Sistema Socio Sanitario

Regione Lombardia

ASST Lecco

Sabato 27 Novembre 2021

RADIOTERAPIA OGGI E DOMANI,

20 (+1) anni della

U.O.C. di Radioterapia dell'Ospedale Manzoni

di Lecco

Stato dell'arte, problematiche attuali e prospettive future nel trattamento delle Neoplasie Ginecologiche

Dott.ssa Annamaria Cerrotta
SC RTO2

Fondazione IRCCS
Istituto Nazionale dei
Tumori di Milano

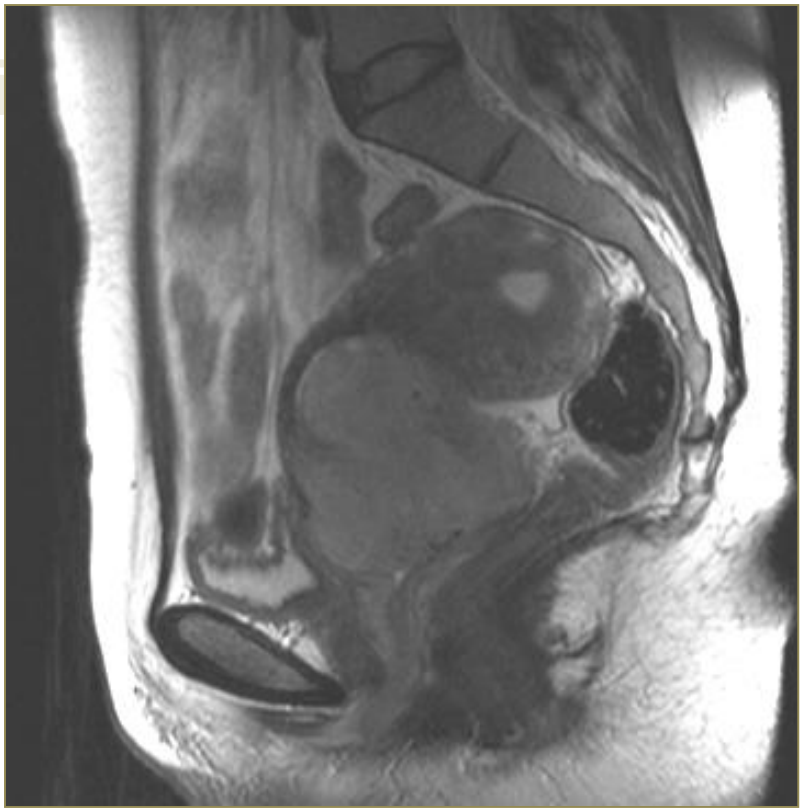
Si dichiara assenza di conflitto di interessi

Neoplasie ginecologiche

- Carcinoma della cervice uterina
- Carcinoma dell’ovaio
- Carcinoma dell’endometrio

Neoplasie ginecologiche

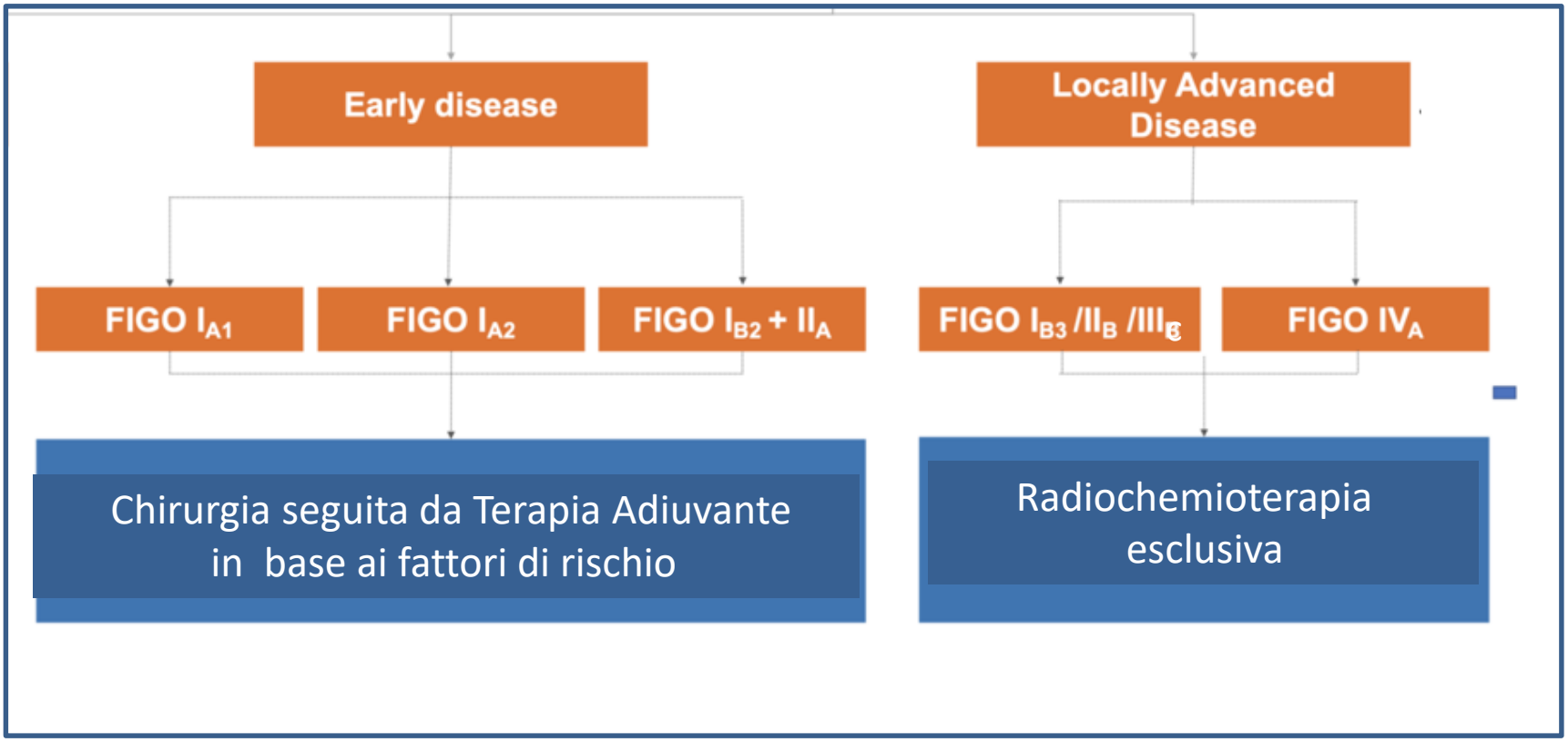
- Carcinoma della cervice uterina
- Carcinoma dell’ovaio
- Carcinoma dell’endometrio



International Federation of Gynecology and Obstetrics Staging of Cervical Cancer 2018

Stage	Description
I	Tumor confined to the uterus
IA	Invasive carcinoma (diagnosed microscopically) with maximum depth of invasion < 5 mm
IA1	Measured stromal invasion < 3 mm in depth
IA2	Measured stromal invasion ≥ 3 mm and < 5 mm in depth
IB	Invasive carcinoma with depth of invasion ≥ 5 mm, limited to cervix uteri
IB1	Invasive carcinoma with ≥ 5 mm stromal invasion and < 2 cm in greatest dimension
IB2	Invasive carcinoma ≥ 2 cm and < 4 cm in greatest dimension
IB3	Invasive carcinoma ≥ 4 cm in greatest dimension
II	Tumor invades outside uterus but not pelvic sidewall
IIA	Without parametrial invasion
IIA1	Invasive carcinoma ≤ 4 cm in greatest dimension
IIA2	Invasive carcinoma ≥ 4 cm in greatest dimension
IIB	With parametrial invasion
III	Tumor invades pelvic sidewall and lower third of vagina, affecting kidney
IIIA	Tumor invades lower third of vagina without pelvic sidewall involvement
IIIB	Tumor invades pelvic sidewall or causes hydronephrosis
IIIC	Tumor involves pelvic or paraaortic lymph nodes, or both, irrespective of tumor size and extent
IIIC1	Pelvic lymph node metastasis only
IIIC2	Paraaortic lymph node metastasis
IV	Bladder or rectal invasion
IVA	Invades mucosa of bladder or rectum
IVB	Spread to distant organs

Carcinoma della cervice uterina



La **Radio-chemioterapia esclusiva** costituisce il trattamento standard nel carcinoma della cervice uterina localmente avanzato

Comprende la radioterapia a fasci esterni,
la chemioterapia concomitante e la brachiterapia endocavitaria

VOLUME 36 · NUMBER 16 · JUNE 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Neoadjuvant Chemotherapy Followed by Radical Surgery Versus Concomitant Chemotherapy and Radiotherapy in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: A Randomized Controlled Trial

Sudeep Gupta, Amita Maheshwari, Pallavi Parab, Umesh Mahantshetty, Rohini Hawaldar, Supriya Sastri (Chopra), Rajendra Kerkar, Reena Engineer, Hemant Tongaonkar, Jaya Ghosh, Seema Gulia, Neha Kumar, T. Surappa Shylasree, Renuka Gawade, Yogesh Kembhavi, Madhuri Gaikar, Santosh Menon, Meenakshi Thakur, Shyam Shrivastava, and Rajendra Badwe

Conclusion

Cisplatin-based concomitant chemoradiation resulted in superior DFS compared with neoadjuvant chemotherapy followed by radical surgery in locally advanced cervical cancer

Neoadjuvant Chemotherapy Followed by Radical Surgery Versus Concomitant Chemotherapy and Radiotherapy in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: A Randomized Controlled Trial

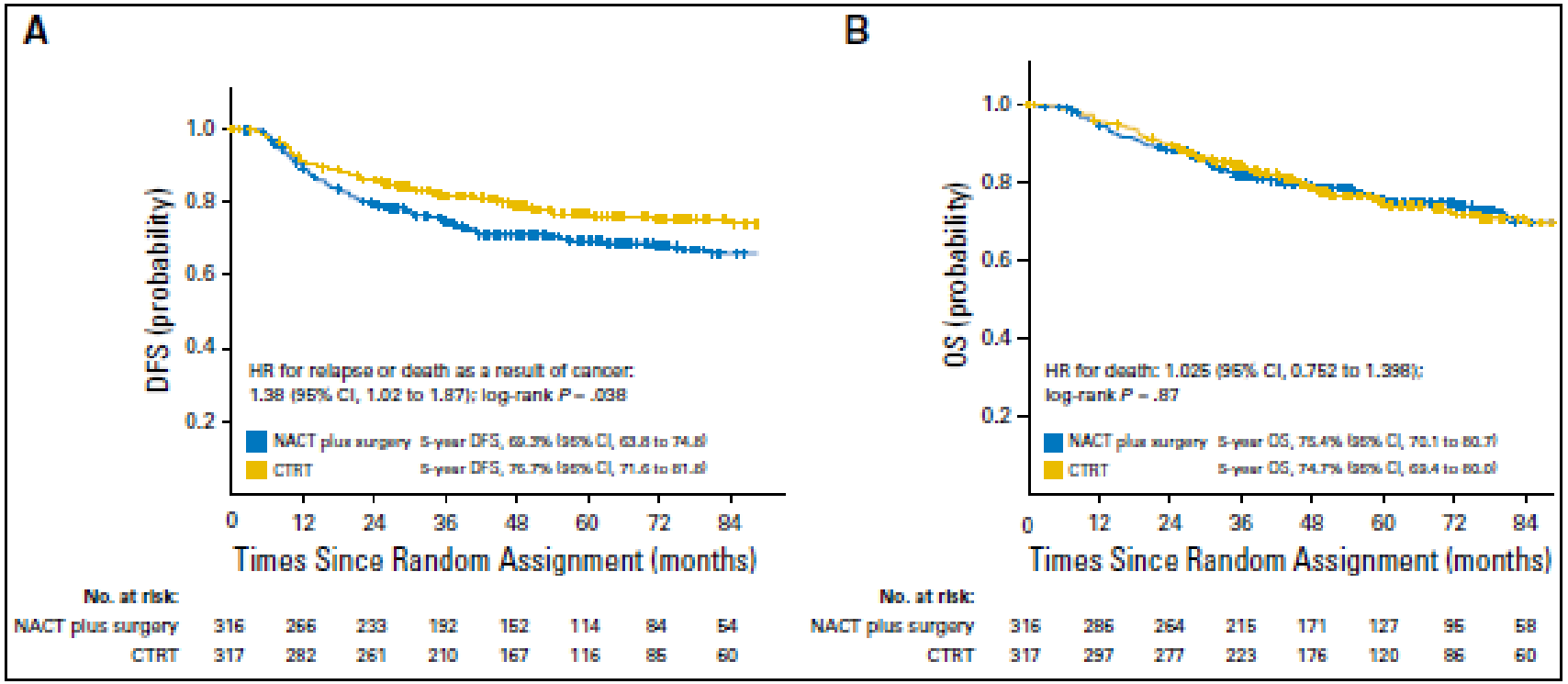
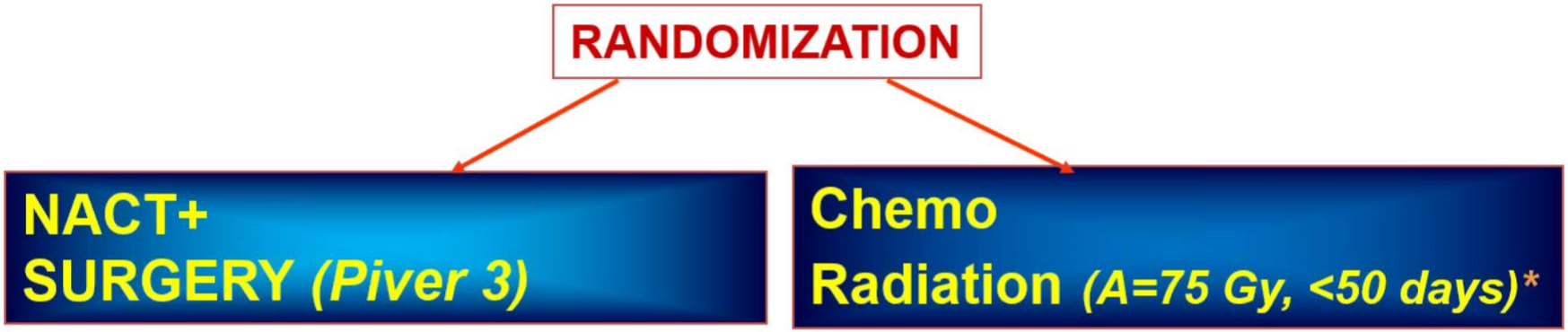


Fig 2. Kaplan-Meier plots for (A) disease-free survival (DFS) and (B) overall survival (OS) in the intent-to-treat population by study group. CTRT, concomitant chemoradiation; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; NACT, neoadjuvant chemotherapy.

Sudeep Gupta, J Clin Oncol 36. © 2018

EORTC prot.55994 *(estimated enrollment=686)*

Cervical Cancer IB2; IIA>4cm; IIB, any histo



HYS optional (not recommended) in case of positive biopsy

Primary outcome: 5-yr OS
Secondary outcomes: PFS, Response, Toxicity, QoL

START date: March 2002

Results from neoadjuvant chemotherapy followed by surgery compared to chemoradiat cervical cancer, EORTC 55994.

Presented Monday, June 3, 2019

Gemma Kenter, Stefano Greggi, Ignace Vergote, Dionyssios Katsaros, Juliusz Kobierski, Leon Massuger, H. C. van Doorn, Fabio Landoni, Jacobus Van Der Velden, Nicholas Simon Reed, Corneel Coens, Iske van Luijk, P. B. Ottevanger, Antonio Casado; Center Gynaecological Cancer Amsterdam, Amsterdam, Netherlands; MITO and Istituto Nazionale Dei Tumori, Naples, Italy; BGOG and University Hospitals Leuven,...

Between May 2002 and June 2014 a total of 620 patients with FIGO stage Ib2-IIb were randomized between neoadjuvant chemotherapy followed by surgery (NACTS, arm 1, N=311) with standard concomitant chemoradiotherapy (CCRT, arm 2, N=309) . In arm 1, radical hysterectomy was required within 6 weeks after completion of cisplatin-based chemotherapy with a cumulative minimum of 225mg/m2, in arm 2, radiation consisted of 45-50 Gy plus boost concurrent with weekly cisplatin chemotherapy (40 mg/m2 per week). Primary endpoint was 5-yrs overall survival (OS).

Results:

Median follow-up time was 8.2 years (95% CI = 7.8 yrs – 8.6 yrs)) and similar between both arms. A total of 191 deaths (31%) occurred. Age, stage and histological cell type were balanced in both arms. Protocol treatment was completed in 459 (74%) patients (71% for NACTS; 82% for CCRT). In arm 1 238 (76%) patients underwent surgery. Main reasons for not having surgery as per protocol, were toxicity (25/74, 34%), progressive disease (18/74, 24%) and insufficient response to NACT (12/74, 16%). Additional radiotherapy was given to 113 patients (36.3%) in arm 1; additional surgery performed in 9 patients (2.9%) in arm 2. Short term severe adverse events (≥G3) occurred more frequently in arm 1 than in arm 2 (35% vs 21%, p < 0.001). The 5 year OS was 72% in arm 1 and 76% in arm 2 (not statistically significant, difference = 4.0% (95%CI: -4% -

Conclusions: *These preliminary results revealed* ***NO DIFFERENCE*** *in 5-year OS between NACT and CT-RT, indicating that quality of life and long term toxicity are important to decide optimal treatment*

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ESGO/ESTRO/ESP guideline

The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer

Radiotherapy and Oncology 127 (2018) 404–416

Management of locally advanced cervical cancer

Treatment strategy should aim for avoiding the combination of radical surgery and postoperative external radiotherapy because of the significant increase in morbidity and no evident impact on survival (grade B).

Contents lists available at ScienceDirect

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journal homepage: www.thegreenjournal.com

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International Journal of Gynecological Cancer 2018

Management of locally advanced cervical cancer

Definitive platinum-based chemoradiotherapy and brachytherapy are the preferred treatment (grade A)

An additional radiation boost to the involved lymph nodes should be applied (grade C)

If cisplatin is not applicable, alternative treatment options are fluorouracil or carboplatin.

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

The ASTRO clinical practice guidelines in cervical cancer: Optimizing radiation therapy for improved outcomes

Junzo Chino [a,*], Christina M. Annunziata [b], Sushil Beriwal [c], Lisa Bradfield [d], Beth A. Ericks
Jane Fitch [g], Matthew M. Harkenrider [h,r], Christine H. Holschneider [i], Mitchell Kamrava [j],
Lilie L. Lin [l], Jyoti S. Mayadev [m], Marc Morcos [n], Chika Nwachukwu [o], Daniel Petereit [p], Ak

Practical Radiation Oncology® (2020) 10, 220-234

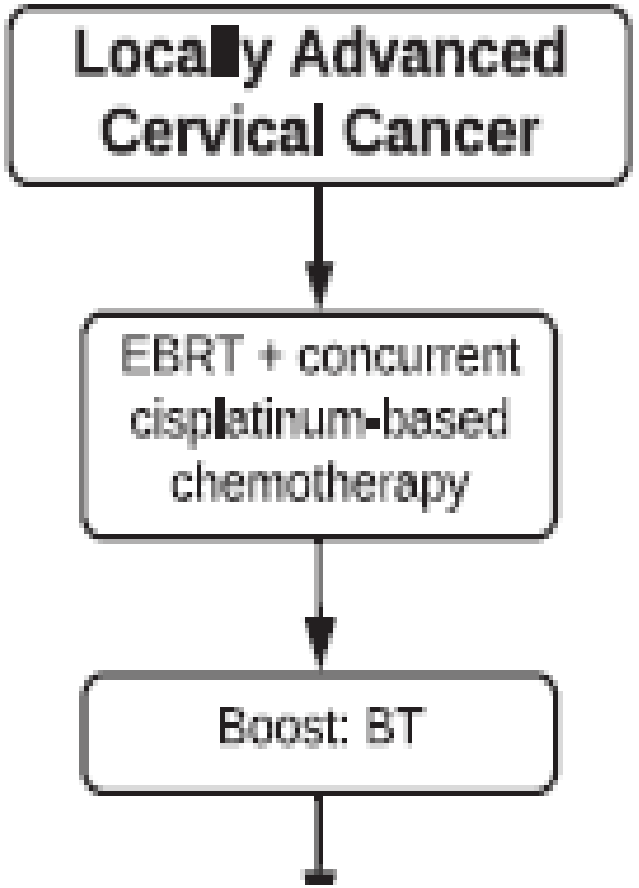
www.practicalradonc.

Clinical Practice Guidelines

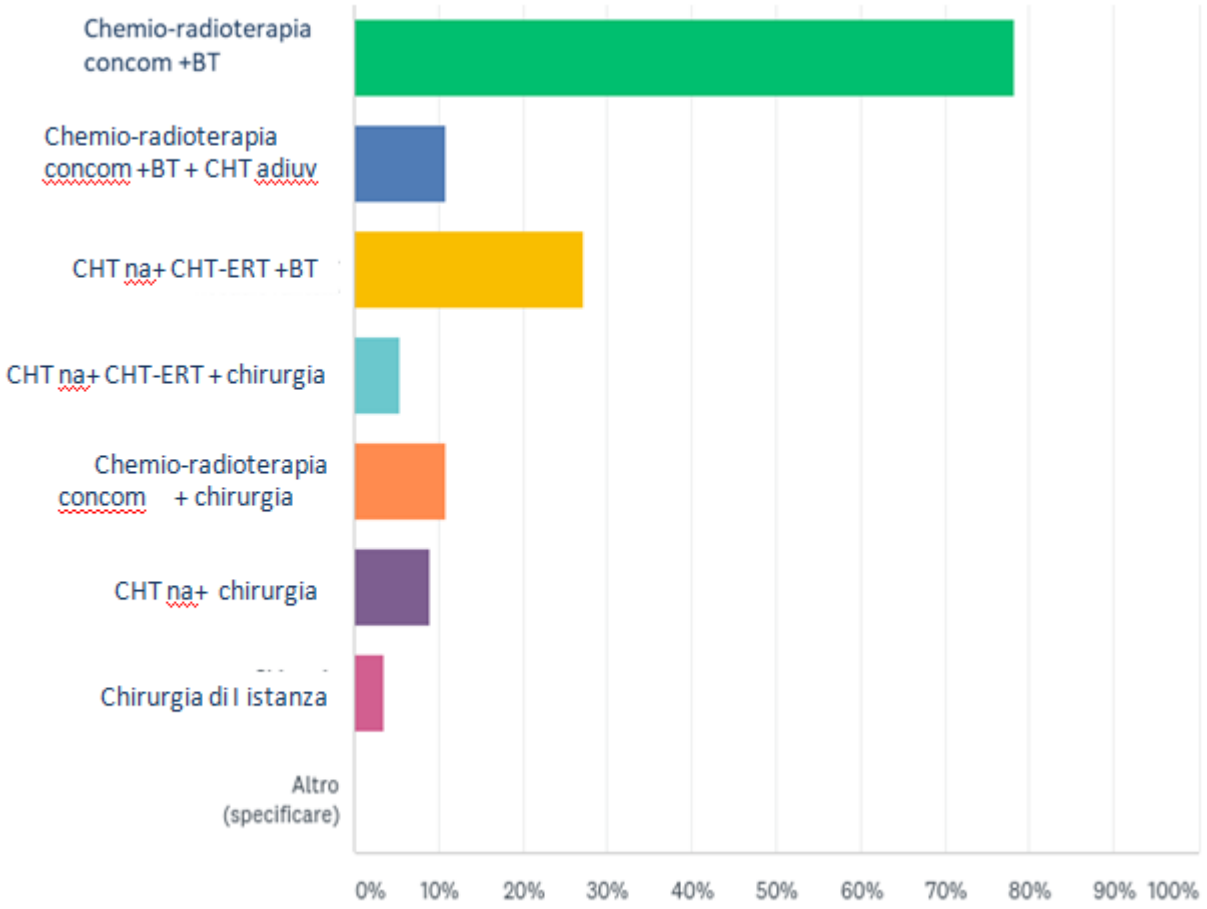
Radiation Therapy for Cervical Cancer: Executive Summary of an ASTRO Clinical Practice Guideline

Junzo Chino, MD,[a,*] Christina M. Annunziata, MD, PhD,[b]

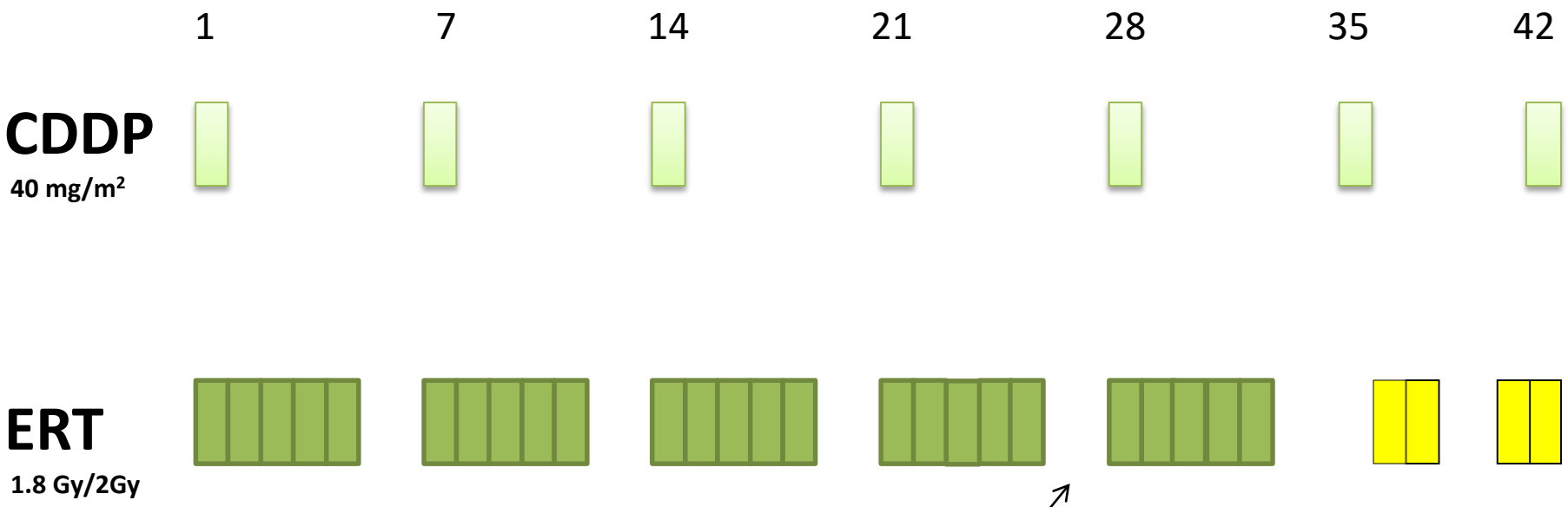
Practical Radiation Oncology: July-August 2020



Quale/i trattamento/i di scelta nel tuo centro per lo stadio FIGO IB2-IVA?



