

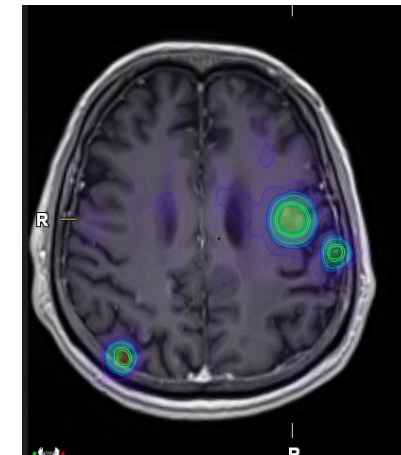
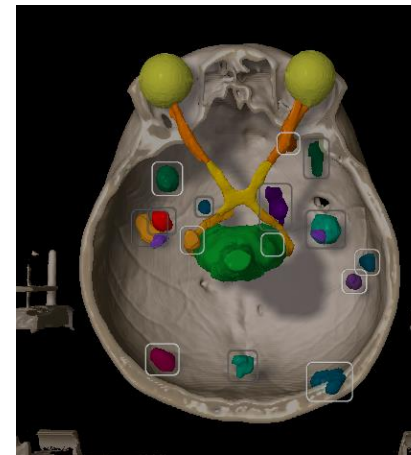
# 1

## Refresher Course en Latinoamérica



**Viernes 1 de septiembre:** speakers by **ASTRO** (en español)

**Sábado 2 de septiembre:** speakers by **ACRO** • **ALATRO** • **ASTRO** (en español)



# Radiocirugía en metástasis cerebrales



**Guillermo Potdevin Stein, MD, PhD.**

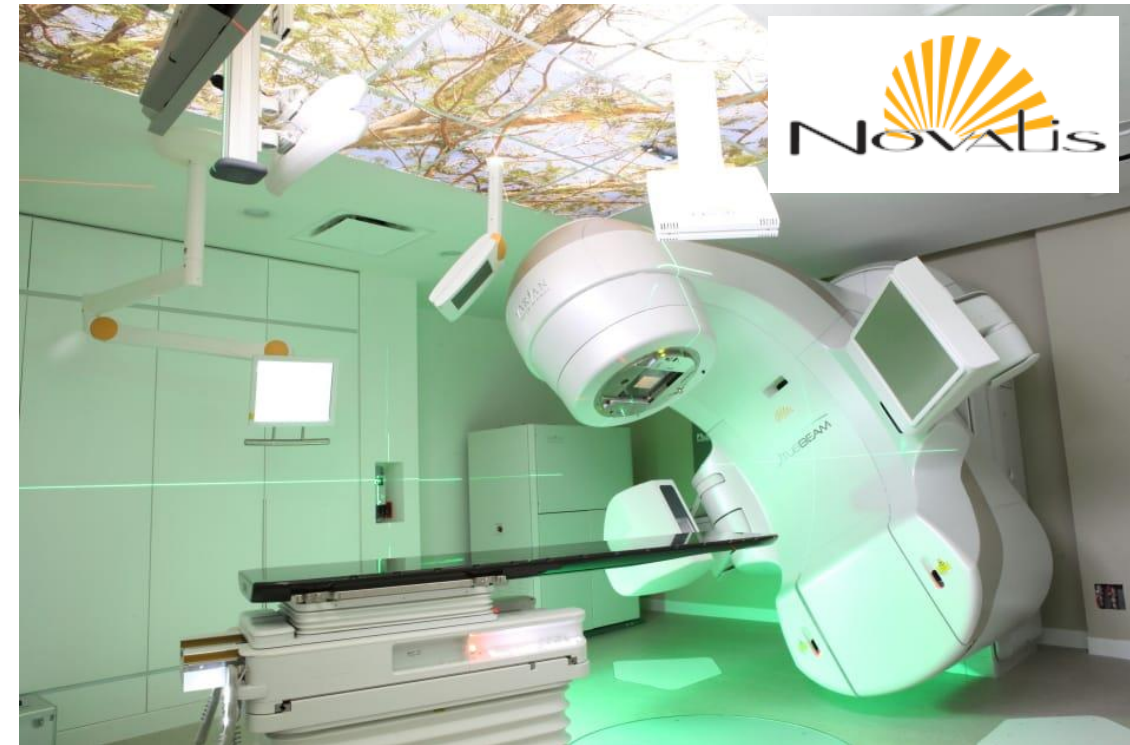
Oncólogo Radioterápico

Fundación Valle del Lili

Sabado 02 de Septiembre 2023

# Trayectoria del Servicio

- En FVL se ha ido evolucionando en función de la tecnología disponible:
  - 1995 Mevatron: 2D
  - 2008 Primus: 3D e IMRT
  - 2014 Artiste: 3D, IMRT (re-introducción), IGRT, SRS (*Con marco*)
  - 2018 Somaton Confidence: Anillo 80 cm, Tomografía 4D
  - Febrero 2019 TrueBeam-Novalis: 3D, IMRT, IGRT, VMAT, SRS (*Sin marco*), SBRT, Gating, DIBH.
  - Junio 2022 TrueBeam (Gemelo): 3D, IMRT, IGRT, VMAT, SBRT, Gating, DIBH.



TrueBeam-Novalis<sup>1</sup>

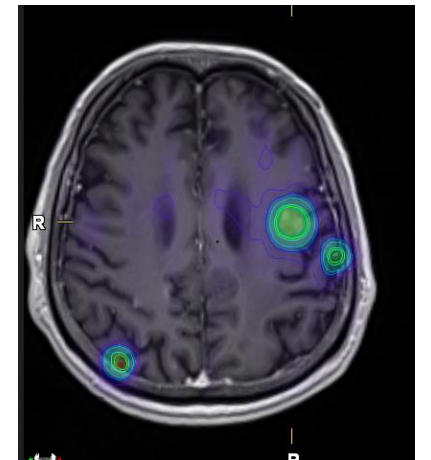
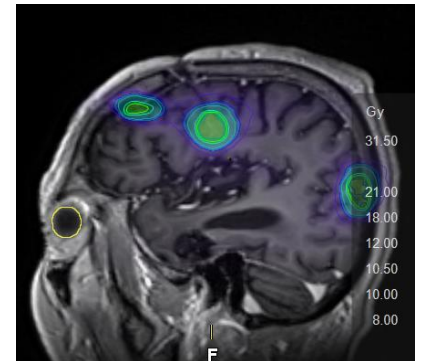
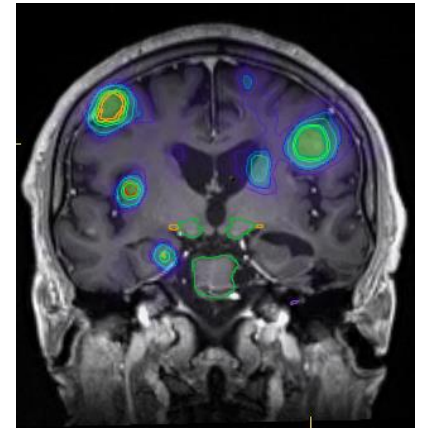
<sup>1</sup> *Primer TrueBeam con Novalis en Colombia.*

# Programa de Radiocirugía FVL

- 2014 se implemento el programa de Radiocirugía:
  - Radiocirugía con marco dosis única y mascara dosis fraccionada.
- En Febrero de 2019 iniciamos los tratamientos de Radioterapia en el TrueBeam.
- En Mayo 2019 empezamos los tratamiento con Novalis (*ExacTrac* y *Elements*).
  - Todas las Radiocirugías sin marco (*frameless*)
- ***Todos los pacientes candidatos a Radiocirugía son discutidos en la Junta de Radiocirugía:***
  - *Una vez a la semana*
  - *Oncología Radioterápica, Neurocirugía, Física Médica, Enfermería Oncológica.*

# Indice

- Introducción
- Caracterización de los pacientes
- Pacientes que se pueden beneficiar de SRS
- Dosis y fraccionamiento
- SRS en lecho quirúrgico
- Terapias dirigidas - Inmunoterapia
- Conclusiones



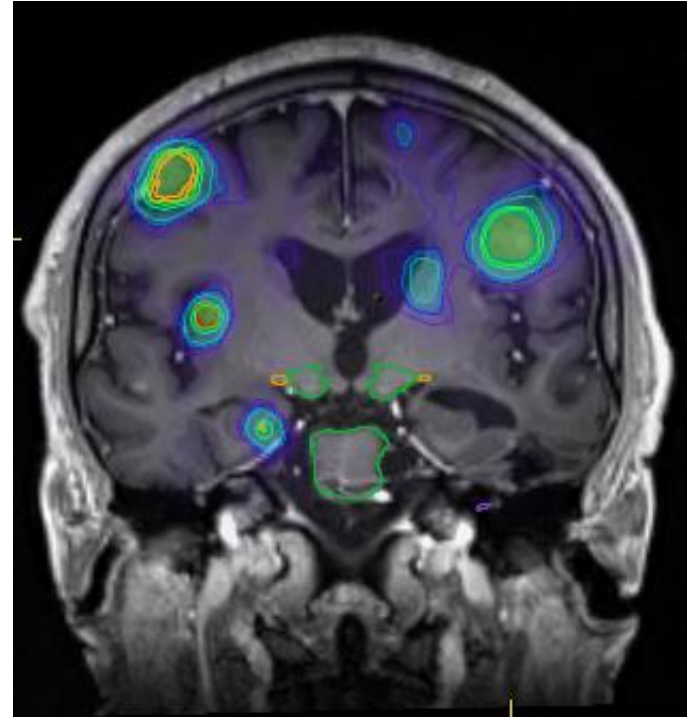
# Introducción

- 20-40% de los pacientes con cáncer desarrollarán metástasis cerebrales (MC) a lo largo de su enfermedad.
- Las MC impactan directamente la calidad de vida y la supervivencia.
- Probabilidad de desarrollo de MC:
  - *Pulmón (19.6%)*
  - *Melanoma (6.4%)*
  - *Renal (4.2%)*
  - *Mama (3.1%)*
  - *Colorectal (1.4%)*
- De las MC diagnosticadas, el pulmón representa el 60% de los casos, Mama 11% y Melanoma 6%.

# Introducción

- Las opciones de tratamiento son:
  - WBRT
  - SRS/fSRS
  - Cirugía
  
- El objetivo del tratamiento es:
  - **Aumentar la supervivencia y mejorar la calidad de vida.**

# Caracterización de los pacientes



# Diagnosis-specific Graded Prognostic Assessment (GPA) - DS-GPA

## Survival in Patients With Brain Metastases: Summary Report on the Updated Diagnosis-Specific Graded Prognostic Assessment and Definition of the Eligibility Quotient

*Sperduto et al 2020, J Clin Oncol 38:3773-3784.*

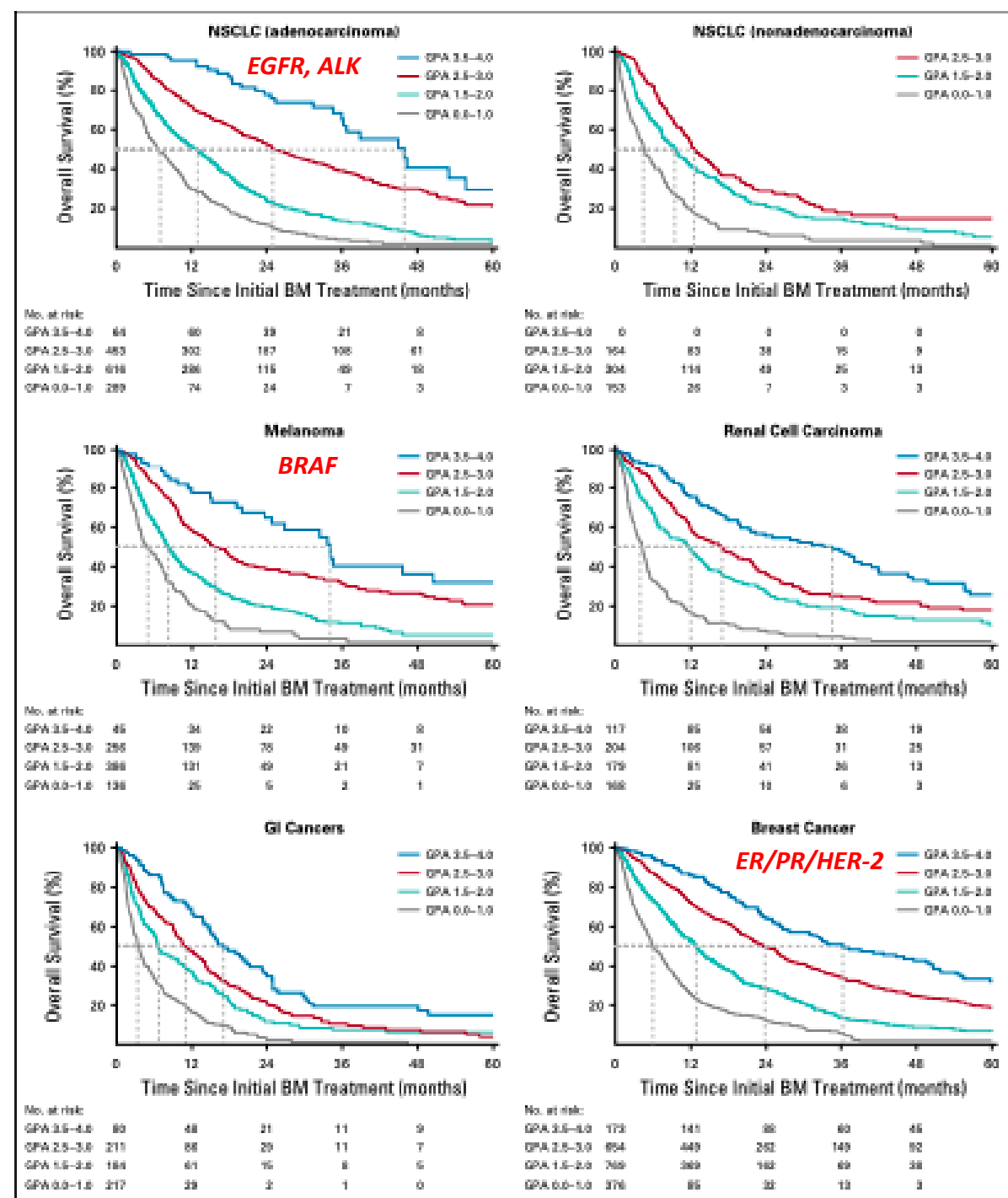
- Edad, (KPS), metástasis extracraneales y número de metástasis cerebrales, histología del primario y perfil molecular .
- 2020 con 6,984 pacientes, entre 2006 y 2017.
- No incluye pacientes con carcinomatosis Leptomeningea ni recurrencia de nuevas metástasis.

