

24-25 Marzo 2023

Ospedaletto di Pescantina (VR)
Centro Congressi Park Hotel Villa Quaranta

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Quali indicazioni per la radioterapia ablativa nel carcinoma mammario metastatico?

Prof Marta Scorsetti

Humanitas University
Humanitas Research Hospital

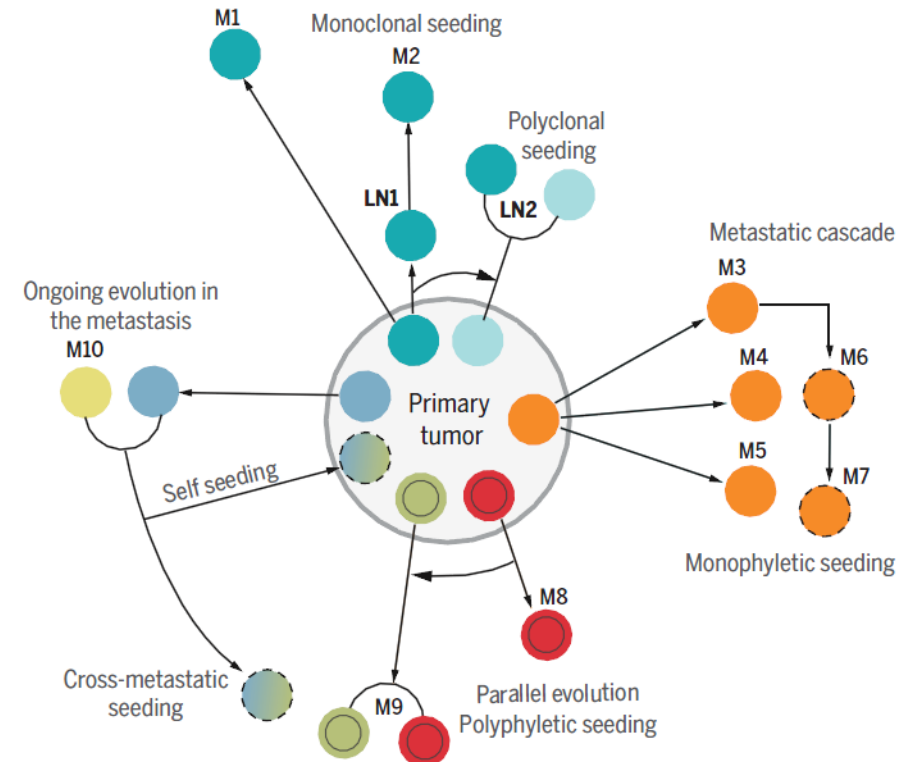
Background

REVIEW

Metastasis as an evolutionary process

Samra Turajlic^{1,2} and Charles Swanton^{1,3*}

**Very complex
reality**



Palma D, WCLC 2018

Oligometastasi: nulla di nuovo

ADENOCARCINOMA OF THE KIDNEY WITH METASTASIS TO THE LUNG

CURED BY NEPHRECTOMY AND LOBECTOMY¹

J. DELLINGER BARNEY AND EDWARD J. CHURCHILL

From the Surgical Services of the Massachusetts General Hospital

Adenocarcinoma of the kidney (hypernephroma) is a neoplasm that on occasion may be treated by removal of the primary growth and an apparently single metastasis. The following case history relates the course of a patient in whom x-ray evidence of a metastatic nodule in the lung was the first sign of disease. A nephrectomy was performed 5 months later, and 15 months following the nephrectomy the pulmonary metastasis was excised by sub-total lobectomy. The patient is surviving 5 years later in good health, without evidence of disease.

Case report. The patient was a white, single woman of 55. The family history was unimportant. Past history was irrelevant except that she spent some months in Greece in 1926, during which time, perhaps owing to excessive dust in the air, she developed a cough and lost about 15 pounds in weight.

Examination by Dr. Donald S. King in November 1931 showed definite dulness at the right apex with increased whispered voice and râles. The left kidney was palpable but was not thought to be enlarged or irregular in outline. The urine showed the slightest possible trace of albumin, but no pus, blood or casts. There was no sputum, nor in fact did it appear at any subsequent time while the patient was under observation.

- 55 year-old woman with primary renal adenocarcinoma and lung metastasis.
- Treated with nephrectomy, radiotherapy to the metastasis (800 rad in 11 fractions)
- Partial lobectomy after progression
- Patient ultimately died of other causes after 23 years.

Palma D. WCLC 2018

Barney Journal of Urology 1939

Oligometastasi: nulla di nuovo

SUMMARY

In the case reported two points are worthy of emphasis:

A lung metastasis from adenocarcinoma of the kidney was not radio-sensitive.

If a metastasis is apparently solitary and accessible to surgical removal, it is definitely worth while to undertake removal of the metastasis as well as the primary growth.

Palma D. WCLC 2018

Barney Journal of Urology 1939

Oligometastasi: definizione

EDITORIAL

Oligometastases

CANCER TREATMENT is based on an often unstated paradigm of disease pathogenesis. Since 1894, when W.S. Halsted^{1,2} clearly elucidated a mechanism of breast cancer spread and used it to design and support the radical mastectomy, surgical and radiotherapeutic approaches to most cancers have been based on this theory. The Halsted theory proposed that cancer spread is orderly, extending in a contiguous fashion from the primary tumor through the lymphatics to the lymph nodes and then to distant sites. Radical en bloc resection, as radical neck dissection in continuity with the primary tumor, radical hysterectomy with regional irradiation for a variety of gynecologic malignancies, and the use of regional irradiation based on this notion of cancer spread have been based on this notion of cancer spread. Another hypothesis has gained prominence in the past decade, suggested with regard to breast cancer.³⁻⁵ This hypothesis proposes that clinically apparent systemic disease. Small tumors are not a manifestation of such systemic disease. The ability of a tumor to metastasize, has already metastasized, or is about to metastasize, is not orderly contiguous extension, but rather a marker of distant disease. Systemic metastases are multiple and widespread, and when subclinical are referred to as micrometastases. Under these circumstances, treatment of local or regional disease should not affect survival.

more about the multistep nature of the development of malignancy.¹¹⁻¹³ Once tumors become invasive, they may gradually acquire the properties necessary for efficient and widespread metastatic spread.¹⁴ Therefore the likelihood, number, and even sites of metastases may reflect the state of tumor development. This suggests that there are tumor states intermediate between purely localized lesions and those widely metastatic. Such clinical circumstances are not accounted for by either the contiguous

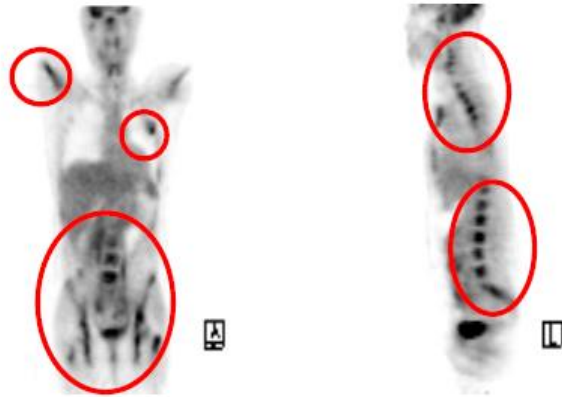
An oligometastatic state is an “intermediate state between purely localized lesions and those widely metastatic”. The state was expounded to be “amenable to a curative therapeutic strategy” and “amenable to localized therapy”.

or concentrate these metastases to a single or a limited number of organs. The likelihood of the oligometastatic state should correlate with the biology of tumor progression, rough clinical surrogates of which, for many tumors, might be primary tumor size and grade. Metastasizing cells may seed specific organs as a function of the seeding

