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Cancer research
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Technological advances in the irradiation of brain metastases

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by SOLTI

- Brain metastases: some years ago
- Brain metastases: **current state**
- Contribution of radiotherapy technology to improve the treatment of brain metastases
  - **Radiosurgery**
  - **Other high conformal techniques**
  - Whole brain radiotherapy with hippocampal avoidance
  - **Intraoperative radiotherapy**
- Conclusions

Twenty years ago

Simple prognosis classification

Class	Variables	Median surviv (months)
Class I	<65 years of age; KPS ≥70; controlled primary tumour; metastases to brain only	7.1
Class II	KPS ≥70, but uncontrolled primary tumour; KPS ≥70, primary controlled, but age ≥65; KPS ≥70, primary controlled, age <65, but metastases to brain and other sites	4.2
Class III	KPS <70	2.3

Gaspar L et al, IJORBP 1997

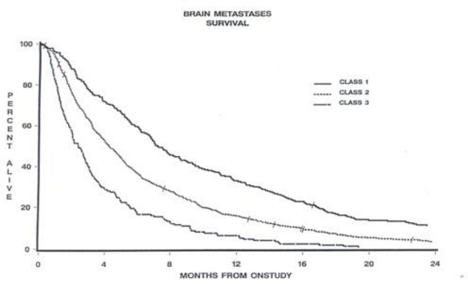
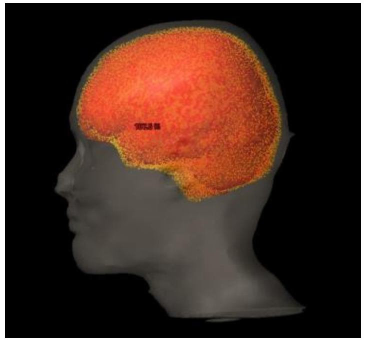
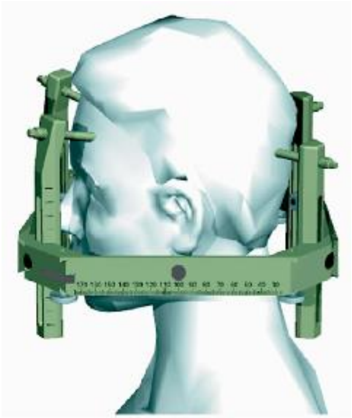


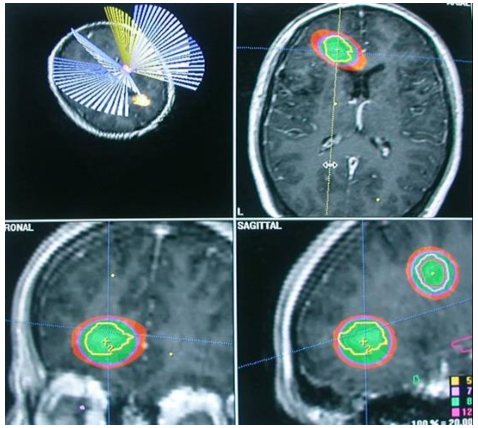
Fig. 2. Survival by RPA class from the RTOG database.

Conventional whole brain radiotherapy



Stereotactic frame based single dose radiosurgery





Brain metastases – current state

- **Diagnostic** improvements optimizing the detection of hidden metastasis
- **Patient selection**: DS-GPA (Diagnose Specific – Graded Assessment Prognosis Scoring Criteria) for each specific cancer subtype, including molecular factors
- The concept of oligometastatic disease – **radical approach**
- **New systemic treatments**
    - Targeted therapies
    - Immunotherapy

  → Prolonged survival for metastatic disease
- Serious concern about **neurocognition and quality of life**

Brain metastases – current state

Prolonged survival for metastatic disease

Better selection of patients (estimated MST > 6 m)

Oligometastatic patients

- More likely are going to be offered a radical approach with surgery or radiosurgery

Multiple brain metastasis

- Tendency to avoid whole brain radiotherapy (WBRT) when possible (feasible and effective systemic treatment, small and asymptomatic lesions...)
- If WBRT is needed, preference for using strategies to prevent neurotoxicity in those patients with favorable long-term prognosis)
- Clinical trials

The question is THE NUMBER

Patient selection – Scoring criteria for prognosis assessment

Non–small-cell and small-cell lung cancer

Prognostic Factor	GPA Scoring Criteria 0	0.5	1.0	Patient Score
Age, years	> 60	50-60	< 50	____
KPS	< 70	70-80	90-100	____
ECM	Present	—	Absent	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.0; 1.5-2.0 = 5.5; 2.5-3.0 = 9.4; 3.5-4.0 = 14.8

Melanoma

Prognostic Factor	GPA Scoring Criteria 0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 4.7; 2.5-3.0 = 8.8; 3.5-4.0 = 13.2

Breast cancer

Prognostic Factor	GPA Scoring Criteria 0	0.5	1.0	1.5	2.0	Patient Score
KPS	≤ 50	60	70-80	90-100	n/a	____
Subtype	Basal	n/a	LumA	HER2	LumB	____
Age, years	≥ 60	< 60	n/a	n/a	n/a	____
Sum total						____

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 7.7; 2.5-3.0 = 15.1; 3.5-4.0 = 25.3

Renal cell carcinoma

Prognostic Factor	GPA Scoring Criteria 0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.3; 1.5-2.0 = 7.3; 2.5-3.0 = 11.3; 3.5-4.0 = 14.8

GI cancers

Prognostic Factor	GPA Scoring Criteria 0	1	2	3	4	Patient Score
KPS	< 70	70	80	90	100	____

Median survival (months) by GPA: 0-1.0 = 3.1; 2.0 = 4.4; 3.0 = 6.9; 4.0 = 13.5

Fig 1. Graded Prognostic Assessment (GPA) worksheet to estimate survival from brain metastases (BM) by diagnosis. Subtype: Basal: triple negative; LumA: ER/PR positive, HER2 negative; LumB: triple positive; HER2: ER/PR negative, HER2 positive. ECM, extracranial metastases; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; KPS, Karnofsky performance score; LumA, luminal A; LumB, luminal B; PR, progesterone receptor.

