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Il trattamento della paziente oligometastatica

Rapporteur

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Il trattamento della paziente oligometastatica:

analisi della letteratura articoli pubblicati nel 2016

Reviews

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OXFORD

Clinical applications of stereotactic radiation therapy for oligometastatic cancer patients: a disease-oriented approach

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ABSTRACT

Oligometastases from solid tumors are currently recognized as a distinct clinical entity, corresponding to an intermediate state between local and widespread disease. It has been suggested that local ablative therapies (including surgery, radiofrequency ablation and radiation therapy) play an important role in this setting, in combination or not with systemic therapies, particularly in delaying disease progression and hopefully in increasing the median survival time. Stereotactic body radiation therapy (SBRT) rapidly emerged in recent years as one of the most effective and less toxic local treatment modalities for lung, liver, adrenal, brain and bone metastases. The aim of this review was to focus on its clinical role for oligometastatic disease in four major cancer subtypes: lung, breast, colorectal and prostate. On the basis of the available evidence, SBRT is able to provide high rates of local tumor control without significant toxicity. Its global impact on survival is uncertain; however, in specific subpopulations of oligometastatic patients there is a trend towards a significant improvement in progression-free and overall survival rates; these important data might be used as a platform for clinical decision-making and establish the basis for the current and future prospective trials investigating its role with or without systemic treatments.

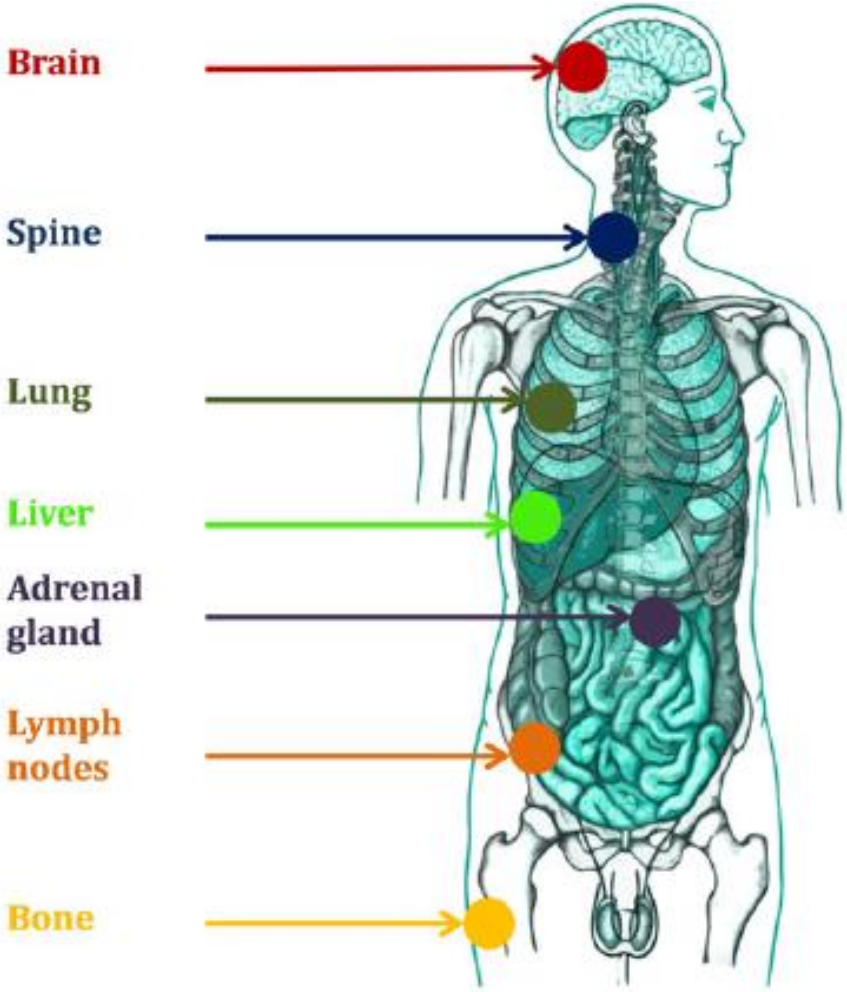

Fig. 1. Metastatic sites treatable with stereotactic radiotherapy.

SBRT FOR OLIGOMETASTATIC NON–SMALL CELL LUNG CANCER

SBRT FOR OLIGOMETASTATIC BREAST CANCER

SBRT FOR OLIGOMETASTATIC COLORECTAL CANCER

SBRT FOR OLIGOMETASTATIC PROSTATE CANCER

FUTURE PERSPECTIVES

SBRT FOR OLIGOMETASTATIC BREAST CANCER

Breast cancer is probably the first model used to illustrate the natural history of solid tumors, and the mechanisms underlying the metastatic spread [2]. Therefore, it is also one of the cancer subtypes where the hypothesis of oligometastases was first formulated, and it served as a model to illustrate the rationale for the use of local therapies to a few metastatic sites, in combination with systemic agents [7].

Very few studies have been published on the use of SBRT for oligometastatic breast cancer patients. The University of Rochester researchers published seminal and most relevant data regarding the use of SBRT in oligometastatic breast cancer [34–36]

As for other oligometastatic tumors, the identification of favorable/unfavorable prognostic groups remains challenging. From surgical series, known favorable prognostic factors are estrogen-receptor positivity, response to systemic therapies, fewer and smaller metastases and longer disease-free interval [38]. Patients receiving ablative radiotherapy for bone-only metastases, single metastases and stable or responding metastases have shown improved outcomes [35].

2. Hellman S. Natural history of small breast cancers. *J Clin Oncol* 1994;12:2229–34.

7. Salama JK, Chmura AJ. The role of surgery and ablative radiotherapy in oligometastatic breast cancer. *Semin Oncol* 2014;41:790–7.

34. Milano MT, Katz AW, Muhs AG, et al. A prospective pilot study of curative-intent stereotactic body radiation therapy in patients with 5 or fewer oligometastatic lesions. *Cancer* 2007;112:650–8.
35. Milano MT, Zhang H, Metcalfe SK, et al. Oligometastatic breast cancer treated with curative intent stereotactic body radiation therapy. *Breast Cancer Res Treat* 2009;115:601–8.
36. Milano MT, Katz AW, Zhang H, et al. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. *Int J Radiat Oncol Biol Phys* 2011;83:878–86.

38. Abbott DE, Brouquet A, Mittendorf EA, et al. Resection of liver metastases from breast cancer: estrogen receptor status and response to chemotherapy before metastasectomy define outcome. *Surgery* 2012;151:710–16.

35. Milano MT, Zhang H, Metcalfe SK, et al. Oligometastatic breast cancer treated with curative intent stereotactic body radiation therapy. *Breast Cancer Res Treat* 2009;115:601–8.

SBRT FOR OLIGOMETASTATIC BREAST CANCER

Table 2. Studies investigating the use of SBRT in oligometastatic breast and colorectal cancer

Study	Patients	Eligibility criteria	Study design	Site of metastases	Therapy	Median follow-up (months)	Median PFS (months)	Median OS (months)	Other therapy (percentage)
Breast cancer									
Milano *et al.* [35]	40	<5 extracranial metastases	subgroup analysis of a prospective Phase II trial	liver, lung, lymph nodes, bone	SBRT	NR	23	not reached	adjuvant chemotherapy/ hormonal therapy (80%)
Colorectal cancer									

4 year OS rate: 59%, 4year PFS rate: 38%, local control almost 90%

[a]Local control rates were compared with metastases from other origins and primary lung cancer, with statistically significant inferiority ($P < 0.05$). SRS = stereotactic radiosurgery, SBRT = stereotactic body radiation therapy, PFS = progression-free survival, OS = overall survival, LC = local control, NA = not applicable, NR = not reported.

SBRT FOR OLIGOMETASTATIC BREAST CANCER

STUDI CLINICI IN CORSO:

NRG BR001-NCT02206334 (fase I) studio di dose-escalation (mammella, polmone, prostata (2-5 metastasi)

SABR- COMET- NCT01446744 (fase II) : SBRT + terapia sistemica vs terapia sistemica +/- RT

NRGBR002 -NCT02364557: (fase II/III) cr mammella con malattia oligometastatica "standard of care" vs "standard of care" + SBRT o chirurgia

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REVIEW

Stereotactic body radiotherapy for oligometastatic breast cancer: a new standard of care, or a medical reversal in waiting?

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ABSTRACT

Metastases-directed therapy via surgery or stereotactic body radiotherapy (SBRT) has become the de facto standard of care in the United States and abroad despite a lack of high quality prospective, randomized trials. Oligometastatic tumors may behave in an inherently more indolent manner secondary to underlying biologic characteristics, including discrepant microRNA expression patterns. This biologic discrepancy suggests that historic improvements in survival observed in retrospective series may stem from the inherent biology of oligometastases and selection biases as opposed to advances in novel localized treatments. In this review, we discuss the theoretical basis for metastases-directed therapies, retrospective data supporting these approaches, recent advances in oligometastasis biology, and ongoing prospective randomized trials designed to compare SBRT and standard of care systemic therapies. We focus on metastases-directed therapy, primarily SBRT, for oligometastatic breast cancer with references to other tumor types when these other tumor types inform oligometastatic breast cancer treatment.

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KEYWORDS
Oligometastases; stereotactic body radiotherapy; metastectomy; medical reversal; breast cancer

A 'medical reversal', as described by Prasad et al., is an accepted medical practice, often widely adopted, that is later found to be no better or worse than a previous standard of care [36,37]

12. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol. 1995;13(1):8–10.

