Radiocirugía intra-craneana en pacientes con más de 5 metástasis cerebrales

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Pregunta: ?¿

- 3 lesiones
- 7 lesiones

EL 10-26% DE PACIENTES QUE MUEREN A CAUSA DE CANCER TENDRAN METASTASIS CEREBRALES

Objetivos del aprendizaje

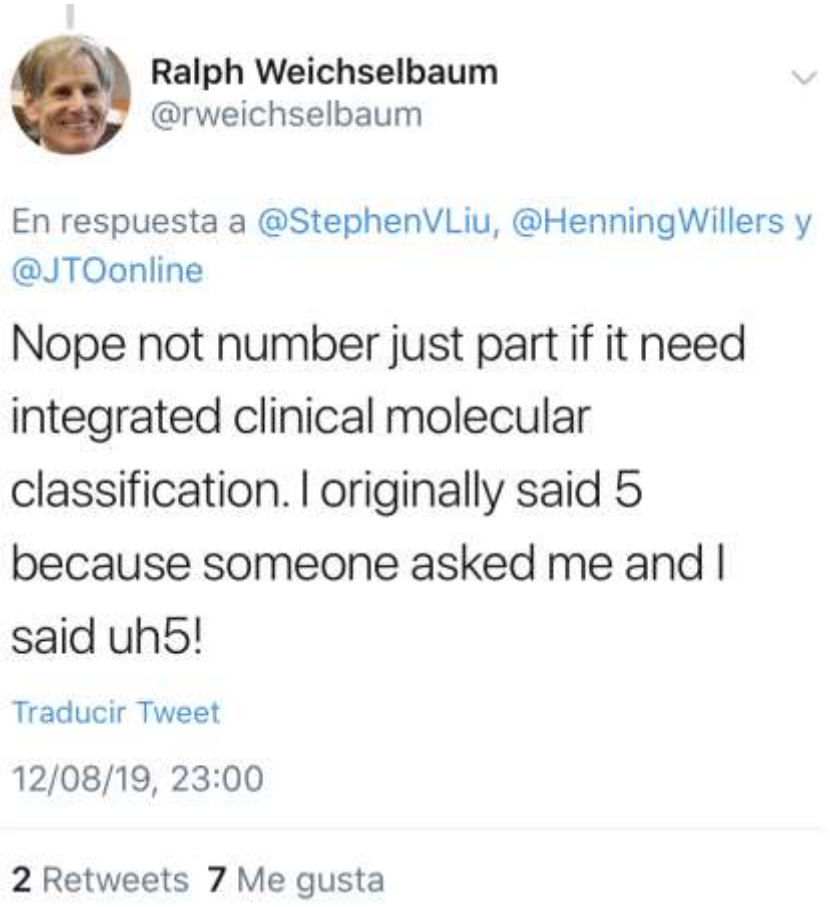
- Beneficio de la radiocirugía en metástasis cerebrales
- Definir el uso de radiocirugía en mas de 4 lesiones metastásicas
- Revisar el papel del volumen de la enfermedad en la decisión de radiocirugía

Introducción

- Enfermedad y tratamiento generan deterioro cognitivo
- El uso de la RMN permite encontrar mas pacientes con enfermedad en SNC
- Tratamiento sistémico : también ofrece control sobre la enfermedad cerebral

Definición de Oligometástasis

- No hay claridad en el número
- No hay claridad en la localización
- Consenso de ASTRO-ESTRO para enfermedad extra-craneana “1-5 metástasis susceptibles de tratamiento”



Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document

Radiocirugía para metástasis cerebrales

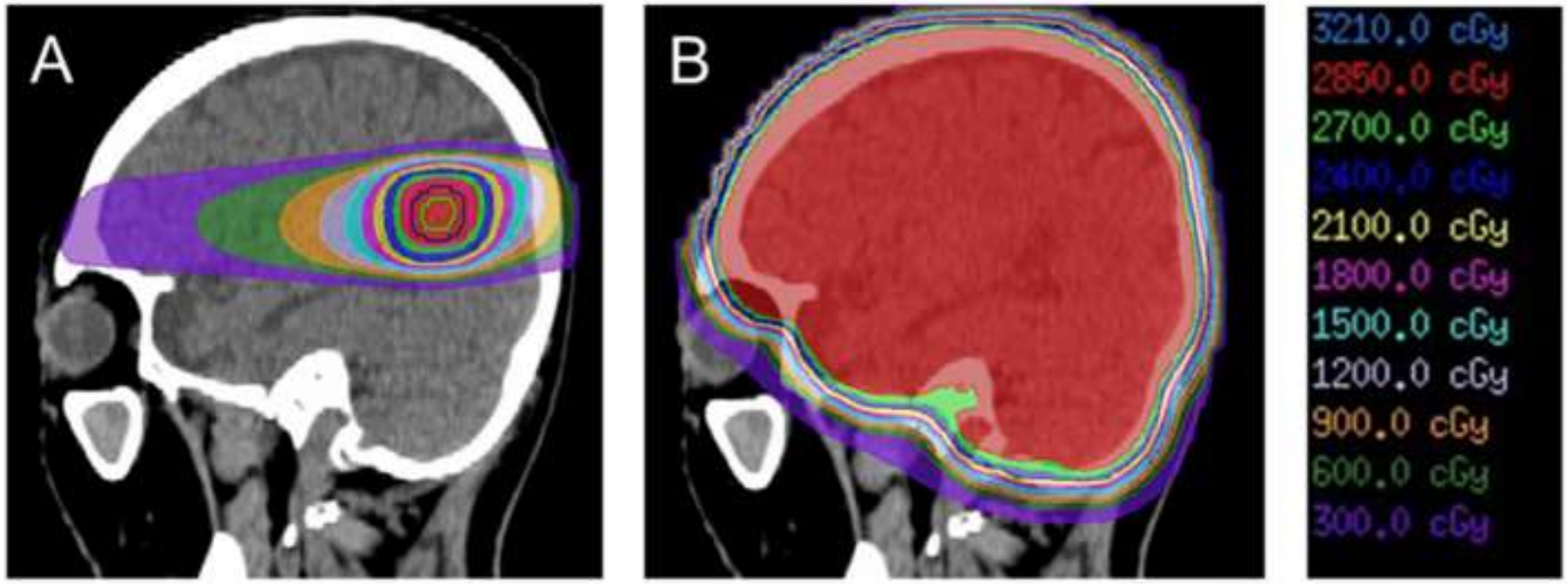


Figure 1. Dose distribution for a metastatic brain tumor calculated by the treatment planning system of (A) stereotactic radiotherapy and (B) whole brain radiotherapy. The red-colored area is receiving 95% of the prescribed dose.

MAYOR PRECISION
MENOS DOSIS INTEGRAL AL CEREBRO

¿Que queremos evitar?

- Deterioro cognitivo
- Deterioro en la calidad de vida
- Toxicidad cerebral temprana y tardía

- Uso de radiocirugía mas radioterapia holoencefálica deterioro en la función de memoria y de aprendizaje del 52% comparado con una del 24%

Chang E.L. et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: A randomised controlled trial. *Lancet Oncol.* 2009;10:1037–1044.

- Deterioro cognitivo del 63.5% con el uso de Radiocirugía comparado con deterioro del 91% con (Diferencia, -28.2%; 90% CI, -41.9% to -14.4%; P < .001).

JAMA. 2016 Jul 26;316(4):401-409. doi: 10.1001/jama.2016.9839.

¿Existe un número a partir del cual no es posible realizar un tratamiento de radiocirugía intra-craneana?

Consideraciones

- Estado funcional del paciente
- Momento de la enfermedad
- Edad
- Escalas pronosticas
- Enfermedad sistémica y su afectación

Acceso a servicios de salud
Acceso a resonancia magnética nuclear

Contexto de la situación actual de radioterapia

- Evidencia clínica mas solida en términos de ensayos clínicos incluye pacientes con 1-3 metástasis
- Los pacientes tienen cada vez supervivencias mas largas
- Perspectiva oncológica integral
- Evaluar múltiples opciones de tratamiento
- Ensayos clínicos que están en curso

Evidencia retrospectiva

Table 1. Retrospective series of patients with more than 4 metastases treated with SRS.

Reference	Year	Number of Metastases	Number of Patients	1 Year Rate of Distant Brain Failure	Median Overall Survival (Months)
Chang et al. [39]	2010	6–10	58	NR	10
		11–15	17	53.1%	13
		>15	33	80.3%	8
Mohammadi et al. [40]	2012	5–20	178	77.6%	4
Bhatnagar et al. [41]	2006	4–18	205	43%	8
Raldow et al. [42]	2013	5–9	84	NR	7.6
		≥10	19	NR	8.3

NR: not reported.

O'Beirn M et al. The Expanding Role of Radiosurgery for Brain Metastases. Medicines (Basel). 2018 Aug 14;5(3):90. doi: 10.3390/medicines5030090.

¿Número de metástasis a tratar?

Metástasis Limitadas: hasta 4 metástasis
Metástasis extensas: 5 o mas metástasis

¿Número de metástasis a tratar?

