, for every patient. Acute and late toxicity were analyzed, according to CTCAE toxicity scale(v. 4.0).

Results: The median fup was 19.4 months. Most of patients received 30 Gy/3 fr, on alternative days: all the patients completed the prescribed SBRT. 18 patients (72%) received androgen deprivation therapy (ADT) concomitant to SBRT. SBRT was well tolerated: only 1 patient experienced G2 acute rectal toxicity but we didn't observe any severe acute or late events (≥G3). Despite the short fup, local control was 100%, distant control was 64% (16/25). All these recurrences were nodal, all out of SBRT field: in 3 of these 9 patients a new SBRT was delivered (30 Gy/3fr): one of these 3 received the third course of nodal salvage SBRT; in the remaining ADT was proposed. At the moment of analysis, all patients were alive.

Conclusions: our experience shows that SBRT for isolated nodal relapse from prostate cancer is a safe treatment, offering a low toxicity profile and an excellent tumor local control. More data and a longer follow up are needed.

P158

HIGH-RISK PROSTATE CANCER AND RADIOTHERAPY: IEO EXPERIENCE AND BENCHMARK FOR AIRC IG 2013-N14300

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Aims: Prostate cancer (Pca) is the second most common male cancer. The prognosis for patients with a diagnosis of high risk PCa is poor. No consensus exists on the most effective treatment. In the last decade hadrontherapy with carbon ions has been considered a suitable strategy for the high-risk Pca, in terms of the dose deposition with a resulting better sparing of organs at risk, based on the promising Japanese results and first Italyn data (CNAO). The aim of this retrospective study was to identify the biochemical progression-free survival and the toxicity profile of localized high-risk prostate cancer patients treated with external beam radiation therapy. These results will constitute a benchmark for a prospective "mixed beam" trial: a boost with carbon ions followed by a pelvic photon intensity modulated radiotherapy. [NCT 02672449 (clinicaltrials.gov)].

Patients and Methods: We retrospectively reviewed the data of 76 patients treated in our Institution with photon radiation therapy according to the inclusion criteria of the

future "mixed beam" trial: cT3a and/or serum prostate-specific antigen >20 ng/ml and/or Gleason score of 8-10, cN0 cM0. Toxicity, biochemical and clinical progression-free survival were assessed.

Results: 76 patients fulfilled our criteria and were treated in our Insitution between 05/2010 and 12/2014. Median age, initial PSA, and GS were 74.9 years, 26.4 ng/mL and 8, respectively. EBRT using IMRT technique consisted in the irradiation of prostate/vesicles or prostate/pelvis for 46 and 30 patients, respectively. Moderate hypofractionation was employed (Fox Chase regimen), median dose was 70.2 Gy (2.7Gy for 26 fractions). In 61 (80.3%) patients androgen deprivation (ADT) was added. The median follow-up was 30.2 months (range 7.2-61.1 months). Biochemical progression was observed in 22 (28,9%) patients after a median time of 20.2 months (range: 5-58.1) from the end of EBRT. 16 patients had clinical progression, in all the cases preceded by biochemical progression. 57 (75%) patients are alive with no evidence of disease, 13 (17.1%) are alive with clinically evident disease, 6 died (3 for PCa). No grade>2 acute and late toxicity, included urinary and rectal complications, was reported.

Conclusions: Our results suggest that a more aggressive treatment is necessary. Local treatment intensification based on the "mixed beam" approach combining carbon ions (with its known radiobiological advantages) and photons might really represent a promising strategy in the high risk prostate cancer and it will be investigated with our prospective clinical trial.

P159

TOXICITY AND QOL IN 300 PROSTATE CARCINOMA PATIENTS TREATED BY MODERATELY HYPOFRACTIONATED IGRT/IMRT-SIB

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Aims: Aim of this study was to evaluate the safety, in terms of acute and late toxicity and QoL in patients (pts) with prostate carcinoma (PCa) treated with moderately hypofractionated IGRT/IMRT-SIB using fiducial markers.

Methods: Three-hundred consecutive PCa pts were treated with daily on-line IGRT based on 2D (6MV) orthogonal images. Low risk pts received 62.1 Gy in 23 fractions to PTV1 (prostate). Intermediate risk pts with probability<15% of lymph nodes involvement (Roach's equation) received 67.5 Gy and 56.25 Gy in 25 fractions to PTV1 and PTV2 (seminal vesicles). In high risk patients with probability>15% of lymph nodes involvement, pelvic lymph nodes (PTV3) received 50 Gy. Acute and late toxicities were prospectively recorded using RTOG-EORTC scale and AUA score. Survival curves were calculated using the Kaplan-Meier method. Androgen suppressive therapy was prescribed based on risk categories.

Results. GI and GU G ≥ 3 acute toxicity were 0.7 % and 2.0 %, respectively. With a median follow-up of 30 months (range: 12-72), late GI ad GU toxicity were recorded in 4 and 18 pts, respectively. Based on IPSS score, no pts reported severe urinary symptoms, and 7.7% of pts reported moderate symptoms only. In terms of QoL, 91.3% declared to be "pleased", 5.7% "mostly satisfied" and 1.3% "mixed" (1.7% not evaluable).

Conclusions: Our experience confirms the safety of moderate hypofractionation delivered with IGRT/IMRT-SIB and a moderate impact on QoL in pts with PCa. Prolonged follow-up is needed to evaluate the results in terms of patients outcome.

P160

RETROSPECTIVE EVALUATION OF PROSTATE HYPOFRACTIONATED STEREOTACTIC ABLATIVE BODY RADIOTHERAPY

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Aims: External beam radiotherapy (EBRT) is a mainstay therapeutic option for prostate cancer and hypofractionated schedules are now proposed as a suitable approach. We tasted Cyberknife (CK) Stereotactic Body Radiotherapy Treatment (SBRT) in men with clinically localized prostate cancer.

Methods: From July 2007 through April 2015 a retrospective analysis was carried out on 199 consecutive patients (pts) with a median age of 74 years (range 52-86), mean prostate volume of 75.6 cc (range 37.03-163.16), and clinically localized prostate cancer. CK was used to deliver fiducials based image guided hypofractionated SBRT. The majority of pts 105 (53%) were low risk, 53 pts (27%) were intermediate risk and 41 pts (20%) were high risk (NCCN criteria). Pre-treatment PSA ranged from 1.51 to 51 ng.mL (median 7.4 ng.mL). 14 pts of 41 high risk received Androgen Deprivation Therapy (ADT), ADT was not administered to any low – intermediate risk patient. All pts were treated with 38 Gy in 4 fractions given daily. Heterogenous dose planning was

used, dose was normalized to the 80% isodose line in order for the prescription dose to cover at least 95% of Planning Target Volume (PTV). Real-time intrafractional motion tracking was used.

Results: With a median follow up of 54 months (range 12-106 months), the six years actuarial PSA relapse free survival rate is 95.6% (CI: 92.4%-98.8%) with 99% for low risk, 90.1% for intermediate risk and 85.8% for high risk. Overall 11 (6%) pts failed biochemical, occurring in 1 low-risk, 4 intermediate-risk and 6 high-risk pts. 23 pts (11%) died during follow up for unrelated causes, only one (0,6%) died for prostate cancer (bone metastases). The patterns of PSA response show a gradual decline with a PSA nadir below 1.0 ng.ml, 12 months after the treatment. Acute urinary symptoms were common with 44% of pts (87) experiencing grade I-II RTOG toxicity and only one patient (0,6%) experienced RTOG grade 3 acute urinary toxicity. In 17% of pts (33) RTOG late grade I-II urinary toxicity was observed, in 8 pts (4%) RTOG late grade 3 urinary toxicity was recorded. In one patient (0,6%) a grade 4 bladder fistula was observed. 0,6% of pts (1) experienced RTOG grade 3 acute and late gastro intestinal toxicity.

Conclusions: CK SBRT represents a non invasive method for the definitive treatment of localized prostate cancer with excellent biochemical control rates at up to 6 years and acceptable early and late toxicity.

P161

EMERGING ROLE OF STEREOTACTIC RADIOTHERAPY IN LYMPH NODAL OLIGORECURRENT PROSTATE CANCER, VERSION 2.0

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Aims: To update our results presented at the XXV AIRO congress concerning clinical outcome of stereotactic body radiotherapy (SBRT) for isolated prostate cancer lymph nodal (LN) recurrence.

Methods: Between 05/2012 and 09/2015, 95 patients (pts) (127 LN) were treated at our Institution. For primary treatment, radical prostatectomy (RRP) (±pelvic LN dissection ±radiotherapy (RT) ±androgen deprivation–AD-) and curative RT (cRT) (±AD) was performed in 74 and 21 pts, respectively. Median age, initial PSA (iPSA), pre-SBRT PSA and Gleason score (GS) were 70 years, 9.8ng/mL, 3.5ng/mL and 7, respectively. SBRT consisted in re-irradiation and first radiotherapy in 9 (10%) and 86 pts, respectively. Median dose was 24Gy/3 fractions. 70 pts were treated for single lymph node and 25 pts were treated for >1 lymph nodes concomitantly. Pelvic/extra-pelvic lymph nodes rate was 60%/40%. In 35 pts AD was added to SBRT (median duration 14.5 months). Toxicity was evaluated using Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) criteria.

Results: Median follow-up was 18.5 months. Acute toxicity included urinary (6, 1 G1 and G2 events, respectively) and rectal events (1 G1 event). Late toxicity included urinary events (2 and 3 G1 and G2 events, respectively). Biochemical response was observed in 64 out of 94 evaluable pts (68%). PSA stabilization and progression was seen in 10 (11%) and 20 (21%) pts, respectively. Clinical progression was observed in 41 pts (44%) after a median time of 15 months (range: 9-18) from SBRT. In-field progression was observed in 12 LN (9%) after a median time of 7 months (range: 4-22). All events of clinical failure were preceded by biochemical progression. 2-year local control and progression free survival rates (PFS) were 84% and 30%, respectively. Age>65years was correlated with better response rate. cRT and pre-SBRT PSA ≥4 ng/mL were correlated with lower response rate. Age>65years, concomitant AD administered up to 12 months and pelvic lymph nodes involvement were correlated with longer PFS. cRT and pre-SBRT PSA≥4 ng/mL showed worse PFS.

Conclusions: SBRT offers excellent in-field tumor control and low toxicity profile. Further investigation is warranted to identify the patients that benefit most from this treatment modality. The optimal combination with AD should also be defined.

P162

MODERATE HYPOFRACTIONATION ON EXTENDED FIELDS AND ANDROGEN DEPRIVATION IN HIGH/VERY HIGH RISK AND OLIGOMETASTATIC PROSTATE CANCER PATIENTS: FIVE YEARS EXPERIENCE BY TOMOTHERAPY

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Aims: to evaluate results of radical extended fields Radiotherapy (RT) with IMRT by Simultaneous Integrated Boost (SIB) technique and daily IGRT using Helical Tomotherapy, in patients with high/very high risk and oligometastatic prostate cancer.

Methods: Between November 2010 and November 2015, 126 patients with high/very high risk and oligometastatic prostate adenocarcinoma, were treated using IMRT-SIB-IGRT technique by Tomotherapy. The mean age was 69.7 years (range: 58-83). The mean iPSA was 27.6 ng/mL (range: 2.3 to 121). 123 patients received long term androgen deprivation therapy (ADT) for 2-3 years with LH-RH analogue. The staging examinations included: bone scan, multiparametric-MRI and choline-

PET, when indicated. The doses were: 75.2 Gy to the prostate volume (32 fractions of 2.35 Gy), 67.2 to 75.2 Gy to seminal vesicles (32 fractions from 2,1 to 2.35 Gy), 54.4 Gy to the pelvic lymph nodes + lumbar-aortic chain (32 fractions of 1.7 Gy), 60,8-66-70,4 Gy on PET/MRI positive nodes (32 fractions of 1, 9 to 2.2 Gy). All organs at risk (OsAR) were contoured and QUANTEC constraints were used for their evaluation. Toxicity was evaluated according to the RTOG-EORTC scale. Outcome was evaluated as biochemical control (defined according to Phoenix criteria).

Results: All patients completed treatment. All constraints for OsAR were met. Mean follow-up (FU) was 35 months (range: 3-60). Acute genitourinary (GU) toxicity>G3, assessed on all patients was 5%; acute gastrointestinal (GI) toxicity>G3 was 3%. Late toxicity was evaluated in 118 patients: the GI>G3 was 2.5% and the GU was observed only in 1 patient. At last FU biochemical disease free survival (bDFS) was 87%. One patient died due to tumor progression, 9% were alive with clinical progression of disease and 1 patient had biochemical recurrence.

Conclusions: This work show the feasibility in terms of patient compliance, acute and late toxicity, despite the moderate hypofractionation and large irradiated volumes. Our data are very promising in a group of patients whose prognosis in terms of bDFS ranges from 55% to 65% at 3 years and from 30% to 45% at 5 years.

Acknowledgments: work supported by 5 per mille 2008 Ministero della Salute-FPRC Onlus and 5 per Mille 2009 Ministero della Salute-FPRC Onlus grant and Eureka 2 protocol of the CHIC EU project grant.

P163

68GA-PSMA PET/CT–GUIDED STEREOTACTIC HYPOFRACTIONATION BODY RADIATION THERAPY (SBRT) IN PATIENTS WITH BIOCHEMICAL PROSTATE CANCER RECURRENCE AFTER PRIMARY TREATMENT

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Aims: Patients with oligometastatic disease can be treated with local therapy, i.e. either surgery or stereotatic body radiotherapy (SBRT). 68Ga-PSMA is a novel tracer which has shown to have higher sensibility and specificity, in terms of detection rate, than other tracers, i.e. choline tracer. Our aim is to investigate the role and impact of PET/CT 68Ga-PSMA for target volume selection and delineation in prostate oligometastatic patients with recurrent disease following salvage tailored SBRT.

Methods: Fifteen pts with oligometastatic recurrent prostate cancer and a number of active synchronous lesions ≤ 4 detected with 68Ga-PSMA PET/CT were treated either with three or five fraction Helical TomoTherapy SBRT. Doses ranged from 24 to 30 Gy in three to five fractions. CT scan and PET/CT PSMA were fused for target delineation. Ten pts received 3 fractions of 8 Gy (total dose 24 Gy) and five pts received 5 fraction of 6 Gy (total dose 30 Gy). Total dose was delivered to PET positive nodes, in respect of organ at risk constraints.

Results: A total of 36 secondary lesions were treated with SBRT. After a median follow-up of 10 months (range 2-12). Ten patients are still in the study and do not present biological or clinical failure or received systemic therapy. Five patients started systemic androgen deprivation therapy (ADT) or systemic chemotherapy. No CTCAE scale grade 2, 3 or 4 toxicity was recorded.

Conclusions: 68Ga-PSMA PET/CT-guided and integrated into the SBRT treatment planning process can be useful for detailed target volume planning. SBRT is very well tolerated and in our experience can be used to defer the beginning of systemic ADT in selected patients with oligometastatic prostate cancer. A prospective study is ongoing to assess impact of 68Ga-PSMA based treatment planning on outcome.

P164

USE OF PALLIATIVE RADIOTHERAPY FOR BONE METASTASES IN PROSTATE CANCER PATIENTS, PRE- AND POST- NEW ANDROGEN RECEPTOR PATHWAY INHIBITORS (ABIRATERONE / ENZALUTAMIDE): EXPERIENCE AT CAMPUS BIO-MEDICO UNIVERSITY

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Purpose: Bone is the third most common site of metastasis in cancer patients, and the first in prostate cancer. Radiotherapy has consolidated role in palliating painful un-complicated bone metastases. More recently, new androgen receptor pathway inhibitors, Abiraterone Acetate (AA) and Enzalutamide (ENZA) have shown a direct impact in bone metastases reducing skeletal events and the use of irradiation.

Materials and Methods: Between January 2013 and May 2016 595 patients with bone metastases were treated with radiotherapy at Radiation Oncology Department of Campus Bio-Medico University. Different fractions regimens were used according to patient's performance status and prognosis (poor risk short course; good risk long course RT). The short-course radiation treatment (1 to 3 fractions) has been reserved for highly painful patients with reduced life expectancy. Instead, the long- course radiation treatment (equal or more than 10 fractions) was carried out in pauci-symptomatic or oligo-metastatic patients. We compared RT treatment in patients with bone metastases from prostate cancer pre AA and ENZA (2013-2014) and post (2015-2016).

Results: Eighty-seven patients (14.6%) had bone lesions from prostate cancer. The rate of prostate cancer patients treated for bone metastasis has not changed along the analysed period ranging from 14 to 15 % (15% in 2013, 14% in 2014, 14.6% in 2015, 14.4% in 2016). In the first period 2013-14, patients were mostly treated with

short course RT (31 pts, 63.3%), than long-course (18 patients, 36.7%). Along 2015 and 2016 (up to May) the data conversed with more patients treated with long course RT (33 pts, 86.8%) instead of short course RT (5 pts, 13.2%).

Conclusions: In the last 2 years, we observed an increasing number of patients with bone metastases from prostate cancer receiving longer radiation treatment reflecting a change in general conditions and life expectancy. These data could be explained by the introduction of AA and ENZA in daily practice. This hypothesis generating data need further evaluation and inclusion of data from other centres.

P165

EXPERIENCE USING ABIRATERONE ACETATE IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

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Aims: The therapeutic management of men with metastatic castration-resistant prostate cancer (mCRPC) has been transformed in recent years. The introduction of a newer androgen receptor (AR) pathway inhibitors, Abiraterone Acetate (AA), has shown to prolong overall survival in both the pre- and post-docetaxel states. We report herein the efficacy and safety of AA in patients treated at two institution.

Methods: Patients with mCRPC were evaluated and treated in pre- and post-chemotherapy setting with AA. Toxicity, according to CTCAE vers. 4.02, with discontinuation due to adverse events, and time to treatment failure have been recorded. All patients were eligible to treatment without any major contraindication. Progression was assessed by means of radiographic, clinical and biochemical exams.

Results: From September 2013 to March 2016 a total of 33 men with metastatic CRPC received therapy with AA. Median age was 72 years. Metastatic sites at treatment beginning were recorded as follows: local (9%, n=3), nodal (15%, n=5), bone (40%, n=13), visceral (6%, n=2), combined (30%, n=10). 13 of these patients were metastatic at diagnosis while the remaining became metastatic after local therapy (prostatectomy 11 pts; and radiotherapy 9 pts). Treatment was discontinued for toxicity in 3 cases: 1 patient for grade 3 diarrhea. 1 patient for increasing in transaminases (G2) and the last one discontinued therapy recording both toxicities (diarrhea G3 and increase in transaminases G2). During therapy with AA 13 patients underwent to radiotherapy, 7 for bone pain and 6 to oligo-metastatic sites. No toxicity was recorded in the combination of both treatment.

Conclusions: Few patients discontinued treatment due to toxicity, and RT could be safely administered during AA.

P166

STEREOTACTIC BODY RADIATION THERAPY INTERMEDIATE/HIGH RISK PROSTATE CANCER: PRELIMINARY ANALYSIS OF ACUTE RADIATION-INDUCED TOXICITIES

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Aims: A Stereotactic Body Radiation Therapy (SBRT) protocol for the treatment of intermediate/high risk prostate cancer is active at the National Cancer Institute. Aim of this analysis is a preliminary evaluation of acute urinary and gastrointestinal (GI)toxicities.

Methods: Intermediate/high risk prostate cancer patients are selected using D'Amico classifier, patients (pts) needing pelvic irradiation are selected. Baseline International Prostate Symptom Score (IPSS) >15 was established as an exclusion criterion. SBRT is performed with Volumetric Modulated Arc Therapy (VMAT). Boost irradiation of the prostate gland (PG) up to 18 Gy (9Gy/fr, once/week) is followed by pelvic irradiation (50Gy, 2Gy/fr).

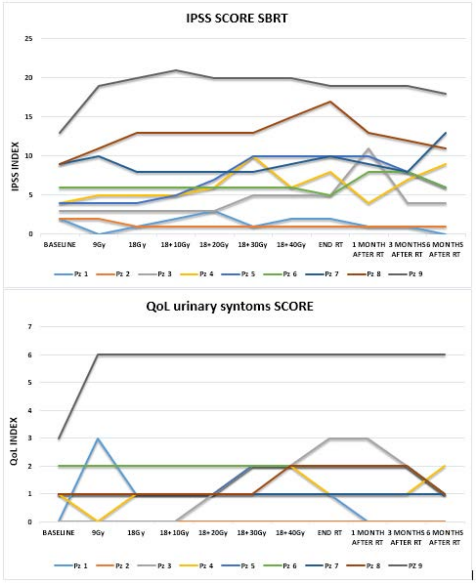

Figure 1.

Contouring of the Clinical Target Volume is based on multi-parametric MRI. The Planning Target Volume for SBRT is defined as the PG plus a 2 mm margin in all directions. A urethral catheter is used to identify the urethra and to keep the bladder filling at a costant volume of 150cc. Imaged Guided RT is performed either by

means of 3 Vigeo Biomarc Gold marker® visualized by kV-cone beam CT or by 3 Calypso® trasponders. All pts are proposed neoadjuvant/adjuvant hormone therapy till 2 years after the end of RT. Urinary and GI toxicity are recorded according to the RTOG scale, at baseline, after each session of SBRT weekly during pelvic irradiation, 3, 6 and 12 months after RT end. Patient reported outcomes are also considered with the same timing: IPSS and the AIROPROS01-02 questionnaire for GI symptoms.

Results: Nine pts were enrolled, all in high-risk class: clinical stage T1c-T4, PSA range 4.89-253 ng/mL, Gleason Pattern Score 7-10. All pts were cN0 and cM0. 4/9 pts(44%) reported acute grade 1 GI toxicity, no grade 2 GI toxicity was scored. 4/9 pts(44%) showed grade 1 acute urinary toxicity and 1 pt (11%) was scored as grade 2. 5/9 pts (55%) reported increase in IPSS during RT. 3/9 pts (33%) reported increased IPSS of at least 5 points at 6 months after RT. Impairment of perceived urinary quality of life (QoL, as measured by question 8 of IPSS) at 6 months was reported by 2 patients, with the patients showing grade 2 urinary toxicity having the highest IPSS at baseline, and the highest IPSS / IPSS increase/worst urinary QoL during the whole follow-up. Detailed results on IPSS and urinary QoL are reported in Figure 1.

Conclusions: This preliminary mono-Institutional analysis indicate good tolerance to an SBRT protocol including both pelvic irradiation an boost to the PG.

P167

LOW-RISK PROSTATE CANCER PATIENTS TREATED WITH IMAGE GUIDED (IGRT) HYPOFRACTIONATED RADIOTHERAPY: RESULTS OF ACUTE AND LATE TOXICITY

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Aims: To evaluate efficacy and toxicity of image-guided hypofractionated radiotherapy (HFRT) in patient with low-risk prostate cancer treated in our institution.

Methods: Between March 2007 and November 2015, 85 patients with biopsy proven low-risk prostate cancer were treated with HFRT associated with IGRT. Median age at diagnosis was 72 years (range 48-82 years). All patients presented cT1/T2a-b N0 M0 clinical stage, a Gleason score of 6 (3+3), and a pretreatment prostate-specific antigen (PSA) serum level <10 ng/mL. All patients performed a simulation CT scan with 2,5 mm slice thickness to execute 3D conformal planning. MRI was used to better delineate the CTV when available. All patients were treated with a total dose of 60 Gy in 20 fractions, 5 times a week, on prostate and the proximal seminal vescicles. Margin from CTV to PTV was 5 mm in all directions. During treatment patients underwent daily cone-beam CT (IGRT). Acute side effects were evaluated according to the RTOG/EORTC late morbidity Scoring Scale.

Results: Median follow-up was 44 months (range 3-108 months) (95% I.C. 36.94-51.02). The actuarial 5-year OS was 96.7% (median not reached). Two deaths occurred for other disorders without any evidence of disease. 5-year CSS was 100% (median not reached), 5-year BRFS was 98.6% (one patient developed biochemical recurrence), 5-year LRFS was 100%. The acute toxicities during the treatment were: grade 1-2 gastrointestinal (GI) toxicity in 13 patients (15.3%), grade 1-2 genitourinary (GU) toxicity in 31 patients (36.5%); grade 3 GU toxicity in 2 patients (2.4%). The toxicities 3 month after the end of the treatment were grade 1-2 GI in 4 patients (4.7%), grade 1-2 GU in 24 patients (28.2%). The toxicities 6 months after the end of the treatment were grade 1-2 GI in 3 patient (4.1%), grade 1-2 GU in 19 patients (26.4%). The cumulative late toxicities observed during follow-up were: grade 1 GI in 2 patients (2.9%), grade 1 GU in 24 patients (34.3%). At the last follow-up grade 1 GI and GU toxicities were observed in 3 (3.5%) and 9 (10.6%) patients respectively. Median of PSA value at diagnosis was 3.27 ng/mL (range 1.69-9.98 ng/mL), at first follow-up was 0.65 ng/mL (range 0.65-10.14 ng/mL) and at the last follow-up was 0.39 ng/mL (range 0.01-2.26 ng/mL).

Conclusions: This study showed that the hypofractionated image-guided radiation therapy in low-risk prostate cancer patients is efficacy and well tolerated with a low rate of high grade toxicity.

P168

TREATMENT PLAN PARAMETERS IN MODERATE HYPOFRACTIONATED RADIOTHERAPY FOR PROSTATE CARCINOMA

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Aims: To evaluate the effect of treatment plan parameters on Volumetric Modulated Arc Therapy (VMAT) target coverage in prostate postoperative hypofractionated radiotherapy (RT).

Methods: From April 2011 to January 2016, 225 patients (pts) with median age 68y (range 48-83) who underwent radical prostatectomy were treated with postoperative hypofractionated radiotherapy at the Pisa University Hospital. According to the treatment objective, all patients were treated with 28 daily fractions of 225cGy, 230cGy or 235cGy . In 146 pts, RT was delivered to prostatic bed with a single arc of gantry rotation (Group1), in 31 pts RT was delivered to prostatic bed but using 2 rotation arcs (Group2), finally 48 pts received prostatic bed and pelvic irradiation using 2 arcs (Group3). VMAT treatment, planned with Varian Eclipse, was delivered to all pts. Statistical analyses, referred to the prostatic bed Planning Target Volume (PTV), were performed using maximum and mean dose (Dmax, Dmean), prostatic bed volume, conformity index (CI), homogeneity

index (HI=Dmax/prescription dose), percentage of PTV receiving 99%, 98% and 95% of prescription dose (D99, D98, D95, respectively). All parameters were compared in the 3 Groups of pts using Mann-Whitney test (by means of IBM SPSS Statistics). We considered correlations significant when $p<0.05$.

Results: Number of arcs and inclusion of pelvic RT significantly related with D99, D98, D95, CI, HI, Dmax and Dmean. In particular, when comparing Group1 with Group2, we observed no difference in terms of D99, D98, D95, Dmean and CI, while Dmax and HI were significantly better in the 2 arcs plans (both with $p<0.0001$). Group1 showed significantly better values for all parameter (D99,D98,D95,Dmax,Dmean,CI,HI) than Group3. Comparing the plans of Group2 and Group3 we found no difference in D99 and Dmean, on the other hand D98, D95, Dmax, CI and HI were better in the plans without pelvic irradiation (ranging from $p<0.048$ to $p<0.002$).

Conclusions: Our data suggest that, when delivering VMAT hypofractionated radiotherapy on the prostatic bed alone, the number of arcs used (1 or 2) has no influence on the coverage of the target, but using 2 arcs may led to a lower Dmax and more homogeneous dose. When delivering RT to prostate bed and pelvic lymphnodes, the prostatic bed may receive a less conformed and homogeneous dose, but the use of 2 arcs could help in obtaining better Dmean and D99. Larger cohorts of data are needed to confirm these results.

P169

LATE TOXICITY OF IMAGE-GUIDED HYPOFRACTIONATED RADIOTHERAPY FOR PROSTATE CANCER: NON RANDOMIZED COMPARISON WITH CONVENTIONAL FRACTIONATION

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Aims: Recent improvement in understanding biology of prostate cancer (high sensitivity to high dose per fraction) and the availability of high precision radiotherapy (image guided radiotherapy, IGRT) allowed for introduction of hypofractionated schedules. The aim of the study is to present the incidence and the predictors for late toxicity comparing the hypofractionated radiotherapy (hypo-IGRT) with conventional fractionation without image guidance (non-IGRT); secondarily to evaluate the tumor control in the two cohorts of patients.

