

**Incontri oncologici Triveneto X Incontro Metastasi Cerebrali da Carcinoma
Mammario HER2-positivo Negrar, 7 Ottobre 2014**

RUOLO DELLA RADIOTERAPIA STEREOTASSICA /RADIOCHIRURGIA

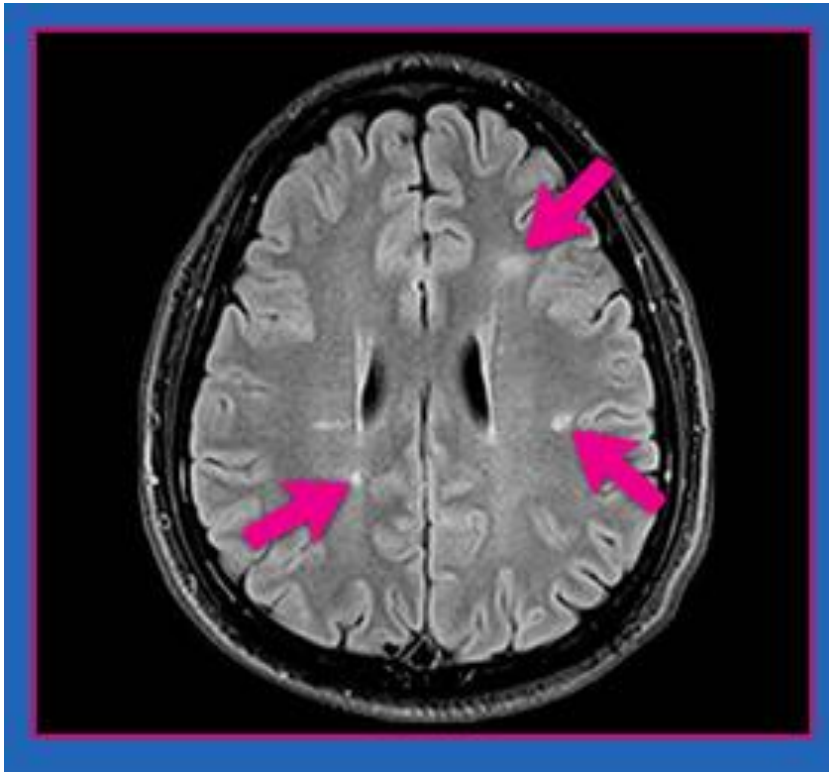
Filippo Alongi
Direttore UOC Radioterapia Oncologica



Ospedale
Sacro Cuore - Don Calabria
Negrar (Verona)



BRAIN METASTASIS IN BREAST CANCER PATIENTS: INTRODUCTION



- **Relapses in the CNS are common (>50%)** and represent a barrier to cure patients with breast cancer.

- Less than 20 % of patients survived 1 year.

- A further **increase in incidence of BM** is seen in breast cancers patients with:
 - estrogen receptor (ER) negative**
 - HER2 positive.**



BRAIN METASTASIS IN BREAST CANCER PATIENTS: PROGNOSTIC FACTORS

Table 1 Median survival duration according to RPA class for patient treated with WBRT

RPA class	Clinical characteristics	All tumors BM MS in m [32]	Breast BM MS in m [31]
1	KPS ≥ 70 and age < 65 and controlled primary tumor and no extra cranial metastases	7.1	15
2	KPS ≥ 70 and age ≥ 65 or uncontrolled primary tumor or extra cranial metastases	4.2	11
3	KPS < 70	2.3	3

MS median survival, *m* months, *KPS* Karnofsky performance status, *BM* brain metastases, *WBRT* whole-brain radiotherapy

