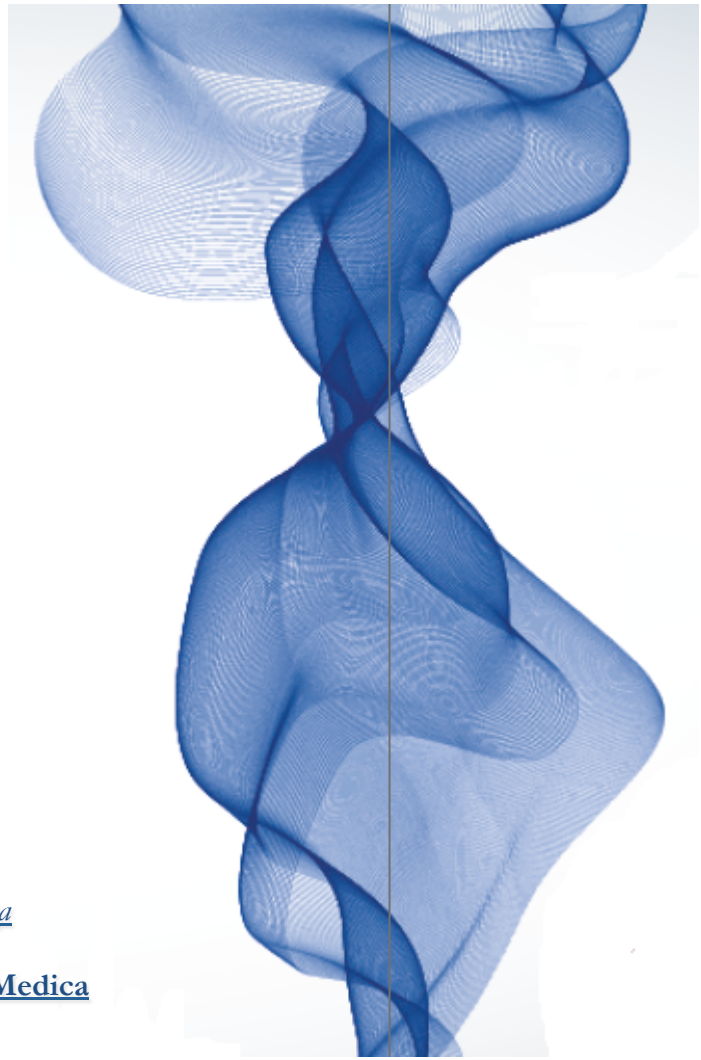
TRATTAMENTO NON CHIRURGICO
DELLE OLIGOMETASTASI

Colonna

Integrazione RT e Ormonoterapia nei tumori di Prostata e mammella



SILVIA CENITI

Azienda Ospedaliera di Cosenza
P.O. Mariano Santo
U.O. Complessa di Oncologia Medica
Direttore: Dr S. Palazzo

VOLUME 31 · NUMBER 11 · APRIL 10 2013

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Extracranial Oligometastases: A Subset of Metastases Curable With Stereotactic Radiotherapy

Kimberly S. Corbin, Samuel Hellman, and Ralph R. Weichselbaum, *University of Chicago Medical Center, Chicago, IL*

The term oligometastases, introduced in 1995[1] and detailed more recently,[2] describes an intermediate state of cancer spread between localized disease and widespread metastases. Metastases from solid tumors are regarded as representative of disseminated cancer and are not considered curable, with the rare exception, such as germ cell tumors.[3,4] By contrast, evidence has emerged that patients with limited metastatic disease, such as liver metastasis from colon or rectal cancer, can be cured by removal of the metastasis, drawing increased focus on the potential for intermediate states of metastatic cancer involvement. The implication of the concept of an oligometastatic state is that metastatic disease may be cured with metastasis-directed therapy. As a further conceptual refinement, Niibe et al[5] have suggested the concept of oligorecurrence to consider patients with a limited number of metastases and controlled primary tumors as a group with an improved prognosis as compared with patients with limited metastasis and uncontrolled primary tumors.[6] The oligometastatic hypothesis is distinct from other potentially important uses of radiotherapy and surgery in metastatic disease, such as consolidation of chemotherapy responses or as an application of the Norton-Simon hypothesis,[7] which predicts that effectiveness of chemotherapy is proportional to the growth rate of the tumor and that the fastest growth rates occur in nonbulky tumors. Aggressive local therapy to metastatic