- JLGK0901
- 1194 pacientes
- Pacientes con 5-10 metástasis tienen supervivencias similares a 2-4 metástasis (**Mediana de supervivencia de 10.8 meses**)

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

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Summary

Background We aimed to examine whether stereotactic radiosurgery without whole-brain radiotherapy (WBRT) as the initial treatment for patients with five to ten brain metastases is non-inferior to that for patients with two to four brain metastases in terms of overall survival.

Methods This prospective observational study enrolled patients with one to ten newly diagnosed brain metastases (largest tumour <10 mL in volume and <3 cm in longest diameter; total cumulative volume ≤15 mL) and a Karnofsky performance status score of 70 or higher from 23 facilities in Japan. Standard stereotactic radiosurgery procedures were used in all patients; tumour volumes smaller than 4 mL were irradiated with 22 Gy at the lesion periphery and those that were 4–10 mL with 20 Gy. The primary endpoint was overall survival, for which the non-inferiority margin for the comparison of outcomes in patients with two to four brain metastases with those of patients with five to ten brain metastases was set as the value of the upper 95% CI for a hazard ratio (HR) of 1·30, and all data were analysed by intention to treat. The study was finalised on Dec 31, 2012, for analysis of the primary endpoint; however, monitoring of stereotactic radiosurgery-induced complications and neurocognitive function assessment will continue for the censored subset until the end of 2014. This study is registered with the University Medical Information Network Clinical Trial Registry, number 000001812.

Findings We enrolled 1194 eligible patients between March 1, 2009, and Feb 15, 2012. Median overall survival after stereotactic radiosurgery was 13·9 months [95% CI 12·0–15·6] in the 455 patients with one tumour, 10·8 months [9·4–12·4] in the 531 patients with two to four tumours, and 10·8 months [9·1–12·7] in the 208 patients with five to ten tumours. Overall survival did not differ between the patients with two to four tumours and those with five to ten (HR 0·97, 95% CI 0·81–1·18 [less than non-inferiority margin], p=0·78; $p_{\text{non-inferiority}}$<0·0001). Stereotactic radiosurgery-induced adverse events occurred in 101 (8%) patients; nine (2%) patients with one tumour had one or more grade 3–4 event compared with 13 (2%) patients with two to four tumours and six (3%) patients with five to ten tumours. The proportion of patients who had one or more treatment-related adverse event of any grade did not differ significantly between the two groups of patients with multiple tumours (50 [9%] patients with two to four tumours *vs* 18 [9%] with five to ten; p=0·89). Four patients died, mainly of complications relating to stereotactic radiosurgery (two with one tumour and one each in the other two groups).

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.

¿Número de metástasis a tratar?

	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)
Died	850 (71%)	310 (68%)	392 (74%)	148 (71%)	0·46
Neurological death*	71 (8%)	32 (10%)	25 (6%)	14 (9%)	0·27
Deterioration of neurological function	146 (12%)	56 (12%)	62 (12%)	28 (13%)	0·53
Local recurrence†	138 (13%)	65 (16%)	54 (11%)	19 (10%)	0·78
New lesions†	625 (58%)	199 (48%)	297 (63%)	129 (69%)	0·12
Leptomeningeal dissemination†	144 (13%)	48 (12%)	61 (13%)	35 (19%)	0·067
Leukoencephalopathy†	9 (1%)	3 (1%)	4 (1%)	2 (1%)	0·68
Salvage SRS procedures	459 (38%)	148 (33%)	221 (42%)	90 (43%)	0·74
1	256 (21%)	76 (17%)	129 (24%)	51 (25%)	0·92
2	113 (9%)	45 (1%)	47 (9%)	21 (10%)	
≥3	90 (8%)	27 (6%)	45 (8%)	18 (9%)	
Salvage WBRT	107 (9%)	36 (8%)	54 (10%)	17 (8%)	0·48
Salvage surgery	23 (2%)	12 (3%)	8 (2%)	3 (1%)	1·00
Systemic anticancer agents	861 (72%)	308 (68%)	387 (73%)	166 (70%)	0·059
Molecularly targeted agents	356 (30%)	123 (27%)	157 (30%)	76 (37%)	0·078

Data are number (%), unless otherwise specified. SRS=stereotactic radiosurgery. WBRT=whole-brain radiotherapy. *Percentages based on the number of patients who died. †Based on 1074 (90%) patients (414 [91%] in group A, 474 [89%] in group B, and 186 [89%] in group C; differences between proportions of patients with data, p=0·64), because MRI results were not available for 120 (10%) patients who had an early death or had remarkable deterioration of clinical state soon after stereotactic radiosurgery.