### Superviciencia:

Pulmón (no microcítico): 7-47 meses  
 Mama: 3-36 meses  
 Melanoma: 5-34 meses  
 Gastro-Intestinales: 3-17 meses  
 Renales: 4-35 meses

### Índice GPA: 0,0 - 4,0

- GPA: 3,5 - 4,0
- GPA: 2,5 - 3,0
- GPA: 1,5 - 2,0
- GPS: 0,0 - 1,0



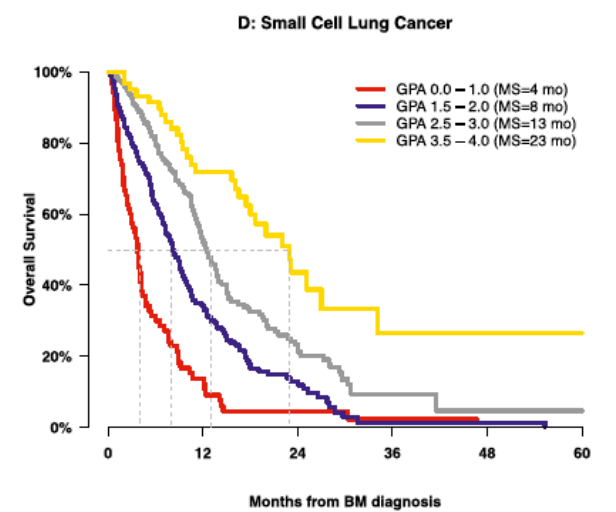
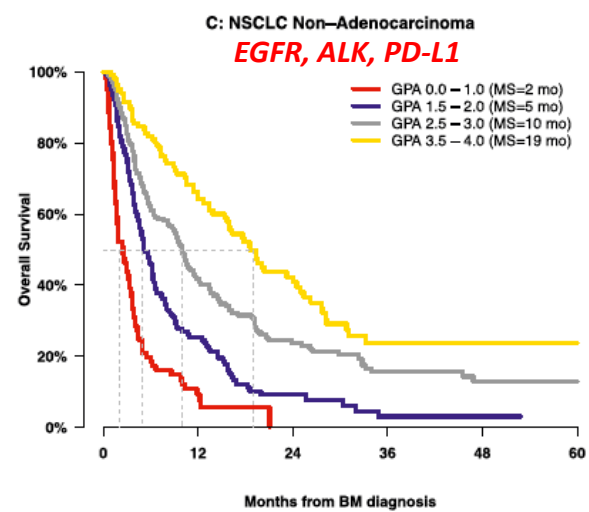
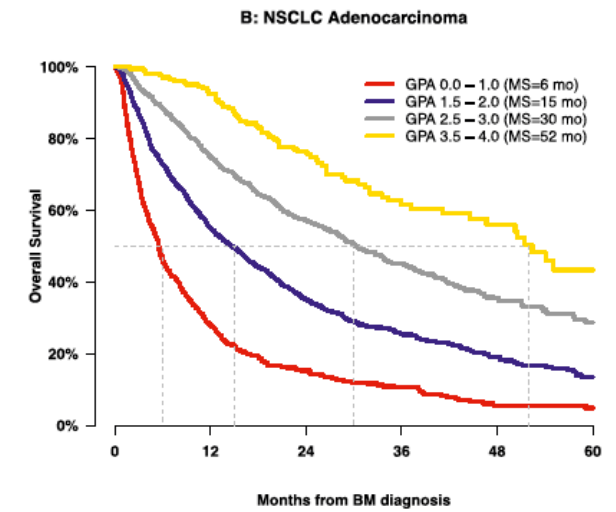
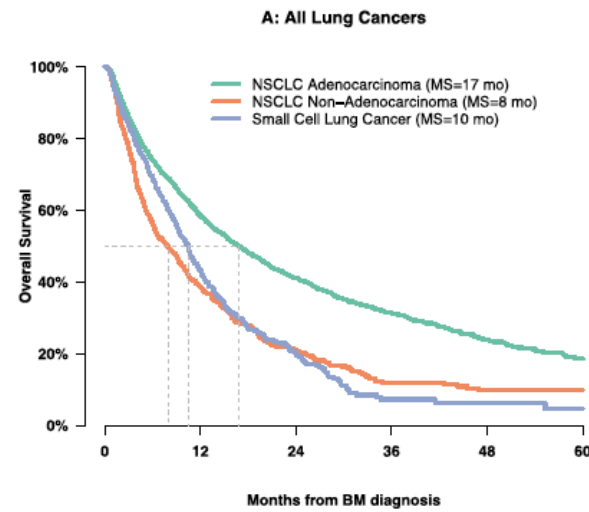
# Graded Prognostic Assessment (GPA) for Patients With Lung Cancer and Brain Metastases: Initial Report of the Small Cell Lung Cancer GPA and Update of the Non-Small Cell Lung Cancer GPA Including the Effect of Programmed Death Ligand 1 and Other Prognostic Factors

Sperduto et al 2022 *Int J Radiation Oncol Biol Phys*, Vol. 114, No. 1, pp. 60–74, 2022

## Supervivencia media:

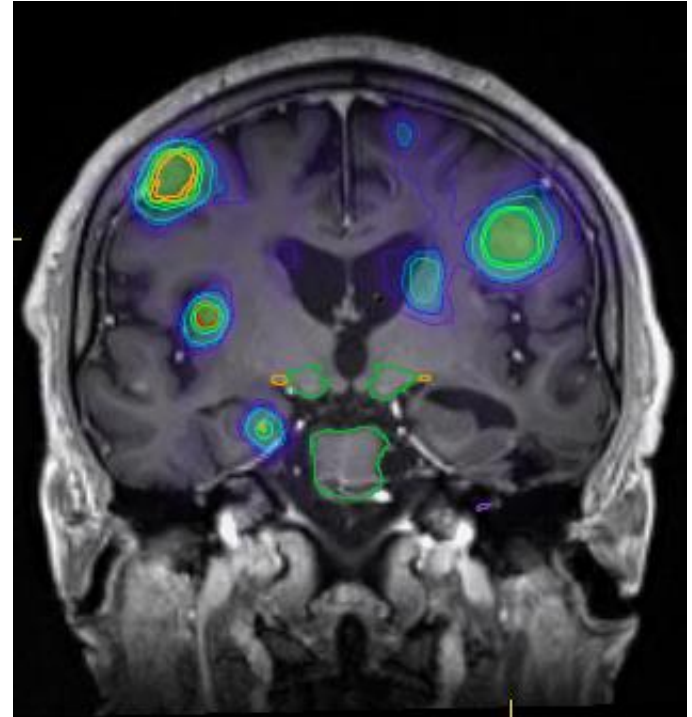
- Adenocarcinoma: 17 meses (6-52)
- No Adenocarcinoma: 8 meses (2-19)
- Microcítico: 10 meses (4-23)

		NSCLC adenocarcinoma				NSCLC nonadenocarcinoma					
		n (%)	MS	HR*	95% CI*	P value*	n (%)	MS	HR*	95% CI*	P value*
EGFR	Positive	777 (26)	25	1.00	Ref	<.01	29 (5)	12	1.00	Ref	.43
	Negative	1813 (60)	16	1.40	1.24, 1.59		253 (41)	9	1.39	0.85, 2.28	
	Unknown	412 (14)	7	2.02	1.59, 2.56		329 (54)	6	1.32	0.67, 2.60	
ALK	Positive	161 (5)	44	1.00	Ref	<.01	7 (1)	8	1.00	Ref	.67
	Negative	2307 (77)	18	2.12	1.66, 2.70		271 (44)	10	0.76	0.28, 2.06	
	Unknown	534 (18)	9	2.24	1.63, 3.07		333 (55)	6	0.93	0.31, 2.81	
PD-L1	75%-100%	318 (11)	24	1.00	Ref	<.01	51 (8)	7	1.00	Ref	.82
	50%-74%	273 (9)	23	1.16	0.92, 1.45		38 (6)	8	1.11	0.65, 1.89	
	25%-49%	105 (3)	22	1.09	0.79, 1.50		24 (4)	7	1.05	0.57, 1.95	
	1%-24%	459 (15)	19	1.29	1.05, 1.58		78 (13)	12	0.98	0.62, 1.56	
	0% (negative)	693 (23)	17	1.41	1.17, 1.70		128 (21)	8	1.11	0.74, 1.68	
	Unknown	1154 (38)	13	1.48	1.23, 1.78		292 (48)	6	1.23	0.82, 1.84	



and  $\geq 50\%$  PD-L1 expression was 17, 19, and 24 months, respectively ( $P < .01$ ), confirming PD-L1 is a significant prognostic factor. EGFR, ALK, and PD-L1 expression were not routinely tested in all patients with lung nonadenocarcinoma or SCLC, and the prognostic significance cannot be determined from the limited numbers.

Qué pacientes se  
benefician de SRS?

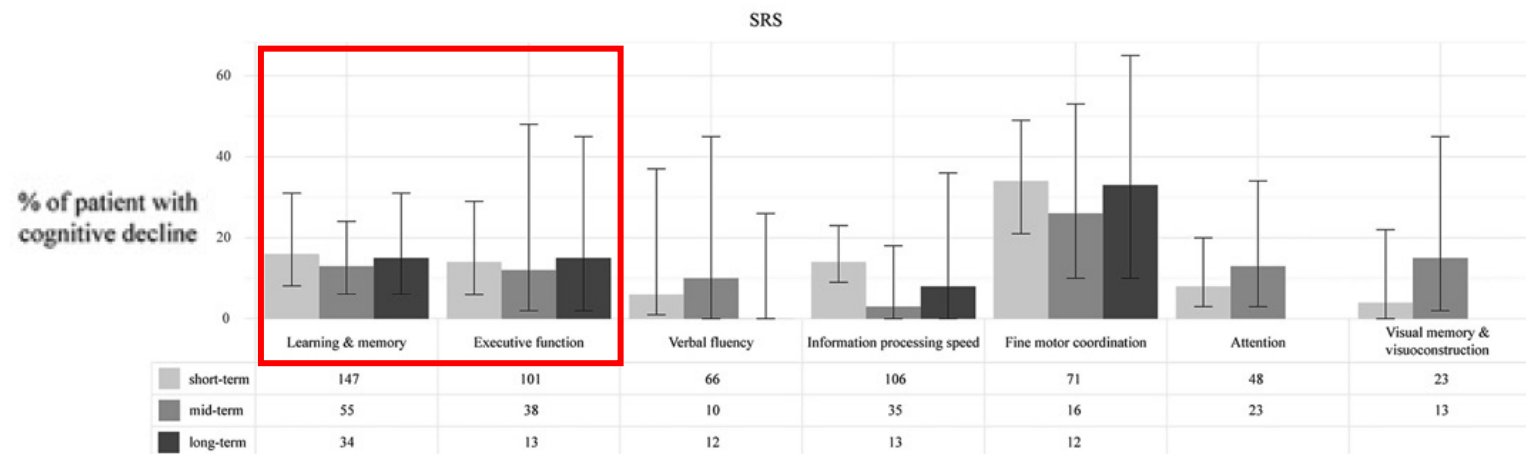
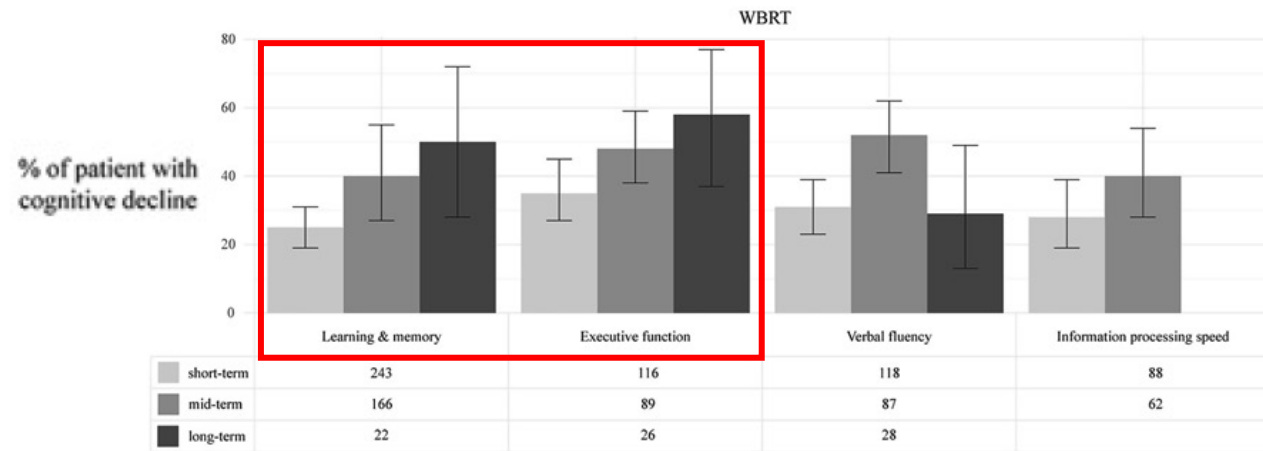


# The Impact of Stereotactic or Whole Brain Radiotherapy on Neurocognitive Functioning in Adult Patients with Brain Metastases: A Systematic Review and Meta-Analysis

Eva Elisabeth van Grinsven<sup>a</sup> Steven H.J. Nagtegaal<sup>b</sup> Joost J.C. Verhoeff<sup>b</sup>  
Martine J.E. van Zandvoort<sup>a,c</sup>

## Abstract

**Background & Objectives:** Radiotherapy is standard treatment for patients with brain metastases (BMs), although it may lead to radiation-induced cognitive impairment. This review explores the impact of whole-brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS) on cognition. **Methods:** The PRISMA guidelines were used to identify articles on PubMed and EmBase reporting on objective assessment of cognition before, and at least once after radiotherapy, in adult patients with nonresected BMs. **Results:** Of the 867 records screened, twenty articles (14 unique studies) were included. WBRT lead to decline in cognitive performance, which stabilized or returned to baseline in patients with survival of at least 9–15 months. For SRS, a decline in cognitive performance was sometimes observed shortly after treatment, but the majority of patients returned to or remained at baseline until a year after treatment. **Conclusions:** These findings suggest that after WBRT, patients can experience deterioration over a longer period of time. The cognitive side effects of SRS are transient. Therefore, this review advises to choose SRS as this will result in lowest risks for cognitive adverse side effects, irrespective of predicted survival. In an already cognitively vulnerable patient population with limited survival, this information can be used in communicating risks and aid in making educated decisions.



# Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases

## A Randomized Clinical Trial

- 213 pacientes con 1-3 MTS entre 2002 y 2013 tratados con SRS vs SRS + WBRT.
- Lesiones de < 3 cm, ECOG  $\leq$  2
- Objetivo Primario: Deterioro cognitivo a los 3 meses.
- Secundarios: Tiempo hasta la recaída intracraneal, Calidad de vida, independencia funcional, estado cognitivo a largo plazo y SG.
- **Conclusión:**
  - SRS en 1-3 MTS vs SRS + WBRT reduce el deterioro cognitivo a los 3 meses.
  - Mejor control de progresión de nuevas lesiones intracraneal y extracraneal SRS + WBRT.
  - No diferencias en SG.
  - 1-3 MTS se recomienda tratamiento con SRS.

Figure 2. Cumulative Incidence of Brain Tumor Progression (Local and/or Distant) After Correcting for the Competing Risk of Survival According to Treatment Group

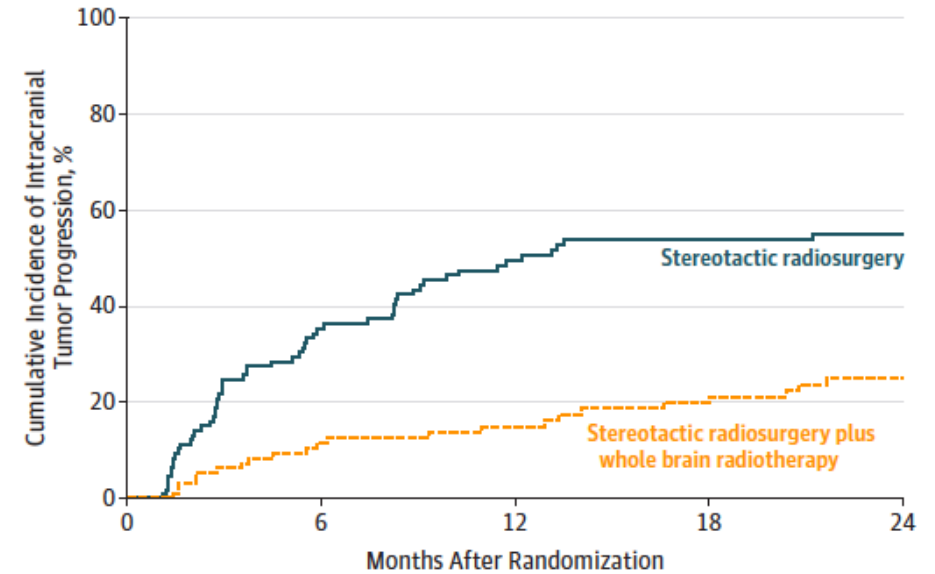
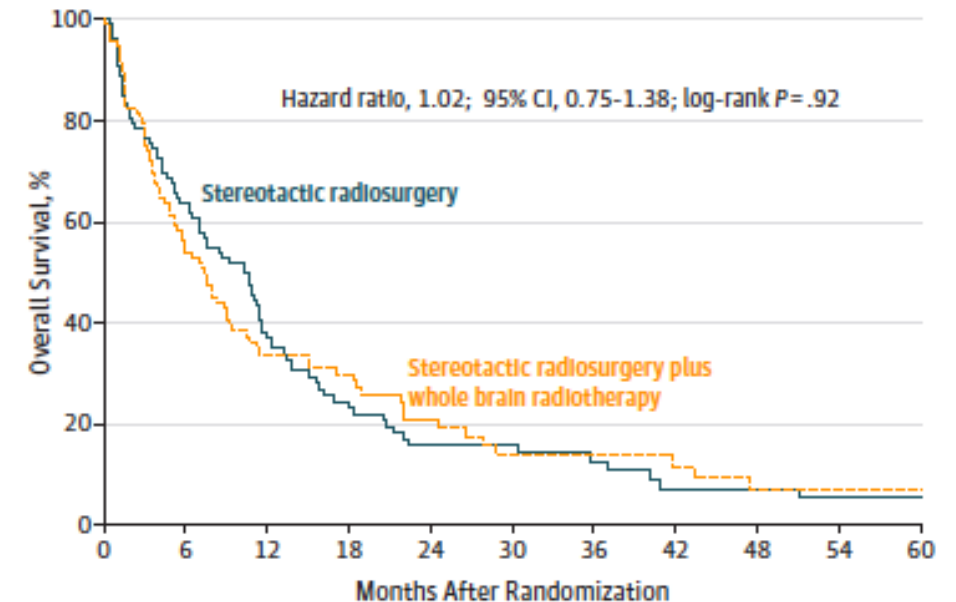


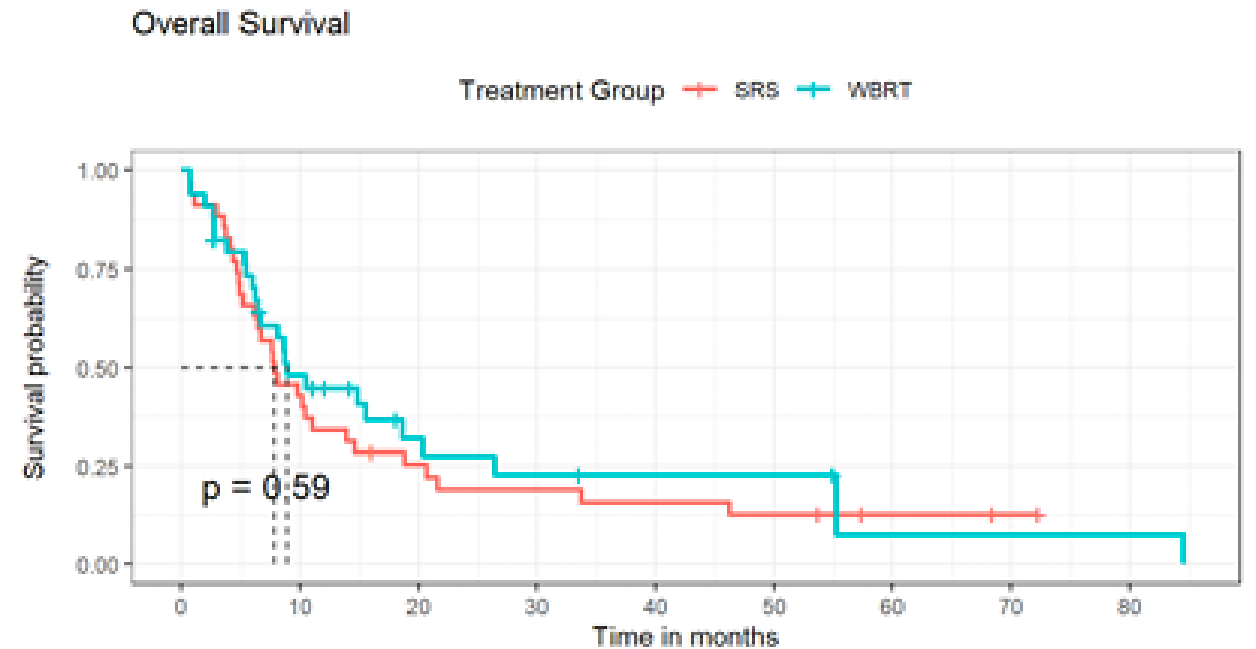
Figure 3. Kaplan-Meier Estimates of Overall Survival According to Treatment Group



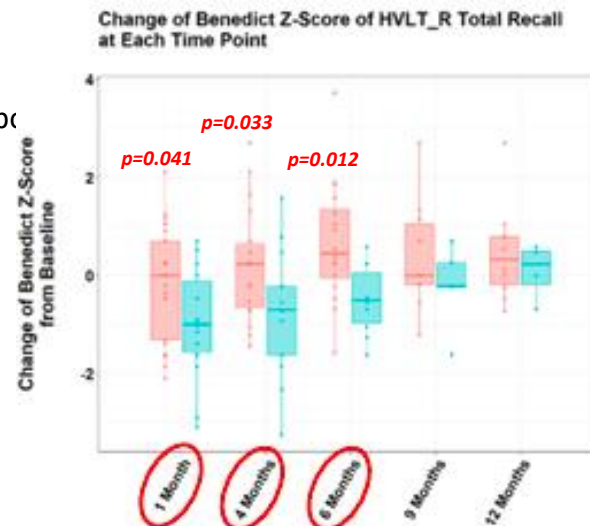
## Stereotactic Radiosurgery versus Whole-brain Radiation Therapy for Patients with 4-15 Brain Metastases: A Phase III Randomized Controlled Trial

J. Li • E.B. Ludmir • Y. Wang • ... E.P. Sulman • P.D. Brown • J.S. Wefel • [Show all authors](#)

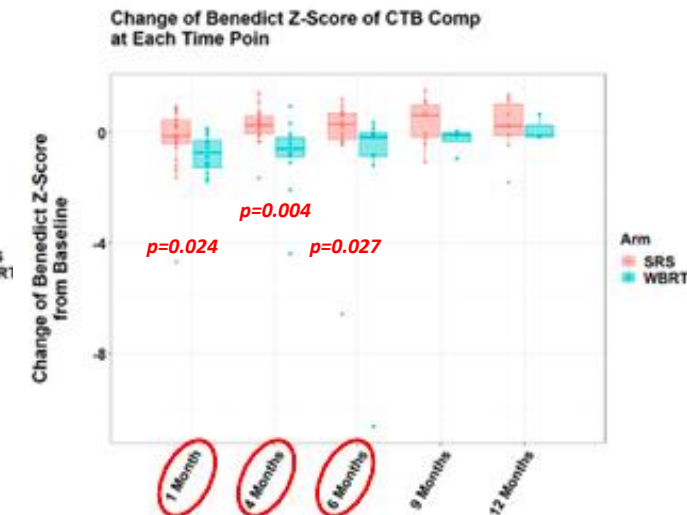
- Estudio randomizado Fase III, 72 pacientes entre 2012 y 2019.
  - Pacientes con 4-15 MTS
  - KPS  $\geq$  70
  - No WBRT previo
  - SRS de 1-3 lesiones > 6 semanas
  - No melanoma o microcítico de pulmón
- Objetivo Principal:
  - Hopkins Verbal Learning Test - Revised Total Recall (HVL-R TR) score:
    - Memoria y función global cognitiva.
  - Control Local a los 4 meses.
- Secundarios:
  - Supervivencia Global, control de la enfermedad extracranial, toxicidad, tiempo para el inicio de QT.
- Conclusiones:
  - **SRS en 4-15 lesiones:**
    - SRS disminución significativa del deterioro cognitivo.
    - No retraso en inicio de manejo sistémico.



### Memory Function at 4 Months



### Global Cognitive Function Measure



## Stereotactic Radiosurgery Compared With Hippocampal-Avoidant Whole Brain Radiotherapy (HA-WBRT) Plus Memantine for 5 or More Brain Metastases



The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. [Know the risks and potential benefits](#) of clinical studies and talk to your health care provider before participating. Read our [disclaimer](#) for details.

ClinicalTrials.gov Identifier: NCT03550391

[Recruitment Status](#) ⓘ : Recruiting

[First Posted](#) ⓘ : June 8, 2018

[Last Update Posted](#) ⓘ : April 14, 2022

See [Contacts and Locations](#)

### Sponsor:

Canadian Cancer Trials Group

### Collaborators:

Alliance for Clinical Trials in Oncology

NRG Oncology

### Information provided by (Responsible Party):

Canadian Cancer Trials Group

### Study Design

Go to

[Study Type](#) ⓘ : Interventional (Clinical Trial)

Estimated [Enrollment](#) ⓘ : 206 participants

Allocation: Randomized

Intervention Model: Parallel Assignment

Intervention Model Description: This is an international multi-centre, open-label, randomized phase III trial comparing stereotactic radiosurgery compared with hippocampal-avoidant whole brain radiotherapy (HA-WBRT) plus memantine for 5-15 brain metastases

Masking: None (Open Label)

Primary Purpose: Treatment

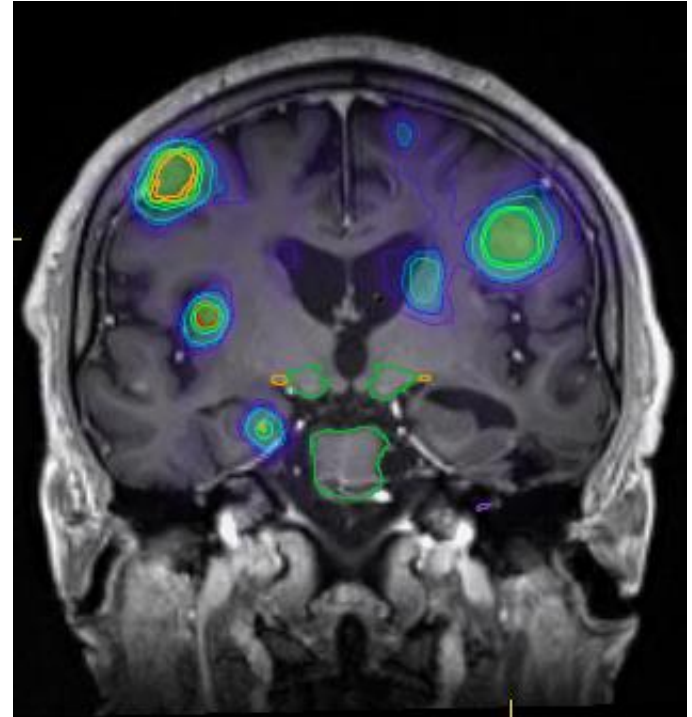
Official Title: A Phase III Trial of Stereotactic Radiosurgery Compared With Hippocampal-Avoidant Whole Brain Radiotherapy (HA-WBRT) Plus Memantine for 5 or More Brain Metastases

Actual [Study Start Date](#) ⓘ : May 25, 2018

Estimated [Primary Completion Date](#) ⓘ : December 31, 2022

Estimated [Study Completion Date](#) ⓘ : June 30, 2023

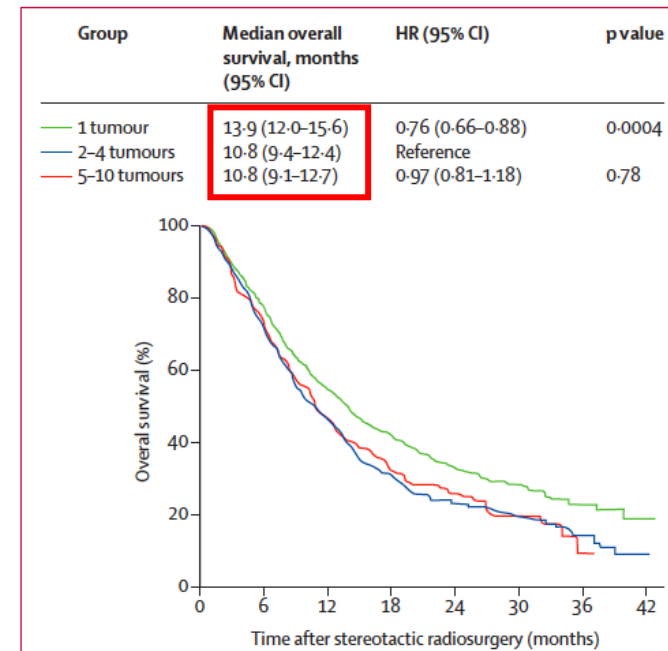
Hasta cuántas lesiones  
podemos tratar?