Hellman S, Weichselbaum RR. JCO 1995

Oligometastasi: definizione

Widely Metastatic Disease



Limited Metastatic Disease



- Distinct clinical state
- Metastases limited in number/destination organ (3 to 5 in 1-3 sites)
- More indolent biology earlier in the metastatic cascade
- Amenable to local ablative approaches

Oligometastasi: classificazione

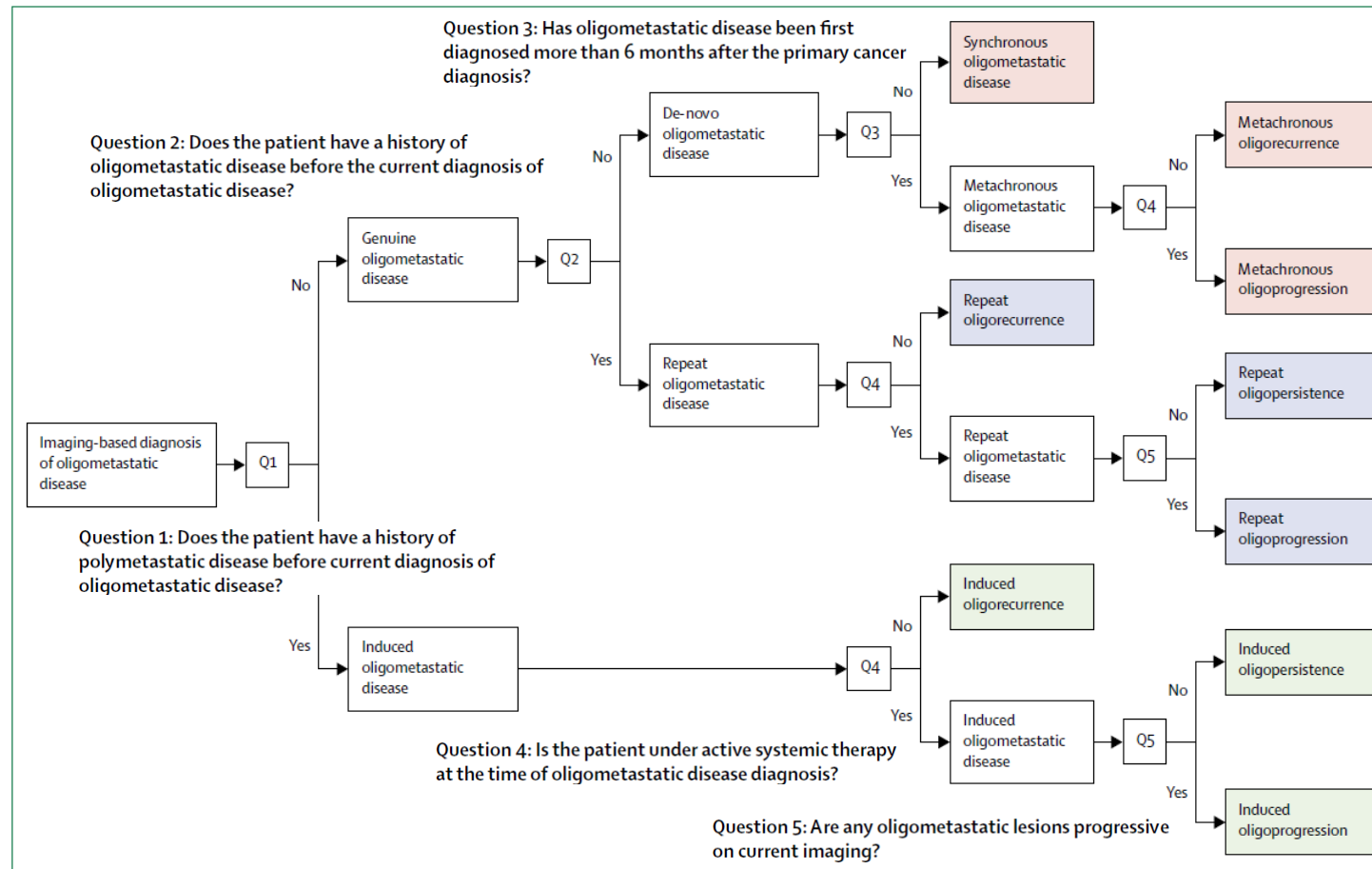
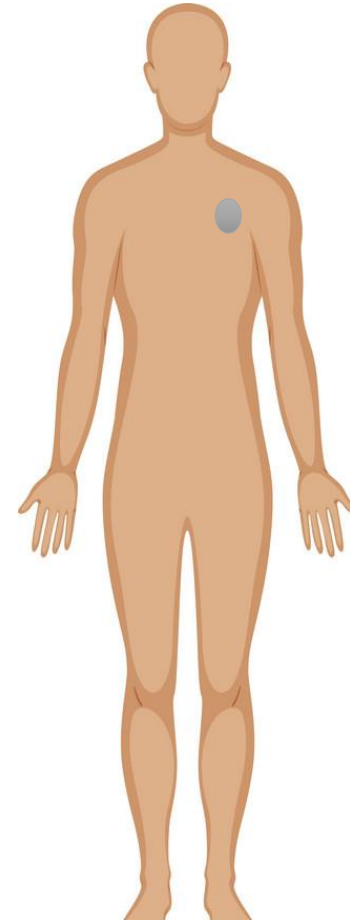


Figure 3: Decision tree for classification of oligometastatic disease

Oligometastasi: classificazione

Solitary metastases:

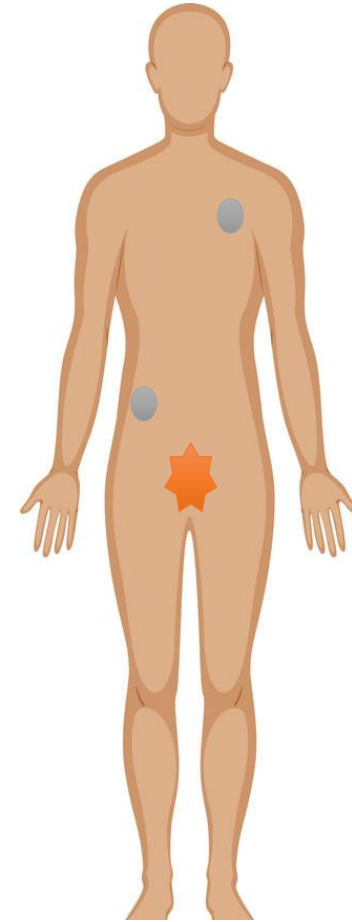
single and isolated metastasis



Oligometastasi: classificazione

Oligometastases de novo:

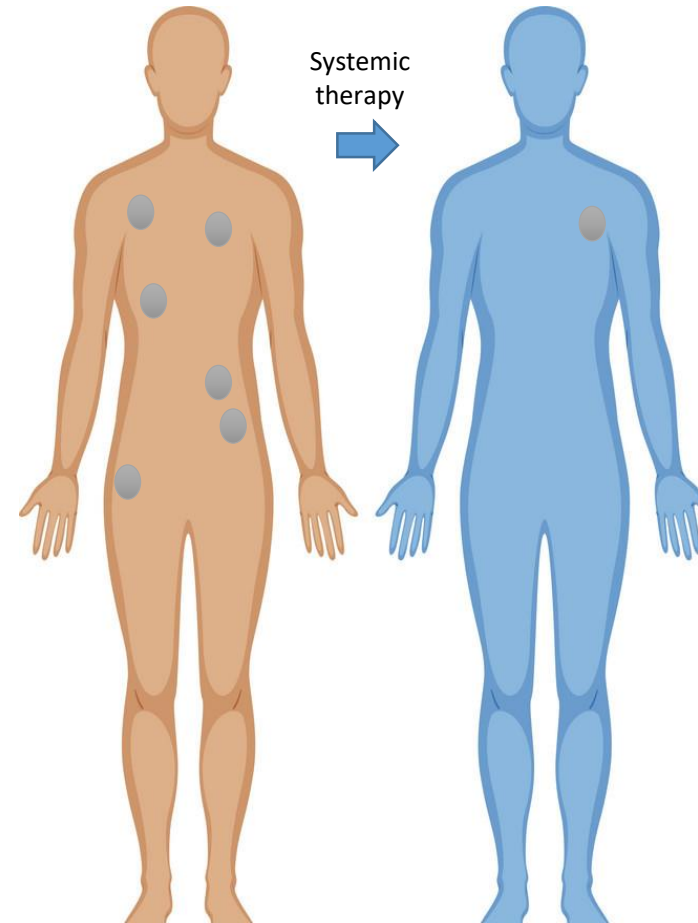
refers to presentation with a limited number of lesions at initial diagnosis



Oligometastasi: classificazione

Induced oligometastases:

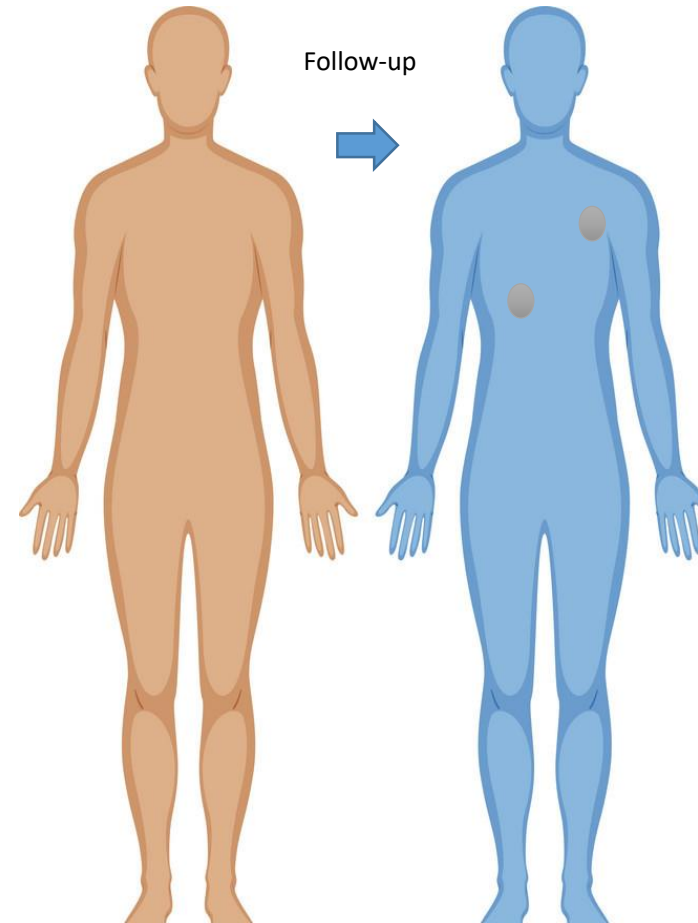
widespread metastases eradicated by systemic therapy that leaves few isolated metastases



Oligometastasi: classificazione

Oligorecurrence:

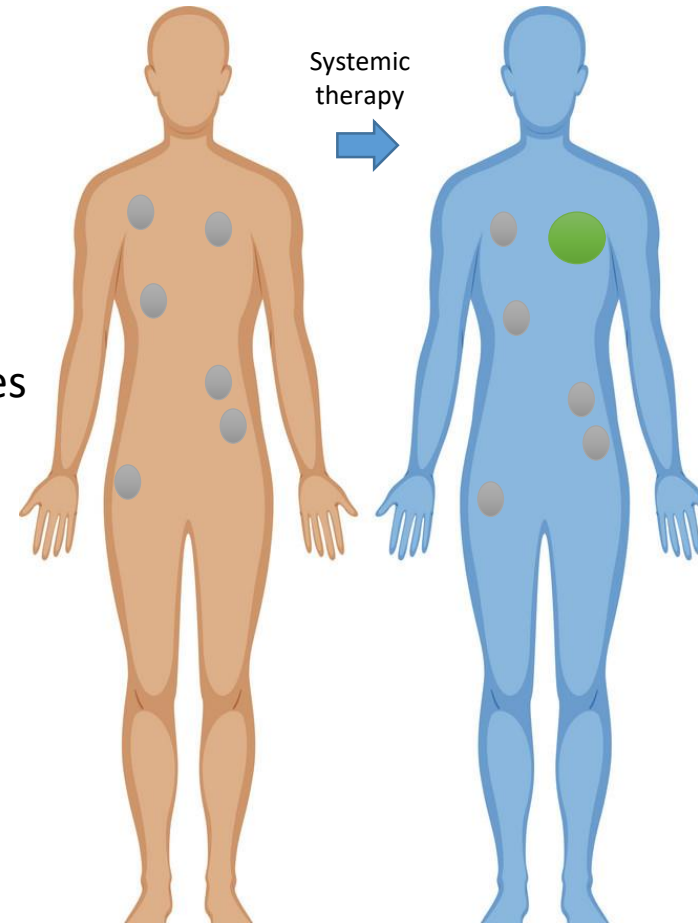
is the metachronous development of new metastases after definitive treatment of primary tumour



Oligometastasi: classificazione

Oligoprogression:

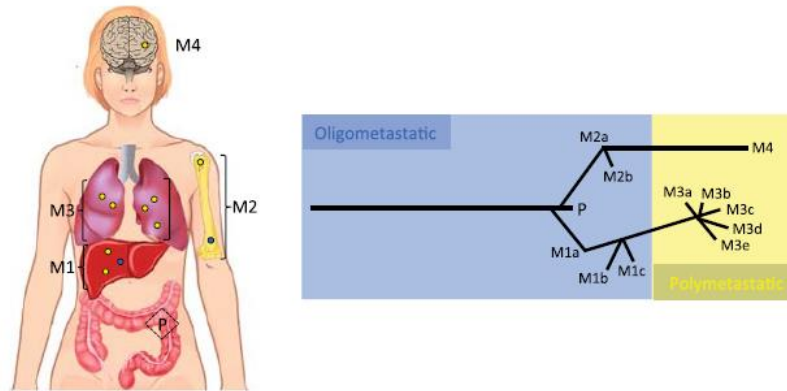
contradictory progression of a few sites of disease despite an overall tumor burden response to systemic therapy



Oligometastasi: rationale per un trattamento locale

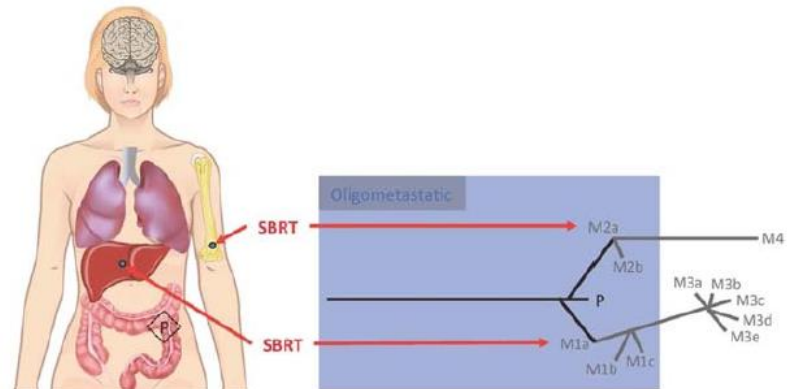
Stereotactic Body Radiotherapy for Oligometastasis *Opportunities for Biology to Guide Clinical Management*