***Table 4*: Treatment outcomes after stereotactic radiosurgery**

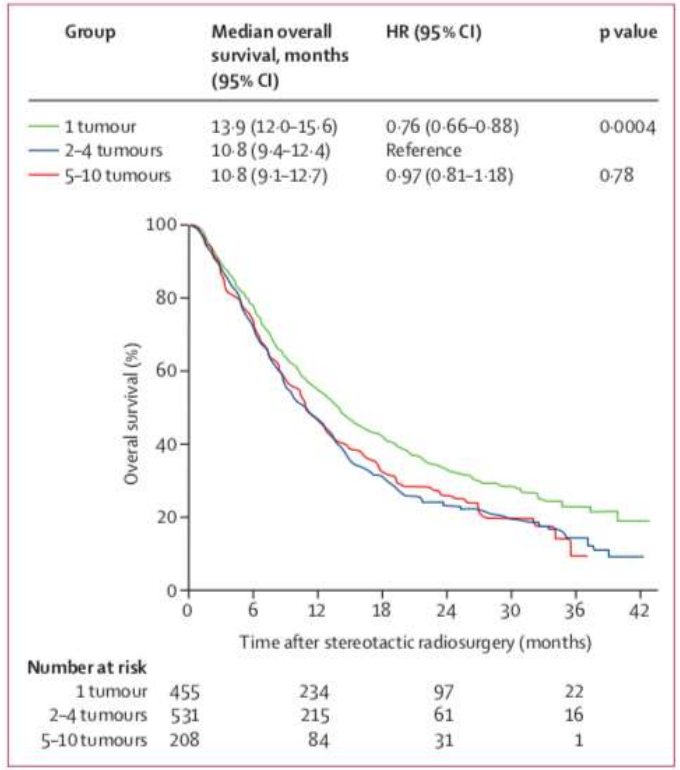

***Figure*: Kaplan-Meier curves of overall survival**
HR=hazard ratio.

CENTRAR NUESTRA ATENCION EN OTRAS VARIABLES

NÚMERO
DE LESIONES

VOLUMEN DE
LESIONES

Perspectiva del numero de lesiones y volumen

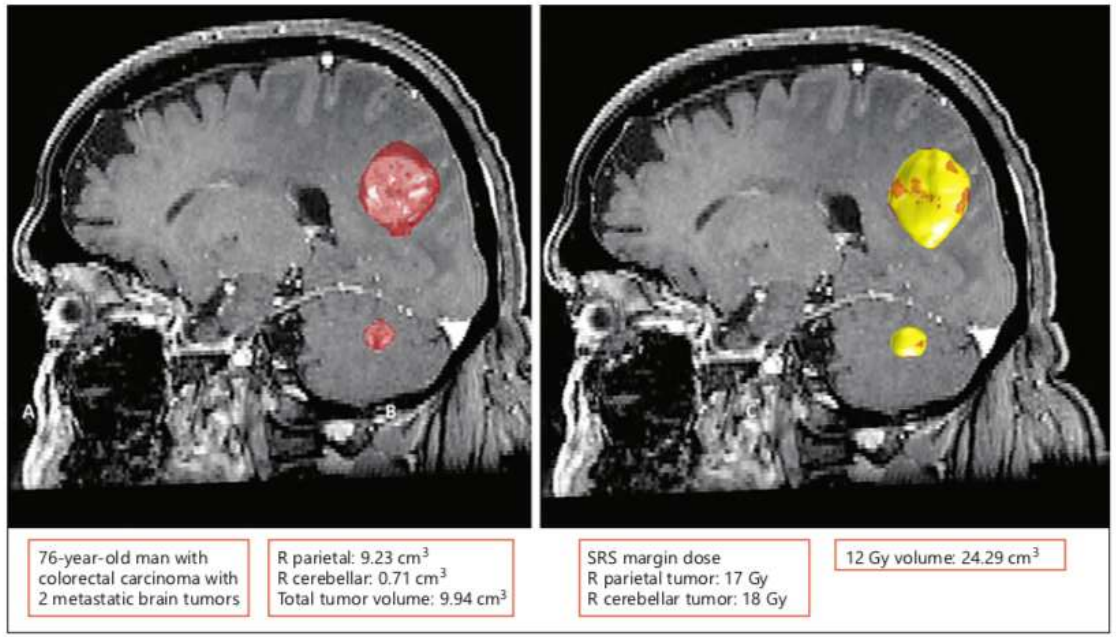

Fig. 1. Radiosurgery dose plan for a patient with only two metastatic tumors. The cumulative tumor volume was about 10 cm^3.