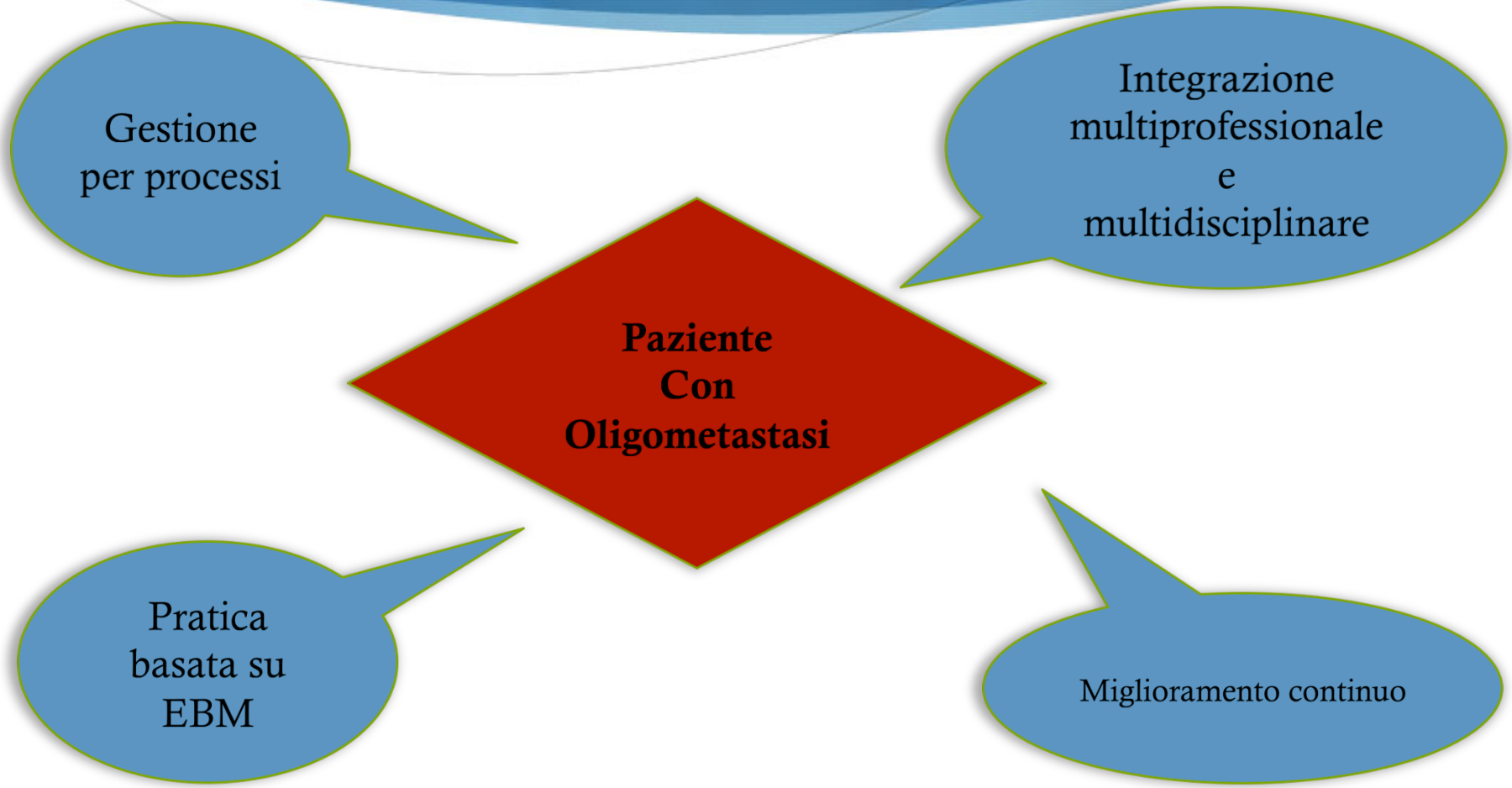
Il Percorso del Pz con Oligometastasi

Integrazione
Terapia locoregionale + Terapia sistemica

Terapia locoregionale

Terapia sistemica

Il Percorso del Pz con Oligometastasi



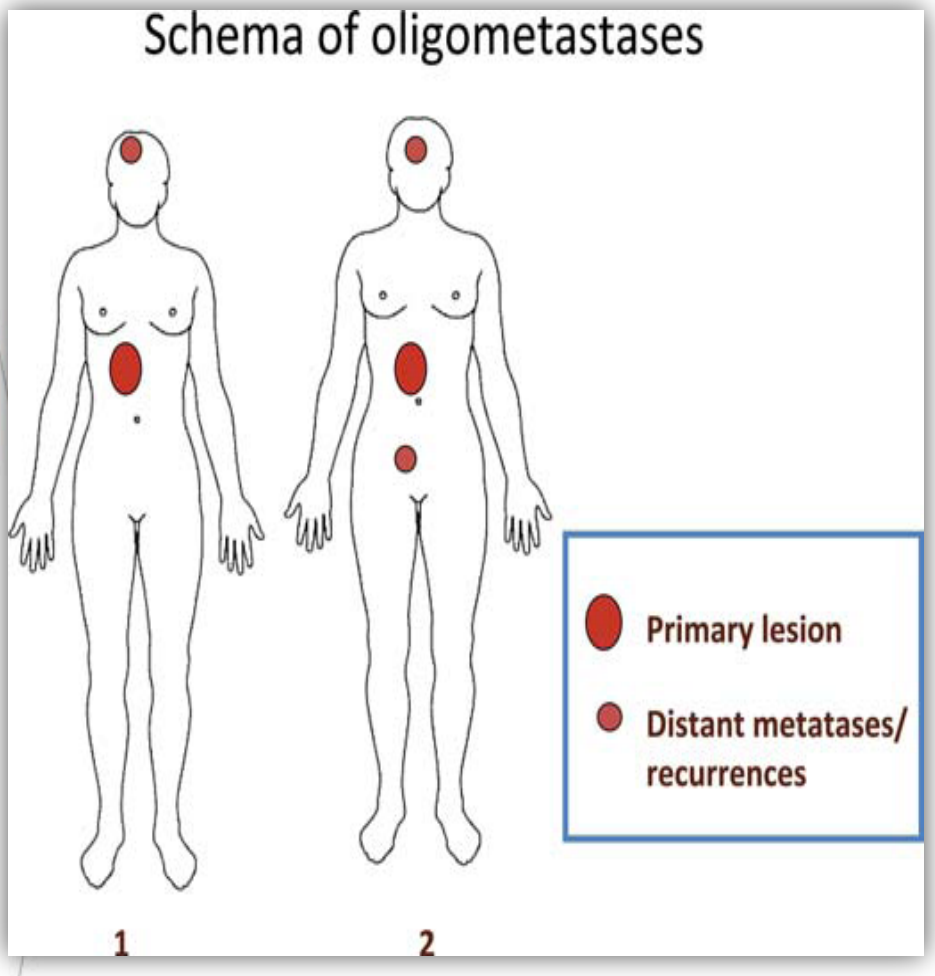

Oncologo
Radioterapista
Radiologo

Oligometastasi

Obiettivi generali cui tendere nell'ambito di una scelta terapeutica condivisa

La sede della malattia è
Il primo fattore discriminante
Nell'indirizzo terapeutico

Selezionare i pazienti con metastasi limitate



Jpn J Clin Oncol 2010;40(2)107–111
doi:10.1093/jjco/hyp167
Advance Access Publication 4 January 2010

Breast Care

Review Article · Übersichtsarbeit

Breast Care 2011;6:363–368
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Does Radiotherapy Have Curative Potential in Metastatic Patients? The Concept of Local Therapy in Oligometastatic Breast Cancer