Linear Progression Model of Metastasis Evolution (with Metastatic Cascades):



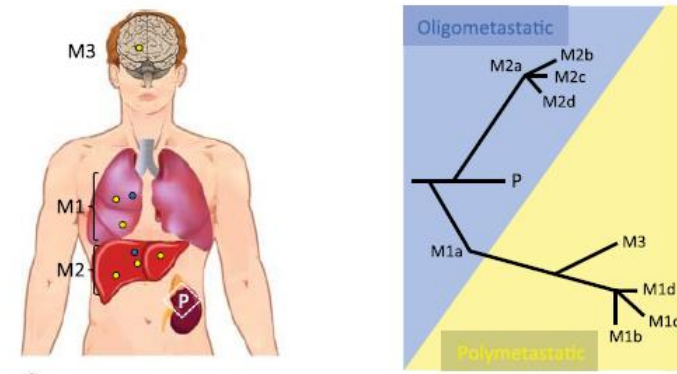
A

Potential Effect of Ablative Therapy:



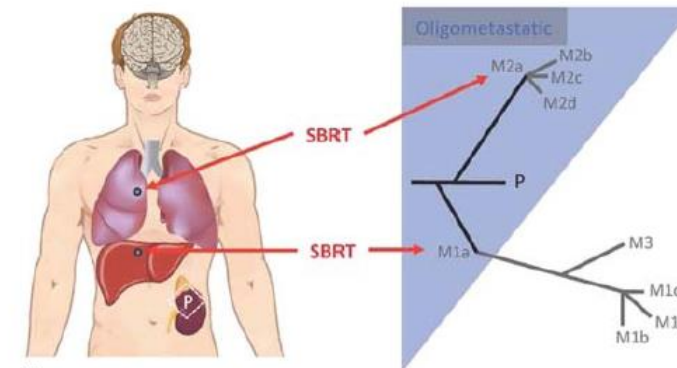
B

Parallel Progression Model of Metastasis Evolution (with Metastatic Cascades):



A

Potential Effect of Ablative Therapy:



B

Oligometastasi: razionale per un trattamento locale

- Aumentare il **controllo locale** per **prevenire sintomi** e mantenere la qualità di vita
- Eliminare tutte le sedi metastatiche visibili per **prolungare la PFS**
- Ridurre il carico di malattia tumorale per **aumentare la OS**
- Eliminare i cloni resistenti per **prolungare l'efficacia delle terapie sistemiche**
- **Ritardare una ulteriore progressione** per ritardare la necessità di iniziare una nuova terapia sistemica
- Avere un **effetto sinergico** con le terapia sistemiche per migliorarne i risultati

Trattamenti locali ablativi: chirurgia

The Rise in Metastasectomy Across Cancer Types Over the Past Decade

Historically, the **role of surgery in patients with metastatic cancer** was predominately limited to **palliative or emergent operations**.

By the 1980s, a few centers were consistently performing **surgical resections for select patients** with metastatic cancer and reporting **promising results**. In addition, theories of cancer biology began to suggest that **in a subset of patients, oligometastatic disease might indeed represent the entire clinically relevant disease burden**.

In these cases, **complete resection was associated with prolonged disease-free survival and**, in some patients, **clinical cure**. As a result, in selected patients surgical resection is now considered for the treatment of oligometastatic disease to most anatomic sites from many different primary cancer types

Trattamenti locali ablativi: chirurgia

Of the 5 most common cancer types, **colorectal cancer** has been the subject of the largest number of studies of metastasectomy with demonstrated **5-year survival rates of >50%, and 10-year survival ranging from 17% to 36%.**

The role of metastasectomy in **other cancer types remains more controversial.** Multiple metastasectomy series have now been published for **breast cancer, lung cancer, and melanoma**, all of which with relatively favorable survival in carefully selected patients, but the series are smaller and less frequently report long-term follow-up.

TABLE 1. National Estimates of Admissions for Metastasectomy by Cancer Type, 2000 Through 2011

	Colorectal Cancer		Lung Cancer		Breast Cancer		Melanoma	
	No.	95% CI	No.	95% CI	No.	95% CI	No.	95% CI
All admissions	87,407	(86,307-88,507)	58,245	(57,453-59,036)	26,271	(25,672-26,870)	20,298	(19,897-20,699)
Mean age (SE), y	62.2	0.10	61.4	0.10	56.8	0.17	58.1	0.22
Female sex	46.0%	(45.3%-46.8%)	45.8%	(44.9%-46.7%)	99.4%	(99.2%-99.6%)	33.6%	(32.2%-35.1%)
Liver metastasectomy	41,312	(40,500-42,125)	503	(405-601)	1663	(1486-1839)	550	(448-652)
Lung metastasectomy	19,590	(18,994-20,185)	NA ^a	NA ^a	6609	(6266-6951)	5839	(5534-6144)
Brain metastasectomy	5588	(5263-5912)	52,944	(52,167-53,720)	16,091	(15,591-16,590)	11,094	(10,718-11,471)
Small bowel metastasectomy	20,916	(20,303-21,529)	2762	(2535-2988)	1724	(1544-1905)	2440	(2233-2646)
Adrenal metastasectomy	599	(493-705)	2067	(1870-2264)	230	(165-295)	471	(377-566)
Mean no. of Elixhauser comorbidities	1.98	(1.96-2.00)	2.72	(2.69-2.75)	1.87	(1.83-1.91)	1.84	(1.80-1.88)
Inpatient mortality rate	2.13%	(1.91%-2.34%)	3.18%	(2.86%-3.51%)	1.91%	(1.54%-2.28%)	1.65%	(1.26%-2.04%)

Trattamenti locali ablativi

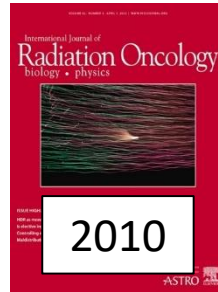
La metastasectomia aumenta il controllo locale e la sopravvivenza di pazienti selezionati, ma...



La maggior parte dei pazienti sono inoperabili per comorbidità o sede delle metastasi



Radioterapia stereotassica



AMERICAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY (ASTRO) AND AMERICAN COLLEGE OF RADIOLOGY (ACR) PRACTICE GUIDELINE FOR THE PERFORMANCE OF STEREOTACTIC BODY RADIATION THERAPY

LOUIS POTTERS, M.D.,* BRIAN KAVANAGH, M.D.,[†] JAMES M. GALVIN, D.Sc.,[‡] JAMES M. HEVEZI, Ph.D.,[§]
NORA A. JANJAN, M.D.,[¶] DAVID A. LARSON, M.D., Ph.D.,** MINESH P. MEHTA, M.D.,^{††}
SAMUEL RYU, M.D.,^{‡‡} MICHAEL STEINBERG, M.D.,^{§§} ROBERT TIMMERMAN, M.D.,^{¶¶}
JAMES S. WELSH, M.D.,*** AND SETH A. ROSENTHAL, M.D.^{†††}

Stereotactic body radiation therapy (SBRT) is an external beam radiation therapy method used to very precisely deliver a **high dose of radiation** to an extracranial target within the body, using either a **single dose or a small number of fractions**.