•• **This seminal paper by Hellman and Weichselbaum introduced the concept of "oligometastases" in 1995.**

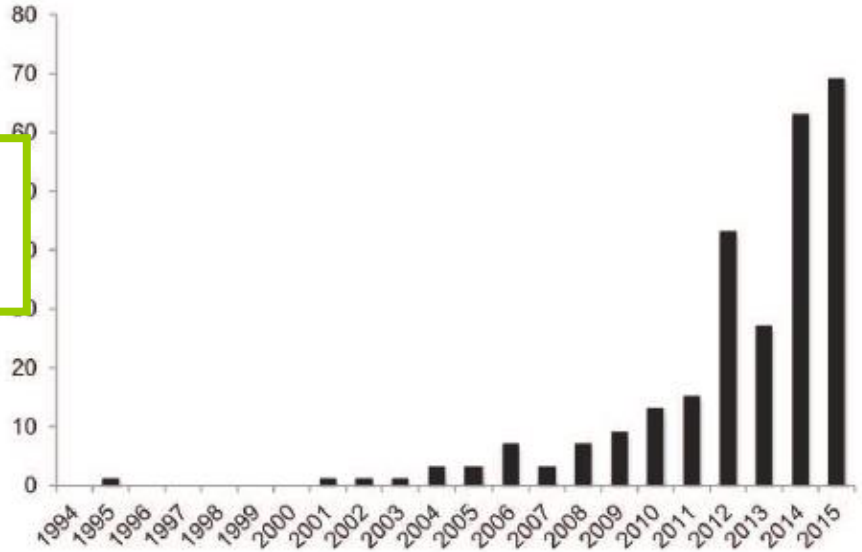

Figure 1. Number of publications, by year, with "oligometastasis", "oligometastases", or "oligometastatic" in title.

Table 1. Proportions of patients that presented with oligometastases in randomized trials for first-line stage IV breast cancer.

Study/Author	Year	*n*	ER/PR (+) (%)	HER2 (+) (%)	≤2 metastases (%)	≤4 metastases (%)	Arms	PFS (months)
Sledge/E1193	2003	739	45	NA	49	NA	1. Doxorubicin 2. Paclitaxel 3. Doxorubicin + Paclitaxel	1. 6.0 (time to failure) 2. 6.3 3. 8.2
Albain	2008	599	32	NA	57	91	1. Gemcitabine + Paclitaxel 2. Paclitaxel	1. 9.9 2. 8.4
Bergh	2012	593	72	100	52	NA	1. Sunitinib + Docetaxel 2. Docetaxel	1. 8.6 2. 8.3
Gianni/AVEREL	2013	424	51	100	50	NA	1. Docetaxel + Trastuzumab 2. Docetaxel + Trastuzumab + Bevacizumab	1. 13.7 2. 16.5
Hurvitz	2013	137	54	100	49.3	NA	1. Docetaxel + Trastuzumab 2. T-DM1	1. 9.2 2. 14.2
Tawfik	2013	30	77	0	50	NA	1. Vinorelbine + capecitabine	8.6 (time to failure)

ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; PFS: progression-free survival; T-DM1: trastuzumab emtansine.

Five-year view

STUDI CLINICI IN CORSO:

SABR- COMET- NCT01446744: SBRT + terapia sistemica vs terapia sistemica +/- RT

NRGBR002 -NCT02364557: (fase II/III) cr mammella con malattia oligometastatica "standard of care" vs "standard of care" + SBRT o chirurgia

CORE trial (fase II) cr mammella, prostata, NSCLC fino a 3 metastasi extracraniche "standard of care" vs "standard of care" + SBRT

Key issues

- A substantial proportion of breast cancer patients recur in an oligometastatic manner, i.e., with a limited number (<5) of metastases in one or two organs.
- Retrospective series demonstrate benefits in progression-free and overall survival for patients with oligometastases who are treated with metastases-directed therapies (surgical metastasectomy or SBRT).
- The majority of radiation oncologists worldwide are utilizing SBRT for the treatment of oligometastases.
- Surgical metastasectomy has been employed for many decades.
- The utilization of metastases-directed therapy has dramatically increased despite a lack of high quality prospective evidence supporting these practices.
- Advances in cancer biology have demonstrated that discrepant microRNA expression patterns may account for the more indolent behavior of some oligometastases.
- Retrospective, uncontrolled case series demonstrating survival benefits of metastases-directed therapy may suffer from selection biases.
- SBRT and surgical metastasectomy carry unique, but substantial, risks for patient morbidity and mortality.
- The rise of metastases-directed therapies despite a lack of high quality prospective evidence increases the risk for future medical reversal.
- Prospective, randomized clinical trials comparing SBRT plus standard of care systemic therapies against standard of care systemic therapies alone are open and accruing patients.

3-4 pz con cr mammella!

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Review

Management of breast cancer brain metastases: A practical review

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ABSTRACT

Brain metastases are a common, and frequently challenging, clinical problem in the contemporary management of metastatic breast cancer. While the management of extracranial metastatic breast cancer is now strongly defined by tumour phenotype, this approach is not so well defined for brain metastases. We review available evidence regarding management of brain metastases, including the limited breast-cancer-specific data. A framework for management according to breast cancer phenotype is proposed.

Prognostic factors

Table 1a
Prognosis scores indicated by the Radiation Therapy Oncology Group (RTOG) Breast Cancer Graded Prognostic Analysis and the MD Anderson Cancer Centre (MDACC) modification*.

	Score				
	0	0.5	1.0	1.5	2.0
RTOG Breast Graded Prognostic Assessment					
KPS	≤50	60	70–80	90–100	–
Phenotype	TNBC	–	HR + BC	HER2HN	HER2HP
Age (years)	≥60	<60	–	–	–
MDACC revalidation of RTOG Graded Prognostic Analysis					
KPS	≤50	60	70–80	90–100	
Phenotype	TNBC	HR + BC	HER2HN	HER2HP	–
Age (years)	>50	≤50	–	–	–
Number	>3	1–3	–	–	–

RTOG = Radiation Therapy Oncology Group; KPS = Karnofsky performance status; MDACC = MD Anderson Cancer Centre, HER2HN = HER2-positive, hormone-negative; HER2HP = HER2-positive, hormone-positive.
* Adapted from Refs. [4,5].

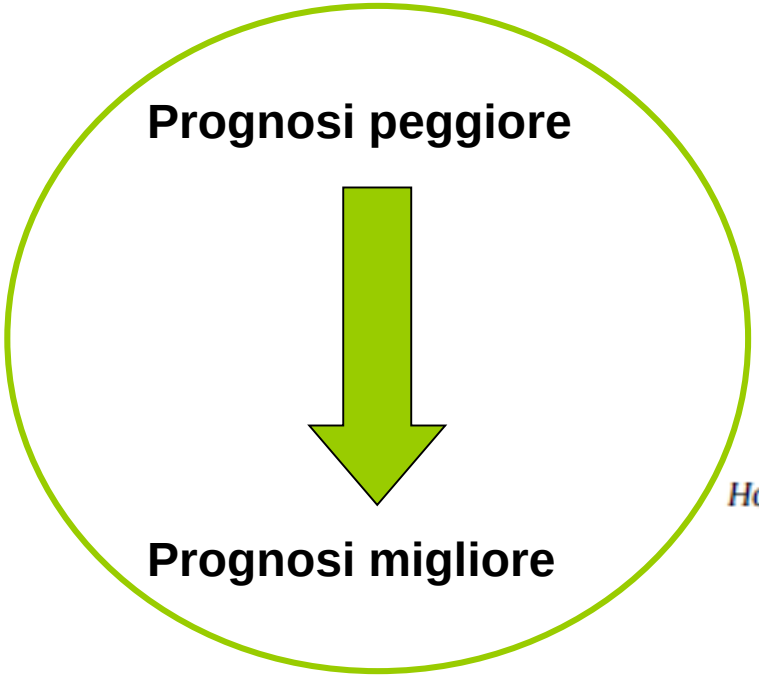
Prognosi peggiore:
lesioni di dimensioni elevate e lesioni localizzate nel tronco dell'encefalo

Table 1b
Radiation Therapy Oncology Group (RTOG) Breast Cancer Graded Prognostic Analysis and MD Anderson Cancer Centre (MDACC) modification scores and overall survival.

RTOG score	Overall survival (months)	MDACC score	Overall survival (months)
0–1.0	3.4	0–1.0	2.6
1.5–2.0	7.7	1.5–2.0	9.2
2.5–3.0	15.1	2.5–3.0	29.9
3.5–4.0	25.3	3.5–4.0	28.8

* Adapted from Refs. [4,5].

Typical disease pattern by phenotype



Triple-negative breast cancer (TNBC)

HER2-positive disease (HER2BC)

Hormone-positive, HER2-negative disease (HR + BC)

Risk of micrometastatic BM

The risk of occult BM relative to lesion number and by phenotype is unknown. A retrospective review of cases treated with radiosurgery without WBRT in one institution found that the 12-month rate of failure in the brain (distant from sites of radiosurgery) was highest in TNBC (79%), intermediate for HR + BC (~47%) and least for HER2BC (36%). The rate of failure by lesion number, extracranial disease status and use of systemic therapies was not reported [17].

[17] Vern-Gross TZ, Lawrence JA, Case LD, McMullen KP, Bourland JD, Metheny-Barlow LJ, et al. Breast cancer subtype affects patterns of failure of brain metastases after treatment with stereotactic radiosurgery. J Neurooncol 2012;110(3):391–8. 1007/s11060-012-0976-3.

Available therapies for brain metastases

Whole-brain radiotherapy (WBRT) | *Stereotactic radiosurgery (SRS)* | *Neurosurgery* | *Systemic therapy*

Table 2
Summary of results of phase III studies for brain metastases.

Whole Brain radiotherapy	
Palliates multiple brain metastases	20 Gy in 10 fractions and 30Gy in 10 fractions are standard of care [19,40]. No survival or palliative benefit from different dose/fractionation schedules [19].
Improves median survival compared with best supportive care	May not do so in poor PS status patients [19,41].
Reduces local and distant brain failure (DBF) after NS or SRS	Approximately halves DBF rate [22,42,43] - Duration of benefit 6–12 months.
Does not improve overall survival compared with NS or SRS alone	For up to 4 BM [22,42,43]
Does not improve and may worsen quality of life after NS of SRS	For up to 3 BM [18,44]
Radiosurgery	
Improves overall survival when added to WBRT	1 lesion [45]
Does not improve overall survival when added to WBRT.	2–4 lesions [45]
May improve survival in good PS patients (post hoc analysis that excluded breast cancer) [46]	
Neurosurgery	
Improves median survival when added to WBRT	1 lesion [47]

SRS Stereotactic radiosurgery; PS Performance Status; NS Neurosurgery; DBF Distant brain failure; BM Brain Metastases; WBRT Whole Brain Radiotherapy.