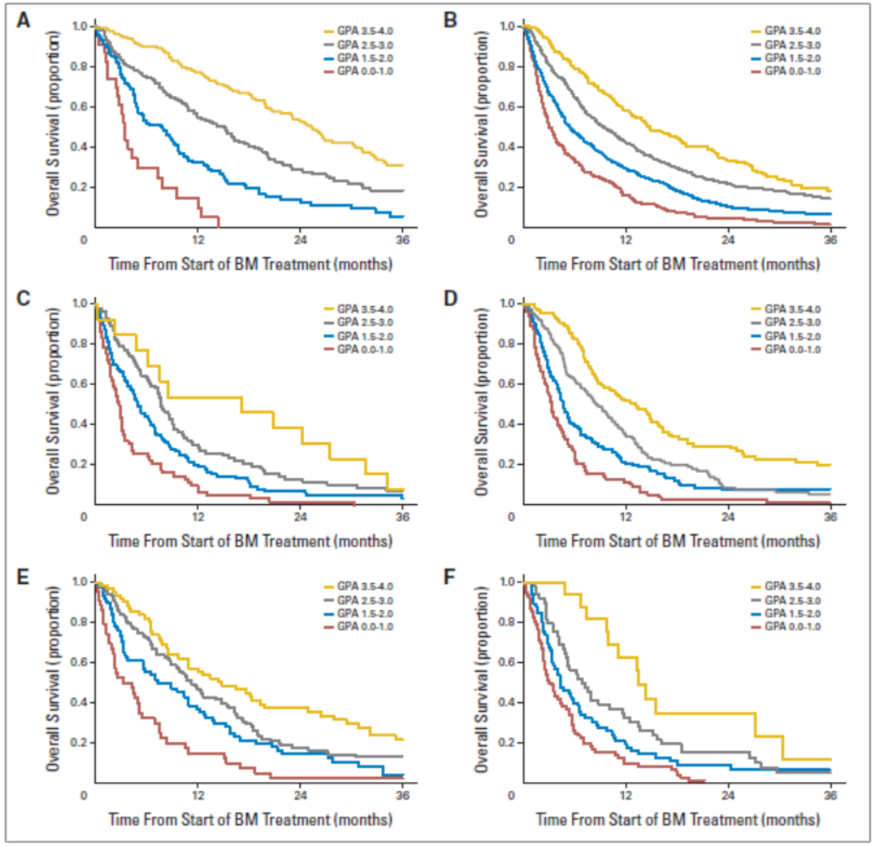


Fig 2. Kaplan-Meier curves for survival for six diagnoses by Graded Prognostic Assessment (GPA) group, demonstrating excellent separation between groups ($P < .001$) for each diagnosis: (A) breast cancer; (B) non–small-cell lung cancer; (C) small-cell lung cancer; (D) melanoma; (E) renal cell carcinoma; and (F) GI cancer. BM, brain metastases.

Sperduto et al, IJORBP 2010 – JCO 2012

Patient selection – Scoring criteria for prognosis assessment

Molecular profile adjusted prognosis factors - molGPA

Lung-molGPA

Table 2. Updated DS-GPA for NSCLC With Brain Metastases (Lung-molGPA) Scoring Chart and Worksheet to Estimate Survival

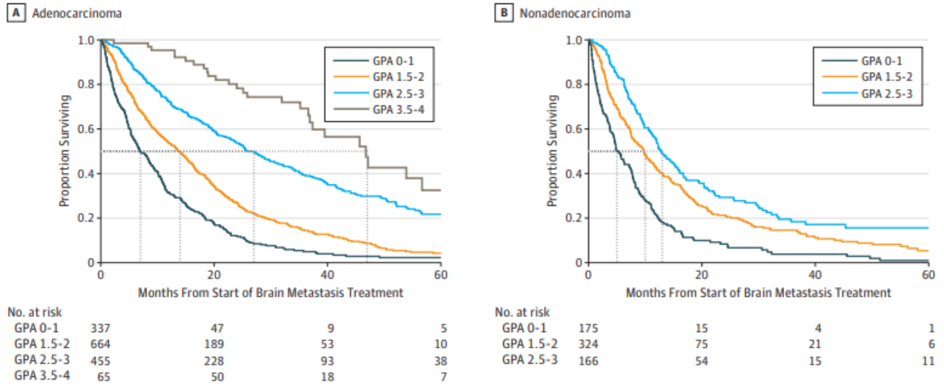
Prognostic Factor	GPA Scoring Criteria[a] 0	0.5	1.0	Patient Score[b]
Age, y	≥70	<70	NA	___
KPS	<70	80	90-100	___
ECM	Present		Absent	___
Brain metastases, No.	>4	1-4	NA	___
Gene status	*EGFR* neg/unk and *ALK* neg/unk	NA	*EGFR* pos or *ALK* pos	___
Total	NA	NA	NA	___

Abbreviations: DS, diagnosis-specific; ECM, extracranial metastases; GPA, graded prognostic assessment; KPS, Karnofsky Performance Status; MS, median survival; NA, not applicable; neg/unk, negative or unknown; NSCLC, non-small-cell lung cancer; pos, positive.

[a] Adenocarcinoma MS in months by GPA: 0-1.0 6.9; 1.5-2.0, 13.7; 2.5-3.0 ,26.5; and 3.5-4.0, 46.8; nonadenocarcinoma MS in months by GPA: 0-1.0, 5.3; 1.5-2.0, 9.8; 2.5-3.0, 12.8.

[b] Evaluating clinician completes this column.

Figure. Kaplan-Meier Curves Showing Survival by the Lung-molGPA for Non-Small-Cell Lung Cancer



GPA indicates graded prognostic assessment.

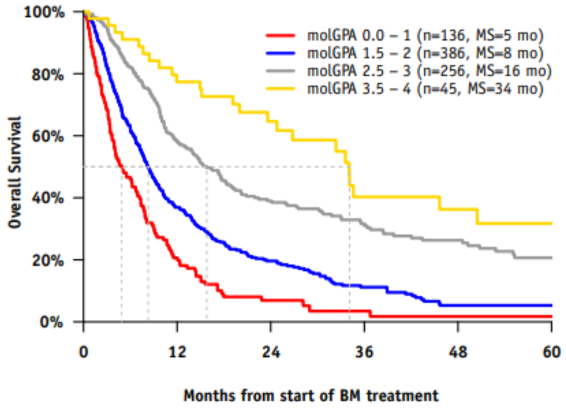
Melanoma-molGPA

Table 2 Melanoma GPA worksheet

Prognostic factor	GPA scoring criteria 0	0.5	1.0	Patient Score
Age, y	≥70	<0		-
KPS	≤70	80	90-100	-
ECM	Present		Absent	-
No. of BM	>4	2-4	1	-
BRAF gene status	Negative/unknown	Positive		-
			Sum	-

Abbreviations: BM = brain metastases; ECM = extracranial metastases; GPA = Graded Prognostic Assessment; KPS = Karnofsky performance status; MS = median survival in months.