Schema di CT- RT nel carcinoma della cervice uterina

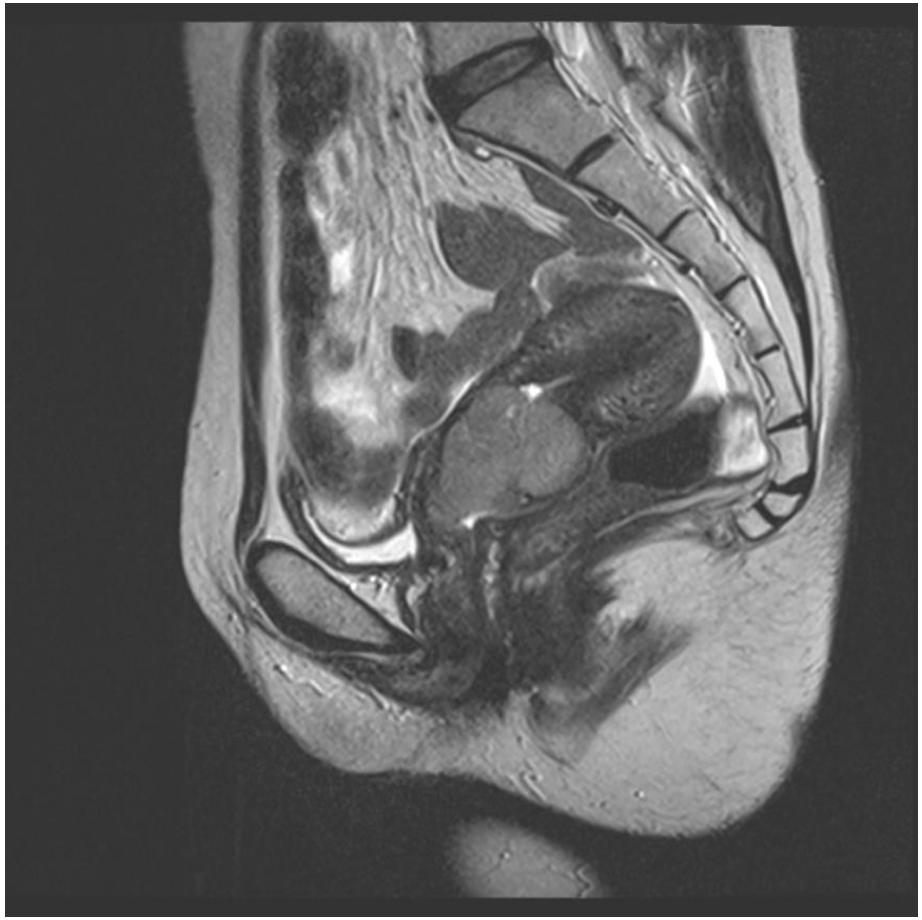


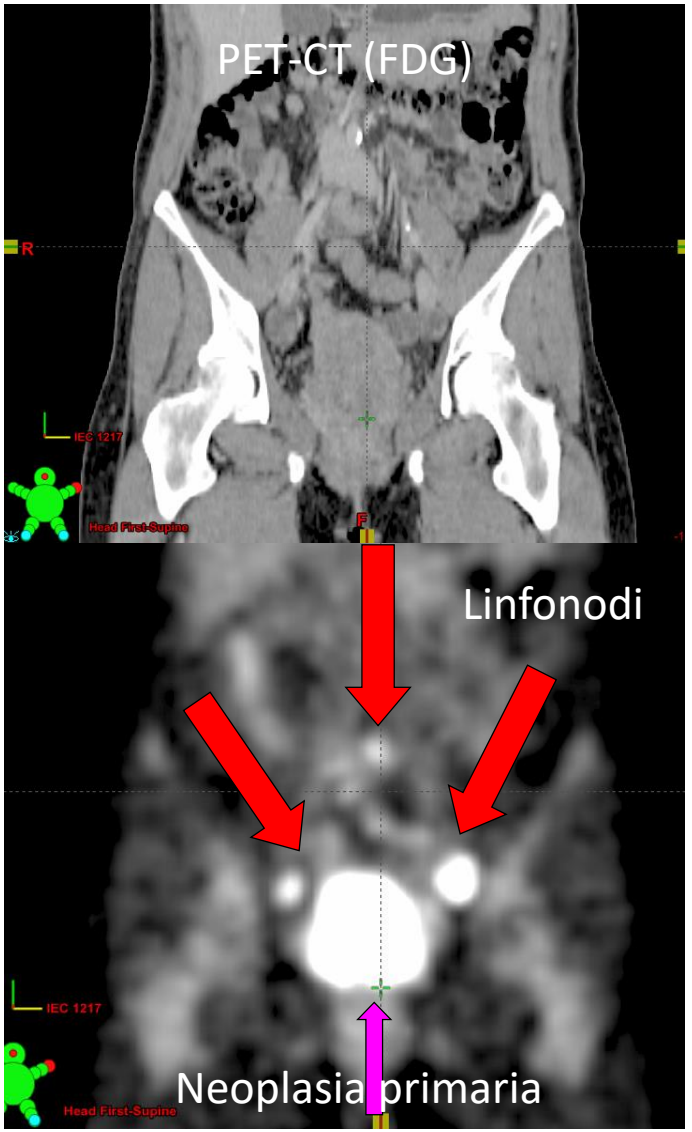
Durata 50-56 gg

Radio-chemioterapia esclusiva

Image Guided Adaptive Radiotherapy (IGART)

RM pelvi



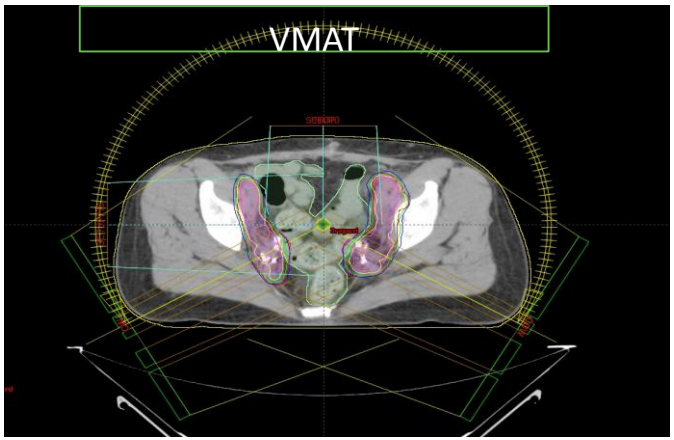


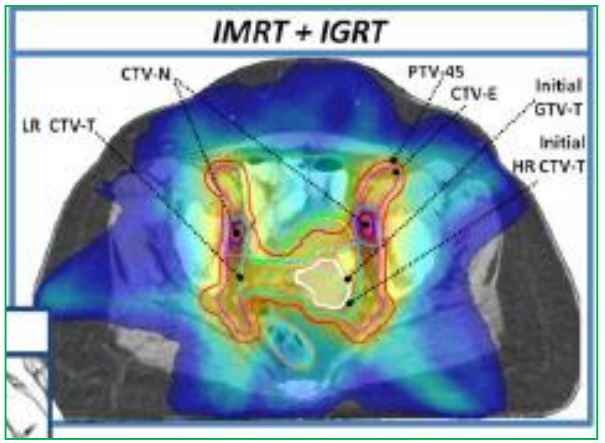
Radio-chemioterapia esclusiva

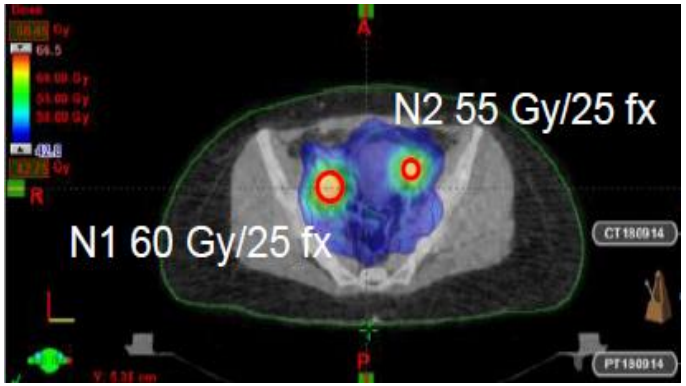
IGART

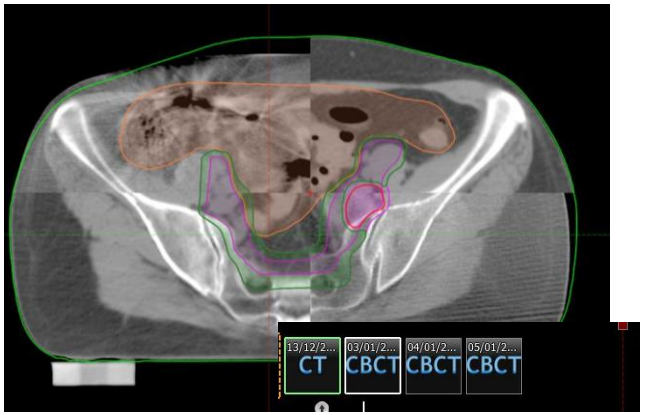
EBRT Linac fotoni X da 6-15 MV:

- **45-50 Gy/25-28 fr (PTV)**
- **55- 60 Gy/25 fr SIB (PTV N)**

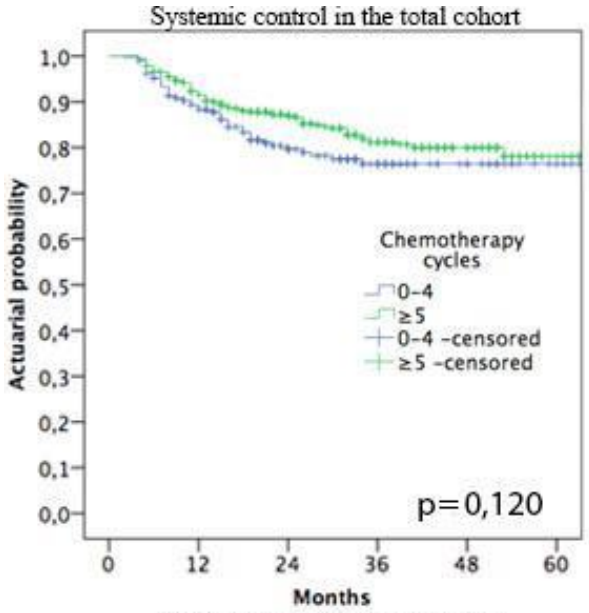


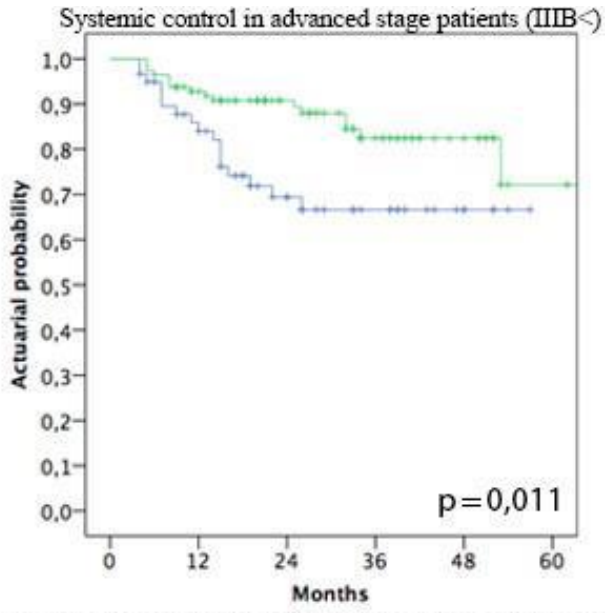


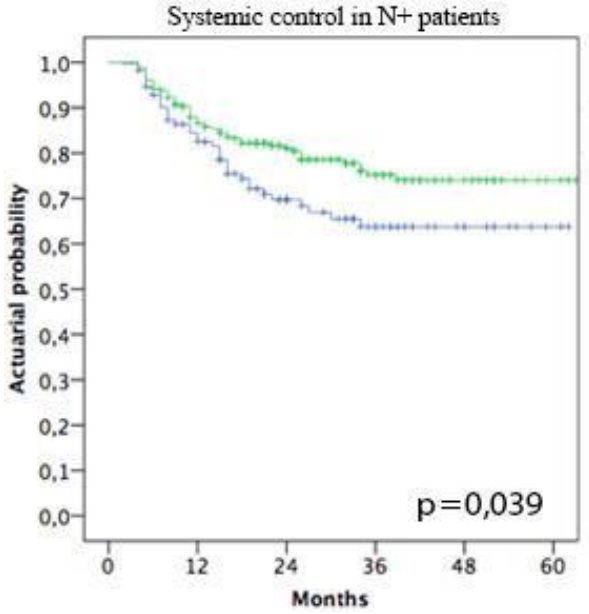


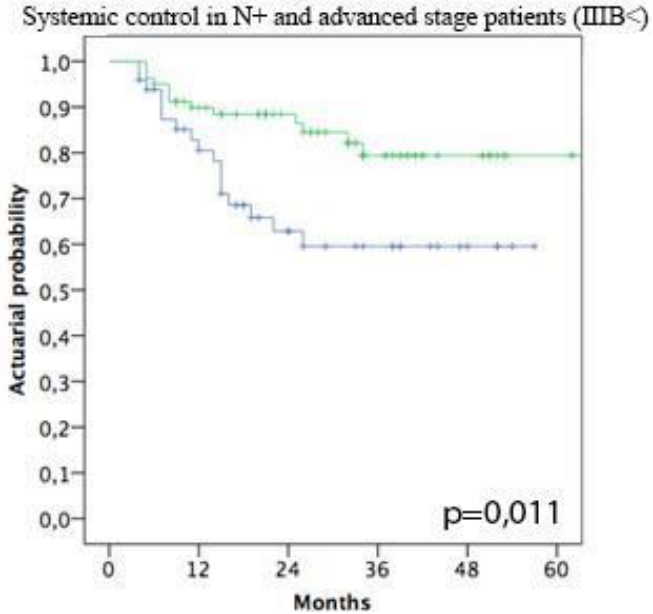


Impact of number of chemotherapy cycles on systemic control.









(Fortin I. ASTRO 2015, EMBRACE network)

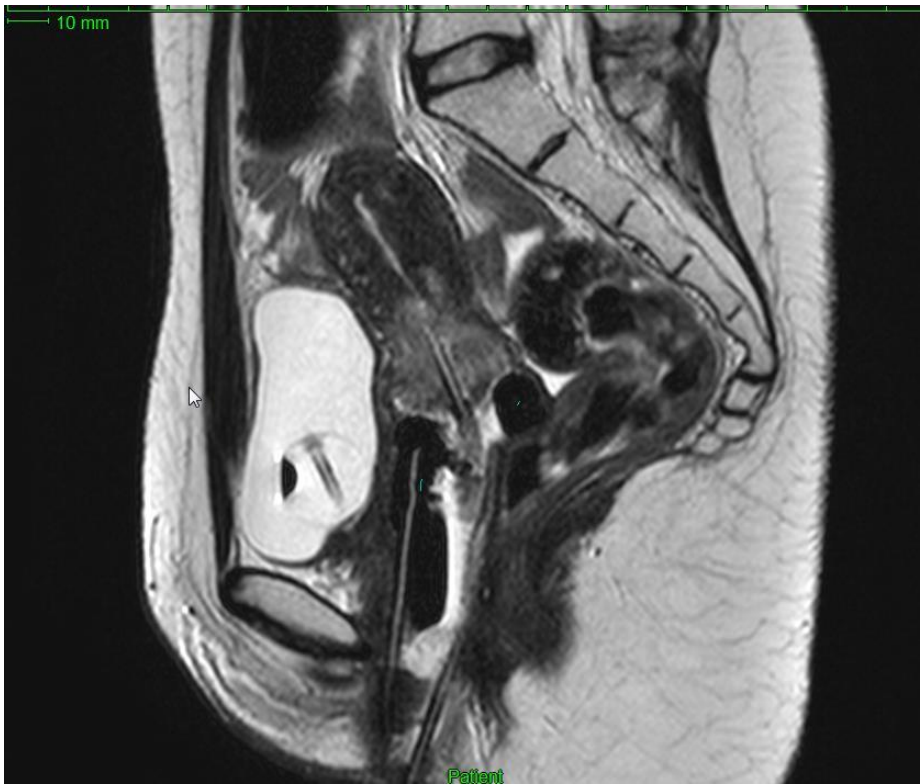
Received Nov 5, 2013. Accepted for publication Nov 6, 2013.

International Journal of
Radiation Oncology
biology • physics

EDITORIAL

Curative Radiation Therapy for Locally Advanced Cervical Cancer: Brachytherapy Is NOT Optional

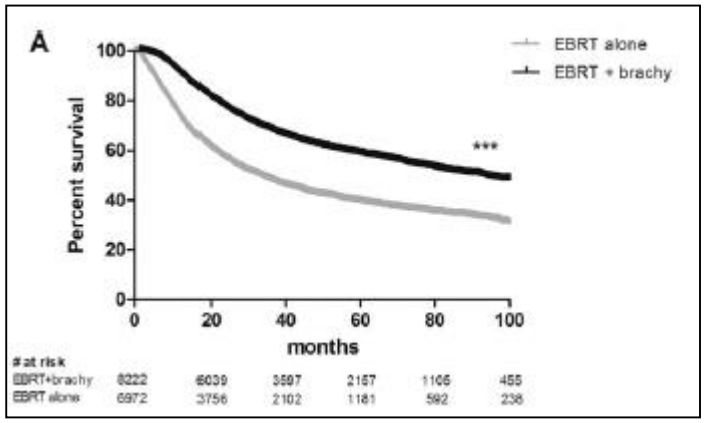
Kari Tanderup, PhD,*,† Patricia J. Eifel, MD,‡ Catheryn M. Yashar, MD,§
Richard Pötter, MD,‖ and Perry W. Grigsby, MD*

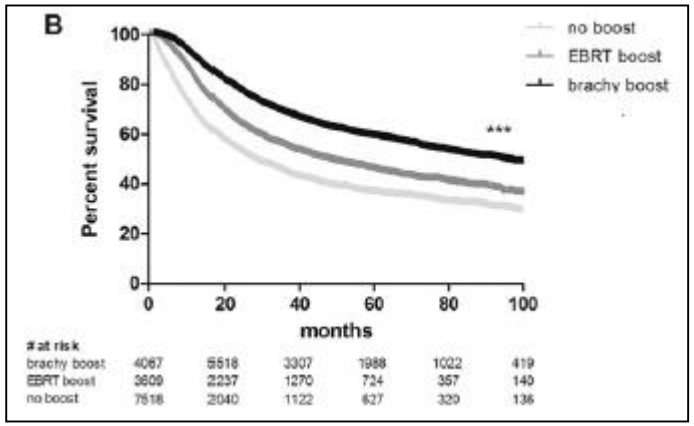


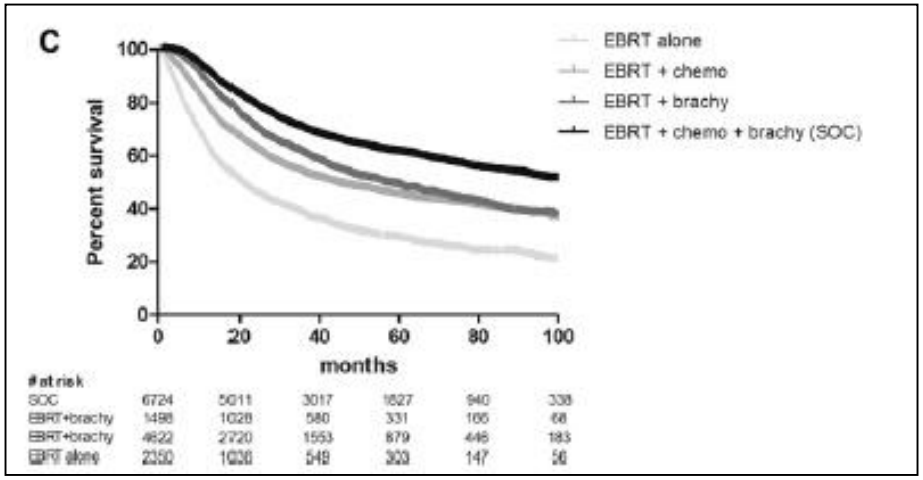
Disparities in standard of care treatment and associated survival decrement in patients with locally advanced cervical cancer

Tyler P. Robin, MD, PhD [a], Arya Amini, MD [a], Tracey E. Schefter, MD [a], Kian Behbakht, MD [b], Christine M. Fisher, MD, MPH [a,*]

Gynecologic Oncology 143 (2016) 319–325







SOC therapy including **chemoradiation and brachytherapy boost confers far superior outcomes** to patients with locally advanced cervical cancer treated with alternative approaches (IMRT or SBRT).