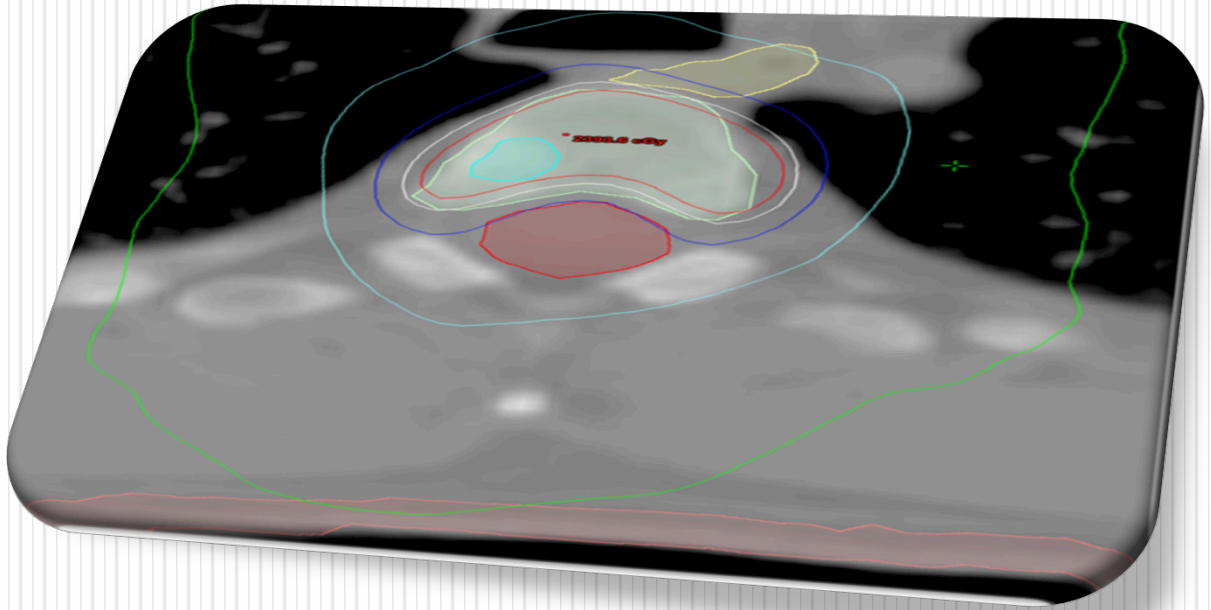
Kathrin Dellas

North European Radiooncological Center Kiel and University of Luebeck, Department of Radiotherapy, Germany

Table 2. Theoretical concept of combining systemic and local therapies in oligometastatic cancer

Diagnostics	The tumor load must be determined as precisely as possible (computed tomography, magnetic resonance imaging, positron emission tomography etc.) to exclude disseminated disease and exactly define the targets of local therapy.
Systemic control and therapy	It is anticipated that the disease can be systemically be controlled. Occurrence of new lesions is unlikely. Control of visible lesions will impact on the further course of disease.
Local therapy	Effective local therapy with minimal side effects is available.
Multimodal treatment concept	Systemic and local therapy can be combined without hindering each other.

Oligometastases: the new paradigm and the new options



Lancet Oncol 2013 Jan;14(1):e28-37. doi: 10.1016/S1470-2045(12)70510-7.

Stereotactic body radiotherapy for oligometastases.

Tree AC, Khoo VS, Eeles RA, Ahmed M, Dearnaley DP, Hawkins MA, Huddart RA, Nutting CM, Ostler PJ, van As NJ.

Source

RoyalMarsden NHS Foundation Trust, London, UK. alison.tree@rmh.nhs.uk

Abstract

The management of metastatic solid tumour shash istorically focuse donsystemic treatment given with palliative intent. However, radical surgical treatment of oligometastases isnow common practice in some settings. The developmentofstereotactic body radiotherapy (SBRT), building on improvements in delivery achieved by intensity-modulated and image-guided radiotherapy, nowallows delivery of ablative doses of radiation to extracranial sites. Many non-randomisedstudieshaveshownthat SBRT for oligometastases issafe and effective, with local control rates of about 80%. Importantly, thesestudiesalsosuggestthat the naturalhistory of the diseaseischanging, with 2-5 yearprogression-free survival of about 20%. Although complete cure might be possiblein afewpatients with oligometastases, the aim of SBRT in thissettingis to achievelocal control and delay progression, and therebyalsopostpone the need for further treatment. Wereviewpublished work showingthat SBRT offersdurablelocal control and the potential for progression-free survival in non-liver, non-lungoligometastaticdiseaseat a range of sites. However, to test whether SBRT reallydoesimproveprogression-free survival, randomised trials will be essential.

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Kimberly S. Corbin, Samuel Hellman, and Ralph R. Weichselbaum, *University of Chicago Medical Center, Chicago, IL*

STEREOTACTIC BODY RADIOTHERAPY FOR OLIGOMETASTASES

Stereotactic body radiotherapy (SBRT) enables highly focal treatment of cancer with single or few fractions of high-dose radiation. SBRT has demonstrated favorable rates of local control for primary and metastatic tumors and provides a treatment option for deep-seated tumors or for those who cannot undergo surgery. Advances in radiotherapy planning have advanced the clinical experience with SBRT for limited metastases, with examples listed in Table 1,[66-79] including a radiation dose–escalation study from our group.[77] SBRT treatment of limited metastases has shown promising local control rates for treated metastases, ranging from 67% to 95%.[66,71,72,74,77,80-84] Two- to 3-year survival rates have been reported in the range of 30% to 64%[73,77,78,85] and

Prostate Cancer

frontiers in ONCOLOGY

ORIGINAL RESEARCH ARTICLE
published: 22 January 2013
doi: 10.3389/fonc.2012.00215

Stereotactic body radiation therapy in the treatment of oligometastatic prostate cancer

Kamran A. Ahmed[1†], Brandon M. Barney[2†], Brian J. Davis[2], Sean S. Park[2], Eugene D. Kwon[3] and Kenneth R. Olivier[2]*

[1] Department of Radiation Oncology, Moffitt Cancer Center, Tampa, FL, USA
[2] Department of Radiation Oncology, Mayo Clinic, Rochester, MN, USA
[3] Department of Urology, Mayo Clinic, Rochester, MN, USA

Table 1 | Patient and disease characteristics at the time of SBRT.

Characteristic	All patients, $n = 17$	HRPC, $n = 11$	Non-HRPC, $n = 6$
Lesions treated (*n*)	21	14	7
Age (year)			
Median	65.0	66.9	60.3
Range	50.6–79.7	52.9–79.7	50.6–74.0
Initial Gleason score (*n*)			
6	1	1	0
7	9	6	3
8	3	1	2
9	4	3	1
Primary therapy at diagnosis (*n*)			
Prostatectomy	15	9	6
EBRT	2	2	0
Time from diagnosis to DM (month)			
Median	50.4	63.0	28.0
Range	1.0–139.2	1.0–139.2	1.0–66.0
Time to development of HRPC (month)			
Median	–	14.0	–
Range	–	4.0–108.0	–
Time from HRPC to SBRT (month)			
Median	–	13.0	–
Range	–	1.0–80.4	–
Site treated with SBRT (*n*)			
Bone	19	12	7
Liver	1	1	–
Retroperitoneal lymph nodes	1	1	–

HRPC, hormone-refractory prostate cancer; EBRT, external beam radiation therapy; DM, distant metastasis; SBRT, stereotactic body radiation therapy.