MS by GPA: 0-1.0 = 4.9, 1.5-2.0 = 8.3, 2.5-3.0 = 15.8, 3.5-4.0 = 34.1.



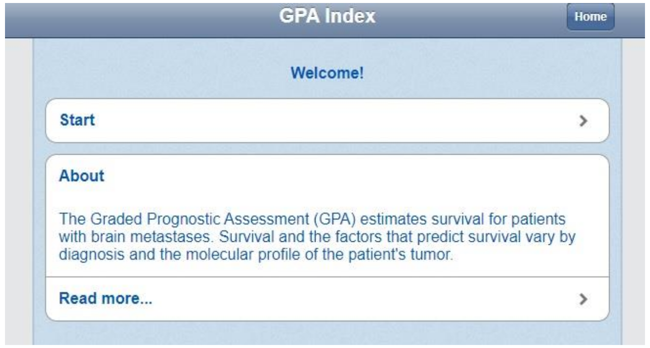
Sperduto et al, JAMA Oncol 2017; Sperduto et al, IJORBP 2017

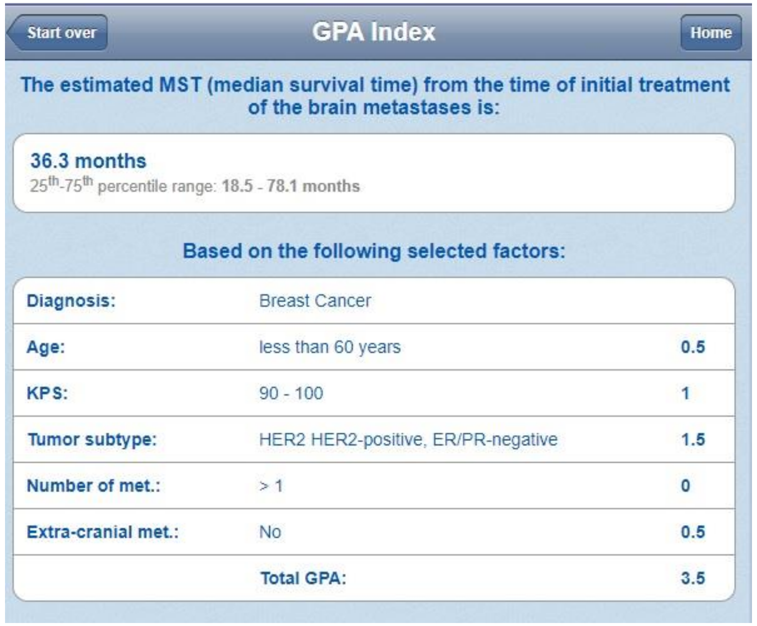
Patient selection – Scoring criteria for prognosis assessment

Updated GPA and Eligibility Quotient

Sperduto et al, JCO 2020

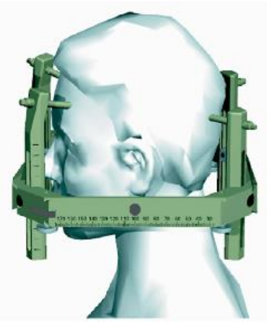
brainmetgpa.com

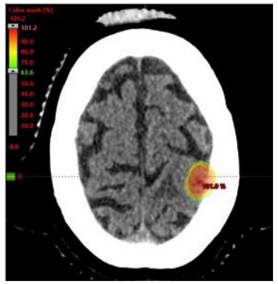


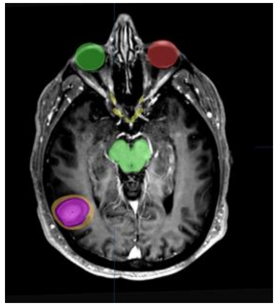


Radiosurgery - definition

- **High precision external beam radiotherapy technique** that delivers **a high radiation dose** in a **small cranial volume**
- It **preserves surrounding tissues** from this high dose (step-dose gradient)
- This technique uses **stereotactic coordinates** to localize the target volumes in relation to the frame
- The irradiation is delivered using multiple non-coplanar beams or arcs to produce a concentrated dose in the target volume
- It requires a highly **accurate immobilization system** (classically, the stereotactic frame) and a special equipment
- A bit of history:
  - It was developed during the 60's, initially designed to treat benign skull base tumors, functional disorders and arteriovenous malformations. Brain metastases were treated during the 80's for the first time
  - At the beginning it was delivered with gamma-units (*GammaKnife*), they were limited to selected centers
  - LINAC-X Knife radiosurgery was developed during the 90s (*LINAC = Lineal Accelerator*) and this enabled the expansion of the technique worldwide
- **Modalities:**
  - Single dose stereotactic radiotherapy (= Radiosurgery or RS)
  - Fractionated stereotactic radiotherapy (SFRT): it's the same technique, but it delivers the dose in several fractions (hypofractionated schemes) and uses a mask instead of the stereotactic frame to immobilize the head. It's preferred for large volumes or locations near risk organs
- The term Radiosurgery is reserved for **intracranial lesions**, in contrast to Stereotactic Ablative Radiotherapy (SABR), which is the delivery of such accurate and high-dose treatment to extracranial small targets