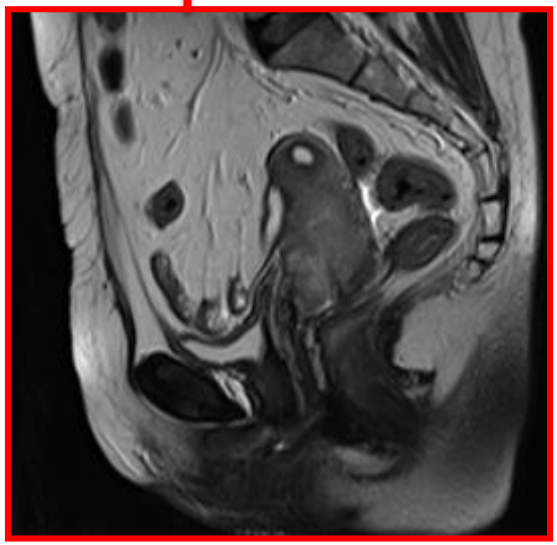
CDDP w +

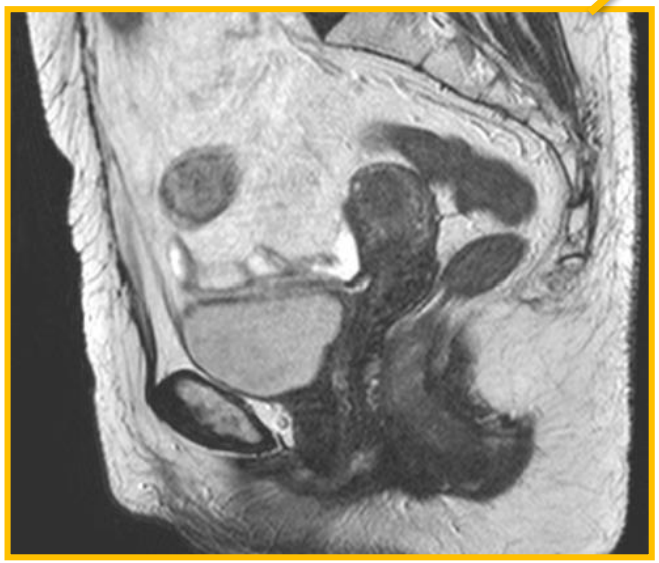
40 mg/m^2

HDR BT 28 Gy/4 fx

ERT

1.8 Gy/2Gy





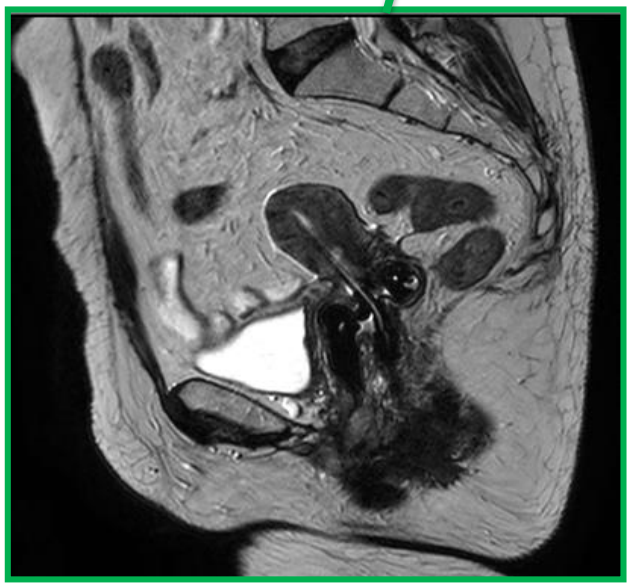
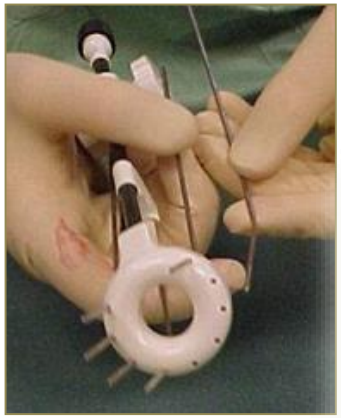


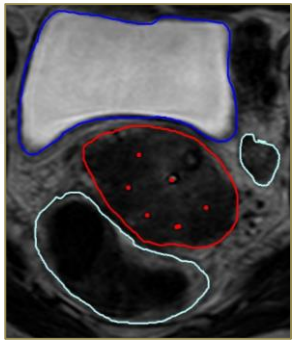
Image Guided Adaptive Brachytherapy (IGABT)

Applicator choice and insertion

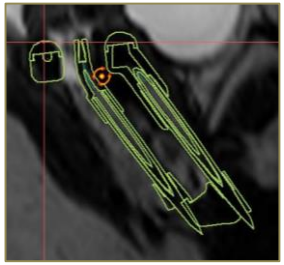


3D imaging

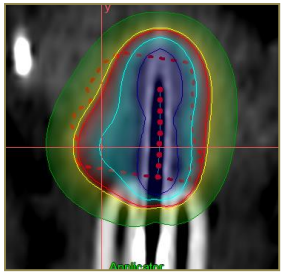
Contouring



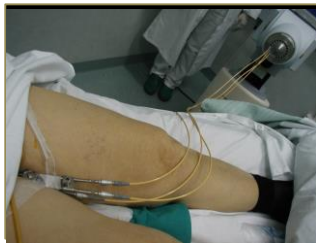
Applicator reconstruction



3D dose planning

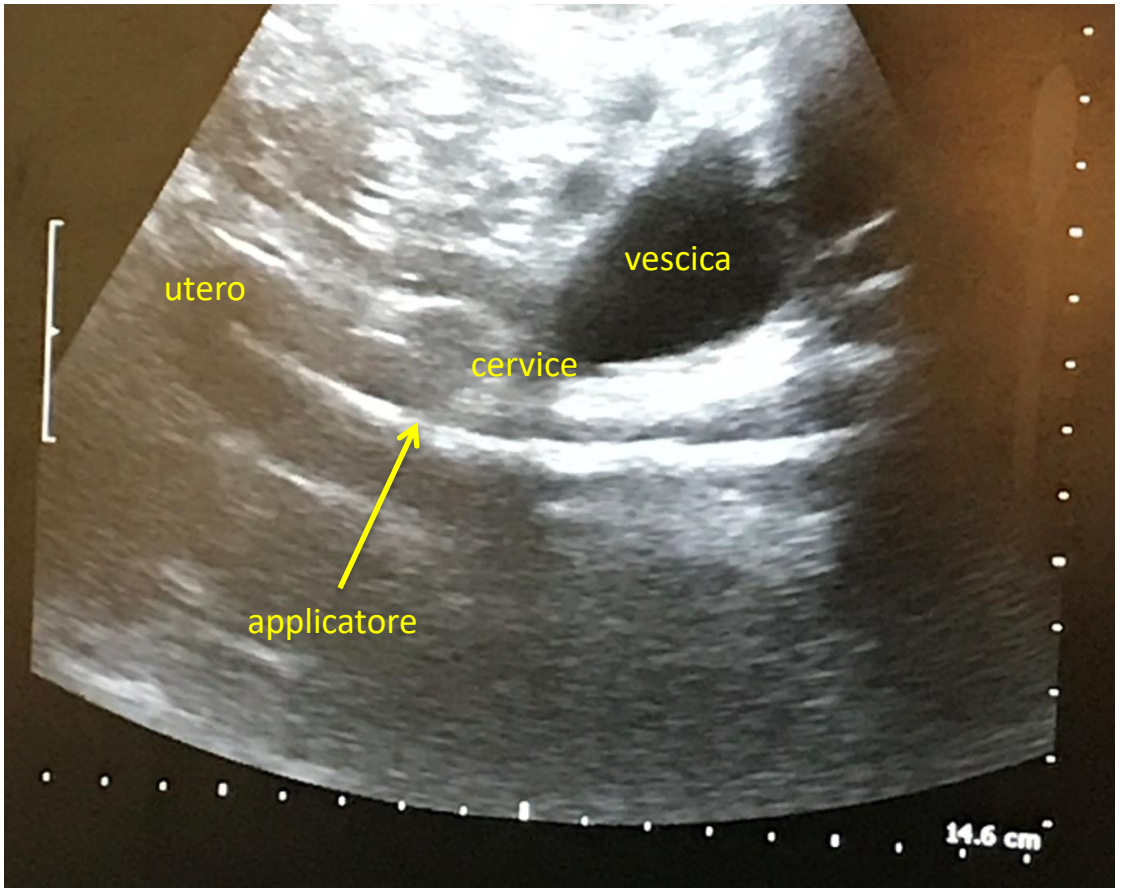


Dose delivery



Il " workflow"

IGABT:
Brachiterapia guidata dalle immagini e “adaptive”

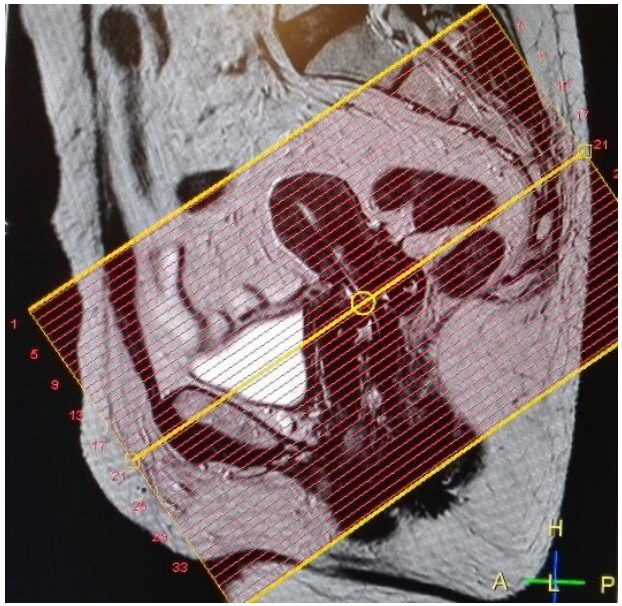


ecografia transaddominale

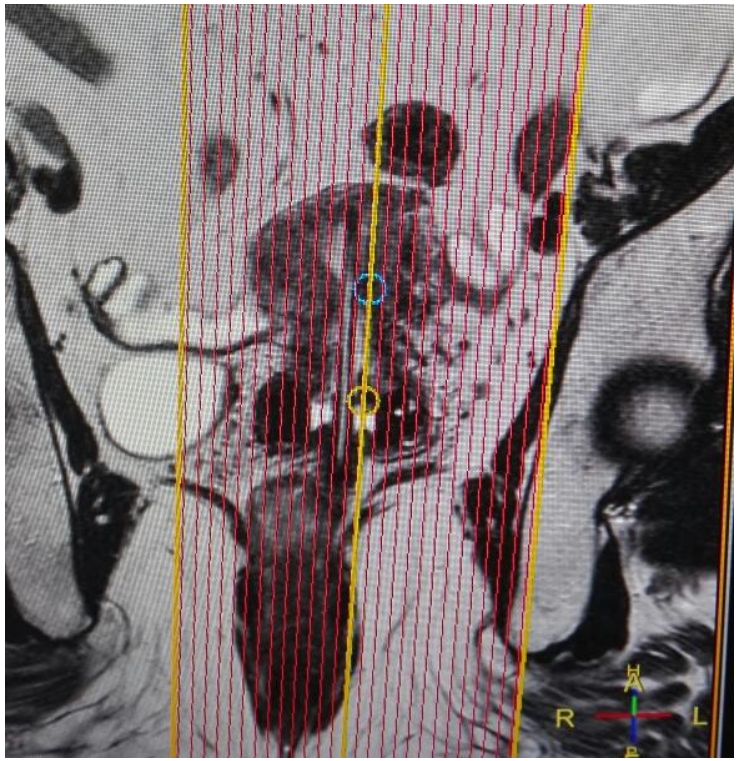
- guida nel corretto posizionamento del tandem
- terapia interstiziale

Requisiti RM

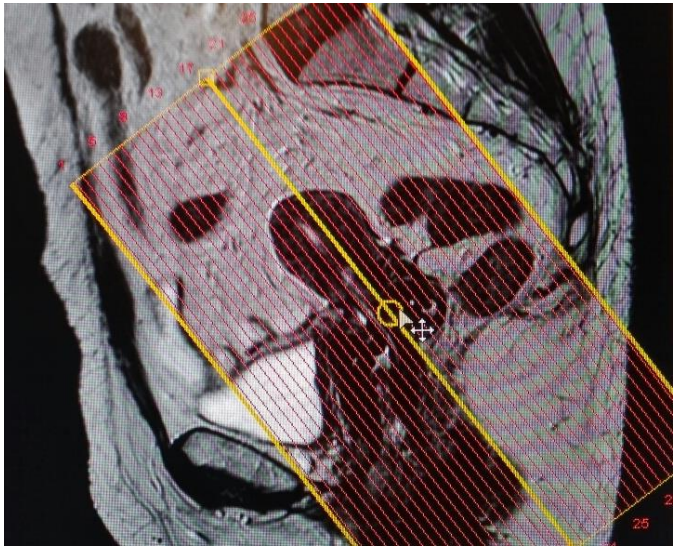
Paratrasversale



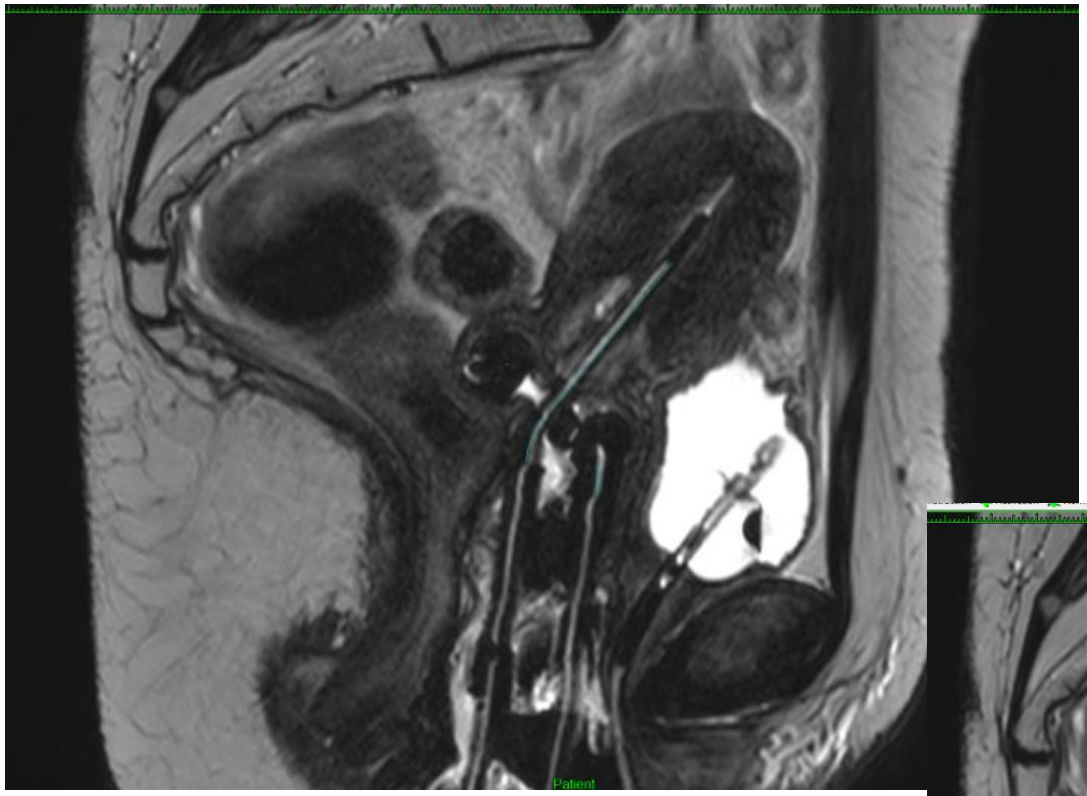
Paracoronale



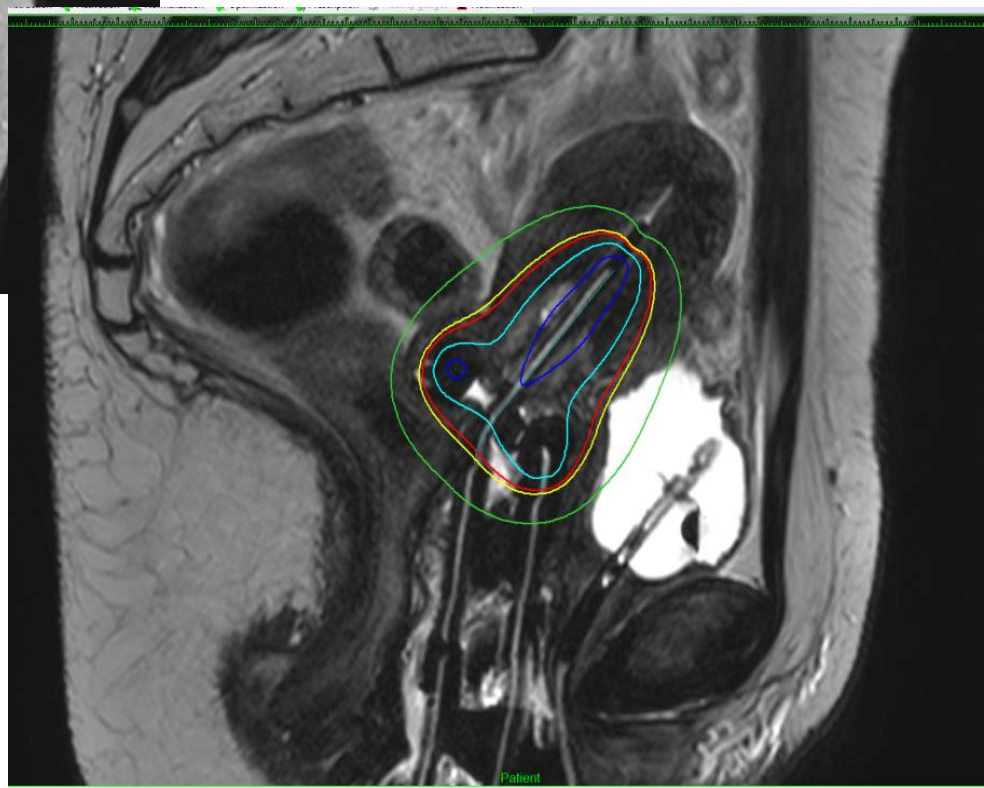
Parasagittale



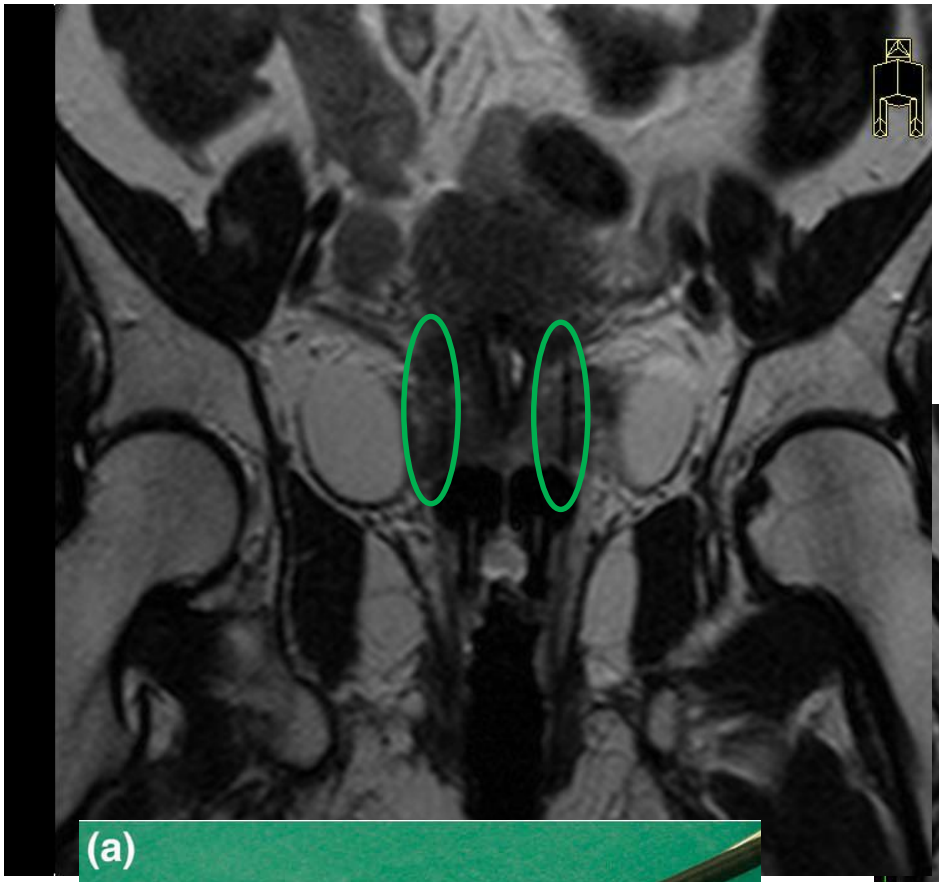
Brachiterapia guidata dalle immagini e “adaptive”



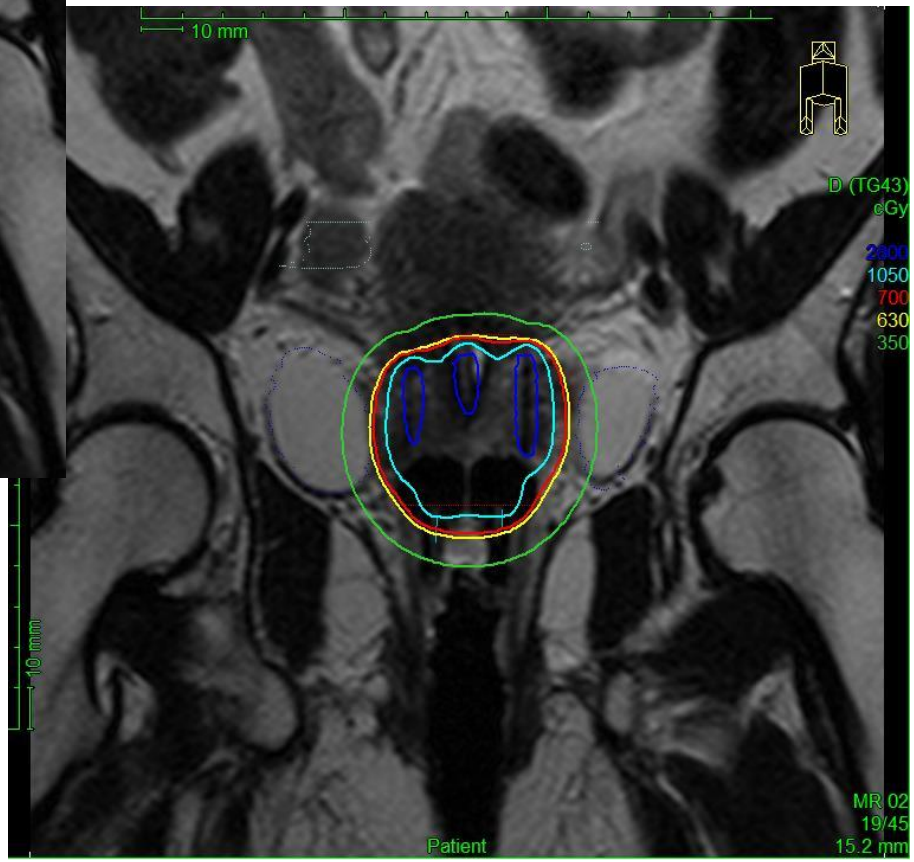
endocavitaria

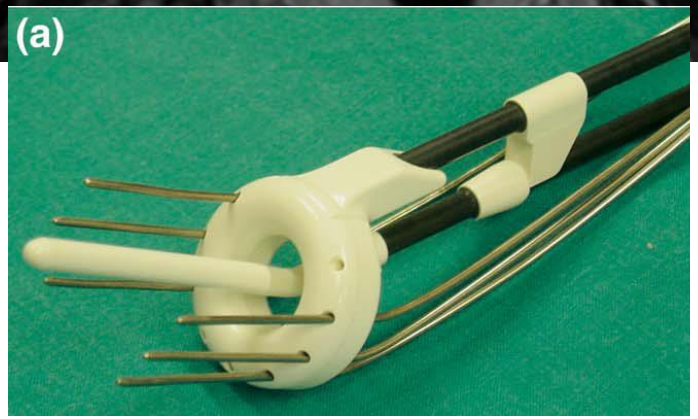


Brachiterapia guidata dalle immagini e “adaptive”



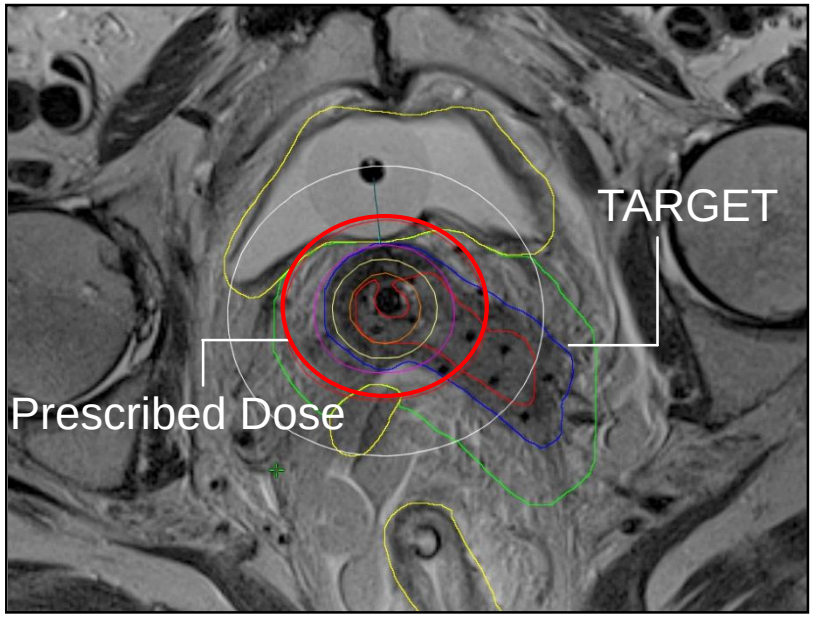
endocavitaria + interstiziale



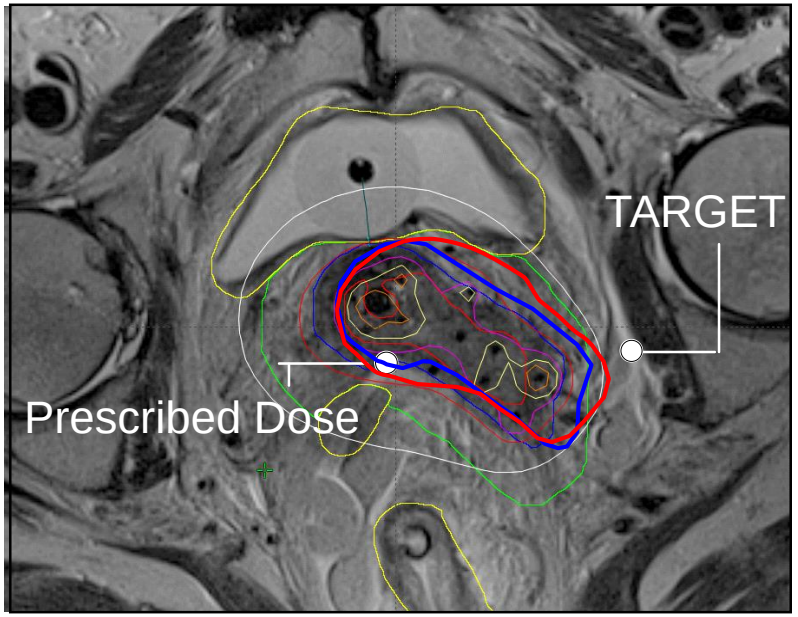


Brachiterapia guidata dalle immagini e “adaptive”