Methods: 179 cT1-T2N0M0 prostate cancer patients were treated within the prospective study with 70.2Gy/26 fractions (equivalent to 84Gy/42 fractions, alpha/beta 1.5 Gy) using IGRT. Their prospectively collected data were compared with data of 174 cT1-3N0M0 patients treated to 80Gy/40 fractions with non-IGRT. Multivariate analysis was performed to define the tumor-, patient- and treatment-related predictors for late toxicity. The recurrence-free survival and overall survival were analyzed for both groups at 5 and 10 years.

Results: Adverse rectal and urinary late toxicity were registered for all but 4 patients. Mainly limited late toxicity was observed: in the hypo-IGRT group included rectal (G1: 22.3%; G2: 8.6%; G3: 6.3%) and urinary events (G1: 34.3%; G2: 21.7%; G3: 3.3%; G4: 1.1%). Late toxicity in the non-IGRT patients included rectal (G1: 12.6%; G2: 5.2%; G3: 2.3%; G4: 1.1%) and urinary events (G1: 29.9%; G2: 8.6%; G3: 0%; G4: 2%). 5 year and 10 year recurrence-free survival in the hypo-IGRT group were 87.7% and 87% vs 80.4% and 55.7% in the non-IGRT. In the recurrences sub-analyses of the hypo-IGRT group were 11.7% of biochemical and 6.7% of clinical failures (local 3.9%, regional 3.9%, and distant 2.2%). The recurrences in the non-IGRT group were biochemical in 31.6% of cases and clinical recurrences in 26.4% of cases (local: 14.4%, regional: 14.4%; distant: 10.9%). The five year and 10 year overall survival were 89.8% and 82.1% in the hypo-IGRT group and 92.2% and 78.6% in the non-IGRT group respectively. Multivariate analysis showed that only hypo-IGRT is correlated with higher late urinary and rectal toxicity.

Conclusions: An increase in late urinary and rectal adverse events but with a significant advantage in local control in the hypo-IGRT patients was observed. Further investigation is warranted in order to exclude the bias due to non-randomized character of the study.

P170

DEGARELIX VS BICALUTAMIDE AS NEOADJUVANT ANDROGEN DEPRIVATION THERAPY FOR PROSTATE VOLUME REDUCTION IN MEN AFFECTED BY PROSTATE CANCER CANDIDATE FOR BRACHYTHERAPY TREATMENT

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Aims: Prostate cancer (PCa) is the most common malignancy in men. Brachytherapy (BRT) is a valid treatment option for low and favorable intermediate risk PCa. However, a gland size >50 cm^3 at time of implantation is an important relative contraindication. In low and favorable intermediate risk patients, androgen deprivation therapy (ADT) is administered before BRT to obtain a volume reduction (VR), but in the latter group it is also used after BRT for its cytotoxic properties. In this study we compared the efficacy in VR of the widely used ADT bicalutamide vs degarelix, a PCa treatment recently approved by EMA.

Materials and Methods: We carried out a retrospective non-randomized study in 20 PCa patients enrolled from January 2015 to May 2016 at the Urology Unit, Brotzu

Hospital, Cagliari. Nine patients TNM category T2aN0M0, Gleason score (GS) 6 (3+3), PSA <10 ng/mL were classified as low risk PCa, 11 patients T2a-T2cN0M0, GS 7 (3+4), PSA 10-20 ng/mL were classified as favorable intermediate risk. Mean age at diagnosis was 67. Total prostate volume (TPV) was assessed by pelvic ultrasound at the first examination. All patients received ADT (10 received degarelix 240/80 mg monthly, 10 bicalutamide 150 mg daily) for three months before BRT and VR was evaluated one week before the procedure. Patients were treated with transperineal ultrasound-based 125-I seeds permanent implantation using an intraoperative 3D conformal treatment planning system. Prescription dose (PD) to cover the target volume (TV, prostate) was 160Gy. Dosimetry implantation parameters for the TV were D90 (dose to 90% of the prostate gland), V100 and V150 (percentage of TV receiving 100% and 150% of the PD, respectively); dose constraints for the organs at risk (OAR) urethra and rectum were based on primary (D2cc and D10 respectively) and secondary (D0.1cc and D30 respectively) parameters.

Results: The PV significantly decreased after three-months ADT treatment, showing a mean percentage reduction of 38,55% +/- 14,54 SD for bicalutamide and 42,64% +/- 8,51 SD for degarelix. Prostate VR (PVR) was more homogeneous in the degarelix group (Fig1). All patients underwent BRT treatment achieving an excellent intraoperative coverage dose of the TV according to constraints dose for OAR.

Conclusions: Degarelix shows non-inferiority to bicalutamide in terms of PVR. The added benefit of degarelix compared to bicalutamide is the monthly administration as a single dose with better patient compliance.

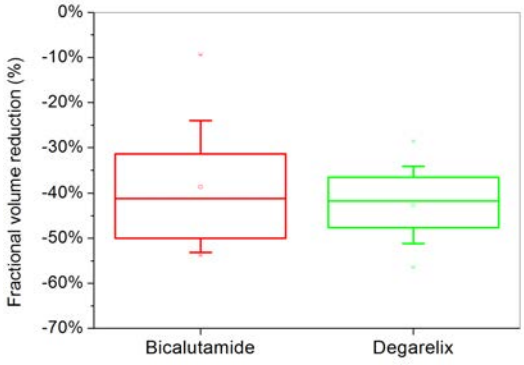

Figure 1.

P171

PROSTATE CANCER (PC) HYPOFRACTIONATION: OUR EXPERIENCE WITH STEREOTACTIC BODY RADIOTHERAPY (SBRT)

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Aims: Pc is the main tumour in men over 50 years (yr). PSA screening has a great role in early detection and mortality decline. Several studies demonstrated a low / ratio for PC, suggesting sensitivity to high dose per fraction schedule, known as hypofractionation. SBRT is a hypofractionated treatment using small and tight margin, with good dose escalation that spare normal tissues and advantageous over traditional techniques. Our purpose is to evaluate the efficacy, feasibility and toxicity of SBRT for PC and possible differences between two alternative schedules: once or twice a week treatments.

Methods: A retrospective study was conducted from July 2014 to June 2016, a total of 20 patients (pts), with low-intermediate risk, was selected. SBRT fractionation was 7 Gy x 5 fr. Failure was assessed using Phoenix definition, toxicity according to CTCAE ver.: 4.0.

Results: The mean follow-up is 13.3 (5-21) months. All pts present a localized disease (T1c-T2cN0M0), with cardiovascular disease or other conditions that contraindicated surgery. Mean age was:70.5 yr (60-81), mean Gleason Score: 6.2 (5-7) and mean PSA:11.5 ng/mL (1.95-20). Nobody has experienced grade 3 or greater toxicity. Acute genitourinary (GU) toxicity of Grade 1 and 2 was found respectively in 6 (30%) and 2 cases (10%); acute gastrointestinal (GI) toxicity of Grade 1 and 2 was found respectively in 3 (30%) and 2 (10%) pts. For chronic toxicity 4 pts (20%) developed GI symptoms with rectal bleeding, negative to colonscopy for tumor, and of this pts, 3 (15%) developed GU toxicity too. Sexual activity was not evaluated. Nobody had PSA failure. Interestingly 15 pts (75%) reported, 30-45 days after SBRT, healing from obstructive symptoms, improvement in urinary function and resolution of nicturia and pollakiuria. The remaining 5 pts (25%) had no benefits but comorbidity, like diabetes or cardiac failure, represent a confounder factors about urinary homeostasis that preclude a definitive answer on real benefits

Conclusions: Our results show that SBRT for localized PC is effective and well tolerated. The lack of PSA failure is a good compromise compared to late GI toxicities, characterized by mild bleeding. Interestingly 75% of pts had a complete resolution of pre-existing urinary symptoms. Of note 3 of the 4 pts who developed chronic toxicities have been treated with twice per week fractionation. Prospective randomized trial with much more pts are necessary to find the better weekly fractionation.

P172

BREATHING-INDUCED PROSTATE MOTION DURING RADIOTHERAPY SESSIONS: AN ACCURATE QUANTIFICATION

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Aims: Intra-session prostate motion during radiotherapy (RT) can negatively affect treatment efficacy and should be carefully evaluated. An electromagnetic system able to localize three transponders permanently implanted in the prostate with sub-millimeter accuracy is currently used at the Fondazione IRCCS Istituto Nazionale dei Tumori for real-time tracking of the tumor. A software was previously developed and validated to filter the signal produced by the transponders. Aim of this study was to apply the software for the quantification of the intra-session prostate motion induced only by patient's breathing.

Methods: Based on a patient-specific analysis of the recorded tracks, the software automatically isolates their main components, i.e. the low frequency motion (long term motion due to physiological movements) and the high frequency harmonic motion (breathing-induced motion). The tracks of 15 patients (pts) who underwent external beam RT in supine position were analyzed for a total of 506 treatment sessions. 35 tracks of a pt treated in prone position were also analyzed. For each session, the amplitude of the breathing-induced prostate motion (BIPM) along the three main directions (L-R, C-C, A-P) was obtained. Average amplitudes, standard deviations and overall amplitude ranges were reported.

Results: The amplitude of the BIPM, averaged over all treatment sessions of the supine pts, resulted 0.23±0.06 mm, 0.45±0.09 mm, and 0.35±0.08 mm for L-R, C-C and A-P directions, respectively (ranges: 0.10÷0.50 mm, 0.21÷0.74 mm and 0.17÷0.62 mm). For the prone pt, the average amplitude resulted 0.26±0.08 mm, 0.75±0.09 mm, and 1.14±0.11 mm for L-R, C-C and A-P directions, respectively (ranges: 0.04÷0.53 mm, 0.49÷1.31 mm and 0.75÷1.78 mm). In general, a very limited intra-pt variation over all treatment sessions was observed for the maximum amplitude of the BIPM, showing that pts tend to behave in the same way over all treatment sessions.

Conclusions: The developed software was able to accurate quantify the intra-session BIPM. The results show that this motion represents a negligible source of intra-session localization uncertainty for pts treated in supine position. On the contrary, the preliminary results for the prone pt show that BIPM can rise almost to 2 mm in A-P direction, suggesting that this setup deserves particular attention in terms of prostate motion management, especially for hypofractionated treatments.

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P173

MODERATE HYPOFRACTIONATION RADIOTHERAPY IN PROSTATE CANCER PATIENTS

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Aims: Analyze retrospectively a cohort of intermediate prostate cancer patients treated with moderate hypofractionated radiotherapy evaluating the clinical efficacy and toxicity profile.

Methods: Prostate intermediate cancer patients received an hypofractionated schedule (61.1 Gy to prostate gland and seminal vesicles and 70.2 Gy to the only prostate gland with a simultaneous concomitant boost in 26 fractions). Two type of Image Guided Radiotherapy (IGRT) was used, Cone Beam Computed Tomography (CBCT) or Clarity transabdominal ultrasound system. The Clarity system is made of two platforms, in CT and treatment room. After CT scan, a free hand axial sweep is acquired. During each treatment session, a free-hand axial sweep is acquired and treatment Positioning Reference Volume (PRV) is aligned with the reference PRV. When the alignment is ideal, the system take into account for final displacements.

Results: A total of 241 patients were treated between January 2009 and December 2015 with a hypofractionated schedule (70.2 Gy/26 fractions) under CBCT (15.8%) guidance or 3DUS guidance with the Clarity platform (84.2%). Median follow up was 42 months. Nineteen patients experienced biochemical failure. Among them, 5 patients went into distant spread with bone lesions, 6 patients with lymphnode disease and 2 patients had a local relapse. Only 3 patients died of disease, while other 10 died of other cause. Biochemical relapse free survival, cancer specific and overall survival were 99.4 (CI: 96-99.9%), 99,8% (CI: 97,6-100%) and 97,8% (CI: 94,2-99,2%) at 36 months, respectively. Acute and late rates toxicities ≥G2 were 22% and 4.1 for genitourinary, while 7.3% and 4.9% for gastrointestinal, respectively.

Conclusions: Three-dimensional ultrasound-based image-guided hypofractionated radiotherapy resulted in being robust and reliable and provides excellent imaging of prostate gland. For patients with a poor prostate ultrasound visualization, CBCT is a valid IGRT system. EBRT delivered employing a hypofractionated schedule under 3DUS based image guidance or under CBCT is a safe and effective treatment with optimal biochemical control and a good toxicity profile. Nowadays we are working with Autoscan probe to evaluate also intra-fraction motion for severe hypofractionation.

P174

EVALUATION OF AN AUTOMATED PLANNING ALGORITHM IN PROSTATE CANCER PATIENTS TREATED WITH MODERATELY HYPOFRACTIONATED RADIOTHERAPY

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Background: Pinnacle Auto-Planning (AP) is a fully automated treatment planning system (TPS) which employs an iterative algorithm to reach and potentially surpass user defined clinical goals. We compared automatically generated plans with historical plans in a cohort of prostate cancer patients.

Table 1.

	PTV Evaluation	
	Historical	Auto-planning
Target Coverage*	99,28	98,68
Homogeneity index**	1,037	1,049

**Volume enclosed by the 95% isodose line. ** The ratio between the dose covering 5% of PTV volume to the dose covering 95% of the PTV volume.*

	Organs At Risk	
	Historical (average cc.)	Auto-planning (average cc.)
Rectum V70	5,26	2,19
Rectum V60	20,79	17,38
Rectum V40	42,29	41,77
Rectum mean dose	34,69	33,03
Bladder V70	5,6	5,23
Bladder V60	19,88	14,88
Bladder V40	34,47	29,47
Bladder mean dose	29,62	24,5
Penile bulb mean dose	19,46	12,87
Femoral heads V30	26,38	8,86

Methods: Twelve consecutive patients treated with volumetric modulated arc therapy for prostate cancer were replanned with AP version 9.10. Plans optimized with Auto-Planning utilize a single model where clinical objectives and priorities for planning target volumes (PTV) and organs at risk (OAR) are defined. In addition to priority, there is a compromise setting which allow for individual OAR priority over targets (es. spinal cord over target). Advanced settings allow the user to set global parameters such as dose fall-off, maximum dose and cold spot management. The dose to PTV, OAR and the effective working time for planning were evaluated in this study. Target coverage was defined as the volume enclosed by the 95% isodose line and the dose homogeneity index (HI) as the ratio between the dose covering 5% of PTV volume to the dose covering 95% of the PTV volume.

Results: The V70, V60, V40 doses and mean doses to rectum, bladder, penile bulb and femoral heads were significantly reduced with AP. In particular, the volume of rectum that received 70Gy were on average 2.19cc. and 5.26cc. in the AP group and historical group respectively The target coverage and HI were on average 98.68 and 1.049 in the AP group and 99.28 and 1.037 in the historical group. The better OAR saving was obtained with little worsening of target coverage and homogeneity. The average effective working time was 10 min in the AP group in comparison to approximately 48 min. in the historical group.

Conclusions: Despite the low number of patients considered in this study, the evaluated automated planning algorithm showed a better OAR saving with similar target coverage in comparison to historical plans. Although it is unknown if these little differences observed are clinically relevant, the effective working time was substantially reduced with Auto-Planning.

P175

LATE TOXICITY AND QUALITY OF LIFE AFTER HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY AS A MONOTHERAPY FOR LOCALIZED PROSTATE CANCER

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Aims: Several randomized trial support the use of higher doses of radiation in the treatment of prostate cancer. However the majority of these studies also demonstrated increased risk of acute and late morbidity . We report prospectively collected toxicity data from a cohort of localized prostate cancer patients treated with Cyberknife (CK) Stereotactic Body Radiation Therapy (SBRT).

Methods: Between July 2007 to April 2011 a retrospective analysis was carried out on 83 consecutive patients with a median age of 74 years (range 60 – 85), mean prostate volume of 67.7 cc (range 37.03 -163.16), and clinically localized prostate cancer treated with CK stereotactic radiosurgery. The majority of patients 39 (47%) were low risk , 27 pts (33%) were intermediate risk and 17 pts (20%) were high risk using the NCCN criteria . Pre-treatment PSA ranged from 1.75 to 51 ng/mL (median 7.6 ngml). 49% of patients had moderate to severe lower urinary tract symptom prior to treatment (baseline AUA>8). The course of radiotherapy consisted of 38 Gy over four fraction given daily to the PTV, which was defined as the prostate (plus seminal vesicles in high risk patients). Real-time intrafractional motion tracking was used. RTOG toxicity grades were assigned for genitourinary (GU) and gastrointestinal (GI)

Results: In total 11 patients died during follow up for unrelated causes. Data to assess GI and GU Toxicity were available for 72 patients with a median follow up of 79 months (range 61-106). Acute urinary symptoms (frequency, dysuria, urgency, hesitancy and nicturia) were common with 57 % of patients experiencing grade I-II

RTOG acute urinary toxicity. No patients experienced RTOG grade 3 acute urinary toxicity, in 4 patients (6%) we recorded RTOG grade 3 late urinary toxicity, in two of them urethral dilatation was required for bulbar urethral stricture. In one patient a grade 4 bladder fistula was observed. No RTOG grade 3 acute and late rectal toxicity was observed. The median time from CK radiotherapy completion to the occurrence of late grade 3-4 GU toxicity was 29 months (range 18-45).

Conclusions: Significant long term toxicities are rare when CK stereotactic Hypofractionated radiotherapy is performed as monotherapy: this probably reflects the ability for current technology to minimize adverse effects of therapy.

P176

PROSTATE RADIOTHERAPY IN OLIGOMETASTATIC PROSTATE CANCER: A SINGLE-CENTER EXPERIENCE OF 17 PATIENTS

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Aims: The current standard of care for patients affected by metastatic prostate cancer (mPCa) at diagnosis is androgen deprivation therapy (ADT) with or without anti-androgen and chemotherapy. Although in other metastatic malignancies the reduction of primary tumor burden is associated with improvement in outcome, the role of local therapy on the prostate in mPCa men remains unclear. The purpose of the study is to evaluate if radiotherapy (RT) on primary improves biochemical control and long-term survival, in order to postpone the need of new systemic therapy.

Methods: We retrospectively reviewed data of patients with prostate adenocarcinoma and bone oligometastases at diagnosis (1Mb according to AJCC TNM stage) treated in our Institution with ADT followed by RT on prostate with or without palliative RT on metastases. Biochemical response, biochemical and clinical failure, overall survival (OS) and RT-toxicity were assessed. All patients were discussed on the multidisciplinary basis.

Results: We identified 17 patients treated with ADT (started at the diagnosis) and external-beam RT on the primary between 6/2008 and 11/2015. All of them were treated also on bone metastases. RT on primary was started after 8.5 months (3.2-52.1) from ADT. RT on prostate was performed with moderately and extremely hypofractionated regimes using image guided intensity- modulated radiotherapy (IMRT), employing 2 systems: image-guide Volumetric Modulated Arc Therapy (Rapid-Arc®, Varian Medical System) and image-guided Static Step and Shoot IMRT by Vero® (BrainLab, D/MHI Japan). After a median follow-up of 27.6 months (6.1-32), 15 patients are alive. Biochemical response was observed in 9 patients. 8 men showed biochemical failure after a median of 21.1 months (14.5-60.9) from the start of ADT, radiological failure was documented after 21.7 months (15.3-75.8). 2 patients developed an in-filed recurrence, 6 both in-field and out-field recurrence. 3-years OS was 83.3%. According to RTOG/EORTC, only one patient developed acute Grade 3 genitourinary toxicity. No late Grade>2 adverse events were observed.

Conclusions: RT on prostate in the presence of bone oligometastases is safe. If compared to historical series (ADT alone), RT on primary seems to improve biochemical control and long-term survival, however this hypothesis should be investigated in prospective studies. Further research is also warranted in order to identify the patients that benefit most from such approach.

P177

CLINICAL COMPARISON OF THREE DIFFERENT SCHEDULES OF RADIOTHERAPY IN LOW/INTERMEDIATE PROSTATE CANCER

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Aims: Here, we examine whether patients experience differences in acute gastrointestinal and genitourinary adverse effects considering conventionally fractionated radiotherapy in 37 fractions (fx) in 3D conformal radiotherapy(3DCRT), hypofractionated radiotherapy with 30 fractions using VMAT, hypofractionated radiotherapy in 5 fractions using CyberKnife® system (CK).

Methods: Clinical data of 23 patients, affected by low/intermediate risk prostatic carcinoma had been collected. All patients were treated with exclusive RT on prostate and seminal vescicles. 10 3DCRT patients were treated with 74 Gy in 37 fractions (2 Gy/fx), 7 CK patients with 35-36,25 Gy in 7 fractions (7-7,25 Gy/fx) and 6 VMAT patients with 72 Gy in 30 fractions (2.4 Gy/fx). It was evaluated acute gastrointestinal and genitourinary toxicity using RTOG scale and the PSA level in the three different treatment types.

Results: The patients mean age was 71,5 years old. Five 3DCRT patients and five VMAT patients received hormonal therapy before RT in order to reduce prostatic gland volume, and only 2 patients underwent TURP. No patients interrupted the treatment due any toxicity. Regarding the acute toxicity it had been reported: the gastrointestinal toxicity was in the 3DCRT group 2 G2 and 1 G1 cases, in the VMAT group 1 G2 case and in the CK group 1 G1 case; the genitourinary toxicity was in the 3DCRT group 4 G1 and 4 G2 cases, none in the VMAT group and in the CK group 3 G1 cases. We also monitored the PSA level variation in the three groups and we saw that in the 3DCRT and CK group the level drop from the start to 6 months after the treatment was statistically

significant with a P<0.01 (P=0.007 and P=0.004), while the value drop in the third group was not significant.

Conclusions: In our experience hypofractioned regimens seem to be safe and reliable in the low/intermediate risk prostate cancer. The better results in 3DCRT group were influenced by hormonal treatment. More patients for each group and longer follow up are necessary in order to evaluate the differences between these different type of RT treatment.

Table 1.

TYPE OF TREATMENT		3DCRT	VMAT	CK
mean age		69,8	70,8	76,3
Hormonal therapy		5	5	0
total dose		74	72	35
number of fractions		37	30	5
Gy/fx		2	2,4	7
BED1,5		172,67	187,2	151,67
Mean CTV (cc)		50,75	53,87	75,36
Mean GTV (cc)		93,32	87,71	132,71
acute genitourinary toxicity	G0	2	0	4
	G1	4	0	3
	G2	4	0	0
	G3	0	0	0
acute gastrointestinal toxicity	G0	7	0	0
	G1	1	0	1
	G2	2	1	0
	G3	0	0	0
Mean PSA	therapy starting	6,409	4,63	10,11
	3 months FU	0,58	3,57	2,42
	6 months FU	0,49	0,45	2,26
	9 monts FU	ND	ND	2,41

P178

STEREOTACTIC RADIOTHERAPY WITH CYBERKNIFE® SYSTEM IN LOCALIZED PROSTATE CANCER: A MONOISTITUTIONAL EXPERIENCE

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Aims: Hypofractionated stereotactic radiotherapy (SRT) is an emerging technique in the treatment of localized prostate carcinoma (LPC). Considering that / ratio prostate cancer is very low (1.5), SRT is advantageous because consent to deliver higher dose/fraction on target respect conventional radiotherapy. In this study we reported our initial experience with SRT using CyberKnife® System (CK) in the treatment of LPC.

Methods: From February 2013 to April 2016 ninety-six patients with LPC, mean age 70,6 years, were treated with CK-SRT. All patients were submitted to the eco-guided implants of 4 intraprostatic fiducial markers 7-10 days before the SRT in order to follow, to detect and to correct the intrafraction target movements. The fusion between CT scan and basal RM was made in order to optimize the contouring for treatment planning. All patients were treated with SRT in 5 fractions of 7-7,25 Gy/fraction for a total dose of 35-36,25 Gy. It was evaluated acute and late gastrointestinal and genitourinary toxicity using RTOG scale, biochemical control using mean decrease of PSA level during the different phases of follow up. In this study we have analyzed the results in the 77 patients with almost 3 months of follow up.

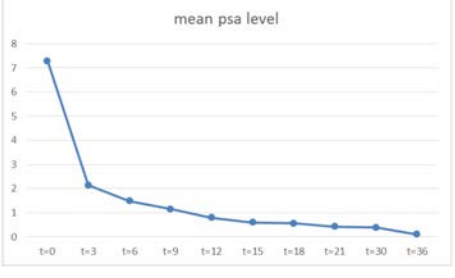
Results: All patients have completed CK SRT without severe complication. Median follow up was 17 months. Three patients died for non related cancer causes. Gastrointestinal acute toxicity G2 for perineal pain and rectal tenesmus was reported in only 13% and was decreased in all patients. Genitourinary acute toxicity G2 for urgency and nicturia was reported in only 4% and G1 for dysuria in 61% of cases which persist in 27,3% of patients. (Table 1). All patients obtained biochemical response with decrease of PSA. The PSA drop between the start of the therapy and at 21 months of follow up, was significant with p<0,01 (p=0,00001).

Conclusions: In our experience CK-SRT seem to be safe and reliable in the LPC. No severe toxicities were reported and the patients were very compliant. Careful patient selection is critical to achieve maximum effectiveness by CK SRT. More patients and longer follow up are necessary in order to evaluate the real advantage of SRT respect to standard fractionation in terms of overall survival, biochemical free survival and late toxicity.

Table 1.

	low risk		intermediate risk	
pts n (%)	40 (52%)		37 (48%)	
HT	9 (11,5%)		11 (14%)	
follow up pts n (%)	3 months	6 months	12months	18 months
	77 (100%)	64 (83%)	50 (65%)	36 (46,7%)
	24 months	30 months	36 months	NCRD
	20 (26%)	9 (11,7%)	4 (5,2%)	3 (3,9%)
acute tox	G0	G1	G2	G3
GI	57 (74%)	10 (13%)	10 (13%)	0
GU	26 (33,8%)	47 (61%)	4 (5,2%)	0
late tox	G0	G1	G2	G3
GI	71 (92,2%)	4 (5,2%)	1 (1,3%)	0
GU	56 (72,8%)	21 (27,2%)	0	0
mean PSA	pre SRT	3 months	6 months	12months
	7,28	2,31	1,48	0,79
	18 months	24 months	30 months	36 months
	0,55	0,4	0,38	0,4

HT hormonal therpy; NCRD non cancer releted death
GI gastrointestinal toxicity; GU genitourinary toxicity



P179

ADJUVANT OR SALVAGE MODERATELY HYPO-FRACTIONATED RADIOTHERAPY IN PROSTATE CANCER: RETROSPECTIVE ANALYSIS

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Aims: We analyzed retrospectively tolerance of a moderately hypofractionated radiotherapy (RT) in salvage or adjuvant setting in patients affected by prostate cancer treated in our Institute.

Methods: Between September 2011 and May 2016, 93 patients have been treated in our Institute after prostatectomy (61 were treated with IMRT and 32 with 3D- CRT). Seventy patients(75.2%) were treated in adjuvant setting, 23(24.8%), received a salvage treatment. Twenty-five patients(26.9%) received elective nodal irradiation(ENI) with IMRT tecnique. Fifty patients received prostate bed conventionally fractioned radiotherapy (CFR); 43 were treated with a moderately hypofractioned scheme (2.3 Gy/fraction). Total doses ranges were 64-70 Gy for CFR group and 59.8-68.2 Gy for hypofractionated RT group. All patients who received ENI were treated with a conventionally fractionated scheme on pelvic lymph nodes.

Results: Median follow-up was 22,7 months(range 1-55). Early grade ≥2 urinary toxicity rates were 6/50(12%) among patients in the CFR group and 10/43(23.2%) in the group who was treated with hypofractionated scheme (p= 0.18). Early grade ≥2 gastrointestinal toxicity were 11/50(22%) in the CFR group and 10/43(23.2%) in the hypofractionated group(p=0.88). Late grade ≥2 urinary toxicity rates were 8/50(16%) in the CFR group and 4/43(9.93%) in the hypofractionated group (p=0.37). Late grade ≥2 gastrointestinal toxicity rates were 5/50(10%)in the CFR group and 2/43(4,6%) in the hypofractionated group(p=0.44). No significative correlation was found between ENI and gastrointestinal toxicity.

Conclusions: In our experience, post-prostatectomy hypofractionated radiotherapy seems to be well tolerated. We have found a moderate trend towards increase of early toxicity in hypofractionated group, but this trend was not statistically significative. Rate of grade ≥2 late toxicity in the hypofractionated group was lower than in CFR group; this difference was not statistically significative.