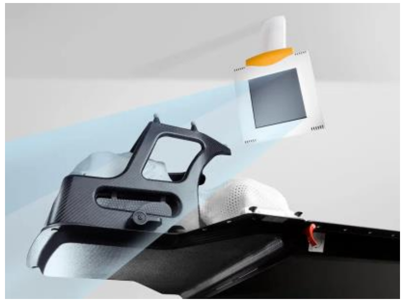


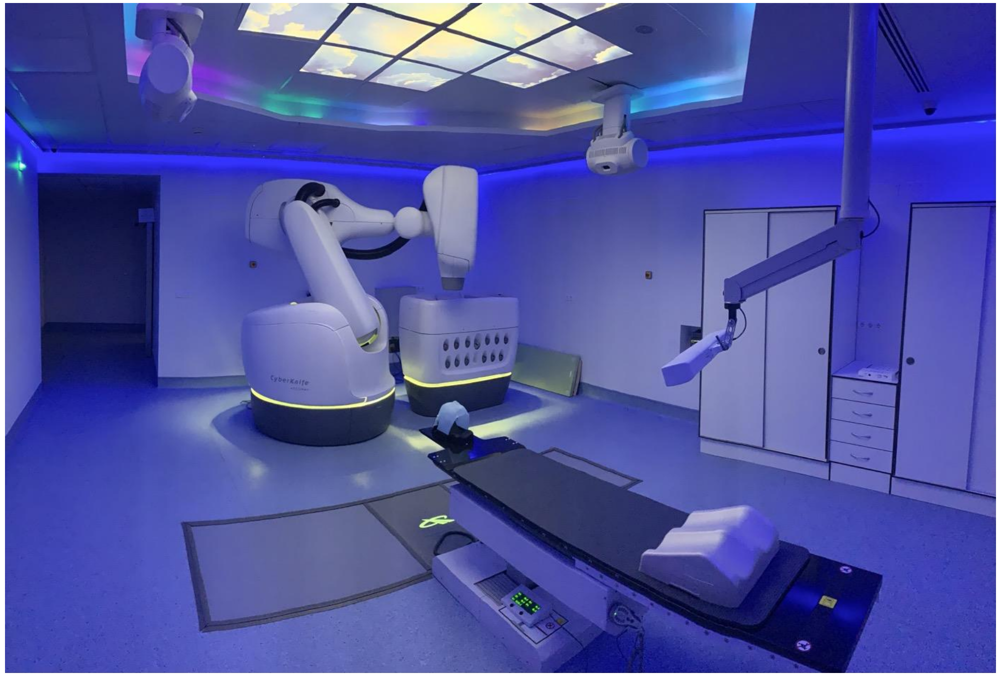




<u>Frameless Radiosurgery</u>:

- The stereotactic and invasive frame is substituted by a **rigid thermoplastic mask**
- It implies the use of **specific equipment with advanced technology** to guarantee the sub-millimeter accuracy in repositioning and monitoring during treatment
- **Image-guided radiotherapy system (X-rays and infrared detectors)**
- Circular cones or dynamic micro-multileaf collimators (dynamically adapted aperture to shape the target)
- Multiple non-coplanar arcs
- Advantages:
    - **Less invasive:** <u>patient comfort</u>, no risk of bleeding or infection
    - Flexibility in scheduling treatment planning (enough time to plan, less pressure for the clinical team)
    - Possibility of <u>repeating treatments</u>





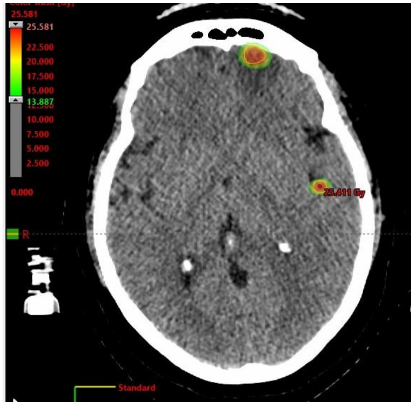
Courtesy of Dr. Fernádez Lizarbe, H.U. Ramón y Cajal

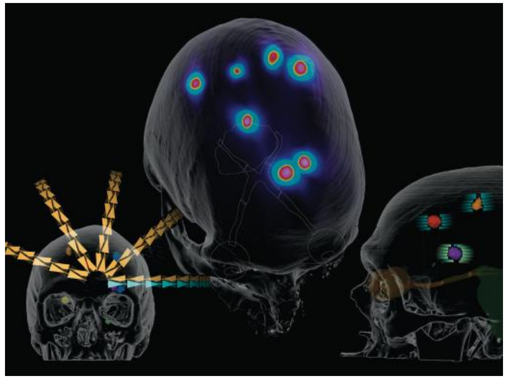
Courtesy of Dr. Luis Aznar, Cromwell Hospital London, Genesis Care

<u>Treatment of multiple brain metastases</u>:

Recent development of specific software for multiple metastasis treatment planning

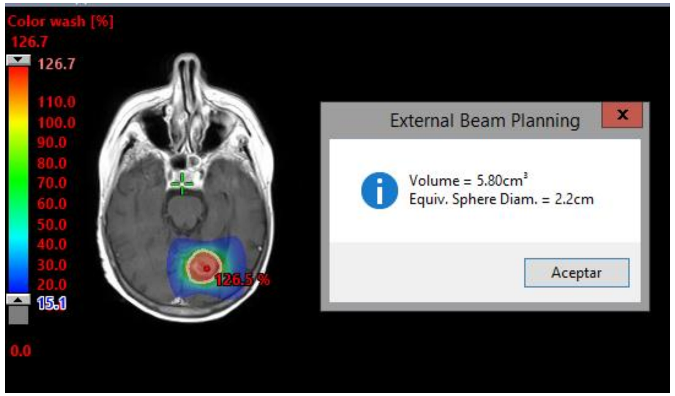
- A volumetric optimized radiosurgical plan is automatically created by the software
- **Simultaneous treatment of all of them with a single isocenter** using intensity modulated techniques or volumetric modulated arc therapy
- Treatment time is fully reduced
- Its availability makes possible the current trend to treat focally a greater number of lesions