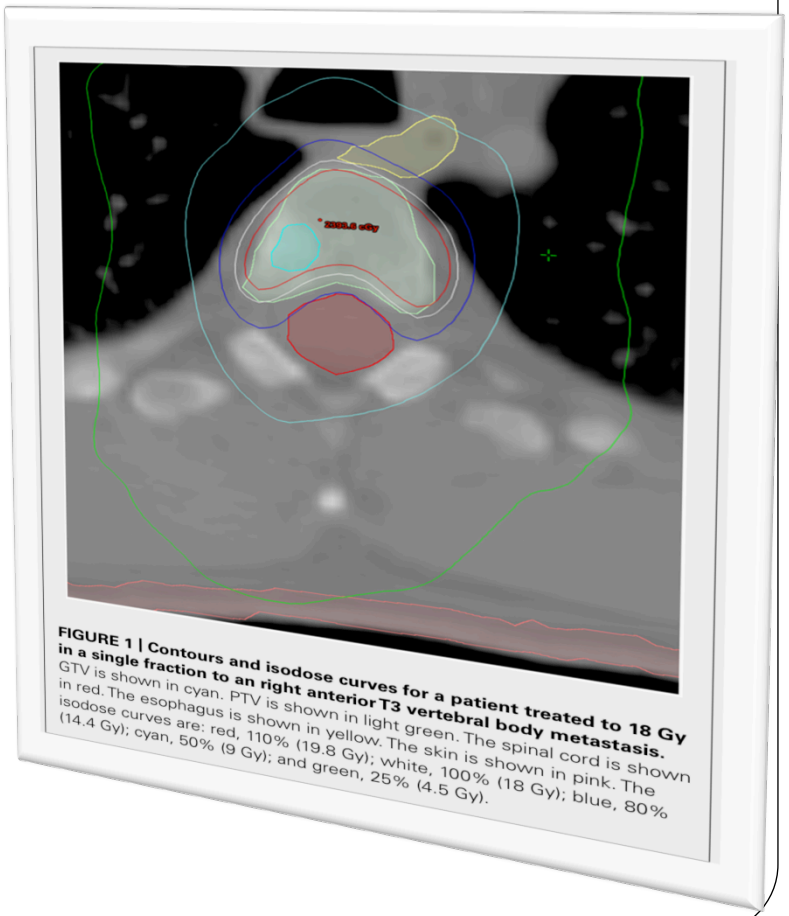

FIGURE 1 | Contours and isodose curves for a patient treated to 18 Gy in a single fraction to an right anterior T3 vertebral body metastasis. GTV is shown in cyan. PTV is shown in light green. The spinal cord is shown in red. The esophagus is shown in yellow. The skin is shown in pink. The isodose curves are: red, 110% (19.8 Gy); white, 100% (18 Gy); blue, 80% (14.4 Gy); cyan, 50% (9 Gy); and green, 25% (4.5 Gy).

frontiers in ONCOLOGY

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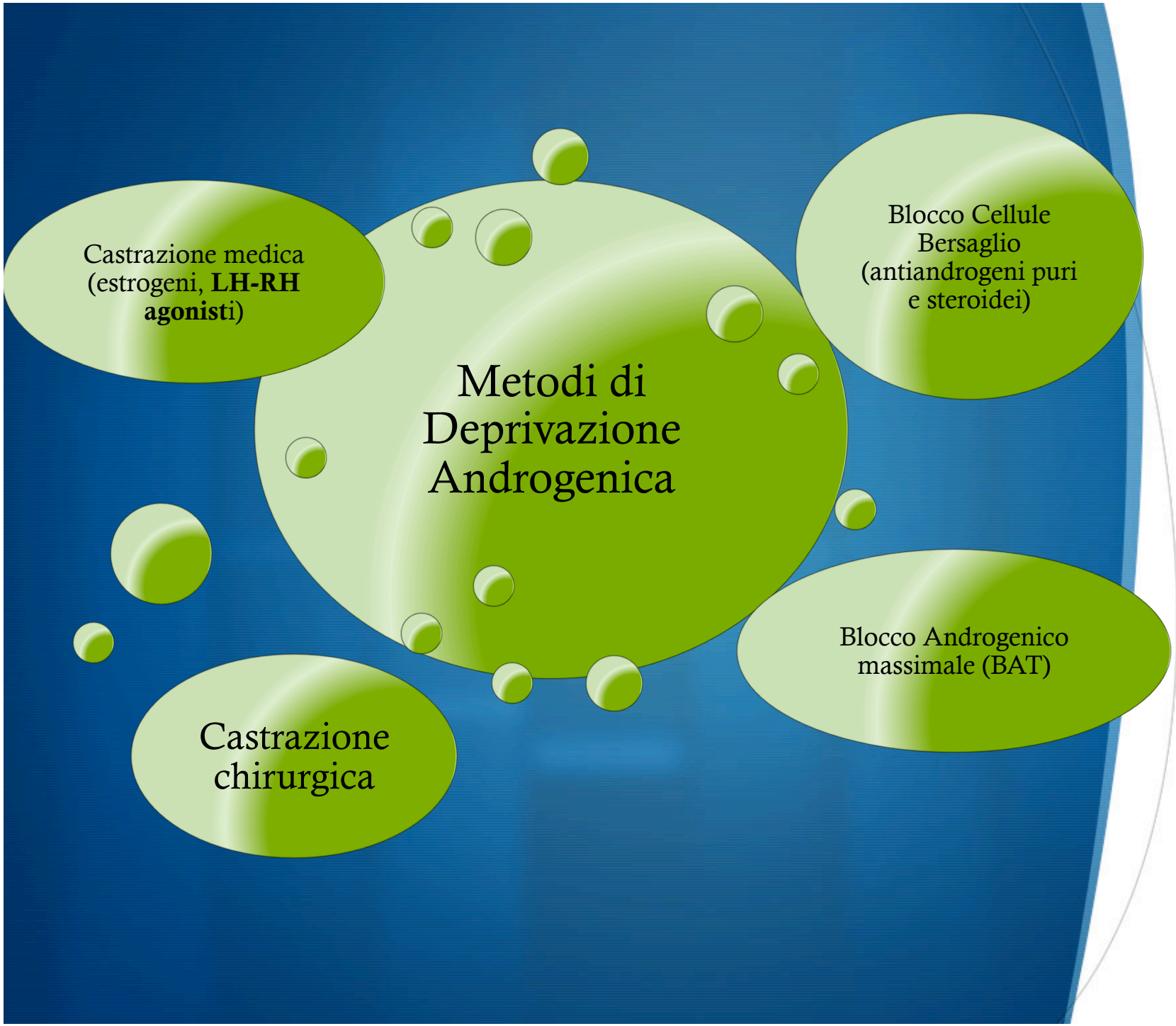
[2] Department of Radiation Oncology, Mayo Clinic, Rochester, MN, USA
[3] Department of Urology, Mayo Clinic, Rochester, MN, USA