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

Masaaki Yamamoto\*, Toru Serizawa\*, Takashi Shuto, Atsuya Akabane, Yoshinori Higuchi, Jun Kawagishi, Kazuhiro Yamanaka, Yasunori Sato, Hidefumi Jokura, Shoji Yomo, Osamu Nagano, Hiroyuki Kenai, Akihito Moriki, Satoshi Suzuki, Yoshihisa Kida, Yoshiyasu Iwai, Motohiro Hayashi, Hiroaki Onishi, Masazumi Gondo, Mitsuya Sato, Tomohide Akimitsu, Kenji Kubo, Yasuhiro Kikuchi, Toru Shibasaki, Tomoaki Goto, Masami Takanashi, Yoshimasa Mori, Kintomo Takakura, Naokatsu Saeki, Etsuo Kunieda, Hidefumi Aoyama, Suketaka Momoshima, Kazuhiro Tsuchiya

- Estudio prospectivo observacional multi-institucional pacientes tratados con SRS exclusivamente:
  - 1 MTS: 455 pacientes
  - 2-4 MTS: 531 pacientes: Volumen Medio 3,45 cc, Volumen máximo 13,9 cc
  - 5-10 MTS: 208 pacientes: Volumen Medio 3,07 cc, Volumen máximo 14,96 cc
  - KPS  $\geq$  70
  - **Dosis de tratamiento:**
    - < 4 cc : 22 Gy
    - 4-10 cc: 20 Gy
- Comparar la no inferioridad en supervivencia global de tratar 5-10 mts vs 2-4 mts.
- 1194 pacientes de 23 centros entre Marzo 2009 y febrero 2012 con seguimiento medio de 20.9 meses.
- **Conclusión: Tratar 5-10 lesiones no es inferior a 2-4 en SG ni en toxicidad.**



	Total (n=1194)	1 tumour (A) (n=455)	2-4 tumours (B) (n=531)	5-10 tumours (C) (n=208)	p value (B vs C)
Treatment-related adverse events*					0.89†
None	1093 (92%)	422 (93%)	481 (91%)	190 (91%)	
Grade 1 and 2	69 (6%)	22 (5%)	36 (7%)	11 (5%)	..
Grade 3	20 (2%)	6 (1%)	10 (2%)	4 (2%)	..
Grade 4	8 (1%)	3 (1%)	3 (1%)	2 (1%)	..
Grade 5	4 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	..
Had MMSE at baseline	1132 (95%)	430 (95%)	504 (95%)	198 (95%)	..
Maintained neurocognitive function‡					
4 months after SRS	623/662 (94%)	243/256 (95%)	263/284 (93%)	117/122 (96%)	0.27
12 months after SRS	333/366 (91%)	141/154 (92%)	139/152 (91%)	53/60 (88%)	0.60
24 months after SRS	120/128 (94%)	55/60 (92%)	47/48 (98%)	18/20 (90%)	0.20
36 months after SRS	28/30 (93%)	14/15 (93%)	10/11 (91%)	4/4 (100%)	1.00

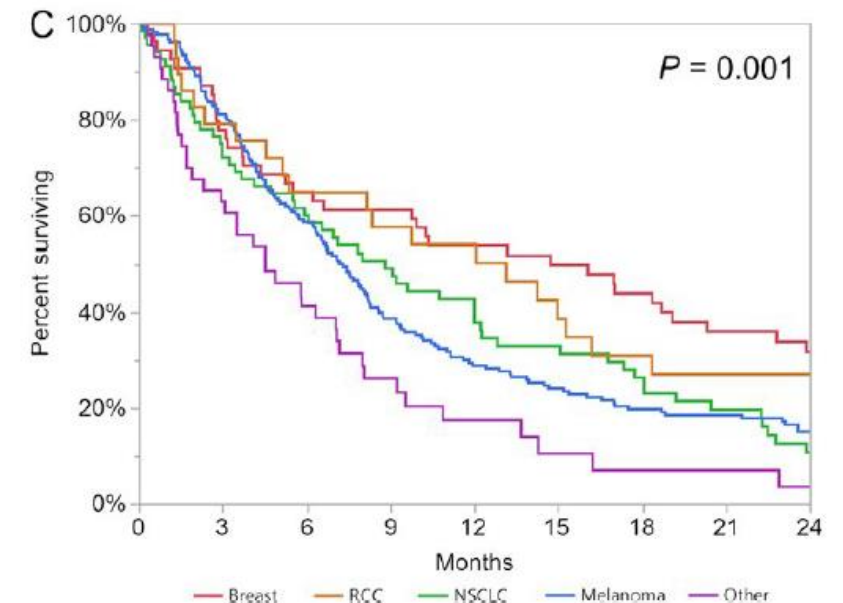
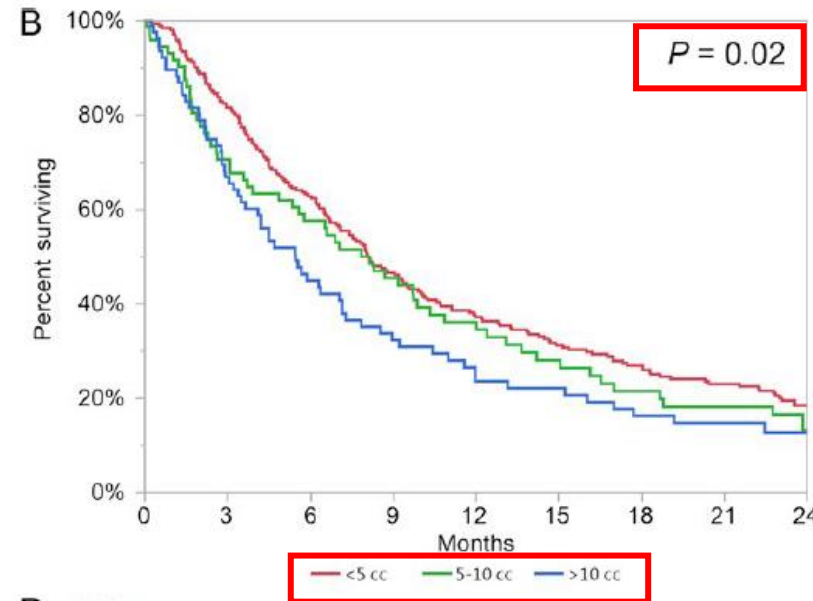
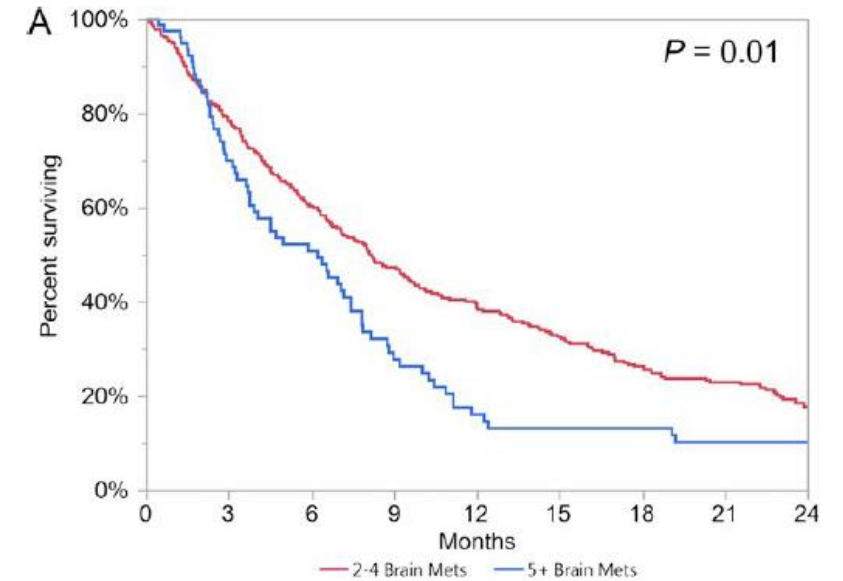
Data are number of patients with one or more adverse event (%), unless otherwise specified. MMSE=Mini-Mental State Examination. SRS=stereotactic radiosurgery. \*Graded according to Common Terminology Criteria for Adverse Events, version 3.0.<sup>26</sup> †p value is for the number of patients with no adverse events versus the number with at least one or more grade 1-5 adverse event across all three tumour number groups. ‡Number of patients whose MMSE score did not decrease by 3 points or more from baseline (ie, same day or one day before or after SRS); percentages are based on the number of patients who completed MMSE at that timepoint.<sup>5</sup>

Table 6: Adverse events and maintenance of neurocognitive function

## The growing importance of lesion volume as a prognostic factor in patients with multiple brain metastases treated with stereotactic radiosurgery

David M. Routman<sup>1,2</sup> , Shelly X. Bian<sup>2</sup>, Kevin Diao<sup>2,3</sup> , Jonathan L. Liu<sup>4</sup>, Cheng Yu<sup>2</sup>, Jason Ye<sup>2</sup>, Gabriel Zada<sup>5</sup> & Eric L. Chang<sup>2</sup>

- Estudio retrospectivo 391 pacientes con >2 mts, tratados entre 1994 y 2015.
  - 2-4 mts: OS 8.1 meses
  - >5 mts: OS 6.2 meses
- Factores de mal pronóstico:
  - **Vol > 10 cc**
  - Histología
  - KPS

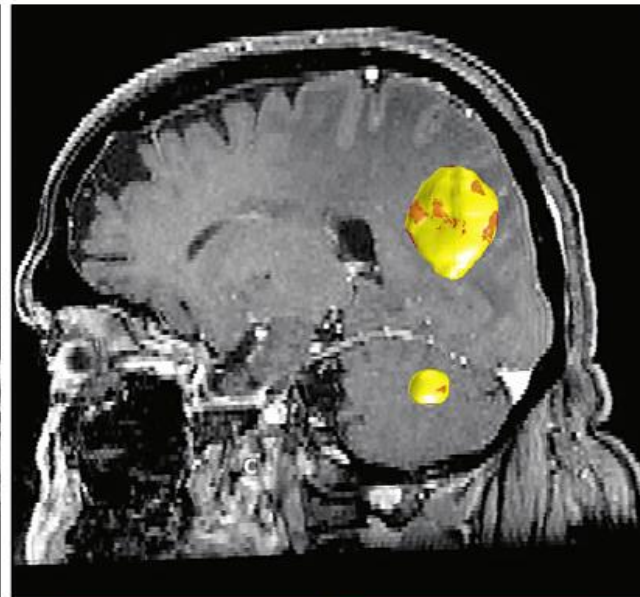
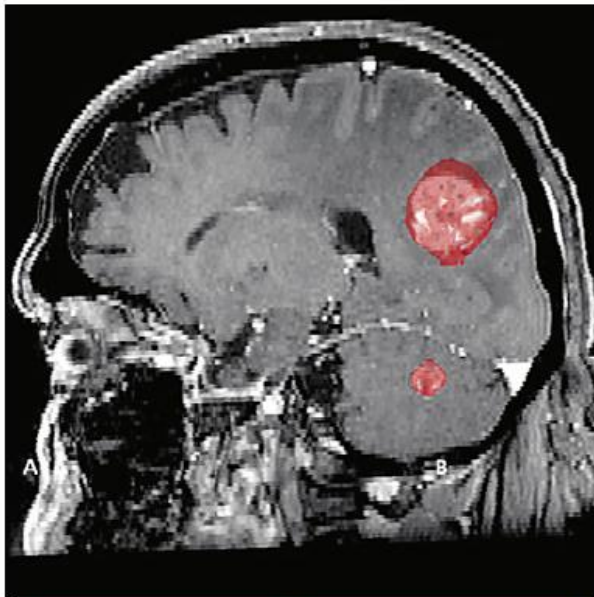


# Guidelines for Multiple Brain Metastases Radiosurgery

Ajay Niranjan<sup>a</sup> Edward Monaco<sup>a</sup> John Flickinger<sup>b</sup> L. Dade Lunsford<sup>a</sup>

<sup>a</sup>Departments of Neurological Surgery and Radiation Oncology, University of Pittsburgh, Pittsburgh, PA, USA;

<sup>b</sup>Center for Image-Guided Neurosurgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA



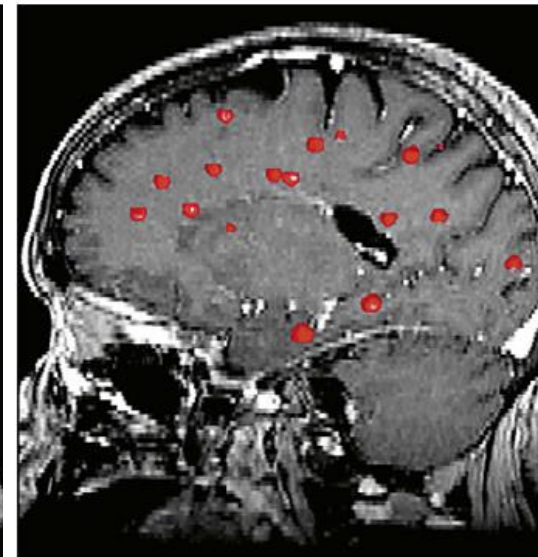
76-year-old man with colorectal carcinoma with 2 metastatic brain tumors

R parietal: 9.23 cm<sup>3</sup>  
R cerebellar: 0.71 cm<sup>3</sup>  
Total tumor volume: 9.94 cm<sup>3</sup>

SRS margin dose  
R parietal tumor: 17 Gy  
R cerebellar tumor: 18 Gy

12 Gy volume: 24.29 cm<sup>3</sup>

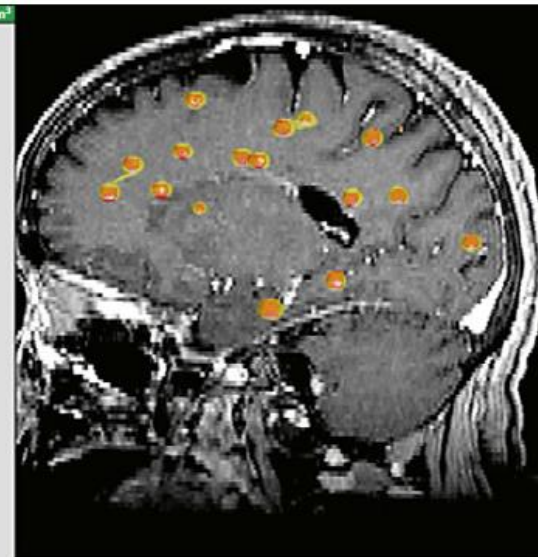
2 lesiones  
Volumen: 10 cm<sup>3</sup>



Met #	Volume in cm <sup>3</sup>
1	0.023
2	0.064
3	0.075
4	0.057
5	0.211
6	0.069
7	0.078
8	0.074
9	0.084
10	0.063
11	0.067
12	0.064
13	0.06
14	0.064
15	0.078
16	0.01
17	0.106
18	0.64
19	0.017
20	0.072
21	0.058
22	0.12
23	0.128
24	0.076
25	0.068
26	0.084
27	0.061
28	0.075
<b>Total GTV</b>	<b>2.707</b>

A 61-year-old female with breast cancer with multiple brain metastases was found to have 28 very small lesions

Total GTV: 2.707 cm<sup>3</sup>

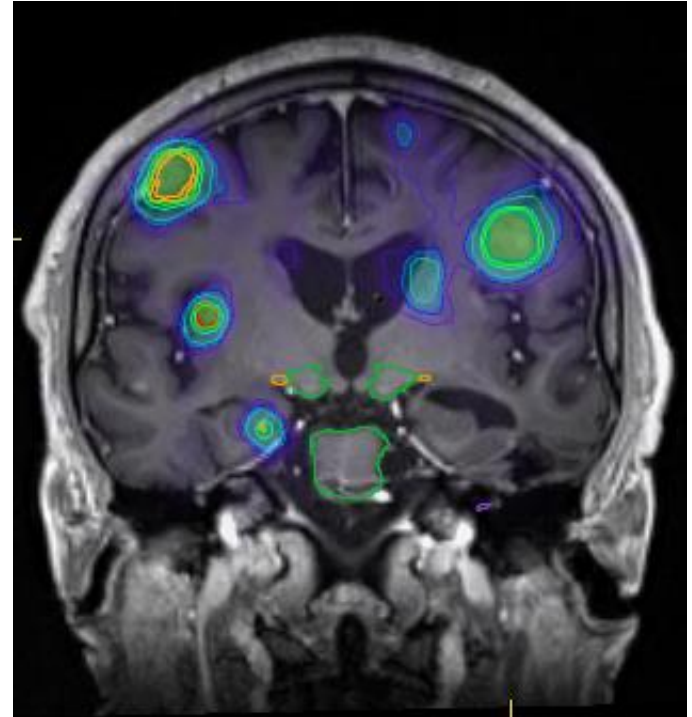


Tumor margin dose: 16 Gy

12 Gy volume: 16.0 cm<sup>3</sup>

28 lesiones  
Volumen: 2,7 cm<sup>3</sup>

Que dosis y  
fraccionamiento usar?



**SINGLE DOSE RADIOSURGICAL TREATMENT OF RECURRENT  
PREVIOUSLY IRRADIATED PRIMARY BRAIN TUMORS AND BRAIN  
METASTASES: FINAL REPORT OF RTOG PROTOCOL 90-05**

EDWARD SHAW, M.D.,\* CHARLES SCOTT, PH.D.,† LUIS SOUHAMI, M.D.,‡ ROBERT DINAPOLI, M.D.,§  
ROBERT KLINE, PH.D.,|| JAY LOEFFLER, M.D.,¶ AND NANCY FARNAN, B.S.†

Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 2, pp. 291-298, 2000

- Estudio de escalada de dosis para identificar la dosis máxima tolerada en lesiones metastásicas o de recidiva de Astrocitomas y Gliomas.
- 156 pacientes entre 1990 y 1994.

Table 3. Accrual by treatment arm and dose

Tumor diameter	Treatment arm/dose/accrual			
≤ 20 mm	Arm 1—> Arm 4—> Arm 7			
	18 Gy <i>n</i> = 12	21 Gy <i>n</i> = 18	24 Gy <i>n</i> = 10	
21–30 mm	Arm 2—> Arm 5—> Arm 8—> Arm II			
	15 Gy <i>n</i> = 15	18 Gy <i>n</i> = 15	21 Gy <i>n</i> = 13	24 Gy <i>n</i> = 12
31–40 mm	Arm 3—> Arm 6—> Arm 9			
	12 Gy <i>n</i> = 21	15 Gy <i>n</i> = 22	18 Gy <i>n</i> = 18	

**Conclusión:**

- ≤ 20 mm: 24 Gy
- 21-30 mm: 18 Gy
- 31-40 mm: 15 Gy



Systematic review

Dose–effect relation in stereotactic radiotherapy for brain metastases.

A systematic review

Ruud Wiggendaad<sup>a,\*</sup>, Antoinette Verbeek-de Kanter<sup>a</sup>, Henk B. Kal<sup>b</sup>, Martin Taphoorn<sup>c,e</sup>, Thomas Vissers<sup>d</sup>, Henk Struikmans<sup>a</sup>

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• Control a los 12 meses:

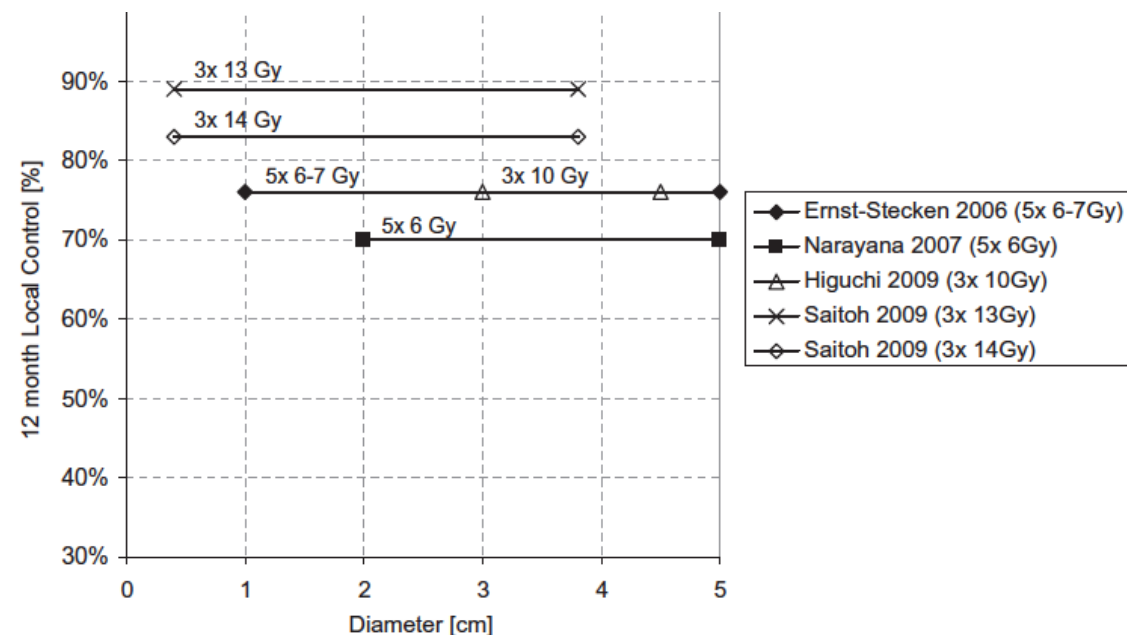
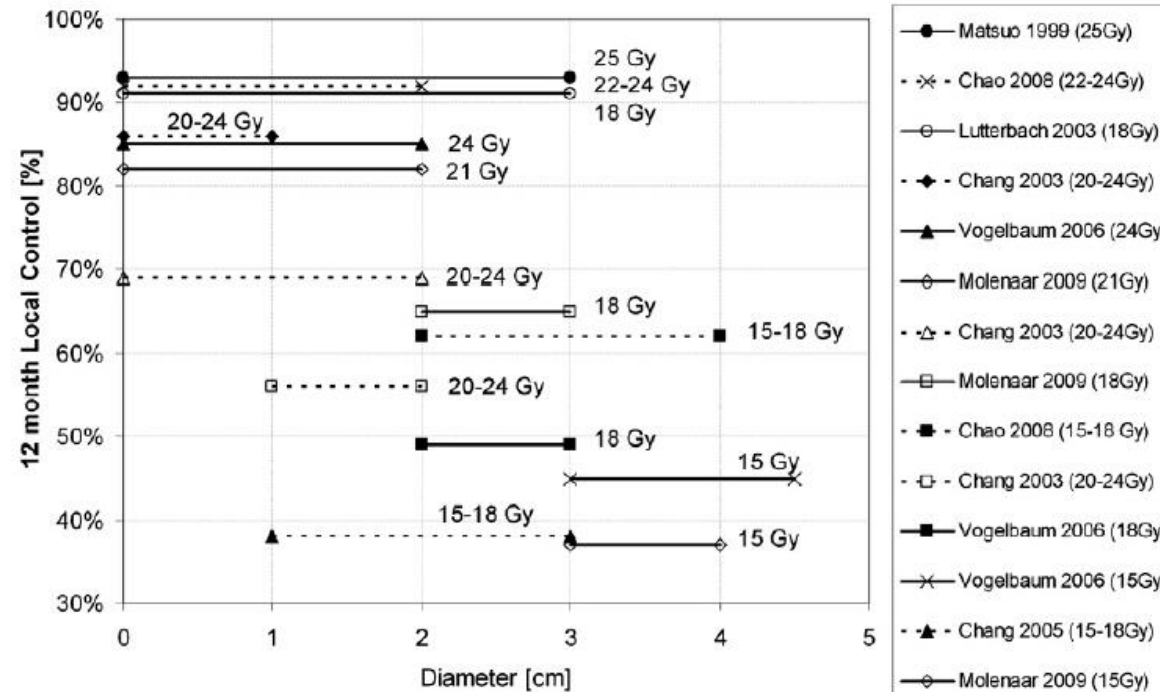
• Dosis única:

- 21 Gy (>80%)
- 18 Gy (>60%)
- 15 Gy (<50%)

• Dosis fraccionada:

- 30 Gy/5 fr
- 35 Gy/5 fr
- 30 Gy/3 fr
- 39 Gy/3 fr
- 42 Gy/3 fr

70-90%





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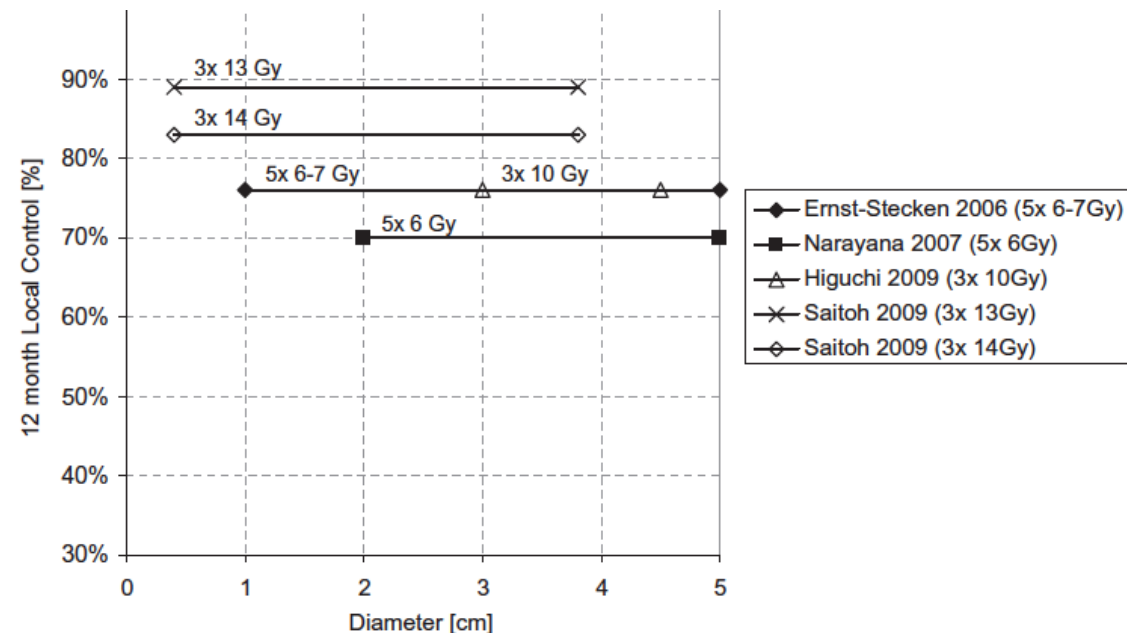
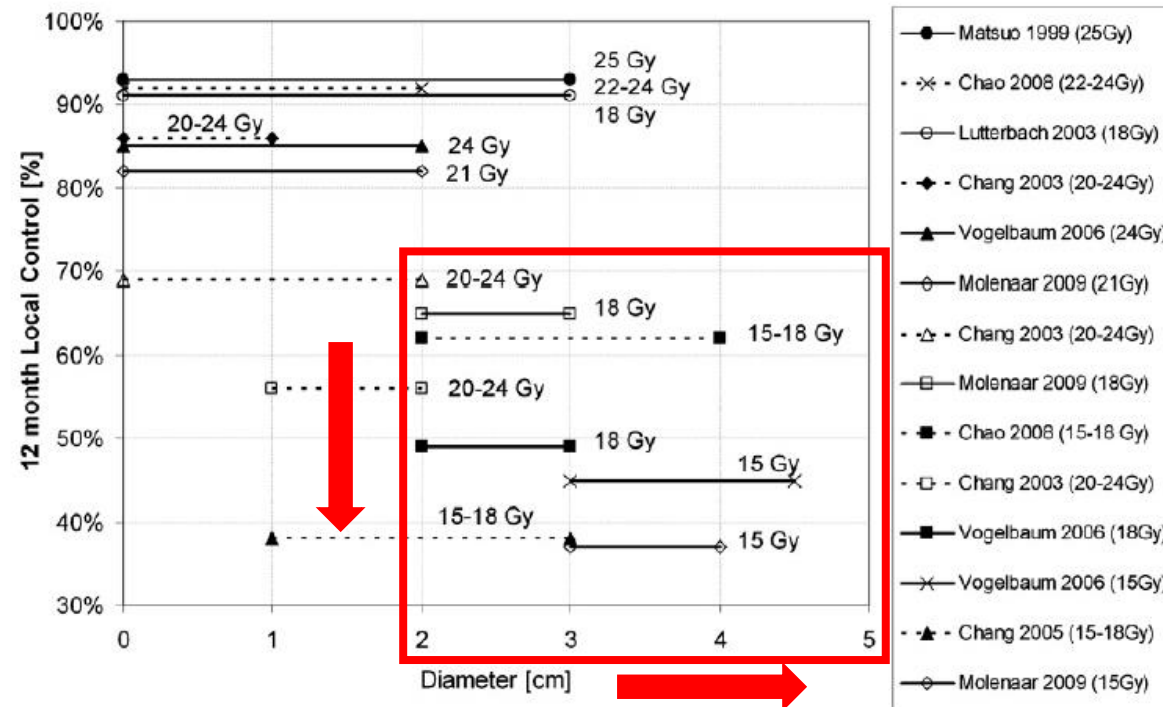
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70-90%





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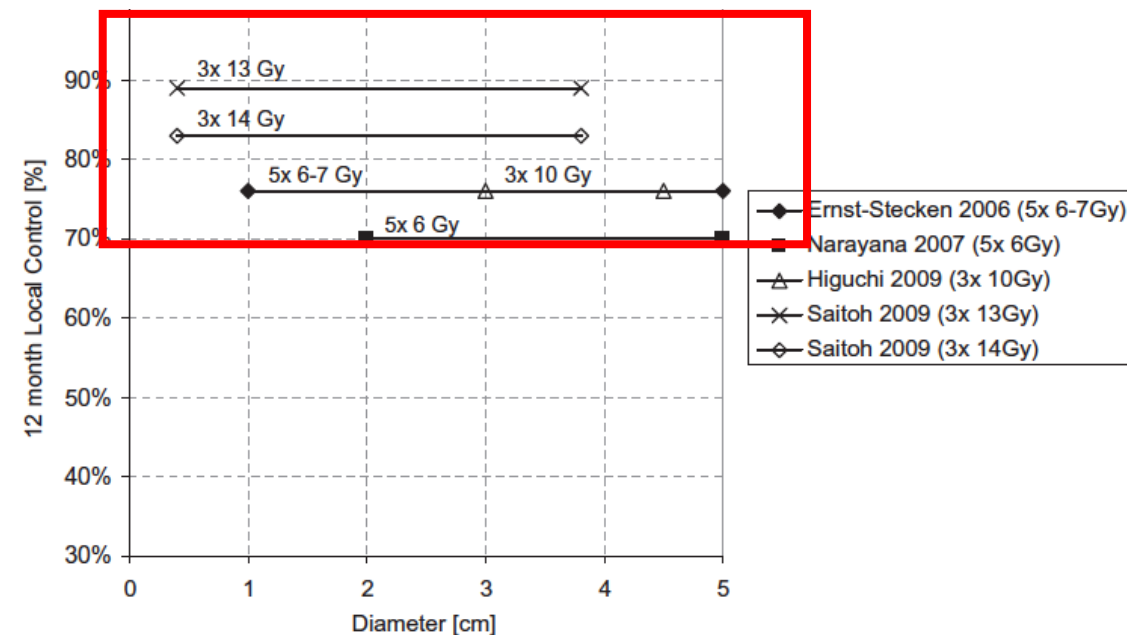
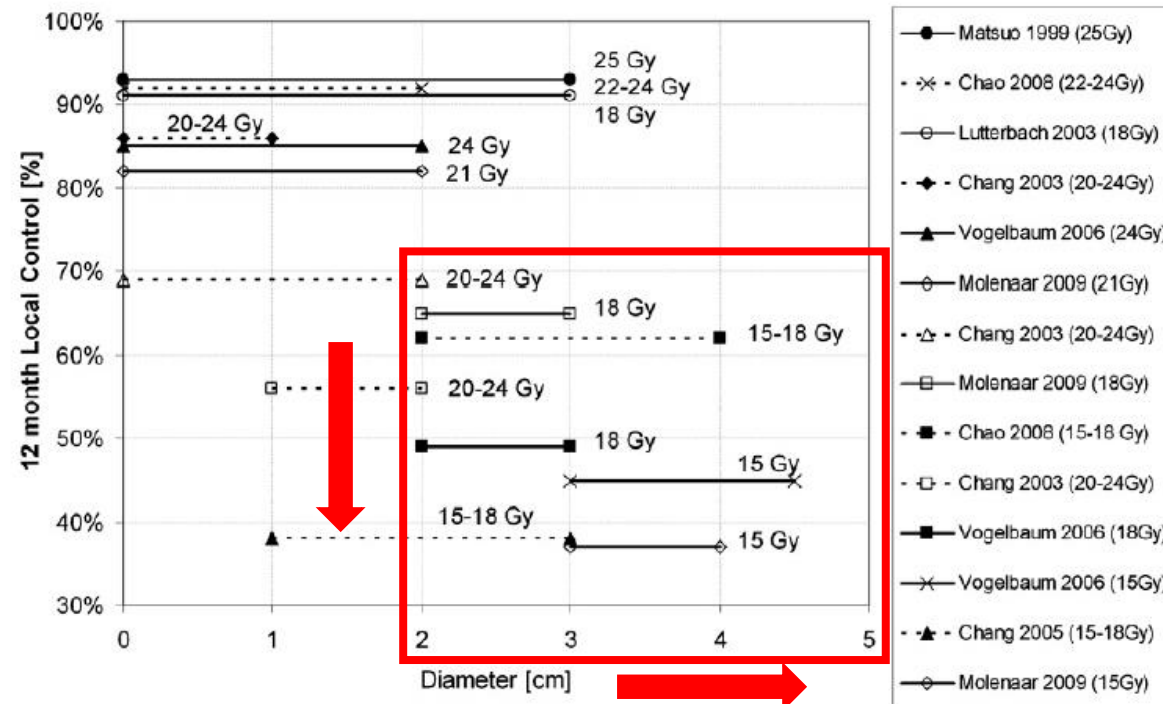
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70-90%





Systematic review

Dose–effect relation in stereotactic radiotherapy for brain metastases.

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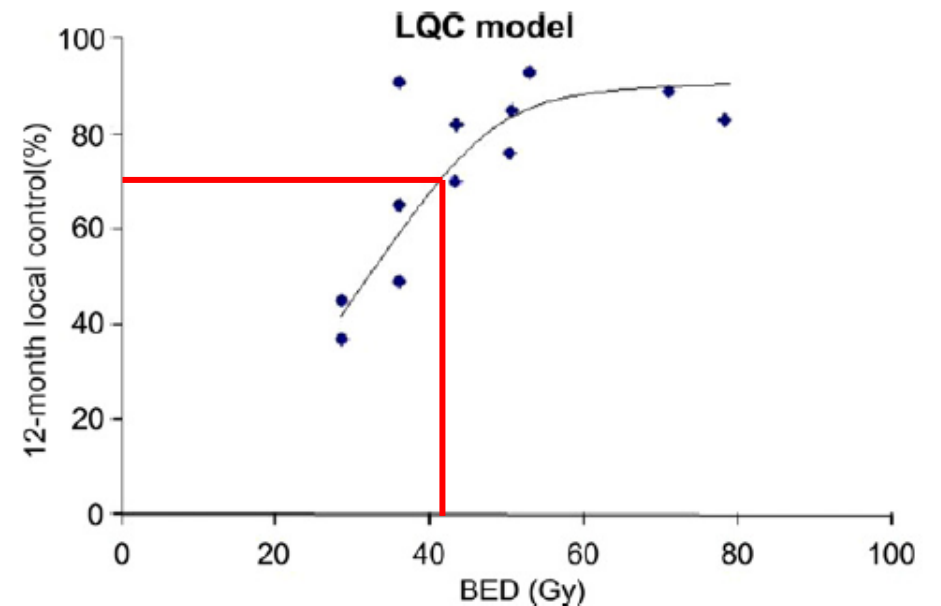
Ruud Wiggendaad<sup>a,\*</sup>, Antoinette Verbeek-de Kanter<sup>a</sup>, Henk B. Kal<sup>b</sup>, Martin Taphoorn<sup>c,e</sup>, Thomas Vissers<sup>d</sup>, Henk Struikmans<sup>a</sup>

Modelo Lineal cuadrático ajustado a altas dosis

$\alpha/\beta$  de 12 Gy ( $BED_{12}$ )

Para obtener un control local a los 12 meses > 70% es necesario tener un  $BED_{12}$  de > 40 Gy, que equivale a 20 Gy/1fr

Dosis Total	Dosis x Fr	# Fr	$BED_{12}$
25 Gy	5 Gy	5	35 Gy
30 Gy	6 Gy	5	45 Gy
35 Gy	7 Gy	5	55 Gy
27 Gy	9 Gy	3	47 Gy
30 Gy	10 Gy	3	55 Gy
39 Gy	13 Gy	3	81 Gy
42 Gy	14 Gy	3	91 Gy



# Single-Fraction Versus Multifraction (3 × 9 Gy) Stereotactic Radiosurgery for Large (> 2 cm) Brain Metastases: A Comparative Analysis of Local Control and Risk of Radiation-Induced Brain Necrosis

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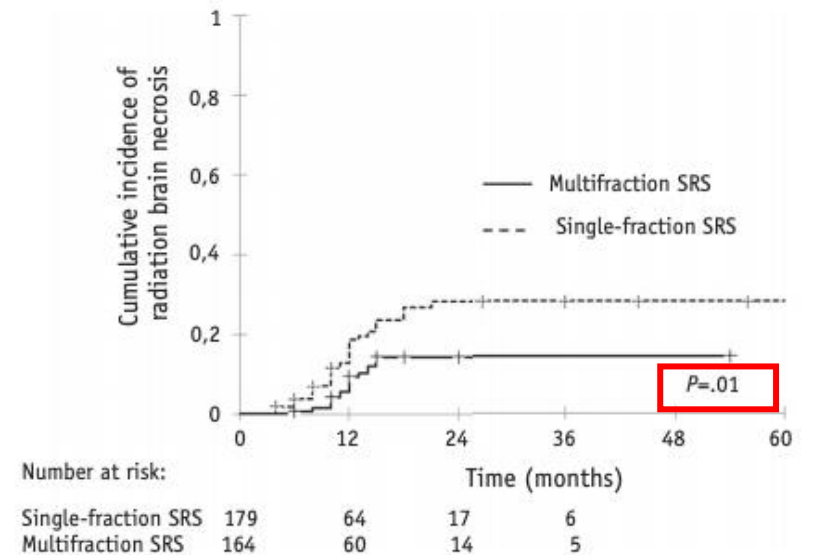
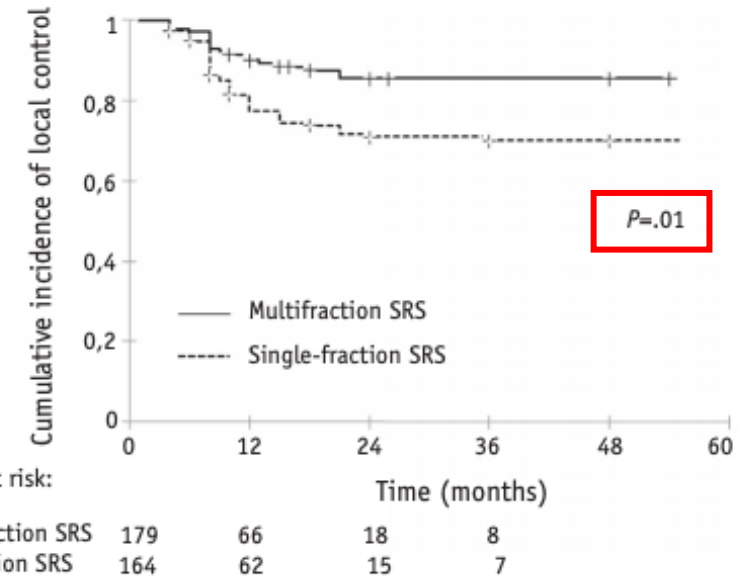
Received Aug 3, 2015, and in revised form Feb 6, 2016. Accepted for publication Mar 11, 2016.