Recommendations for management

Imaging | *Medical management of BM symptoms* | *Multidisciplinary meeting*

Making treatment decisions

Published guidelines

[36] Tsao MN, Rades D, Wirth A, Simon S, Danielson B, Gaspar L, et al. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol 2012;2:210–25. http://dx.doi.org/10.1016/j.prro.2011.12.004.

[37] Soccianti S, Ricardi U. Treatment of brain metastases: review of phase III randomized controlled trials. Radiother Oncol 2012;102:168–79. http://dx.doi.org/10.1016/j.radonc.2011.08.041.

Management framework

Table 4
Framework steps for treatment of breast cancer brain metastases.

Characteristic	Questions
Step 1: Consider the patient	
Performance status	Life expectancy?
Symptoms	Will surgery palliate best?
	Asymptomatic. Is treatment for brain metastases needed at this time?
Fitness for surgery	Co-morbidities?
	Anticoagulation? Antiplatelet therapy?
Step 2: Consider the disease	
Phenotype	Likely natural history?
	Estimated median survival?
Extracranial disease	Present? Absent? Progression?
Systemic therapy	Number of lines of therapy?
	Any more therapies available?
	Likelihood of response in extracranial disease? In brain?
Number	1, ≤3–4 or >4?
Size	Should surgery be considered?
	Is stereotactic radiosurgery feasible?
Location	Is neurosurgery feasible?
Extent of oedema	Extensive and of concern? Moderate? Minimal?
De novo or progressive disease	Prior therapy?

Il trattamento della paziente oligometastatica:

analisi della letteratura articoli pubblicati nel 2016

Original articles

Original Article

Clinical and Molecular Markers of Long-Term Survival After Oligometastasis-Directed Stereotactic Body Radiotherapy (SBRT)

Anthony C. Wong, MD, PhD[1]; Sydeaka P. Watson, PhD[2]; Sean P. Pitroda, MD[1]; Christina H. Son, MD[1]; Lauren C. Das, MD[1]; Melinda E. Stack, MD[3]; Abhineet Uppal, MD[3]; Go Oshima, MD[3]; Nikolai N. Khodarev, PhD[1,4]; Joseph K. Salama, MD[5]; Ralph R. Weichselbaum, MD[1,4]; and Steven J. Chmura, MD, PhD[1]

BACKGROUND: The selection of patients for oligometastasis-directed ablative therapy remains a challenge. The authors report on clinical and molecular predictors of survival from a stereotactic body radiotherapy (SBRT) dose-escalation trial for oligometastases. **METHODS:** Patients who had from 1 to 5 metastases, a life expectancy of >3 months, and a Karnofsky performance status of >60 received escalating SBRT doses to all known cancer sites. Time to progression, progression-free survival, and overall survival (OS) were calculated at the completion of SBRT, and clinical predictors of OS were modeled. Primary tumor microRNA expression was analyzed to identify molecular predictors of OS. **RESULTS:** Sixty-one evaluable patients were enrolled from 2004 to 2009. The median follow-up was 2.3 years for all patients (range, 0.2-9.3 years) and 6.8 years for survivors (range, 2.0-9.3 years). The median, 2-year, and 5-year estimated OS were 2.4 years, 57%, and 32%, respectively. The rate of progression after SBRT was associated with an increased risk of death (hazard ratio [HR], 1.44; 95% confidence interval [CI], 1.24-1.82). The time from initial cancer diagnosis to metastasis (HR, 0.98; 95% CI, 0.98-0.99), the time from metastasis to SBRT (HR, 0.98; 95% CI, 0.98-0.99), and breast cancer histology (HR, 0.12; 95% CI, 0.07-0.37) were significant predictors of OS. In an exploratory analysis, a candidate classifier using expression levels of 3 microRNAs (miR-23b, miR-449a, and miR-449b) predicted survival among 17 patients who had primary tumor microRNA expression data available. **CONCLUSIONS:** A subset of oligometastatic patients achieves long-term survival after metastasis-directed SBRT. Clinical features and primary tumor microRNA expression profiling, if validated in an independent dataset, may help select oligometastatic patients most likely to benefit from metastasis-directed therapy. ***Cancer* 2016;122:2242-50**. © *2016 American Cancer Society.*

KEYWORDS: oligometastases, stereotactic body radiotherapy, microRNA, biomarker, classifier.

Cancer July 15, 2016

TABLE 1. Patient and Tumor Characteristics

Characteristic	No. of Patients [Months]	% [Range]
Primary sites (histology)		
Breast	7	11.5
Colon/rectum	6	9.8
Head and neck squamous cell	5	8.2
Nonsmall cell lung	11	18
Renal	8	13.1
Sarcoma	5	8.2
Small cell lung	5	8.2
Other (gallbladder, ovary, skin, thymus, thyroid, parotid, PNET)	14	23
Induced oligometastases		
Yes	8	13.1
No	53	86.9
Oligometastases per patient: No. treated on protocol		
1	33	54.1
2	12	19.7
≥3	16	26.2
Distant metastasis-free interval, mo		
0 (metastatic at initial diagnosis)	7	11.5
0-3	12	19.7
3-6	5	8.2
6-12	8	13.1
12-24	5	8.2
24-48	11	18
>48	13	21.3
Median	[11.6]	[0-302]
Time from metastasis to SBRT, mo		
0-3	15	24.6
3-6	4	6.6
6-12	17	27.9
12-24	12	19.7
24-48	9	14.8
>48	4	6.6
Median	[9.9]	[1-86]
Time to progression after SBRT, mo		
0-3	20	32.8
3-6	13	21.3
6-12	8	13.1
12-24	7	11.5
24-48	5	8.2
>48	1	1.6
Never progressed	7	11.5
Median among progressors	[4.3]	[1-64]

Abbreviations: PNET, primitive neuroectodermal tumor; SBRT, stereotactic body radiotherapy.

MATERIALI E METODI

Novembre 2004-Novembre 2009:

61 pz 113 metastasi

Cr mammella pz:7/61

1-5 metastasi,
aspettativa di vita >3 mesi,
KPS>60
metastasi ≤ 10 cm o ≤ 500mL
no RT in precedenza
no CT concomitante, solo OT

Micro RNA in 17 campioni del tumore primitivo di pazienti arruolati ma solo 1 pz con cr mammella!!!

Treatment and Endpoints

Details of radiation treatment planning and delivery have been previously described.[15] A 3 × 3 dose-escalation schema was used with cohorts for each anatomic site escalated in 6 gray (Gy) increments (2 Gy per fraction). The starting dose for all sites was 24 Gy, and the ceiling for all cohorts was 60 Gy in 3 fractions; however, the trial closed with the 48 Gy cohort, before reaching the maximum tolerated dose. In general, the radiation dose was prescribed to the planning target volume edge, typically to the 80% to 90% isodose line, with 95% of the planning target volume required to receive 95% of the planned dose.

The primary endpoint was determination of the maximum tolerated dose and dose-limiting toxicity (defined as grade 4-5 hematologic toxicity or grade 3-5 nonhematologic toxicity, excluding nausea, vomiting, and alopecia) of SBRT for each of 5 anatomically defined cohorts: head and neck, lung, liver, abdomen, and extremities. The secondary endpoints were response rate, OS, progression-free survival (PFS), and patterns of failure.

Follow-Up

Patients returned every 2 weeks for 1 month, monthly for 3 months, and quarterly thereafter. Acute toxicities were scored according to the Common Terminology Criteria for Adverse Events (version 3.0.16).[16] Late toxicities were scored according to the Radiation Therapy Oncology Group late toxicity scoring system.[17] Each metastasis was a target lesion that was independently assessed for response. Patterns of progression were determined by assessing all treated metastases and untreated tumors (primary tumors and metastases) on all follow-up studies.

RISULTATI

median follow-up:
2,3 y (0,2-9,3 y) for all patients
6,8 y (2,0-9,3y) for survivors