All but two patients received some form of anti-androgen therapy after completing SBRT

completing SBRT. **Results:** Local control (LC) was 100%, and the PSA nadir was undetectable in nine patients (53%). The first post-SBRT PSA was lower than pre-treatment levels in 15 patients (88%), and continued to decline or remain undetectable in 12 patients (71%) at a median follow-up of 6 months (range, 2–24 months). Median PSA measurements before SBRT and at last follow-up were 2.1 ng/dl (range, 0.13–36.4) and 0.17 ng/dl (range, <0.1–140), respectively. Six (55%) of the 11 patients with HR PCa achieved either undetectable or declining PSA at a median follow-up of 4.8 months (range, 2.2–6.0 months). Reported toxicities included one case each of grade 2 dyspnea and back pain, there were no cases of grade ≥3 toxicity following treatment. **Conclusion:** We report excellent LC with SBRT in oligometastatic PCa. More importantly, over half the patients achieved an undetectable PSA after SBRT. Further follow-up is necessary to assess the long-term impact of SBRT on LC, toxicity, PSA response, and clinical outcomes.


Castrazione medica (estrogeni, **LH-RH agonist**i)
Metodi di Deprivazione Androgenica
Blocco Cellule Bersaglio (antiandrogeni puri e steroidei)
Blocco Androgenico massimale (BAT)
Castrazione chirurgica

INDICAZIONI ALLA TERAPIA ORMONALE

- Neoadiuvante pre RT o PR
- Adiuvante dopo RT o PR
- Carcinoma in stadio avanzato
- Ripresa di malattia dopo RT o PR

ANTIANDROGENI

Blocco Cellule Bersaglio

Antiandrogeni steroidei : ciproterone acetato, megestrolo, medrossiprogesterone

Antiandrogeni non steroidei:

Flutamide,
Bicalutamide,
Nilutamide

LH-RH ANALOGHI

- Goserelin
- Triptorelina
- Buserelin
- Leuprolide

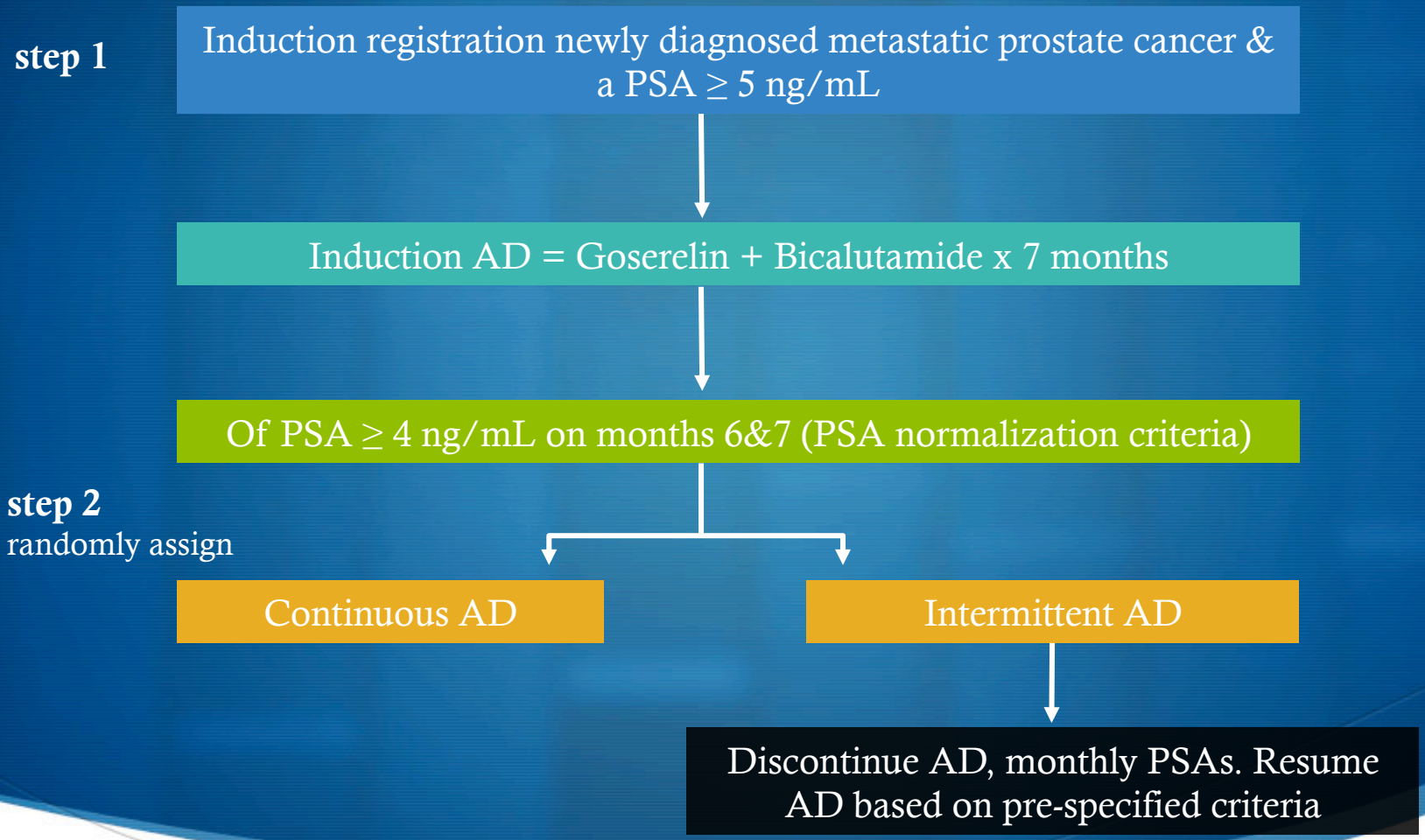
- Prostate cancer

Intermittent versus continuous androgen deprivation in hormone sensitive metastatic prostate cancer patients: Results of SWOG 9346 (INT.-6162) an International Phase III Trial

Hussain M, et al.