The ability to deliver a **single or a few fractions of high-dose ionizing radiation** with **high targeting accuracy** and rapid dose falloff gradients encompassing tumors within a patient provides the basis for the development of SBRT.

Radioterapia stereotassica

Gli obiettivi sono:

- Riduzione dei margini:
 - Riduzione del volume di tessuto sano irradiato
 - **Ridurre la tossicità**
- Aumento della dose per frazione:
 - Erogare dosi ablative
 - **Aumentare l'efficacia**



Radioterapia stereotassica

● SBRT PRO

- Non invasiva
- Bassa tossicità
- Fattibili in quasi tutti i pazienti e in tutti i distretti corporei
- Possibilità di trattare multiple lesioni simultaneamente
- Possibilità di essere erogata in concomitanza con la maggior parte delle terapie sistemiche

● SBRT CONS

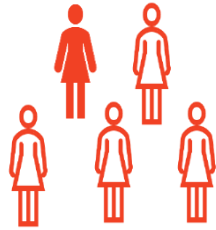
- Mancanza di una conferma istologica
- Mancanza di tessuto per ulteriori analisi



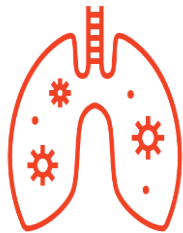
E nella patologia mammaria?



Oligometastasi nel tumore mammario

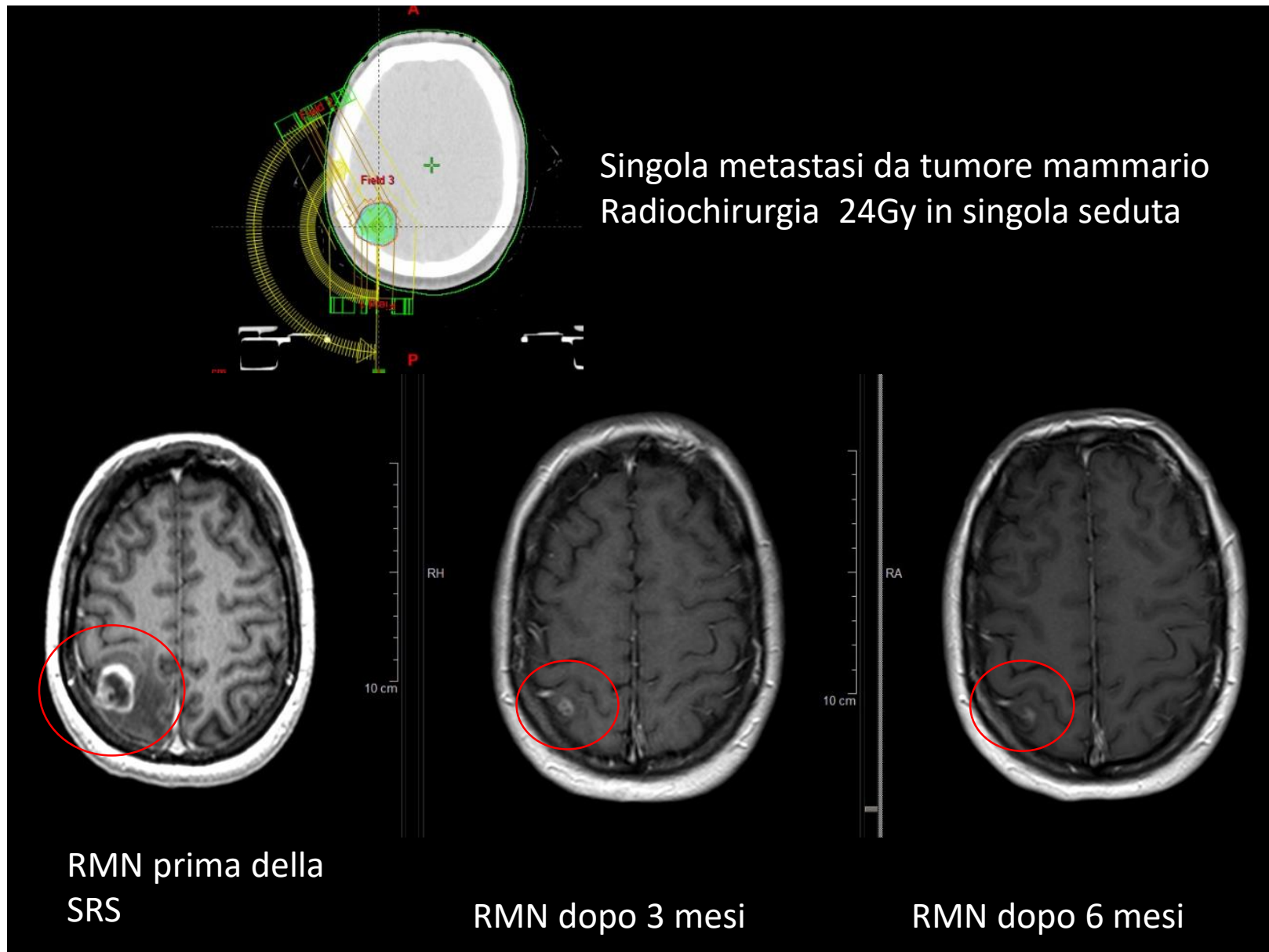


- 5-10% delle pazienti si presenta con **metastasi all'esordio** di malattia
- 20% delle pazienti con malattia localizzata **svilupperà metastasi a distanza** nei 5 anni dopo la diagnosi



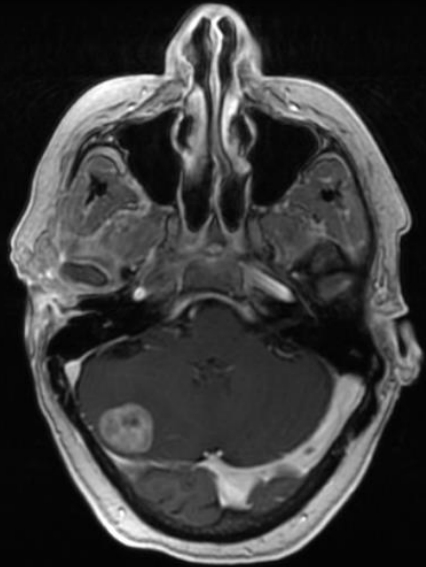
- La malattia tende a recidivare nelle sedi dove si era già localizzata precedentemente
- Le **oligometastasi** nel tumore mammario sono circa il **20% della casistica**

Casi clinici: metastasi encefaliche



Casi clinici: metastasi encefaliche

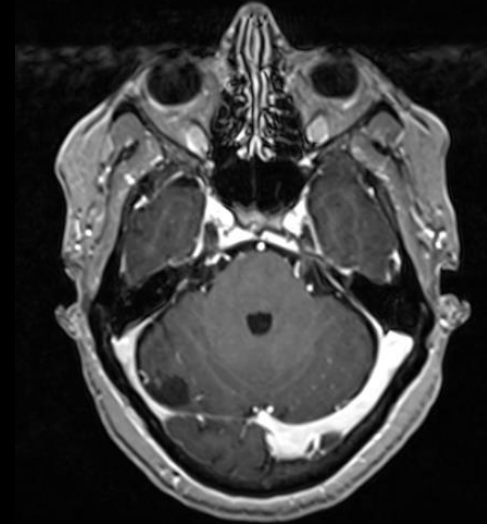
Metastasi da neoplasia mammaria
trattata con radiochirurgia