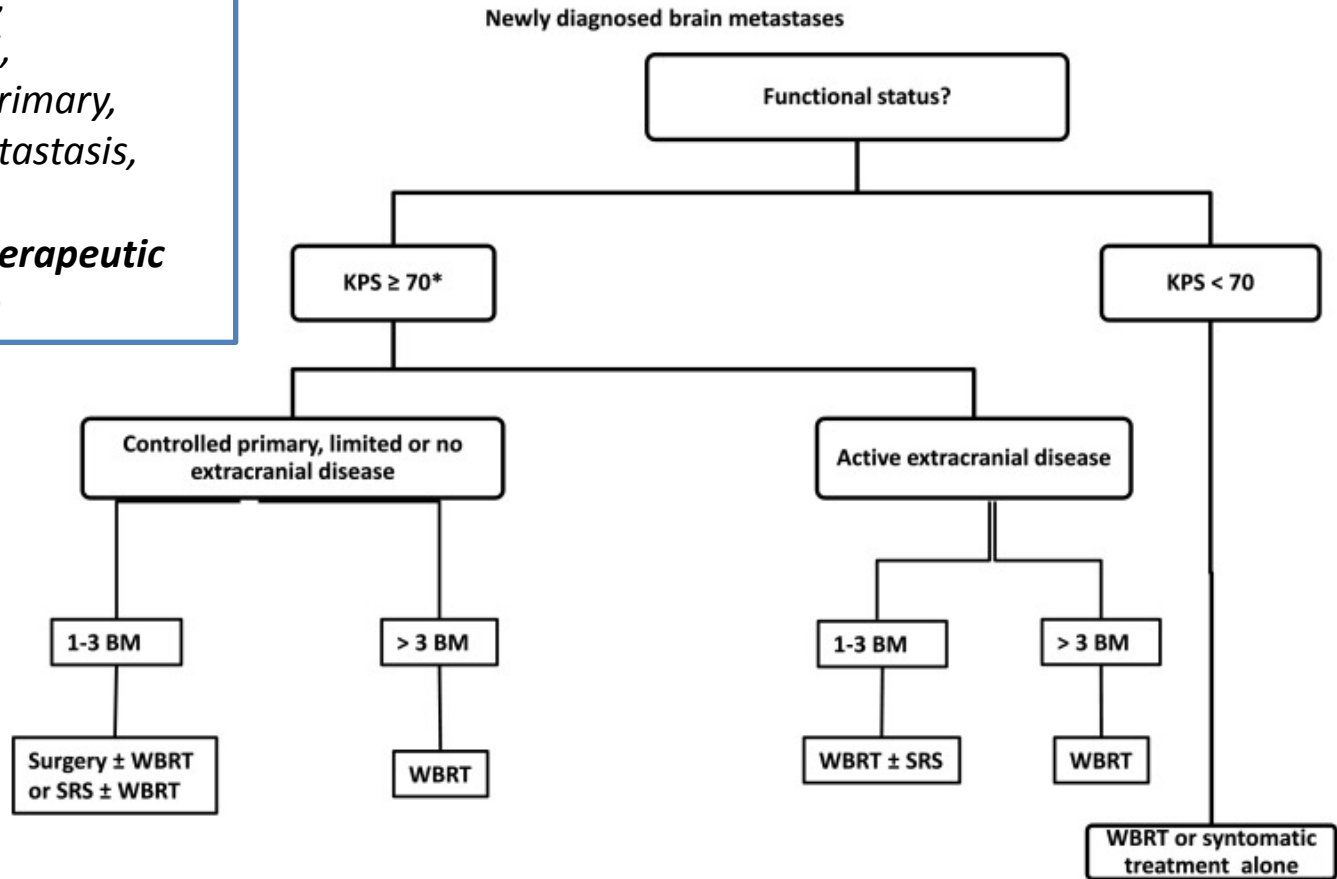
- *KPS* < 70 ,
 - *age* > 65 ,
 - *uncontrolled Primary*,
 - *extracranial metastasis*,
- are “**prognostic factors**”
and...



BRAIN METASTASIS IN BREAST CANCER PATIENTS: Therapeutic ALGORITHM

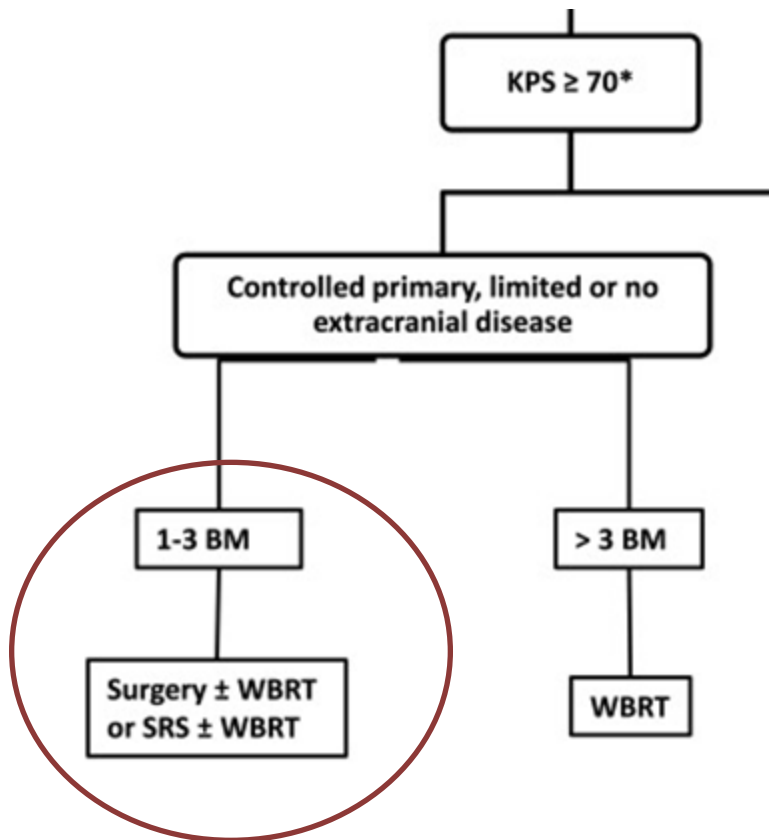
• *KPS < 70,*
• *age > 65,*
• *uncontrolled Primary,*
• *extracranial metastasis,*