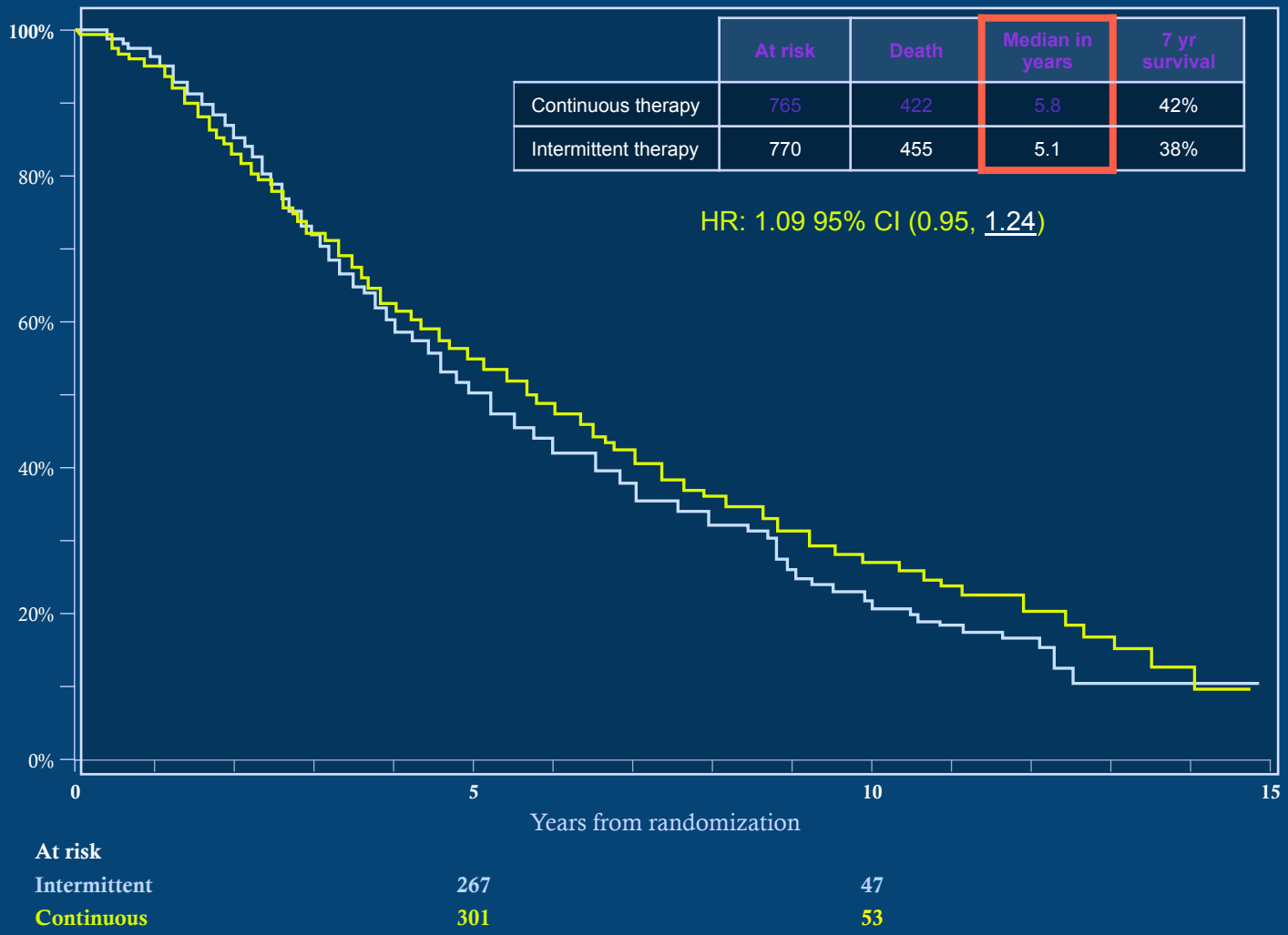
Hussain M et al. ASCO 2012, Abstract n. **4**

Study design



Hussain M et al. ASCO 2012, Abstract n. 4

Overall survival: Intermittent therapy is inferior compared to continuous therapy



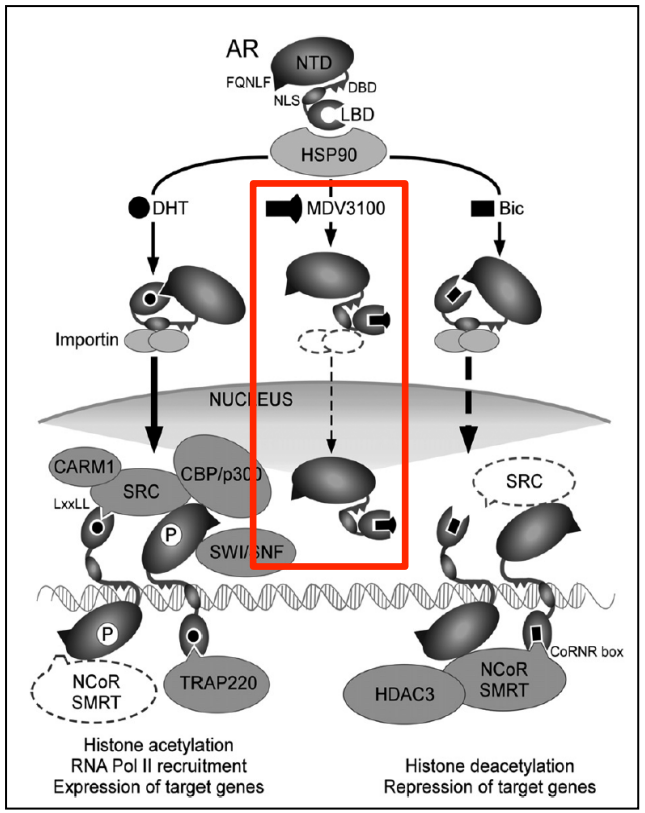
	At risk	Death	Median in years	7 yr survival
Continuous therapy	765	422	5.8	42%
Intermittent therapy	770	455	5.1	38%