A longer follow-up is needed to confirm these results.

P180

HYPOFRACTIONATED RADIOTHERAPY AND ABIRATERONE IN PATIENTS WITH METASTATIC CASTRATE RESISTANT PROSTATE CANCER

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Aims: Palliative radiotherapy (pRT) is primarily employed for palliation of bone pain in patients with castrate-resistant prostate cancer (CRPC).We describe a series of patients treated with abiraterone acetate and undergoing palliative radiotherapy for bones metastasis with a moderately hypofractionated scheme.

Methods: We retrospectively analyzed 13 patients with CRPC that received abiraterone and concomitant pRT in our Department between June 2013 and November 2015. Seven patients underwent surgery and subsequently adjuvant or salvage radiotherapy, three were subjected to radiotherapy alone and three had initially metastatic disease. All patients developed CRPC which previously progressed on luteinizing hormone-releasing hormone (LHRH) analogue therapy and maximal androgen blockade. All patients were treated with Zoledronic acid, to prevent skeletal-related complications. Five patients were treated with docetaxel and one was treated with Radium-223. The average time between the onset of the disease and the appearance of metastases was six years. All patients were treated with abiraterone and concomitant hypofractionated RT of at least one and up to 5 bony lesions. The lesions of spine and pelvis predominated (48% and 29% correspondingly). Total radiation dose varied between 8 Gy to 30 Gy (median dose 20 Gy in 4 fractions). Pain palliation was assessed in patients who had clinically significant baseline pain. All patients were also receiving synchronous prednisone and LHRH analogue therapy.

Results: The average follow-up was 9,5 months. All patients demonstrated an excellent biochemical response. Median PSA level was significantly reduced from 30 ng/mL (range 7-180) to 2 ng/mL (range 0,5-138) after pRT. pRT resulted in pain palliation in 80% of symptomatic patients and side effects were mild.

Conclusions: Hypofractionated radiotherapy is an effective tool for palliation of symptoms commonly caused by metastatic prostate cancer, concomitant use of abiraterone is feasible and effective in the treatment of bone metastasis from prostate cancer.

P181

POSTOPERATIVE HYPOFRACTIONATED RADIOTHERAPY IN PROSTATE CANCER: A SINGLE INSTITUTION EXPERIENCE WITH TOMOTHERAPY

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Aims: During the last decades, many studies of hypofractionated radiotherapy have been published in the prostate cancer field, due to the stronger radiobiological evidences of a low alpha/beta ratio for the prostate cancer ranging around 1.5 , demonstrating a trend in improvement in the hypofractionated groups in terms of Local Control and Biochemical Control if compared to the standard fractionation, with a substantial equivalence of acute and late

toxicities. Very few publications are at the moment available in the postoperative setting. This is a single institution experience with Tomotherapy of hypofractionated radiotherapy in adjuvant and salvage treatments. We report the preliminary results of acute and late toxicities.

Methods: Between February 2012 and October 2015 27 patients underwent an hypofractionated radiotherapy with Tomotherapy in our Institute. Eigth pts received adjuvant treatment for the presence of risk factors for local relapse at hystological examination at the surgery, while 20 pts underwent a salvage radiotherapy for biochemical relapse after prostatectomy. All patients did a regimen in 23 fractions for a total dose of 57.5 Gy and 59.8 Gy. Patients characteristics are reported in Table 1

Table 1.

MEAN AGE	66,59 (56-76)
MEDIAN AGE	67
Surgical Gleason score	6 (3+3): 4
	7 (3+4): 9
	7 (4+3): 8
	8 (4+4): 2
	9 (4+5): 3
	10 (5+5): 1
Surgical T staging	pT2a: 1
	pT2b: 1
	pT2c: 7
	pT3a: 13
	pT3b: 5
Surgical Margins	R0: 14
	R1: 13
Nodal surgical status	p N0: 5
	p N1: 4
	p Nx: 18
Adjuvant RT	7
Salvage RT	20
Type of Surgery	Robotic: 9
	Laparoscopic: 18
Prostatic bed + Pelvic irradiation	9
Prostatic bed irradiation only	18
Fractionation schedule:	
- Fraction dose /n° fr	2,5 Gy /23 fr: 20 pz
- Total dose:	2,6 Gy/23 fr: 8 pz
	57,5 Gy
	59,8 Gy
mean iPSA	7.75 (4.3-42.7)
median iPSA	6.02
Mean Pre RT PSA	0.77 (0-4.06)
Median pre RT PSA	0.47

Results: The acute and late urinary and rectal toxicities have been evaluated by the use of the C.T.C.A.E. 4.02 and the SOMA-LENT modified Scales. We lost 2 patients during the follow up period (1 patients died for other cause and 1 patients was not found anymore). The acute and late toxicities are reported in Table 2. The acute GU-G2 and GI-G2 toxicities were 18.5% and 14.8% respectively. One patient experimented a subacute rectal toxicitiy ≥ G3, (dilatation for rectal substenosis within 6 months from the end of RT), while the late GU-G2 and GI-G2 toxicities were 8% and 0% respectively. Only 1 patient had a urinary late G3 toxicity (urethral dilations for substenosis) while none patients had a rectal late toxicity ≥ G3.

Conclusions: Many of the randomized and not randomized trials regarding hypofractionation have been published in the elective treatment setting with very few datas available in the postoperative group with the alert for the acute and late toxicities reported in the different published series. Even if this is a very small experience with a limited number of patients, we had very few toxicities but future and larger series are necessary to better understand the real impact of hypofractionated radiotherapy in postoperative prostate cancer setting.

P182

HYPOFRACTIONATED IMRT IN PATIENTS WITH LOCALIZED PROSTATE CANCER: EVALUATION OF TOXICITY

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Purpose: assessment of hypofractionated radiotherapy toxicity in patients with localized prostate cancer.

Methods: We performed a literature review, from 2006 to 2016 , for the evaluation of toxicity genitourinary (GU) and gastrointestinal (GI), by selecting those studies that evaluated patients with prostate cancer at low-intermediate risk. In all studies were compared conventional fractionation and hypofractionated regimen IMRT technique. The RTOG system was used to evaluate the toxicity GU and GI. Patients treated with conventional fractionation received a median dose of 80 Gy in 40 sessions, patients treated with hypofractionated IMRT received a median dose of 7Gy for 5 fractions.

Results: In the evaluated studies were not found G4 GU and GI toxicity. It was evidenced G1 - G2 GI and G2 - G3 GU toxicity . The comparison between conventional fractionation and hypofractionated RT showed no difference in severe GU and moderate-severe GI toxicity, while the moderate GU toxicity results higher in hypofractionated schemes.

Conclusions: The use of hypofractionated RT resulted effective and safe and it can obtain a good control of the disease while maintaining acceptable the risk of toxicity. This create the conditions for the use of higher hypofractionated regimes in patients with localized prostate cancer.

P183

PROSTATE MOTION DURING HYPOFRACTIONATED RADIOTHERAPY AND EVALUATION OF CORRECT PTV MARGIN

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Aims: To evaluate inter and intra-fraction prostate motion during prostate hypofractionated radiotherapy and personalization of PTV's margins for each patient.

Methods: In 6 consecutive prostate cancer patients were implanted 3 gold fiducial markers. All patients were classified as low or intermediate risk and the radiotherapy prescription was 70 Gy in 28 fractions. They were treated with single arc VMAT and daily IGRT, performed with BrainLab ExacTrac 6D X-Ray system, associated to 6D couch. The acquisition protocol for each patient, in order to evaluate prostate motion, provided four x-ray exposures in all fraction. The first exposure was used to correct patient setup (translation and rotations) with the automatic registration tool based on pelvic bones anatomy; the second to correct prostate's position with a manual technique based on markers position, while the other two images were acquired during and at the end of the treatment (we don't apply any correction during therapy). In off-line review mode, 672 images were analyzed to report all the shifts. For every treatment session of every patient, all the images were analyzed first with the automatic tool and after manually (using gold markers). This approach allowed to manage both bony anatomy (patient setup) and prostate motion every day. With daily IGRT systematic errors are null; only random errors within the same patient and between fractions were analyzed. A statistical analysis of the results was performed and the PTV's margins calculation was done using the van Herk's formula $2.5\Sigma + 0.7\sigma$, which takes into account systematic (Σ) and random errors (σ).

Results: Concerning set-up positioning, mean recorded shifts are 3.4 mm, 1 mm and 2.3 mm for vertical, lateral and longitudinal directions, with angular shift of 0.35°, -1° and 1.5°, respectively. While intra-fraction and inter-fraction standard deviation of organ motion was less than 2 mm. No variation of organ motion amplitude during all the treatment was recorded, for every patient analyzed.

Conclusions: By daily IGRT with gold markers and ExacTrac System, systematic errors are avoided, and we assessed that intra-fraction movement is limited. More studies are needed to evaluate if it is possible to safely adapt and reduce patient's PTV after first 5 fractions and if it is safe to increase the daily dose, provided a reduction of toxicity to organs at risk in radical prostate hypofractionated radiotherapy.

P184

HYPOFRACTIONATED REGIMEN IN PROSTATE CANCER PATIENTS. UPDATE OF A MULTICENTER STUDY

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Aims: To evaluate feasibility and toxicity of hypofractionated regimen in the treatment of prostate cancer using 3D conformal technique or IMRT.

Methods: Patients with localized prostate cancer were treated with hypofractionated regimen of 2,7 Gray die with a total dose of 67,5-70,2 Gray on the prostate. Seminal vesicles were put out of the fields when a total dose of 45,9 Gray was delivered. Dose constraints were: rectum: V50<33%; femoral heads: V36<50%; bladder V59<50%. In all patients toxicities were evaluated weekly during treatment.

Results: From 22.04.2010 to 01.04.2016 a total of 106 patients entered on the study. Median age was 78 years old (range 62-88). All had adenocarcinoma with a median Gleason Score 6 (3+3) (range 5-9). A median value of PSA at diagnosis was 10,20 (range 4,4-28,20). 30 patients were submitted to total androgenic block. Late genitourinary toxicity was: G0 (85 pts: 80%), G1 (21 pts: 20%). 34 patients (32%) had G1 rectal toxicity and G3 toxicity was reported in eigth patients (8%).

Conclusions: The hypofractionated regimen used in this study seems to be feasibile with very low toxicity profiles. Longer follow-up is necessary to evaluate long term results.

P185

SBRT "PRE-BOOST" PLUS EXETERNAL BEAM RADIATION THERAPY IN INTERMEDIATE AND HIGH RISK PATIENTS WITH PROSTATE CANCER: PRELIMINARY RESULTS

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Aims: We evaluated the feasibility and toxicity of localized prostate cancer (LpC) patients in intermediate and high risk treated with Stereotactic Body Radiotherapy (SBRT) anticipate boost and 3D conformal radiotherapy or Intensity Modulated Radiation Therapy (3DCRT/IMRT).

Methods: LpC patients with prostate volume $\leq$ 90 cc, no previously submitted to trans-urethral prostate resection, without any oncological disease, excluding cuta-

neous basal cell carcinoma were enrolled in the present study. Patients were treated with SBRT and EBRT. SBRT was performed using a CyberKnife System "simulating" an HDR brachyterapy treatment and a Fiducial Tracking System.

Results: From February 2011 to December 2015 nine patients for SBRT and EBRT of the prostate plus seminal vesicles and/or pelvic nodes (9.5 Gy/two fractions plus 46 Gy/23 fractions EBRT) were enrolled. Median age was 76 (73-84 years). Androgen deprivation therapy (ADT) was administered in 4/9 patients. The median pre-treatment PSA was 7.42 (range, 0.16–19.35) ng/ml. All patients completed the planned therapy. Acute genitourinary (GU) Grade 1 toxicity was observed in 4/9 (44%) patients; acute genitourinary (GU) Grade 2 toxicity was observed in 3/9 (33%) patients. Acute gastrointestinal (GI) Grade 1 toxicity was observed in 2/9 (22%) patients. The median PSA nadir was 1.81 (range,0.02–1.4) ng/mL. Late GU grade 1 toxicity was observed in 2/9 (22%) patients. No late GI was observed. Median follow up was 22 (range, 8–63) months.

Conclusions: Our preliminary results of SBRT "simulating" HDR for LpC as anticipated boost plus EBRT confirm feasibility in intermediate and high risk prostate cancer patients with optimal PSA control and low acute and late toxicity.

P186

MODERATE HYPOFRACTIONATED INTENSITY-MODULATED RADIOTHERAPY FOR LOW-INTERMEDIATE RISK PROSTATE CANCER: INITIAL EXPERIENCE AT UNIVERSITY OF CATANIA

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Aims: In the last few years, Hypofractionated Radiotherapy (H-RT) for prostate cancer has become of growing interest with the recognition of a potential improvement in therapeutic outcome with treatment delivered in moderately larger daily fractions. In addition, hypofractionation offers a reduction in fraction number and increased convenience for patients, reducing the overall cost of treatment including linear accelerators occupancy and patient transportation. The purpose of this trial is to give a detailed analysis of our initial experience on the efficacy of H-RT in patients with low and intermediate risk prostate cancer.

Methods: From January 2013 to January 2015, we have treated a total of 21 patients (pts) with low and intermediate risk prostate cancer. Pts treated with radical mild H-RT (72.5 Gy in 29 fractions over 5.8 weeks) by means of a step-and-shoot IMRT technique. Our patients were aged between 58 and 82 years with the following features: a clinical classification of T1b to T2c, a Gleason score of 6 (3+3) or 7 (3+4), and a prostate-specific antigen (PSA)<20 ng/mL. In all pts, radical irradiation was preceded by a neoadjuvant/concomitant hormonal therapy (HT), with a complete androgen blockade, of at least 6 months, in order to reduce the prostate volume. Volume measurements were done by means of an MR scan at recruitment and after 6 months of HT, before H-RT. Volume of prostate gland ranged between 43 and 73 cm3 Target volume was defined as the whole prostate gland and the lower part of seminal glands, plus a circumferential margin of 1 cm in all directions, 0,7 cm posteriorly. Pts were treated in prone position, with empty rectum and full bladder, and they were immobilized by means of a vacuum cushion or a thermoplastic body mask. Additional criteria were ECOG performance status<2, and no prior local treatments for prostate cancer.

Results. A total of 21 patients were treated with mild H-RT and had follow-up information. Median follow-up was 25 months. Dose-volume constraints, according to QUANTEC guidelines, of the bladder (V60 ranged between 37-42%) and of the rectum (V50 ranged between 38-48%) were respected in all patients. At this time, the disease-free survival (DFS) and the overall survival (OS) are 100%. Acute grade I-II gastrointestinal and genitourinary acute adverse events were observed in 5 patients treated with H-RT. No grade III or more acute toxicity was reported. Late rectal bleeding was seen in 4 pts, none of grade III or more.

Conclusions: In men with low and intermediate risk prostate cancer, the efficacy of mild H-RT (72,5 Gy in 29 fractions over 5,8 weeks) allows a good DFS and OS. The rate of acute and late gastrointestinal and genitourinary toxicity was comparable to that of conventional fractionated IMRT treatments.

P187

HYPOFRACTIONATED IMRT WITH SIB IN HIGH RISK PROSTATE CANCER PATIENTS AFTER RADICAL PROSTATECTOMY: PRELIMINARY RESULTS

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Aims: There are few data on postoperative hypofractionated radiation therapy of high risk prostate cancer patients. In our study we evaluated the feasibility and toxicity of IMRT with simultaneous integrated boost (SIB) of the prostate Bed and the pelvic nodes.

Methods: We enrolled patients with indications for adjuvant or salvage radiation therapy (≥ pT3 and/or R+ and/or N+). The primary end point was the evaluation of the Gastrointestinal (GI) and genitourinary (GU) toxicities according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Median follow up was 22 (range, 8–63) months.

Results: From February 2013 to December 2015 10 patients were enrolled for IMRT with simultaneous integrated boost (SIB) of the prostate Bed and the pelvic nodes. Patients received 50.4 Gy in 28 fractions to the pelvic nodes and 61.6 to 72.8 Gy in 28 fractions on the prostate bed with SIB-IMRT. Median age was 66 (55-78

years). Androgen deprivation therapy (ADT) was administered in 5/9 patients. All patients completed the planned therapy. Acute genitourinary (GU) Grade 1 toxicity was observed in 5/10 (50%) patients; acute genitourinary (GU) Grade 2 toxicity was observed in 2/10 (20%). Acute gastrointestinal (GI) Grade 1 toxicity was observed in 3/10 (30%) patients. Acute gastrointestinal (GI) Grade 2 toxicity was observed in 2/10 (20%) patients. Late GU grade 1 toxicity was observed in 4/10 (40%) patients. Late GI grade 1 toxicity was observed in 2/10 (20%) patients. 1/10 patient had biochemical failure.

Conclusions: SIB-IMRT is feasible for prostate cancer patients after prostatectomy, with acceptable rates of acute/late toxicities. Prospective randomized controlled trials are encouraged to confirm its equivalence to conventional scheme.

P188

STEREOTACTIC BODY RADIOTHERAPY IN OLIGOMETASTATIC PROSTATE CANCER PATIENTS WITH ISOLATED LYMPH NODES OR BONE INVOLVEMENT: A PRELIMINARY EXPERIENCE

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Purpose: Stereotactic body radiotherapy (SBRT) is emerging as a treatment option in oligometastatic cancer patients. The purpose of this study is to report an initial clinical experience with SBRT in oligometastatic prostate cancer patients with isolated lymph nodes or bone involvement trated at our center in Barletta.

Materials and Methods: Between March 2015 to May 2016, 10 patients were treated with SBRT, delivered using LINAC with daily cone beam CT. All patients underwent [(11)C] choline-positron emission tomography/computed tomography before SBRT: 8 patients had isolated nodal metastases and 2 isolated bone metastases. Four patients received androgen deprivation therapy(ADT) concomitant to SBRT and two ADT and abiroterone; four patients didn't receive hormonal therapy concomitamt to SBRT. The median PSA pre-SBRT was 2.5 ng/mL (1.2-4.3). Prescribed doses and schedule of fractionation was 30 Gy in 5 fractions . Response to treatment was assessed with periodical PSA evaluation. Toxicity was registered according to RTOG/EORTC criteria.

Results: The median follow-up was of 6 months (range 2-14). A significant reduction of PSA was observed in 7 cases, while PSA was stable in 2 cases and raised in 1 case who experienced a relapse of disease in other sites . At the time of analysis, all patients are alive. SBRT was well tolerated: one patient experienced G1 acute gastrointestinal toxicity. Late toxicity was evaluated in patients with more than 6 months of follow-up, and no toxicity was relevated.

Conclusions: Despite the small number of patients and the minimum follow-up, our experience shows that SBRT is a safe treatment, effective, and minimally invasive in the eradication of limited nodal or bone metastases from prostate cancer.

P189

HYPOFRACTIONATED PELVIC RADIOTHERAPY FOR HIGH-RISK PROSTATE ADENOCARCINOMA: A PRELIMINARY STUDY

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Aims: The role of pelvic elective nodal irradiation (ENI) in the management of prostate cancer is controversial. We report on acute toxicity in high-risk localized prostate cancer patients treated with hypofractionated pelvic radiotherapy employing a simultaneous integrated boost.

Methods: A consecutive series of 15 patients affected with prostate cancer was treated with intensity-modulated radiotherapy using a hypofractionated schedule and a simultaneous integrated boost consisting of 70 Gy (2.5 Gy daily) to the prostate gland (PTV1), 63 Gy (2.25 Gy daily) to the seminal vesicles (PTV2) and 53.2 Gy (1.9 Gy daily) to the pelvic nodes (PTV3) delivered in 28 fractions. Assuming an / of 1.5 for tumor control, the hypofractionated schedule carries BED values of 186.6 Gy (PTV1),157.5 Gy (PTV2),120.5 Gy (PTV3) whereas BED values showed with conventionally sequential fractionated schedule are 186.6 Gy (PTV1), 158.6 Gy (PTV2), 116.6 Gy (PTV3). For acute responding normal tissues, assuming an / 5 for rectum and an / 6 for bladder, the hypofractionated schedule carries BED values of 105 Gy for rectum and 99 Gy for bladder; while conventionally fractionated schedule shows BED values of 112 Gy and 106.6 Gy for the same organ at risk (OARs). Daily cone-beam computed tomography was applied. Androgen deprivation was prescribed for a median duration of 24 months. The acute gastrointestinal and genitourinary toxicity was assessed according to CTCAE. v3.

Results: The median follow-up time was 5 months (range, 1 to 8 months). The rates of Grade 1 acute genitourinary (GU) and gastrointestinal (GI) toxicities were 20% and 14% and grade 2 acute GU and GI were 19% and 13%, respectively. None of the patients experienced grade ≥3 acute GU and GI toxicities.

Conclusions: Our hypofractionated schedule delivered with intensity-modulated radiotherapy and a simultaneous integrated boost approach proved to be a safe option with a low acute toxicity for patients with prostate cancer.

P190

IMMUNOTHERAPY AND STEREOTACTIC RADIATION THERAPY FOR MELANOMA BRAIN METASTASES: ANALYSIS OF ACUTE NEUROTOXICITY IN 17 PATIENTS

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Aims: Stereotactic radiotherapy (SRT) is a standard treatment for the management of melanoma brain metastases (BM). Preliminary data suggest that high doses of radiotherapy administered with limited number of fractions promote productive interaction between tumors and the immune system and this interaction can be enhanced using active immunotherapy. Therefore, there is an emerging interest to investigate the clinical benefits of incorporating immunotherapeutic agents with SRT, in particular using drugs acting on the immune checkpoint blockade such as Ipilimumab (anti-CTLA-4), Pembrolizumab and Nivolumab (anti-programmed death-1 -anti-PD-1). However, limited data still exist about the safety of these drugs when combined with radiation. Aim of our study is to evaluate toxicity of concomitant administration of immunotherapy and SRT for melanoma BM.

Methods: Seventeen patients (pts) with melanoma BM treated with SRT and concomitant (within 6 months) Ipilimumab or Pembrolizumab or Nivolumab were treated at our Institution between 2010 and 2016. Primary end point of this analysis was neurotoxicity assessment using both clinical evaluation and/or radiologic images (CT or MRI) performed after at least 8 weeks from the end of SRT.

Results: SRT (using a Cyberknife system) was administrated before, during and after immunotherapy in 4 (23,5%) pts, 9 (53 %) pts, and 4 (23,5%) pts, respectively. The majority (14) of pts were treated for a single lesion, while 3 pts for 2 lesions. Median dose of SRT was 20 Gy in a single fraction (range 16-24 Gy). Prophylactic steroid administration during RT treatment was used for all pts. Median follow-up was 3 months (range 1-24 months). At the time of the assessment 15 pts (88,2%) died for cancer related disease and 2 pts (11,8) were alive with evidence of metastatic disease. Neurological assessment was available for all patients. No treatment-related neurologic toxicity (headaches, nausea) was reported, except for 1 patient with focal weakness and 1patient with one episode of seizure. For 13 pts a radiologic exams was performed. Five pts presented mild perilesional edema and 1 patient had necrosis of the treated lesion. Both pts had no associated neurologic symptoms.

Conclusions: In our series SRT resulted to be well tolerated in patients with melanoma BM who received concomitant administration of immunotherapy agents. Ongoing analysis are evaluating patients' clinical outcomes.

P191

BIWEEKLY HYPOFRACTIONATED RADIATION THERAPY FOR THE TREATMENT OF EPITHELIAL SKIN CANCER IN VERY ELDERLY PATIENTS

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Aims: Radiotherapy is a well established treatment option for epithelial skin cancer with high response rates. Epithelial skin cancer frequently occur in elderly population, sometimes in advanced stage, when intensive and, sometimes, disfiguring treatments are needed. The aim of our study is to evaluate the efficacy and tolerability of hypofractionated radiotherapy in a population of very elderly patients with locally advanced stage epithelial skin cancer. Because epithelial skin cancers are locally aggressive, our primary endpoint was local control (LC) and compliance to treatment. Secondary endpoints were, socio-economic impact, overall survival (OS), cancer specific survival (CSS) and toxicity.

Methods: Twenthy-six tumors in 21 patients were treated with two different hypofractionated schedules: 6 Gy in 10 bi-weekly fractions and 5 Gy in 12 bi-weekly fractions (total dose 60 Gy). Median age at the treatment was 88 (range 77-100), 13 (62%) patients had a PS(Ecog) of 1-2 and 8 (38%) patients had a PS(Ecog) of 3-4. Life expectancy was ≤5 years in 19 (90.5%) patients and >5 years in 2 (9.5%) patients. Eighteen tumors were at Stage I-II (69%), 2 (8%) cases were at stage III and 6 (23%) at stage IV.

Results: The overall response rate was 96.1% (25/26 lesions) with a rate of complete response of 92.4% (24 tumors). Four cases (15.3%) had a G3 acute local toxicity, while late toxicity occurred in 3 (11.5%) cases. Tolerability and compliance to treatment were good; adherence to treatment was 92.4%, with 2 cases of interruption who did not completed therapy. All patients experienced an improvement of the symptoms and a reduction of pain and medications. Median OS in our series was 28 months (95% c.i. =4.7-51.2). At the time of analysis 11/21 (52.3%) patients are dead. Median CSS was not reached. One and 2 years CSS were 95%.

Conclusions: Hypofractionated RT is an effective option of treatment and can be safely administered also in elderly patients, with low toxicity and optimal results. The toxicity is acceptable and the rate of withdrawal is low. Considering the high rate of local control achieved with both schedules, we suggest the use of the 6 Gy in 10 (biweekly) fractions schedule in this setting of elderly patients, mainly due to the shorter duration of the course and in the view of administer a treatment more sustainable by these frail patients and to reduce the costs.

P192

EFFICACY OF PALLIATIVE HYPOFRACTIONATED RADIOTHERAPY FOR ADVANCED NON-MELANOMA SKIN CANCER IN ELDERLY PATIENT

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Aims: In this study we assessed the rate of tumor response and symptom palliation after hypofractionated radiotherapy (HRT) in elderly patients affected by advanced non-melanoma skin cancer (ANMSC).

Methods: Between 2008 and 2016, 18 patients affected by ANMSC were treated, at our Radiotherapy Department, with palliative HRT. Age, gender, tumor histology, grading, location, size, borders, primary/recurrent tumor, speed of growth, presenting symptoms (pain, neurologic symptoms, bleeding), immunosuppression and radiation treatment characteristics were recorded at baseline. Tumor size and tumor-related symptoms were monitored at each fraction and at follow-up visits. Patients were treated with photon or electron beam, and received 24-36 Gy in 4-6 fractions (1 fraction/week). After the end of RT course, follow-up visits were planned: first visit was performed at 8-12 weeks after treatment, and subsequently every 3–4 months. Tumor response, symptom palliation and local recurrence rates were analyzed; treatment response (tumor size and symptoms) was evaluated for patients observed for at least one follow-up visit or basing on the response observed at the time of the last available clinic visit.

Results: We treated a total of 18 patients, with 26 ANMSC. Mean age was 89 years (range 77-110); 9 patients were men, 9 women. Mean tumor size at presentation was 2.2 cm (range 0.5-4.5 cm). Most of the tumors were squamous (12), 4 patients had a basal cell histology, while 2 a Kaposi Sarcoma. No patient presented immunosuppression or rapidly growing tumors. About location site 9 tumors occurred within the "mask area" of the face, 7 in scalp/neck/forehead region, 2 tumors occurred on extremities. At presentation, 5 patients referred neurologic symptoms, 10 bleeding, 3 presented both neurologic symptoms and bleeding. 17 patients were evaluable for the follow-up (mean: 16 weeks, range 3-102 weeks). At the time of the end of RT course or at the last follow-up visit, tumor response rate was 52.9% (complete response 5/17; partial response 4/17). Two patients experienced in field local recurrence. Presenting symptoms were alleviated in 58.3% (7/13) of symptomatic sites.

Conclusions: Palliative HRT in ANMSC offers significant response rate and palliation symptoms, although the duration of response is not known. Furthermore, being administered 1 day/week, HRT provides a good treatment option especially for elderly patients where ANMSC are more frequent.