Standard loading pattern



Optimized loading pattern



Radiotherapy and Oncology 120 (2016) 434–440

Contents lists available at ScienceDirect

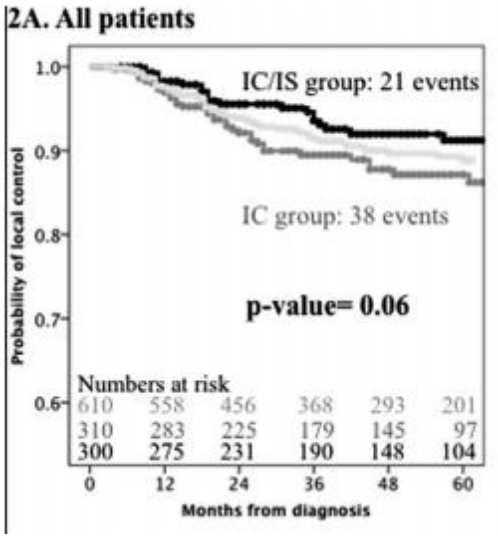
Radiotherapy and Oncology

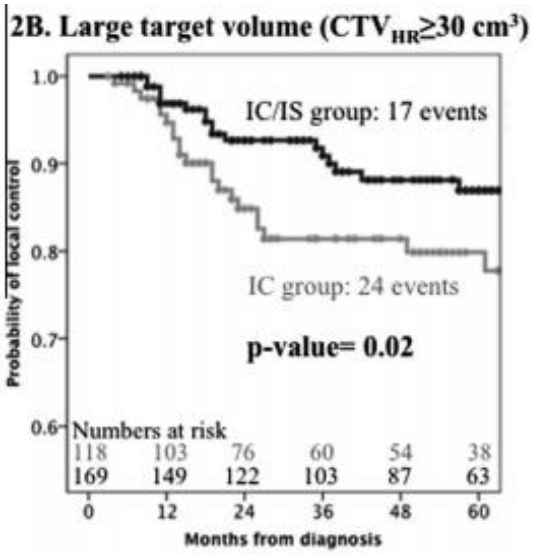
journal homepage: www.thegreenjournal.com

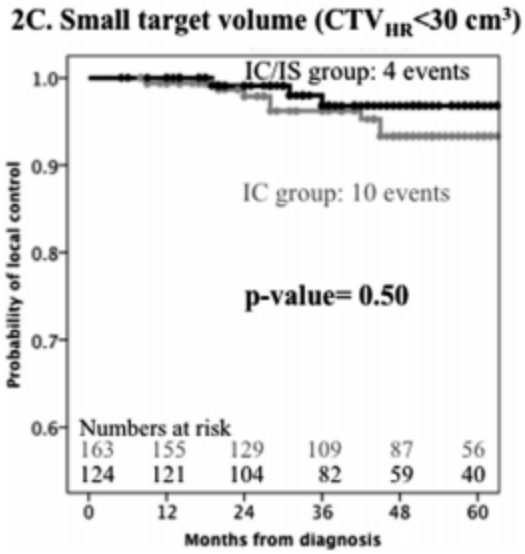
Image guided brachytherapy in cervical cancer

Image guided adaptive brachytherapy with combined intracavitary and interstitial technique improves the therapeutic ratio in locally advanced cervical cancer: Analysis from the retroEMBRACE study

Lars Fokdal [a,*], Alina Sturdza [b], Renaud Mazeron [c], Christine Haie-Meder [c], Li Tee Tan [d], Charles Gillham [e], Barbara Šegedin [f], Ina Jürgenliemk-Schultz [g], Christian Kirisits [b], Peter Hoskin [h], Richard Pötter [b], Jacob C. Lindegaard [a], Kari Tanderup [a]







Combined IC/IS brachytherapy improves the therapeutic ratio in LACC by enabling a tumour specific dose escalation resulting in significantly higher local control in large tumours without adding treatment related late morbidity

ICRU REPORT No. 89

PRESCRIBING, RECORDING, AND REPORTING BRACHYTHERAPY FOR CANCER OF THE CERVIX

Treatment planning and performance of BT is based on the recommendations of the "ICRU 89/GEC ESTRO Report" on "Prescribing, Recording and Reporting Brachytherapy for Cancer of the Cervix" (ICRU report 89)

THE INTERNATIONAL COMMISSION ON RADIATION UNITS AND MEASUREMENTS
PREPARED IN COLLABORATION WITH
Groupe Européen de Curiethérapie –
European Society for Radiotherapy and Oncology (GEC-ESTRO)
(Published June 2016)

Journal of the ICRU Volume 13 No 1–2 2013
Published by Oxford University Press

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MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study

*Richard Pötter, Kari Tanderup, Maximilian Paul Schmid, Ina Jürgenliemk-Schulz, Christine Haie-Meder, Lars Ulrik Fokdal, Alina Emiliana Sturdza, Peter Hoskin, Umesh Mahantshetty, Barbara Segedin, Kjersti Bruheim, Fleur Huang, Bhavana Rai, Rachel Cooper, Elzbieta van der Steen-Banasik, Erik Van Limbergen, Bradley Rumwell Pieters, Li-Tee Tan, Remi Abubakar Nout, Astrid Agatha Catharina De Leeuw, Robin Ristl, Primoz Petric, Nicole Nesvacil, Kathrin Kirchheiner, Christian Kirisits, Jacob Christian Lindegaard, EMBRACE Collaborative Group**

Lancet Oncol 2021

	Number of patients	CTV_{HR} volume, cm^3*	CTV_{HR} $D_{90\%}$ $EQD2_{10}$, Gy	Local failure (n)	Pelvic failure (n)	Any failure (n)	Patients dead (n)	5-year local control (95% CI)	5-year pelvic control (95% CI)	5-year disease-free survival (95% CI)	5-year overall survival (95% CI)
IB1	124	22 (17–27)	91 (87–95)	2	6	20	24	98% (94–100)	95% (87–98)	76% (67–83)	83% (75–89)
IB2	119	26 (20–38)	89 (84–93)	9	18	36	35	92% (84–96)	84% (75–90)	65% (56–73)	73% (64–81)
IIA1	38	23 (14–31)	91 (85–96)	3	4	6	7	91% (73–97)	88% (71–95)	75% (58–86)	80% (63–90)
IIA2	31	34 (24–42)	87 (80–91)	3	6	10	8	89% (68–96)	77% (55–89)	65% (44–79)	74% (53–87)
IIB	693	27 (19–36)	90 (86–95)	55	78	146	152	91% (88–93)	88% (85–90)	73% (69–76)	78% (75–82)
IIIA	13	30 (24–35)	84 (82–88)	0	0	2	3	100%	100%	76% (43–92)	76% (42–91)
IIIB	190	40 (30–56)	88 (83–91)	15	24	61	78	92% (86–95)	86% (79–90)	59% (52–66)	64% (57–71)
IVA	34	57 (39–89)	86 (78–89)	3	6	10	17	91% (75–97)	81% (62–91)	47% (28–63)	52% (33–68)
IVB	98	34 (22–47)	89 (85–92)	8	16	40	38	89% (79–95)	81% (70–88)	48% (37–58)	61% (49–70)
Total	1341†	28 (20–40)	90 (85–94)	98	158	331	363†	92% (90–93)	87% (85–89)	68% (65–70)	74% (72–77)

Data are n, median (IQR), or Kaplan-Meier estimates (95% CI). *Mean dose delivered over all fractions. †One patient with unknown FIGO stage. FIGO=The International Federation of Gynaecology and Obstetrics. CTV_{HR}= high-risk clinical target volume. $D_{90\%}$=minimal dose to 90% of the clinical target volume. $EQD2_{10}$=equi-effective dose in 2 Gy per fraction of 10 Gy.

Table 3: CTV_{HR} volume, and dose and clinical outcomes according to $FIGO_{2009}$ stage

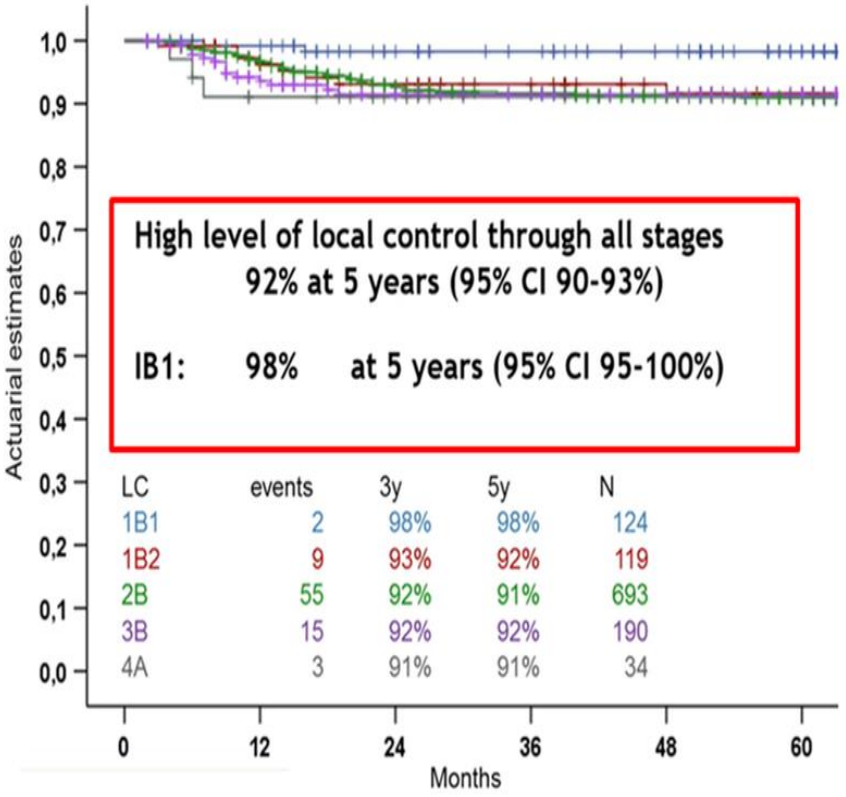
Chemoradiotherapy and MRI-based IGABT result in effective and stable long-term local control across all stages of locally advanced cervical cancer, with a limited severe morbidity per organ.

ESTRO 2020

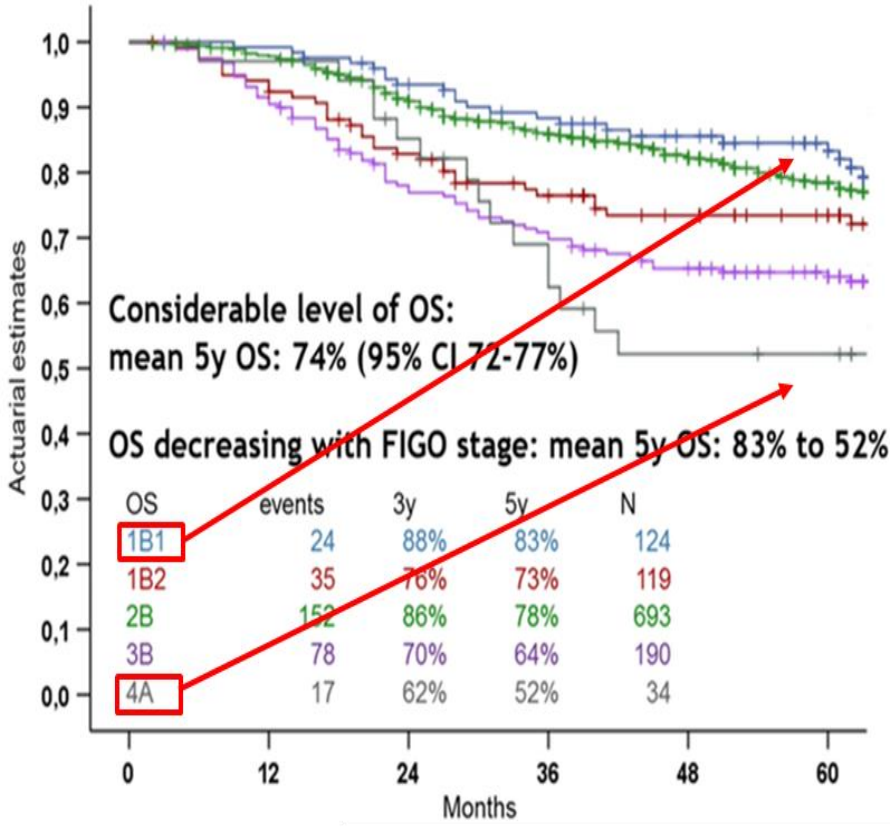
EMBRACE

R. Pötter

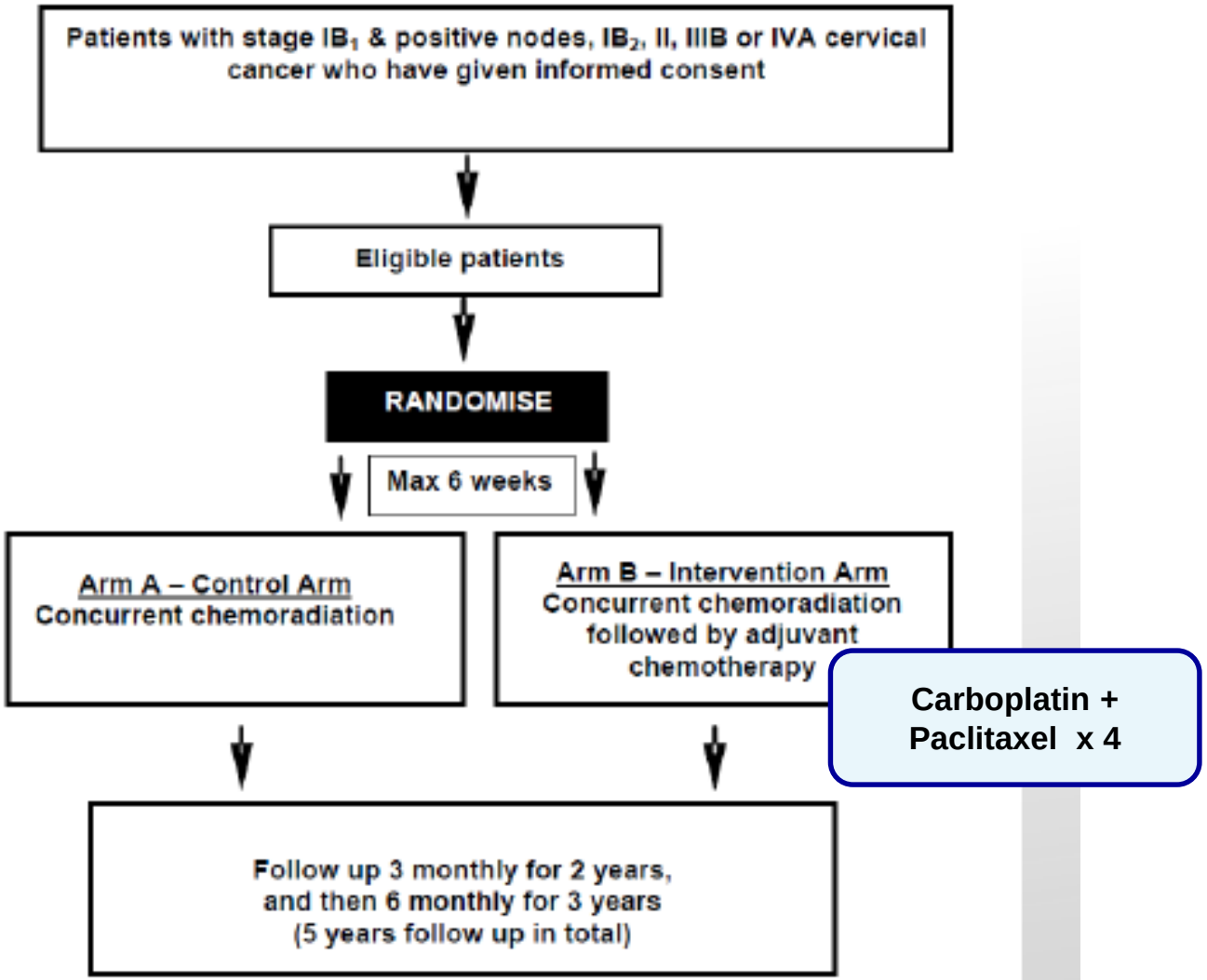
Local control and FIGO$_{2009}$ stage EMBRACE I (KM estimates)



Overall survival and FIGO$_{2009}$ stage EMBRACE I (KM-estimates)



STUDY SCHEMA - OUTBACK



2021 ASCO ANNUAL MEETING

Adjuvant chemotherapy following chemo-radiation as primary treatment for locally advanced cervical cancer compared to chemo-radiation alone: The randomised phase 3 OUTBACK Trial (ANZGOG 0902, RTOG 1174, NRG 0274)

Linda Mileshkin*, Kathleen N Moore*, Elizabeth H Barnes, Val Gebski, Kailash Narayan, Nathan Bradshaw Yeh Chen Lee, Katrina Diamante, Anthony Fyles, William Small Jr, David K Gaffney, Pearly Khaw, Susan Brooks,
Spencer Thompson, Warner Huh, Matthew J Carlson, Cara Matthews, Danny Rischin, Martin Stockler, Bradley J Monk