...influence the therapeutic algorithm





BRAIN METASTASIS IN BREAST CANCER PATIENTS: LOCAL TREATMENT FOR SINGLE/FEW MTS



Case of best prognostic factors:

- Surgery?
 - SRS?
 - Adding WBRT?
- ...No consensus!!!***



BRAIN METASTASIS IN BREAST CANCER PATIENTS: Surgery(plus WBRT) vs WBRT



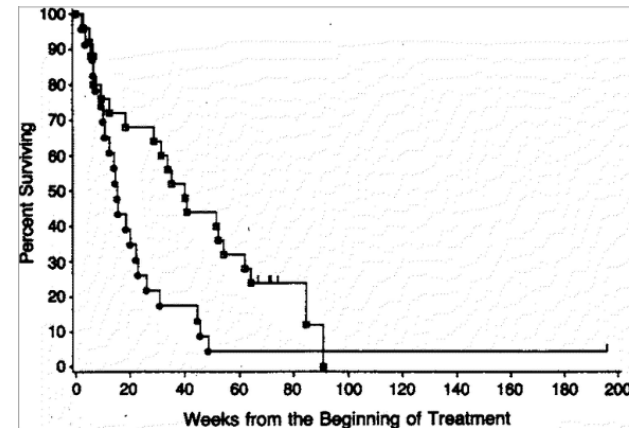
The NEW ENGLAND
JOURNAL of MEDICINE

1990(!!)

A RANDOMIZED TRIAL OF SURGERY IN THE TREATMENT OF SINGLE METASTASES TO THE BRAIN

ROY A. PATCHELL, M.D., PHILLIP A. TIBBS, M.D., JOHN W. WALSH, M.D., ROBERT J. DEMPSEY, M.D.,
YOSH MARUYAMA, M.D., RICHARD J. KRYSZCIO, PH.D., WILLIAM R. MARKESBERY, M.D.,
JOHN S. MACDONALD, M.D., AND BYRON YOUNG, M.D.

- Brain recurrence (BR) was less frequent in the surgical group than in the radiation alone group (20 vs 52 %; $p>0.02$).
- Median OS was significantly longer in the surgical group than in the radiation group (40 vs 15 weeks; $p<0.01$).





BRAIN METASTASIS IN BREAST CANCER PATIENTS: Surgery (plus WBRT) vs WBRT

...Thus, Surgery (plus WBRT) is the best option??

• **Operative mortality** has to be weighed against any possible benefit from surgery. In earlier series of patients with single brain metastases who were treated with surgery, operative mortality rates were in the range of 10-34%

...What about SRS??



RADIOSURGERY

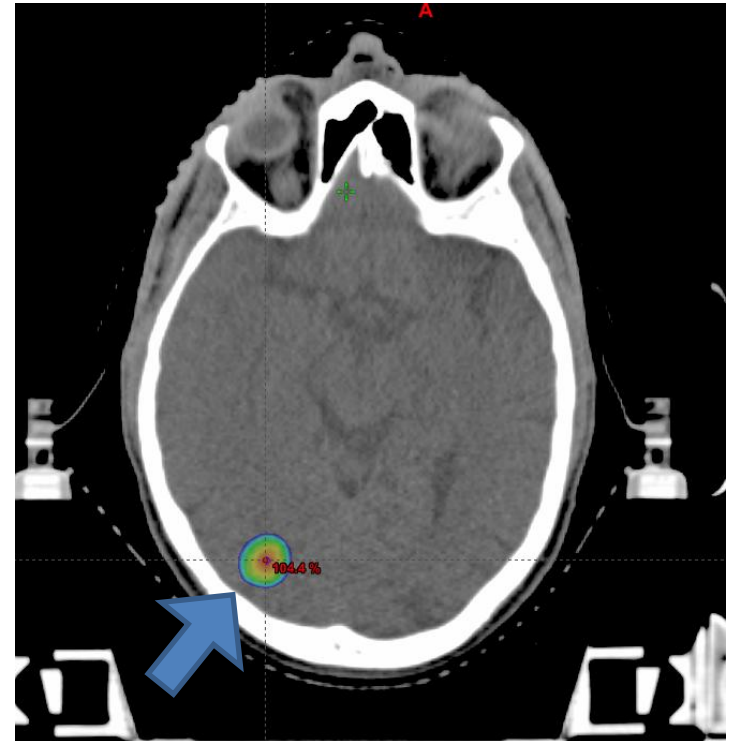
Stereotactic radiosurgery (SRS)