P193

COMBINATIONS OF RADIOTHERAPY AND IMMUNE AND/OR TARGETED THERAPIES FOR MELANOMA BRAIN METASTASES

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Aims: Immunotherapy and Targeted therapies has been, in the recent years, an important therapeutic goal to improve the prognosis in patients affected by metastatic melanoma. We presented our preliminary experience in patients treated with palliative radiotherapy of multiple brain metastases performed concurrently with these new drugs.

Methods: From 2011 to 2016 we treated 10 patients (pts) affected by multiple brain metastases (MBM) from stage IV melanoma. The mean age was 49 years (range: 29-75). BRAF mutation was present in 7/10 pts. The brain progression disease (PD) was detected by Magnetic Resonance (MRI) in 6 cases and by Computed Tomography (CT) in 4 cases. Systemic therapies (ST) started after brain progressive disease (BPD) in 5 cases, others pts continued previous ST for complete systemic response. ST was: immunotherapy in 3 cases (1 ipilimumab, 2 pembrolizumab) and target therapy in 7 cases (5 dabrafenib + trametinib, 1 dabrafenib, 1 vemurafenib + cobimetinib). Two pts received previous stereotactic brain radiotherapy (SRS) for single brain metastasis (2 years and 6 months before BPD). Nine pts received whole brain irradiation (WBI), doses and fractionations were 30 Gy/10 fractions (fr) in 6 cases, 20 Gy/5 fr in 3 cases, 25 Gy/3 fr in 1 case by SRS. Acute and late toxicity were evaluated according to the RTOG-EORTC scale.

Results: One pt died during WBI. Three pts showed a partial response (PR) and 1 pt stable disease (SD) at the control imaging, with a mean time of 2,9 months; 6 pts showed BPD. The mean overall survival (OS) was 4 months (range 9,5 -1), the radiological time to progression (TTP) was 1,5 months (range 0-5), the clinical TTP was 2,7 months. Three pts showed lesion bleeding not due to the WBI and 1 pts showed intestinal bleeding from abdominal lesions. One pt developed skin radio sensitivity after WBI.

Conclusions: Our little experience showed a good tolerance to the associated treatments. The skin toxicity developed by 1 pt, outside radiotherapy field, is described in the recent literature. Our survival results are in agreement with the results showed in the literature data, according to the stage of the disease and the clinical history of these pts that received several previous therapies. More pts, a better selection and a correct definition of treatment timing are needed to achieve more data and better conclusions.

P194

HYPOFRACTIONATED EXTERNAL BEAM RADIOTHERAPY OR BRACHYTHERAPY FOR NON-MELANOMA SKIN CANCER: ACUTE AND LATE TOXICITY AND CLINICAL OUTCOMES

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Aims: To retrospectively review failure, cosmesis, and outcomes of patients with epithelial skin cancer treated with hypofractionated external beam Radiotherapy (EBRT) or Brachytherapy (BT).

Materials and Methods: The records of 32 patients having 42 lesions treated from 2003 to 2015 were analyzed. Mean age at the time of treatment was 83 years (range 64-99). Histology was basal cell carcinomas in 12 cases and squamous cell carcinomas in 27 cases. In 3 cases, pathologic assessment was not feasible. In 86% of cases, the lesions were localized in the mask areas of the face and scalp. In 21 cases, EBRT followed surgical excision: 18% had negative margins, 45% had microscopically positive margins, 14% macroscopic positive margins, 23% close margins (<5mm). Median size of the lesions was 30 mm (range 5-70). In 88% of cases, EBRT was used: electron beam irradiation (79%), megavoltage photons (7%) or mixed technique (2%). In half of EBRT cases, a bolus was used. A Valencia applicator was used for HDR-BT form January 2015 and five cases were treated with superficial lesions <30 mm, (40 Gy in 10 fractions). All the treatments were delivered with a hypofractionated schedule: the median total dose was 49.75 Gy, the median dose/fraction was 2.5 Gy once daily (range 2.25-4). Acute toxicity was evaluated according to the RTOG Acute Toxicity Scale.

Results: At a median follow up of 8 months (range 0-70), local relapse was observed in 8 cases (19%), mainly marginal relapses, lymph nodal relapse was observed in 4 patients (10%). Only 1 patient presented distant metastases. The median time of local relapse was 7 months (range 0-60) while the median time of regional relapse was 5 months (range 0-12). Among the 21 patients treated with primary RT, 85% obtained a complete clinical response, while only 3 patients had persistent or progressive disease. The median time to observe a complete response was 4 months (range 1-11). In the group of postoperative treatments, patients treated with EBRT after 2 or more surgical excisions of the primary and of subsequent local relapses were more likely to develop local relapses (38%) than patients treated soon after the first surgical excision (0%). The rate of local relapse was non related to the site of the target (plane areas vs irregular surface areas). No patient had >G3 acute skin toxicity, 38% had G1 skin toxicity, 43% G2, 17% G3. Only 3 patients showed a significant (>G2) cutaneous late toxicity, mainly fibrosis and depigmentation. No cases of tissue necrosis was found. All patients completed the planned course of RT.

Conclusions: Radiotherapy remains an excellent treatment modality for epithelial skin cancer both in the primary and in the postoperative setting, with a low rate of local relapses (19%) and late sequelae (7%). Hypofractionation with EBRT or BT is feasible and allows elderly patients to complete the planned course of RT with a minimal discomfort. Postoperative RT should be performed soon after the first surgical excision rather than after two or more relapses to obtain an optimal local control.

P195

COMPLETE REGRESSION OF CERVICAL LYMPH NODE METASTASIS IN IV CLARK LEVEL MELANOMA: A CASE REPORT

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Aims: To report a case of complete regression of cervical lymph node metastasis in a 79 years old female suffering from skin cancer localized in left temporal region.

Methods: In 2015 a 79-year-old female due to a large metastatic node was enrolled for palliative radiotherapy. She had in 2004 a diagnosis of melanoma localized in the cutis of left parotid area and, in 2007, had a intraparotid nodal recurrence treated with surgery. In November 2011 she underwent to lymph node neck dissection (I and II level) for recurrent disease. In 2012 a third recurrence in laterocervical node has been diagnosed and histo-pathologic studies demonstrated a BRAF mutation; the patient was submitted to targeted therapy with Vemurafenib (from August 2012 to July 2013, 11 courses), Ipilimumab (from October 2014 to April 2015, 4 courses), and with Pembrolizumab (from May 2015 to July 2015, 3 courses). In 2015 a PET-TC showed disease in 7th cervical vertebrae, lateracervical nodes (DT max: 6,5 x 4,22 x 3,80 cm) and lung.

Results: We treated the lymphadenopathy using a serial volumetric technique (24 Gy in three fractions, at day 0-7- 21, 8Gy per fraction) on left neck and 8 Gy/1 fr on 7th cervical vertebrae. Node-disease PTV was obtained expanding the GTV to 5 mm in all direction adjusting the volume in correspondence of the skin. Radiotherapy was used in order to reduce bulky disease. Patient showed complete regression of cervical lymph node metastasis. A follow-up TC performed in February 2016 showed complete regression in lateral neck region.

Conclusions: 0, 7, 21 regimen, demonstrated to obtain some responses in the treatment of malignant mucosal melanoma. This is the first report on the use of this scheme in treating nodal melanoma metastases in association with monoclonal antibodies. The clinical results obtained in the present patient encourage the use of this fractionation in the palliative treatment of nodal disease in melanoma.

P196

FACIAL SKIN CANCER TREATED WITH HDR SURFACE BRACHYTHERAPY WITH LEIPZIG

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Aims: Radiotherapy has a key role in skin cancers treatment, especially when they occur in elderly people and in the face. The purpose of this study is the retrospective evaluation of cosmetics results, toxicity and clinical outcomes in patients (pts) with facial skin cancer treated with high dose rateo (HDR) surface brachytherapy performed with Leipzig applicator. Methods:We recruited 25 pts with facial skin cancer who underwent accelerated hypofractionation performed with HDR surface brachytherapy with Leipzig applicator. The histological types were: 14 basal cell cancer, 9 squamous cell cancer, 1 basosquamous cell cancer and 1 dermatofibrosarcoma. Median age was 69 (50-98). All lesions were limited at a depth of <3mm. 24/25 pts, previously underwent surgery, showed positive margins in 13 pts and negative in 11. Among these 11 pts, 5 underwent to surgery for tumor recurrence, 6 showed deep tumor infiltration. Lesions were located in the nose, in the lip and in the eyelid. One 98 years old pt, with dermatofibrosarcoma in medial canthus of the right eye, refused surgical excision (NCCN 2016). We used Leipzig applicator with diameter range of 1-3 cm. To ensure reproducibility treatment conditions, all pts had skin markers. The prescription dose was 40Gy in delivered 8 fractions (5Gy/fr), considering / =10, with a biological effective dose (BED) of 60 Gy at a depth ≤ 4 mm. Patients with lesions>3 cm in diameter, were treated with electron beam therapy with a prescription dose of 48-50 Gy in 24-25 fractions.

Results: Acute skin toxicity was evaluated according RTOG toxicity scale, through weekly regular visits performed during treatment. To prevent or reduce acute toxicity effects we have recommended use of topical creams. We observed G1 acute toxicity in 10 pts and G2 acute toxicity in only 1 pt. Average follow-up was 18 months (range 12-24), with no evidence of any severe late toxicity; only one pt showed teleangectasia. We reported 24 pts with no evidence of recurrence. Only one pt showed recurrence of disease and underwent surgical excision.

Conclusions: In pts with superficial skin cancer, HDR brachiterapy with Leipzig applicator provides excellent results for both cosmetic results and skin toxicity, offering a good local control, and granting a uniform dose distributionit. Furthermore, showing equal efficacy when compared to “electron beam therapy”, it also allows to complete the treatment in few sessions, reducing overall treatment time.

P197

HYPOFRACTIONATED RADIOTHERAPY IN NON-MELANOMA SKIN CANCER ≥ 3 CM IN ELDERLY PTS

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Aims: To evaluate clinical outcome of an Hypofractionated schedule in elderly pts with NMSC ≥3cm.

Methods: From 2010 to 2016 we treated 17 pz, median age 78 years, with diagnosis of NMSC (5/17 basal cell carcinoma, 11/17 squamous cell carcinoma, 1/17 trichilemmal carcinoma), ≥3cm (range 3-8 cm diameter), GTV median volume was 32cc (range 5-60 cc). Only 1 pt presented extremity disease (malleolar region) and the others had head region disease. Total dose was 36 Gy in 6 Gy/fractions twice a week. Pts were evaluated 1 month after the end of treatment and then every 3 months. At the follow up pts were assessed for acute and late toxicity according to the Radiation Therapy Oncology Group criteria and treatment response according to Recist criteria.

Results: Median follow up was 12 months. We reported CR in 9/17 pts (53 %), PR in 8/17 pts (47.%) at one month after the end of the treatment. No PD was observed. No pts had acute side effect that required treatment interruption. Acute toxicity was grade 1 RTOG in 3/17 pts. 1/17 had grade 2 RTOG late skin toxicity with moderate fibrosis and discromia.

Conclusions: The Hypofractionated schedule of 36 Gy in 6 Gy/fractions 2/week in elderly pts gave good results in term of treatment response and of acute and late side effects even in lesions ≥3cm. The treatment was well tolerated in all cases and the shorter regime facilitates compliance of elderly pts reducing the number of Hospital visits.

P198

HYPOFRACTIONATED RADIOTHERAPY IN ELDERLY PATIENTS WITH NON-MELANOMA SKIN CANCER

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Aims: The objective of this study is to evaluate the efficacy of the hypofractionated radiotherapy in elderly patients with non-melanoma skin cancer and the rate of tumor response to the radiotherapy regimen used at our department (8 Gy/fraction once per week).

Methods: From October 2009 to March 2015, 5 patients (3 males, 2 females) underwent radiotherapy and 6 lesions (histologically 3 Basal cell Carcinomas and 3 Squamous Cell Carcinoma) were examined. The

median patients'age was 84 years (range 75-92). The patients presented a red and firm lump with flat, crustle or ulcerated patchs and they suffered of symptoms as bleeding, skin pain, odour and anaemia. Before treatment all patients are evaluated by a dermatologist and plastic surgeon, who had ruled out the feasibility of surgical resection or other local treatment. The tumors are located on the forehead/temple (1 lesion), outer ear (1 lesion), scalp (3 lesions) and foot (1 lesion). Treatment is performed by an Elekta Precise linear accelerator. Radiotherapy is delivered using electrons (6-9 MeV) or photons (6 MV) depending on tumor site and depth. The field size choice depended on the lesion size and localization. Total radiotherapy dose was 48 Gy in 6 fractions or 56 Gy in 7 fractions, 8 Gy fraction per week.

Results: Presenting symptoms are alleviated in all patients (5/5). An initial treatment response is noted after the third fraction (day 21) as flattening of the lesions. At the time of the last follow up (median 12 months) 5/6 lesions has complete response and one of these, after 3 months, showed local recurrence and 1/6 partial response. No acute and subacute toxicities were seen.

Conclusions: This radiotherapy regimen offers impressive response rates, with excellent tolerability. The hypofractionated treatment by 8 Gy per week, total dose 56 Gy in 7 fractions or 48 Gy in 6 fractions, can be regarded the radiation schedule of choice.

P199

EFFECTIVENESS OF SBRT IN OLIGOMETASTATIC MERKEL CELL CARCINOMA: A CASE REPORT

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Aims: Our purpose is to present the effectiveness of stereotactic radiotherapy in a case of metastatic Merkel cell carcinoma (MCC). It is a rare and aggressive neuroendocrine skin cancer that predominantly occurs in older patients. Main features are: high frequency of local recurrence, regional nodal and distant metastasis and a high rate of mortality.

Materials and Methods: We report the case of an oligometastatic MCC in a woman aged 68. In her clinical history there are surgery, irradiation and chemoterapy. She underwent surgical removal of right leg skin lesion in May 2008 (histological examination: MCC), followed by right inguinal lymphadenectomy. After five years, she underwent a new lymphadenectomy for a voluminous (50x40 mm) metastatic external iliac lymph node, followed by pelvic irradiation (50 Gy / 25 fractions). In November 2014, a CT scan showed a lesion of right adrenal gland (28x32 mm) and patient underwent platinum-based chemotherapy for 6 cycles, until June 2015. Unfortunately, in August 2015, a CT scan demonstrated progression of disease: a dimensional increase at right adrenal gland (61x67 mm) and evidence of new localizations in caval nodal region and left adrenal gland.

Results: In september 2015, the patient underwent SBRT both to adrenal lesions and caval lymph nodes. Patient was immobilized using a thermoplastic mask with abdominal compressor. Initial PTV volumes were 316 cc and 25 in right (adrenal gland and adjacent nodes) and left (adrenal gland) side, respectively. Treatment was performed by linear accelerator True Beam STX (Varian) with Rapid-Arc technique with flattening filter free photon beams (6X FFF). Total delivered dose was 50 Gy in 5 fractions, with daily cone-beam CT. At third fraction, both targets appeared unexpectedly decreased of 46 %. This imposed the re-planning to optimize treatment. No toxicity were reported at the end of radiotherapy. After 6 months, a PET-CT scan showed a complete response. No other disease localizations were found. No late toxicity was reported.

Conclusions: There is no globally and clear consensus on management of MCC. In our patient, stereotactic radiotherapy led to a very good result in terms of local control and toxicities, despite the dimension of lesions. In oligometastatic patients, deep hypofractionation could be considered to improve local control.

P200

SAFETY AND EFFICACY OF STEREOTACTIC BODY RADIOTHERAPY (SBRT) AS A BOOST ON VAGINAL CUFF (VC) COMPARING TO BRACHYTHERAPY (BT)

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Aims: SBRT is an innovative form of highly conformal, noninvasive, radiation therapy that delivers a high radiation dose to target with an optimal healthy tissues sparing. BT, a consolidated technique where a radiation source is directly placed to the target area, plays a key role in the adjuvant treatment of many gynecologic cancers as a boost to the VC. Our purpose is to assess the efficacy and safety of SBRT compared with BT, as a boost on VC, after whole pelvis radiation (WPR).

Methods: A retrospective study was conducted on patients (pts) that undergone radical surgery followed by WPR and boost to the VC, between March 2006 and May 2016. A total of 29 pts, who refused BT, received SBRT for treatment of their malignancies in the adjuvant setting. The mean age was 58,5 years (range, 35-82 years). Mean WPR dose was 45-50,4Gy. Mean SBRT dose was 25Gy, delivered in five fractions. Toxicities were acquired according to Common Terminology Criteria for Adverse Events vers.: 4.0

Results: The mean follow up was 18 months (from 4 to 26 months DS: 5,8). Clinical International Federation of Gynecology and Obstetrics (FIGO 2009) for Stages I, II, III, and IV, was respectively 48%, 14%, 31% and 0%. Only one had a local recurrence in the VC. During the radiation treatment 45% pts had acute genitourinary toxicity, 54% of grade-2 and 46% of grade-1. Gastrointestinal acute toxicity was observed in 35%, 50% of grade-2 and 50% of grade-1. Acute gynecologic toxicities was found

in 7% of 2 grade only. There was no grade-3 or greater toxicities during or within 3 months after SBRT. No chronic genitourinary toxicities were found. Instead chronic toxicities were found in 20% of pts that developed vaginal dryness and one bleeding by chronic vaginitys. Gastrointestinal chronic toxicity was found in 14%, with rectal bleeding resolved by cauterization of the rectal vessels. There were no other reported late toxicities

Conclusions: Our results suggest that SBRT to vaginal cuff, as a boost treatment on high risk areas, is well tolerated, feasible and easily performed. Furthermore the procedure show acceptable toxicity and good local control, with minimally invasive technique. Additional and prospective studies are necessary to understand if SBRT may be a reasonable options when BT is not feasible or refused by pts.

P201

A MODERATE IPOFRACTIONATION SCHEDULE WITH INTENSITY MODULATED RADIOTHERAPY IN PREOPERATIVE LOCALLY ADVANCED CERVICAL CANCER

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Aims: To analyze the efficacy and tolerability of intensity modulated radiation therapy (IMRT) simultaneous integrated boost (SIB) associated to cisplatin based chemotherapy in preoperative setting of patients with locally advanced cervical cancer.

Methods: From September 2014 to December 2015, we analyzed patients with locally advanced cervical cancer undergone to neoadjuvant intensity-modulated extended-field chemoradiation plus simultaneous integrated boost. A radiation dose of 39.6 Gy, 1.8 Gy/fraction, was delivered to the pelvis plus a radiation dose to the primary tumor delivered with SIB-IMRT strategy for a total of 50.6 Gy, 2.3 Gy/fraction in 25 fractions. Cisplatin based chemotherapy was delivered associated to radiotherapy. Radical hysterectomy plus pelvic with or without aortic lymphadenectomy was performed within 6 to 8 weeks from CRT. Statistical analysis was performed using Systat program.

Results: 29 patients (median age: 52 years; The International Federation of Gynecology and Obstetrics (FIGO) stage IB2: 1, IIB: 19, IIIA: 1; IIIB: 5; IVA: 3) were analyzed. The treatment was well tolerated with a good compliance: no patients had grade 3/4 gastrointestinal or genitourinary toxicity; grade 3 leukopenia and neutropenia were reported in only 1 case (stage FIGO IVA) without interruption of the treatment.pCR was documented in 15 cases (51%) and 4 patients (13%) had a microscopic residual disease (persistent tumor foci of 3 mm maximum dimension). At median follow-up of 12.5 months (range: 7-19 months), the 1-year local control was 95%, whereas the 1-year disease-free and overall survival rates were 95% and 100%, respectively.

Conclusions: The treatment was globally well tolerated with a good compliance. Results in terms of efficacy were comparable with literature data. Local control and overall survival will be further evaluated with a longer follow-up.

P202

USE OF HELICAL TOMOTHERAPY IN LOCALLY ADVANCED CERVICAL CANCER: OUR INSTITUTE EXPERIENCE

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Aims: The purpose of this study is the evaluation of clinical outcomes and acute-late toxicity in patients unfit for Brachytherapy, treated with Helical Tomotherapy (HT) in locally advanced cervical cancer.

Methods: Between January 2013 and March 2016 we retrospectively enrolled 18 patients (pts) with locally advanced cervical cancer. According to FIGO 2009 classification: 16.7% were IIA; 50% were IIB; 11.1% were IIIA; 11.1% were IIIB; 11.1% were IV. Pts were classified into 2 groups: 11 pts (Group A) underwent 3DCRT pelvic irradiation plus cervical boost with HT, and 7 pts (Group B) treated with IMRT-IGRT pelvic irradiation plus Simultaneous Integrated Boost (SIB) in HT. For Group A, Mean Total Dose (MTD) was 47.7 Gy (range 45-50.4) for pelvic target, followed by HT boost with MTD of 18.8 Gy (14-20) administered in 6-10 fractions; for Group B, MTD was 48.35 Gy (45-54) for pelvis and 59.02 Gy (53-69.56) for SIB. Neoadjuvant chemotherapy was administered in 27% of Group A, and in 43% of Group B. Concurrent chemotherapy platinum-based was administered in 64 % of Group A and 71% of Group B. We weekly evaluated gastrointestinal (GI) and genitourinary (GU) toxicities during treatment and at every follow-up visit, according to CTCAE v4.0 scale.

Results: With a median follow-up of 7 months (2-39), we observed G1 GU acute toxicity in 18% of Group A, and in 28% of Group B; G2 GU acute toxicity was 9% in Group A, and 14% in Group B, reporting no G3-4 GU toxicity. G1 GI acute toxicity was reported in 36% of Group A, and in 14% of Group B; no G2-3 GI toxicities occurred. Late toxicity was evaluated in 67% of pts, only reporting one case of G3 GU toxicity. Regarding response rate, we observed in Group A complete response (CR) in 55% of pts, partial response (PR) in 9% and stable disease (SD) in 18%; progression disease (PD) occurred in 18%. Among pts of Group B, we registered CR in 58% of cases, PR in 14%, SD in 14% and PD occurred in 14%.

Conclusions: In our experience HT represented a safe alternative to endocavitary Brachytherapy; in our sample we recorded a superior incidence of GU acute toxicity in

Group B, that might be correlated to a higher dose to the bladder delivered with SIB. Regarding clinical outcomes assessment, we reported comparable response rates between two groups, that might be given to the presence in Group B of pts with more advanced disease. For a more accurate evaluation of the survival rates, a longer follow-up is required.

P203

SAFETY AND EFFICACY OF FRACTIONED STEREOTACTIC BODY RADIATION THERAPY (FSBRT) IN OLIGO-METASTATIC RECURRENT OVARIAN CANCER (ROC). A MONOISTITUTIONAL RETROSPECTIVE EXPERIENCE

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Aims: Epithelial Ovarian Cancer is the leading cause of death among gynaecological malignancies. Standard treatment is a combination of cytoreductive surgery and platinum based chemotherapy. Although many patients are disease free after primary therapy, 40-85% of them will relapse and response rate decrease with each subsequent CT regimen while toxicities cumulate. The need for additional effective therapy is recognized. Despite that Radiation Therapy has usually played a marginal role. Intensity Modulate Radiotherapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) are improvement of radiation therapy technology that make irradiation safe and well tolerated and they could be a valid option for patients with ROC after primary surgery, selected by type of recurrence and biological characteristics.

Methods: Between April 2013 and February 2016, 12 patients affect by lymphonodal reccurence were selected and 21 treatments were administrated to them. All patients underwent surgery (6 patients had secondary cytoreductive surgery after desease progression) and had chemotherapy before radiation, median 2 lines (range 1-5 lines), including adjuvant chemotherapy, based on carboplatin/paclitaxel regimen. Median age was 48 year (range 39-65 yrs), clinical FIGO stage was II in 3 pts (25 %), IIIC in 7 pts (58%) and IV in 2 pts (17%); histological subtype was serus carcinoma G3 in 10 pts (83%) and endometrioid adenocarcinoma G3 in 2 pts (17%). BRCA 1/2 mutation was present in 6 pts (50%), 4 pts refused test and 2 pts were wild tipe. We treated 1 to 3 lesion in each patient, diameter range between 1,5 and 4,7 cm. Target volume was delineated on CT/PET imaging according to ICRU 83 and received 35 Gy in 5 fc (BED 59,5 Gy). Tumor recurrence was assessed by CA 125 biomarker, abdominal TC scan, Abdominal Magnetic Resonance Imaging (MRI) and 18-FDG-PET WB at baseline and during the follow up.

Results: All pts had a CR after RT. All pts treated with radiotherapy are alive at a median follow up (FU) of 24 months (range 3-31 months). 8 pts (66%) have no evidence of disease. 4 pts receved new lines of CT and 4 pts receved new RT treatment post progression. Patients with BRCA1/2 mutation had the best response and a long FU without evidence of diasese. No toxicities treatment related were recorded.

Conclusions: FSBRT and VMAT are feasible and effective in nodes ROC, especially in patient with BRCA 1/2 mutation. More studies with more patients enrolled are required.

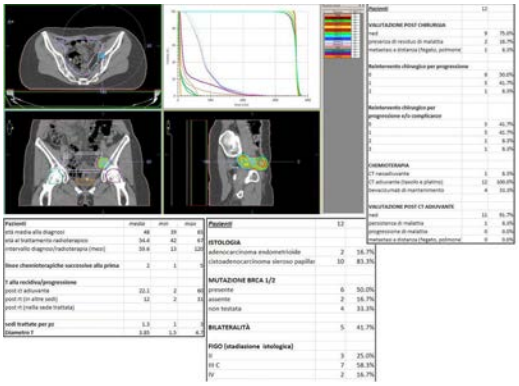

Figure 1.

P204

HYPOFRACTIONATION IN CERVICAL CANCER BY HELICAL TOMOTHERAPY PLUS BRACHYTHERAPY BOOST AND CONCOMITANT CHEMOTHERAPY: A DOUBLE DOSE ESCALATION

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Aims: Traditionally, curative radiation treatment for squamous cervical cancer (SCC) is associated to concomitant chemotherapy platinum based. Doses on the pelvic volume and on the present disease were limited by tolerance of health tissues, especially by small bowel. The possibility of dose escalation (DE) was achieved by intracavitary brachytherapy (BRT) boost, the most classical and proven hypofractionation technique. More modern technologies and techniques, like Helical Thomoterapy (HT), allowed a safe and concomitant dose escalation in this setting of patients (pts) and we need to show our experience in terms of outcome, tolerance and feasibility.

Methods: From 2011 to 2015 we treated 34 pts affected by SCC, 22 with curative intent (4 recurrences). The mean age was 58 years (range 32-88). Grading was: G2 in 10 pts and G3 in 12pts. Stage was: IIA in 4 pts, IIB in 14 pts, IIIA in pt, IIIB I in 2 pts and IV in 1 pt. All pts

received concurrent chemotherapy (CHT) with cisplatin and/or taxanes. All patients were treated with Intensity Modulated Radiation Therapy with Simultaneous Integrated Boost Image Guided Radiation Therapy (IMRT-SIB-IGRT) using @Helical Tomotherapy (HT). External beam radiotherapy (EBRT) was planned on PET-CT images acquired in treatment position. Tumor doses ranged from 60 to 70.4 Gy in 30 fractions (fr) with a moderate hypofractionation; dose to the pelvis ranged from 50.4 to 54 Gy. Lumbar-aortic chain was treated In 4 pts (51 Gy); 13 pts received a boost on PET positive lymph nodes with dose ranging from 60 to 66 Gy. All pts were treated with high dose rate BRT boost with dose/fraction of 6-15 Gy in 1-3 fr.

Results: All pts completed the treatment. Mean follow up was 13,6 months (range 1-26). Three pts recurred: 1 pt in lumbar-aortic chain, 2 pts in pelvic region. Mean time to progression was 3,3 months. Overall survival was 82% with a mean time of 10 months. Two pts died for distant metastases, two for peritoneal progression. No acute or late gastro-intestinal (GI) toxicity>G2 were observed; only one pt developed a G3 acute and late genitourinary toxicity. No severe late hematological toxicity was observed; only one pt developed a G4 acute neutropenia requiring medical therapy.

Conclusions: Our experience of double DE by HDR+ EBRT with concurrent chemotherapy, showed to be effective and safe and well tolerate with a low rate of complications.

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P205

IS VOLUMETRIC STEREOTACTIC TECNIQUE (VMAT) FOR DELIVER BOOST TO VAGINAL CUFF IN PATIENTS WITH GYNECOLOGIC CANCER, A SAFE ALTERNATIVE TO HDR BRACHYTHERAPY?

