Radiocirugía Intracraneal (SRS/SRT): actualización desde el punto de vista clínico

Tarek Hijal

McGill University – Montreal - Canada

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Radiocirugía estereotáctica

- Técnica de radioterapia caracterizada por la administración precisa de altas dosis de radiación, en una sola sesión, a objetivos intracraneales pequeños, estereotácticamente definidos, de tal manera que la caída de la dosis fuera del volumen objetivo es muy aguda.

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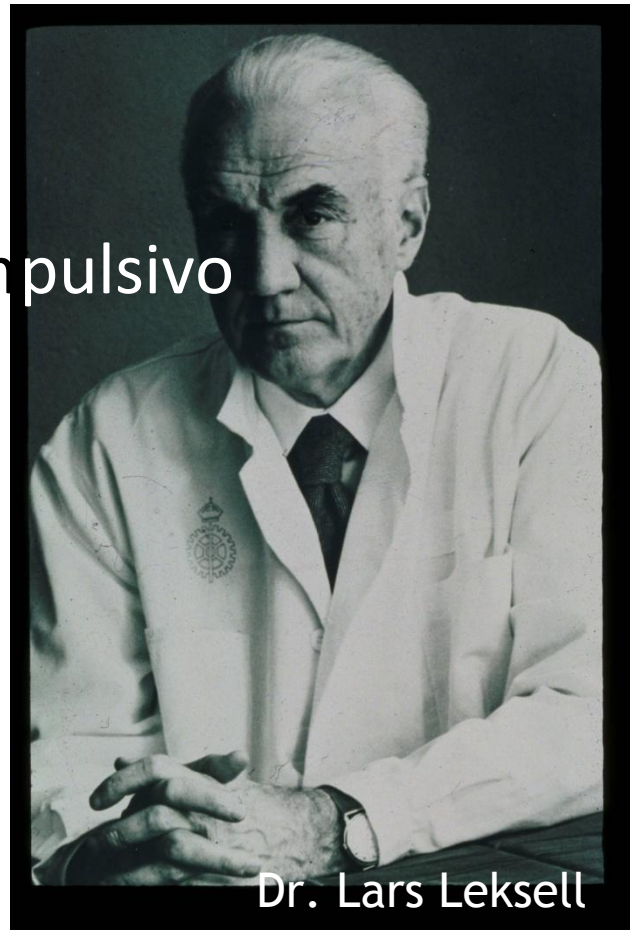
Orígenes de la radiocirugía

- Técnica diseñada para tratar trastornos funcionales
- El primer paciente tratado en 1951 tenía un trastorno compulsivo
- Técnicas de imagen limitadas


Dr. Lars Leksell

McGill

RADIOSURGERY

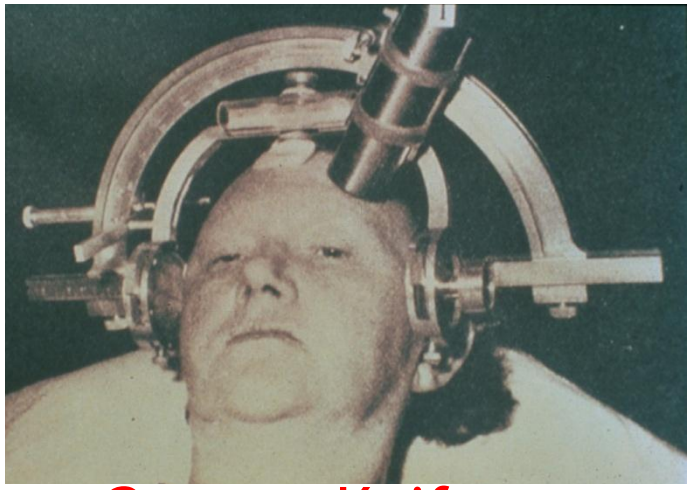
The Stereotaxic Method and Radiosurgery of the Brain.