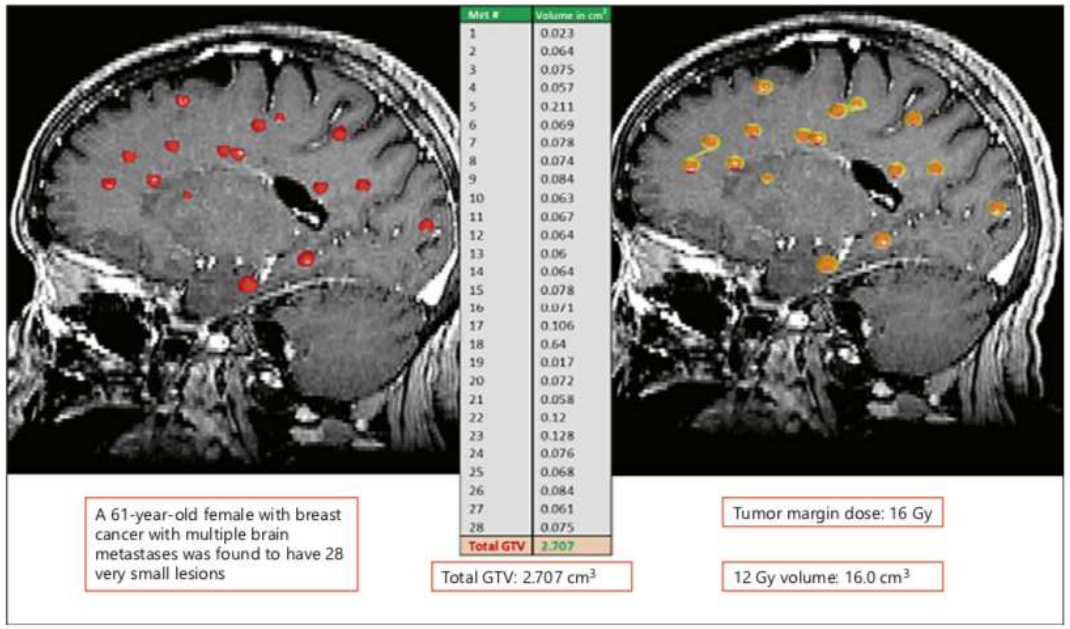

Fig. 2. Radiosurgery dose plan of a patient with 28 metastatic tumors. The cumulative tumor volume was about 2.7 cm^3.

Niranjan A, Lunsford LD, Kano H (eds): Leksell Radiosurgery.
Prog Neurol Surg. Basel, Karger, 2019, vol 34, pp 100–109 (DOI: 10.1159/000493055)

Volumen es mas importante que el número

61 pacientes con 10 lesiones o mas

Mediana de volumen por lesión: 0.37 cm3

Mediana del volumen tumoral total : 4.86 cm3
Media 8.05

95% de control local
81.6% de pacientes no progresión intracraneal

See the corresponding editorial in this issue, pp 234–236.

J Neurosurg 117:237–245, 2012

Stereotactic radiosurgery using the Leksell Gamma Knife Perfexion unit in the management of patients with 10 or more brain metastases

Clinical article

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Object. To better establish the role of stereotactic radiosurgery (SRS) in treating patients with 10 or more intracranial metastases, the authors assessed clinical outcomes and identified prognostic factors associated with survival and tumor control in patients who underwent radiosurgery using the Leksell Gamma Knife Perfexion (LGK PFX) unit.

Methods. The authors retrospectively reviewed data in all patients who had undergone LGK PFX surgery to treat 10 or more brain metastases in a single session at the University of Pittsburgh. Posttreatment imaging studies were used to assess tumor response, and patient records were reviewed for clinical follow-up data. All data were collected by a neurosurgeon who had not participated in patient care.

Results. Sixty-one patients with 10 or more brain metastases underwent SRS for the treatment of 806 tumors (mean 13.2 lesions). Seven patients (11.5%) had no previous therapy. Stereotactic radiosurgery was the sole prior treatment modality in 8 patients (13.1%), 22 (36.1%) underwent whole-brain radiation therapy (WBRT) only, and 16 (26.2%) had prior SRS and WBRT. The total treated tumor volume ranged from 0.14 to 40.21 cm^3, and the median radiation dose to the tumor margin was 16 Gy. The median survival following SRS for 10 or more brain metastases was 4 months, with improved survival in patients with fewer than 14 brain metastases, a nonmelanomatous primary tumor, controlled systemic disease, a better Karnofsky Performance Scale score, and a lower recursive partitioning analysis (RPA) class. Prior cerebral treatment did not influence survival. The median survival for a patient with fewer than 14 brain metastases, a nonmelanomatous primary tumor, and controlled systemic disease was 21.0 months. Sustained local tumor control was achieved in 81% of patients. Prior WBRT predicted the development of new adverse radiation effects.