- “Stereo”: “solid” or “3-dimensional”
- “Tact”: (to touch)

Thus it means: *“3 dimensional arrangement to touch”*



Able to delivery :
“High doses to small volume with maximum
surrounding organ sparing”



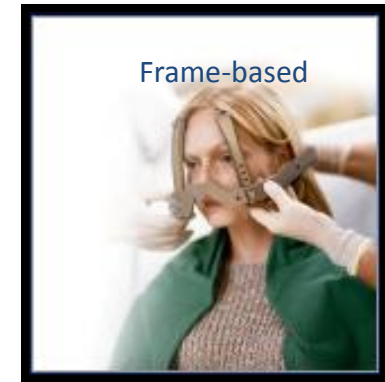
*Isolated brain metastasis from Breast Ca.
Dose prescription: 25 Gy in single session (ICRU)*



RADIOSURGERY FOR SINGLE/FEW BRAIN METS



Invasive



Non-Invasive





BRAIN METASTASIS IN BREAST CANCER PATIENTS: SRS

Radiosurgery is intended to provide:

- > local tumor control,
- improve clinical symptomatology,
- enhance survival.

All of these radiosurgical goals are generally achieved with:

- low morbidity,
- low cost,
- essentially zero mortality

*Noyes et al, Radiosurgery 1996;
Rutigliano et al, Neurosurgery 1995*



BRAIN METASTASIS IN BREAST CANCER PATIENTS: Surgery vs SRS

- **NO randomized trials** comparing surgical metastasectomy with SRS
- → Retrospective reports support comparable outcomes.

- The SELECTION of treatment should depend on patient- and disease-related factors (**SIR/RPA**).

*Noyes et al, Radiosurgery 1996;
Rutigliano et al, Neurosurgery 1995*



BRAIN METASTASIS IN BREAST CANCER PATIENTS: Surgery+WBRT vs SRS+WBRT

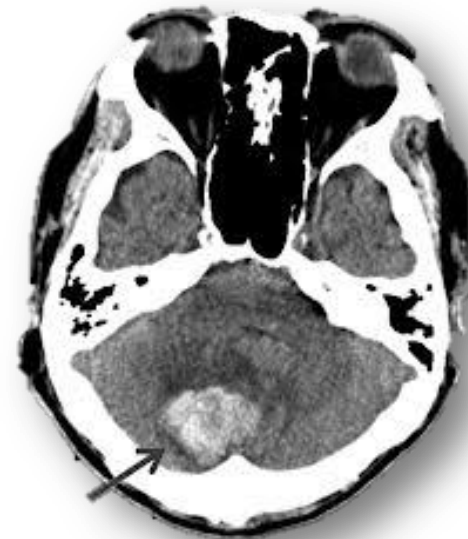
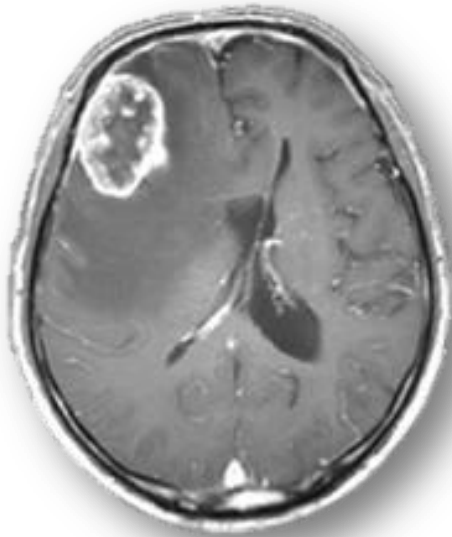
Several retrospective studies have compared S + WBRT with SRS + WBRT.

All of them reported **no significant differences on OS** or longer time to BR

(...except for one, that showed an improvement for S+WBRT, although probably there may have been a selection bias, since SRS patients were poor candidates for surgery. *Bindal AK et al, J Neurosurgery 1996*)



FRACTIONATED STEREOTACTIC RADIOSURGERY



Lesion diameter >3 cm $\left\{ \begin{array}{l} \rightarrow 3 \text{ FRACTIONS } (>8 \text{ Gy per fraction}) \\ \rightarrow 2 \text{ FRACTIONS } (> 11.5 \text{ Gy per fraction}) \end{array} \right.$



RADIOSURGERY FOR SINGLE/FEW BRAIN METS

*WBRT has been routinely added to SRS for single/few mets...
... until this paper*