- 354 pacientes con lesiones > 2 cm.
- Dosis única:
  - 2 – 3 cm: 18 Gy
  - >3 cm: 15-16 Gy
- Fraccionada:
  - 27 Gy en 3 fr de 9 Gy
  - ( $BED_{12}$  47 Gy)

LC: 77%  
RN: 20%

LC: 91%  
RN: 8%

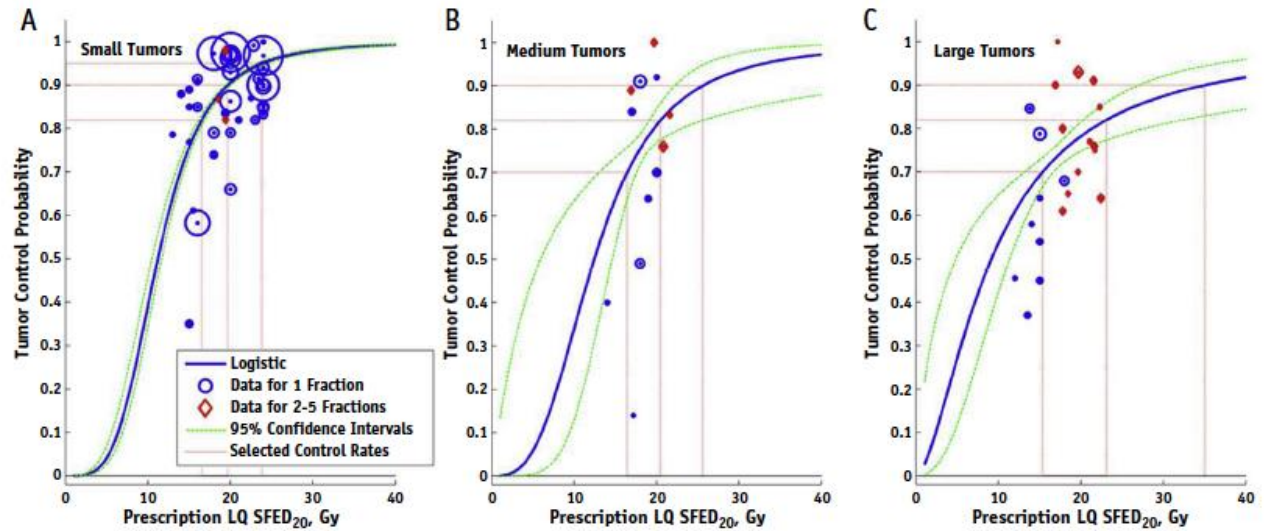
**Conclusions:** Multifraction SRS at a dose of 27 Gy in 3 daily fractions seems to be an effective treatment modality for large brain metastases, associated with better local control and a reduced risk of radiation-induced radionecrosis as compared with SF-SRS. © 2016 Elsevier Inc. All rights reserved.



# Tumor Control Probability of Radiosurgery and Fractionated Stereotactic Radiosurgery for Brain Metastases

Kristin J. Redmond, MD,\* Chengcheng Gui, BS,\* Stanley Benedict, PhD,† Michael T. Milano, MD,‡ Jimm Grimm, PhD,§ J. Austin Vargo, MD,|| Scott G. Soltys, MD,¶ Ellen Yorke, PhD,# Andrew Jackson, PhD,# Issam El Naqa, PhD,\*\* Lawrence B. Marks, MD,†† Jinyu Xue, PhD,‡‡ Dwight E. Heron, MD, MBA,§§ and Lawrence R. Kleinberg, MD\*

Received Oct 7, 2020. Accepted for publication Oct 25, 2020.



## Control Local a 1 año:

### Dosis Única:

- ≤ 20 mm:
  - **18 Gy: >85%**
  - **24 Gy: 95%**
- 21 – 30 mm:
  - **18 Gy: 75%**
- 31-40 mm:
  - **15 Gy: ~69%**

### Fraccionada:

- 21 – 40 mm:
  - **27-35 Gy en 3-5 fr: 80%**

**Results:** Of 2951 potentially eligible manuscripts, 56 included sufficient dose-volume data for analyses. Accepting that necrosis and pseudoprogression can complicate the assessment of LC, for tumors ≤20 mm, single-fraction doses of 18 and 24 Gy corresponded with >85% and 95% 1-year LC rates, respectively. For tumors 21 to 30 mm, an 18 Gy single-fraction dose was associated with 75% LC. For tumors 31 to 40 mm, a 15 Gy single-fraction dose yielded ~69% LC. For 3- to 5-fraction fSRS using doses in the range of 27 to 35 Gy, 80% 1-year LC has been achieved for tumors of 21 to 40 mm in diameter. **Conclusions:** TCP for SRS and fSRS are presented. For small lesions <20 mm, single doses of ≈ 18 Gy appear generally associated with excellent rates of LC; for melanoma, higher doses seem warranted. For larger lesions >20 mm, local control rates appear to be ≈ 70% to 75% with usual doses of 15 to 18 Gy, and in this setting, fSRS regimens should be considered. Greater consistency in reporting of dosimetric and LC data is needed to facilitate future pooled analyses. As systemic and biologic therapies evolve, updated analyses will be needed to further assess the necessity, efficacy, and toxicity of SRS and fSRS.

# Single- and Multifraction Stereotactic Radiosurgery Dose/Volume Tolerances of the Brain

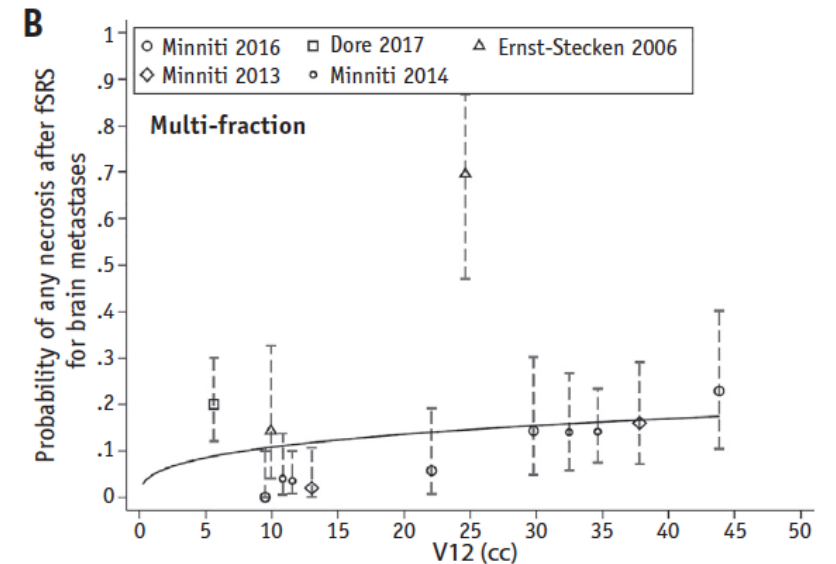
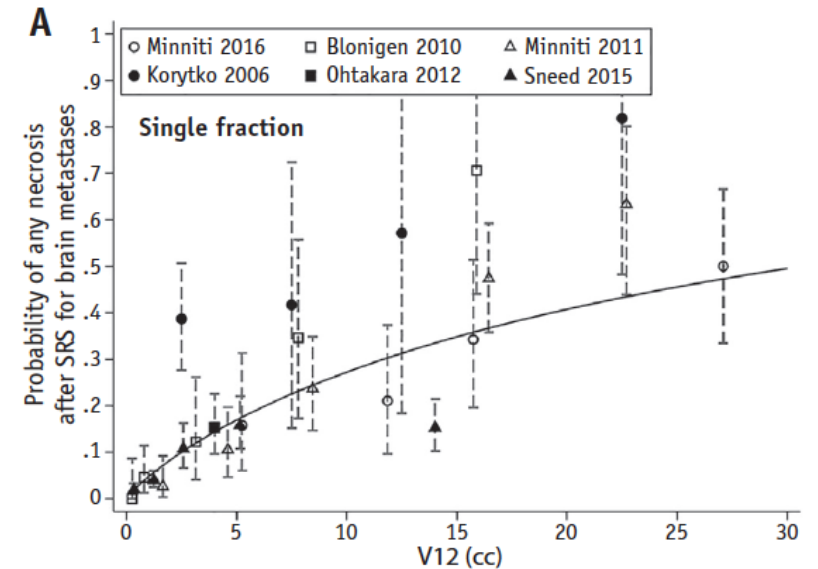
Michael T. Milano, MD, PhD,\* Jimm Grimm, PhD,†  
 Andrzej Niemierko, PhD,‡ Scott G. Soltys, MD,§ Vitali Moiseenko, PhD,||  
 Kristin J. Redmond, MD,¶ Ellen Yorke, PhD,# Arjun Sahgal, MD,\*\*  
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Received Aug 3, 2020. Accepted for publication Aug 3, 2020.

Keywords: stereotactic radiosurgery, brain metastases, radionecrosis, NTCP modeling, AVM data.

**Results:** Data from 51 reports are summarized. There was wide variability in reported rates of radionecrosis. Available data for SRS/fSRS for brain metastases were more amenable to NTCP modeling than AVM data. In the setting of brain metastases, SRS/fSRS-associated radionecrosis can be difficult to differentiate from tumor progression. For single-fraction SRS to brain metastases, tissue volumes (including target volumes) receiving 12 Gy (V1) of 5 cm<sup>3</sup>, 10 cm<sup>3</sup>, or >15 cm<sup>3</sup> were associated with risks of symptomatic radionecrosis of approximately 10%, 15%, and 20%, respectively. SRS for AVM was associated with modestly lower rates of symptomatic radionecrosis for equivalent V12. For 3-fraction fSRS for brain metastases, normal brain tissue V18 <30 cm<sup>3</sup> and V23 <7 cm<sup>3</sup> were associated with <10% risk of radionecrosis.

**Conclusions:** The risk of radionecrosis after SRS and fSRS can be modeled as a function of dose and volume treated. The use of fSRS appears to reduce risks of radionecrosis for larger treatment volumes relative to SRS. More standardized dosimetric and toxicity reporting is needed to facilitate future pooled analyses that can refine predictive models of brain toxicity risks. © 2020 Elsevier Inc. All rights reserved.



# Single- and Multifraction Stereotactic Radiosurgery Dose/Volume Tolerances of the Brain

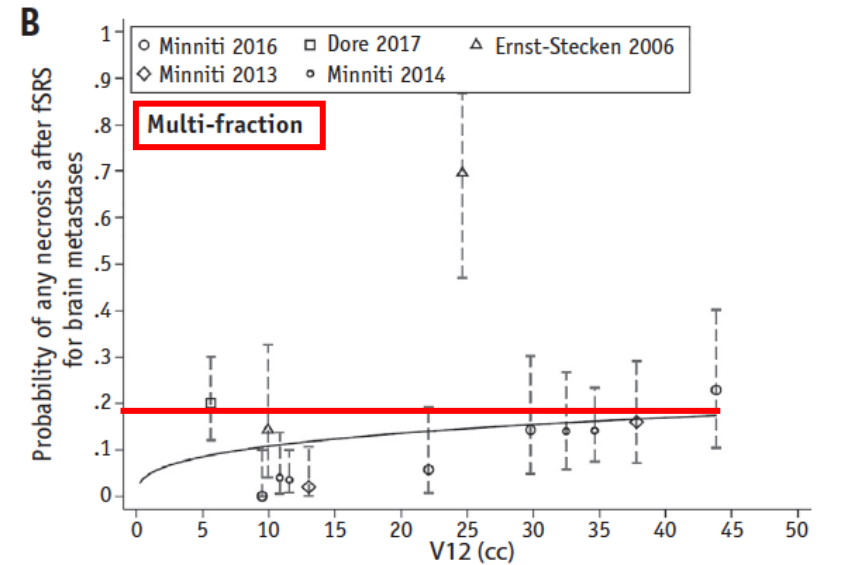
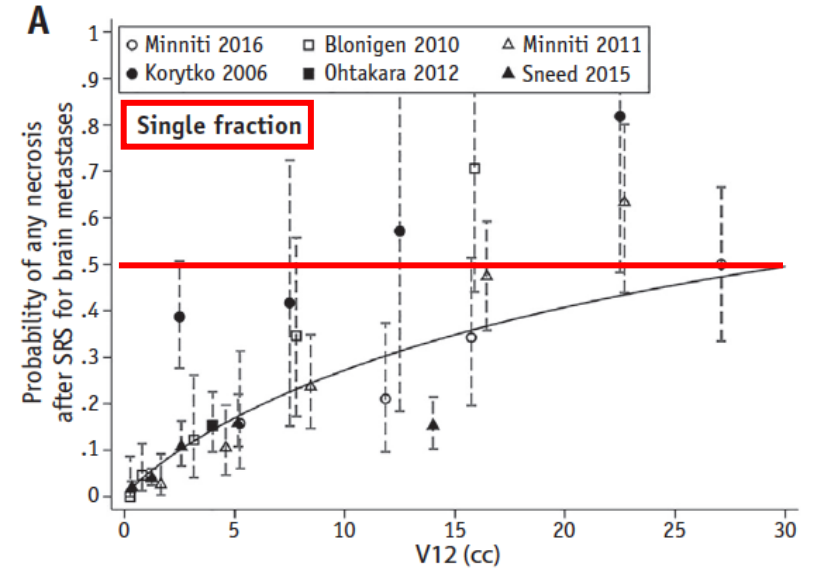
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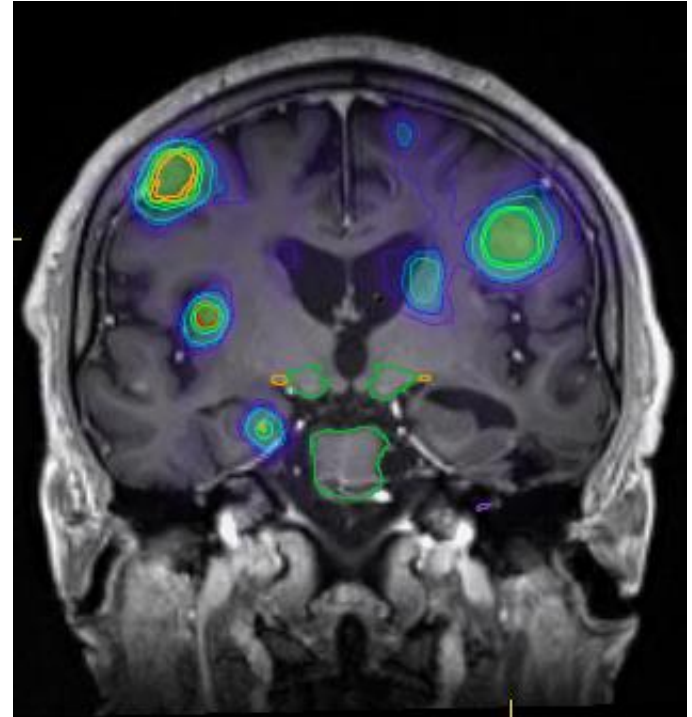
Keywords: stereotactic radiosurgery, brain metastases, radionecrosis, NTCP modeling, AVM, fSRS, SRS, V12, V18, V23, V1, V2, V3, V4, V5, V6, V7, V8, V9, V10, V11, V12, V13, V14, V15, V16, V17, V18, V19, V20, V21, V22, V23, V24, V25, V26, V27, V28, V29, V30, V31, V32, V33, V34, V35, V36, V37, V38, V39, V40, V41, V42, V43, V44, V45, V46, V47, V48, V49, V50.