6th June, 2021

* Equal; first authors

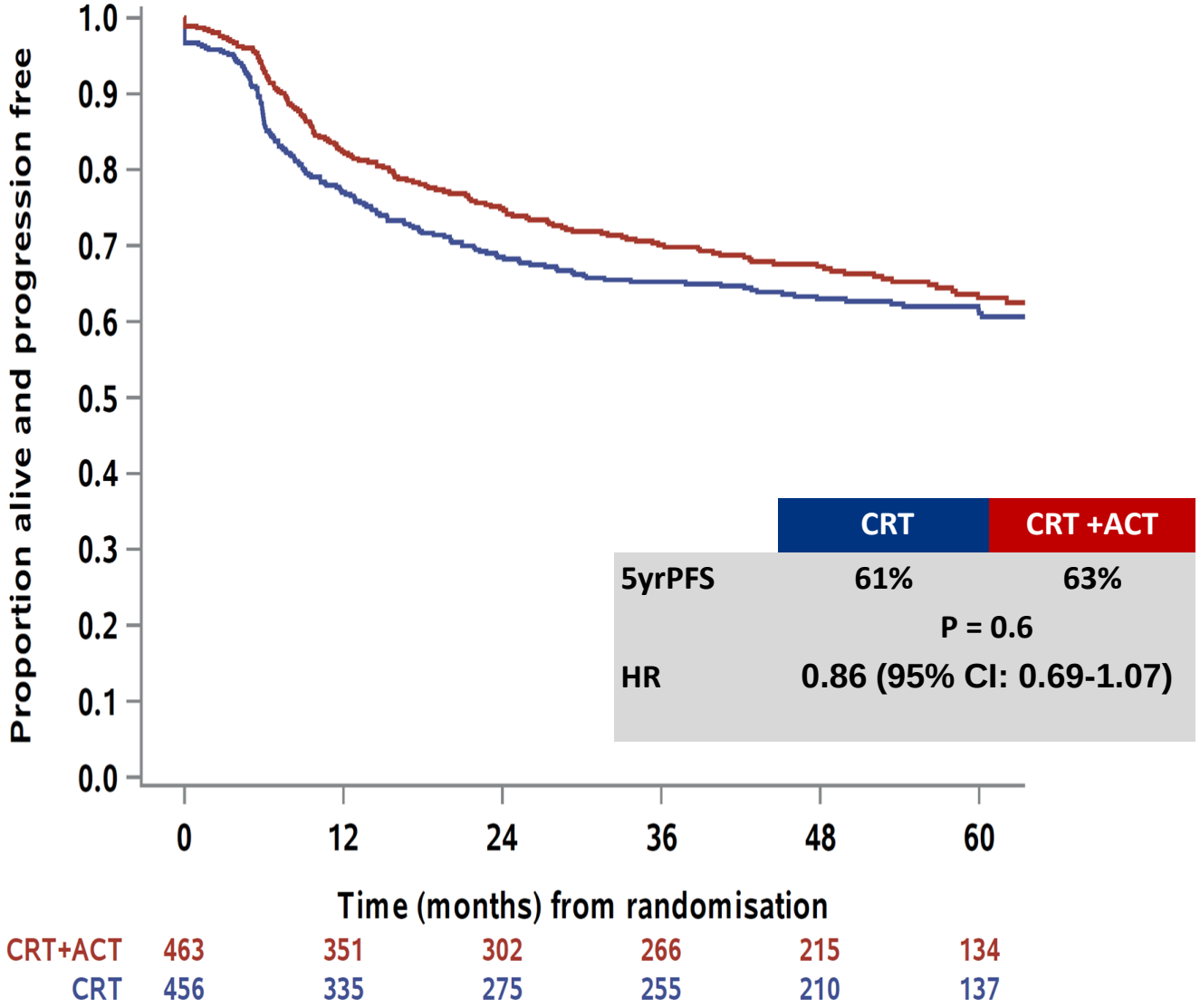
ANZ GOG

NRG ONCOLOGY
Advancing Research. Improving Lives.™

GCIG GYNECOLOGIC CANCER INTERGROUP

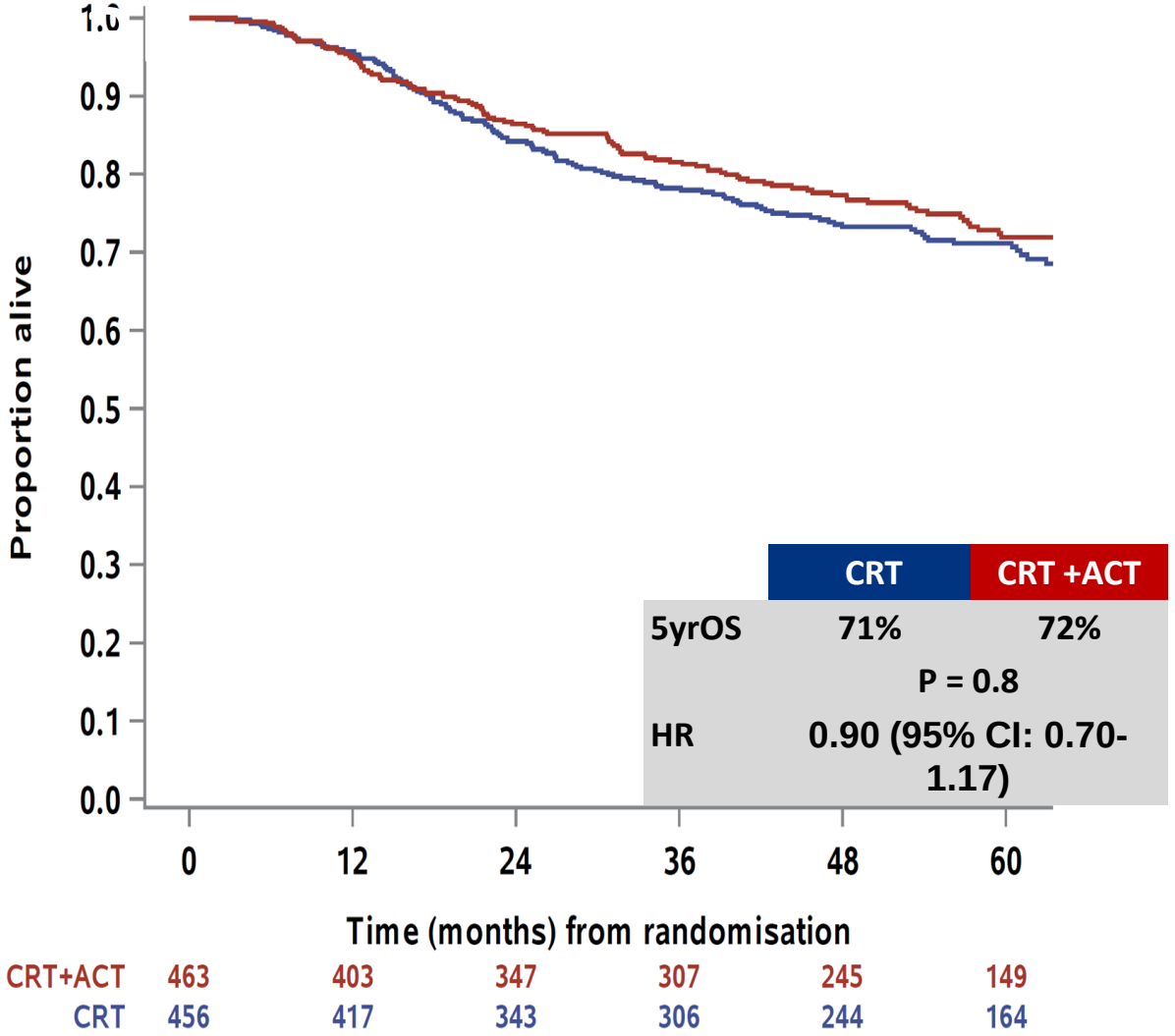
NHMRC Clinical Trials Centre

Progression-Free Survival



Linda Mileshkin - ASCO Meeting 2021

Overall Survival



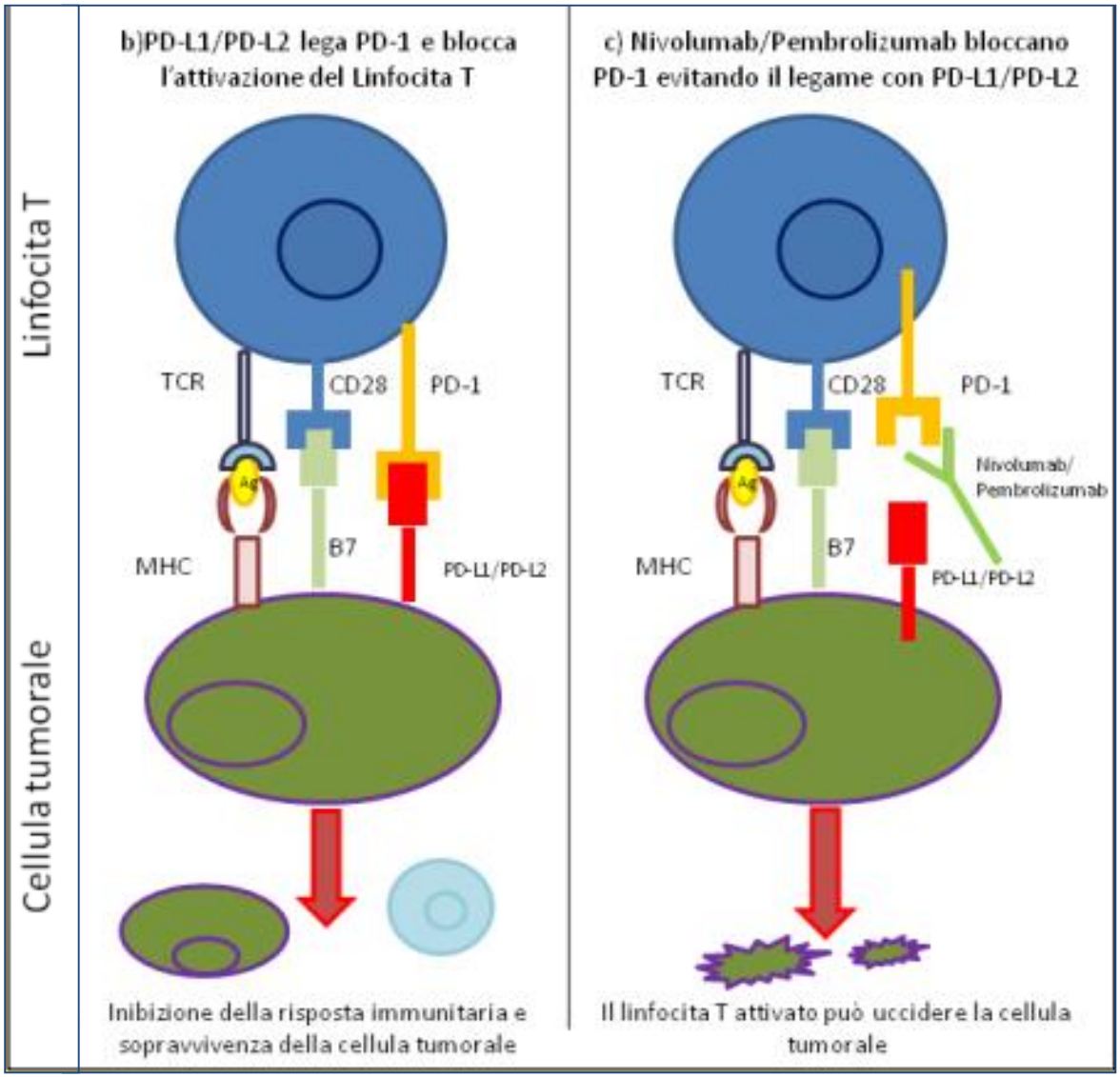
These findings do not support the use of adjuvant chemotherapy with carboplatin and paclitaxel after chemoradiation with weekly cisplatin

Linda Mileshkin - ASCO Meeting 2021

Cervical Cancer Treatment: The Immune Checkpoint Inhibitor Era

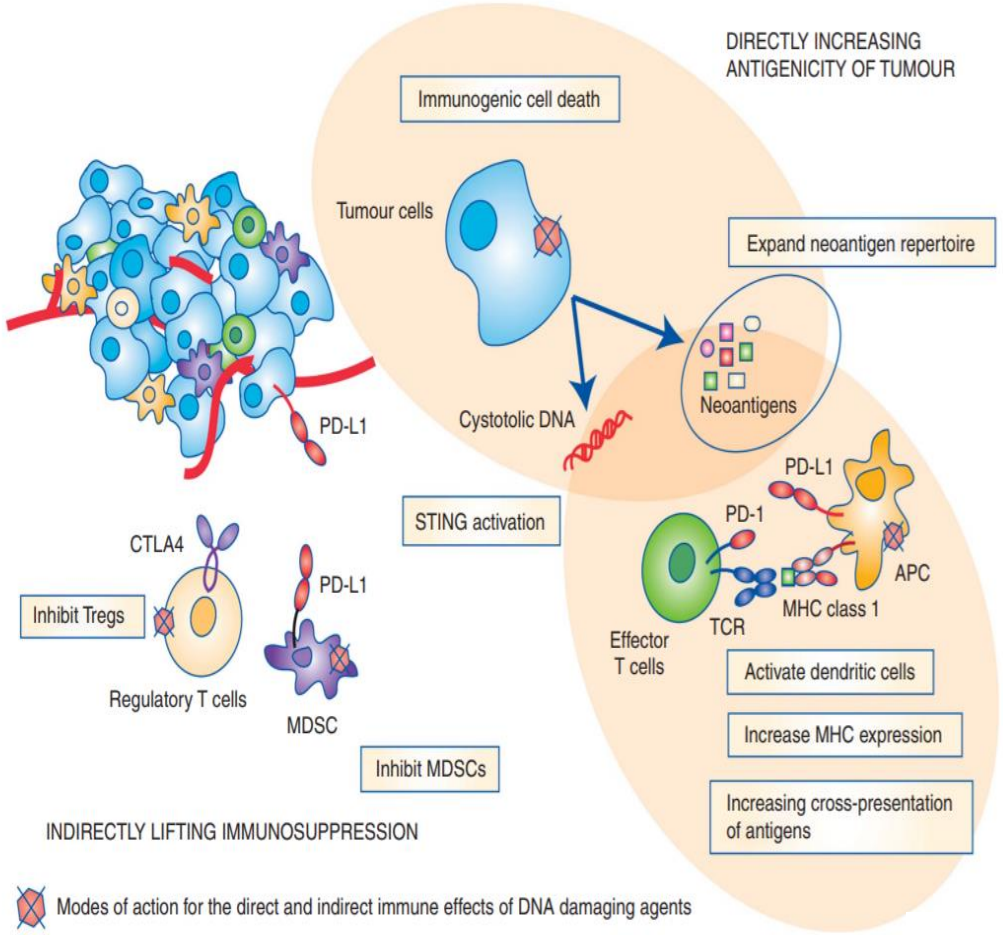
- **A strong scientific rationale exists for combining IO in cervical cancer and with chemoradiotherapy (CRT)**
  - Cervical cancer is an overwhelmingly HPV-drive cancer: HPV DNA detected in >90% of tumors
  - PD-1 is highly expressed in Cervical Cancer
  - Pembrolizumab binds with the PD1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2 thus preventing the down modulating of the immune response by tumor cells
  - KN158 demonstrated responses with durability in 2L+ cervical cancer
  - CRT appears to modulate tumor microenvironment favorably for IO (e.g., PACIFIC in Stage III NSCLC RT)
  - Preliminary data with pembrolizumab with CRT in H&N are supportive: ORR 89%, acceptable safety profile (Powell, ASCO 2017)

Meccanismo d'azione del Pembrolizumab



Scientific Rationale for Chemoradiation + IO

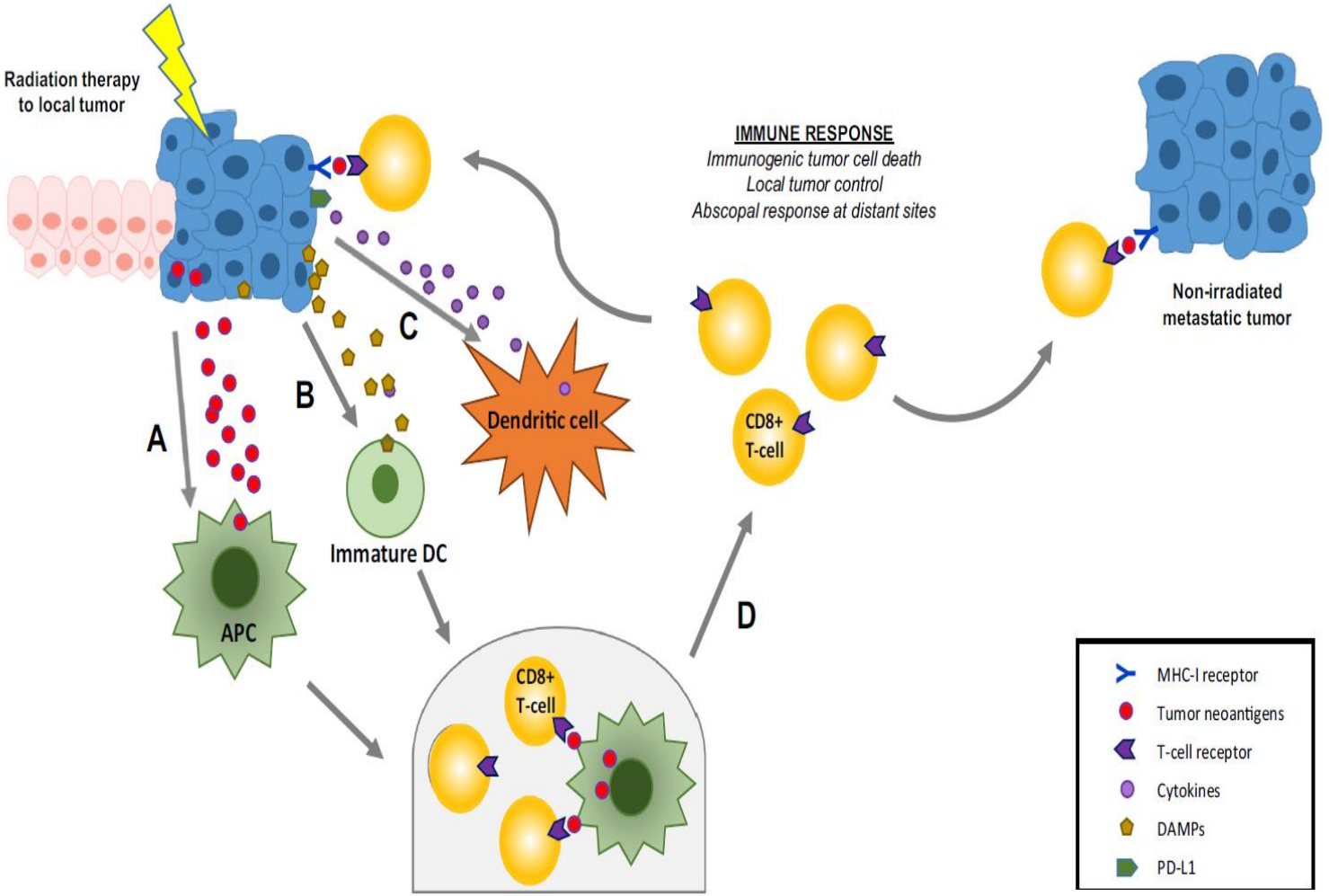
- Mechanisms by which DNA damaging agents (e.g. cisplatin) affect the immunogenicity of tumors



Brown JS et al. Br J Cancer 2018

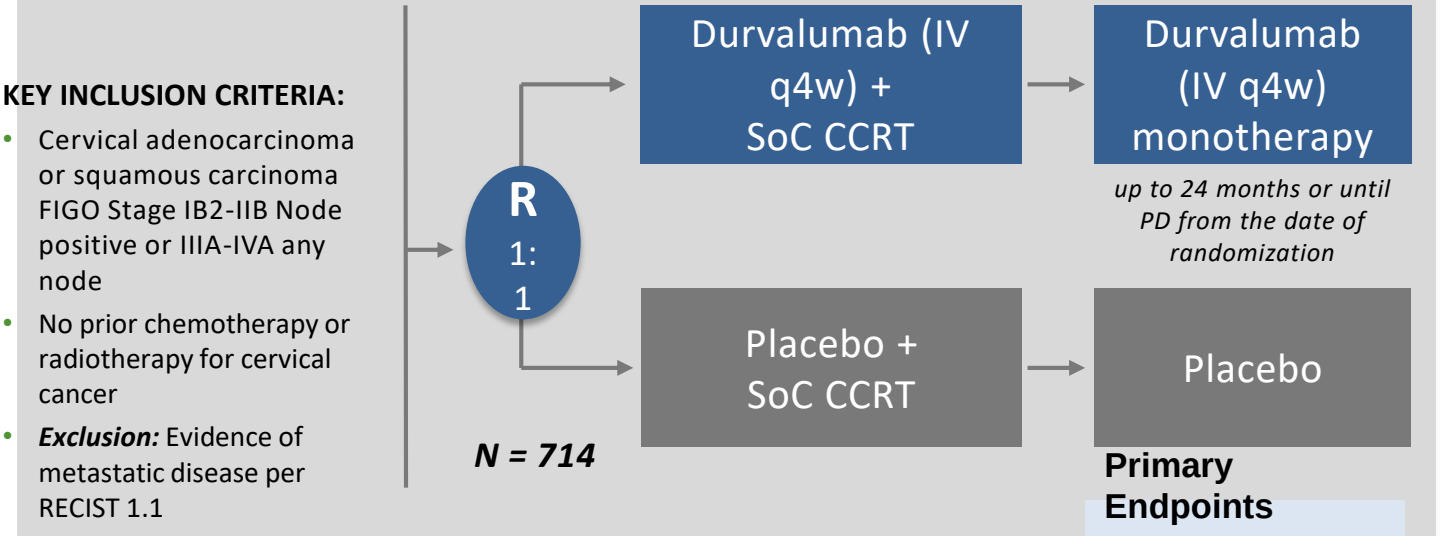
Scientific Rationale for Chemoradiation + IO

- Mechanisms by which radiation affects the immunogenicity of tumors



Lee L & Matulonis U, Gynecol Oncol 2019

CALLA Study Design



KEY INCLUSION CRITERIA:

- Cervical adenocarcinoma or squamous carcinoma FIGO Stage IB2-IIB Node positive or IIIA-IVA any node
- No prior chemotherapy or radiotherapy for cervical cancer
- ***Exclusion:*** Evidence of metastatic disease per RECIST 1.1

First Posted Feb 5, 2019

Actual Start Date : Feb 15, 2019

PCD: Aug, 2023

Primary Endpoints

- PFS

Secondary Endpoints

- OS, CR rate[1)], ORR, DoR, HRQoL

Key Considerations

- Study cites in US, LATAM, Asia, South Africa and limited cites in Europe.[2)]
- PFS is only primary endpoint
- Either cisplatin or carboplatin is allowed for CCRT

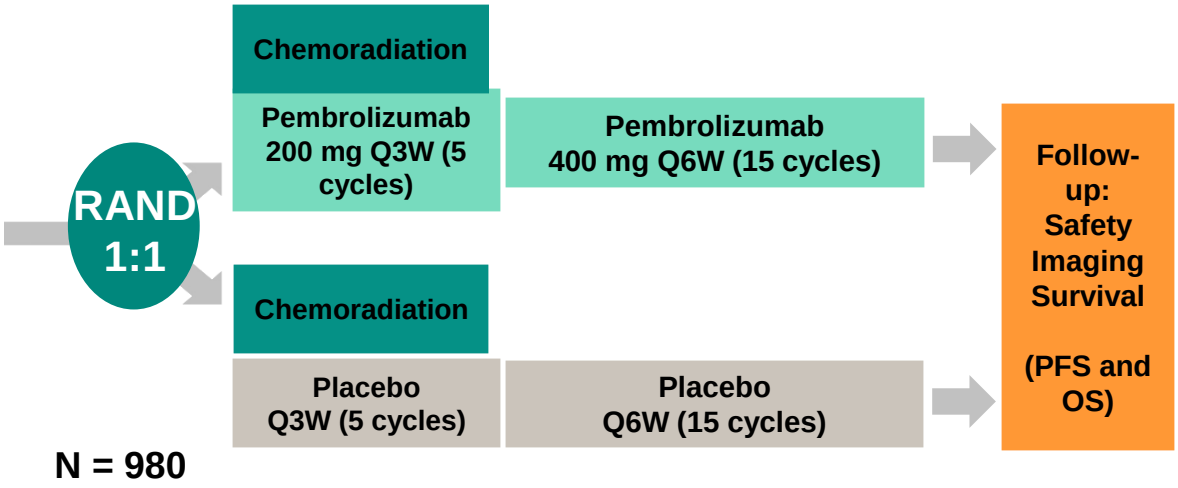
1. The analysis of CR rate at the first tumor assessment after chemoradiotherapy
2. US, LATAM(Brazil, Chile, Mexico, Peru), Asia(India, Japan, South Korea, Philippines, Taiwan), South Africa, Europe (Hungary, Russia)

Source: https://clinicaltrials.gov/ct2/show/study/NCT03830866

ENGOT-CX11/GOG-3047/MK-3475-A18 Trial Design

Key eligibility criteria:

- FIGO 2014 stage IB2-IIB (node- positive disease) OR FIGO 2014 stage III-IVA (either node-positive or node-negative disease)
- RECIST 1.1 measurable or non-measurable disease
- Treatment naïve
- ECOG 0 or 1



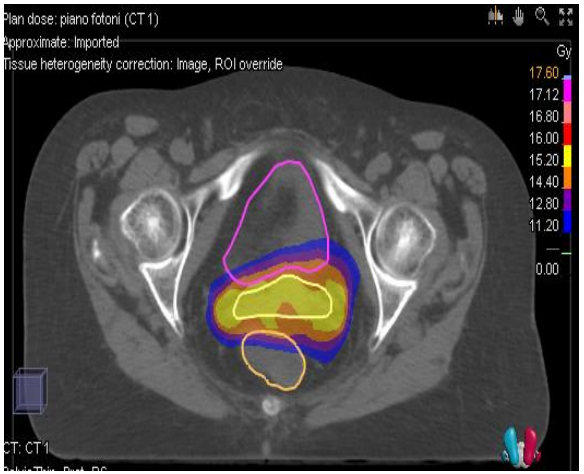
A Randomized, Phase 3, Double-Blind Study of Chemoradiotherapy With or Without Pembrolizumab for the Treatment of High-risk, Locally Advanced Cervical Cancer

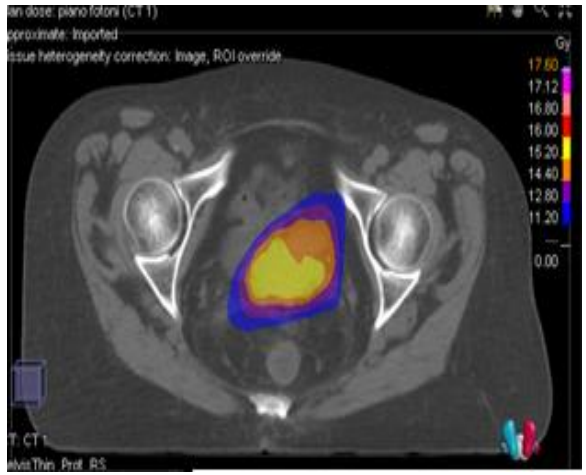
CABLE: Carbon ion rAdiotherapy as Boost for Locally advanced cErvical cancer unfit for brachytherapy

Indicazioni	Pazienti con diagnosi di tumore localmente avanzato della cervice uterina “poor responder/non responder ongoing”alla prima fase di trattamento e/o unfit per BT
Sperimentazione clinica	Sovradosaggio con ioni carbonio (3-4.8 GyRBE per 8 frazioni) sulla malattia residua sequenziale ad RT/CT o NACT + RT/CT
Obiettivi dello studio	Endpoint primario: Controllo locale Endpoint secondario: • OS • PFS • tossicità • QOL