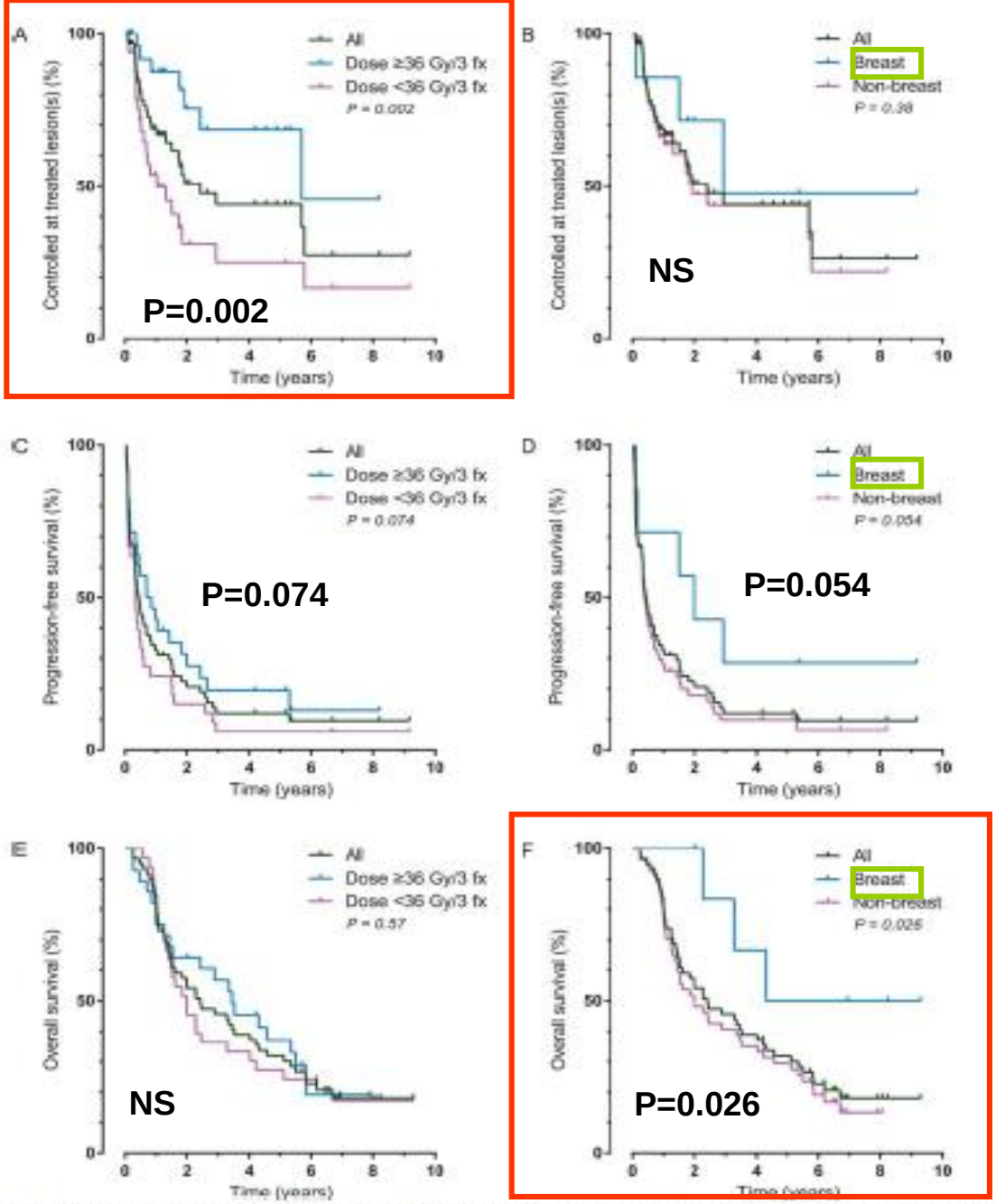
Toxicity

Acute toxicity for this cohort was previously reported.[15] Only 2 patients experienced grade 3 acute toxicity: 1 patient in the 30 Gy liver cohort experienced grade 3 vomiting, and 1 patient in the 42 Gy lung cohort experienced grade 3 fatigue. There were no grade 4 acute toxicities. Six episodes of grade 3 late toxicity were described in the previous update of this cohort. Since then, there were no additional episodes of grade ≥3 toxicity.

Patterns of Progression and TMC

Seven patients (11.5%) never progressed after protocol therapy. In another 7 patients (11.5%), first progression occurred only in treated metastases; 4 of those patients received relatively low SBRT doses of 24 or 30 Gy as part of the dose-escalation protocol. Thirty-eight patients (62.3%) had initial progression only outside of protocol-treated metastases. Nine patients (14.8%) progressed initially at both treated and untreated sites.

"The median, 2-year and 5-year estimated OS were 2.4 years, 57% and 32% respectively"



Controlled at treated lesions

PFS

OS

Figure 1. Treated metastasis control (A) is improved with radiation doses ≥36 gray (Gy) in 3 fractions (fx), but (B) does not differ based on breast cancer histology. Trends (C) for improved progression-free survival with radiation doses ≥36 Gy in 3 fx and (D) for breast cancer histology are illustrated. Improved overall survival (E) is not observed with increasing radiation dose but (F) is observed in patients with breast cancer.

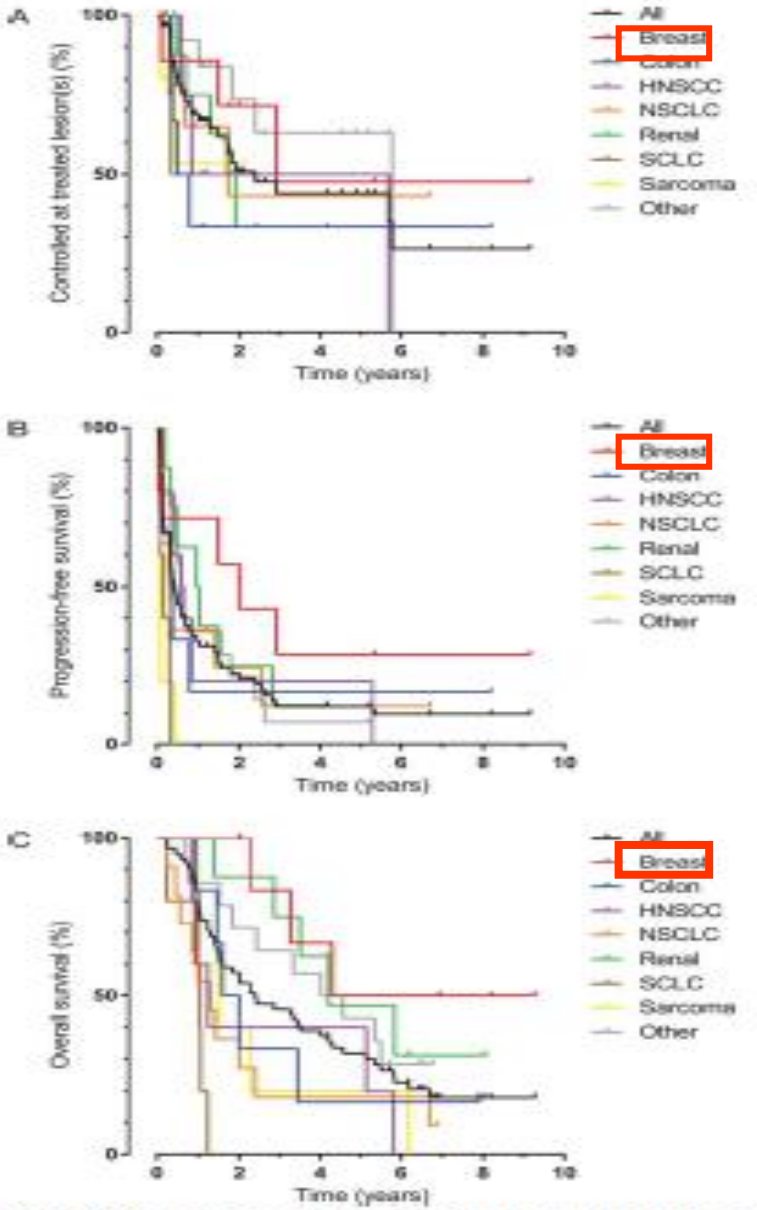


Figure 2. Kaplan-Meier estimates of (A) treated metastasis control, (B) progression-free survival, and (C) overall survival are illustrated for histologic subgroups that included at least 5 patients. HNSCC indicates head and neck squamous cell carcinoma; NSCLC, nonsmall cell lung cancer; SCLC, small cell lung cancer.

Controlled at treated lesions

PFS

OS

TABLE 2. Characteristics Associated With Survival on Univariate and Multivariate Cox Regression Analyses

Characteristic	HR for Mortality	95% CI	*P*
Univariate analysis			
Distant metastasis-free interval	0.86	0.77-0.93	< .001
Breast cancer histology	0.32	0.08-0.89	.026
Time from metastatic diagnosis to protocol treatment	0.81	0.64-1.00	.046
Rate of progression	1.06	1.03-1.20	< .05
Induced oligometastatic state	1.81	0.78-3.70	.16
Progression at protocol-treated lesion	1.41	0.79-2.50	.24
Solitary oligometastasis	1.22	0.69-2.20	.48
Age	1.00	0.98-1.03	.87
Dose < 36 Gy/3 fractions	1.18	0.67-2.10	.57
Multivariate analysis			
Breast cancer histology	0.12	0.07-0.37	< .05
Distant metastasis-free interval	0.98	0.98-0.99	< .05
Time from metastatic diagnosis to end of protocol treatment	0.98	0.98-0.99	< .05
Rate of progression	1.44	1.24-1.82	< .05

Abbreviations: CI, confidence interval; Gy, gray; HR, hazard ratio.

CONCLUSIONI

In conclusion, our long-term data demonstrate that patients with oligometastases can receive ablative radiotherapy to all malignant sites with limited acute and late toxicity, leading to reasonable rates of TMC with sufficient dose escalation. A subset of these patients, especially those with breast cancer, may achieve long-term survival. MicroRNA classifiers may help predict tumor biology and clinical outcome. Research to validate microRNA expression profiling in the selection of optimal patients for oligometastasis-directed therapy is ongoing.

Clinical Investigation

Radiosensitivity Differences Between Liver Metastases Based on Primary Histology Suggest Implications for Clinical Outcomes After Stereotactic Body Radiation Therapy

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Summary

We have previously validated a multigene expression index for tumor radiosensitivity (RSI). The current analysis reveals significant differences in RSI based on primary histology of liver metastases with colorectal adenocarcinoma found to be more radioresistant. Differences in RSI were validated in a cohort of 33 patients treated with stereotactic body radiation therapy (SBRT) to 38 liver metastases. This analysis reveals primary histology to be an important factor to consider in SBRT radiation dose selection.