Lancet Oncol 2009; 10: 1037-44

Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial

Eric L Chang, Jeffrey S Wefel, Kenneth R Hess, Pamela K Allen, Frederick F Lang, David G Kornguth, Rebecca B Arbuttle, J Michael Swint, Almon S Shiu, Moshe H Maor, Christina A Meyers



	Stereotactic radiosurgery plus whole-brain radiotherapy (N=11)	Stereotactic radiosurgery alone (N=20)	p (A>B)
Total recall	52%	24%	96%
Delayed recall	22%	6%	86%
Delayed recognition	11%	0%	86%

p (A>B)=Bayesian probability that the proportion with a significant neurocognitive worsening is higher in stereotactic radiosurgery plus whole-brain radiotherapy than stereotactic radiosurgery alone.

*WBRT could reduce neurocognition...
But what about Outcome?*

***Brain metastases:
SRS vs SRS + WBRT
randomized clinical trials***

Courtesy of Dr. E. Maranzano, Terni

Randomized phase III trials in brain metastases

SRS vs SRS + WBRT:

	# of patients	Intracranial progression free survival (months)	Overall survival (months)
<i>Aoyama 2006</i>	132 (67 SRS vs 65 SRS+WBRT)	Favour to SRS + WBRT	No difference
<i>Chang 2009</i>	58 (30 SRS vs 28 SRS+WBRT)		
<i>Kocher & Soffiatti 2010</i>	359 (179 SRS/Surg. vs 180 SRS/Surg + WBRT)		
<i>Mondschein 2010</i> (Abst ASTRO) MELANOMA	74 45 SRS vs 29 SRS+WBRT		



FRACTIONATED STEREOTACTIC RADIOSURGERY AND WHOLE BRAIN RADIOTHERAPY

Lancet Oncol 2009; 10: 1037-44

Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial

Eric L Chang, Jeffrey S Wefel, Kenneth R Hess, Pamela K Allen, Frederick F Lang, David G Kornguth, Rebecca B Arbuckle, J Michael Swint, Almon S Shiu, Moshe H Maor, Christina A Meyers

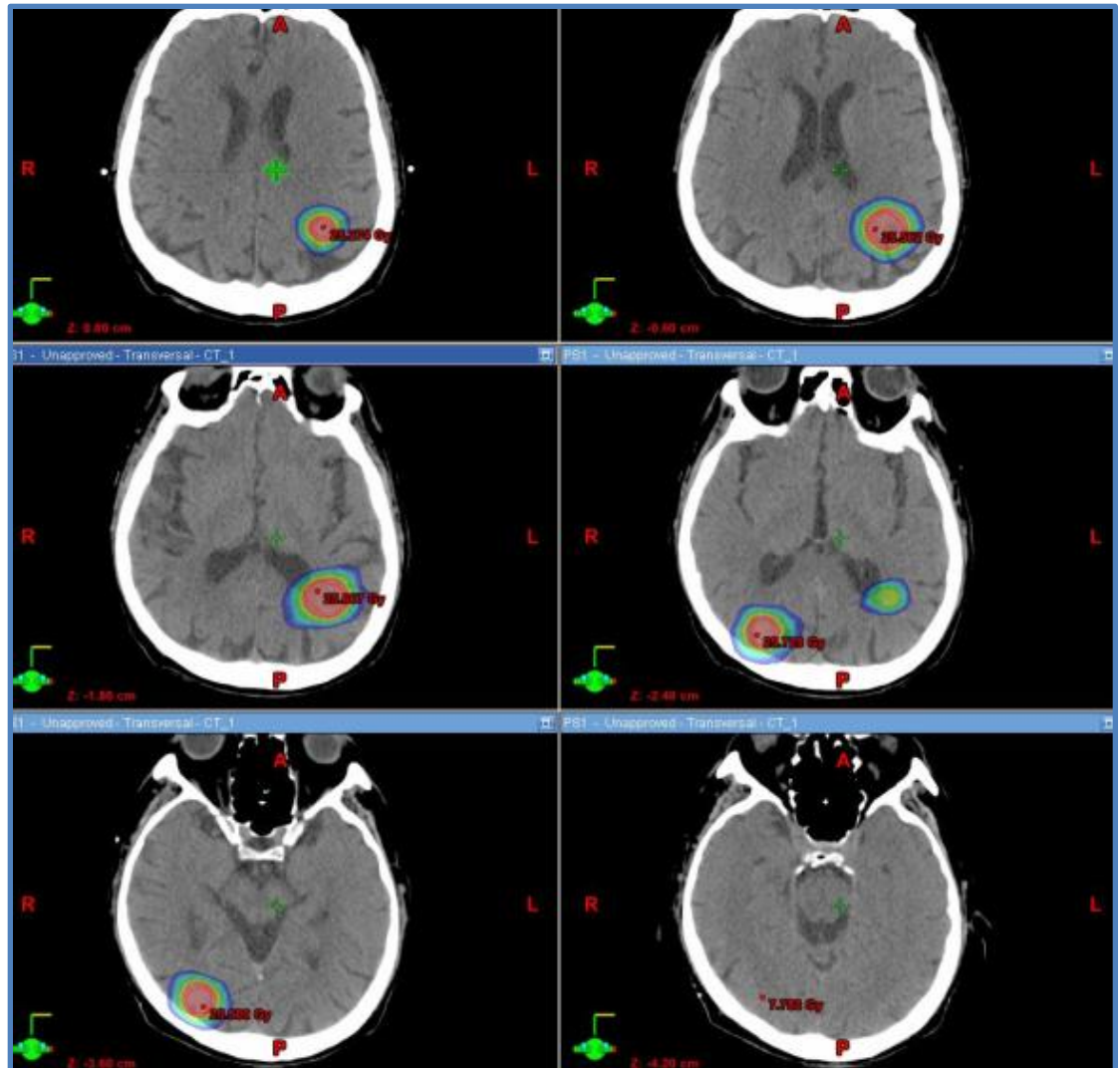
- 1. WBRT causes a decline in learning and memory function by 4 months compared with the group that received SRS alone.**
- 2. In patients 1-3 brain metastases initial treatment should be SRS**
- 3. clinical close monitoring is recommended for early diagnosis of relapse**
- 4. WBRT should be reserved only as a salvage therapy**