Conclusions. Stereotactic radiosurgery safely and effectively treats intracranial disease with a high rate of local control in patients with 10 or more brain metastases. In patients with fewer metastases, a nonmelanomatous primary lesion, controlled systemic disease, and a low RPA class, SRS may be most valuable. In selected patients, it can be considered as first-line treatment.
(*http://thejns.org/doi/abs/10.3171/2012.4.JNS11870*)

KEY WORDS • stereotactic radiosurgery • Gamma Knife surgery • brain metastasis • morbidity

¿Es 10 metástasis el limite?

- Estudio multi-institucional
- No diferencias significativas para supervivencia global en pacientes 2-4 metástasis versus 5-15 metástasis
- 9.5 meses versus 7.5 meses

International Journal of Radiation Oncology biology • physics
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Clinical Investigation

Initial SRS for Patients With 5 to 15 Brain Metastases: Results of a Multi-Institutional Experience

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Table 2 Univariate and multivariate Cox proportional hazards analyses of overall survival

	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age				
<65 y	Ref	-	Ref	-
≥65 y	1.43 (1.30-1.58)	<.01	1.40 (1.26-1.56)	<.01
Sex				
Female	Ref	-	Ref	-
Male	1.36 (1.23-1.50)	<.01	1.21 (1.08-1.36)	<.01
Extracranial disease burden				
None	Ref	-	Ref	-
Oligometastatic	1.49 (1.25-1.77)	<.01	1.47 (1.21-1.80)	<.01
Widespread	2.07 (1.75-2.44)	<.01	2.03 (1.67-2.48)	<.01
Extracranial disease status				
Stable	Ref	-	Ref	-
Progressive	1.51 (1.34-1.69)	<.01	1.26 (1.11-1.42)	<.01
Primary				
Breast	Ref	-	Ref	-
Lung	1.34 (1.15-1.55)	<.01	1.32 (1.11-1.58)	<.01
RCC	1.16 (0.95-1.41)	.15	0.91 (0.72-1.15)	.42
Melanoma	1.56 (1.32-1.85)	<.01	1.28 (1.05-1.56)	.02
Other	1.68 (1.37-2.04)	<.01	1.42 (1.13-1.80)	<.01
No. of BM				
1	0.71 (0.64-0.79)	<.01	0.73 (0.65-0.82)	<.01
2-4	Ref	-	Ref	-
5-15	1.15 (0.97-1.35)	.10	1.11 (0.93-1.36)	.25
Margin dose (Gy)	0.97 (0.95-0.99)	<.01	0.96 (0.94-0.98)	<.01
Treatment era				
1991-2007	Ref	-	-	-
2008-2013	1.04 (0.92-1.18)	0.52		

Abbreviations: BM = brain metastasis/metastases; CI = confidence interval; HR = hazard ratio; NC = not calculated; RCC = renal cell carcinoma; Ref = reference.