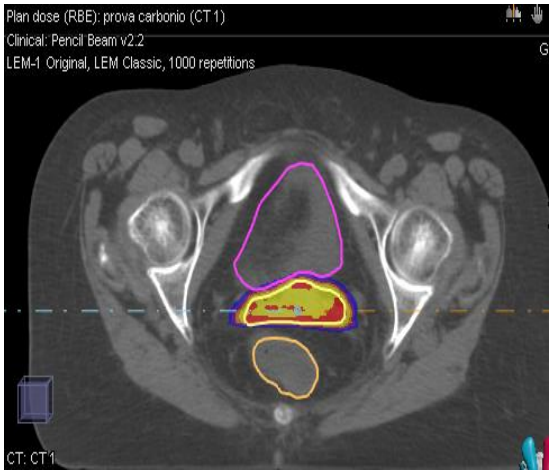
Studio in silico: CIRT vs IMRT/VMAT

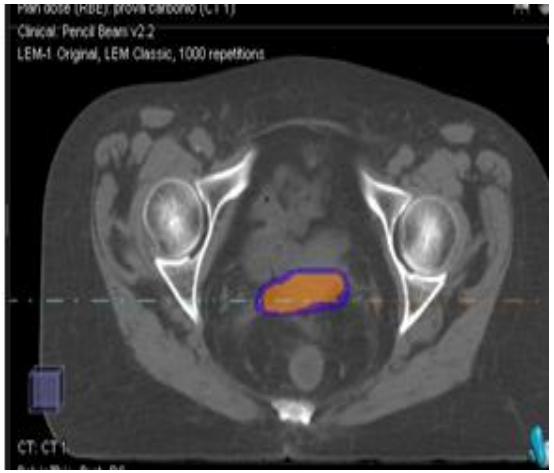
Fotoni





CIRT





Studio in corso in CNAO con AOU Pisana & IEO

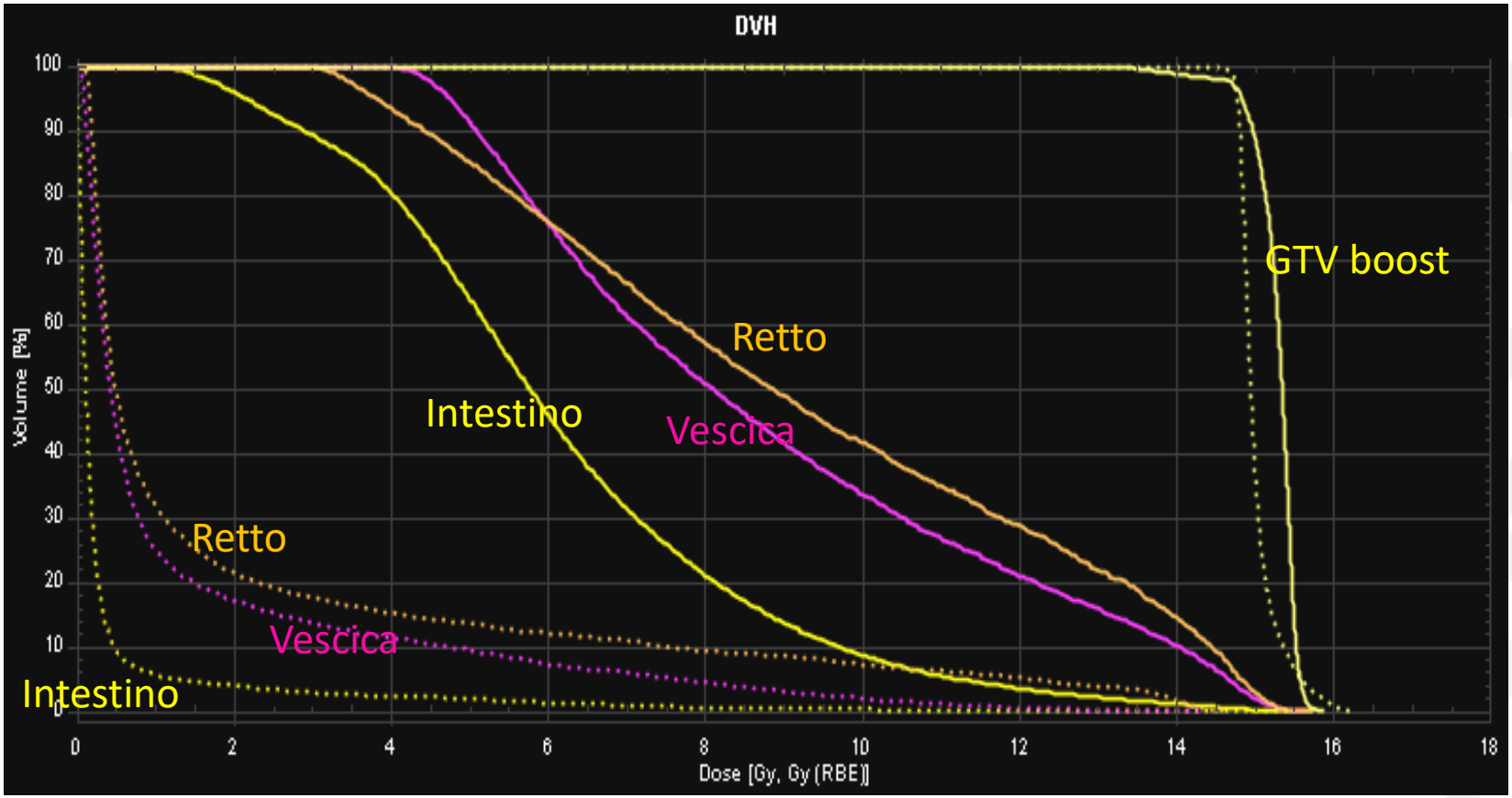
Razionale:
-Selettività spaziale
-Vantaggi radiobiologici
-Dati giapponesi

Studio in silico: CIRT vs IMRT/VMAT

Studio in corso in CNAO con AOU Pisana & IEO

CIRT ---------

Fotoni _____



Advances in Radiotherapy

Proton and carbon ion therapy

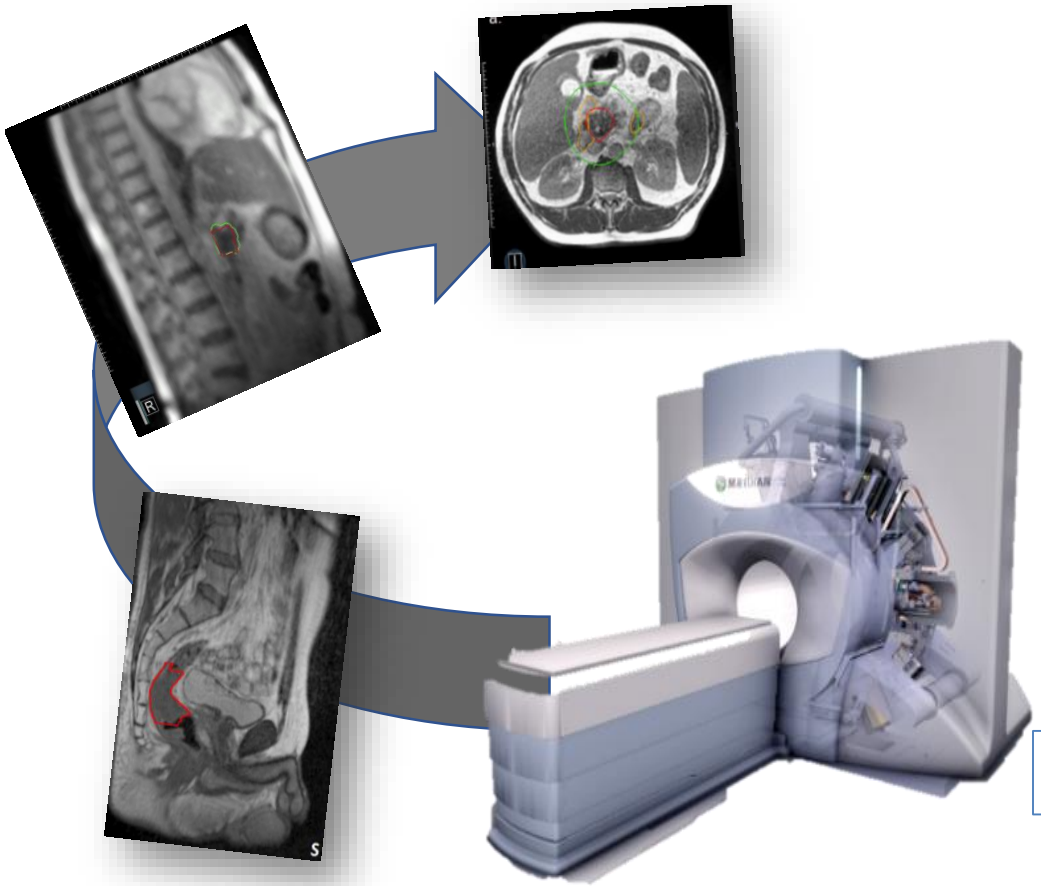
may allow further reduction of normal tissue irradiation particularly bowel and bladder

Proton therapy combined with brachytherapy to reduce toxicity in locally advanced cervical cancer treatment**: toward proEMBRACE**

Ipotesi
Sostituire la fase EBRT con PT per un selezionato gruppo di pazienti, mantenendo IGABT boost necessario per il controllo della malattia

Advances in radiotherapy

Application of MR guided EBRT



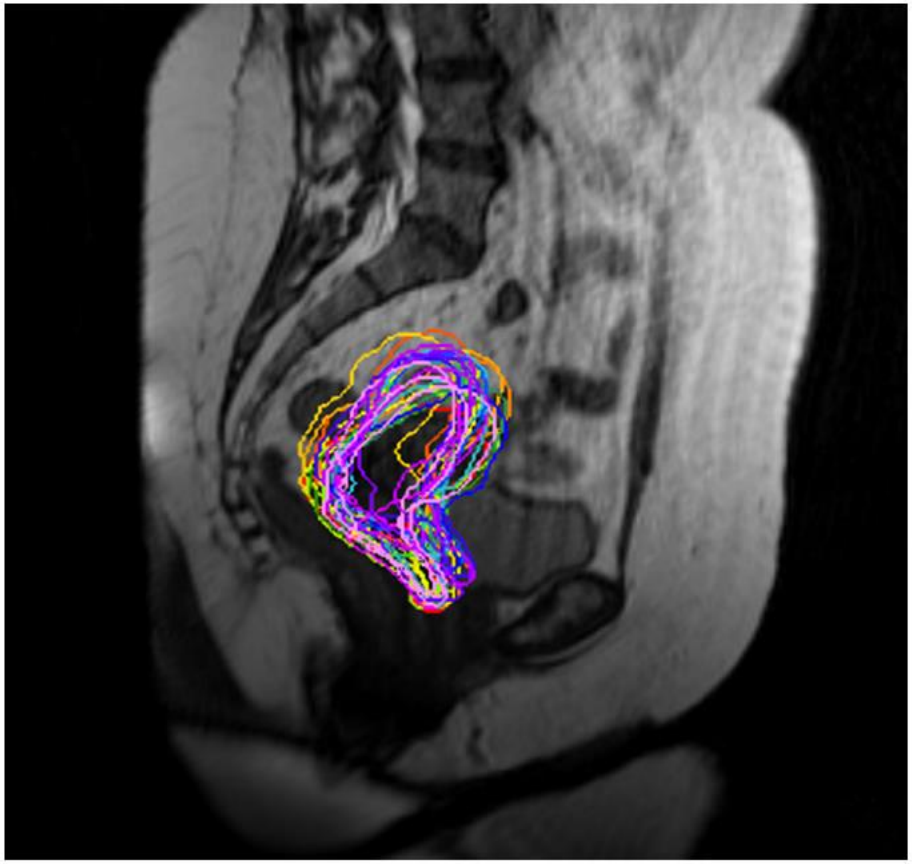
1. To see
2. To gate
3. To adapt

Treatment personalization

MR linac : adaptive RT strategies and customization of RT margins can offer potential solutions to maximize PTV coverage and minimize OAR dose.

Results

- 15 LACC patients
- A total of 232 pre-treatment 0.35 T MR scans
- Median volume reduction: 32.4% (26.2%-53.6%).



Courtesy of A. Romano- Policlinico Gemelli

14 Dicembre 15.00-18.00

LA CONTORNAZIONE DELLA PELVI FEMMINILE: ORGANI A RISCHIO EMERGENTI NELLA PRATICA CLINICA QUOTIDIANA

15.00-15.05 **Introduzione** *(D.ssa A. Cerrotta)*

15.05-15.25 **Il trattamento del carcinoma della cervice uterina localmente avanzato** *(D.ssa G. Macchia-D.ssa A. Cerrotta)*

15.25-15.45 **L'utilizzo della risonanza magnetica per la definizione delle strutture pelviche** *(D.ssa B. Seccia)*

15.45- 17.25 **Organi a rischio emergenti nella pelvi femminile: limiti anatomici sulla risonanza magnetica e sulla TC di centratura**

- *15.45-16.05* **Collo e base della vescica** *(D.ssa A. Augurio)*
- *16.05-16.25* **Sfintere anale esterno, sfintere anale interno, muscolo puborettale, muscolo elevatore dell'ano** *(D.ssa A. Vinciguerra)*
- *16.25-16.45* **Vagina** *(D.ssa V. De Sanctis)*
- *16.45-17.05* **Midollo osseo** *(D.ssa R. Autorino)*
- *17.05-17.25* **Ovaie** *(D.ssa C. Delle Curti)*

17.25-17.45 **Presentazione caso clinico** *(D.ssa F. Di Guglielmo)*

17.45-18.00 **Discussione e conclusioni** *(D.ssa A. Cerrotta)*

CREDITI ECM: 4,5

La FAD sincrona prevede la partecipazione all'attività formativa attraverso piattaforma Zoom, che sarà fruibile in diretta attraverso una connessione ad internet. Se non ha mai usato Zoom, la invitiamo a scaricare preventivamente l'App al seguente indirizzo https://zoom.us/support/ download e a nominare il dispositivo con il quale accede con Cognome e Nome per esteso. Questo è importante ai fini del rilevamento della sua presenza.

La sincronicità della partecipazione prevede il collegamento dei discenti agli orari prestabiliti dal programma formativo, garantendo l'interattività con i docenti attraverso un sistema di messaggistica via chat. La partecipazione viene rilevata attraverso la registrazione degli accessi e della permanenza su piattaforma Zoom durante la sessione di formazione che verrà registrata e resa disponibile per una fruizione asincrona/ripetibile, come supporto alla compilazione del questionario ECM sulla piattaforma http://ecm.radioterapiaitalia.it/. La verifica di apprendimento verrà effettuata tramite questionario a risposta multipla da effettuare entro 3 giorni dalla data dell'evento sulla piattaforma suindicata e si ricorda che per ottenere i crediti ECM dovrà obbligatoriamente compilare anche il questionario di gradimento. Riceverà istruzioni dal Provider.

Associazione Italiana Radioterapia e Oncologia Clinica, Gruppo di studio ginecologico

Neoplasie ginecologiche

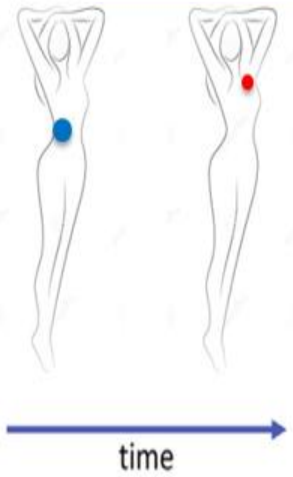
- Carcinoma della cervice uterina
- Carcinoma dell'ovaio
- Carcinoma dell'endometrio

Malattia oligo-metastatica/persistente/recidivante e radioterapia stereotassica

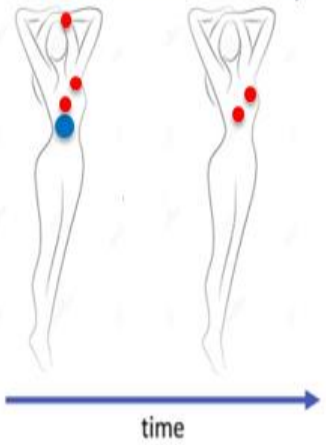
OLIGOMETASTATIC DISEASE SCENARIOS

De novo synchronous oligometastastic disease

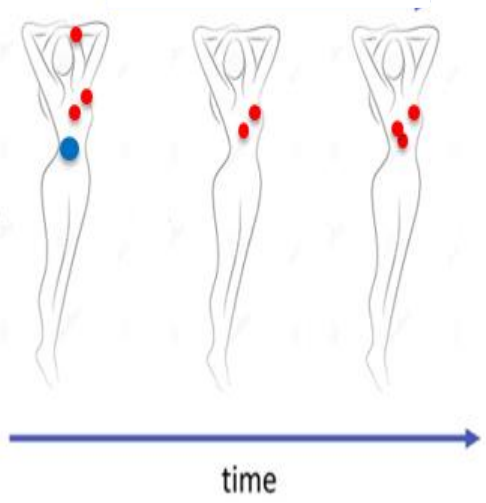
De novo metachronous oligometastastic disease



Oligopersistent disease



Oligoprogression

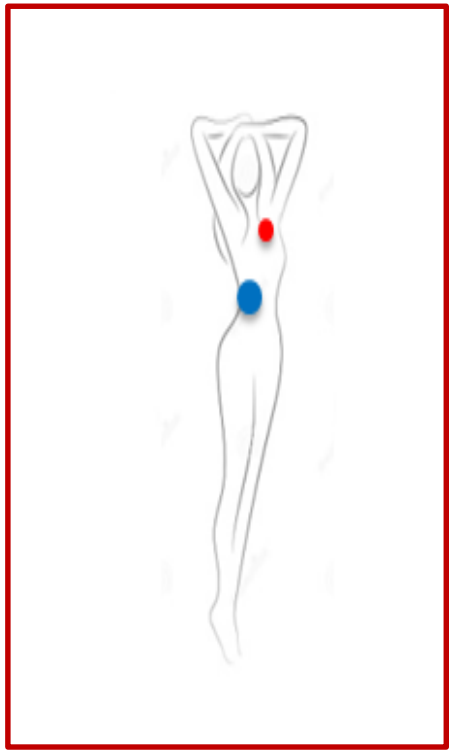


Systemic chemotherapy→ Platinum, Bevacizumab, PARP inhibitors, immunotherapy

Stereotactic Body Radiotherapy (SBRT)

ROC >70% within two years

from diagnosis



High dose/short time

Minimally invasive

High local control

Minimal toxicities

Retreatment

Safely administered during CT

Active in chemoresistant disease

Immune response activator

Synergic with immunotherapy and PARPi

	Trippa et al. 2016 (22)	Iftode et al. 2018 (23)	Lazzari et al. 2018 (24)
N° patients **N° lesions**	11 20	26 44	82 156
Inclusion criteria	Limited lymph node relapse at imaging	≤4 lesions Maximum diameter 5 cm Life expectancy> 6 months PS≥2	Oligorecurrent/oligoprogressive/ oligopersistent ovarian cancer Unfit for other local therapies
Exclusion criteria	-	Brain metastases	Bone or brain metastases
Site of lesions	LN (mediastinal, lomboaortic, pelvic sites)	LNs Visceral metastases (liver, lung)	LNs Visceral metastases (head and neck, thorax, abdomen, pelvis)
Total dose, fractionation: N. lesions (%)	25 Gy (5 Gy, 5 fractions): 5 (25) 30 Gy (6 Gy, 5 fractions): 3 (15) 35 Gy (7 Gy, 5 fractions): 2 (10) 40 Gy (8 Gy, 5 fractions): 10 (50)	LNs: median total dose: 45 Gy (range, 36-60 Gy) in 6 fractions (range, 4-8) Liver: median total dose 75 Gy (range, 45-75 Gy) in 3 fractions (range, 3-6) Lung: 48 Gy in 4 fractions	24 Gy (8 Gy, 3 fractions): 89 (57.0) 25 Gy (5 Gy, 5 fractions): 35 (22.4) 30 Gy (10 Gy, 3 fractions): 10 (6.4) Other regimens: 22 (14.1)
BED α/β 10Gy	-	-	Median, Gy: 43.2 Range, Gy: 28-112.5
Equipment	Linear accelerator	Linear accelerator (Varian Medical Systems, USA)	VERO System Cyberknife System
Technique	5MV photons: coplanar dynamic arcs	6-10MV photons: flattened or unflattened beams single or multiple coplanar partial arcs (RapidArc)	6-MV photons: Dynamic arcs or multiple modulated fixed beams (VERO) Nonisocentric and noncoplanar technique (Cyber)
Dose prescription	Isocenter	Target mean	75% to 80% isodose line
GTV	Median 5.35 cc Range, cc 1.5-18.3	Median 7.04 mL Range, 1.27-62.45mL	Median, cc 3.15 Range, cc 0.19-90.5
Reference constraints	-	Personalized	Timmerman RD. 2008
IGRT	Yes (MV portal imaging)	Yes (gating, cone beam CT)	Yes (Xsight spine, cone beam CT, ExacTrac system)
Clinical Response	CR:11 (100%)	CR: 26 (59.1%) PR: 9 (20.5%) SD: 6 (13.6%) PD: 3 (6.8%)	CR: 76 (61.8%) PR: 17 (13.8%) SD: 19 (15.5%) PD: 11 (8.9%)
Median follow up	24 months	28.5 months (range, 6-86)	17.4 months (range, 2.2-51.4)
Toxicity Grade, N. patients	0	Grade 2 Acute toxicity: 5 Grade 3/4: 0	Grade 1-2 Acute toxicity: 22 Grade 1-2 Late toxicity: 23 Grade 3/4: 0
2-yr actuarial LPFS[a]	73%	92.9%	68%
2-yr actuarial PFS	-	38.0%	18%
2-yr actuarial OS	78%	92.7%	71%

MPR-OC and SBRT

The Oncologist®

Radiation Oncology

A Large, Multicenter, Retrospective Study on Efficacy and Safety Of Stereotactic Body Radiotherapy (SBRT) in Oligometastatic Ovarian Cancer (MITO RT1 Study): A Collaboration of MITO, AIRO GYN, and MaNGO Groups

Gabriella Macchia,[a,†] Roberta Lazzari,[b,†] Nicoletta Colombo,[c] Concetta Laliscia,[d] Giovanni Capelli,[e] Giuseppe Roberto D'Agostino,[f] Francesco Deodato,[a] Ernesto Maranzano,[g] Edy Ippolito,[h] Sara Ronchi,[b] Fabiola Paiar,[d] Marta Scorsetti,[f,i] Savino Cilla,[j] Rossana Ingargiola,[b,k] Alessandra Huscher,[l] Anna Maria Cerrotta,[m] Andrei Fodor,[n] Lisa Vicenzi,[o] Donatella Russo,[p] Simona Borghesi,[q] Elisabetta Perrucci,[r] Sandro Pignata,[s] Cynthia Aristei,[r] Alessio Giuseppe Morganti,[t] Giovanni Scambia,[u,v] Vincenzo Valentini,[a,y,w] Barbara Alicja Jereczek-Fossa,[b,k,††] Gabriella Ferrandina[u,v,††]

261 patients, 449 lesions CR+PR: **89**%

mFUP: 22 months 2y-LPFS: **81.9**%; 2y-PFS: 15.4

2y-OS:**73.6**%

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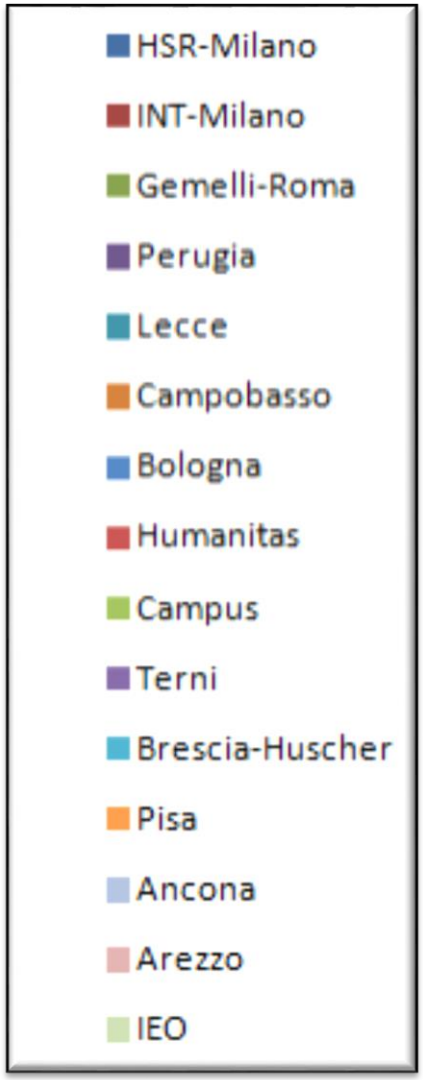
Macchia G, et al. The Oncologist 2020; 25(2):e311-e320..