By

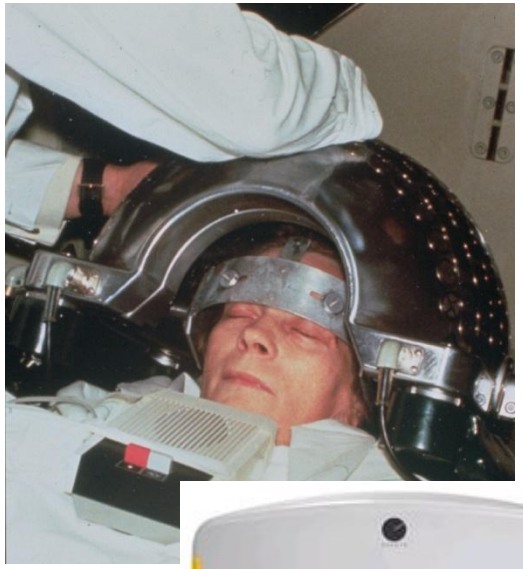
LARS LEKSELL.

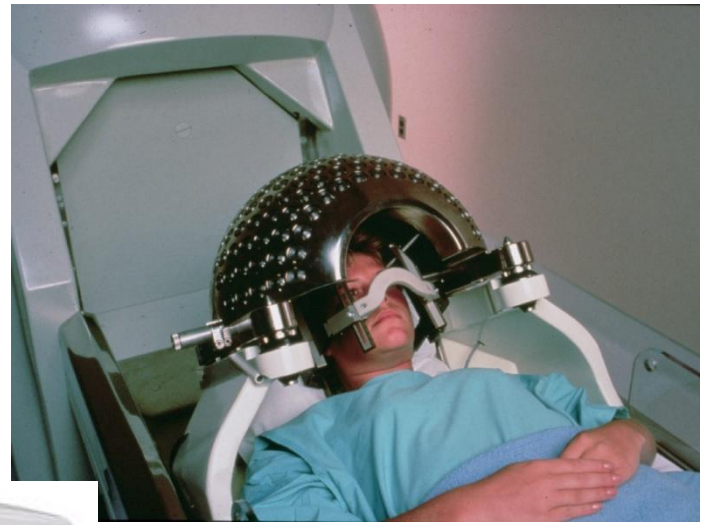
The stereotaxic technique enables the accurate insertion of a needle electrode into any given structure of the brain and its destruction by electrolysis or electrocoagulation (HORSLEY & CLARKE, 1908; SPIEGEL *et al.* 1947). It would therefore seem feasible to replace the needle by narrow beams of radiant energy directed at the target in the brain and thereby produce a local destruction of the tissue.

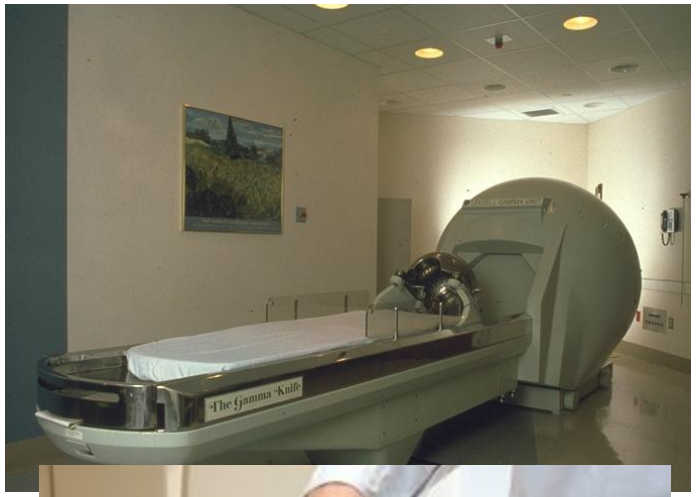
Acta Chir. Scand. **102**, 316-319 (1951).

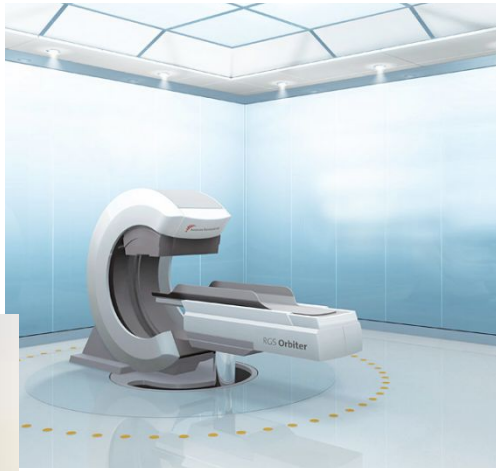


Gamma Knife









Radiocirugía a base de acelerador lineal

- 1983 - Betti & Derenchinsky – B Aires
- 1984 – Colombo – Vicenza
- 1985 – Hartmann – Heidelberg
- 1986 – Podgorsak - Montreal