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Aims: Purpose of this study is to demonstrate the safety and efficacy of volumetric stereotactic technique (VMAT) as an alternative to HDR brachytherapy (HDR-BT) to deliver a boost to the vaginal cuff (VC) after pelvic adjuvant radiotherapy (PRT) and in vaginal recurrences in patients with gynecologic cancer, by comparing our data with those reported in literature in terms of Relapse Free Survivor (RPS) , Gastrointestinal (GI) and Genitourinary (GU) toxicity and Sexual Wellness (SW).

Methods: Between December 2010 and January 2016 , we recruited 42 patients with gynecological cancer, 23 cervix and 19 endometrial cancer (Nine of these were relapsed), who rejected the HDR-BT. In adjuvant setting (78.6 %, 33 Pts) all patients were treated with radiotherapy to the whole pelvis (45-50.4 Gy 25-28) followed by boost on the VC , with dose range of 12-15 Gy in 3 daily fractions, and vaginal recurrences (21.4%, 9 Pts) were treated with dose range of 20-30 Gy in 5-6 daily fractions, in all cases using VMAT. For CT scanning and treatment delivery, we placed a vaginal dilator with radiopaque reference , to distend the wall and the VC, for a better target volume (TV) delineation. The planning treatment volume (PTV) was outlined following the guidelines for HDR – BT, covering 5 cm of distal vagina and adding 3 mm of margins in all directions. The dose distribution to the TV and organs at risk (OAR) was compared with data in literature for HDR - BT. GU and GI early and late toxicity was evaluated according to CTCAE v4.0 , the BS was evaluated by anonymous questionnaire EORTC QLQ - CX24 . The median follow up was 30 months (range 4-64)

Results: The dose distribution shows a good coverage of the VT, comparable to that obtained with HDR - BT , with respect of dose constraints to bladder and rectum according to QUANTEC. Grade 2 toxicity GI and GU was found in 4 (9%) and 3 patients (7%) respectively In 65% of cases (28 patients) was reported vaginal dryness and dyspareunia 3 months after treatment. At 30 months follow up LC results of 95 % .

Conclusions: In terms of LC, toxicity, and BS data emerged from our experience are in line with those reported in literature for HDR - BT, which leads us to consider VMAT as a viable alternative to the HDR - BT to deliver a boost to the vaginal cuff in adjuvant schedule as well as in case of recurrence.

P206

STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR METASTATIC LYMPH NODES IN GYNECOLOGICAL TUMORS: OUR EXPERIENCE

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Aims: Usually , the therapeutic approach for patients with oligometastatic / oligorecurrence disease is a systemic therapy alone. There isn't a standard approach for the management of patients with oligometastatic lymph nodes. In the last years, several evidences have blossomed, supporting the use of stereotactic body radiotherapy (SBRT) for oligometastases or oligorecurrence. We evaluated the outcome and toxicities after Stereotactic Body fractionated radiotherapy in patients treated for oligometastatic lymph nodes from primary gynecological tumors.

Methods: In this study 9 patients, with metastatic lymph nodes were enrolled (for a total of 15 treatment), who undergone to SBRT in our Department from January 2013 to March 2016. All patients were affected by different gynecological cancers (3 patients with endometrial cancer, 2 patients were suffering by cancer of the cervix and 4 affected by ovarian cancer) . All patients had undergone to surgery as first therapeutic approach; 3 patients undergone external beam radiotherapy (Total Dose 45Gy in 25 fractions) after surgery, only one patient has been submitted to boost to the vaginal cuff with HDR-Brachitherapy (5 Gy in 3 fractions). The lymph nodes

were located in different sites: 11/15 lumbo-aortic, 2 liac, 1 ileo-epatic, and 1 in the left laterocervical site. All treatments were carried out in 3 fractions with doses ranging from 16 to 27 Gy with different prescription isodose lines (range: 65-82%). Only one treatment was delivered with a dose of 16 Gy in 3 fractions to respect abdominal constrains.

Results: The lumbo-aortic lymph node treated with a dose of 16 Gy has relapsed and was, therefore, reirradiated with a single fraction of 8 Gy. The follow-up carried out after 50 days, showed that the metastatic lymph node was regressed, and no toxicity was referred by the patient. At the follow up, all treated lymph nodes underwent a volume reduction; unfortunately, 4 patients had a disease progression in different sites and are currently undergoing antiblastic systemic therapy. No toxicity was reported by the patients who undergone SBRT for metastatic lymph nodes.

Conclusions: Stereotactic body radiotherapy in the treatment of oligometastatic and/or oligorecurrence lymph node localization is a valid and safe therapeutic approach.

P207

ENDOMETRIAL CANCER TREATED WITH HIGH DOSE RATE INTRAVAGINAL BRACHYTHERAPY +/- EBRT: OUR EXPERIENCE

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Aims: The current standard treatment for early-stage endometrial cancer is abdominal hysterectomy with bilateral salpingo-oopherectomy. Adjuvant radiotherapy is often required depending on clinical and pathologic characteristics. External-beam radiation therapy (EBRT), high dose rate brachytherapy (HDR-BT) or the combination of both treatments could be necessary. This study aims to evaluate efficacy and toxicity of adjuvant HDR-BT in women with endometrial cancer with or without the use of EBRT.

Methods: Between June 2014 and December 2015, thirty patients with endometrioid endometrial cancer were treated at Radiotherapy Department in Taranto with HDR-BT. Mean age was 65 years (range: 51-84). Pathological stage was I FIGO for 50%, II FIGO for 23.3% and III FIGO for 26.7% of patients. The tumor grading was well differentiated for 13.3%, moderately differentiated for 70% and poorly differentiated for 16.7% of patients. All patients were treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy and 83.3% of them underwent also lymphadenectomy. Adjuvant chemotherapy (carbon-platinum/taxol) was administered in 26.6% of patients. Pelvic external radiotherapy was administered with a total dose of 45 Gy (1.8 Gy/die) in 50% of patients. HDR iridium-192 intravaginal brachytherapy was administered with a total dose of 15 Gy (5 Gy per fraction) for patients who received EBRT and with a total dose of 25 Gy for HDR-BT alone. Computed Tomography scans of the whole pelvis were obtained, also for HDR-BT, in order to contour Clinical Target Volume (one-half to two-thirds of the length of the vagina), Planning Target Volume and organs at risk (bladder and rectum). We proceeded with plan optimization and DVH evaluation: doses for bladder and rectum were respectively ≤110% and ≤100% of the prescribed doses. Toxicity was evaluated according to the RTOG-EORTC scale.

Results: Median follow-up was twelve months (range 4-22 months). Acute gastro-intestinal (GI) toxicity was observed only in patients treated with EBRT (G1 in 6.6% of patients and G2 in only one patient). Acute genitourinary (GU) toxicity was G1 in 23.3% of patients. No late GI toxicity was observed while late GU toxicity was respectively 20% and 6.6% (for G1 and G2). No locoregional recurrences and no distant metastases were observed.

Conclusions: Our experience, although with a short follow-up time, showed that HDR-BT +/- EBRT for high- and intermediate-risk patients with endometrial carcinoma is safe offering good results in terms of disease control. CT-based tridimensional conformal brachitherapy should be used in order to reduce dose at organs at risk and improve target dose distribution with less toxicity.

P208

VERTEBRAL INTRAOPERATIVE RADIATION TECHNIQUE (V-IORT): A NEW MULTIMODALITY APPROACH TO SPINE METASTASIS. THE EUROPEAN INSTITUTE OF ONCOLOGY EXPERIENCE

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Aims: About 50% of bone metastasis are in the spine and do need radiation therapy to relieve pain and prevent fractures. A combination of vertebroplasty and intraoperative radiation therapy can be performed using the Intrabeam, Carl Zeiss AG mobile platform with flexible arm.

Methods: Between 11/2015 and 5/2016 10 patients have been evaluated at the European Institute of Oncology to undergo V-IORT and 5 of them judged suitable for the treatment. Indication to V-IORT are lesion from T4 to L3. Primary malignancy was breast, kidney and pancreas in 2, 2 and 1 pt respectively. 3 of the 5 patients had already recently undergone radiation therapy at the same site. The treatment was performed after a careful estimation of previous RT data and discussion of radiological images with the interventional radiologist and physicists. A preplanning evaluation based on basal

CT scan was performed to estimate the most adequate positioning of the applicator and to define dose to the spinal cord. A dose of 8 Gy has been delivered in all pts, prescribed at 7, 8 and 10 mm in 1, 3 and 1 pt. In the operating room fluoroscopy was performed to confirm the optimal positioning of the radiation source and for last 2 pts a C-arm digital fluoroscopy was used to carefully identify the posterior wall of the vertebrae. A biopsy was performed before giving RT. After the intraoperative RT, vertebroplasty was performed. The total treatment time was about 2 hours while the irradiation time was around 2 minutes. Follow-up consisted in clinical examination and CT scan or PET after 2-4 months when possible.

Results: 1 pt died for visceral progression of disease 2 months after the procedure and 4 pts are alive. Radiological evaluation has been performed in one pt and showed complete reconstruction of the vertebrae without disease. The other 3 pts will be evaluated in the coming weeks. Clinically, with the mean time from V-IORT of 2 months (range, 0-4) no acute toxicity has been registered. In particular, no neurological event has been observed.

Conclusions: V-IORT is a promising technique to treat or re-treat vertebral metastasis. Our experience confirms that the procedure is fast and safe in terms of neurological complications. Longer follow-up and larger series is necessary to define the pts that benefit most from this approach.

P209

SINGLE CENTRE RANDOMIZED CLINICAL TRIAL: IMPACT ON THE REDUCTION OF ACUTE URINARY POST-BT LDR WITH PERMANENT SEEDS IMPLANTATION IN LOW-INTERMEDIATE RISK PROSTATE CANCER AFTER ORAL ADMINISTRATION OF HYALURONIC ACID, CHONDROITIN SULFATE, CURCUMIN AND QUERCETIN (IALURIL• SOFT GELS)

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Aims: Irritative urinary symptoms have peaked after one month from permanent seeds implantation in prostate cancer (PCa). Aim of our study is to determine whether the oral use of Ialuril® soft gel reduces acute genito-urinary toxicity, induced by Iodine125 BT LDR , in particular LUTS (lower urinary tract symptoms).

Methods: From april 2015 to February 2016, 40 men undergoing Iodine125 BT LDR permanent seed implantation as monotherapy with diagnosis of low-intermediate risk of PCa, according to National Comprehensive Cancer Network (NCCN) risk group and ASTRO-EAU-EORTC guidelines, were enrolled. They were randomly assigned in two groups: the first assumed Ialuril® soft gel after BT-LDR for a month, while other group received no preventive therapy. All patients were discharged on first day post-BT. The International Prostate Symptom Score (IPSS) questionnaire was administered in all cases before BT-LDR and after a month. We analized GU toxicity according to Common Terminology Criteria (CTCAE) for Adverse Events scale v4.0.

Results: Of the 20 patients that have Ialuril® soft gel oral administration, prior to therapy 15 tox G0 and G1 in 5 patients, while patients who haven't been given no adjuvant therapy showed G0 in 16 patient and 4 G1. After one month, patients who were prescribed adjuvant therapy showed G0 in 16 cases and 4 G1, while patients without therapy 8 G0, toxicity G1 in 11 patients and one case G2, as shown in the attached charts.

Conclusions: Ialuril Soft Gels® in this small study, seems to improve the acute toxicity GU in patients undergoing BT LDR with permanent seeds implantation in PCa.

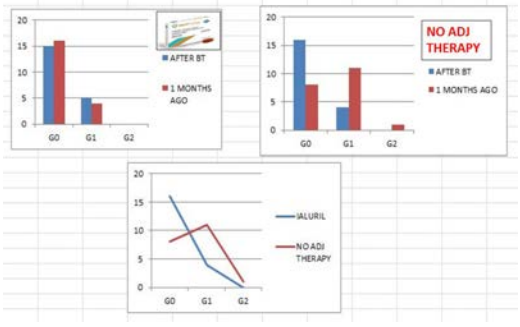

Figure 1.

P210

THE ROLE OF HYALURONIC ACID IN THE TREATMENT OF ACUTE AND LATE TOXICITY AFTER HIGH DOSE RATE (HDR) ENDOVAGINAL BRACHYTHERAPY

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Aims: The aim of our study was to evaluate the effectiveness of hyaluronic acid (HA) in the prevention of acute and late vaginal toxicities in patients (pts) with endometrial cancer treated with endovaginal HDR Brachytherapy (BT).

Methods: From January 2011 to January 2015 we retrospectively analyzed 126 pts affected by low risk endometrial cancer. All pts were treated with extrafascial or radical hysterectomy with lymphadenectomy +/- adjuvant Chemotherapy (CT) and received adjuvant HDR endovaginal BT. Before Computerized Tomography simulation a vaginal applicator (diameter size range 2-3.5 cm), depending on vaginal extension, was positioned. Target delineation was contoured according to American Brachytherapy Society Consensus Guidelines. The total dose prescription was 21 Gy in 3 fractions delivered 1

fraction for week. We prescribed 1 ovule containing 5 mg of HA every evening in pts without symptoms and twice a day in pts with symptoms and we suggest to continued local therapy 2 weeks after BT. Acute and late toxicity was evaluated according to CTCAE vs 4.02.

Results: The mean age of pts was 67 years (range 27-90) and the median follow-up was 29 months (range 3-59). According to FIGO 2009 classification we observed 39 pts (30.9 %) FIGO IA, 73 pts (57.9%) FIGO IB, 11 pts (8.8%) FIGO II and 3 pts (2.4%) FIGO III. The last received only BT for comorbidity and old age (>85 years). 33 pts (26.2%) received adjuvant CT. Overall acute toxicities occurred in 24 pts (19%): vaginal inflammation (G1/G2) in 18 pts (14.3 %), dyspaneuria (G1/G2) in 7 pts (5.5%) and haemorragy (G2) in 1 pts (0,8%). Two pts (1.6%) had more than one acute toxicity. Overall late toxicity was observed in 20 pts (15.9%): fibrosis (G1/G2) in 14 pts (11.1%), telangectasias (G1/G2) in 7 pts (5.5%), dryness (G1/G2) in 6 pts (4.8%) and stenosis (G1) in 2 pts (1.6%). Six pts (4.8%) had more than one late toxicities. No G3 or higher acute or late toxicities were observed.

Conclusions: The incidence of HDR-BT vaginal toxicity is variably reported in literature with ranges wide from 12.7% to 88.0%. Compared with literature data, our results suggest that the use of topical therapy with HA can reduce vaginal toxicities and can play a key role in heling process of damaged tissue after endovaginal adjuvant BT. Further studies with higher number of pts and longer follow-up are necessary to define our findings and to determine the optimal doses and duration of topical therapy with HA.

P211

HDR VS LDR VAGINAL BRACHYTHERAPY: A COMPARISON IN TERMS OF OUTCOMES AND TOXICITY

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Aims: To compare the outcomes in terms of survival and toxicity for endometrial carcinoma patients treated with either HDR or LDR vaginal brachytherapy (VBT) after external beam radiotherapy.

Methods: From January 2000 to December 2014, patients with endometrial cancer after radical hysterectomy +/- pelvic and/or lombo-aortic lymphadenectomy were treated with adjuvant radiotherapy (45 Gy, 1.8 Gy/day on the whole pelvis) and subsequential VBT boost (HDR dose was 7 Gy in one fraction prescribed to 0.5 cm from the surface of the applicator; LDR dose was 25 Gy to the vaginal mucosa). The outcomes of patients were evaluated in terms of local control (LC), overall survival (OS) and toxicity (according to CTCAE v 4.0).

Results: We retrospectively analyzed 200 patients treated with external beam radiation therapy followed by a HDR VBT boost in 78 patients and LDR VBT boost in 122 patients. Patients characteristics are summarized in Table 1. With a median follow-up of 25 months (range 1-163), 5-ys overall suvival (OS) was 98% vs 97% in LDR and HDR group respectively (p=0.37) and 5-ys local control (LC) was 93%, similar in the two groups (p=0.81). At multivariate analyses, any factors (age, stage, grading) seems to have impact on OS (p=0.37) and LC (p=0.81). Patients treated with LDR VBT after external beam radiotherapy had an higher gastrointestinal acute toxicty; probably, this is due to development of radiation tecnique over the years of this study. No differences was found in terms of acute genitourinary and hematological toxicity. Late toxicity such as vaginal stenosis was registered during regular follow-up visit by clinical evaluation. We didn't find statistically significant differences between the two modalities (p=0.67).

Conclusions: With the limits of a restrospective review, there were no differences in survival and late toxicity outcomes for patients receiving LDR or HDR brachytherapy. HDR is safe technique in comparison to LDR modality. A larger database analysis will confirm outcomes and toxicity of HDR VBT in postoperative endometrial cancer.

Table 1.

Patient characteristics	TOTAL	HDR	LDR
Age (Median)	63 (31-88)	64 (36-88)	62 (47-88)
Histology • Adenocarcinoma	200	78	122
Stage • IA • IB • IC • II • IIIA • IIIB • IIIC	14 55 59 44 13 3 12	12 39 2 10 5 2 8	2 16 57 34 8 1 4
Grading • Well differentiated • Moderately well-differentiated • Poorly differentiated	25 97 78	4 32 42	16 66 40
Miometrial Invasion • < 50% • > 50%	55 145	24 54	30 92

P212

HYPOFRACTIONATED BRACHYTHERAPY BOOST; REVERSE OR TRADITIONAL? AN ANALYSIS OF EFFECTIVENESS ON SURVIVAL

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Aims: To evaluate survival curves of two different treatment schedules of high dose rate hypo-fractionated brachytherapy in gynaecological cancers.

Methods: From November 2008 to April 2012 95 pts. with endometrial cancer (no recurrences) were treated in postoperative setting as out patients according to this treatment schedule: 18 Gy in 3 fractions as Boost after external-beam pelvic irradiation (50 Gy in 5 weeks) or Reverse boost 18 Gy in 3 fractions before the same exter-

nal-beam pelvic irradiation. Dose was prescribed to 5 mm from the surface of the applicator, 3,5 cm the active length of the source. The implant optimisation was performed recognizing the bladder dose and the rectal dose as average of almost 3 points for each critical organ with a semi-3D technique aided by simulator, the optimal target-dose volume was determined with radiopaque marker into the rectum and Foley catheter balloon in the bladder. The comparison of survival curves with the Kaplan Meier method.

Results: Two groups: Boost (45 pts.) versus Reverse (50 pts.). The median follow-up of the entire population was 5,35 years (range 1,13-7,33); in the Boost recorded median age 58 (range 31-84); stage distribution was pT1b 7 pts., pT1c 26, pT2 11, other stages 1; G1 11 cases, G2 32, G3 2; lymph node status performed in 38 pts. (N0=36, N1=2) in other 7 NX; in the Reverse median age 69 (range 41-84); stage distribution was pT1b 12 pts., pT1c 25, pT2 10, other stages 3; G1 9 cases, G2 32, G3 9; lymph node status performed in 43 pts. (N0=39, N1=4) in other 7 NX. The late toxicity as G3- G4 was 4 pts. in Boost group and 2 in Reverse population. The relapse recorded only in 1 (still alive) of group Boost. The groups resulted comparable for these parameters. We also evaluated the gap after external beam in Boost group and it resulted a median of 35 days (range 7-134). The survival comparison resulted slightly favourable to Reverse group median 5,83 versus 4,81 years (P=0,70).

Conclusions: The second schedule of high dose rate brachytherapy is more effective in gynaecological cancers with acceptable toxicity compared to the first schedule. To explain these data, the hypothesis is that reverse boost is a method to minimize the chance of geographic miss in pts. with the vaginal cuff without damage like fibrosis or stenosis by external radiotherapy.

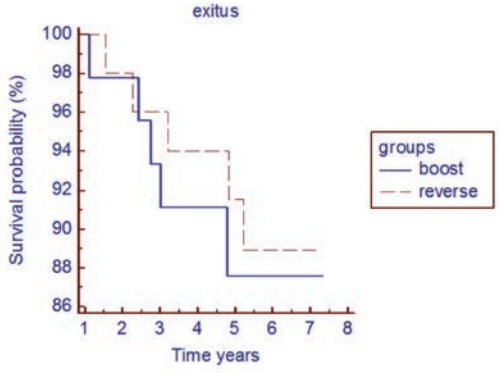

Figure 1.

P213

SALVAGE LDR-BRACHYTHERAPY FOR RECURRENT PROSTATE CANCER AFTER EBRT: RESULTS FROM A SINGLE INSTITUTION WITH FOCUS ON TOXICITY

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Aims: Salvage brachytherapy (along with surgery and criotherapy) are among the most used salvage therapies for locally recurrent prostate cancer after primary radiation therapy. These techniques, in particular when applied to the whole gland, carry a high risk of toxicity and, frequently, a deterioration of the patient's quality of life. Our aim is to evaluate the results of whole gland salvage BT after primary EBRT in terms of toxicity (primary endpoint) and efficacy (secondary endpoint).

Matherials and Methods: We retrospectively analyzed clinical data of 19 patients treated with salvage BT at our institution from June 2012 to November 2015. Local recurrences were identified with PET choline (with or without MRI)after biochemical recurrence according to Phoenix criteria (nadir + 2). All patients received 130 Gy LDR-BT. At the time of salvage BT only 2 patients were receiving ADT (local recurrent CRPC). Acute and late toxicities were graded using CTCAE 4.0. Data from IPSS and IIEF questionnaires at 6-12 and 24 months after salvage BT were also reported (higher IPSS and lower IIEF indicate deterioration). Univariate analysis was performed to identify predictors of biochemical control and toxicities.

Results: Median follow up after salvage BT was 24 months. We observed only 1 case of acute G3 cystitits. Severe late toxicities were observed: 2/19 G3 cystitis (10,2%) and 1/19 G4 proctitis (5,3%). Median IPSS score pre- salvage BT and after 6-12-24 months were respectively 4, 11, 12 and 5. Median IIEF score pre-salvage BT and after 6-12-14 months were respectively 5,2,4 and 4. At the time of analysis only 2 patients showed biochemical relapse (3-years FFBF 85,2%). At univariate analysis only interval to relapse after initial treatment (p=0,05) were significant in predicting further biochemical failure. No statistically significant correlations between pre IPSS and IIEF status and toxicity post treatment were found.

Conclusions: Salvage BT for recurrent prostate cancer after primary EBRT seems to be a feasible treatment for selected patients. The severity of the observed toxicities showed a "peak" after 6 months/1 year after treatment and then decreased. Good results were observed in terms of treatment efficacy. Longer follow up and further accrual of patients is needed to confirm these results.

P214

DEFINITIVE HIGH-DOSE-RATE BRACHYTHERAPY FOR CERVICAL CANCER: A SINGLE INSTITUTION 20 YEARS EXPERIENCE

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Aims: To evaluate the results, efficacy and tolerability of definitive high-dose-rate (HDR) intracavitary brachytherapy for cervical cancer patients, in a single institution experience.

Methods: From September 1994 through December 2015, 77 patients with primary cervical cancer were radically treated in our radiotherapy department with high-dose-rate intracavitary brachytherapy, using a remote after-loading Iridium-192 source with a Ring or Fletcher applicator (chosen depending on patient anatomy). The mean age was 67 (range, 39-90). The great majority of those patients received also an external beam radiation therapy (EBRT) treatment (74 patients, 96.1%) with different timing (median interval between EBRT and HDR was 7 days, range 0-31) and different total doses (range, 23.4-64 Gy, with conventional fractionation), 28.6% had a parametrial boost, and 5.2% a lombo-aortic nodes EBRT treatment. Of the patients, 76.6% had a locally advanced disease (41.5% in IIB stage, 3.9% in IIIA stage and 31.2% in IIIB stage), and the histology was squamous-cell carcinoma for 76 patients and adenocarcinoma for only 1 patient. HDR median total dose to Point A was 14 Gy (range, 7-31 Gy) erogated in 2 fractions (range, 1-4). Twenty-four patients also received a chemotherapy treatment (1 to 3 cycles, in a platinum-based asset).

Results: With a median follow-up of 52 months (range, 3-258), no acute or late toxicities of grade 3 or 4 were observed (especially genitourinary nor gastrointestinal). Complete clinical and instrumental response was observed in 65 patients, while 6 patients had a partial response and 6 patients had no response or local disease progression after HDR treatment completion. The overall survival and disease-free survival rates at 5 years were 52.7% (95% confidence interval, 42%-66%) and 63.2% (95% confidence interval, 53%-76%), respectively, and 6 patients had evidence of distant metastases.

Conclusions: Definitive high-dose-rate brachytherapy for cervical cancer is a well-tolerated treatment, with excellent disease local control rates. Overall survival rates are still limited by the high age of patients.

P215

EXCLUSIVE INTERSTITIAL HIGH-DOSE-RATE BRACHYTHERAPY FOR LIP CANCER: REPORT ON A SERIES OF 8 PATIENTS

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Aims: To evaluate outcome of patients with lip cancer treated using high-dose-rate (HDR) brachytherapy alone.

Methods: We examined the medical records of 8 patients with lip cancer treated with exclusive HDR interstitial brachytherapy, using a remote afterloading unit, between June 2005 and May 2015. The mean age was 79 years (range 43-83). There were 6 men and 2 women and all patients had a squamous cell carcinoma, but one with a mixed form (basaloid and epidermoid). The tumor was located on the lower lip in 6 patients, in the upper lip and in the left commissure in another one. Clinical stage was T4N0 in one case, T3N0 in 4 case, T2N0 in 3 cases including 3 recurrent tumors. The implantation procedure was performed in all cases after local anesthesia. The implanted volume included an amount of healthy tissue around the gross disease, with a safety margin of 1 cm, depending on the position of the tumor. Tumor volumes were implanted with 2-4 needles spaced by about 10 mm. A dose of 45 Gy in 9 fractions (5 Gy per fraction twice a day from Monday to Friday) was delivered in all cases, with a minimum interval of 6 hours between fractions.

Results: The implantation procedure was well tolerated, with no immediate complications. No patients experienced severe pain or discomfort during treatment. After a median follow-up of 31.5 months (range 5-124), the disease free survival rate (DSF) was 75% and the overall survival (OS) rate was 75%. Two patients had a histologically confirmed neck nodal recurrence, occurred at 15 and 20 months from procedure, respectively. One of them underwent a therapeutic neck dissection followed by adjuvant radiotherapy and died 72 months after salvage surgery free from disease. Instead the other patient refused any treatment and died 14 months after diagnosis of recurrence. None of our patients had a local recurrence. The proper functioning of lips and mouth was maintained in all cases, with good cosmetic results in all patients, except two: the first one had a carcinoma of the oral commissure and developed a mild oral stenosis (in part already known before the treatment); the second one had a carcinoma of the upper lip and developed an unsightly retraction. No serious late toxicity was recorded.

Conclusions: In our retrospective study, exclusive HDR interstitial brachytherapy resulted a feasible and safe conservative option for the treatment of lip cancer, and offered an excellent local control with good functional and aesthetic results.

P216

EXCLUSIVE HDR BRACHYTHERAPY IN POST-OPERATIVE ENDOMETRIAL CANCER PATIENTS: CLINICAL OUTCOMES

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Aims: To evaluate disease local control in terms of overall survival, disease-free survival and the toxicity rates of patients with early stage endometrial cancer treated with brachytherapy alone.

Methods: From September 2007 to December 2016, 52 patients with endometrial cancer were retrospectively analyzed. The mean age was 65 years (range, 47-76 years). Surgery consisted of total hysterectomy and bilateral salpingo-oophorectomy (TH/BSO). Pathological stage was defined according to the International Federation of Gynecology and Obstetrics surgical staging system (FIGO-2009). The stage distribution was as follows: IA in 27/52 patients (52%); IB in 25/52 patients (48%). About histological grading: 4/52 (7.7%) patients were G1, 33/52 (63.5%) patients G2, 15/52 (28.8%) patients were G3. All patients received post-operative HDR (high dose-rate) VBT (vaginal brachytherapy) delivered to a dose of 21 Gy given in 3 fractions of 7 Gy. Acute and late toxicities were evaluated according to RTOG scale. Overall survival, disease-free survival were based on Kaplan-Maier statistical analysis.