HR: 1.09 95% CI (0.95, 1.24)

Hussain M et al. ASCO 2012, Abstract n. 4

NUOVE TERAPIE ORMONALI

MDV 3100

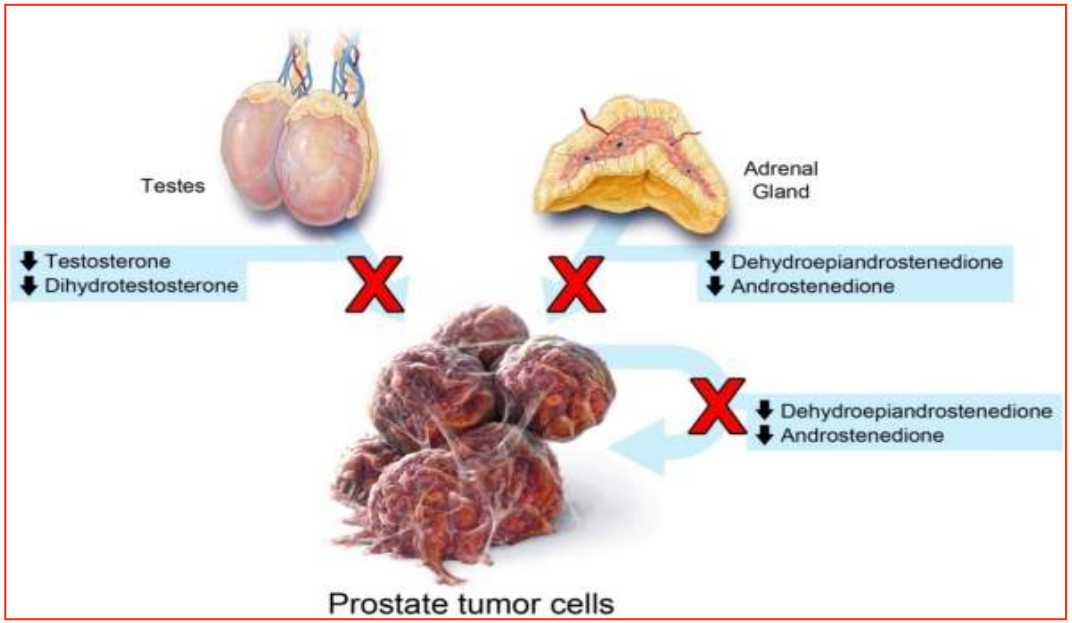


Adattata da Shen et al, Cancer Cell 2009

-ABIRATERONE: steroideo

-TAK-700 (Orteronel): non steroideo

Inibitori selettivi di 17-20 liasi -> inibizione della sintesi surrenalica, testicolare, prostatica di testosterone



Attard et al, JCO 2009

NUOVE TERAPIE ORMONALI, NUOVE INDICAZIONI

-Indicazione attuale: CaP metastatico, resistente alla castrazione, in progressione sierologica e strumentale dopo CT I linea con Docetaxel

-Studi clinici di fase III in atto:

-> CaP metastatico, resistente alla castrazione, con progressione sierologica e strumentale (prima di CT I linea)

-> CaP metastatico, androgeno-sensibile

-> CaP avanzato

Breast Cancer

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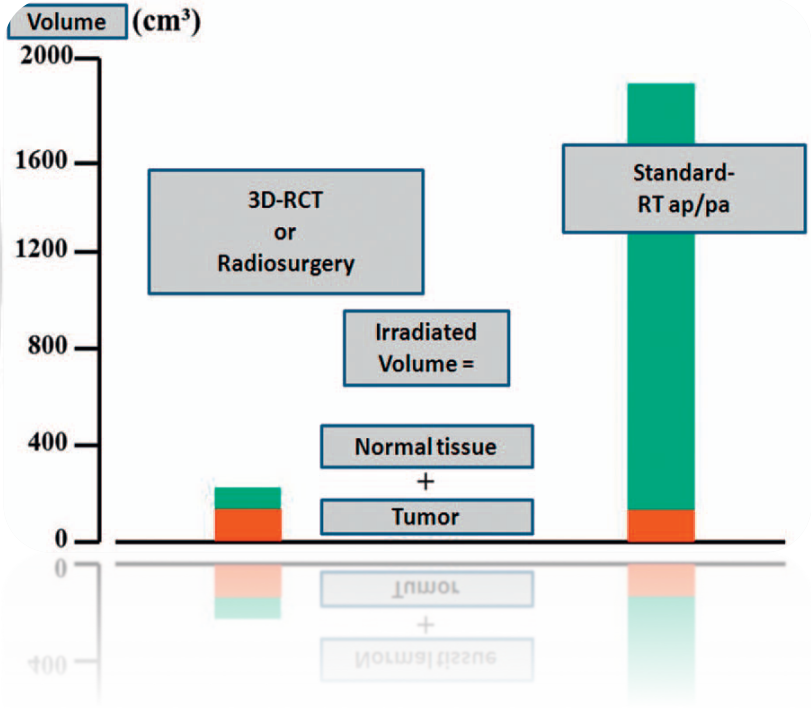

Breast Cancer Research and Treatment
June 2009, Volume 115, Issue 3, pp 601-608

Oligometastatic breast cancer treated with curative-intent stereotactic body radiation therapy

Michael T. Milano, Hong Zhang, Su K. Metcalfe, Ann G. Muhs, Paul Okunieff

Abstract

PURPOSE:

Prospective pilot study to assess patient outcome after stereotactic body radiation therapy (SBRT) for limited metastases from breast cancer.

METHODS:

Forty patients with < or =5 metastatic lesions received curative-intent SBRT, while 11 patients with >5 lesions, undergoing SBRT to < or =5 metastatic lesions, were treated with palliative-intent.

RESULTS:

Among those treated with curative-intent, 4-year actuarial outcomes were: overall survival of 59%, progression-free survival of 38% and lesion local control of 89%. On univariate analyses, 1 metastatic lesion (versus 2-5), smaller tumor volume, bone-only disease, and stable or regressing lesions prior to SBRT were associated with more favorable outcome. Patients treated with palliative-intent SBRT were spared morbidity and mortality from progression of treated lesions, though all developed further metastatic progression shortly (median 4 months) after enrollment.

CONCLUSIONS:

SBRT may yield prolonged survival and perhaps cure in select patients with limited metastases. Palliative-intent SBRT may be warranted for symptomatic or potentially symptomatic metastases.