Retrospective, multicenter study in very large, real life dataset of ROC patients

MITO-RT1:



15 Centri, 261 pazienti, 449 lesioni

Aims:

- activity
- safety
- potential predictors of clinical outcome

MITO-RT1

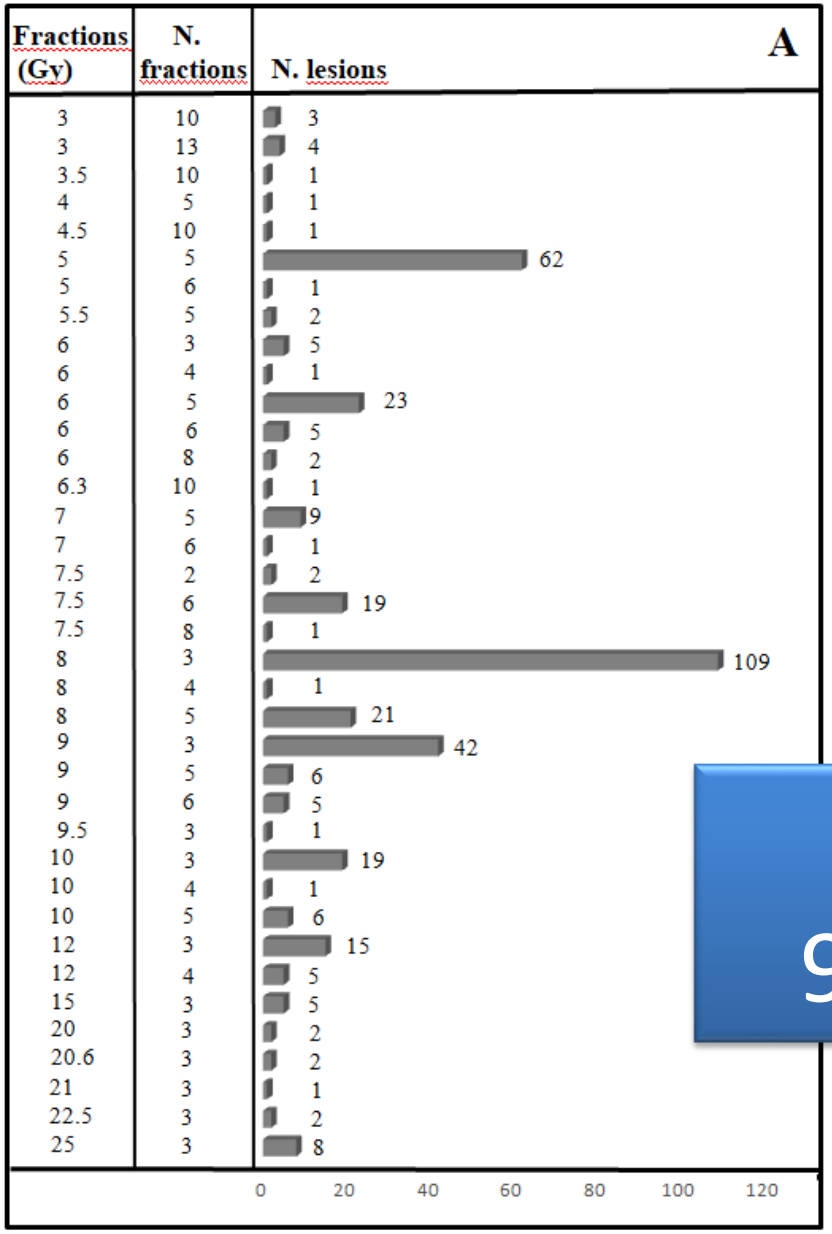
Histotype	
High grade serous cell	186 (71.3)
Endometrioid	36 (13.8)
Clear cell	11 (4.2)
Undifferentiated	6 (2.3)
Mixed mullerian/carcinosarcoma	6 (2.3)
Other	16 (6.1)
N. patients undergoing surgery before SBRT[c]	
No	3 (1.2)
Yes	253 (98.8)
n.a.	*5*
N. of previous surgery	
Median (range)	1 (0-7)
N. patients undergoing chemotherapy before SBRT[c]	
No	0
Yes	256 (100)
n.a.	*5*
N. of lines of previous chemotherapy	
Median (range)	2 (1-11)
N. patients undergoing previous in site radiotherapy[c]	
No	247 (96.5)
Yes	9 (3.4)
n.a.	*5*

MITO-RT1

	N.(%)
Type of lesion(s)	
Lymph node	292 (65.0)
Parenchyma	157 (35.0)
Anatomical district	
Abdomen	248 (55.2)
Pelvis	85 (18.5)
Thorax	66 (14.7)
Brain	37 (8.2)
Neck	13 (5.2)
N. of patients bearing	
1 lesion	146 (55.9)[a]
2 lesions	70 (26.8)
3 lesions	28 (10.7)
4 lesions	9 (3.4)
5 lesions	6 (2.3)
6-7 lesions	2 (0.8)[b]

Equipments	
Linear Accelerator (LINAC)	401 (89.3)
CyberKnife	34 (7.6)
Tomotherapy	11 (2.4)
GammaKnife	3 (0.7)
GTV	
Median, range (cc)	4.5 (0.04-68.4)
PTV	
Median, range (cc)	17.9 (0.04-136.4)
Total dose, Gy	
Median (range)	25 (5-75)
N. of fractions	
Median (range)	4 (1-13)
Dose/fraction, Gy	
Median (range)	8 (3-30)
$BED_{\alpha/\beta 10}$	
Median (range)	50.7 (7.5-262.5)
Type of treatment	
SBRT, stereotactic radiotherapy (more fractions)	396 (88.2)
SRS, stereotactic radiosurgery (single fraction)	53 (11.8)
Referral dose	
Specific isodose	235 (52.3)
Isocenter	159 (35.4)
Target mean	55 (12.3)

Courtesy of Gabriella Macchia



65.2% clinical CR

96.4% Clinical Benefit

Courtesy of Gabriella Macchia

Table 3. Univariate and multivariate analysis of variables predicting clinical complete response to SBRT on a per lesion basis

Variable	N.	Complete response N. (%)	Univariate			Multivariate		
			Odds ratio	95% CI	p value[a]	Odds ratio	95% CI	p value[a]
All lesions	446	291 (65.2)	-	-	-	-	-	-
Age, years								
>60	213	129 (60.6)	1°			1°		
≤60	233	162 (69.5)	1.486	1.004, 2.198	**0.048**	1.616	1.056, 2.472	**0.027**
Histotype								
Serous	320	206 (64.4)	1°		0.538	-	-	-
Others	126	85 (67.5)	1.147	0.741, 1.777				
Type of lesions								
Parenchyma	155	76 (49.0)	1°			1°		
Lymph nodes	291	215 (73.9)	2.940	1.953, 4.428	**<0.001**	2.937	1.888, 4.569	**<0.001**
Total dose, Gy								
≤ 25	226	147 (65.0)	1°					
> 25	220	144 (65.4)	1.018	0.689, 1.504	0.928	-	-	-
N. fractions								
≤ 4	271	176 (64.9)	1°					
> 4	175	115 (65.7)	1.034	0.694, 1.543	0.868	-	-	-
Dose/fraction, Gy								
≤ 8	172	107 (62.2)	1°					
> 8	274	184 (67.1)	1.242	0.834, 1.849	0.286	-	-	-
BED_{10}, Gy								
≤70	314	202 (64.3)	1°					
>70	132	89 (67.4)	1.147	0.746, 1.766	0.531	1.979	1.214, 3.227	**0.006**
PTV[b], cc								
>18	187	106 (56.7)	1°					
≤18	232[b]	162 (69.8)	1.768	1.182, 2.646	**0.006**	1.857	1.207, 2.857	**0.005**

[a] calculated with logistic regression, [b] 27 missing

Independent predictors of high chances of clinical CR

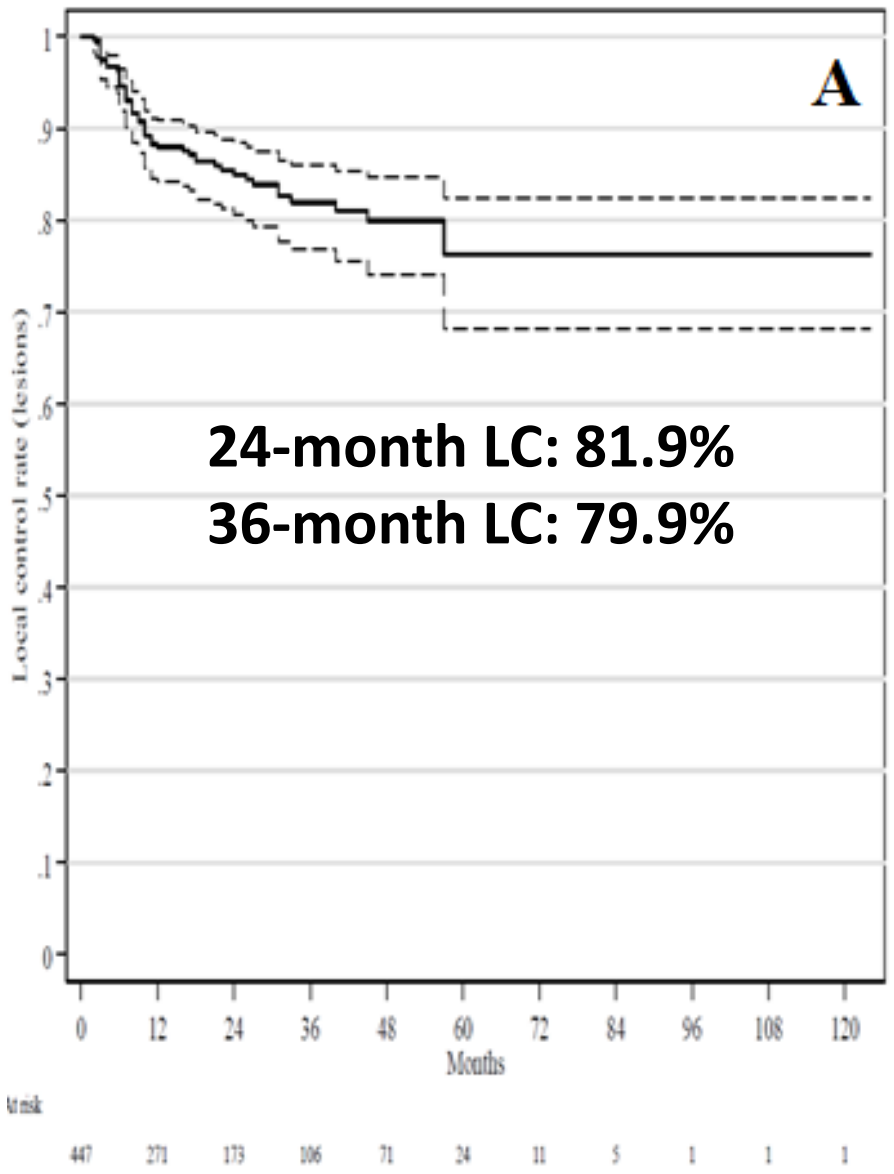
age $\leq$60

PTV$\leq$18 cc

LN disease

BED_{10}>70

Courtesy of Gabriella Macchia



PD: 61/446 irradiated lesions (13.7%)

20.6% low grade acute toxicity,
2-year late toxicity free survival: **95.1%**

half of patients >60 years
46% → ≥2 previous CT lines and at least 1 major surgery

Safety also in unfit setting

Courtesy of Gabriella Macchia

Future perspectives

Trial record **1 of 8** for: SBRT | Ovary Cancer

U.S. National Library of Medicine

ClinicalTrials.gov

Previous Study | Return to List | Next Study

Efficacy and Safety of SBRT in Oligo-metastatic/Persistent/Recurrent Ovarian Cancer (MITO-RT3/RAD)

Clinical trial

Efficacy and safety of stereotactic body radiotherapy (SBRT) in oligometastatic/persistent/recurrent ovarian cancer: a prospective, multicenter phase II study (MITO-RT3/RAD)

Gabriella Macchia [1], Barbara Alicja Jereczek-Fossa [2, 3], Roberta Lazzari [2], Annamaria Cerrotta [4], Francesco Deodato [1] Edy Ippolito [6], Cynthia Aristei [7], Maria Antonietta Gambacorta [5, 8], Giovanni Scambia [9, 10], Vincenzo Valentini [5, 8] and Gabriella Ferrandina [9, 10]

Correspondence to Dr Gabriella Macchia, Radiotherapy Unit, Gemelli Molise, Campobasso, Molise, Italy; macchiagabriella@gmail.com

INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER

12 center started accrual

(Ethical Committee approval)

70 lesions (46 patients) at September 2021

Macchia G, et al. Int J Gynecol Cancer 2021

Table 1. Schedules of treatment and dose prescription according to target sites

TYPE OF LESIONS		Dose Gy	N. fractions	Total dose Gy	BED_{10} Gy	
LYMPH NODES		6	5	30	48	
		10	3	30	60	
		8	5	40	72	
		7	5	35	59.5	
		9	5	45	85.5	
		10	5	50	100	
PARENCHYMA		9	3	27	51.3	Brain Bone
		8	5	40	72	Liver Lung Bone (vertebra)
		12	3	36	79.2	Bone (non vertebra)
		15	3	45	112.5	Lung
		10	5	50	100	
	Tumor size					
BRAIN	*<15 mm*	20	1	20	60	Cyberknife *(dose prescription 80%)*
	15 mm-4 cm	9	3	27	51.3	
	>4 cm	6	5	30	48	

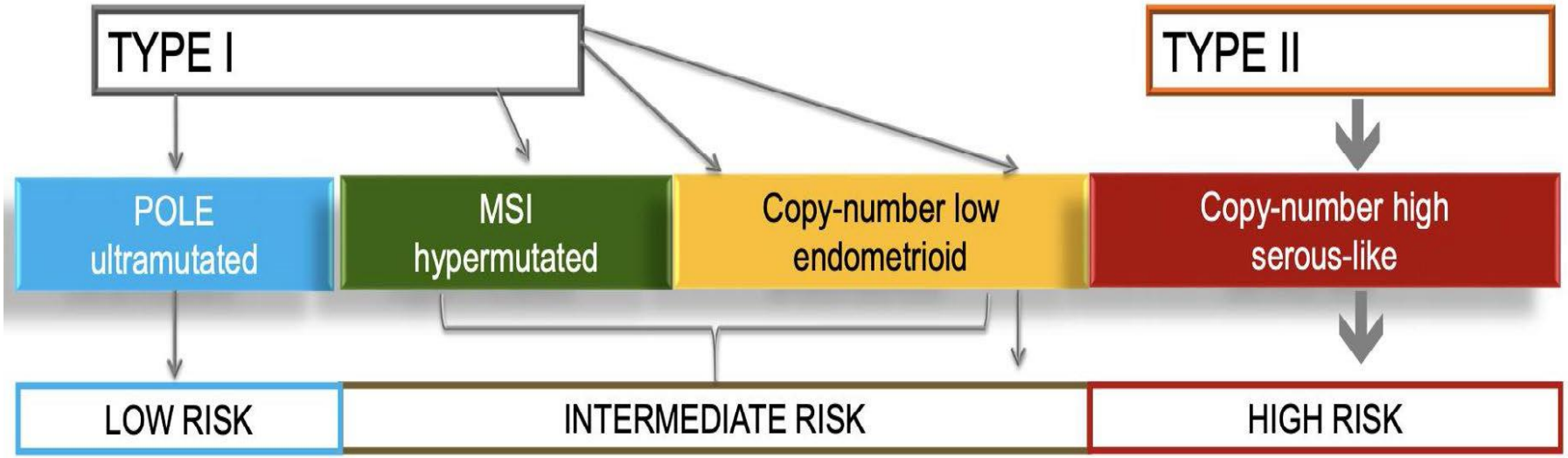
Neoplasie ginecologiche

- Carcinoma della cervice uterina
- Carcinoma dell’ovaio
- Carcinoma dell’endometrio

Fattori di rischio per il Carcinoma Endometriale

- Grado istologico
- Tipo istologico
- Profondità di interessamento del miometrio
- Infiltrazione degli spazi linfovascolari
- Stadio
- Età

Classificazione del TCGA(The Cancer Genomic ATLAS)



Genomic based approach del carcinoma endometriale:

- **POLE ultramutati: a prognosi favorevole;**
- ***copy-number low endometrioidi: a prognosi intermedia;***
- **MSI ipermutati: a prognosi intermedia;**
- ***copy-number high (serous-like): a prognosi peggiore***

2013

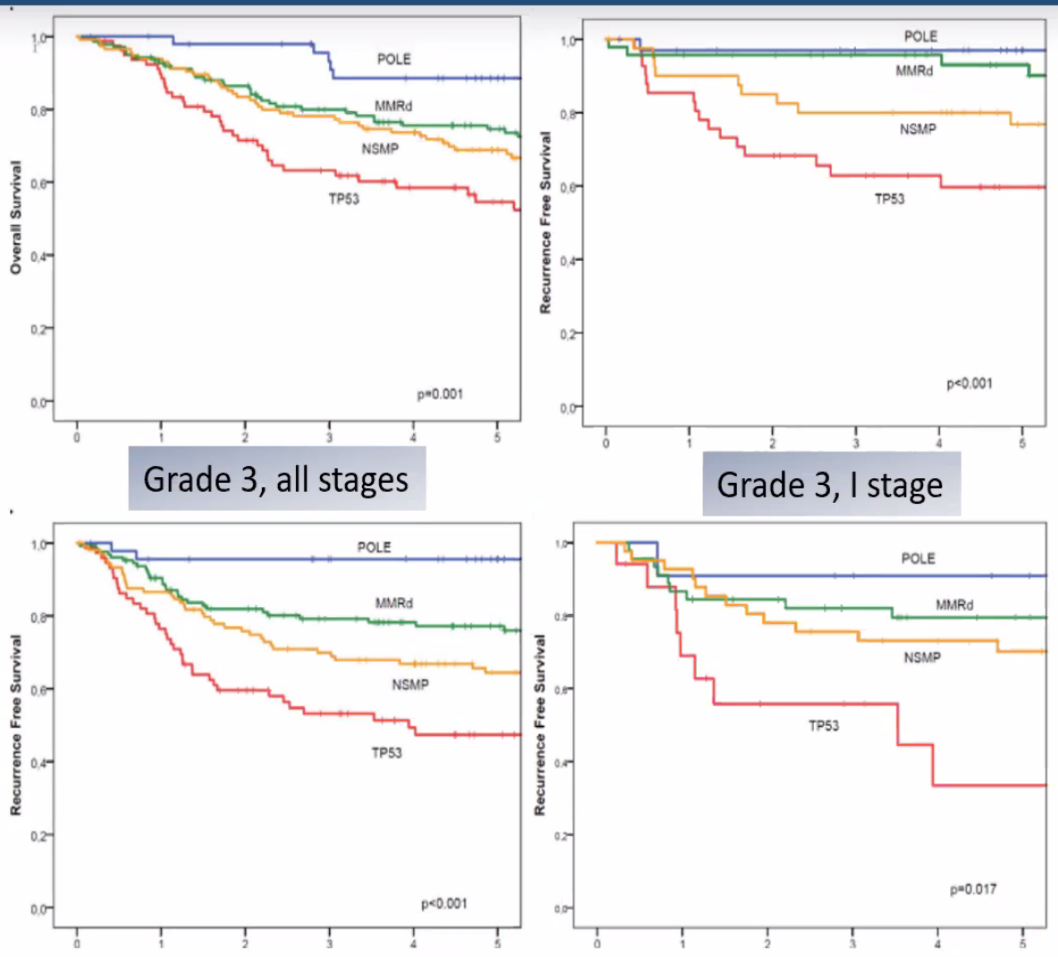
A Genomic-Based Approach Has Identified 4 Distinct Molecular Subgroups of Endometrial Cancer [1,2]

	POLE ultramutated EC	MMRdeficient EC	NSMP EC	P53mutant EC
Estimated prevalence	**5-15%**	**25-30%**	**30-40%**	**5-15%**

MOLECULAR CLASSIFICATION OF HIGH GRADE ENDOMETRIAL CANCER

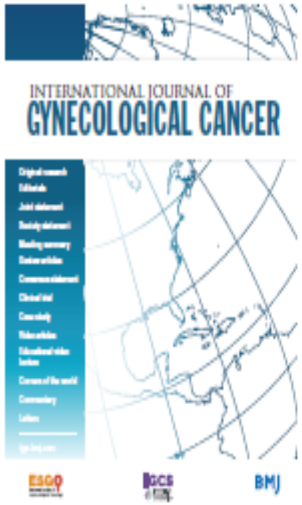
2018,
381 patients, Grade 3 EEC
international collaboration

- Grade 3 endometrial cancer is not a homogeneous “high risk” cohort .
- TGCA molecular groups have clear prognostic impact in high-grade EC.
- Prognostic strenght of molecular classification is independent of stage.
- POLE almost zero events also in grade 3 disease



Bosse et al, Am J Surg Pathol 2018

Joint statement



ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

Nicole Concin [1,2] Xavier Matias-Guiu,[3,4] Ignace Vergote,[5] David Cibula,[6] Mansoor Raza Mirza,[7] Simone Marnitz,[8] Jonathan Ledermann [9] Tjalling Bosse,[10] Cyrus Chargari,[11] Anna Fagotti,[12] Christina Fotopoulou [13] Antonio Gonzalez Martin,[14] Sigurd Lax,[15,16] Domenica Lorusso,[12] Christian Marth,[17] Philippe Morice,[18] Remi A Nout,[19] Dearbhaile O'Donnell,[20] Denis Querleu [12,21] Maria Rosaria Raspollini,[22] Jalid Sehouli,[23] Alina Sturdza,[24] Alexandra Taylor,[25] Anneke Westermann,[26] Pauline Wimberger,[27] Nicoletta Colombo,[28] François Planchamp,[29] Carien L Creutzberg[30]

Concin N, *et al. Int J Gynecol Cancer 2020;0:12–39. doi:10.1136/ijgc-2020-002230*

Valutazione terapia adiuvante secondo i fattori di rischio molecolari

Classe di rischio	
Basso	I Stadio IA (G1 e G2) endometrioide (MMRd e NSMP) e LVSI assenti o focali
	Stadio I/II POLEmut
Intermedio	Stadio IA G3 endometrioide (MMRd e NSMP) e LVSI assente o focale
	Stadio IA non endometrioide (sieroso, a cellule chiare, carcinoma indifferenziato, carcinosarcoma, misto) e/o tumori p53 abn senza invasione miometriale e nessuna o focale LVSI
	Stadio IB (G1 e G2) endometrioide (MMRd e NSMP) e LVSI assente o focale
	Stadio II Grado 1 endometrioide (MMRd e NSMP) e LVSI assente o focale
Intermedio/Alto	Stadio I endometrioide (MMRd e NSMP) qualsiasi grado e qualsiasi profondità di infiltrazione con LVSI sostanziale
	Stadio IB G3 endometrioide (MMRd e NSMP) indipendentemente da LVSI
	Stadio II Grado 1 endometrioide (MMRd e NSMP) con LVSI sostanziale
	Stadio II Grado 2-3 endometrioide (MMRd e NSMP)
Alto	Tutte gli stadi e tutte le istologie con p53abn e invasione miometriale
	Tutti gli stadi di carcinoma sieroso o indifferenziato compreso il carcinosarcoma con invasione miometriale
	Tutti gli stadi III e IVA senza tumore residuo, indipendentemente dall'istologia e indipendentemente dal sottotipo molecolare

Joint statement

ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

Risk Group	Molecular Classification Unknown	Molecular Classification Known[Δ,*]
Low	• Stage IA endometrioid + low-grade** + LVSI negative or focal	• Stage I-II ***POLE*mut** endometrial carcinoma, no residual disease • Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade** + LVSI negative or focal

For low-risk endometrial carcinoma, no adjuvant treatment is recommended (I, A)

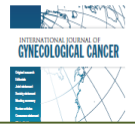
When molecular classification is known:

• EC stage I–II, *POLE-mutation,* omission of adjuvant treatment should be considered (III, A)

•EC stage III-IVA, POLE-mutation, there are no outcome data without a treatment. Prospective registries are recommended (IV, C)

Concin N, *et al. Int J Gynecol Cancer 2020*

Joint statement



ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

Risk Group	Molecular Classification Unknown	Molecular Classification Known[Δ],*
Intermediate	• Stage IB endometrioid + low-grade** + LVSI negative or focal • Stage IA endometrioid + high-grade** + LVSI negative or focal • Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	• Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade** + LVSI negative or focal • Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade** + LVSI negative or focal • Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion

Recommendations

• Adjuvant brachytherapy can be recommended to decrease vaginal recurrence (I, A).

• Omission of adjuvant brachytherapy can be considered (III, C), especially for patients aged <60 years (II, A).

•For p53abn carcinomas without myometrial invasion, adjuvant therapy is generally not recommended (III,C)

Concin N, *et al. Int J Gynecol Cancer 2020*

PORTEC-2 & Swedish; Nout et al, Lancet 2010; Wortman et al BJC 2018; Ortoft et al 2013; Sorbe et al, 2012

ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

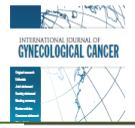
Risk group	Molecular classification unknown	Molecular classification known*†
High–intermediate	▶ Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ▶ Stage IB endometrioid high-grade‡ regardless of LVSI status ▶ Stage II	▶ Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion ▶ Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade‡ regardless of LVSI status ▶ Stage II **MMRd/NSMP** endometrioid carcinoma

High–intermediate risk (pN0 after lymph node staging)

- Adjuvant brachytherapy can be recommended to decrease vaginal recurrence (II, B)
- EBRT can be considered for substantial LVSI and for stage II (I, B)
- Adjuvant chemotherapy can be considered, especially for high-grade and/or substantial LVSI (II, C).
- Omission of any adjuvant treatment is an option (IV,C)

Concin N, *et al. Int J Gynecol Cancer 2020*

PORTEC-1 and -2 & GOG-249 & NSGO/EORTC; Nout et al, Lancet 2010; Randall et al, JCO 2019; Hogberg et al EJC 2010



ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

Risk group	Molecular classification unknown	Molecular classification known*†
High–intermediate	▶ Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ▶ Stage IB endometrioid high-grade‡ regardless of LVSI status ▶ Stage II	▶ Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion ▶ Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade‡ regardless of LVSI status ▶ Stage II **MMRd/NSMP** endometrioid carcinoma

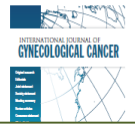
High–intermediate risk cN0/pNx **(lymph node staging not performed**)

- Adjuvant EBRT is recommended, especially for substantial LVSI and/or for stage II (I, A).
- Additional adjuvant chemotherapy can be considered, especially for high-grade and/or substantial LVSI (II, B).
- Adjuvant brachytherapy alone can be considered for high-grade LVSI negative and for stage II grade 1 endometrioid carcinomas (II, B)

Concin N, *et al. Int J Gynecol Cancer 2020*

PORTEC-1 and -2 & GOG-249 & NSGO/EORTC; Bosse et al, 2015; Wortman et al, BJC 2018; Randall et al, JCO 2019; Hogberg et al EJC 2010

Joint statement



ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

Risk group	Molecular classification unknown	Molecular classification known*†
High	▶ Stage III–IVA with no residual disease ▶ Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	▶ Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ▶ Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease ▶ Stage I–IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease

EBRT with concurrent and adjuvant chemotherapy (I, A) or alternatively sequential chemotherapy and radiotherapy is recommended (I, B).