Int J Radiation Oncol Biol Phys, Vol. 95, No. 5, pp. 1399–1404, 2016

MATERIALI E METODI

Radiosensitivity signature

RadioSensitivity Index (RSI) is directly proportional to tumor radioresistance → **RSI: high index = radioresistance**

Methods and Materials: Radiosensitivity (determined by survival fraction at 2 Gy) was modeled as a function of gene expression, tissue of origin, ras status (mut/wt), and p53 status (mut/wt) in 48 human cancer cell lines. Ten genes were identified and used to build a rank-based linear regression algorithm to predict an intrinsic radiosensitivity index (RSI, high index = radioresistance). This model was applied to three independent cohorts treated with concurrent chemoradiation: head-and-neck cancer (HNC, $n = 92$); rectal cancer ($n = 14$); and esophageal cancer ($n = 12$).

studiati come target per effetto radiosensibilizzante implicati in: "radiation signalling", regolazione dl ciclo-cellulare, "DNA damage", apoptosi, proliferazione cellulare, deacetilazione degli istoni

Gene name
Androgen receptor
c-Jun
STAT1
PKC
RelA (p65)
c-Abl
SUMO-1
CDK1 (p34)
HDAC1
IRF1

$$\begin{aligned} RSI = &-.0098009 * AR + 0.0128283 * cJun + 0.0254552 \\ &* STAT1 - 0.0017589 * PKC - 0.0038171 * RelA \\ &+ 0.1070213 * cABL - 0.0002509 * SUMO1 \\ &- 0.0092431 * CDK1 - 0.0204469 * HDAC \\ &- 0.0441683 * IRF1 \end{aligned}$$

Int. J. Radiation Oncology Biol. Phys., Vol. 75, No. 2, pp. 489–496, 2009

RISULTATI

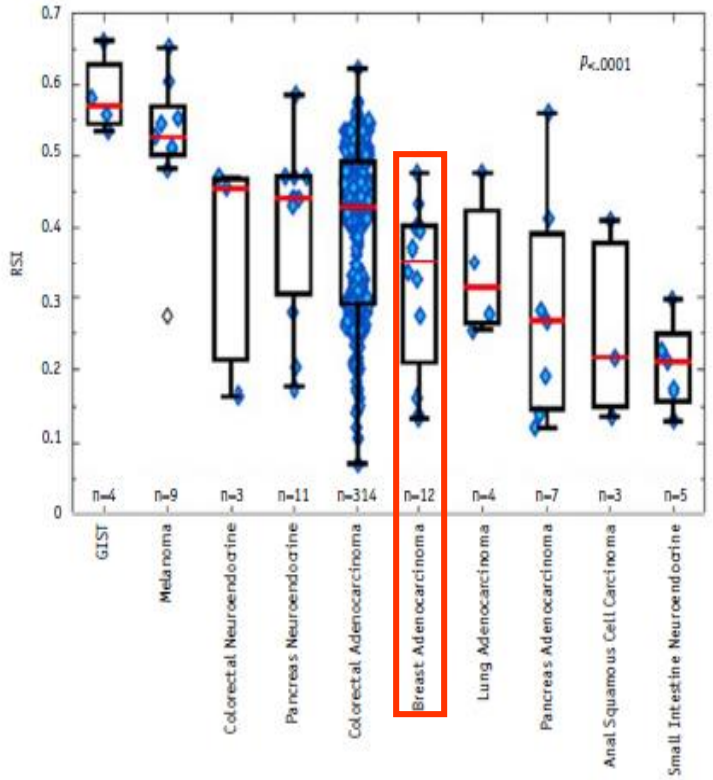

Fig. 1. Box plot of radiosensitive index (RSI) values of liver metastases based on primary histology. *Abbreviation:* GIST = gastrointestinal stromal tumor. Unfilled diamonds represent outliers using the standard 1.5 interquartile range rule.

RSI: high index = radioresistance

The median RSI for all liver lesions was 0.43 (quartile [Q]1, 0.28; Q3, 0.49). There were significant differences in RSIs of liver metastases based on primary histology. The median RSIs for liver metastases in descending order of radioresistance were gastrointestinal stromal tumor (GIST) (0.57), melanoma (0.53), colorectal neuroendocrine (0.46), pancreas neuroendocrine (0.44), colorectal adenocarcinoma (0.43), breast adenocarcinoma (0.35), lung adenocarcinoma (0.31), pancreas adenocarcinoma (0.27), anal squamous cell cancer (0.22), and small intestine neuroendocrine (0.21) ($P<.0001$). A box plot of RSI of liver metastases based on primary histology is displayed in Figure 1.

372 pazienti (almeno 3 campioni)
tumore primitivo:
cr colon-retto 314 pz (84,4%)
cr mammella 12 pz (3,2%)
cr pancreas neuroendocrino 11pz (3%)
melanoma 9 pz (2,4%)
altre istologie

SBRT patient cohorts

Table 1 Clinical characteristics of colorectal and noncolorectal liver metastases

Characteristic	Colorectal	Noncolorectal	*P* value
Patients (n)	22	11	
Age, y (range)	67 (39-89)	60 (46-74)	.11
Male/female	11/11	2/9	.08
Lesions (n)	27	11	
Diameter of lesion, cm (range)	2 (0.6-6.7)	2.7 (1.2-5.1)	.29
Dose 50 Gy/60 Gy	8/19	2/9	.69
Number of lines of previous chemotherapy (range)	2 (0-5)	2 (1-4)	.59
Follow-up, mo (range)	20.5 (3-44.9)	28.4 (2.5-38.6)	

33 pazienti , 38 metastasi epatiche
Non colorectal: 4 cr mammella, 5 cr anale squamoso, 2 cr polmonre NSCLC
median follow-up: 21,2 mesi (range 2,5-44,9 mesi)

SBRT patient cohorts

An independent retrospective analysis was conducted on all consecutive patients treated with a dose of **50 or 60 Gy in 5 fractions given over 1 week.**

Patients underwent placement of fiducial markers before simulation, guided by either computed tomographic (CT), endoscopic, or angiographic approaches. An individualized motion management strategy was chosen after conventional simulation with fluoroscopy to determine the amount of respiratory-associated fiducial marker motion with an intended technique of either incorporating an abdominal compression device or respiratory gating using an infrared reflector on the patient's chest.

PTV =GTV+ 5 mm - maximum doses: bowel and stomach 30 Gy, cord and esophagus 20 Gy - mean dose to the kidneys <10 Gy, liver-GTV V15 <700 cc, lung V10 <1500 cc, and heart mean <10 Gy - PTV covered by 90% of the prescribed dose.

After treatment, patients were followed up by the treating radiation oncologist or medical oncologist with imaging at 2- to 3-month intervals. An independent review of imaging to assess LC was undertaken by 2 radiation oncologists (K.A.A. and J.J.C.) and a radiologist (G.E.H.). Local failure was defined by an increase in the size of the previously irradiated area according to the Response Evaluation Criteria in Solid Tumors criteria, version 1.1 (19).

RISULTATI

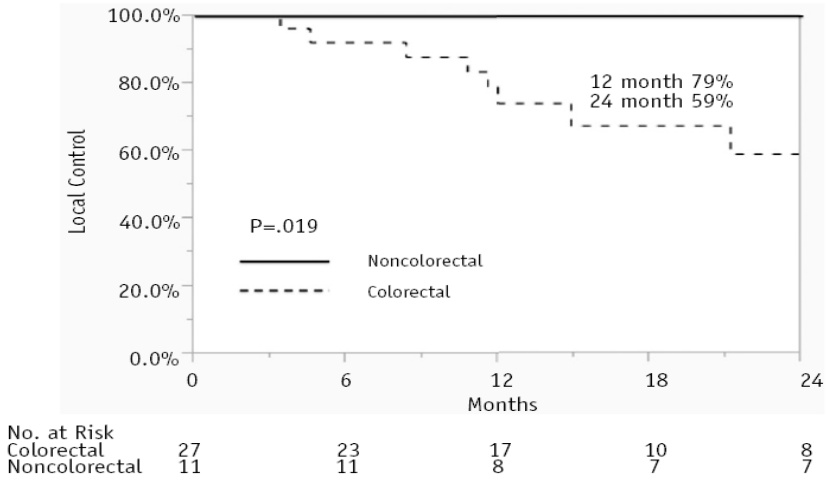

Fig. 2. Kaplan-Meier local control rates for colorectal and noncolorectal liver metastases.

The 12-month and 24-month Kaplan-Meier rates of local control (LC) for colorectal lesions from the independent clinical cohort were 79% and 59%, compared with 100% for noncolorectal lesions (P=.019), respectively.

OS non differenze statisticamente significative:

ANALISI UNIVARIATA

There was a trend toward SBRT dose predicting response on univariate analysis: 50 Gy versus 60 Gy (hazard ratio 3.0; 95% confidence interval [CI]: 0.82-11.0; $P=.10$). Other factors including size ≥ 2 cm/ <2 cm ($P=.47$) and number of lines of previous chemotherapy $\geq 2/1$ ($P=.42$), age ($P=.12$), and gender ($P=.47$) were not found to be significant factors predicting LC.

ANALISI MULTIVARIATA

When factors that were trending on univariate analysis (age and dose) were taken into account, colorectal histology remained significant for local failure ($P=.04$) on multivariate analysis.

CONCLUSIONI

In this analysis assessing radiosensitivity of liver metastases based on primary histology, we noted significant differences based on primary histology. Primary histology played a significant role in determining radiosensitivity, with colorectal metastases found to be more radioresistant than histologies such as anal squamous cell cancer, breast adenocarcinoma, and lung adenocarcinoma. These findings correlated with clinical outcomes in an independent dataset of patients treated with liver SBRT. This study paves the way for a future clinical trial with genomically guided dose selection based on primary histology and RSI.

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Original article

Stereotactic body radiation therapy: A promising chance for oligometastatic breast cancer

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ABSTRACT

Background: Multidisciplinary management of oligometastatic breast cancer with local therapy could improve disease control. The aim of our study is the assessment of safety and efficacy of Stereotactic Body Radiation Therapy (SBRT) in selected subset of patients.

Patients and methods: Oligometastastic patients from breast cancer were treated with SBRT for 1–3 lung and liver lesions, in an observational study. Inclusion criteria were: age >18 years, ECOG 0-2, diagnosis of breast cancer, no extrapulmonary and/or extrahepatic disease, other metastatic sites stable or responding after chemotherapy were allowed, no life threatening conditions, less than 5 lung and liver lesions (with maximum diameter <5 cm), chemotherapy completed at least 3 weeks before treatment, written informed consent. Prescription dose ranged between 48 and 75 Gy in 3 or 4 consecutive fractions. Primary end-point was local control (LC). Secondary end-points were toxicity, overall survival (OS) and progression-free survival (PFS).

Results: From April 2010 to June 2014, 33 patients for a total number of 43 lesions were irradiated. Median follow up was 24 months (range 3–59). Actuarial LC rates were 98% at 1 year and 90% at 2 and 3 years. Complete response, partial response and progressive disease were detected in 25 (53.2%), 16 (34%), and 6 (12.8%) lesions, respectively. Median OS was 48 months. Actuarial OS rates at 1 and 2 years were 93% and 66% respectively. Median PFS was 11 months, with a PFS rate at 1 and 2 years of 48% and 27%, respectively. At univariate analysis DFI >12 months, hormonal receptor positivity, medical therapies after SBRT showed a significant impact on OS. Treatment was well tolerated, with no G3-4 toxicities.

Conclusions: SBRT is a safe and feasible alternative treatment of liver and lung oligometastases from breast cancer, in selected patients not amenable to surgery, with good local control and survival rate.