Results: The median follow-up observed was 35 months (range 5-77 months). The five-year overall survival was 97,6%. The five-year disease-free survival was 91.3%. 47/52 patients (90.4%) presented a complete response to the treatment. No local relapse (pelvic or vaginal) was observed. One patients died after 14 months of follow up for intercurrent causes without evidence of disease, while one patient died due to disease progression after 8 months of follow up. Four patients presented distant disease: 2 patients presented pulmonary disease, one patient had inguinal lymph nodes metastases, and one patient showed systemic metastases. Acute VBT-related toxicity was seen in 12 (23%%) patients: 3 patients (5.8%) developed grade 1-2 gastrointestinal toxicity and 9 patients (17.3%) developed grade 1-2 genitourinary toxicity. Diarrehea was the most common adverse effect (25%). We recorded late toxicities GU in 7 patients (13.5%): particularly, vaginal grade 1-2 toxicities were observed. No GI toxicities were observed. There was no evidence of grade 3-4 toxicity.

Conclusions: Adjuvant VBT in patients with early stage endometrial cancer showed good outcomes in terms of disease local control with an acceptable toxicity profile.

P217

CURATIVE RADIATION THERAPY (EBRT+BT) FOR LOCALLY ADVACED CERVICAL CANCER: MONO-INSTITUTIONAL EXPERIENCE ON 39 PATIENTS

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Purpose: The aim of this study is illustrate our experience in curative treatment of advanced cervical cancer by using external beam radiation (EBRT) and concomitant chemotherapy followed by brachytherapy (BT).

Materials and methods: This study includes 39 patients with cervical cancer treated in our center from 2010 to 2015. The mean age was 58 years old (range 30-83), 11/39 patients (28,2%) had more than 60 years at diagnosis. The mean value of the widest tumor diameter was 45,4mm (range 19-87 mm). FIGO STAGE: 2/39 was IB1, 1/39 was IB2, 3/39 was IIA, 18 was IIB, 3/39 was IIIA, 5/39 was IIIB, 4/39 was IVA, 2/39 was IVB. 13/39 patients (33,3%) presented regional lymph nodes involvement. Only 2 patients had positive para-aortic lymph nodes. Five/39 patients (12,8%) made neoadjuvant chemotherapy: the patients were considered not respondent, therefore surgical approach was excluded and a curative radiochemotherapy was planned. Thirty-four/ 39 (87,1%) patients were treated with chemio-radiotherapy plus brachytherapy and 5 with exclusive radiotherapy plus brachytherapy. The concomitant chemo-therapy was given once a week (the median of cicle was six), with Cisplatin 40mg/mq2.

Twenty-two/39 patients (56,4%) were treated with IMRT tecnique, and 17 of them (77,3%) received IMRT-SIB (2.2 Gy x 28 fractions on GTV-cervix and GTV-LNs PET-positive, 1.8 Gy x 28 fraction on pelvis ± LN lombo-aortics). The means total BT dose was 21 or 28 Gy in 3-4 fractions of 7 Gy for fraction with the aim to achive a total dose (EBRT plus BT) in the range of 85-90 Gy.

Results: The mean follow up was 26 months (Range 4-60 months). 1/39 patients (2,6%) was lost to follow-up and it is not possible to evaluate the response to treatment. At the first control (3 months from the end of treatment) the complete response rate was recorded in 31/38 (81,6%) patients, while 4/38 patients (10,5%) showed a systemic progression with lung metastatis in 2 patient and 2 patients had lymph-nodes nodes progression (inguinal nodes and lombo-aortic nodes, respectively), all the patients showed complete regression of the cervical disease. Finally, 3/38 (7.9%) patients were considered not respondent. Only 1/31 patients (3.2%) had cervical relapse 18 month after the end of treatment. Overall, after a median follow-up of 26 months, 3 patients died for progressive disease. Early radiation reactions were recorded in 25/38 patients (65,8%). Most of toxicity were of grade 1-2 and involved gastrointestinal and genito urinary system. Chronic toxicity on tissues mainly concerned the vaginal mucosa with vaginal dryness, atrophy and vaginal stenosis.

Conclusions: The results show that locally advanced cervical cancer, treated with curative chemo-radiotherapy plus brachytherapy presents a high complete response rate with good compliance to treatment regarding to acute and chronic toxicity.

P218

HYPOFRACTIONATED HDR BRACHYTHERAPY: A LONG TERM ANALYSES OF A MONOISTITUTIONAL EXPERIENCE IN PATIENTS AFFECTED BY SOFT TISSUE SARCOMAS

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Aims: The purpose of our study has been the evaluation outcomes and toxicity of adjuvant high dose rate hypofractionated brachytherapy combined or not with 3D-conformal radiation therapy in the management of patients affected by soft tissue sarcomas

Patients and Methods: In this retrospective analysis, the inclusion's cryteria was diagnosis of sarcoma and adjuvant treatment with hypofractionated brachytherapy HDR (250-700 cGy per fraction). The outcomes of patients were evaluated in terms of toxicity, local control and overall survival

Results: From June 2003 to april 2016 19 patients were treated with high-dose rate brachytherapy (HDR). Out of nineteen 53% were male and 47% female. Median age was 59 years (range 44-70). In 15 patients (78.9%) the tumour was located in an extremity while in 4 (21.1%) in retroperitoneum. Only three patients (15.8%) were treated with HDR alone whereas for the remaining ones a combination of brachytherapy and external irradiation was used. Total dose was selected depending on type of implant and proximity to vessels or skin; one patient received 10 Gy in 4 fractions, 3 pts 15 Gy in 3 fractions , 3 patients 20 Gy in 5 fractions, 8 patients 16 Gy in 4 fractions and 3 patients 30 Gy in 6 fractions and only 1 patient received 35 Gy in 5 fractions.). Acute toxicity was mild (G1-2) and occurred only in patients whose treatment with HDR was followed by external beam irradiation. Local control was recorded in 68.4% of the patients; 6/19 patients developed local recurrence during the follow-up period, of which three have been affected by retroperitoneal sarcomas. Distant metastasis occurred in 4/19 patients (21%). Median overall survival was 90 months while median local control was 114 months.

Conclusions: Hypofractionated HDR brachytherapy is safe and well tolerate.

P219

IS HDR INTERSTITIAL BRACHYTHERAPY BOOST TOLERATE AND FEASIBLE IN PROSTATE CANCER? A SCHEDULE EVALUATION

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Aims: Brachytherapy (BT) is a consolidate method to create dose-escalation and steep dose gradients between target and organs at risks (OAR). Aim of this analysis was to evaluate acute genitourinary (GU) and gastrointestinal (GI) toxicity after one fraction of High Dose Rate BT (HDR-BT) and External Beam Radiation Therapy (EBRT) in prostate cancer patients.

Methods: Patients with prostate cancer, histologically confirmed, were enrolled. Selection criteria included: M0; high-risk features (Stage T3 and/or Gleason Score>7 and/or prostate specific-antigen level>20 ng/mL) or intermediate-risk features (Stage T2c and/or GS>7 and/PSA>10 ng/mL and<20 ng/mL); no Trans-Urethral resection of the prostate (TURP) in the previous sixth months; no anesthesiological contraindications. All patients received one fraction of HDR. The total dose was 15 Gy on high risk zone (periferical zone) during a hospitalization. Under spinal anesthesia, a pre-planning was performed before the procedure for studying the optimal implant geometry. The definitive treatment planning was realized on US imaging acquired in the bunker. After two weeks later BT, all patients received EBRT (46 Gy in 23 daily fractions), by volumetric IMRT/Arc therapy. All patients assumed androgen deprivation therapy. Dosimetrical parameters and acute Toxicity (according to the Common Toxicity Criteria for Adverse Event Version 4.03-CTAE v4.03, by the National Cancer Institute) were collected.

Results: Between June 2014 and January 2016, 9 patients were treated by the reported schedule. For HDR-BT, hospitalization lasted three days; no post-HDR procedure complications were detected in all patients. In 8 patients the procedure resulted feasible in terms of workload organization. In 1 patient due to US artefacts we performed a CT simulation. Median follow-up was 6 months. The dosimetrical constraints evaluated were D2cc<12Gy e V100<15Gy for rectal volume, and D10cc<17.5 Gy and D30cc<16.5 Gy for urethra. They were respected in 100% of cases. The schedule was well tolerated. No patient developed GI and GU acute and late toxicity of any grade.

Conclusions: This schedula is feasible and very well tolerated with low morbidity. Ongoing and planned accrual of more patients and a longer follow-up will allow confirming these preliminary results. Moreover, in the future we planned to define the high risk zone of prostate using MR imaging and US-MR imaging fusion software.

P220

INTENSITY MODULATED RADIATION THERAPY (IMRT) FOLLOWED BY PULSED-DOSE-RATE BRACHYTHERAPY BOOST (PDR-BT) IN THE CURATIVE TREATMENT OF UTERINE CERVICAL CANCER: THE EUROPEAN INSTITUTE OF ONCOLOGY EXPERIENCE

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Aims: The aim of study was to evaluate the outcomes in terms of local and distant control, disease progression, overall survival (OS) and the toxicity profile for patients (pts) treated with curative-intent with Intensity Modulated External Beam Radiotherapy (IMRT) followed by Pulsed-Dose-Rate Brachytherapy (PDR-BT) for uterine cervical carcinoma.

Methods: Between 3/2011 and 2/2014, 44 pts (39 squamous cell carcinoma, 6 adenocarcinoma) were treated with PDR-BT boost after IMRT. The median patient age at diagnosis was 50.9 years (range 28.2 – 86.9). According to FIGO classification there were 2 stage IA, 12 IB, 2 IIA, 14 IIB, 1 IIIA, 11 IIIB, 2 IVB. 24 patients had positive nodes. 39 pts received concomitant platinum based chemotherapy +/- paclitaxel . The treatment consisted of pelvic +/- lomboaortic tract IMRT using RapidArc® to a total dose of 45-50.4 Gy/25-28 fractions, 5 fr/week. PDR-BT boost, after a median time of 15 days (range, 1-92 days), was performed by a median CTV prescribed dose of 30 Gy (range 24-30 Gy). The median dose-rate was 0.5 Gy/h (range 0.4 to 0.6 Gy/h), delivering 1 pulse/h, 24/24h by a cable-driven remote afterloaded Iridium-192 source. Acute and late toxicity were evaluated by RTOG scoring criteria and SOMA-LENT criteria, respectively.

Results: The median follow-up was 26.7 m. (range, 4.4 - 42.7). At the end of BT 4 pts (8.8%) referred a grade 1-2 genito-urinary (GU) symtoms. Acute toxicity (within 6 m.) was observed in 23 pts (52.2%) with a grade 1-2 in one or more of the following sites: skin, vagina, mucosae, GU or gastrointestinal (GI) tract. Grade 1-2 GI and vaginal late toxicity (after 6 m.) occurred in 21 pts (46.6%) while grade 3-4 in 6 pts (13.6%): 4 pts developed a G4 rectal complications requiring colostomy (1 stage IB, 2 IIB, 1 IIIA at diagnosis) and 2 pts had a G3 vaginal stenosis. OS, disease-free-survival and local control at last follow up were 84% (37/44), 72.7% (32/44) and 88.6% (39/44), respectively. Distant mets occurred in 18.18% (8/44), pelvic relapse in 6.8 % (3/44), both pelvic and distant mets in 4.5% (2/44).

Conclusions: Our study confirms that the combination of IMRT and PDR BT can be considered a safe and effective treatment for cervical cancer. Despite high percentage of advanced disease pts, local control was very high (near 90%). Patterns of failure with metastatic dissemination claims for the optimization of the systemic approach.

P221

INCIDENCE AND TREATMENT OF OROPHARYNGEAL CANDIDOSIS IN CANCER PATIENTS: RESULTS OF OBSERVATIONAL MULTICENTRIC TRIAL

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Aims: An Italyn multicentric observational trial was conducted to describe the oropharyngeal candidiasis (OPC) incidence and correlated treatment in cancer patients undergoing radiotherapy, alone or combined with chemotherapy.

Materials and Methods: We retrospectively analyzed patients with non-metastatic tumors; inclusion criteria were: age ≥ 18 years, histologically confirmed diagnosis of head and neck SCC in stage I-IV, renal, colon rectal or lung cancer that underwent to radiotherapy alone or associated to chemotherapy or biological therapies and normal renal/liver function. Exclusion criteria were: metastatic disease, previous or concomitant diagnosis of second cancer, previous head and neck RT, psychiatric disorders, chronic use of antimycotic drugs, severe infection treated with intravenous antibiotic agents and diagnosis of mycotic or bacterial infection of oral cavity or systemic mycosis. OPC treatment depended on behavior of single centre, topic or systemic drugs were allowed. Primary end point was OPC incidence, secondary endpoint was to evaluate impact of prophylactic therapy on OPC. Ethical Board approval by every participating center was required.

Results: From January 2014 to July 2015 we identified 133 patients. 36 were female and 97 male, median age was 63 years. Primary tumor was head and neck district, colon rectum and lung in 112 (84%) pts (oropharynx 41 pts, oral cavity 36 pts, larynx 26 pts, salivary glands 7 pts and nasopharynx 2 pts), 17 (13%) pts and 4 (3%) pts, respectively. 71/133 pts underwent to cisplatin based chemotherapy associated to RT and 62/133 to radiotherapy alone. 110/133 pts reported complete data on OPC, data on remaining 23 pts were incomplete. 60/110 (55%) pts developed OPC. 28/60 (47%) underwent to prophylactic therapy: 23 pts with topic treatment (miconazole – also mucoadhesive tablets - 20 pts, fluconazole 3 pts) and 5 pts with systemic itraconazole.

Conclusions: OPC is a common disorder occurring in

cancer pts, thus prophylactic treatment seems to be a clinical practice largely used especially in the management of some solid tumors (i.e head and neck cancer). Our analysis underlines that miconazole is the main agent prescribed in this setting even if it remains to assess its role in clinical practice on a larger number of patients.

P222

DEVELOPMENT AND APPLICATION OF A METHOD TO REDUCE PROTON THERAPY SKIN TOXICITY: FROM EMPIRICAL OBSERVATION TO CLINICAL PRACTICE

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Aims: The increased skin toxicity is a renowned pitfall of proton therapy (PT), which conflicts with the superiority of protons in terms of depth dose distribution compared with x-ray therapy. No standard strategies to reduce PT skin toxicity have been described so far. Here, we report our in-house development of a method to reduce acute skin complications for proton irradiated patients.

Methods: The clinical observation (March, 2016) of the irradiated skin of a chordoma patient at the end of PT (74 Gy Rbe in 32 fractions) showed (Figure 1) a toxicity spared area surrounded by a wide region affected by intense skin reaction. The spared region exactly matched the area below the film dressing used to protect skin tattoos during treatment. A dosimetric verification showed no impact of the film dressing on proton dose distribution. The medical board consequently decided to test the application of film dressings on patients at risk for severe acute skin toxicity.

Results: Between April and May, 2016, the medical device was successfully tested on six patients at risk for severe acute skin toxicity. The results of the application of the film dressing on the skin of 1) a giant cell sacral tumor treated with postoperative proton therapy (62 GY RBE in 32 fractions) and 2) a recurrent maxillary sinus cancer patient undergoing proton reirradiation (63 Gy RBE in 35 fractions) are showed in figures 2, 3 and 4,5 respectively. At the end of treatment the skin regions below the film dressing were completely spared by acute severe toxicity (Figures 4,5).

Conclusions: The application of a film dressing upon the regions at risk for skin toxicity during PT treatment seems a feasible and effective method to reduce proton therapy surface toxicity. Several biological and physical hypothesis, without a definite conclusion, have been made regarding the exact mechanism leading to film dressings' skin toxicity sparing.[1] Our empirical finding translated into daily clinical practice in our center and confirmed the initial independent experiences recently reported by other PT facilities.[2]

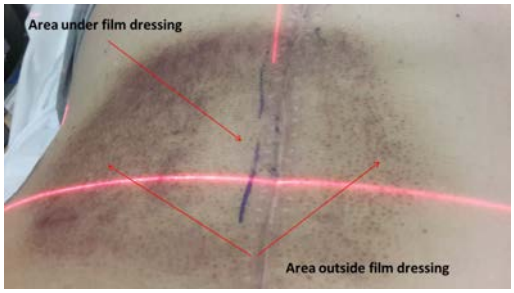

Figure 1.

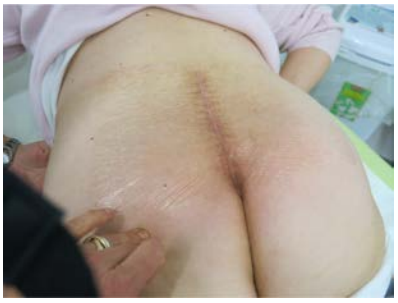

Figure 2. Start of treatment: application of film dressing.

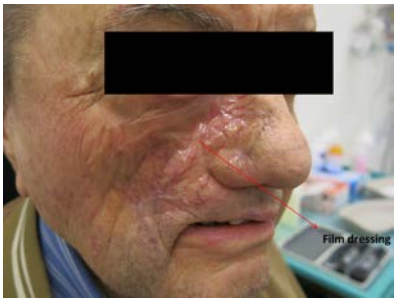

Figure 3. Start of treatment: application of film dressing on region at risk for severe toxicity (already irradiated area).

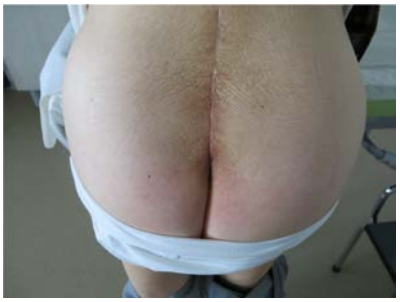

Figure 4. End of treatment: no skin toxicity observed.

Figure 5.

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P223

EFFICACY AND SAFETY OF AN HALF BODY IRRADIATION SCHEDULE IN PATIENTS WITH MULTIPLE BONE METASTASES: A PHASE I-II TRIAL

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Aims: To evaluate the efficacy of an half-body irradiation (HBI) schedule on pain relief in multiple bone metastases cancer patients. The secondary aim was to evaluate the safety of this short course hypofractionated treatment.

Methods: From August 2003 to February 2016, patients with widespread symptomatic bone metastases and no previous history of large field radiotherapy were enrolled. The pain score (pain evaluation obtained by multiplying severity frequency) and the drug score (analgesic assumption evaluation obtained by multiplying severity frequency) as well as the visual analog scale (VAS) for pain were used to record and monitor pain. Data on pain status and dosage/frequency of analgesic consumption were recorded before treatment (baseline evaluation) and during follow-up. HBI encompassed the lower half body (pelvic bones, lumbo-sacral vertebrae and upper third of femurs). Prostate cancer metastases received 15 Gy/3Gy fraction along 5 days. Skeletal metastases due to other primary tumors received accelerated HBI (3 Gy fractions twice daily, 6–8 h apart, on 2 consecutive days, up to 12 Gy).

Results: 258 patients (M/F 102/156; median age: 64; range 29-95) were enrolled and completed the treatment. After HBI, a significant reduction of pain, as evaluated by VAS, was recorded (pre- treatment versus post- treatment mean VAS: 5.4 versus 2.7, CI 2.2-3.2; p=0.0001). Moreover, 62 patients (24%) had complete pain relief and 64 patients (25%) showed more than a 30% VAS reduction. Overall response rate for pain was 53% (CI 0.95: 46.2% - 60.4%). In 182 patients (71%) Pain and Drug scores before and after treatment were valuable. Statistical analysis showed a significant reduction of Pain and Drug scores especially concerning patients with the highest scores before treatment (Chi squared test: p=0.001). In particular, 26 patients (14%) achieved a Drug Score's reduction and 40 patients (22%) discontinued analgesic therapy. Nineteen percent of all series exhibited no treatment related complications, and an additional 79% experienced only mild or moderate (transitory) toxicity. As a whole, Grade>3 toxicity (severe) was seen in four patients (2%): haematologic G3 (1 pt) and gastro-intestinal G3 (2 pts). Only 1 Grade 4 haematologic toxicity was registered. 111 patients (43%) presented pain flare's phenomenon.

Conclusions: HBI is safe and effective, providing long lasting pain reduction in patients with multiple bone metastases.

P224

C-MYC SUSTAINS TRANSFORMED PHENOTYPE AND PROMOTES RADIORESISTANCE OF EMBRYONAL RHABDOMYOSARCOMA CELL LINES

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Aims: We have previously reported that the MEK/ERK pathway sustains in vitro and in vivo transformed phenotype and radioresistance of embryonal rhabdomyosarcoma (ERMS) cell lines. Furthermore, we found that aberrant MEK/ERK signaling activation promotes c-Myc oncoprotein accumulation. In this study, the role of c-Myc in sustaining the ERMS transformed and radioresistant phenotype is characterized.

Methods: RD and TE671 cell lines conditionally expressing MadMyc chimera protein, c-Myc-dominant negative and shRNA directed to c-Myc were used.

Results: Targeting c-Myc counteracted in vitro ERMS adherence and in suspension, growth motility and the expression of pro-angiogenic factors. c-Myc depletion decreased MMP-9, MMP-2, u-PA gelatinolytic activity, neural cell adhesion molecule sialylation status, HIF-1 , VEGF and increased TSP-1 protein expression levels. Rapid but not sustained targeting c-Myc radiosensitized ERMS cells by radiation-induced apoptosis, DNA damage and impairing the expression of DNA repair proteins RAD51 and DNA-PKcs, thereby silencing affected ERMS radioresistance.

Conclusions: c-Myc sustains ERMS transformed phenotype and radioresistance by protecting cancer cells from radiation-induced apoptosis and DNA damage, while promoting radiation-induced DNA repair. This data suggest that c-Myc targeting can be tested as a promising treatment in cancer therapy.

P225

VITAMIN D PROTECTS ENDOTHELIAL CELLS FROM IRRADIATION-INDUCED SENESCENCE AND APOPTOSIS BY MODULATING MAPK/SIRT1 AXIS

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Aims: Radiotherapy toxicity is related to oxidative stress-mediated endothelial dysfunction. Here, we investigated on radioprotective properties of Vitamin D (Vit.D) on human endothelial cells (HUVEC).

Methods: HUVEC, pre-treated with Vit.D, were exposed to ionizing radiation (IR): ROS production, cellular viability, apoptosis, senescence and western blot for protein detection were performed. The role of MAPKs pathway was investigated by using U0126 (10 M) MEKs/ERKs-, SB203580 (2.5 M) p38-inhibitor or by over/expressing MKK6 p38-upstream activator.

Results: Vit.D reduced IR-induced ROS production protecting proliferating and quiescent HUVEC from cellular apoptosis or senescence, respectively, by regulating MAPKs pathways. In proliferating HUVEC, Vit.D prevented IR-induced apoptosis by activating ERKs while in quiescent HUVEC counteracted IR-induced senescence by inhibiting the p38-IR-induced activation. MEKs&ERKs inhibition in proliferating or MKK6/ mediated p38 activation in quiescent HUVEC, respectively, reverted anti-apoptotic or anti-senescent Vit.D properties. SirT1 protein expression levels were up-regulated by Vit.D. ERKs inhibition blocked Vit.D-induced SirT1 protein up-regulation in proliferating cells. In quiescent HUVEC cells, p38 inhibition counteracted the IR-induced SirT1 protein down-regulation, while MKK6 transfection abrogated the Vit.D positive effects on SirT1 protein levels after irradiation. SirT1 inhibition by sirtinol blocked the Vit.D radioprotective effects.

Conclusions: Vit.D protects HUVEC from IR induced/oxidative stress by positively regulating the MAPKs/SirT1 axis.

P226

ANALYSIS OF ACUTE OCULAR TOXICITY IN A RETROSPECTIVE SERIES OF 35 CONSECUTIVE PATIENTS (PTS) TREATED WITH ENDOSCOPIC SURGERY FOLLOWED BY POSTOPERATIVE IMRT/VMAT (PORT) FOR SINONASAL NEOPLASMS

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Aims: To investigate acute ocular toxicity in a retrospective series of 35 consecutive pts with sinonasal neoplasms after primary endoscopic surgery and PORT.

Methods: Between Jan 2010 and Dec 2015, 35 pts (30 M and 5 F; mean age: 68.5 yrs, range: 34-80) received endoscopic surgery for ITAC=21 pts (60%), squamous cell carcinoma=7 pts (20%), esthesioneuroblastoma=2 pts (6%), other histologies=5 pts (14%) and PORT: 19 IMRT (54%) and 16 VMAT (46%). TNM 2010 was: pT1N0M0=2 pts (6%), pT2N0M0=9 pts (26%), pT3N0M0=7 pts (20%), pT4N0M0=17 pts (48%). Grading: G1=1 pt (3%), G2=19 pts (54%), G3=12 pts (34%), GX=3 pts (9%). Resection margins: R0=14 pts (40%), R1/R2=8 pts (23%), RX=13 pts (37%). In all pts CTV consisted of surgical bed with adequate margins to cover pre-operative local extension and local diffusion pathways; 12 pts (34%) received also elective neck irradiation. 95% of PTV volume had to be covered by at least 95% isodose; prescription doses were: 1.8-2.0-2.2 Gy/fract. up to 54-60-66 Gy (ICRU 83) to low-, intermediate-, and high risk regions, respectively. All pts completed PORT without treatment interruptions.

Results: Acute conjunctivitis was investigated weekly during PORT; no G3 reactions were reported. 1 st week G0=35 pts (100%); 2 nd week G0=29 pts (83%), G1=6 pts (17%); 3rd week G0=25 pts (71%), G1= 9 pts (26%), G2=1 pt (3%); 4th week G0=22 pts (63%), G1=13 pts (37%); 5 th week G0=16 pts (46%), G1=18 (51%), G2=1 pt (3%); 6 th week G0=15 pts (43%), G1=18 pts (51%), G2=2 pts (6%). No other ocular acute reactions were reported in this series.

Conclusions: Our preliminary data show that in these patients IMRT/VMAT PORT after endoscopic surgery allows for excellent PT coverage and result s in very mild acute toxicity to conjunctiva, that does not interfere with proper treatment delivery.

P227

ACUTE AND LATE TOXICITIES IN PATIENTS AFFECTED BY ORAL CANCER TREATED WITH INTENSITY-MODULATED RADIOTHERAPY (IMRT)

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Aims: The aim of the study was to analyze acute and late toxicities in patients (pts) with oral cancer treated with IMRT.

Methods: From January 2011 to January 2016, 58 pts (mean age 62.9 yrs; range 42-87) with oral cancer underwent adjuvant RT or exclusive RT-CT were analyzed. The RT was performed with IMRT technique and LINAC DHX of Varian System. The dose prescribed was 66Gy (2.2Gy/ff) for PTVs high risk; 60 Gy (2.0Gy/ff) for PTVs intermediate risk and 54 Gy (1.8Gy/ff) for PTVs low risk. Acute and late toxicity was evaluated according to CTCAE scale vs. 4.0 by weekly examination during RT treatment and every 3 months after RT.

Results: At analysis 41 pts (70%) were male and 17 (30%) female. The median follow-up was 23.3 months (range 3-63months). Overall, 36 pts (62%) underwent surgically treatment and 22 (38%) exclusive RTCT treatment. RTCT or RT plus molecular-target therapy was prescribed in 27 pts (47%); 22 pts (81%) received CDDP 40 mg/mq q7 and 5 pts (19 %) received RT plus Cetuximab 250 mg/mq q7. Acute toxicity: G1/G2 mucositis occurred in 52 pts (89 %) and G3 in 2 pts (3.5 %); G1/G2 dysphagia in 35 pts (60%) and G3 in 3 (5%) pts; G1/G2 odynophagia was observed in 40 (69%) pts and G3 in 4 pts (8%); G1/G2 dysgeusia in 49 pts (84%) and G3 in 2 (3.5 %) pts. Finally, G1/G2 weight lost was observed in 29 pts (50%) and G3 in 3 pts (5%). Patients with G3 dysphagia or weight lost underwent parenteral nutrition and the with G2 required nutritional support. Only 1 pts required the placement of PEG due to a significant weight loss (10 kg). Late toxicity: G1/G2 mucositis occurred in 5 pts (9%); G1/G2 dysphagia in 24 pts (41%) and G3 in 3 (5%) pts; G1/G2 odynophagia in 26 pts (45%) and G3 in 1 (1.7%) pts; G1 dysgeusia occurred in 23 pts (40%) and G3 in 2 (3.5%) ; G1/G2 xerostomia was observed in 15 pts (26%) and G3 in 1 pts (1.7%). Finally, G1/G2 weight lost occurred in 6 pts (10%) and G3 in 1 (1.7%) pts. Overall G3 late toxicity was observed in 8 pts, of them 6 pts required nutritional support and 2 pts placement of PEG due to weight lost and dysphagia.