RADIOSURGERY FOR SINGLE/FEW BRAIN METS

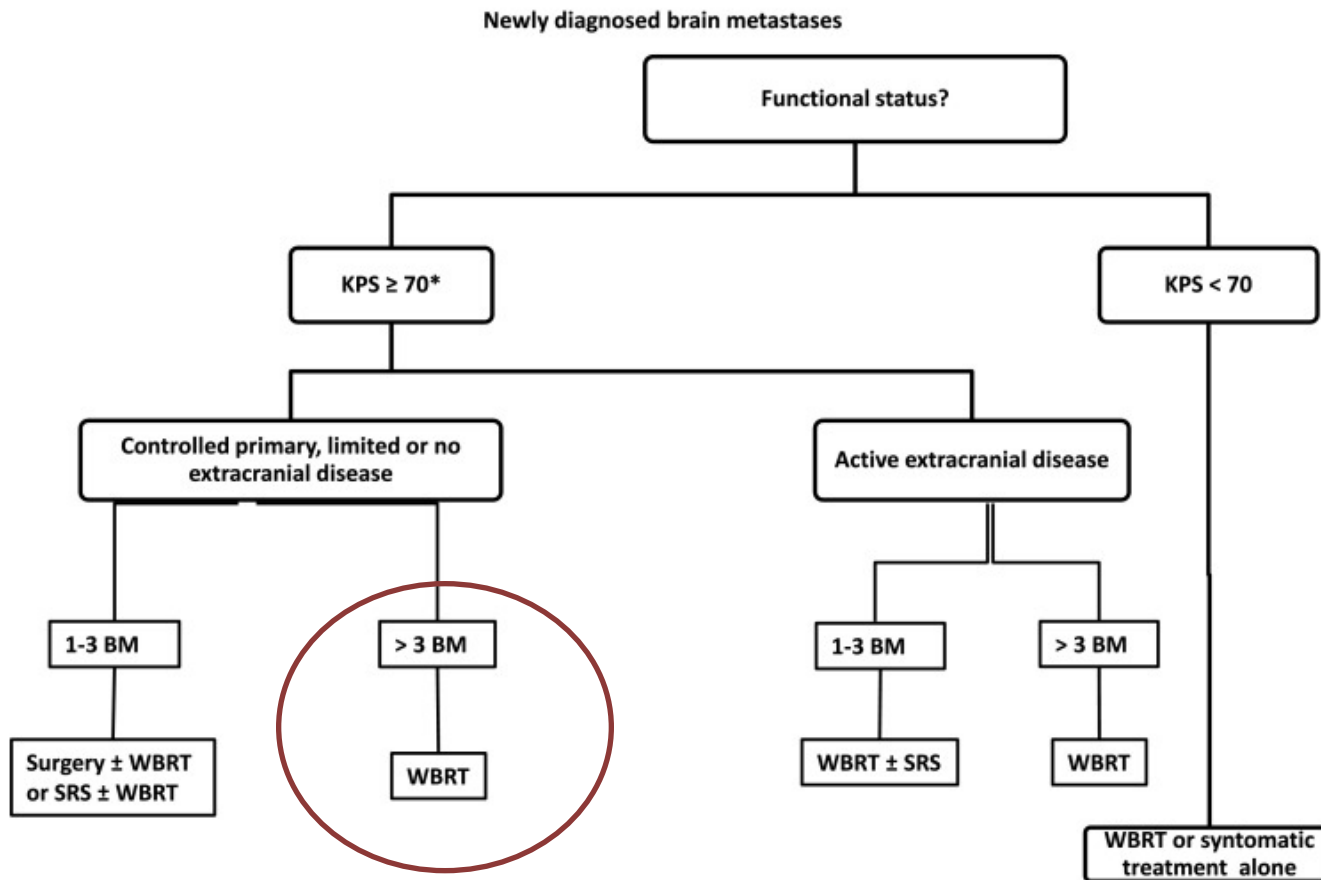
Patient with 2 brain metastases.