MATERIALI E METODI

Material and methods

This observational study was approved by the local ethical committee. From April 2010 until June 2014 oligometastatic patients with liver or lung metastases from breast cancer were treated with SBRT in our institution. Inclusion criteria were: age >18 years, ECOG 0-2, diagnosis of breast cancer, no extrapulmonary and/or extrahepatic disease, other metastatic sites stable or responding after chemotherapy were allowed, no life threatening conditions, less than 5 lung and liver lesions (with maximum diameter <5 cm), chemotherapy completed at least 3 weeks before treatment, written informed consent for the treatment. Systemic therapies other than chemotherapy were allowed during RT (i.e hormonal therapies and/or immunotherapy). Patients were excluded from these analysis if pregnant. All patients gave written informed consent for treatment.

Primary end point was local control (LC), secondary end points were toxicity, progression free survival (PFS) and overall survival (OS).

All patients were staged with thorax and abdomen CT and PET/CT to confirm the oligometastatic state. Abdominal MRI was required in patients with liver metastases.

Table 2

Characteristics of patients treated with SBRT for lung or liver metastases.

	Number
Number of patients	33
Age (years)	Mean 57 years
Hormonal receptor positive	23 (69.7%)
HER2 3+	16 (48.5%)
Systemic therapies for metastatic disease before SBRT	30 (90.9%)
Sites of treated oligometastases	Liver 23 (69.7%)
	Lung 10 (30.3%)
Number of treated oligometastases	
1	21 (63.6%)
2	10 (30.3%)
3	2 (6.1%)
Extrahepatic/pulmonary stable disease	16 (48.5%)
Sum of ITVs Liver	Mean 20.06 cc
Lung	Mean 10.96 cc

SBRT: stereotactic body radiation therapy, ITV: internal target volume.

Table 1
Normal tissue tolerances used for planning, in brackets the more relaxed constraints for the fractionation schemes with 4–8 fractions.

Normal tissue	Constraints
Healthy liver	$>700\ cm^3 < 15$ Gy
Spinal cord	$D^3_{0.1\,cm} < 18\ (20)$ Gy
Kidneys	$V_{15Gy} < 35\%$
Stomach	$D^3_{1cm} < 21\ (36)$ Gy
Duodenum	$D^3_{1cm} < 21\ (36)$ Gy
Small bowel	$D^3_{1cm} < 21\ (36)$ Gy
Large bowel	$D^3_{1cm} < 21\ (36)$ Gy
Lungs	Mean < 4 Gy
	$V_{20Gy} < 10\%$
Heart	$D^3_{1cm} < 30$ Gy
Oesophagus	$D^3_{0.1cm} < 30$ Gy

All patients were treated with a volumetric modulated arc technique (VMAT). All SBRT/VMAT plans were optimized by inverse planning to ensure maximal dose conformity and rapid dose falloff toward critical structures. SBRT/VMAT was delivered with 6- or 10-MV photons, using modulated dynamic arcs. Dose was prescribed as the mean dose to PTV ensuring that more than 98% of PTV would receive 95% of prescribed dose. Normal tissues tolerances used for planning are showed in Table 1.

RISULTATI

Table 3
Sites of first disease progression and patients'treatment characteristics.

Patient	Site of progression	Site of treated metastases	Dose of SBRT
1	Thoracic wall and axilla	Liver (1)	56.25 Gy in 3 fr.
2	Lymph nodes	Liver (1)	56.25 Gy in 3 fr.
3	Thoracic wall and lymph nodes	Liver (1)	75 Gy in 3 fr.
4	Liver (other site)	Liver (2)	61.8 Gy in 3 fr.
5	Pleura, lymph nodes, bone	Liver (1)	75 Gy in 3 fr.
6	Lung	Liver (2)	75 Gy in 3 fr.
7	Bone, lymph nodes, liver (other site)	Liver (2)	67.5 Gy in 3 fr.
8	Liver (other site)	Liver (3)	75 Gy in 3 fr.
9	Liver (other site)	Liver (1)	75 Gy in 3 fr.
10	Lymph nodes, liver (other site)	Liver (1)	61.8 Gy in 3 fr.
11	Liver (other site)	Liver (1)	75 Gy in 3 fr.
12	Liver (other site)	Liver (3)	75 Gy in 3 fr.
13	Liver (other site)	Liver (1)	66 Gy in 3 fr.
14	Liver (other site)	Liver (1)	75 Gy in 3 fr.
15	Lymph nodes	Liver (1)	75 Gy in 3 fr.
16	Liver (other site)	Liver (1)	75 Gy in 3 fr.
17	Liver (other site)	Liver (1)	61.8 Gy in 3 fr.
18	Liver (other site)	Liver (2)	75 Gy in 3 fr.
19	Liver (other site)	Liver (2)	75 Gy in 3 fr.
20	Brain, bone, lung	Lung (1)	48 Gy in 4 fr.
21	Pleura	Lung (1)	48 Gy in 4 fr.
22	Bone	Lung (2)	48 Gy in 4 fr.
23	Lymph nodes	Lung (1)	60 Gy in 3 fr.
24	Lung	Lung (2)	48 Gy in 4 fr.

During treatment patients were evaluated the first and the last day of RT, or more frequently if required; patients were evaluated again 4 weeks after the end of treatment for acute toxicity. Toxicities were graded according to Common Terminology Criteria for Adverse Events version 4.0.

No CT concomitante
14 pz trastuzumab
20 pz OT non specificata

Tossicità G1-G2

No patients experienced radiation-induced liver disease (RILD, both classic or non-classic) or any grade ≥3 toxicity. In twenty-one cases (63.6%) we did not record any acute or late toxicity. Nausea and vomiting G1-2 were the most represented side effects (18%). Regarding late toxicity, during follow up we recorded one case of G2 gastritis and one case of G2 cough.

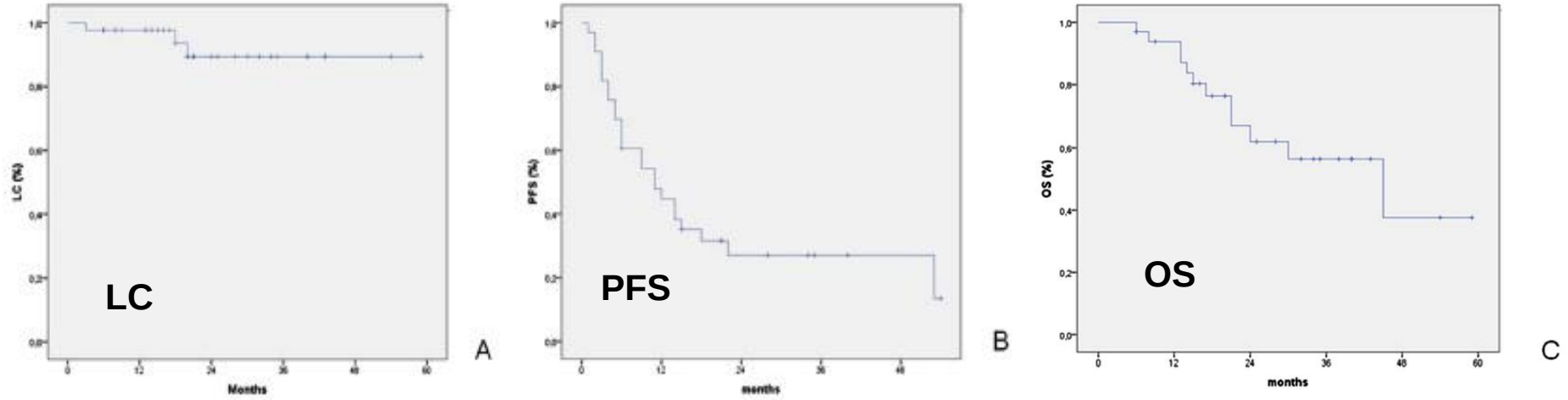


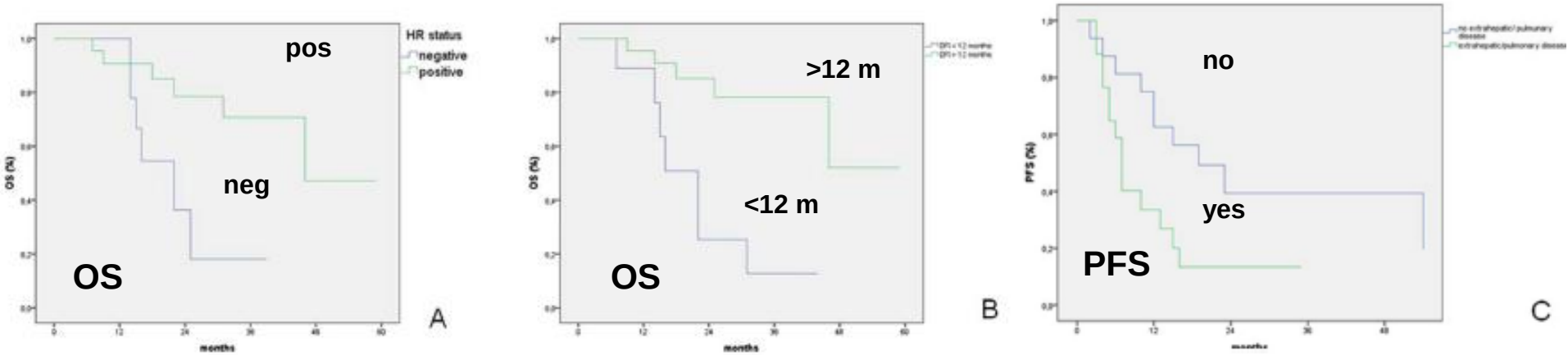
Fig. 2. Local control (A), Progression free survival (B) and Overall survival (C) curves.

In our experience, we report an excellent local control of 98% at 1 year and 90% at 2 years, in line with published literature [15–18].

Follow-up mediano: 24 mesi (range 3-59)

Median overall survival (OS) was 48 months (IC 95%, 18.6–71.3). Actuarial OS rate at 1 and 2 years 93% and 66%.