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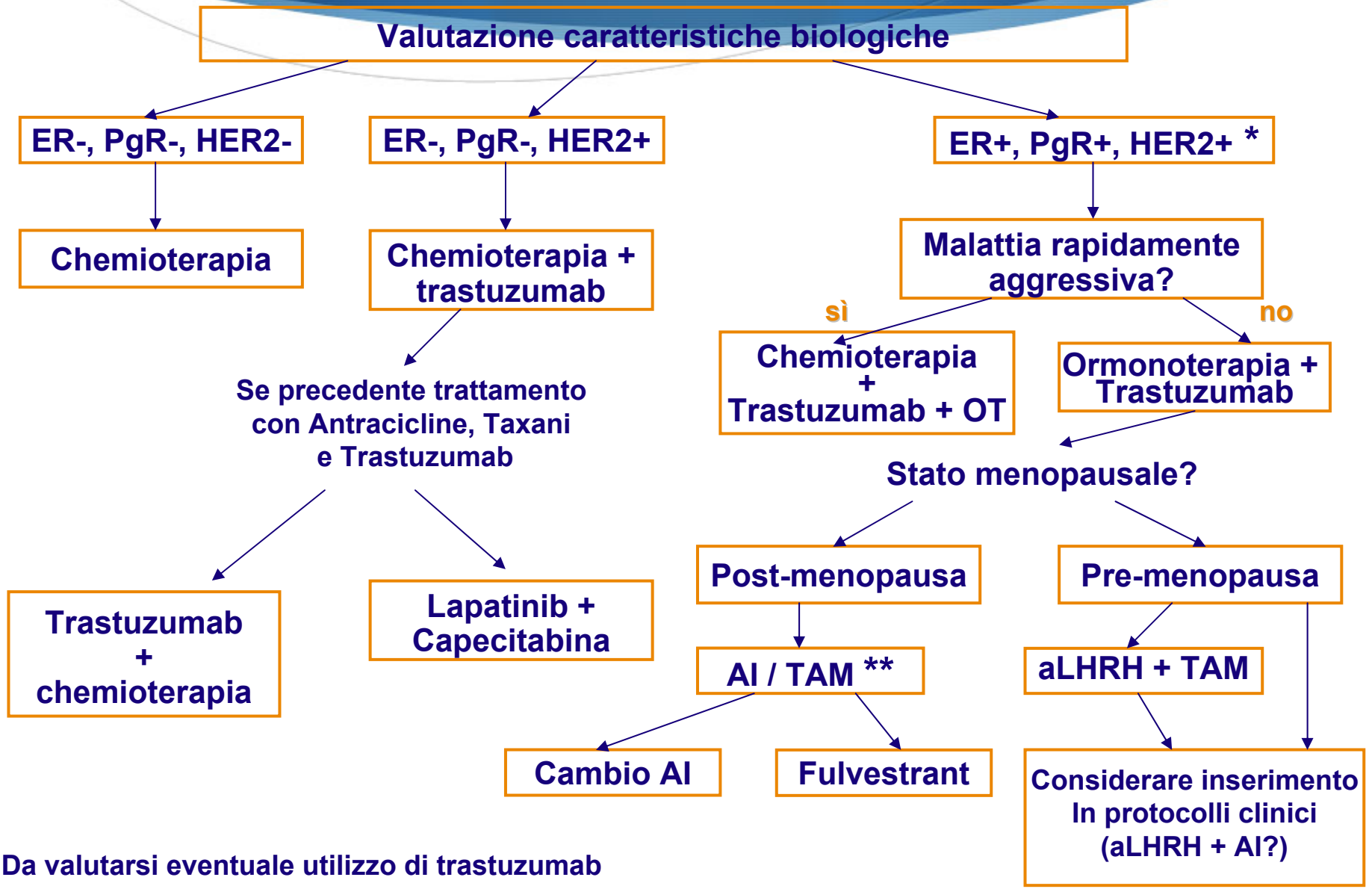
North European Radiooncological Center Kiel and University of Luebeck, Department of Radiotherapy, Germany

Combining Irradiation and Systemic Therapy

In patients with locally advanced breast cancer, best results are achieved by combining local radiation and systemic therapy [24, 32]. Although some in vitro experiments [32–34] demonstrated a decreased sensitivity to ionizing radiation after incubation of MCF-7 cell lines with tamoxifen, an antagonistic effect of ionizing radiation and treatment with tamoxifen has not been confirmed in animal studies [35, 36]. In contrast, several large randomized clinical studies [37] comparing adjuvant tamoxifen, radiation therapy and placebo, and combined radiation therapy and tamoxifen demonstrated best results [38]. Thus, the experimental endpoints of the in vitro studies may not have been relevant for the in vivo situation, and there is no clinical data for an adverse effect of combined tamoxifen and radiation. Instead, the clinical data argue for a synergistic effect.

TERAPIE SISTEMICHE

Breast Cancer



* Da valutarsi eventuale utilizzo di trastuzumab

** scelta sulla base della eventuale OT e delle comorbidità della pz

ORMONOTERAPIA

- **In tutte le pz ormonoresponsive (ER+, PgR+)**, con strategia diversificata in caso di:
  - **Pz pre-menopausa** → analogo LHRH e tamoxifene
  - **Pz post-menopausa** → tamoxifene, inibitori dell'aromatasi, fulvestrant

- L'ampia scelta di composti ormonali permette la pianificazione di una sequenza di tipologie endocrinoterapiche per le successive linee metastatiche

- Ormonoterapia per la fase avanzata

- Phase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer.
- First efficacy results from the LEA study

Martin M, et al.

Mod da: Martin M, et al. SABCS 2012, Abstract n. S1-7

Study design and treatment

Binational, multicentric, randomized open label phase III study

N=380 patients
unresecable locally advanced
or
metastatic breast cancer HR+/HER-

Stratification criteria
- Adjuvant AI (yes/no)
- N lesions (one/multiple)
- Measurable lesions (yes/no)
- Country (Spain/germany)

R

ET
Letrozole (2.5 mg/d) or fulvestrant 250 mg i.m. 1 q 28

Till disease progression

ET-B
Letrozole (2.5 mg/d) or fulvestrant 250 mg i.m. q 28 + bevacizumab (15 mg/kg q3w)

ET: Endocrine therapy; B: Bevacizumab

Mod da: Martin M, et al. SABCS 2012, Abstract n. **S1-7**

APPROCCIO MULTIDISCIPLINARE