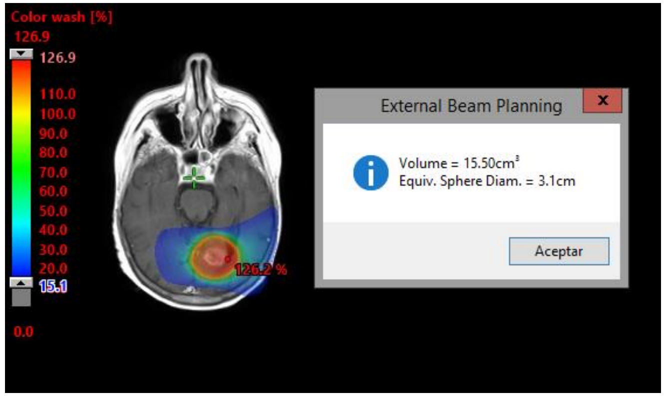


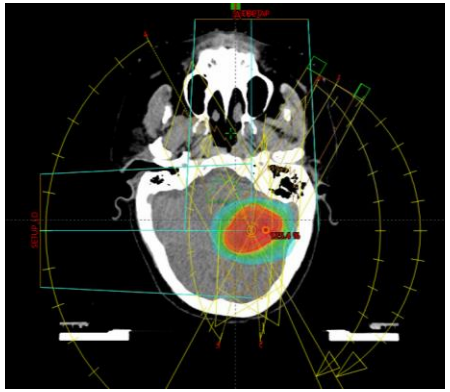


Other conformal techniques

- Radiosurgery is unavailable in most radiation oncology centers
- However, other high conformal techniques such as Volumetric arc therapy (VMAT), which has features of intensity-modulated radiotherapy IMRT) as well as arc therapy, are widely distributed and available in most centers
- Once mastered extracranial high conformal techniques to treat small volumes (SBAR), many centers have begun to use them to focally treat brain metastases as well, however using hypofractionated schemes instead of single dose
- They could be **quite equivalent for targets over 2 cm**, such as large brain metastasis or postsurgical cavities
- This option **improves patient comfort** while reducing transfers to distant centers
- <u>But be cautious with small lesions!!!</u>



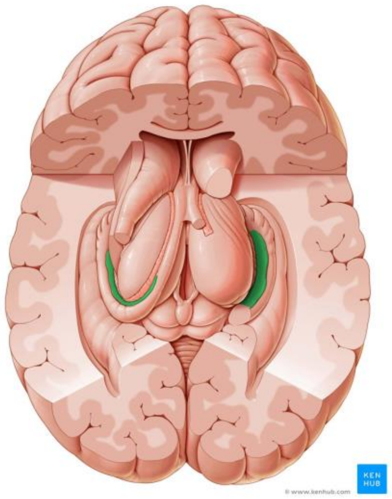




Hippocampal sparing whole brain radiotherapy

Concern about cognitive deterioration after WBRT

- Neuroprotective drugs: memantine
- Hippocampal avoidance



<u>Rationale for hippocampal sparing during WBRT</u>:

Preclinical and clinical studies have suggested that relatively low doses of radiation received by the neural stem cell within the subgranular zone of the hippocampal dentate gyrus may contribute to radiotherapy induced cognitive toxicity

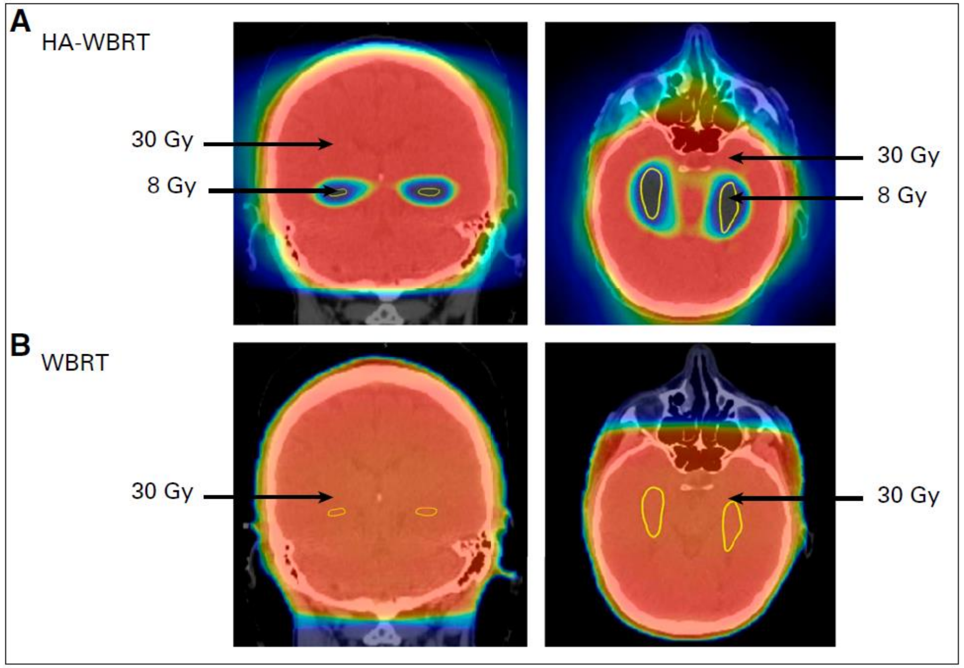
Monje ML et al, Nat Med 2002; Gondi V et al, IJORBP 2013

Memantine

- It's a N-methyl-D-aspartate (NMDA) receptor antagonist that blocks pathologic excessive stimulation of NMDA receptors
- It has been shown to be beneficial in dementia and Alzheimer
- Preclinical models demonstrated that could be beneficial as neuroprotector in brain irradiation
- **RTOG 0614 trial** compared memantine to placebo in 554 patients with brain metastases receiving WBRT. While it did not find a significant difference in its primary outcome – preservation of cognitive function at 24 weeks on the HLVT-R DR instrument – it did find clinically meaningful and statistically significant benefits in other cognitive outcomes, including cumulative incidence of cognitive failure and cognitive function measured by the Mini Mental State Examination instrument
- Memantine was well tolerated
- In USA, Memantine is a standard of care for patients with better prognosis receiving WBRT
- A twice-daily dose is prescribed as follows: 5-mg morning dose (week 1), 5-mg twice a day (week 2), 10-mg morning dose and 5-mg evening dose (week 3) and 10-mg twice a day (weeks 4-24)

Reisberg B et al, NEJM 2003; Brown PD et al, Neuro Oncol 2013

Hippocampal sparing whole brain radiotherapy



Whole brain radiotherapy with or without hippocampal sparing

- Intensity modulated RT (IMRT) or helical tomotherapy to successfully deliver **therapeutic doses of WBRT while limiting radiation dose to the bilateral hippocampal dentate gyri**
- Bilateral hippocampal contours generated on the fused thin-slice MRI and expanded 5 mm to determinate the hippocampal avoidance (HA) region ("U-shape"),
- Accurate delineation of hippocampus is critical
- Hippocampal dose usually limited under 9-10 Gy in 98% of volume // D40 < 7.3 Gy
- PTV = whole-brain parenchyma excluding the HA region