Median progression-free survival (PFS) was 11 months (IC 95%, 4.5–17.4 months), with a PFS rate at 1 and 2 years of 48% and 27%, respectively (Fig. 2).



Hormonal receptors **Disease Free Interval** **Extra hepat/pulm disease**

Fig. 3. Overall survival curves according to hormonal receptors (HR) (A) and Disease free interval (DFI) (B); Progression free survival (PFS) curve according to extra hepatic/pulmonary disease (C).

Table 4
Prognostic factors affecting LC, OS and PFS rates on univariate analysis.

Factor	Univariate analysis		
	LC	OS	PFS
Tumor size	ns[a]	ns	ns
extra	ns	ns	0.03
DFI>12 months	ns	0.005	ns
HER +++	ns	ns	ns
Rec+	ns	0.03	ns
CT *	ns	0.01	ns
OT *	ns	0.04	ns
Trastuzumab	ns	ns	ns
Local control	ns	ns	ns

[a] ns: not significant.
* After SBRT

At multivariate analysis, none of the analyzed parameters showed a significant correlation with LC, OS and PFS.

CONCLUSIONI

SBRT as ablative local treatment for oligometastatic disease is becoming more and more popular. This approach can guarantee an excellent local control as in the series we report. This advantage can probably translate in a PFS and OS, with a not negligible, although still theoretical, chance of cure, especially if local therapies are integrated with efficient systemic treatments. Breast cancer patients are excellent candidate for this kind of approach, because of the natural behavior of the disease, with the frequent occurrence of an oligometastastic state. As we showed in this study, also patients with visceral metastases, heavily treated with systemic therapies, take a significant advantage from SBRT, despite their historically dismal prognosis.

However, we must not forget that ablative local therapies, although commonly prescribed, are not yet the standard of care for breast oligometastatic patients. All possible efforts must be made to enroll patients in phase III trials that will hopefully confirm that local therapies can have a positive impact on metastatic patients' survival.

Il trattamento della paziente oligometastatica:

analisi della letteratura articoli pubblicati nel 2016

radioterapia e T-DM1

nature COMMUNICATIONS

ARTICLE

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Anti-tubulin drugs conjugated to anti-ErbB antibodies selectively radiosensitize

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Tumour resistance to radiotherapy remains a barrier to improving cancer patient outcomes. To overcome radioresistance, certain drugs have been found to sensitize cells to ionizing radiation (IR). In theory, more potent radiosensitizing drugs should increase tumour kill and improve patient outcomes. In practice, clinical utility of potent radiosensitizing drugs is curtailed by off-target side effects. Here we report potent anti-tubulin drugs conjugated to anti-ErbB antibodies selectively radiosensitize to tumours based on surface receptor expression. While two classes of potent anti-tubulins, auristatins and maytansinoids, indiscriminately radiosensitize tumour cells, conjugating these potent anti-tubulins to anti-ErbB antibodies restrict their radiosensitizing capacity. Of translational significance, we report that a clinically used maytansinoid ADC, ado-trastuzumab emtansine (T-DM1), with IR prolongs tumour control in target expressing HER2+ tumours but not target negative tumours. In contrast to ErbB signal inhibition, our findings establish an alternative therapeutic paradigm for ErbB-based radiosensitization using antibodies to restrict radiosensitizer delivery.

CASE REPORT Open Access

Expansive hematoma in delayed cerebral radiation necrosis in patients treated with T-DM1: a report of two cases

Mitsuya et al. BMC Cancer (2016) 16:391
DOI 10.1186/s12885-016-2464-1

Koichi Mitsuya[1*], Junichiro Watanabe[2], Yoko Nakasu[1], Nakamasa Hayashi[1], Hideyuki Harada[3] and Ichiro Ito[4]

Abstract

Background: Multiple new targeted agents have been developed for patients with human epidermal growth factor receptor type 2 (HER2) – positive breast cancer. Patients with HER2– positive breast cancer will develop brain metastases with greater incidence than patients with non-HER2 cancers, and many of them will undergo stereotactic radiosurgery (SRS) or other CNS radiotherapy. The interaction between radiation effects and new targeted agents is not well understood. We report two cases suggesting a novel adverse effect of T-DM1 (trastuzumab emtansine) on symptomatic enlargement of radiation necrosis (RN) after SRS.

Case presentation: Two patients with HER2-positive breast cancer had received SRS for single brain metastasis more than 5-years ago. They had been heavily treated for HER2-positive metastatic breast cancer (trastuzumab and pacritaxel, lapatinib and capecitabine). They initiated T-DM1 therapy for progressive systematic disease 5. 5 years after stereotactic irradiation, when a small RN was recognized on brain MR images of each patient. The RN lesions increased in size and became symptomatic during 13 or 14 months of T-DM1 treatment. The patients underwent surgical resection of the lesion. Pathological examination revealed necrosis, hematoma, granulation tissue and telangiectasia without neoplastic cells.

Conclusions: A potential enhancement of RN by T-DM1 in the brain may be one of important adverse events associated with the use of T-DM1 for patients after SRS. These cases highlight the need of careful follow-up when combining new systemic targeted therapies and SRS for brain metastases.

Keywords: Brain metastasis, Breast cancer, Human epidermal growth factor receptor type 2, Radiation necrosis, Stereotactic radiosurgery, Trastuzumab emtansine

Caso clinico n 1

Pz di 67 anni con cr mammario stadio IV
8 anni prima metastasi cerebrale di 8 mm trattata con SRS D95=25 Gy
5,5 anni dopo SRS inizia T-DM1
dopo 8 mesi dall'inizio di T-DM1 lesione asintomatica: RM,TC e chirurgia: RADIONECROSI

Inizio T-DM1 **14 mesi** **15 mesi**

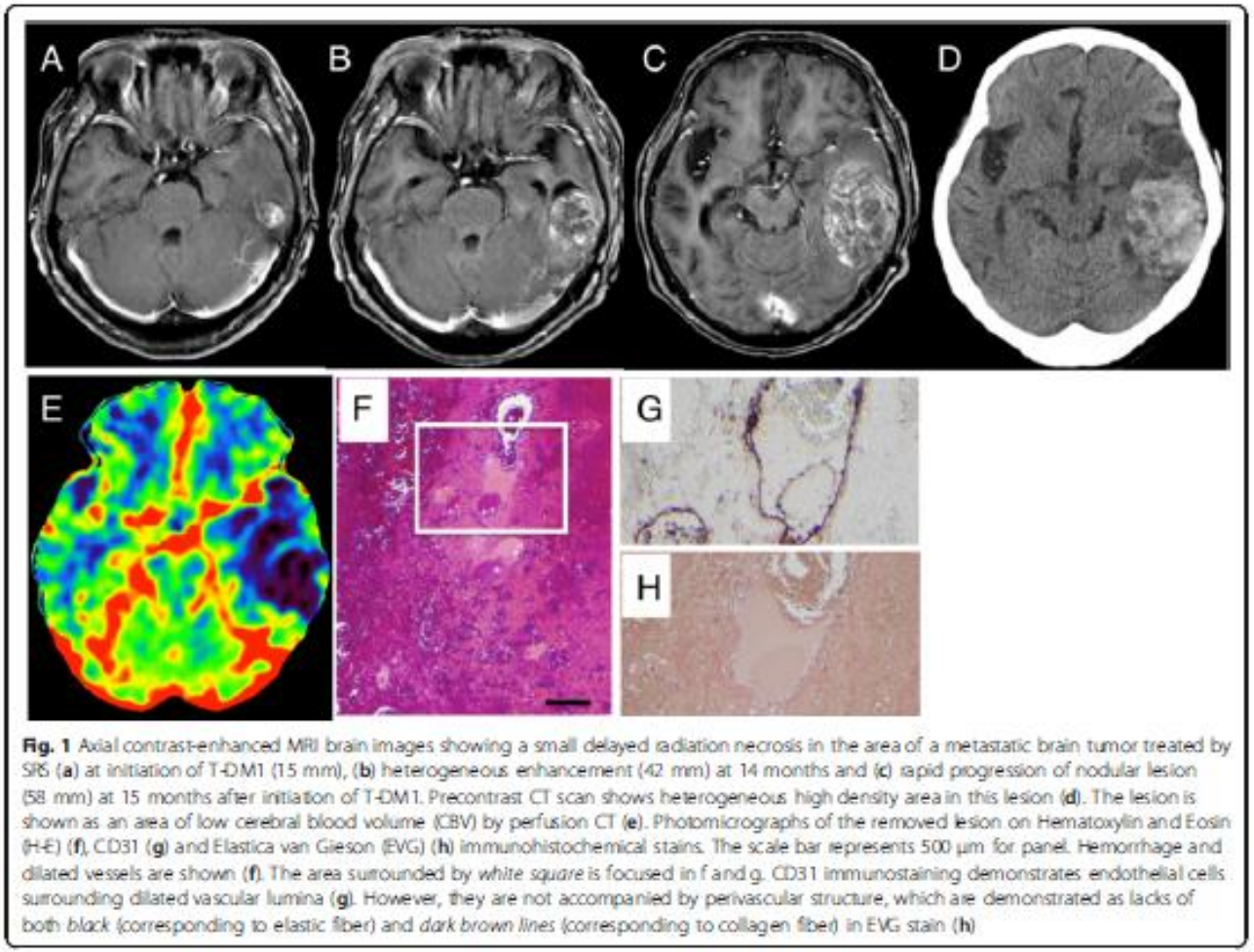

Fig. 1 Axial contrast-enhanced MRI brain images showing a small delayed radiation necrosis in the area of a metastatic brain tumor treated by SRS (**a**) at initiation of T-DM1 (15 mm), (**b**) heterogeneous enhancement (42 mm) at 14 months and (**c**) rapid progression of nodular lesion (58 mm) at 15 months after initiation of T-DM1. Precontrast CT scan shows heterogeneous high density area in this lesion (**d**). The lesion is shown as an area of low cerebral blood volume (CBV) by perfusion CT (**e**). Photomicrographs of the removed lesion on Hematoxylin and Eosin (H-E) (**f**), CD31 (**g**) and Elastica van Gieson (EVG) (**h**) immunohistochemical stains. The scale bar represents 500 μm for panel. Hemorrhage and dilated vessels are shown (**f**). The area surrounded by *white square* is focused in f and g. CD31 immunostaining demonstrates endothelial cells surrounding dilated vascular lumina (**g**). However, they are not accompanied by perivascular structure, which are demonstrated as lacks of both *black* (corresponding to elastic fiber) and *dark brown lines* (corresponding to collagen fiber) in EVG stain (**h**)