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# SRS en lecho quirúrgico



## Radiation Therapy for Brain Metastases: An ASTRO Clinical Practice Guideline

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 Mateo Ziu, MD,<sup>s</sup> and Paul D. Brown, MD<sup>f</sup>

**Table 4** Indications for observation, postoperative SRS, WBRT, or preoperative SRS

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
1. For patients with resected brain metastases, radiation therapy (SRS or WBRT) is recommended to improve intracranial disease control.	Strong	High 13,50,51
2. For patients with resected brain metastases and limited additional brain metastases, SRS is recommended over WBRT to preserve neurocognitive function and patient-reported QoL.	Strong	Moderate 52
3. For patients whose brain metastasis is planned for resection, preoperative SRS is conditionally recommended as a potential alternative to postoperative SRS.	Conditional	Low 53,54

*Abbreviations:* KQ = key question; QoL = quality of life; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy.

*Regine W. et al., 2004  
 Kocher M. et al., 2011  
 Mahanan A. et al., 2017*

*Brown P. et al., 2017*

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**Table 5 Recommended postoperative cavity single-fraction SRS dosing guidance<sup>52</sup>**

Cavity volume (cm <sup>3</sup> )*	Single-fraction SRS dose (cGy)
<4.2 cm <sup>3</sup>	2000 cGy
≥4.2 to <8.0 cm <sup>3</sup>	1800 cGy
≥8.0 to <14.4 cm <sup>3</sup>	1700 cGy
≥14.4 to <20.0 cm <sup>3</sup>	1500 cGy
≥20.0 to <30.0 cm <sup>3</sup>	1400 cGy
≥30.0 cm <sup>3</sup> to <5.0 cm max	1200 cGy

*Abbreviation:* SRS = stereotactic radiosurgery.  
 \* Given the irregular shape of surgical cavities, the total prescribed dose should be based on the surgical cavity volume with a maximum cross-sectional diameter of <5.0 cm.

*Brown P. et al., 2017*

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## Single Fraction Stereotactic Radiosurgery Compared With Fractionated Stereotactic Radiosurgery in Treating Patients With Resected Metastatic Brain Disease

### Study Design

Study Type ⓘ: Interventional (Clinical Trial)  
 Actual Enrollment ⓘ: 242 participants  
 Allocation: Randomized  
 Intervention Model: Parallel Assignment  
 Masking: None (Open Label)  
 Primary Purpose: Treatment

Official Title: Phase III Trial of Post-Surgical Single Fraction Stereotactic Radiosurgery (SRS) Compared With Fractionated SRS for Resected Metastatic Brain Disease

Actual Study Start Date ⓘ: October 11, 2019

Estimated Primary Completion Date ⓘ: March 2025

Estimated Study Completion Date ⓘ: March 2028

### Investigators

Study Chair: Paul D. Brown, MD Mayo Clinic

Go to ▾

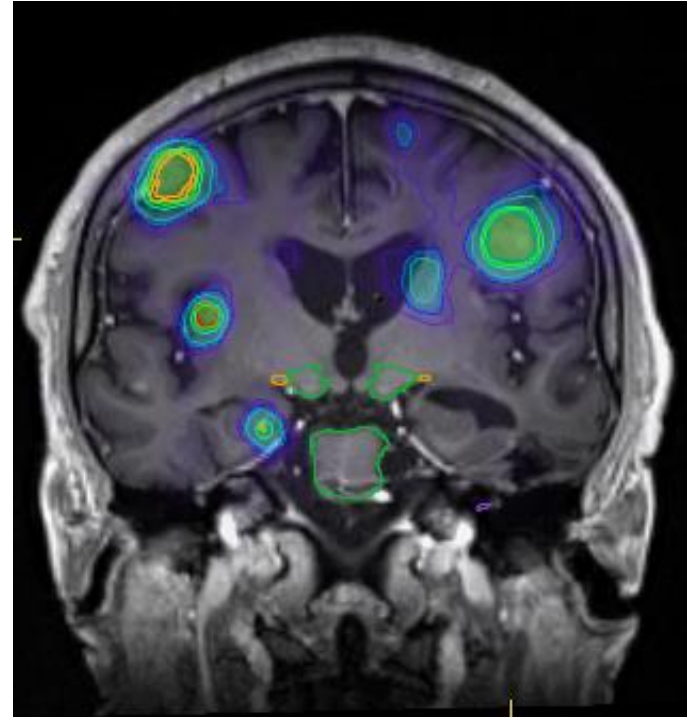
**SRS 12-20 Gy en una fracción**

**VS**

**27 Gy /3 fr (Lesiones < 3 cc)**

**30 Gy /5 fr (Lesiones >3 cc)**

# Terapias dirigidas - Inmunoterapia



# Radiation Therapy for Brain Metastases: An ASTRO Clinical Practice Guideline

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**Table 3** Indications for SRS alone for intact brain metastases

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
1. For patients with an ECOG performance status of 0-2 and up to 4 intact brain metastases, SRS is recommended.	Strong	High 13-18
2. For patients with an ECOG performance status of 0-2 and 5-10 intact brain metastases, SRS is conditionally recommended.	Conditional	Low 19-21
3. For patients with intact brain metastases measuring <2 cm in diameter, single-fraction SRS with a dose of 2000-2400 cGy is recommended.  <u>Implementation remark:</u> If multifraction SRS were chosen (eg, V12 Gy >10 cm <sup>3</sup> [see KQ4]), options include 2700 cGy in 3 fractions or 3000 cGy in 5 fractions.	Strong	Moderate 5, 13, 16, 19, 22
4. For patients with intact brain metastases measuring ≥2 to <3 cm in diameter, single-fraction SRS using 1800 cGy or multifraction SRS (eg, 2700 cGy in 3 fractions or 3000 cGy in 5 fractions) is conditionally recommended (see KQ4).	Conditional	Low 22-24
5. For patients with intact brain metastases measuring ≥3 to 4 cm in diameter, multifraction SRS (eg, 2700 cGy in 3 fractions or 3000 cGy in 5 fractions) is conditionally recommended.  <u>Implementation remarks:</u> <ul style="list-style-type: none"> <li>• If single-fraction SRS were chosen, doses up to 1500 cGy may be used (see KQ4).</li> <li>• Multidisciplinary discussion with neurosurgery to consider surgical resection is suggested for all tumors causing mass effect, irrespective of tumor size.</li> </ul>	Conditional	Low 23, 24
6. For patients with intact brain metastases measuring >4 cm in diameter, surgery is conditionally recommended, and if not feasible, multifraction SRS is preferred over single-fraction SRS.  <u>Implementation remark:</u> Given limited evidence, SRS for tumor size >6 cm is discouraged.	Conditional	Low 19, 22-24
7. For patients with <b>symptomatic</b> brain metastases who are candidates for local therapy and CNS-active systemic therapy, upfront local therapy is recommended.	Strong	Low 25, 26
8. For patients with <b>asymptomatic</b> brain metastases eligible for CNS-active systemic therapy, multidisciplinary and patient-centered decision making is conditionally recommended to <b>determine whether local therapy may be safely deferred.</b>  <u>Implementation remark:</u> The decision to defer local therapy should consider factors such as brain metastasis size, parenchymal brain location, number of metastases, likelihood of response to specific systemic therapy, access to close neuro-oncologic surveillance, and availability of salvage therapies.	Conditional	Expert opinion

Abbreviations: CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; KQ = key question; SRS = stereotactic radiosurgery. Local therapy is defined as brain metastasis-directed radiation therapy and/or surgery.

# Radiation Therapy for Brain Metastases: An ASTRO Clinical Practice Guideline

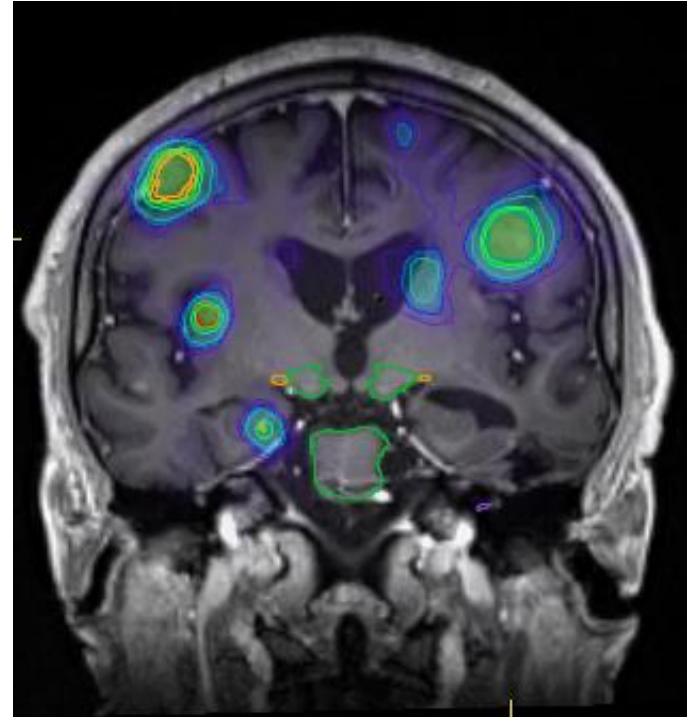
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**Table 3** Indications for SRS alone for intact brain metastases

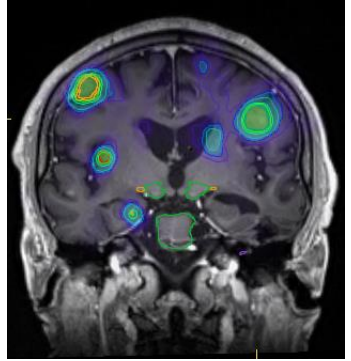
KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
1. For patients with an ECOG performance status of 0-2 and up to 4 intact brain metastases, SRS is recommended.	Strong	High 13-18
2. For patients with an ECOG performance status of 0-2 and 5-10 intact brain metastases, SRS is conditionally recommended.	Conditional	Low 19-21
3. For patients with intact brain metastases measuring <2 cm in diameter, single-fraction SRS with a dose of 2000-2400 cGy is recommended.  <u>Implementation remark:</u> If multifraction SRS were chosen (eg, V12 Gy >10 cm <sup>3</sup> [see KQ4]), options include 2700 cGy in 3 fractions or 3000 cGy in 5 fractions.	Strong	Moderate 5, 13, 16, 19, 22
4. For patients with intact brain metastases measuring ≥2 to <3 cm in diameter, single-fraction SRS using 1800 cGy or multifraction SRS (eg, 2700 cGy in 3 fractions or 3000 cGy in 5 fractions) is conditionally recommended (see KQ4).	Conditional	Low 22-24
7. For patients with <i>symptomatic</i> brain metastases who are candidates for local therapy and CNS-active systemic therapy, upfront local therapy is recommended.	Strong	Low 25, 26
8. For patients with <i>asymptomatic</i> brain metastases eligible for CNS-active systemic therapy, multidisciplinary and patient-centered decision making is conditionally recommended to determine whether local therapy may be safely deferred.  <u>Implementation remark:</u> The decision to defer local therapy should consider factors such as brain metastasis size, parenchymal brain location, number of metastases, likelihood of response to specific systemic therapy, access to close neuro-oncologic surveillance, and availability of salvage therapies.	Conditional	Expert opinion Low 19, 22-24
8. For patients with <i>asymptomatic</i> brain metastases eligible for CNS-active systemic therapy, multidisciplinary and patient-centered decision making is conditionally recommended to determine whether local therapy may be safely deferred.  <u>Implementation remark:</u> The decision to defer local therapy should consider factors such as brain metastasis size, parenchymal brain location, number of metastases, likelihood of response to specific systemic therapy, access to close neuro-oncologic surveillance, and availability of salvage therapies.	Conditional	Expert opinion Low 25, 26

Abbreviations: CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; KQ = key question; SRS = stereotactic radiosurgery. Local therapy is defined as brain metastasis-directed radiation therapy and/or surgery.

# Conclusiones



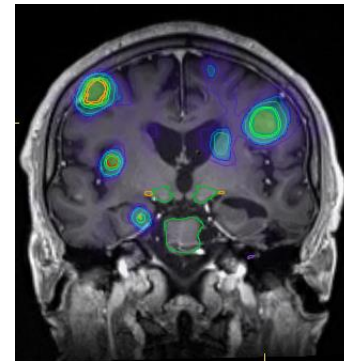
# Radiocirugía en metástasis cerebrales



## • Conclusiones

- El tratamiento de metástasis con SRS reduce el deterioro cognitivo comparado con WBRT
- Pacientes con supervivencia estimada > 3-4 meses (*DS-GPA*):
  - 1-4 metástasis: *SRS primera opción*
  - 5-10 metástasis: *SRS siempre se debe considerar como opción*
  - > 10 metástasis: *SRS según cada caso*
  - Se debe hacer tratamiento adyuvante si resección quirúrgica (*preferiblemente con SRS para disminuir el deterioro cognitivo*)
  - Pacientes asintomáticos candidatos a terapias dirigidas o inmunoterapia: *Discutir en comité multidisciplinar*

# Radiocirugía en metástasis cerebrales



## • Conclusiones

- Definir la dosis de tratamiento y el fraccionamiento en función de:
  - *Tamaño, localización, número de lesiones, objetivo de control local, tecnología con la que se cuenta, experiencia con la que se cuenta.*
- Lesiones < 20 mm: 20-24 Gy
- Lesiones 20-30 mm: 18 Gy\* o 27 Gy/3 fr o 30 Gy/5 fr
- Lesiones 30-40 mm: 27 Gy/ 3fr o 30 Gy/5 fr

*\*Si por cumplir el  $V_{12}$  bajamos dosis, tener en cuenta que bajamos igualmente el control local.*



Gracias.

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