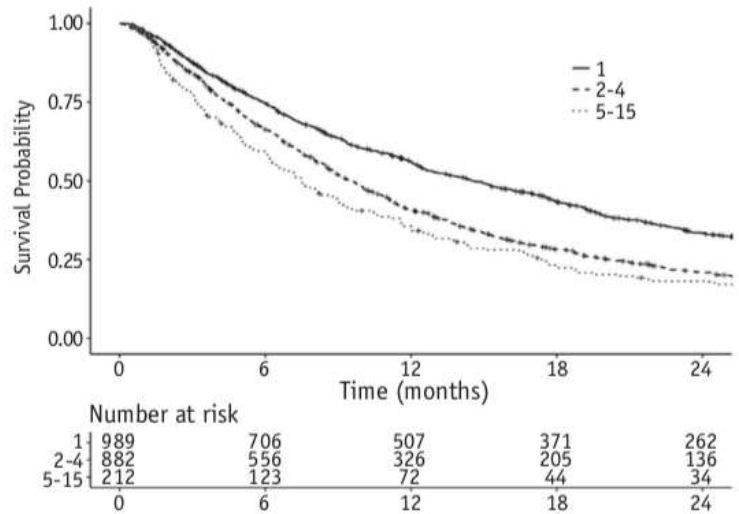
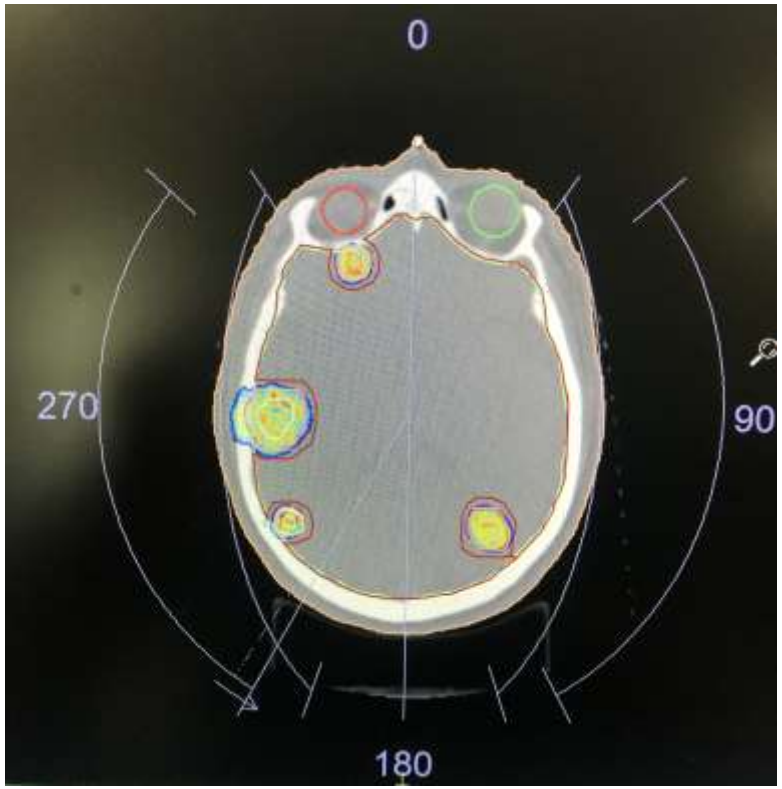
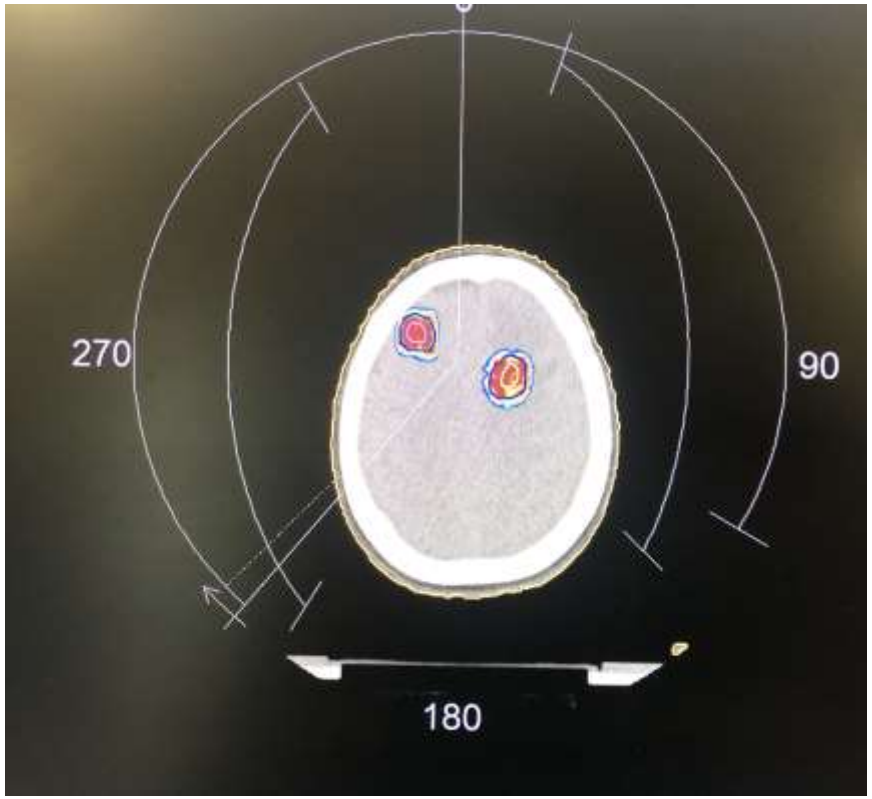


Fig. 1. Kaplan-Meier plot of overall survival by number of brain metastases treated with initial stereotactic radiosurgery.