RMN prima della
SRS



SRS in singola seduta

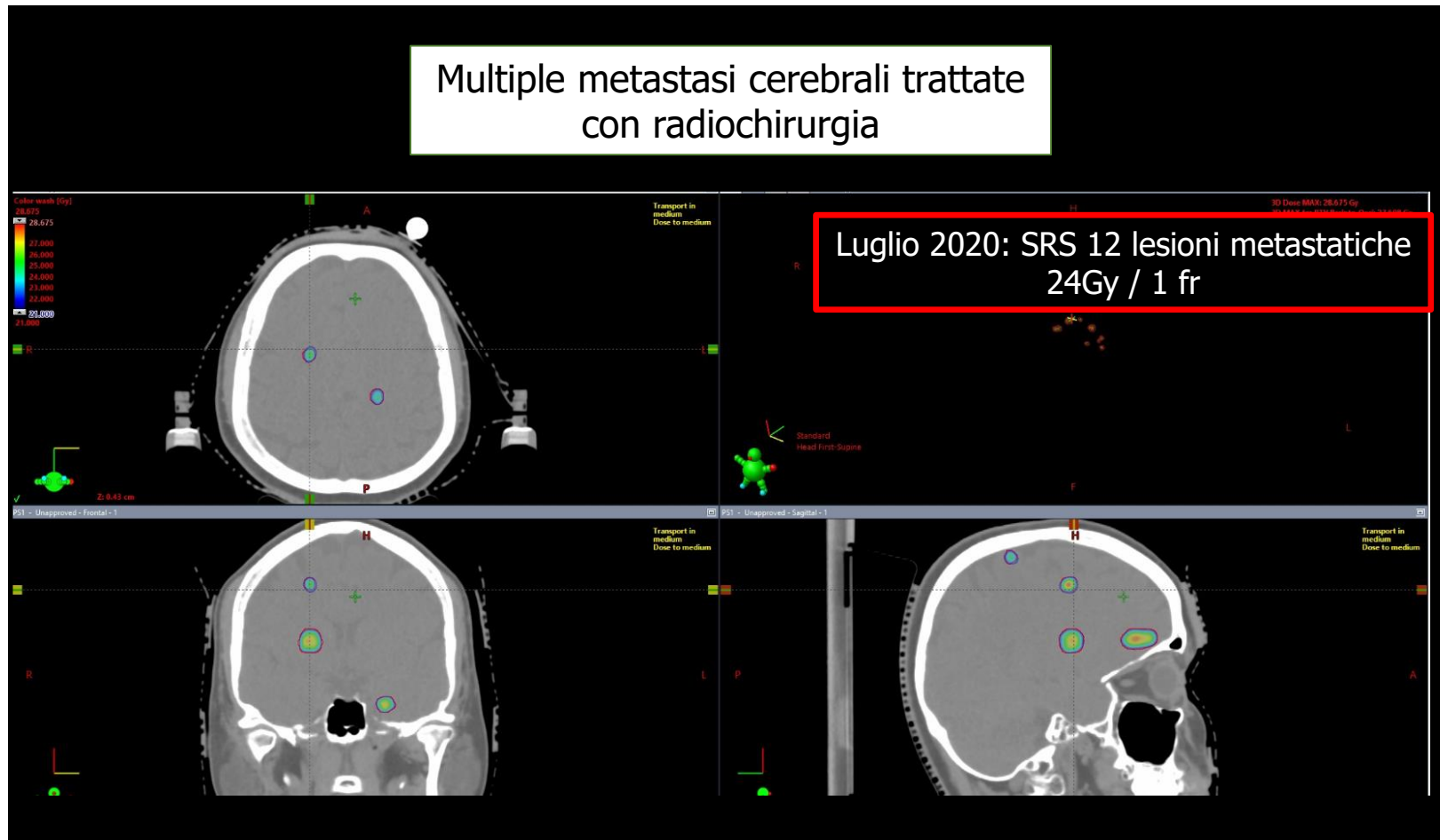


RMN dopo 6 mesi

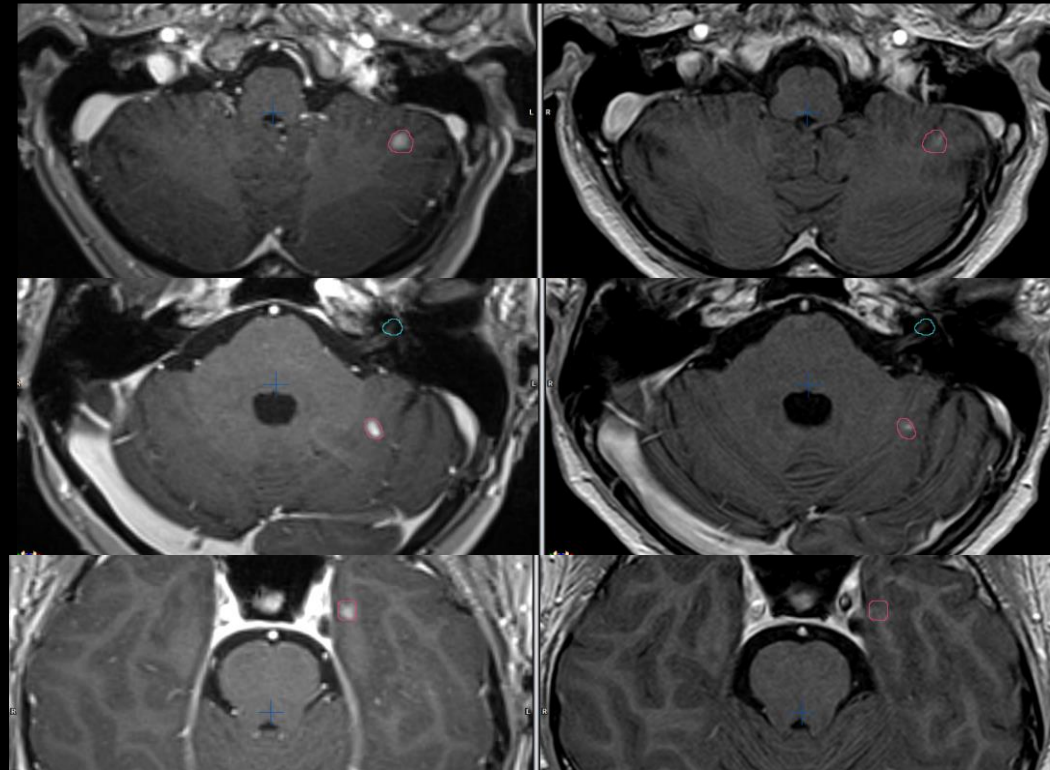
Casi clinici: metastasi encefaliche

Multiple metastasi cerebrali trattate
con radiochirurgia

Luglio 2020: SRS 12 lesioni metastatiche
24Gy / 1 fr



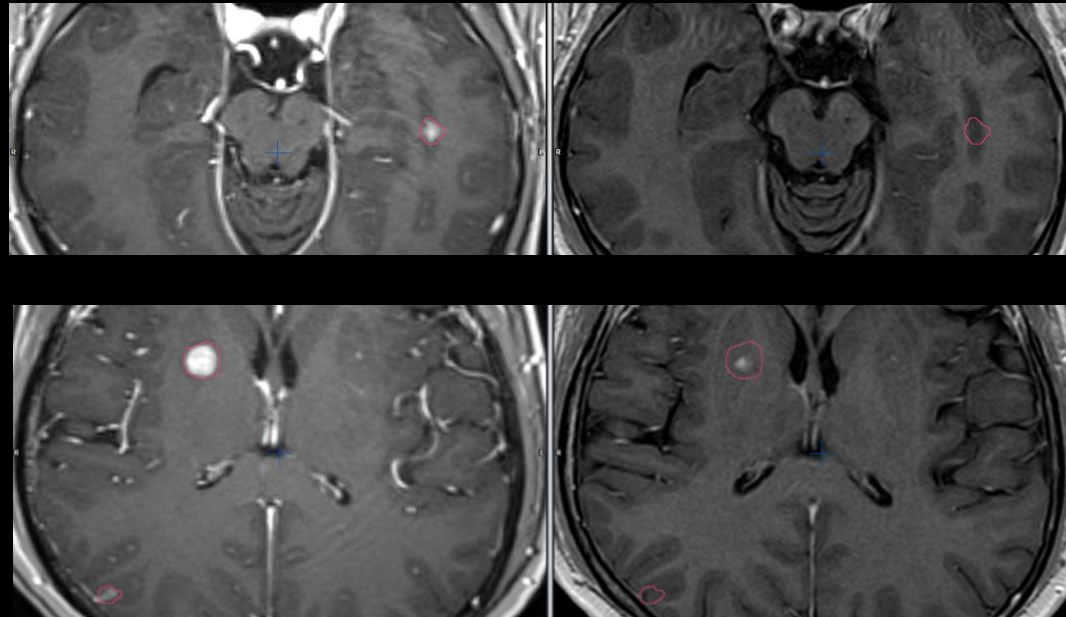
Casi clinici: metastasi encefaliche



RMN prima della SRS

RMN dopo 1 anno

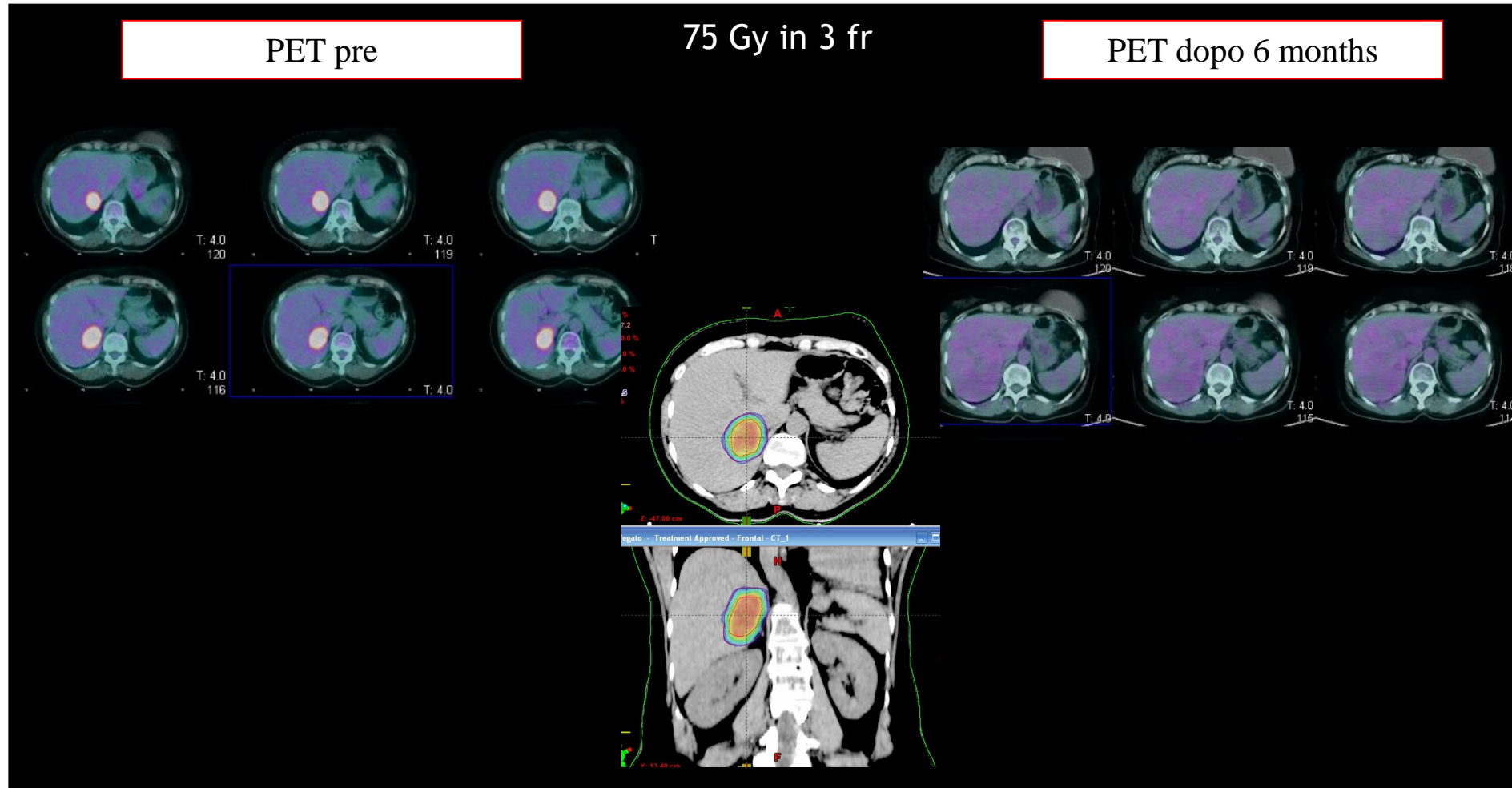
Casi clinici: metastasi encefaliche



RMN prima della SRS

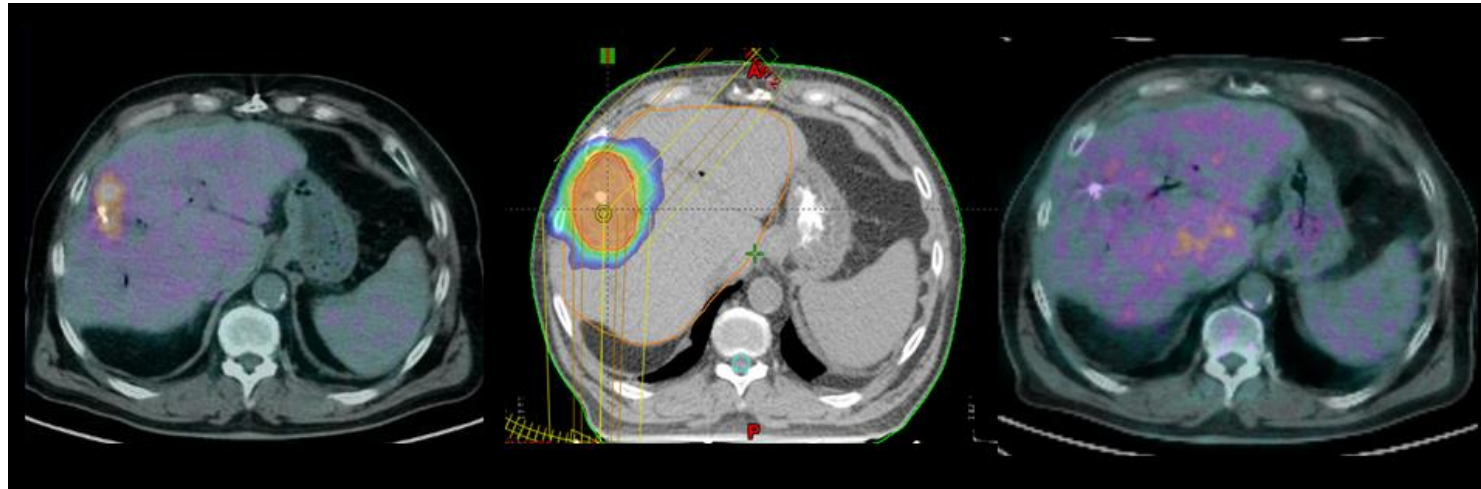
RMN dopo 1 anno

Casi clinici: metastasi epatiche



Casi clinici: metastasi epatiche

Metastasi epatica singola da tumore mammario operato trattata con SBRT



PET – CT pre-trattamento

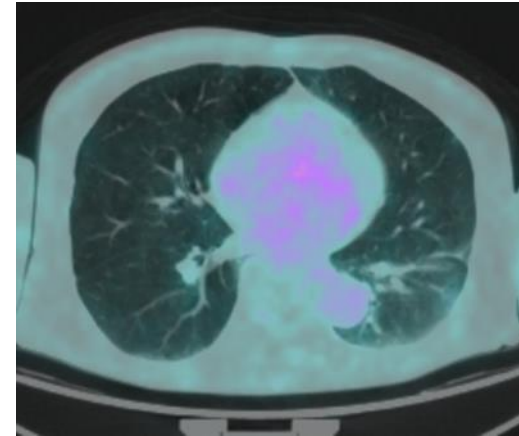
PET – CT post-trattamento

Casi clinici: metastasi polmonari

Metastasi polmonare singola
da neoplasia mammaria
operata
48Gy/4 fr



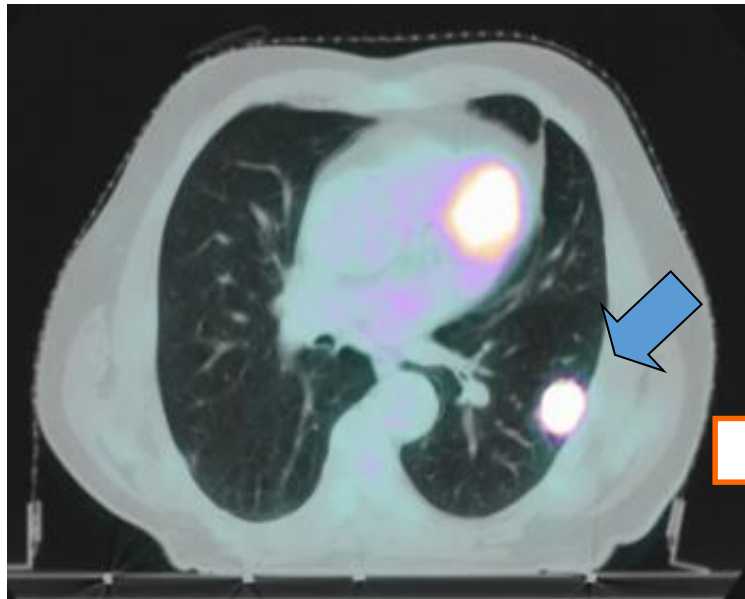
Pre-RT PET/CT



Post-RT PET/CT
Risposta completa dopo 6
mesi

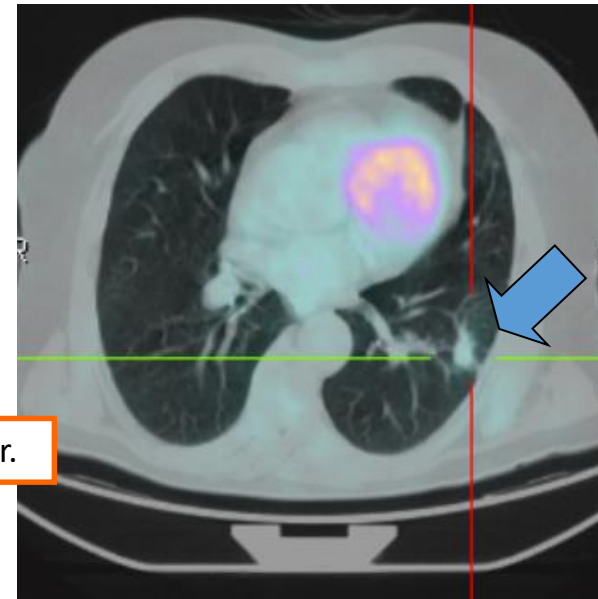
Casi clinici: metastasi polmonari