Gondi V et al, R&O 2010; Gondi V et al, IJORBP 2013; Brown PD et al, JCO 2020

Hippocampal sparing whole brain radiotherapy

VOLUME 32 · NUMBER 34 · DECEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY   ORIGINAL REPORT

Preservation of Memory With Conformal Avoidance of the Hippocampal Neural Stem-Cell Compartment During Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase II Multi-Institutional Trial

Vinai Gondi, Stephanie L. Pugh, Wolfgang A. Tome, Chip Caine, Ben Corn, Andrew Kanner, Howard Rowley, Vijayananda Kundapur, Albert DeNittis, Jeffrey N. Greenspoon, Andre A. Konski, Glenn S. Bauman, Sunjay Shah, Wenyin Shi, Merideth Wendland, Lisa Kachnic, and Minesh P. Mehta

- 42 analyzable patients at 4 months
- Mean relative decline in HVLT-R DR from baseline was 7% (95% CI, 4.7%-18.7%), significantly lower in comparison with the historical control (p<0.001)
- No decline in QOL scores

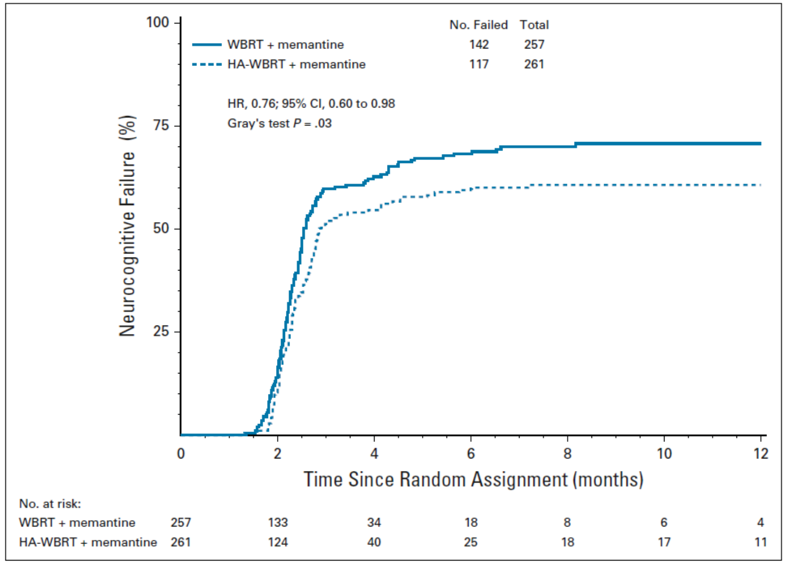
original reports

Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC001

JCO 2020

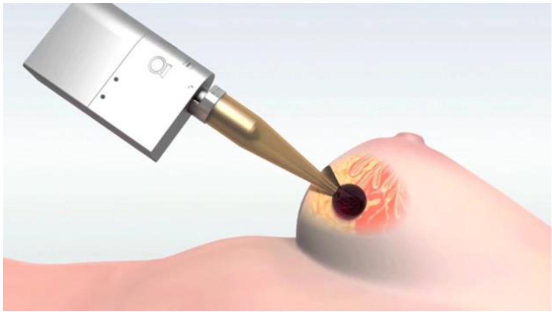
Paul D. Brown, MD[1]; Vinai Gondi, MD[2]; Stephanie Pugh, PhD[3]; Wolfgang A. Tome, PhD[4]; Jeffrey S. Wefel, PhD[5]; Terri S. Armstrong, PhD[6]; Joseph A. Bovi, MD[7]; Cliff Robinson, MD[8]; Andre Konski, MD, MBA[9]; Deepak Khuntia, MD[10]; David Grosshans, MD, PhD[5]; Tammie L. S. Benzinger, MD, PhD[8]; Deborah Bruner, PhD[11]; Mark R. Gilbert, MD[6]; David Roberge, MD[12]; Vijayananda Kundapur, MD[13]; Kiran Devisetty, MD[14]; Sunjay Shah, MD[15]; Kenneth Usuki, MD[16]; Bethany Marie Anderson, MD[17]; Baldassarre Stea, MD, PhD[18]; Harold Yoon, MD[19]; Jing Li, MD[5]; Nadia N. Laack, MD[1]; Tim J. Kruser, MD[20]; Steven J. Chmura, MD, PhD[21]; Wenyin Shi, MD[22]; Snehal Deshmukh, MS[3]; Minesh P. Mehta, MD[23]; and Lisa A. Kachnic, MD[24] for NRG Oncology

In conclusion, use of HA during WBRT with memantine effectively spares the hippocampal neuroregenerative niche to better preserve cognitive function and patient-reported symptoms. No differences were observed in toxicity, intracranial PFS, or OS compared with standard WBRT and memantine.



Intraoperative Radiotherapy in brain mets

- It consists of the irradiation of the **surgical bed**, in the operating room, **immediately after the tumorectomy** of the corresponding lesion
- **High dose** of radiation **precisely delivered** to the target area with minimal exposure of surrounding tissues
- Importance of changes in the tumor microenvironment following IORT (provide superior LC)
- <u>Advantages</u>: precision, no waiting time to complementary treatment after surgery, eliminates or reduces external radiotherapy
- <u>Inconveniences</u>: adapted operating room, specific equipment, extends surgery time
- Uses: breast cancer, sarcoma, digestive cancer
- Miniaturized mobile linear accelerator