Caso clínico

Paciente con Adenocarcinoma de pulmón ALK positivo. Cefalea leve. Tac de cráneo 3 lesiones. RMN cerebro 12 Lesiones en cerebro
Plan: HSRS 27 Gy en 3 fx





PLANEACION: UN SOLO ISOCENTRO

Seguimiento

Tolerancia al tratamiento sin efectos secundarios significativos

<u>Continua jugando golf</u>

Al 1.5 años progresión osea y pulmonar
Estabilidad de lesiones en SNC
No progresión SNC
Fallece

Tips para tratamiento

- Disminuir el margen del GTV
- Menos radionecrosis
- Mas radionecrosis y NO diferencia en control local con margen de 3 mm versus 1 mm (Kirkpatrick IJROBP 2014) ni en 2 mm versus 0 mm (Nataf IJROBP 2008)

Dosis de órganos a riesgo

Table 2 Summary of NTCP[a] estimates after SRS/SBRT from the HyTEC reports[*]

Organ	Volume segmented	Number of fractions	Endpoint	Dose (Gy) or dose-volume parameters	Rate (%)[a]	Notes
Brain; for metastasis	Total brain including target	1	Symptomatic necrosis	$V_{12Gy} \leq 5\ cm^3$	10%	From Table 3 and Figs. 4 and 5 in paper.
		1	Symptomatic necrosis	$V_{12Gy} \leq 10\ cm^3$	15%	Consistent with QUANTEC.
		1	Symptomatic necrosis	$V_{12Gy} \leq 15\ cm^3$	20%	Prior whole brain RT appears to not markedly increase risks in most reports (with the exception of brain stem).[†] However, repeat SRS/fSRS to the same area has been associated with markedly increased risks.
		3	Edema or necrosis	$V_{20Gy} \leq 20\ cm^3$	$\leq 10\%$	
		3	Edema or necrosis	$V_{20Gy} \leq 30\ cm^3$	$\leq 20\%$	
		5	Edema or necrosis	$V_{24Gy} \leq 20\ cm^3$	$\leq 10\%$	
		5	Edema or necrosis	$V_{24Gy} \leq 30\ cm^3$	$\leq 20\%$	
Brain; SRS for arteriovenous malformation	Total brain including target	1	Symptomatic necrosis	$V_{12Gy} \leq 10\ cm^3$	$\leq 10\%$	From Figure 2 in paper
Optic pathway	Optic nerves and chiasm	1	Neuropathy	$D_{max} < 10$-12 Gy	< 1%	From Table 3 in paper. Consistent with QUANTEC. Prior RT exposure of the optic pathway (either whole brain RT or SRS/fSRS) appears to markedly increase risks.
		3	Neuropathy	$D_{max} < 20$ Gy	< 1%	
		5	Neuropathy	$D_{max} < 25$ Gy	< 1%	

HyTEC Introduction

High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic (HyTEC): An Overview

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Guía ASTRO 2022

ASCO special articles

Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

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abstract

PURPOSE To provide guidance to clinicians regarding therapy for patients with brain metastases from solid tumors.

METHODS ASCO convened an Expert Panel and conducted a systematic review of the literature.

RESULTS Thirty-two randomized trials published in 2008 or later met eligibility criteria and form the primary evidentiary base.

RECOMMENDATIONS Surgery is a reasonable option for patients with brain metastases. Patients with large tumors with mass effect are more likely to benefit than those with multiple brain metastases and/or uncontrolled systemic disease. Patients with symptomatic brain metastases should receive local therapy regardless of the systemic therapy used. For patients with asymptomatic brain metastases, local therapy should not be deferred unless deferral is specifically recommended in this guideline. The decision to defer local therapy should be based on a multidisciplinary discussion of the potential benefits and harms that the patient may experience. Several regimens were recommended for non–small-cell lung cancer, breast cancer, and melanoma. For patients with asymptomatic brain metastases and no systemic therapy options, stereotactic radiosurgery (SRS) alone should be offered to patients with one to four unresected brain metastases, excluding small-cell lung carcinoma. SRS alone to the surgical cavity should be offered to patients with one to two resected brain metastases. SRS, whole brain radiation therapy, or their combination are reasonable options for other patients. Memantine and hippocampal avoidance should be offered to patients who receive whole brain radiation therapy and have no hippocampal lesions and 4 months or more expected survival. Patients with asymptomatic brain metastases with either Karnofsky Performance Status ≤ 50 or Karnofsky Performance Status < 70 with no systemic therapy options do not derive benefit from radiation therapy.

Additional information is available at www.asco.org/neurooncology-guidelines.

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Recommendation 3.4

SRS, WBRT, and the combination of SRS plus WBRT are all reasonable options for patients with more than four unresected or more than two resected brain metastases and better performance status (eg, KPS ≥ 70). SRS may be preferred for patients with better prognosis or where systemic therapy that is known to be active in the CNS is available (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Conclusiones

- La radiocirugía permite disminuir el deterioro cognitivo de los pacientes
- El uso o no de la radiocirugía no depende solo del numero de lesiones
- Se debe examinar al PACIENTE y considerar la enfermedad oncológica, terapias sistémicas disponibles el curso de la enfermedad, la enfermedad a distancia y el volumen de la enfermedad

Gracias

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