Conclusions: The IMRT technique was feasible for treatment of oral cancer with acceptable acute and late toxicities. Overall, G3 acute and late toxicities occurred in 26% and 13% respectively. Our study showed better results compared with the data in literature. Nevertheless, is essential to identify the pts with high risk of severe toxicity to better clinical management of this subset of pts.

P228

STEREOTACTIC BODY RADIOTHERAPY (SBRT) IN THE TREATMENT OF LUNG, ABDOMINAL AND BONE RENAL CELL CARCINOMA (RCC) METASTASES

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Aims: RCC tumors are not too radio-resistant as previously thought, considering that SBRT of metastases from RCC is associated to a good local control and long-term palliation. So, SBRT is a new treatment option for metastatic RCC. We report our experience on lung, abdominal and bone RCC metastases treated with SBRT.

Method: 15 patients with 17 metastases (5 bone, 6 lung, 5 lumbar-aortic lymph node) from RCC were treated. Male/female ratio was 13/2, median age was 68y (range, 62-80), median KPS was 100% (range, 80-100). In 3 patients metastases were synchronous, whereas in the others metastases occurred after a median time of 11 months (range 2-48) from first diagnosis. At the time of irradiation, 12 patients receiving target therapy with tyrosine-kinase inhibitor (TKI), stopped it for 14 days (7 days before and 7 after SBRT). Patients with synchronous diagnosis of metastatic RCC received SBRT after nephrectomy and before to start target therapy. All lesions were treated with 5 fractions and various single doses (12Gy, 10Gy, 8Gy, 7Gy, 6Gy and 5Gy in 2,2,2,4,4, and 3 lesions, respectively). All but 2 patients were treated in only 1 site. The 3 patients with bone metastases had pain requiring opioids.

Results: At a median follow-up of 25 months (range, 11-84), all patients were evaluable. Radiographic response using RECIST criteria 3 months after treatment was obtained in 100% of lesions, 12 were stable, 3 were in partial response and 2 in complete remission. After SBRT opioids were reduced, TKI were started again without delay 7 days later. 2 patients (one with a bone and one with a lung metastasis) relapsed in-field after 6 and 14 months from irradiation. Remaining 13 patients not experienced progression in the irradiated sites. 10 patients had a systemic progression of disease after a median time of 24 months, 2 were treated with SBRT, 2 were submitted to surgery, 1 to radiosurgery for brain progression, and remaining 5 received second line target therapy. No G3-G4 toxicity was registered.

Conclusions: Our experience confirms a high response rates after SBRT of lung, abdominal and bone RCC metastases. SBRT is safe and effective for this setting of patients and may delay the need to start or change target therapy.

P229

XEROSTOMIA IN PATIENT REPORTED OUTCOMES (PROS). XEROSTOMIA QUALITY OF LIFE SCALE (XEQOLS) QUESTIONNAIRE: THE TRANSLATION INTO ITALIAN LANGUAGE

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Aims: to translate the Xerostomia Quality of Life Scale (XeQoLS) into italyn language (XeQoLS-IT). Xerostomia is the most relevant acute and late toxicity in patients with head and neck cancer treated with radiotherapy (RT) or radiochemotherapy (RTCT). Patient-Reported Outcome (PRO) instruments are subjective reports on patient perception of their health status. The majority of PROs are in english language. The XeQoLS developed at the University of Michigan consists of 15 items and measures the impact of salivary gland dysfunction and xerostomia on the four major domains of oral health-related QoL: physical, personal/psychological, social functioning, and pain/discomfort issues. Patients answered the questions by checking the box that describes best how true each statement was during the past 7 days (not at all, a little, somewhat, quite a bit, very much), with a Likert 1-5 scale. Higher scores represent greater degree of symptoms.

Table 1.

	Mean	Range
Debriefing 1: the clarity of instruction and of items on a five point Likert scale (1=not at all; 2=somewhat; 3=moderately; 4=very; 5=completely)	4,5	3-5
Debriefing 2: the ease to complete the items on a five point Likert scale (1=not at all; 2=somewhat; 3=moderately; 4=very; 5=completely)	4,5	3-5
Words/Item unclear	Item 9 (2 patients)	
Suggestion	Add item about night xerostomia (4 patients) Add item about the role of xerostomia in quality of voice (1 patient)	

Methods: The XeQoLS-IT was created through a linguistic validation multi-step process. The three main steps were: forward translation (TF), backward translation (TB) and administration of the questionnaire to 35 italyn patients with head and neck cancer during RT treatment or in follow-up. 2 Radiation Oncologists created independently two italyn versions. The two versions were compared and modificated to obtain a reconciliated version (version 1). This version was translated back into English. Discrepances were arbitreated by a third consultant, and solutions were reached by consensus (version 2). To evaluate version 2, patients completed the XeQoLS-IT and also a cognitive debriefing about the clarity of instructions, the easiness to complete the items and any recommendable changes.

Results: the mean time to compile the questionnaire was 4.5 minutes. The questionnaire was considered simply by patients. The clarity of the instructions and the easiness to answer questions had a mean value of 4.5 (± 0.71) on a scale from 1 to 5. Four patients suggested to add an item on the night dryness.1 patient suggested to consider the role of xerostomia on quality of voice. Two patients considered item 9 not so clear. The aim of the study was to make a good translation and so we did not include any variation respect to the original version.

Conclusions: A multi-step process led the creation of the final version of the XeQoLS-IT, a suitable instrument for the perception of xerostomia in patients treated with RT or RT-CT.

P230

XEROSTOMIA IN HEAD AND NECK CANCER: A PILOT STUDY ON FEASIBILITY AND UTILITY OF XEROSTOMIA QUALITY OF LIFE SCALE-ITALIAN VERSION QUESTIONNAIRE

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Aims: to conduct a pilot study on feasibility and utility of Xerostomia Quality of Life Scale-italyn version (XeQoLS-IT) questionnaire recently translated. Given to head and neck cancer patients the questionnaire focuses on the role of salivary gland dysfunction and xerostomia in the Health Related Quality of Life (HRQoL) four major domains (physical, personal/psycological, social functioning and pain/discomfort issues).

Methods: from January to April 2016, 35 patients (29 males and 6 females) with head and neck cancer, who received radiotherapy (RT) treatment or had completed radical RT (8 and 27 patients respectively), were enrolled to prospectively self-complete the XeQoLS-IT questionnaire and a Cognitive Debriefing (CD). Relatively to age, three groups were defined: 18-50 years (n=1), 51-65 years (n=17) and 66-83 years (n=17). Time for compilation was recorded for each patient. Patients characteristic were reported in table 1. CD consisted of two questions on a five-point Likert scale, the first (Debriefing 1) about clarity of instruction and items and the second one (Debriefing 2) on how ease it is to complete the items itself. Debriefing also included open questions to improve the items of questionnaire. Patients demografic, clinical and treatment details were recorded and correlated with the items, the 4 domains of HRQoL and the debrifing score.

Results: the majority of the patients easily answered the questionnaire (86%). Score about clarity of instruction and questions, and easiness to answer ranged from 3 to 5 of Likert scale (mean=4.5). Debriefing 1 score was more high in female patients (p=0.02), in age 51- 65 years (p=0.004) and in higher degree of education (p =0.01). Debriefing 2 was correlated with age, 51-65 years, (p=0.02), level of education (p=0.05) and nondrinker patients (p=0.02). In this analysis the questionnaire score suggests a greater impact on 3 domains of HRQoL (physical, personal/psycological and social functioning) in female gender and in patients in RT treatment. PS, working status, smoking or non smoking patients and pre-

sence of partner were not significant.

Conclusions: the CD suggested that XeQoLS-IT questionnaire is simple and clear to use, is understandable by patients (mean value of the debriefing 1 and 2 was 4.5/5) and the time of completion is quick 4.5 minutes. It can be a useful tool for evaluating the xerostomia and helping clinicians in the management of radiation-induced xerostomia.

P231

SENSORINEURAL HEARING LOSS IN PATIENTS WITH HEAD AND NECK CANCER TREATED WITH CISPLATIN-BASED CHEMO-RADIOTHERAPY

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Aims: Concurrent chemo-radiotherapy remains the standard of care for patients with locally advanced, high-risk head and neck squamous cell carcinoma (HNSCC). Sensorineural hearing loss (SNHL) is a common adverse event after radiotherapy (RT), with higher incidence when cisplatin-based chemotherapy (CHT) is used. The aim of this study was to evaluate the SNHL in patients with locally advanced, high-risk HNSCC treated with concurrent RT and cisplatin-based CHT.

Methods: In a retrospective cohort study, we selected 18 consecutive patients (14 male, 4 female; median age 58.5 years) affected by HNSCC (11 patients with diagnosis of oropharynx carcinoma, and 7 patients with nasopharynx carcinoma). Median follow-up was 9 months (average follow-up, 12.7 months). All patients were treated between July 2014 and March 2016. Ten patients underwent Intensity Modulated Radiotherapy technique (IMRT) and 8 with Simultaneous Integrated Boost IMRT (SIB-IMRT) with a dose ranging from 50 to 54 Gy on low-risk CTV, 60 Gy on intermediate-risk CTV, and from 67.5 to 70 Gy on GTV and high risk CTV in 30 and 35 fractions, respectively. In addition, all patients received concurrent CHT with cisplatin at 100 mg/m2 day 1 and day 21. Dosimetry was performed using the value of mean dose to the cochlea with a constraint of ≤ 45 Gy. Audiometry was performed before and after treatment. All of the audiometric evaluations used bone conduction (BC) measurements at frequencies of 0.5, 1, 2 and 4 kHz. Pure tone averages (PTA) were calculated at PTA 0.5-1-2. SNHL was defined as an increase in BC threshold >10 dB at frequencies PTA 0.5-1-2 or 4 kHz alone.

Results: Audiograms were conducted in all of the 18 patients (36 ears) before and after treatment. Twelve patients (66.6%) showed an increment in BC at high frequency 4 kHz after treatment; 4 of them developed low frequency SNHL (PTA 0.5-1-2 kHz). In 4 of these patients (8 ears), mean cochlear dose was >45 Gy, while in 8 patients (16 ears) mean cochlear dose was<45 Gy.

Conclusions: Radio-chemotherapy remains the standard of care in patients with locally advanced, high-risk HNSCC. SNHL is a common adverse event after RT, with higher incidences after concomitant cisplatin-based CHT. Our data suggest that SNHL could be related to concomitant cisplatin-based CHT as the RT hearing damage is still not detectable due to the short follow up. More interesting data about SNHL are expected as long as follow up continues.

P232

TOXICITY IN RADIOTHERAPY IN COMBINATION WITH CETUXIMAB FOR LOCALLY ADVANCED HEAD AND NECK CANCER

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Aims: To evaluate the toxicity of the combined treatment with radiotherapy and Cetuximab for locally advanced head and neck cancer (oropharynx, larynx and oral cavity).

Methods: From January 2011 to April 2016, 22 patients (18 M-5 F; mean age 56 ys.; PS 0-1) with advanced head and neck carcinoma (Stage IV A) were treated with Radiotherapy and Cetuximab 400 mg/m^2 as loading dose following 250 mg/m^2 once per week concomitant to radiotherapy for a total of 7 cycles. The dose is delivered by IMRT-SIB (52,7-68 Gy/30 fractions). The acute and late toxicity rate is defined according to CTCAE vers.4.0. All patients are examined every week during treatment and every 3 months after therapy.

Results: All patients completed radiotherapy. The concomitant treatment is completed in only 2 patients (9%). The other patients interrupted cetuximab for acute toxicity: 1 patient (4%) received 6 cycles, 4 pts(18%) 5 cycles, 3 pts (14%) 4 cycles, 9 pts (41%) 3 cycles and 3 pts (14%) only 2 cycles of medication. The adverse effects was mucositis in 15 patients (68%) with 27% grade 4, 53% grade 3 and 20% grade 2; skin reaction in 21 patients (95%) with 19% grade 4, 57% grade 3 and 24% grade 2. Eleven patients (50%) developed dysphagia: 36% grade 3 and 64% grade 2.

Conclusions: Our results seem comparable to those in the literature. Patients have a low compliance to Cetuximab concomitant to RT due to increased of acute toxicity rates. Longer follow-up is necessary to evaluate late toxicities.

P233

VASCULAR STENOSIS IN PATIENTS IRRADIATED ON ABDOMINAL NODES AFTER SURGERY FOR TESTICULAR SEMINOMA

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Aims: To evaluate vascular damage to subdiaphragmatic main vessels and to investigate associated risk factors in patients irradiated after surgery for testicular seminoma.

Methods: Between 2003 and 2012, 42 male patients underwent surgery for testicular seminoma at our institution. Postoperatively 16 patients had chemotherapy or observation, while 26 were treated with radiation therapy (RT) on abdominal nodes with a median dose of 25 Gy. All patients underwent echo color-Doppler of abdominal arteries, namely, renal, aorta, upper mesenteric, iliac and celiac trunk. For 18 out of 26 irradiated patients dose maps were retrievable for dosimetric analysis. Univariate logistic regression analysis was performed to evaluate correlations between clinical factors, treatment parameters and the incidence of vascular damage. For the dosimetric analysis, two groups of abdominal arteries were considered: the stenotic arteries versus the normal ones.

Results: At a median follow up of 77.4 months (range, 12-120 months), 8 stenosis were recognized by echo color Doppler. All stenosis were detected in the irradiated group only. At the univariate analysis, age at treatment was the only clinical factor significantly associated with stenosis ($p< 0.01$) with older age at irradiation time entailing a lower risk. From the dosimetric analysis we found the mean dose to the vessels significantly associated ($p<0.05$) with stenosis.

Conclusions: Radiation therapy, even at the moderate doses used for testicular seminoma, is associated with augmented risk of developing arterial stenosis of the abdominal vessels. Our study indicates age and mean dose to the vessels as predictive parameters for stenosis.

P234

DIETARY SUPPLEMENTARY WITH LACTIC FERMENTS (CANDIREX FORTE®) IN THE PREVENTION OF ACUTE RADIO-INDUCED GASTRO-INTESTINAL TOXICITY IN PATIENTS WITH RECTAL CANCER AND IRRADIATED IN THE PELVIC REGION

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Aims: To investigate the efficacy of a support therapy with a dietary supplementary with lactic ferments (Candirex forte®) on prevention and/or progression of acute gastro-intestinal toxicity.

Methods: 39 patients with rectal cancer were prospectively enrolled and randomly assigned to take daily Candirex forte® or not from the beginning of radiation therapy. Radiation therapy consisted of 45 Gy in the pelvic region given by 1.8 Gy daily fractions with 3D conformal radiation therapy. Weekly it was evaluated GI toxicity (diarrhea, constipation, abdominal pain) according to CTCAE v4.0. scale toxicity.

Results: Between Jenuary 2014 and February 2016, 39 consecutive patients affected by rectal cancer were enrolled in the study. Median age was 61.5 years; 19 patients with stage II and 20 patients with stage III; 17 patients were treated preoperatively and 22 postoperatively; all patients received concomitant chemotherapy with fluoropyrimidine agents. The maximum grade of toxicity in terms of constipation recorded in the study was G1 in both groups ($p= 0.90$) and in terms of abdominal pain was G2 in both groups ($p=0.41$). Diarrhea incurred in 30% of patients (6) in the Candirex forte ® group and in all patients (100%) in the control group ($p=0.000005$). There was a statistically significant dependence between grade of toxicity and time of occurrence ($p=0.002$) and it was different in both groups ($p=0.003$) with a lower grade of diarrhea from second week of treatment in the Candirex forte® group which was stationary until the end of the treatment.

Conclusions: a dietary supplementary with lactic ferments (Candirex forte®) during radiation therapy on pelvic region reduced the grade and the progression of acute GI toxicity (diarrhea).

P235

BAICALIN COMBINED WITH BROMELAIN AS THERAPY FOR THE PREVENTION OF EDEMA AND RADIODERMATITIS CAUSED BY RADIOTHERAPY

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Aims: The aim of this work was to test the use of Baicalin combined with Bromelain and Aescin (Lenidase®) per os as prevention and as solution for the inflammatory edema and radiodermatitis caused by radiotherapy, on a group of patients suffering from breast cancer. Baicalin performs a strong anti-inflammatory and antiedema activity, while Bromelain has an anti-inflammatory effect, so their combination favours the drainage of bodily fluids as well as the control of the anti-inflammatory process.

Methods: From April 2014 to May 2015, 150 patients suffering from breast cancer and between an age of 30 and 80 years old, with an median age of 55 years old, have been recruited con the test. Every patient has assumed the formula of Baicalin combined with Bromelain in dosage of 1cpr x 2/die during the radiotherapy treatment and for the 2 weeks following the end of it. All the patients have been in positive general conditions. ECOG 0, without significant comorbidities. The patients already showed a mammary pathology of stadium I in the 60% of the cases and of stadium II in the 40% of the cases. Every patient has undergone surgery (Quadrantectomy + removal of the sentinel node), the 20% of patients has undergone axillary dissection, the 30% has undergone CHT adjuvant and the 80% has undergone hormonal treatment Each patient has been radiated on the residual mammary gland: the 92% of these patients has been radiated with the WBRT technique (complete radiation of the breast)

with a varied dosage from 50 Gy (2 Gy/die in 25 fractions) to 42,56 Gy (2,66 Gy/die in 14 fractions) + additional boost of 10 Gy on the operating Table. The 8% of patients have been radiated with a technique composed by non-conventional dosage APBI (Accelerated Partial Breast Irradiation) for a total dosage of 38,5 Gy in 10 fractions /3,85 Gy/die).

Results: The 100% of patients have assumed the integrator without interruption and without any collateral effect. All the patients have completed the radiation treatment in the designated times. The 50% of patients have preventively assumed the product from the first session of radiotherapy, the remaining 50% have assumed it with the arising acute inflammatory edema. A local edema has not been found in the percentage of the patients who have preventively assumed the integrator, only a mild skin rash that has healed in 3 weeks from the end of the radiation treatment, has been observed. However, in the remaining 50% of patients a partial, but sensible reduction of the local edema caused by the radiation therapy has been observed, side effect that has been resolved in 30 days from the end of the radiotherapy.

Conclusions: Our experience has highlighted the utility of Baicalin combined with Bromelain in the reduction and prevention of acute collateral effects of radiation treatment of the breast, with a faster resolution of the edema of the residual mammary gland and of the skin rash.The administration of the integrator has proved itself manageable without causing toxicities.

P236

ASSESSMENT OF TOXICITY OF ADJUVANT THERAPY IN 300 PATIENTS WITH ORAL CANCER

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Aims: To evaluate the toxicity in 300 patients (pz) suffering from oral cancer treated with 3D-RT + Cetuximab or 3D-RT alone after surgery (CH).

Methods: From 2008 to 2016, at the Radiotherapy of A.O. ""Pugliese-Ciaccio"" of Catanzaro, 248 pz were treated with CH + 3D-RT and 52 pz were treated with CH + 3D-RT + Cetuximab. The patients selected for this study had an ECOG status of 0-1. All patients were followed for a follow-up (FU) in order to evaluate toxicity. The 45% of pz (134) received a dose of ≤ 50.4 Gy, 17% (52) of the pz received a dose>50.4 Gy, but ≤ 60 Gy, the remaining 38% (114) received a dose>60Gy , but ≤ 70.2 Gy. Toxicities were evaluated according to the scale of RTOG / EORTC.

Results: After a median of 14 months FU (range 2-48), 41 pz (14%) are living, while the remaining 259 pz (86%) died due to disease progression. In the group of pz treated with CH + 3D-RT + Cetuximab 31 pz (60%) presented mucositis G1-G2 and 21 pz (40%) had dysphagia. In the group of pz treated with CH + 3D-RT 103 pz (42%) presented mucositis G2-G3, 83 pz (33%) had dysphagia, 10 pz (4%) had mandibular fistula, 10 pz (4%) have presented cutaneous fistula and 42 pz (17%) had no toxicity.

Conclusions: The results of our work show that the acute toxicity after surgery, does not increase in the group of patients treated with Cetuximab + RT compared to the group treated with 3D-RT alone.

P237

QUALITY OF LIFE (QOL) AND NEURO-COGNITIVE EVALUATION (NC) IN PATIENTS TREATED WITH RADIATION THERAPY FOR BRAIN METASTASIS: AN OBSERVATIONAL PROSPECTIVE CLINICAL TRIAL – AIRO-SNC GROUP

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Aims: The possible neurocognitive (NC) effect of radiation therapy(RT) has become one of the main issues when choosing treatment for patients with brain metastases. The main aim of this study (supported by the AIRO-SNC group) is therefore to evaluate neuro-cognitive and QoL outcome in patients (pts) treated with RT for brain metastases.

Methods: Pts had a NC evaluation and QoL testing before treatment, during RT and during follow up (mini mental status examination - MMSE, trail making test - TMT A and B, clock drawing test - CDT; EORTC QoLC30 and BN20). Differences in basal points were analyzed with ANOVA test.

Results: In the last two years, 77 patients were enrolled (M/F=31/46). Median age was 58 (range 28-77); 63% and 37% of the pts were in RPA class 1 and 2, respectively; 33% had GPA score between 1.5-2, and 53% between 2.5-3. The primary tumor was lung in 43%, breast in 30% and melanoma in 12%. 51% of the pts had no neurological symptoms at diagnosis; 16% of the symptomatic patients had headache. 55% of the pts had only one lesion, 13% and 16% respectively 2 and 3 lesions. 61% of the pts had cortical and 38% subcortical localizations. At presentation, a surgical approach was chosen in 40% of cases. Forty-eight patients (62%) received whole brain irradiation(WB); 9 of them were also submitted to simultaneous integrated boost(SIB) and 2 had stereotactic RT(SRS) after WB; 29 pts had SRS (38%) without WB; 19% of pts received also concomitant chemotherapy. Fifty-three pts (69%) were receiving steroids before RT. Basal MMSE was between 24-30 (no neurological alteration) in 94% of the pts, 4% had a score of 20-23 (suspected neurological alteration); none showed a score under

21. Basal MMSE and CDT mean points did not differ in patients treated with WB vs SRS. Mean TMT A, B, A+B were 65, 158, 92 and 44, 91, 46 respectively in WB and SRS group. Twenty patients(26%) had anti-epileptic drugs before RT. During treatment, 12% and 15% of the pts reported respectively G1 and G2 headache; G1 and G2 fatigue was recorded respectively in 27% and 15% of the evaluable pts. The use of steroid increased during RT in 15 pts(20%). Figure 1 shows the Consort diagram of the study (16 pts still in follow-up; some pts lost at three months died later).

Conclusions. NC and QoL testing has been time consuming but feasible. Almost all the patients (94%) had no neurocognitive disturbance at diagnosis. The mature data of the study and the NC scoring evolution after RT will be presented.

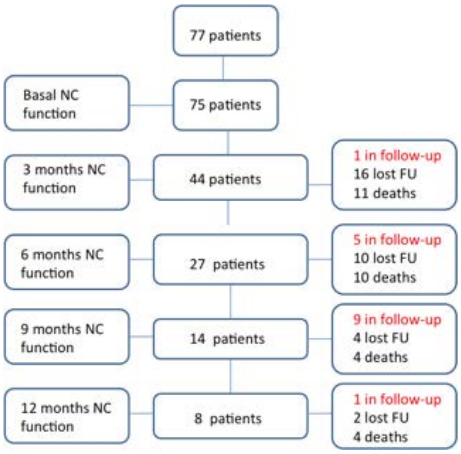

Figure 1.

P238

IVIM (INTRAVOXEL INCOHERENT MOTION) MAGNETIC RESONANCE IN THE EVALUATION OF HPV POSITIVE AND NEGATIVE OROPHARYNX HEAD AND NECK CANCER: PREDICTION OF RESPONSE TO TREATMENT AND TOXICITY

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AIMS: the goal of this study is to identify, in patients treated with curative chemo-radiation for oropharynx head and neck cancer, an MRI signal pattern that can be predictive of (1) changes (during treatment) of disease and organs at risk that can identify parameters of early response and toxicity; (2) early locoregional recurrences that can benefit from a curative salvage therapy; (3) patients at risk of developing severe toxicity that can become chronic and can represent an enduring problem in the long-term survivivors.

Methods: The sample size of 58 patients has been calculated on the basis of risk-of-recurrence data derived from studies on “”functional imaging”“ methods (MRI and PET). The model assumes that the IVIM method can detect the recurrences earlier. Inclusion criteria: (1) age> 18 years, (2) histological diagnosis of oropharyngeal squamous neoplasia with pathologic determination of HPV, (3) general condition and associated diseases that do not contraindicate the execution of chemotherapy or radical radiation therapy, (4) general condition and associated diseases that do not contraindicate performing repeated MRI over time, (5) other non-surgical treatments, chemotherapy or radiotherapy for cancer of the cervical-cephalic or other locations with the exception of non-melanoma skin cancers or in-situ of the cervix cancer and other solid tumors whose radical treatment has been completed more than five years before enrollment in the study and for which the patient remained free of disease (6) accessibility to follow-up, (7) signature of informed consent. MRI exams are scheduled before the start of treatment (baseline), during treatment (at the dose of 36 Gy in standard fractionation or equivalent doses with alternative fractionations) and during follow-up at 3, 6, 12, 18 and 24 months. Figure 1 shows the flow-chart of the study.

Results: The study was approved by the local etical commitee on August 2015. Since then 8 patients have been enrolled. The reaserch team is looking forward to possible multicentric collaborations.

Conclusions: The study is ongoing and preliminary results on the predictive value of this innovative “”functional imaging”“ method will hopefully be available soon.

	Base line	Treatment							End of treatment	Follow-up									
		1 w	2 w	3 w	4 w	5 w	6 w	7 w		15 d	30 d	3 m	6 m	9 m	12 m	15 m	18 m	21 m	24 m
Informed consent	X																		
Demographic form	X																		
Diagnosis form	X																		
Biochemical exams	X	X	X	X	X	X	X	X		X		X	X	X	X		X		X
RMN-IVIM	X				X							X	X		X		X		X
Neck US	X											X	X		X		X		X
Systemic staging	X													X				X	
Clinical evaluation + fiber optic endoscopy	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Radiotherapy		X	X	X	X	X	X	X											
Chemotherapy		X	X	X	X	X	X	X											
End of treatment form									X										
Symptoms evaluation (VHNSS-IT survey)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Toxicity evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Follow up form										X	X	X	X	X	X	X	X	X	X

Figure 1. Flow-chart.

P239

MULTIPARAMETRIC MRI AND TARGETED PROSTATE BIOPSY WITH MOLECULAR BIOLOGICAL BIOMARKERS ANALYSIS: IMPROVEMENTS IN RISK ASSESSMENT? PRELIMINARY DATA OF SUBSTUDY OF AIRC-IG 13218

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Aims: Patient Specific Antigen (PSA) for risk categorization of prostate cancer (PCa) is not enough, as it is an organ- but not cancer-specific biomarker. In the context of the ongoing clinical trial "Short-term radiotherapy for early prostate cancer with concomitant boost on the dominant lesion (DIL)", it is possible for the patient to undergo a magnetic resonance imaging (MRI)-guided biopsy of the DIL to investigate the presence of aggressive phenotype markers. An immunohistochemical (IHC) assay is performed to determine a panel of biomarkers (Ki67, Phosphatase And Tensin Homolog - PTEN) known to be related to PCa progression. The aim of this study is to study the correlation between tumor aggressiveness and clinical outcomes in PCa patients treated with ultra-hypofractionated RT.

Material and Methods: The patient enrollment of the clinical trial started in July 2015, and the recruitment of 65 consecutive patients should be completed by the end of 2016. The tumor samples were collected via a MRI-guided biopsy of the DIL from the 14th recruited patient onward. Ki67 and PTEN status are assessed by an IHC assay and a re-evaluation of the Gleason Score (GS) is performed.

Results: At present, 8 patients performed a MRI-guided biopsy of the DIL without complications. The obtained IHC analysis of Ki67 and PTEN will be correlated with the clinical outcomes at the end of RT course, after a suitable follow-up period. As far as the re-evaluation of GS is concerned, for 4 patients the MRI-guided analysis was confirmed as compared to the results of the first random-biopsy. On the contrary, for 4 patients an upgrade of GS was found, with 2 patients classified as intermediate-risk instead of low-risk, 1 patient as high-risk instead of intermediate-risk and for 1 patient the opposite.