RADIOSURGERY:
Dose prescription: 25 Gy in single fraction.





BRAIN METASTASIS IN BREAST CANCER PATIENTS: Only WBRT for more than 3??





BRAIN METASTASIS IN BREAST CANCER PATIENTS: Only WBRT for >3 mts??

Lancet Oncol 2014; 15: 387-95

Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

•**M&M:** 1194 pts treated with SRS (1 → 10 brain mets)

•**RESULTS:** Overall survival → 1-5 BM = 5-10 BM

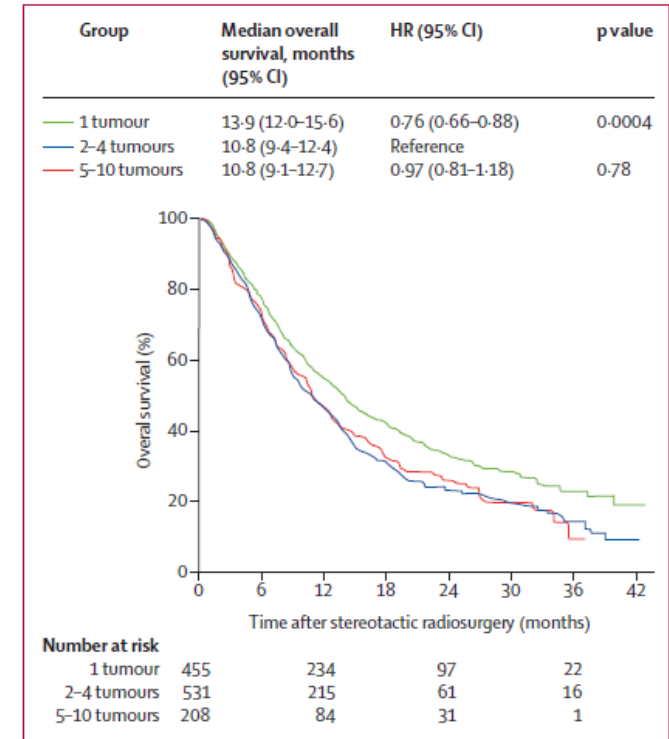


Figure: Kaplan-Meier curves of overall survival
HR=hazard ratio.

Interpretation Our results suggest that stereotactic radiosurgery without WBRT in patients with five to ten brain metastases is non-inferior to that in patients with two to four brain metastases. Considering the minimal invasiveness of stereotactic radiosurgery and the fewer side-effects than with WBRT, stereotactic radiosurgery might be a suitable alternative for patients with up to ten brain metastases.



BRAIN METASTASIS IN BREAST CANCER PATIENTS: Only WBRT for >3 mts??

THE LANCET Oncology

Volume 15, Issue 7, June 2014, Pages e246–e247



Correspondence

Stereotactic radiosurgery for patients with brain metastases

Filippo Alongi^a, Alba Fiorentino^a , Pierina Navarria^b, Lorenzo Bello^c, Marta Scorsetti^b

^a Department of Radiation Oncology, Sacro Cuore Hospital, Negrar-Verona 37134, Italy

^b Department of Radiotherapy and Radiosurgery, Istituto Clinico Humanitas Cancer Center, Milano, Italy

^c Department of Neurosurgery, Istituto Clinico Humanitas Cancer Center, Milano, Italy

Available online 26 May 2014

..Despite the relevance of Yamamoto and colleagues' study, its messages need to be interpreted carefully. Oversimplification of oncological treatment should be avoided...

...Whole-brain radiotherapy is the standard treatment for non-oligometastatic patients.