Caso clinico n 2

Pz di 45 anni con cr mammario stadio IV
SRS (D95=25 Gy) per mestatasi lobo parietale dx 10 mm,
dopo 1 anno recidiva a livello cerebrale intervento chirurgico e SRT postoperatoria 30Gy /5 Gy
dopo 5,5 inizia T-DM1 lieve disorientamento spazio-temporale- RM,TC e chirurgia: RADIONECROSI

Inizio T-DM1 **12 mesi** **15 mesi**

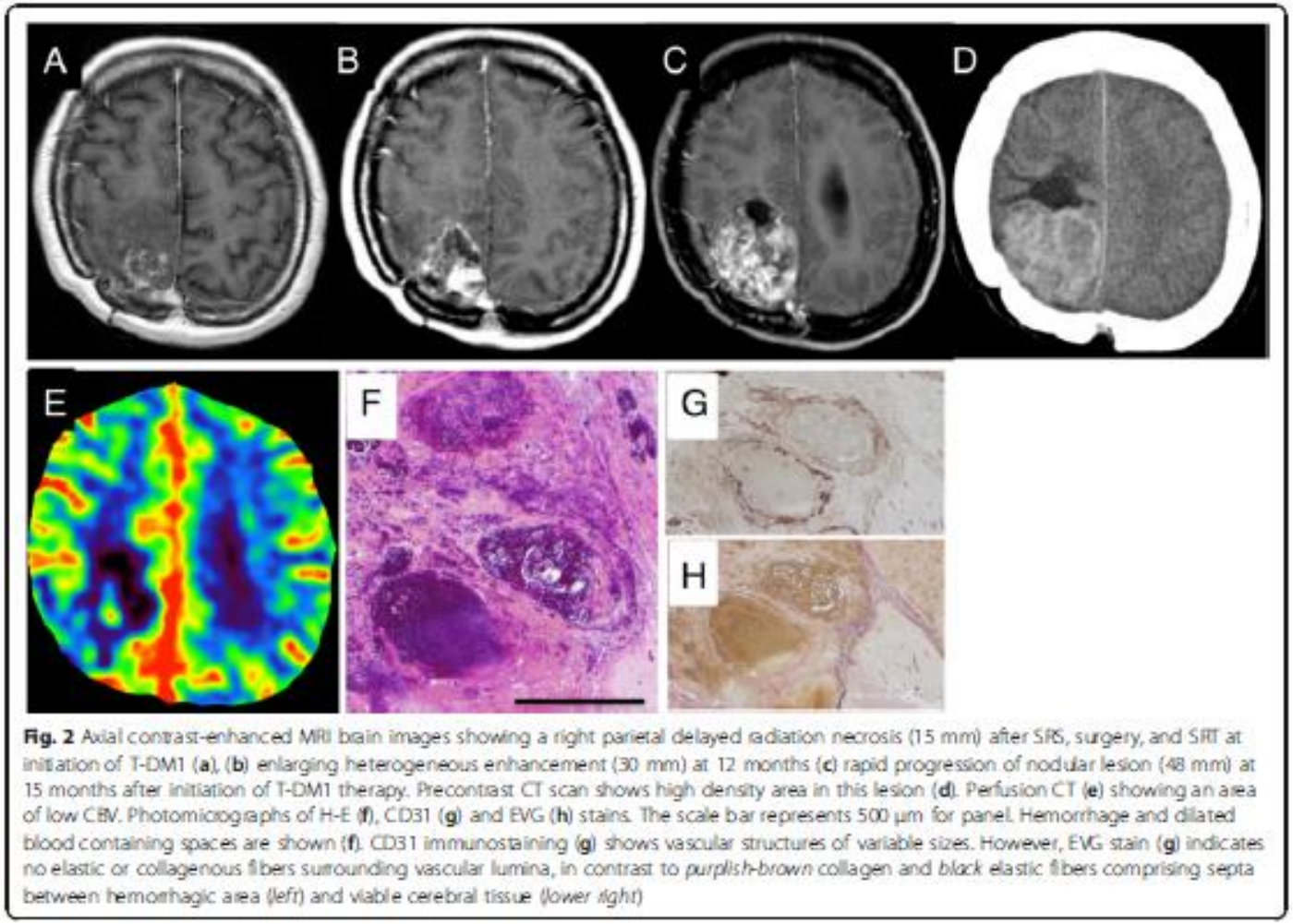

Fig. 2 Axial contrast-enhanced MRI brain images showing a right parietal delayed radiation necrosis (15 mm) after SRS, surgery, and SRT at initiation of T-DM1 (**a**), (**b**) enlarging heterogeneous enhancement (30 mm) at 12 months (**c**) rapid progression of nodular lesion (48 mm) at 15 months after initiation of T-DM1 therapy. Precontrast CT scan shows high density area in this lesion (**d**). Perfusion CT (**e**) showing an area of low CBV. Photomicrographs of H-E (**f**), CD31 (**g**) and EVG (**h**) stains. The scale bar represents 500 μm for panel. Hemorrhage and dilated blood containing spaces are shown (**f**). CD31 immunostaining (**g**) shows vascular structures of variable sizes. However, EVG stain (**g**) indicates no elastic or collagenous fibers surrounding vascular lumina, in contrast to *purplish-brown* collagen and *black* elastic fibers comprising septa between hemorrhagic area (*left*) and viable cerebral tissue (*lower right*)

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CLINICAL STUDY

Studio retrospettivo

Preliminary experience of the concurrent use of radiosurgery and T-DM1 for brain metastases in HER2-positive metastatic breast cancer

Arthur Geraud[1] · Hao Ping Xu[1] · Philippe Beuzeboc[2] · Youlia M. Kirova[1]

Abstract This is preliminary study assessing the efficacy and safety of concurrent use of radiation therapy (RT) and T-DM1 for the treatment of brain metastases (BM) in patients with HER2-positive metastatic breast cancer (BC). We retrospectively studied 12 patients treated for BM at the Institut Curie in 2014–2015 with T-DM1 and concurrent (4) or sequential (8) radiosurgery with or without whole brain irradiation. The following variables were studied: local control, clinical and radiological response as well as early and late side effects. The mean age of the population was 38 years at the time of diagnosis of BC and 46 years at of BM. All patients were with good PS. The response rate of the concurrent treatment group was 75% with 1 complete response, 1 partial response, one stable disease and 1 progression. Comparatively, the response rate in the sequential group was as follows: two complete responses, two partial responses, six cases of stable disease and two cases of local progression. No patient experienced interruption of irradiation because of side effects. About 50% of patients were asymptomatic after treatment. Radiation necrosis was observed in 50% of patients in the concurrent group and 28.6% of patients in the sequential group with a similar rate of oedema in the two groups. We found that the combination of T-DM1 and radiosurgery was feasible but can increase the incidence of radiation necrosis. Larger prospective studies with longer follow-up are needed to more clearly evaluate this association.

12 pazienti (arruolamento 2014-2015)
4 pz radiochirurgia contemporaneamente a T-DM1
8 pz radiochirurgia dopo (intervallo >1 mese)T-DM1

RADIONECROSI:

RT e T-DM1 concomitante: 50%
RT e T-DM1 sequenziale: 33.3%

EDEMA:

RT e T-DM1 concomitante: 25%
RT e T-DM1 sequenziale: 28.6%

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Letter to the editor

Preliminary results of the concurrent use of radiotherapy for bone metastases and trastuzumab emtansine in patients with HER2-positive metastatic breast cancer

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Table 1
Preliminary results of the concurrent use of radiotherapy for bone metastases and trastuzumab emtansine in HER2-positive metastatic breast cancer patients: characteristics and treatment at first presentation and bone metastatic evolution.

	Patient 1	Patient 2	Patient 3
Initial disease			
Age	35 years	30 years	53 years
Histology (grade)	Invasive ductal carcinoma (III)	Invasive ductal carcinoma (II)	Invasive ductal carcinoma (II)
Tumour stage	T1 N2 M0	T3 N1 M0	T4N1M1
Local and systemic treatment	Lumpectomy + lymph node dissection Radiotherapy breast + boost (66) + supraclavicular (50) Mastectomy for disease recurrence Adjuvant chemotherapy, hormonal therapy and trastuzumab	Mastectomy + SN Radiotherapy breast (50) + internal mammary chain and supraclavicular (45) Adjuvant and neoadjuvant chemotherapy, adjuvant hormonal therapy and trastuzumab	Mastectomy + lymph node dissection Breast (45), supraclavicular (45) Chemotherapy and trastuzumab before surgery/radiotherapy
Bone metastatic evolution			
Age at bone metastatic localizations	50 years	38 years	58 years
Others metastatic sites	Brain, liver, lung	Brain	Brain, liver
Systemic treatment	Chemotherapy, trastuzumab	Chemotherapy, lapatinib, trastuzumab	Chemotherapy, hormonal therapy, lapatinib, trastuzumab
Trastuzumab emtansine duration	4 months	11 months	5 months
Stop: yes or no (cause)	Stopped after liver progression	Continued	Continued
Bone radiotherapy			
Localization	Dorsal vertebras	Sacrum	Left shoulder
Type of treatment	D3–D7		
Dose	15 Gy 5 fractions	15 Gy 5 fractions	8 Gy 1 fraction
Symptoms before radiation	Motor deficit, pain	Pain	Pain
Pain control after radiotherapy	Good pain relief	Good pain relief	Good pain relief
Neurologic evolution after radiotherapy	Partial response	N/A	N/A
Side effects related to the concurrent use of radiotherapy and trastuzumab emtansine	No side effects (12 months after treatment)	No side effects (9 months after treatment)	No side effects (3 months after treatment)

CONCLUSIONI…

In attesa di avere i risultati degli studi in corso…

ACCURATA SELEZIONE DELLE PAZIENTI!!!

Grazie per l'attenzione!