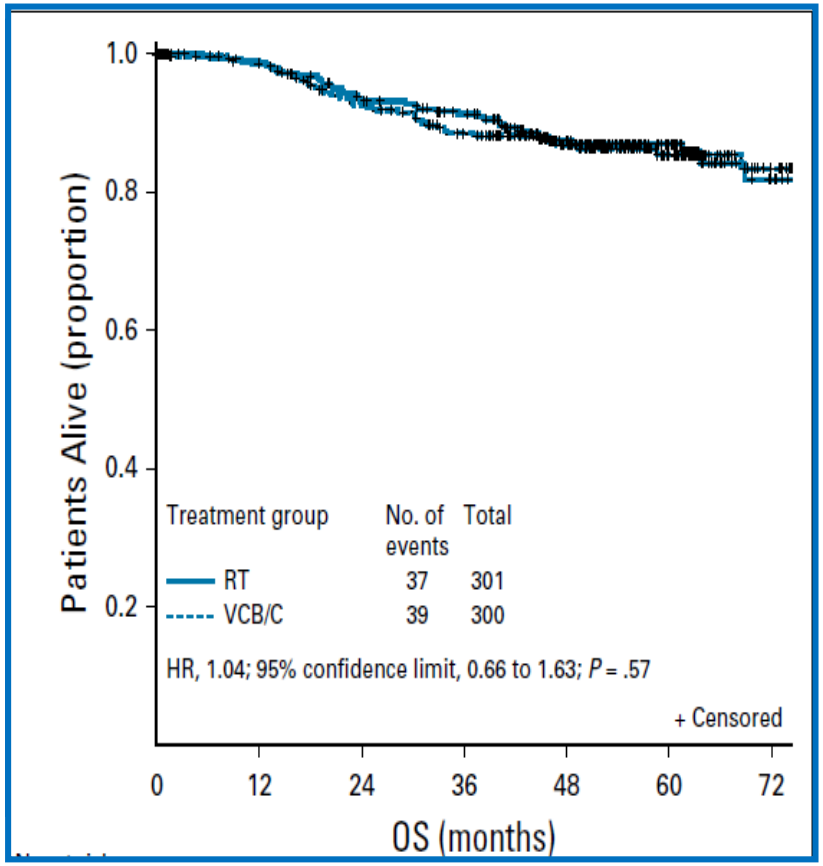
Chemotherapy alone is an alternative option (I, B).

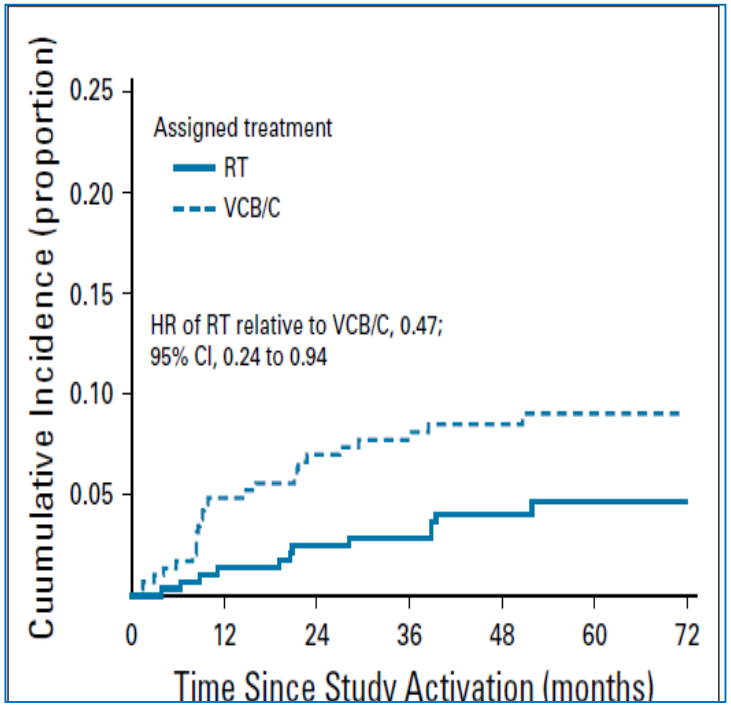
Carcinosarcomas should be treated as high-risk carcinomas (IV,B)

Concin N, *et al. Int J Gynecol Cancer 2020*

PORTEC-3 & GOG-258 & NSGO/EORTC; de Boer et al, Lancet Oncol 2019; Matei et al, NEJM 2019; Randall et al, JCO 2019; Travaglino et al, Gynecol Oncol 2021

Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/ Carboplatin in High-Intermediate and High-Risk Early-Stage Endometrial Cancer





Pelvic nodal recurrences

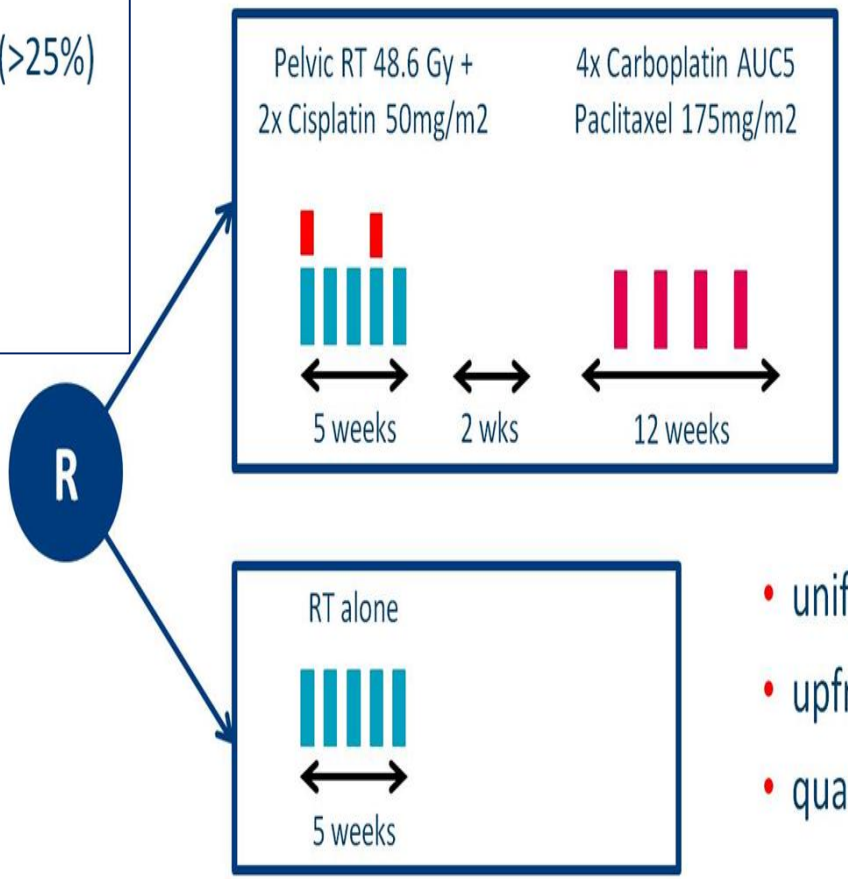
- Acute toxicity greater with VCB/C; late toxicity similar

Pelvic RT remains an appropriate treatment for High Intermediate risk endometrial carcinoma.

Randall, JCO 2019

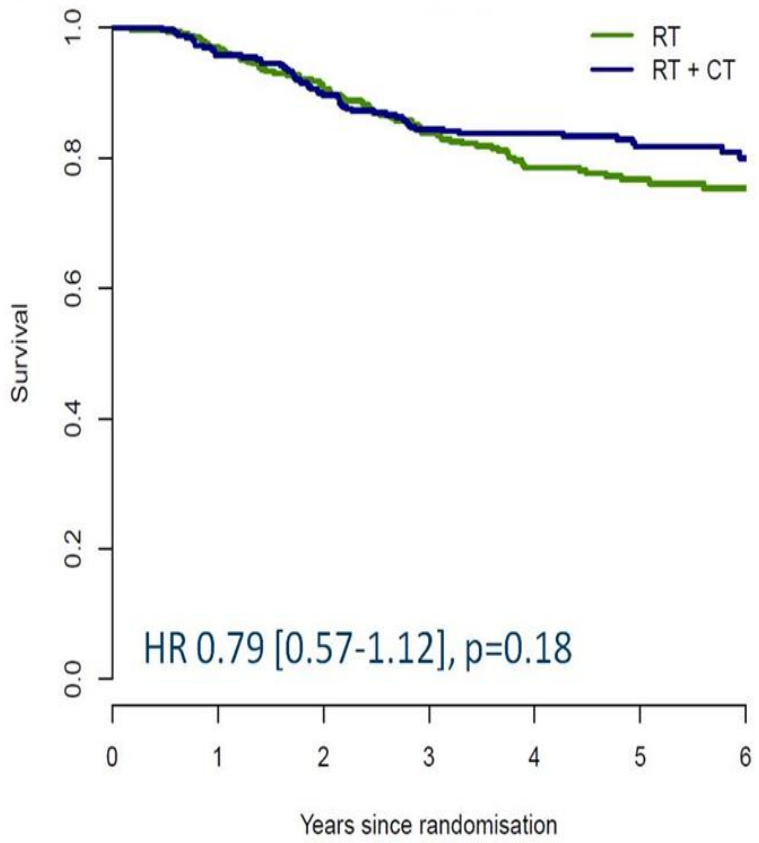
RANDOM RT vs RCT – PORTEC-3

- Endometrial carcinoma
  - stage I grade 3, with deep invasion or LVSI+
  - stage II - III
  - stage I-III serous or clear cell cancers (>25%)
- WHO PS 0-2
- No residual macroscopic tumor after surgery
- Pathology review before randomisation

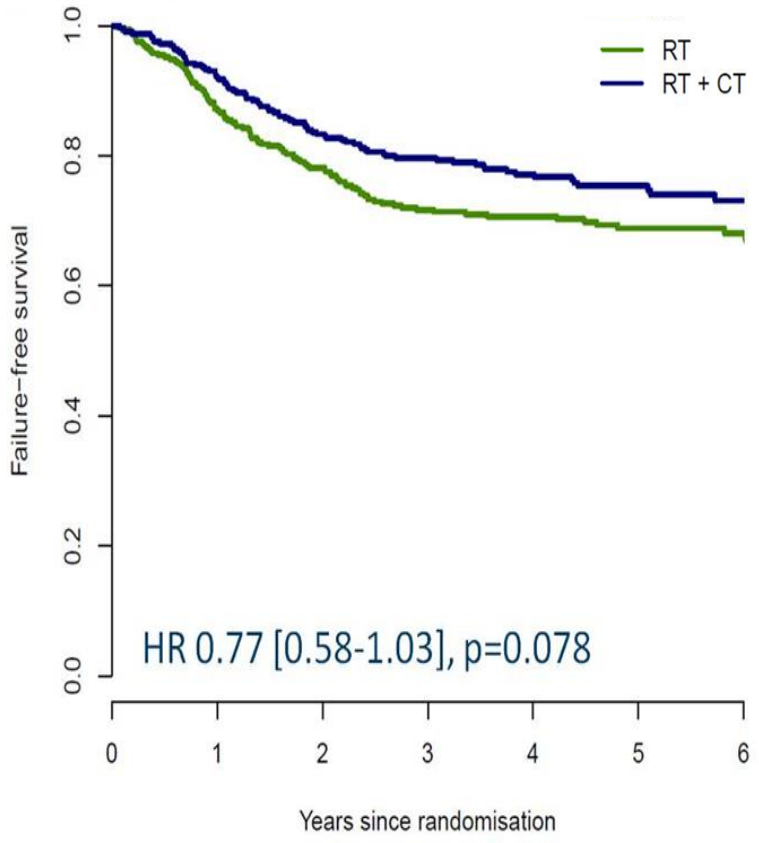


- uniform treatment schedule
- upfront pathology review
- quality of life analysis

Survival (OS and FFS)



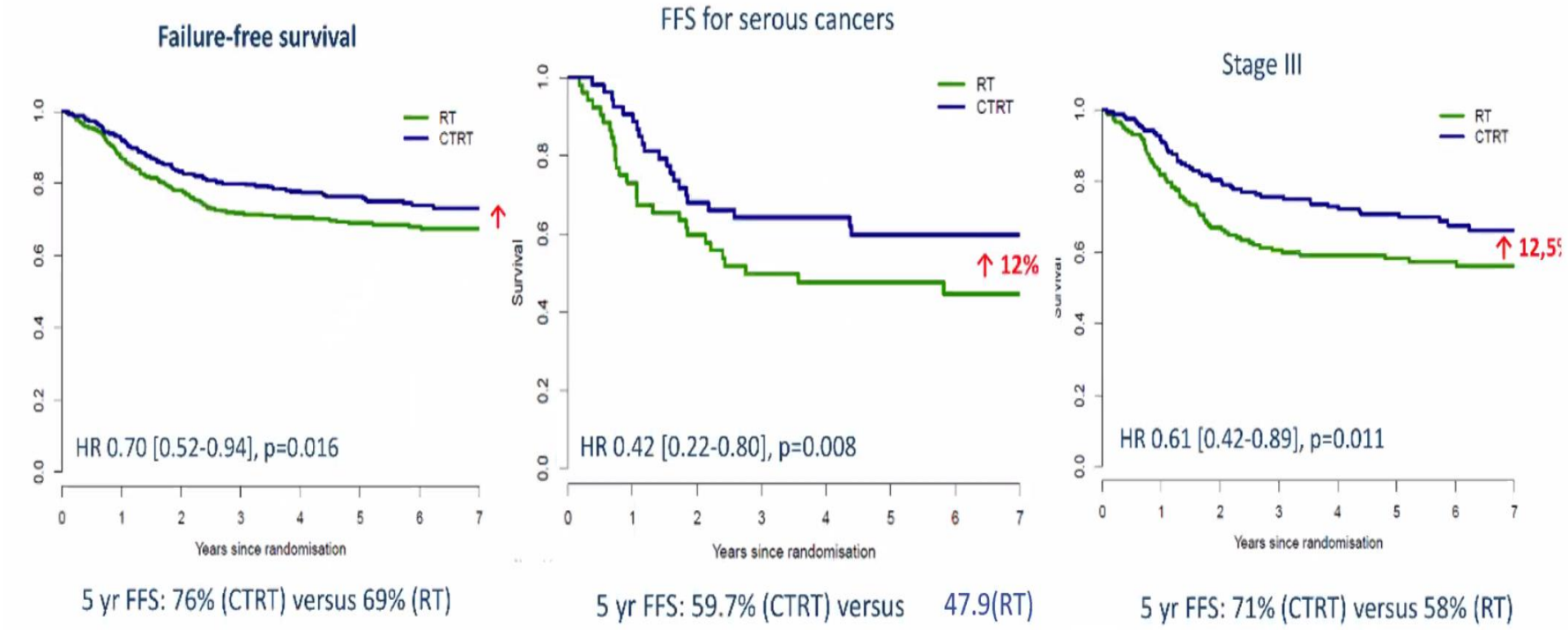
5 yr OS: 82% (CTRT) versus 77% (RT)



5 yr FFS: 76% (CTRT) versus 69% (RT)

This treatment schedule not to be recommended for Stage I-II EC

PORTEC-3 trial results: FFS

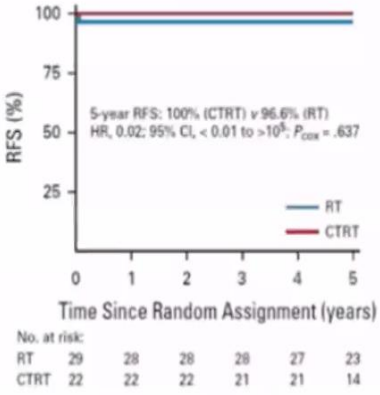


Improved 5-year overall and failure-free survival with chemoradiotherapy compared with radiotherapy alone for women with stage III disease

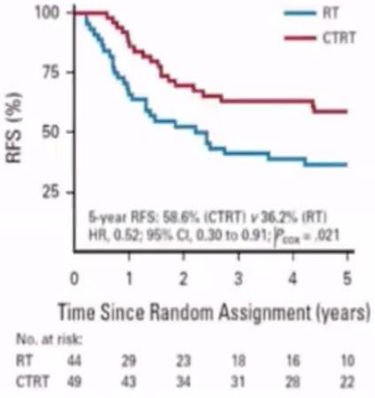
PORTEC-3 translational results

Predictive potential of molecular classification for adj platinum-based treatment

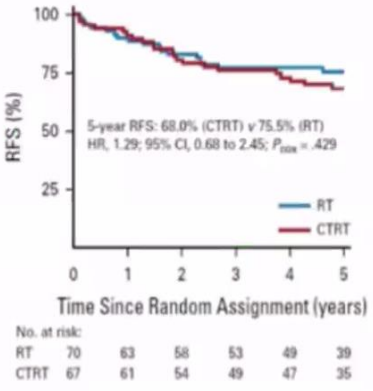
POLEmut



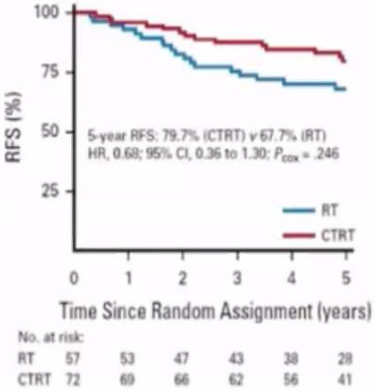
p53abn



MMRd



NSMP



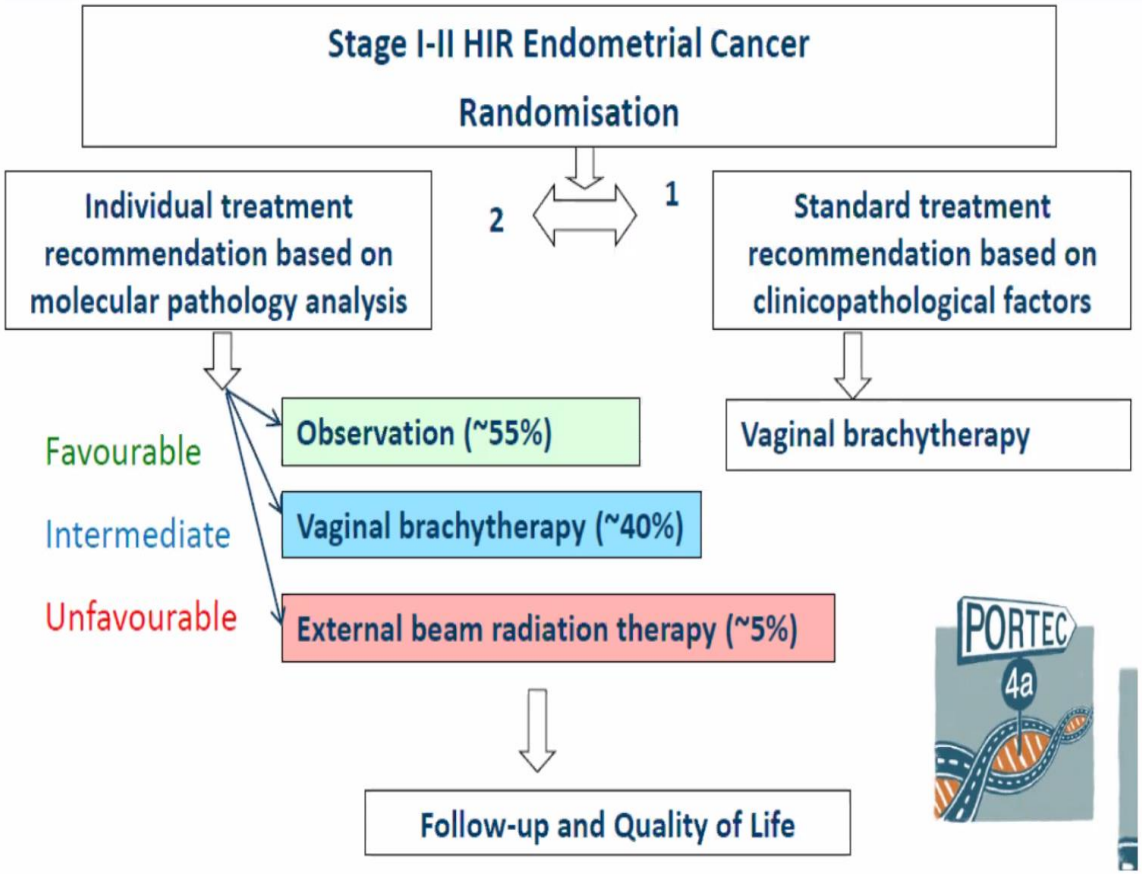
ESGO-ESTRO-ESP EC Guidelines

Specific treatment recommendations for POLEmut stage I/II and p53 mut EC based on current level of evidence

Leon-Castillo et al, JCO 2020

PORTEC-4a trial

Molecular integrated vs standard indication for adjuvant treatment



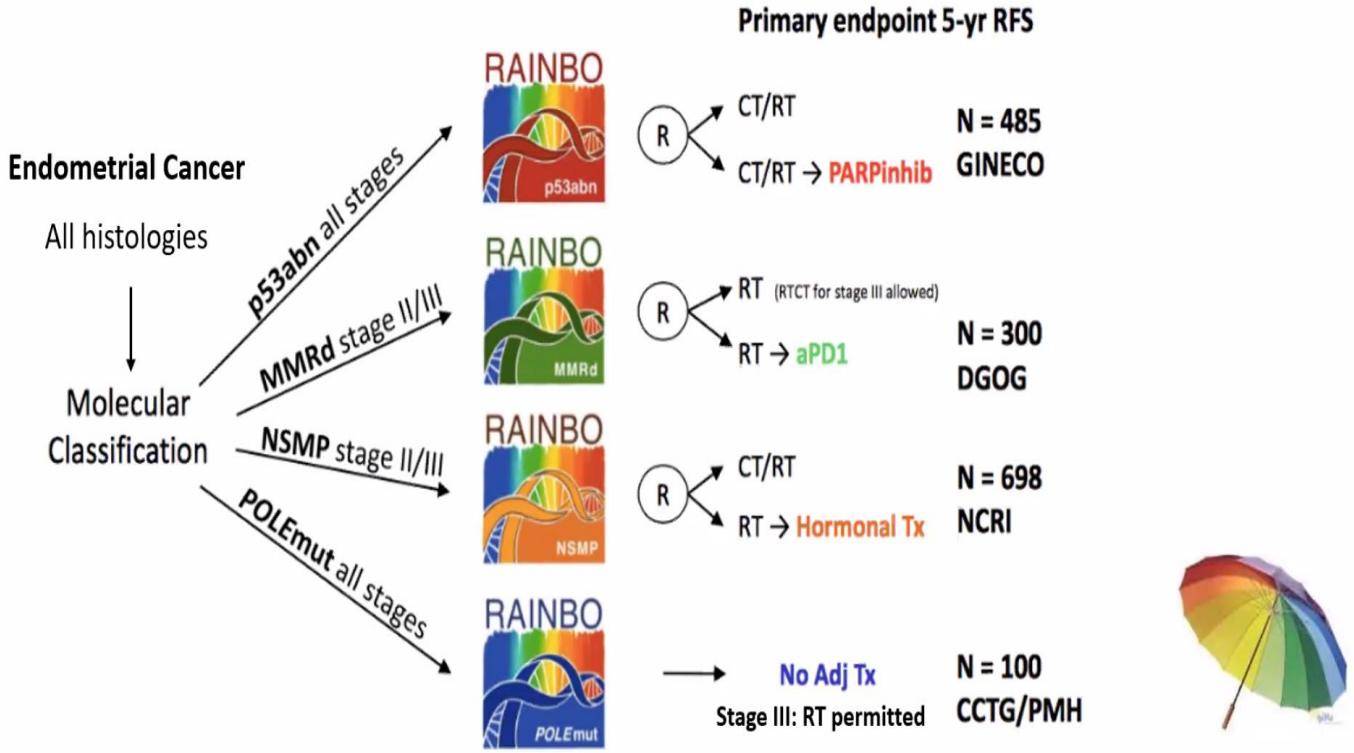
RAINBO

TransPORTEC

TransPORTEC-RAINBO program
International program of trials based on molecular group

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Refining **A**djuvant treatment **IN** endometrial cancer **B**ased **O**n molecular profile



Conclusions

Molecular subgroups classification is certainly prognostic and probably predictive

TGCA molecular characterization is changing the treatment approach

Immunotherapy is becoming an important tool in treatment strategy for EC

Grazie!

annamaria.cerrotta@istitutotumori.mi.it