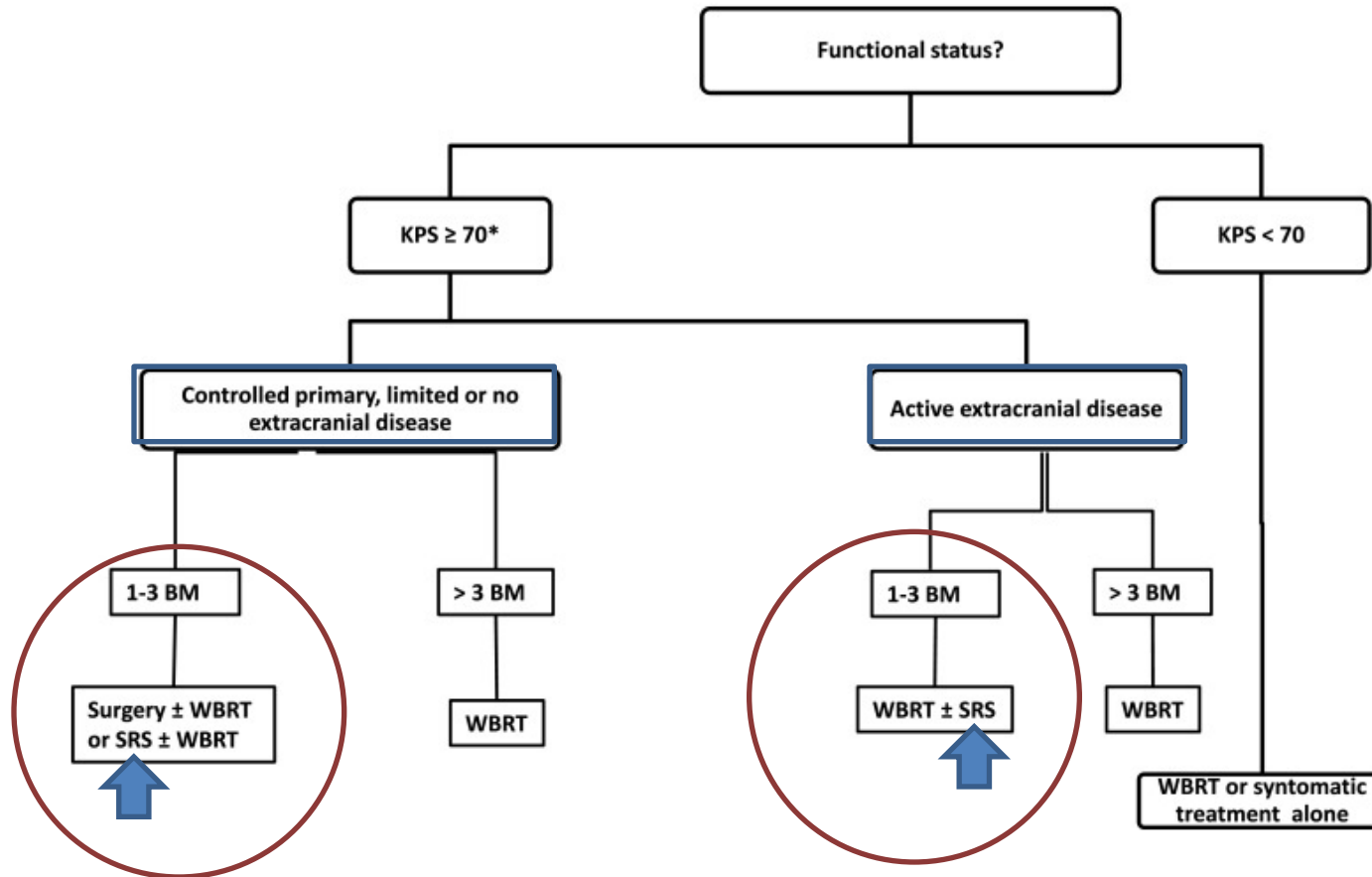
Referred to by Masaaki Yamamoto, Toru Serizawa, Takashi Shuto, Atsuya Akabane, Yoshinori Higuchi, Jun Kawagishi, Kazuhiro Yamanaka, Yasunori Sato, Hidefumi Jokura

Stereotactic radiosurgery for patients with brain metastases – Authors' reply



BRAIN METASTASIS IN BREAST CANCER PATIENTS: TAKE HOME MESSAGE

Newly diagnosed brain metastases



1) SRS should be considered a routine treatment owing to better neurocognitive outcomes and a lower risk of late adverse effects in limited BM (1-3)

2) Whole-brain radiotherapy is still the standard treatment for non-oligometastatic patients.



BRAIN METASTASIS IN BREAST CANCER PATIENTS: CONCLUSIONS

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Cranial Stereotactic Radiosurgery: Current Status of the Initial Paradigm Shifter

2014

Jason P. Sheehan, Chun-Po Yen, Cheng-Chia Lee, and Jay S. Loeffler

...Although the concept of radiosurgery has been present for more than six decades, radiosurgery continues to be refined and expanded.

Thus, the paradigm shift is not yet complete.



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