Conclusions: Preliminary data could suggest the higher accuracy of the MRI-guided biopsy in GS definition . Moreover, it is well known that the random biopsy strategy is often subject to sampling error, which might results in downgrading of the class risk. MRI-guided prostate biopsy of the DIL may improve also the risk stratification, but without changing the actual RT course. Further investigations will be performed towards the identification of a pattern in the tumor aggressiveness-response in PCa treated with ultra-hypofractionated RT. Moreover, a possible relationship between biomarker analysis and imaging textural features will be also explored.

P240

EXTRACRANIAL STEREOTACTIC RADIOTHERAPY BOOST IN PATIENTS WITH OLIGOMETASTATIC DISEASE: A PHASE I DOSE ESCALATION CLINICAL TRIAL

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Aims. To determine the maximum tolerated dose (MTD) of fractionated extracranial stereotactic radiotherapy (ESRT) delivered as a boost after a prior radiotherapy.

Methods. A Phase I ESRT clinical trial is still ongoing in our Center. Patients have been enrolled in 2 different arms, based on previous radiotherapy dose:<50 Gy and>50 Gy. ESRT has been delivered in five fractions over 5 days. Dose has been prescribed according to ICRU 62. A four no-coplanar beams class solution or a volumetric technique (VMAT) have been applied in all patients. The planning target volume (PTV) has been defined as gross tumour volume (GTV) plus 5-15 mm. According to different arms, the first cohort received an ESRT dose of 25 or 20 Gy, and subsequent cohorts received higher doses up to the maximum planned dose of 35 or 30 Gy. Dose-limiting toxicity (DLT) was any grade>3 acute toxicity or any grade>2 late toxicity. The MTD was exceeded if 2 of 6 or 4 of 12 patients in a cohort experienced DLT.

Results. Characteristics of the 44 patients enrolled were: M/F: 25/19; median age: 67 yrs (range 43-83); 50 lesions (18 local recurrences, 26 nodal recurrences, 6 distant metastases). 32 lesions received a prior radiotherapy dose<50 Gy and 18 lesions received a previous radiotherapy dose>50 Gy. With a median follow-up time of 18 months (range, 3-104 months), overall response rate was 86% (Complete and Partial Response: 76% and 10%, respectively; Stable or Progressive Disease: 4% and 2%, respectively); 4 lesions were not evaluable. Up to a dose of 35 Gy, only 2 patients experienced a DLT (1 enterocutaneous fistula and 1 colonic stenosis surgically treated).

Conclusions. Fractionated ESRS delivered as a boost after prior radiotherapy treatment up to 35 Gy in five daily fractions is well tolerated; further dose escalation is ongoing.

P241

PHASE II MULTI-INSTITUTIONAL CLINICAL TRIAL OF PELVIC INTENSITY MODULATED RADIOTHERAPY (IMRT) COMBINED WITH A CARBON ION BOOST FOR HIGH-RISK PROSTATE CANCER

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**Affiliation at the beginning of the study*

Aims: The definition of the optimal treatment schedule for high risk prostate cancer is still under debate. A combination of photon intensity modulated radiotherapy (IMRT) on pelvis with a carbon ion boost might be the optimal treatment scheme to escalate the dose to the prostate and deliver curative dose with respect to normal tissue and quality of dose distributions. In fact, carbon ion beams offer the advantage to deliver hypofractionated RT using a significantly smaller number of fractions compared to conventional RT without increasing risks of late effects.

Methods/Design: This study is a prospective phase II clinical trial exploring safety and feasibility of a mixed beam scheme consisting of a carbon ion boost on prostate followed by photon IMRT on pelvis. The study is designed to enroll 65 patients with localized high risk prostate cancer at three different Oncological Centers: Istituto Europeo di Oncologia (IEO), Fondazione IRCCS Istituto Nazionale dei Tumori (INT) and Centro Nazionale di Adroterapia Oncologica (CNAO). Primary endpoint is the evaluation of safety and feasibility with acute toxicity scored up to 1-month after the end of RT. Secondary endpoints are evaluations of treatment early- (3 months after the end of RT) and long-term tolerability, quality of life and efficacy.

Discussion: The present clinical trial aims at improving the current treatment for high risk prostate cancer, evaluating safety and feasibility of a new RT mixed-beam scheme including photons and carbon ions. Encouraging results are coming from carbon ion facilities worldwide, on the treatment of different tumors including prostate cancers. In fact, carbon ions combine physical properties allowing for high dose conformity and advantageous radiobiological characteristics. The proposed mixed beam treatment has the advantage to combine a photon IMRT phase with high conformity standard of care with a hypofractionated carbon ion boost delivered in a short overall treatment time.

Trial registration: Clinical Trial Identifier: NCT 02672449 (clinicaltrials.gov)

P242

OPTIMAL DOSE PRESCRIPTION IN LINAC-BASED SBRT USING VMAT: A "PARETO FRONTS" APPROACH

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Aims. Pareto fronts are a powerful mathematical strategy to formalize the trade-off between a given set of mutually contradicting objectives. We use this strategy to determine the optimal block margin and prescription isodose for both optimal target coverage and normal tissue sparing for VMAT treatments in extracranial stereotactic radiotherapy.

Methods. Three spherical-shaped targets of different dimensions (20cc, 55cc and 101cc) were selected from our database. GTV included macroscopic disease defined on CT. PTV was defined based on internal margin and setup margin. Healthy liver was considered whole liver minus GTV. A single fraction dose of 26 Gy was prescribed (PD=Prescription Dose). VMAT plans were generated with Ergo++ (Elekta) using a 10MV single arc. Pareto fronts based on (i) different MLC block margin around PTV (ranging from +4mm to -2mm with 1 mm step) and (ii) different prescription isodose line (IDS) ranging from 50% to 100% of PD were produced. For each block margin, the greatest IDS fulfilling the criteria: 95% of PTV volume reached 100% of PD was considered as providing the optimal clinical plan for target coverage. The liver mean dose, V7Gy and V12Gy were used together with the PTV coverage (1-V100) to generate the fronts. The ratio of the prescription isodose surface volume to PTV volume (conformity index CI), gradient index (GI=V50/V100), the ratio of normal tissue volume receiving 50% of prescription dose and PTV volume (NTV50/PTV), homogeneity index (HI=D2%/PD) and healthy liver irradiation in terms of mean dose, V7Gy and

V12Gy were calculated to compare different plans

Results. A total of about 450 plans were calculated. Pareto fronts generated for one of the lesions are plotted in figure 1a,b. For all block margins, PTV coverage is deteriorated with the decrease of liver Dmean, V7Gy and V12Gy. The front for 1mm MLC margin is situated below and on the left of the other fronts for all the three different target sizes. Figure 1c,d show the GI plotted against theIDS and the HI for optimal clinical plans. GI shows a U-shaped behaviour with minimum values at 1 mm for all metrics, independent of tumor dimensions. Minimal GI values were found at HI values approximately equal to 1.3.

Conclusions. Pareto fronts provide a rigorous strategy to choice clinical optimal plans in SBRT treatments. Our evaluation shows that a 1mm MLC block margin provides the best results with regard healthy liver tissue irradiation and steepness of dose fallout.

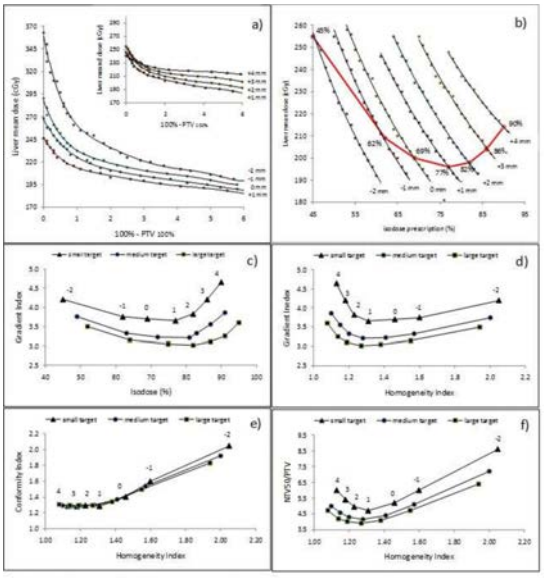

Figure 1: (a) Pareto fronts obtained for liver mean doses vs target coverage for all block margin. Each dot represents a single plan; (b) Pareto fronts obtained for liver mean dose and isodose lines prescriptions. Bold red line connects plans with same optimal dose coverage for different block margins (i.e. the clinical optimal plans obtained with the greatest IDS fulfilling the two criteria: 95% of PTV volume reached 100% of PD and 90% of PTV reached 99% of PD); (c) gradient index vs isodose line prescription for the clinical optimal plans, (d) gradient index vs homogeneity index for the clinical optimal plans, (e) conformity index vs homogeneity index for the clinical optimal plans, and (f) normal tissue volume receiving 50% of PD for the clinical optimal plans. In figure (c) to (f) numbers represent the block margins.

P243

SHORT COURSE PARTIALLY ABLATIVE RADIOTHERAPY FOR LARGE MASS TUMORS USING SIMULTANEOUS INTEGRATED BOOST: A PROOF OF CONCEPT

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Aims: To assess the feasibility in the delivery of highly heterogeneous doses to symptomatic large tumor using VMAT technique and simultaneous integrated boost during a short course palliative accelerated radiotherapy.

Table 1.

	Dose level 1	Dose level 2	Dose level 3
PTV (excluding BTV)			
Prescription dose (Gy)	20	20	20
D98% (Gy)	18.8	18.7	18.6
D95% (Gy)	19.1	19.2	19.1
D50% (Gy)	20.4	22.1	22.9
D2% (Gy)	28.9	33.6	38.5
Dmean (Gy)	21.6	23.4	24.8
BTV			
Prescription dose (Gy)	30	35	40
D98% (Gy)	28.9	33.6	38.3
D95% (Gy)	29.3	34.2	38.8
D50% (Gy)	31.1	36.1	40.3
D2% (Gy)	32.0	37.6	41.5
Dmean (Gy)	31.1	36.2	40.4
Healthy tissue			
Dos Int (cGy*mL)	9.74E+06	9.77E+06	9.79E+06
V5 (%)	22.7	23.0	23.5
V10 (%)	10.6	10.8	11.1
V15 (%)	5.3	5.3	5.5
V20 (%)	0.5	0.9	1.0
Conformity and dose contrast indexes			
CI_PTV	1.18	1.19	1.20
DC	1.50	1.75	2.00
DCI	1.44	1.55	1.63
NDC	0.96	0.88	0.81

Methods: For the dosimetric analysis we selected a patient with a large symptomatic sarcoma. A Planning Target Volume (PTV) and a Boost Target Volume (BTV) were defined as the GTV plus and minus 1 cm, respecti-

vely. Two different doses were simultaneously delivered to the PTV and BTV according to a dose-escalation protocol. Three dose levels were planned: Level 1 (PTV: 20/5Gy; BTV: 30/7.5Gy), Level 2 (PTV: 20/5Gy; BTV: 35/8.75Gy), Level 3 (PTV: 20/5Gy; BTV: 40/10Gy). The aim was to irradiate the central part of the tumor up to 10Gy/fraction while maintaining the border area of the tumor and the surrounding healthy tissues with <5Gy/fraction. SIB-VMAT plans were generated using Oncentra Masterplan TPS, in the dual-arc modality. The mean dose, D98%, D95% and D2% doses were scored for each target. A conformity index, PTV_CI, defined as the volume encompassed by the PTV 95% isodose divided by the PTV volume, was calculated. A dose contrast index (DCI) was defined as the mean dose to the BTV divided by the mean dose to the PTV (excluding BTV). For healthy tissue, an integral dose, Dint, was defined as the product of mean dose and volume of normal tissue, excluding the PTV. This was reported together with the irradiated volumes at the dose levels of 5, 10, 15 and 20 Gy (V5, V10, V15 and V20).

Results: Overall results are reported in Table 1. When BTV dose escalated up to 200% of PTV prescription, the PTV_CI increase was <2% (from 1.18 to 1.20), proving that SIB strategy was able to reduce the dose to the BTV surrounding volume despite the dose escalation. Similarly the percentage increase of ID to normal tissues was 1%. The increase in healthy tissues receiving more than 5,10,15 and 20 Gy was less than 1%. Deviation from the ideal contrast dose slightly increased with increased BTV dose.

Conclusions: We quantified the capability of SIB-VMAT to deliver highly heterogeneous doses in the treatment of large tumors. We showed that despite the major dose escalation in the BTV, the dose conformity to PTV and the integral dose to the normal tissue minimally increased, with a dose spillage from PTV to normal tissue almost constant. The safe delivery of ablative dose in the central part of the tumor has the potential to greatly improve the palliative effect.

P244

ADVANCED SOLID CANCERS IN ELDERLY PATIENTS: RESULTS OF A SHORT-COURSE ACCELERATED PALLIATIVE RADIOTHERAPY

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Aims: To assess the efficacy and safety of a SHort-course Accelerated RadiatiON therapy (SHARON) regimen in the palliative treatment of locally advanced or metastatic cancers in elderly patients.

Methods: Eligibility criteria of this analysis (pooled analysis of 3 phase II studies) were: patients with histologically confirmed solid cancers, age ≥ 80 years, patients with an expected survival>3 months and Eastern Cooperative Oncology Group (ECOG) performance status of ≤3. The primary endpoint was to evaluate the symptoms response rate produced by a radiotherapy regimen based on the delivery of 4 radiotherapy fractions (5 Gy per fraction) with a twice daily fractionation in two consecutive days.

Results: Twenty-four patients were included in this analysis. Characteristics of the patients were: male/female: 17/7; median age: 87.0 years (range: 80-98). ECOG performance status was<3 in 16 patients (66.7%). Six patients (25.0%) had locally advanced thoracic cancers, 13 patients (54.2%) had advanced primary or metastatic H&N tumors and 5 patients (20.8%) had complicated bone metastases. With a median follow-up time of 5.0 months (range, 1 to 8 months), eleven G1-G2 acute skin (45.9%) and G1-2 mucositis (12.5%) toxicities were recorded. One patient (4.2%) experienced G1 acute gastro-intestinal toxicity and only 1 patient (4.2%) experienced G3 acute mucositis. Of 24 symptomatic patients, 19 showed an improvement or resolution of baseline symptoms (overall palliative response rate: 79.2%). Three-months overall survival was 89.7% (median survival time: 7.0 months; 95%CI 5.4-8.6 mo). Median survival without symptoms progression was 5.0 months (95%CI: 2.5-7.5 mo). In 23 patients with pain, a significant reduction of this symptom was recorded in terms of VAS (mean baseline VAS vs mean VAS after treatment: 3.9 versus 1.7, p=0.001).

Conclusions: Short-course accelerated radiotherapy in locally advanced or metastatic cancers is effective in terms of symptom relief and well tolerated even in older patients.

P245

ELIOT- BOOST FOLLOWED BY HYPOFRACTIONATED EBRT AFTER CONSERVATIVE SURGERY IN PATIENTS WITH EARLY BREAST CANCER: PRELIMINARY RESULTS FROM A NON RANDOMISED- PHASE II CLINICAL TRIAL

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Aims: The trial is aimed to evaluate the incidence of in-breast tumour recurrence (IBR) and the acute and late toxicity in patients affected by early breast cancer (BC), undergoing conservative surgery and electron intraoperative radiation (ELIOT) boost, followed by hypofractionated external beam radiotherapy (EBRT).

Methods: From February 2012 to January 2016, 83 early BC patients underwent conservative surgery and ELIOT boost, followed by EBRT at Papa Giovanni XXIII Hospital in Bergamo (Italy). Patients inclusion criteria are: infiltrating carcinoma histology (T1-2, N0-1, M0), unifocality or multifocality (maximum distance between two lesions ≤ 2 cm), PS (ECOG) ≤ 2, age>18, premenopausal status. ELIOT boost was delivered for all patients at the level of tumour bed by a dedicated linear accelerator NOVAC 7 HITESYS (NRT, Italy), using 9 MeV electron beam, a single dose of 12 Gy at 90%. EBRT was given at the whole breast in 13 daily fractions of 2.85 Gy Fifteen patients underwent adjuvant chemotherapy and 74 patients underwent hormone therapy. IBR is any local relapse within the treated breast. Acute and late toxicity were assessed using RTOG toxicity scale.

Results: Forty-seven patients (56.6%) started EBRT boost in 28 days after ELIOT boost procedure. Current median follow up was 23 months and is too short to evidence any IBR. After ELIOT, 2 patients underwent mastectomy, after the identification of another breast metachronous nodule and BRCA1 mutation respectively. Four patients underwent conventional scheduled EBRT: 3 for the presence of unfavourable prognostic disease factors as discovered on the surgical specimen and 1 for severe post-surgical side effects. Most patients had slight local post-surgical oedema: 1 patient had necrosis of the scar area. After EBRT, slight skin erythema (G1) was evidenced in all patients. Considering late toxicity, slight scar fibrosis (G1) was assessed in most patients: 1 patient showed scar retraction and 1 dehiscence of surgical scar.

Conclusions: The advantages of the ELIOT-boost followed by hypofractionated EBRT in early BC are the reduction of treatment duration and skin toxicity with better cosmetic results, the delineation of tumour bed under direct visual and palpable evaluation, no adjuvant chemotherapy delay and the immediate inhibition of cells repopulation. With these preliminary results, it seems to be manageable with acceptable acute toxicity. A longer follow up is needed in order to show IBR and late effects rate.

P246

SHORT-COURSE PALLIATIVE RADIOTHERAPY FOR COMPLICATED BONE METASTASES: FINAL RESULTS OF A PHASE II STUDY

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Aims: To assess the efficacy of a SHort-course Accelerated RadiatiON therapy (SHARON) regimen in the palliative treatment of complicated bone metastases.

Methods: A phase II clinical trial was planned based on optimal two-stage Simon's design. Eligibility criteria included patients with an Eastern Cooperative Oncology Group (ECOG) performance status of ≤3. The primary endpoint was to evaluate the symptoms response rate produced by a radiotherapy regimen based on the delivery of 4 radiotherapy fractions (5 Gy per fraction) with a twice daily fractionation in two consecutive days.

Results: Twenty-nine patients were enrolled in this trial. Characteristics of the patients were: male/female: 16/13; median age: 66 years (range: 46-87). ECOG performance status was <3 in 25 patients (86.2%). With a median follow-up time of 5.0 months (range, 1 to 36 months), 9 G1-2 gastro-intestinal (31%), 2 G1 haematological (6.8%) and 6 G1 skin (20.7%) toxicities were

recorded. Only 1 patient (3.4%) experienced G3 acute gastro-intestinal toxicity. Of 29 symptomatic patients, 27 showed an improvement or resolution of baseline symptoms (overall palliative response rate: 92.6%). Three-month overall survival was 92.2% (median survival time: not reached). In 25 patients with pain, a significant reduction of this symptom was recorded in terms of Drug Score (mean baseline Drug Score vs mean Drug Score at follow-up: 5.3 vs 4.0; p=0.04).

Conclusions: Short-course accelerated radiotherapy on complicated bone metastases (20 Gy in twice daily fractions for 2 consecutive days) is tolerated and effective in terms of symptom relief. A phase III comparison against a standard palliative regimen (30 Gy in 10 fractions) has been planned in this patient population.

P247

SINGLE DOSE OF RADIOTHERAPY IN A BENIGN PATHOLOGY: THE HETEROTOPIC OSSIFICATION

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Aims: the Heterotopic Ossification (HO), an atypical formation of ectopic bone in soft tissue, is a severe risk in patients who receive elective arthoplasty. The degree of ossification is commonly evaluated using the Brooker classification system. The use of Radiotherapy (RT) to prevent this complication is well described in literature. Our aim is evaluate the outcome in patients treated with prophylatic and therapeutic RT after arthroplasty to prevent and cure the HO.

Methods: From 2010 to 2015 at S. Donato Hospital of Arezzo, 10 patients, 2 females and 8 males, were treated with multidisciplinary approach for benign diseases with arthoplasty and RT. The mean age of the patients was 61,6 years. Nine patients underwent arthoplasty for hip osteopathy and 1 patient for elbow osteopathy. Eight patients received preventive RT treatment in a single fraction of 7 Gy 24-72 hours after arthroplasty. These patients were defined as “High risk for developing HO” because they had previously performed the same surgery in contralateral site and had developed heterotopic ossification. Two patients, who didn’t receive profilatic radiotherapy after arthoplasty, have developed HO at 6 and 7 months and they were treated with curative aim with 7 Gy in a single fraction for discomfort and pain.

Results: All patients tolerated the treatment well. Complication following RT treatment were not observed. At 10 months patients who received profilatic radiotherapy did not manifest any HO. Two patients with curative radiotherapy pain were controlled at 10 months.

Conclusions: in patients at high risk for developing HO, postoperative RT appears to be safe and effetive in prevention of HO recurrence or to control the pain. A singole dose of 7 Gy seemed effective.

P248

HYPOFRACTIONATED RADIOTHERAPY AND TARGETED THERAPY: SURVEY OF THE INTERREGIONAL AIRO GROUP “EMILIA ROMAGNA-MARCHE”

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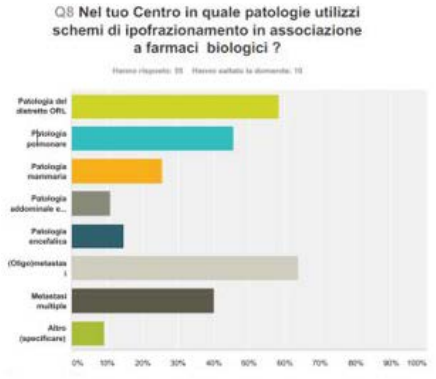
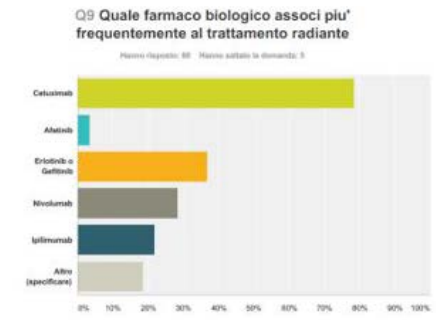
Aims: In the past two decades, thanks to significant technological advances in radiation therapy (RT) planning and delivery, the use of hypofractionation (Hypo) has been widely explored with palliative or curative intent, as well as, the role of targeted therapies (Tp) has been increasingly studied in several cancer types. Nevertheless, only few prospective trials focused the attention on the combination of these two therapeutic options. In this scenario the Interregional AIRO Group “Emilia Romagna-Marche” proposed a brief survey to explore the Italyn pattern of practice in the use of HypoRT and targeted Tp.

Methods: We performed an online survey addressed to all Italyn RT Centers belonging to AIRO during a 15-day period; it included 15 questions with an overall estimated time for finishing the questionnaire of 10 minutes. Results were evaluated using descriptive statistics. Results: 66 centers filled out the survey. 57% of all participating centers consider moderate Hypo dose/fractions>250 cGy while 38%>210 cGy; 40% of all participants define extreme Hypo delivering RT doses greater than 800 cGy, 31%>500 cGy and 29%>1000 cGy. Participants use Hypo with curative intents in several disease presentations especially for oligometastases (82%), prostate, breast and lung cancers (79%, 77% and 70% respectively), brain tumors (67%). Palliative

HypoRT is delivered for multiple metastases and it is also used especially for lung cancers (83%), brain tumors (91%) and pelvic diseases (71%). Italyn centers use the combination with targeted Tp most frequently in oligometastatic setting (62,5%), head and neck and lung cancers (57% and 45%) or multiple metastases (40%) [Figure 1]. Among the most accepted integration, 78% of participants combine HypoRT with Cetuximab, 37% with Erlotinib or Gefitinib and 28% with Nivolumab [Figure 2]; 84% select the combined treatment modality after a multidisciplinary discussion with Oncologists and when Hypo is the treatment of choice, 91% evaluates to stop targeted Tp before starting RT. Among participating radiation oncologists, 42% considers as they have enough knowledge about targeted Tp, 12% even a good one but 46% reveal inadequate experience with them. For 69% participants, medical meeting for updating on targeted Tp could be very useful and 97% are interested in participating in multicenter prospective trials on the combination of HypoRT and targeted drugs especially in oligometastatic diseases (60%), lung and head and neck cancers (58% and 37%), pelvic masses and multiple metastatic setting (28% both). Conclusions: This survey highlights a large heterogeneity in the definition of Hypo regimens and in their use in combination with targeted Tp despite a wide use of HypoRT in many clinical settings for palliative and curative purposes. Refresher courses on targeted Tp and new prospective clinical trials are necessary for a better and safe use of the combined treatment.





Figures 1 and 2.

P249

HADRONTHERAPY FROM THE RADIATION ONCOLOGIST POINT OF VIEW: FACE THE REALITY. THE ITALIAN SOCIETY OF ONCOLOGICAL RADIOTHERAPY (AIRO) SURVEY

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Aims: Growing evidence is accumulating for the use of carbon ions in radioresistant tumors such as soft tissue sarcomas, mucosal melanomas and adenocystic carcinomas of salivary glands. Furthermore, increasing number of patients are being treated worldwide with proton therapy because of advantageous physical properties that allows dose escalation in skull base and paraspinal tumors, eye melanomas and pediatric treatment.

So far approximately 100.000 patients have been treated worldwide with protontherapy, more than 10.000 with carbon ion radiotherapy (RT). In Italy hadrontherapy started in 2011 at CNAO National Center for Oncological Hadrotherapy in Pavia with more than 800 cancer patients treated up to now.

Considering the spreading of the technique in Italy and worldwide, real advantage of hadrontherapy compared to photon RT has become a matter of debate at congresses, and level I evidence with controlled randomized trials comparing photon with particle therapy has been advocated from the scientific community. Waiting for results from ongoing clinical trials, with this survey we aim first of all at investigating the perception of hadrontherapy among the Italyn Radiation Oncologists (RO)

Methods: An electronic survey with 18 items regarding Hadrontherapy was sent via email to about 1000 RO within the collaboration of the Italyn Society of Oncological Radiotherapy (AIRO) inside a project supported by the Associazione Italyna per la Ricerca sul Cancro (AIRC IG 2013-N14300)

Results: Two-hundred and twenty-four (22.4%) physicians completed the survey. Among them, 44.3% are RO with more than 5 years of clinical practice, and only 10.4% RO in training. Median age was 46 years (range 27-77). 56.6% admitted poor knowledge of heavy particles radiobiology rationale and the differential clinical indication for the use of protons versus carbon ions. 80.7% declared lack of knowledge concerning ongoing particle therapy clinical trials. Radioresistant and pediatric tumors are perceived as principal indications for 44.4% and 72%, respectively. Re-irradiation is highly recommended for 78%. Strikingly, only for 16% of RO hadrontherapy is considered an option in their clinical practice. On the other side 52.6% claimed need for at

least 3 up to 5 particle therapy centers in Italy.

Conclusions: Our survey highlights the interest of the Italyn RO community for particle therapy. Better definition of the indications for hadrotherapy and the optimal patient selection is warranted.

P250

HYPOFRACTIONATION IN THE TREATMENT OF BONE METASTASES IN PATIENTS WITH HORMONE REFRACTORY PROSTATE CANCER

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Aims. The hypofractionated radiotherapy plays a fundamental role in the treatment of bone metastases. At our center, we evaluated the feasibility and effectiveness of two schemes hypofractionation: 8 Gy single dose and 8 Gy in two fractions to be made within a week of each other. The two irradiation techniques have been associated with the new molecules used in medical therapy.

Methods. From July 2014 to March 2016 they were treated 21 patients with bone metastases from hormone refractory prostate cancer . The median age of patients studied was 71 years with bone metastasis respectively localized in the dorsal and lumbar spine in 50% of cases, 30% at the level of bilateral lower limbs and the remaining 20% at the level of the pelvis. Radiation therapy was by hand in a single dose in 60% of cases in patients with worse P.S. while in the remaining 40% it was backed bifractionation treatment. All patients were administered simultaneously, the abiraterone acetate 1 g / day in combination with LHRH analogue every three months.

Results. All patients were reassessed after 30-40 days of therapy. In no case were registered signs of toxicity. In 80% of cases there has been a reduction in their analgesic therapy administered dose.

Conclusions. In our experience, the radiotherapy hypofractionated 8 Gy in a single session or, alternatively, 8 Gy in two weekly sessions in conjunction with the abiraterone acetate was well tolerated and had a good impact both as regards the control of the pain is the improvement of quality of life.