Paziente trattata con SBRT su metastasi polmonare da neoplasia mammaria



PET/CT prima della SBRT

48Gy/4 fr.



PET/CT: risposta completa 6 mesi dopo la SBRT

Direzioni future

Easily accessible



Difficult
availability

Selection of patients

- Clinical
- Imaging
- Genetic/epigenetic

Less informative



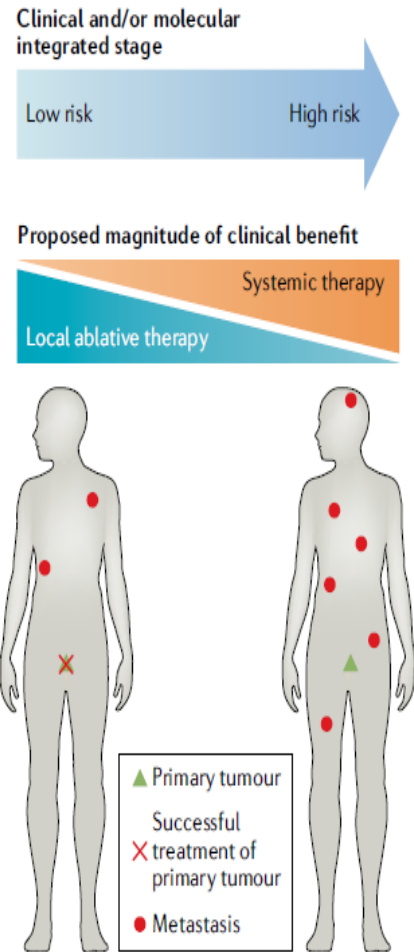
Highly
informative

ESTRO & EORTC initiative:
OligoCare

**A Pragmatic Observational Basket
Study to Evaluate Radical Radiotherapy
for Oligo-Metastatic Cancer Patients**



Medicina personalizzata



Box 1 | Characteristics of indolent clinical metastases

Clinical

- Low number (typically 1–5 lesions)
- Metachronous presentation
- No involvement of lymph nodes
- Slow rate of progression (typically <0.6 new lesions per year)
- Limited organ sites (typically 1–2 sites)
- Favourable histology (including, but not limited to, breast, prostate and kidney)

Biological

- Activation of innate and adaptive immunity
- Absence of mesenchymal features
- Low degree of tumour aneuploidy
- Low degree of intratumoural heterogeneity
- Intact 14q chromosomal arm
- Expression of microRNAs that suppress genes associated with metastasis

Treatment

Local ablative interventions (with stereotactic body radiotherapy, radiofrequency ablation or surgery) tend to be more beneficial for these patients than systemic therapy

Take Home Message

- *La patologia oligometastatica mammaria* esiste, anche se per ora è poco studiata e poco rappresentata negli studi clinici
- *La radioterapia* rappresenta il trattamento ideale per le oligometastasi grazie all'alta efficacia e bassa tossicità
- *Studi clinici* focalizzati sulle oligometastasi da mammella sono necessari e auspicabili per permettere una migliore comprensione della biologia tumorale
- *L'identificazione e la selezione dei pazienti* sono cruciali nella neoplasia mammaria, data la sua eterogeneità. La ricerca traslazionale è necessaria
- *Differenti tipi* di patologia oligometastatica potrebbero richiedere lo stesso trattamento ma con *obiettivi diversi*, consideriamo anche endpoint innovativi

Consideriamo la SBRT come un'altra "linea di terapia" nell'armamentario per il trattamento della neoplasia mammaria metastatica.

Grazie per l'attenzione