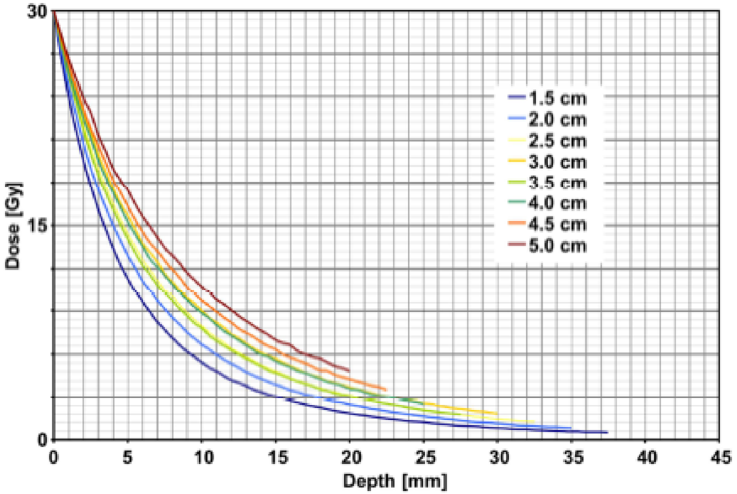


Intraoperative radiotherapy in brain mets

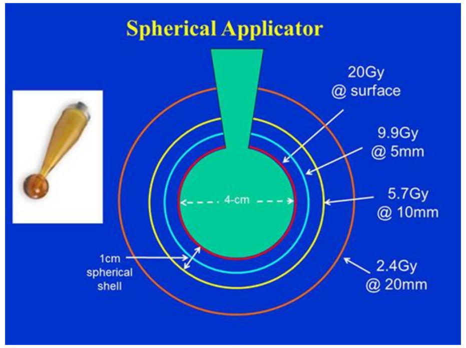
- It uses low X-rays mini-lineal accelerators
- Depending on the device, the applicator is a rigid sphere (Intrabeam®) or an inflatable balloon (Xoft®), both designed to perfectly fit the resected cavity, being able to contact the entire wall, applying pressure but not traumatically
- Energy: low energy of 50 kV (higher radiobiological effect, EBR 1.3-1.5)

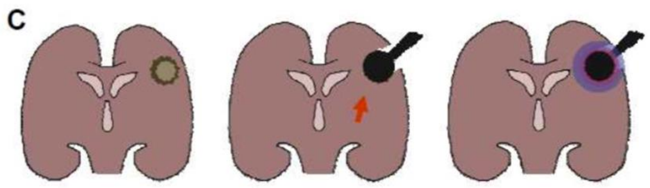
Xoft®

Intrabeam®



Dose distribution



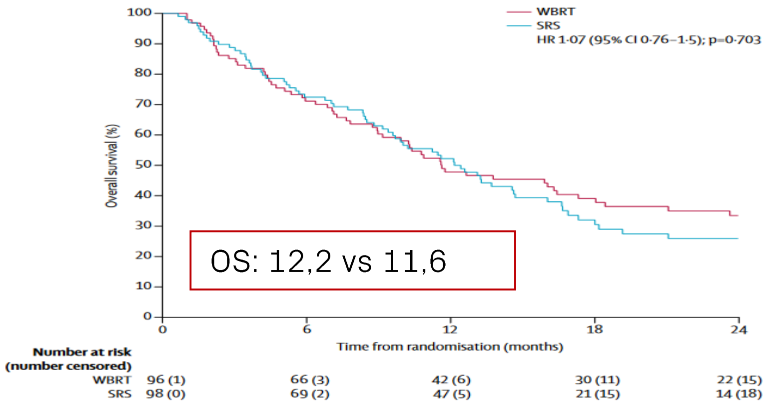


Intraoperative radiotherapy in brain mets

- Almost 50% of resected brain metastasis relapse after surgery
- Traditionally the adjuvant treatment has been whole brain radiotherapy
- However, recent studies has shown that **local irradiation can be delivered instead of WBRT**, without an impairment on survival, while remaining useful at reducing the risk of recurrence
- Postoperative irradiation of the cavity is delivered with radiosurgical techniques (single-dose initially, more recently with fractionated schemes)

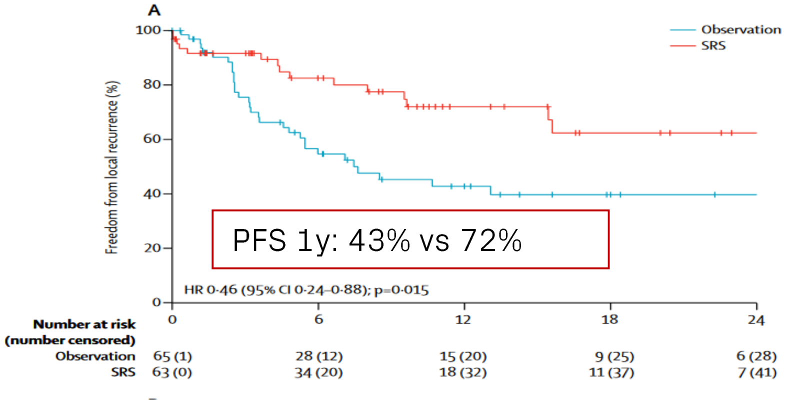
Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial

Paul D Brown, Karla V Ballman, Jane H Cerhan, S Keith Anderson, Xiomara W Carrero, Anthony C Whitton, Jeffrey Greenspoon, Ian F Parney, Nadia N I Laack, Jonathan B Ashman, Jean-Paul Bahary, Costas G Hadjipanayis, James J Urbanic, Fred G Barker II, Elana Farace, Deepak Khuntia, Caterina Giannini, Jan C Buckner, Evanthia Galanis, David Roberge



Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial

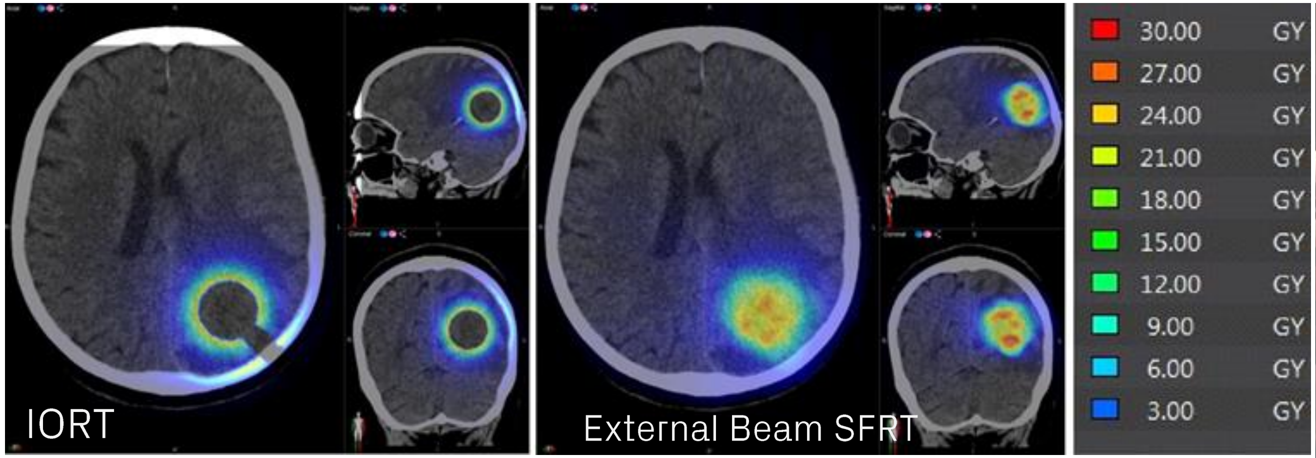
Anita Mahajan, Salmaan Ahmed, Mary Frances McAleer, Jeffrey S Weinberg, Jing Li, Paul D Brown, Stephen Settle, Sujit S Prabhu, Frederick F Lang, Nicholas Levine, Susan McGovern, Erik Sulman, Ian E McCutcheon, Syed Azeem, Daniel Cahill, Claudio Tatsui, Amy B Heimberger, Sherise Ferguson, Amol Ghia, Franco Demonte, Shaan Raza, Nandita Guha-Thakurta, James Yang, Raymond Sawaya, Kenneth R Hess, Ganesh Rao

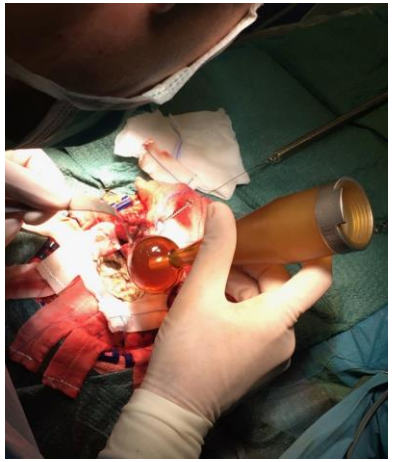


Brown PD et al, Lancet 2017; Mahajan A et al, Lancet 2017

Intraoperative radiotherapy IN BRAIN METS

- It’s being tested as an option to **adjuvantly treat brain cavities after surgical resection**
- First feasibility prospective study was published in 2015 (23 patients)
- Theoretical calculation for dose prescription was published in 2018
- First retrospective series have been recently published (54 patients in 2019 and 40 patients in 2021)
- They all conclude that IORT is a safe and effective means of delivering adjuvant radiation to the brain metastases cavity with a high rate of local control, low incidence of radionecrosis and increased homogeneity to target dose beyond traditional RS plans
- **Phase II trials are ongoing**



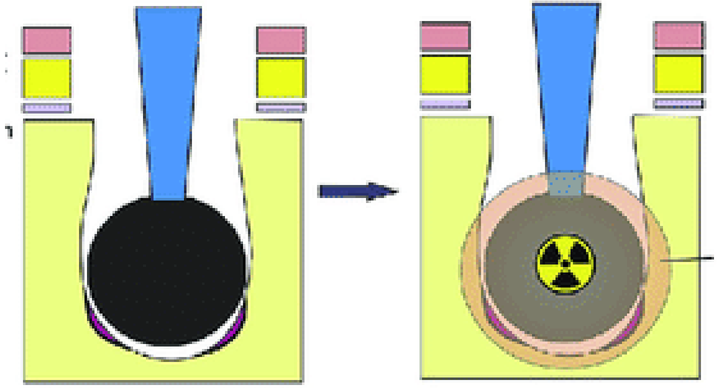


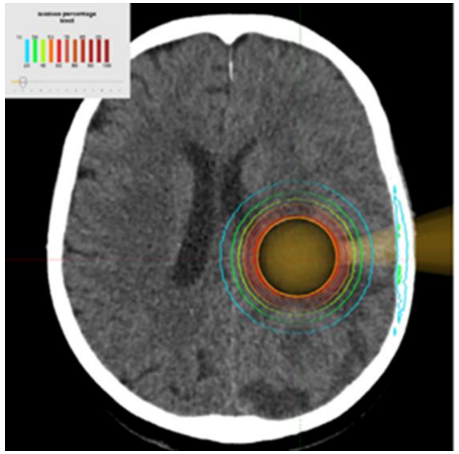
Weil RJ et al, J Neurosurg 2015; Vargo JA et al, 2018; Cifarelli CP et al, J Neuro-Oncol 2019; Kahl KH et al, Strahlent Oncol 2021

Intraoperative radiotherapy IN BRAIN METS

Advantages:

- Immediacy
  - no waiting time to complementary treatment after surgery
  - eliminates the necessity of external beam radiotherapy
  - eliminates the risk of not complementing adjuvant treatment
  - reduces the delay to start additional treatments
  - patient comfort
- Radiobiological and biological effects
  - avoidance of tumor repopulation
  - high dose
  - single dose
  - changes in microenvironment following IORT
  - higher tissue radiosensibility after surgery
- Accuracy
  - RT is easily and precisely delivered
  - Better dose fall-off
  - Minimal exposure of surrounding tissues
  - Avoids the difficulties and uncertainties in the contouring with external beam RT





Conclusions

Prolonged survival of metastatic patients has led to a new scenario in which neurocognition and quality of life as become real concerns. In the setting of radiotherapy this means that **focal treatments** are going to be preferred (when possible) and health **brain parenchyma is going to be protect** in patients with favorable prognosis classes. Technology is helping us to achieve these goals

- ✓ Radiosurgery has been technologically improved with advanced equipment and software. This has made possible **frameless radiosurgery** and has made easier and feasible the focal treatment of **multiple brain metastases**
- ✓ Radiosurgery is now more comfortable, and this allows the possibility of easy **repeat of the procedure**
- ✓ The widespread of **non-radiosurgical high conformal techniques** allows focal treatment of selected large lesions and cavities in many centers
- ✓ When WBRT is needed, in patients with favorable prognosis **neurocognition can be protected avoiding the irradiation of hippocampal region**
- ✓ **Intraoperative radiotherapy** is emerging as a promising option to adjuvantly treat resection cavities (phase II trials ongoing)

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