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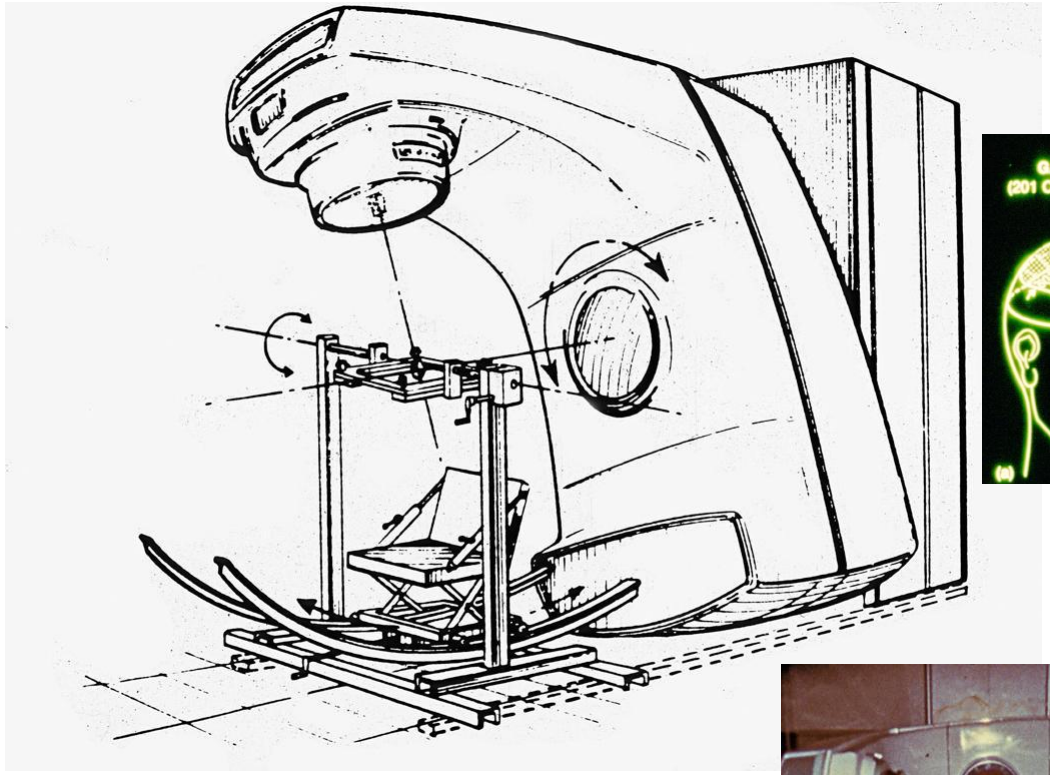
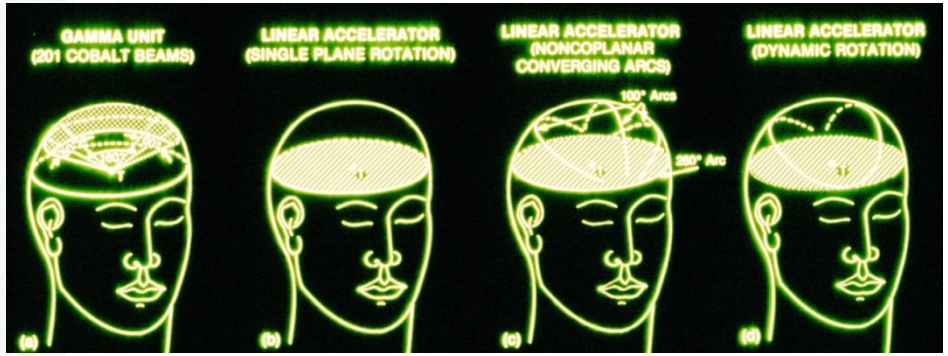
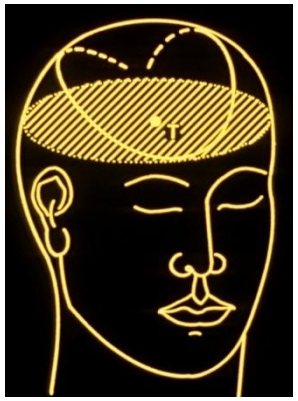
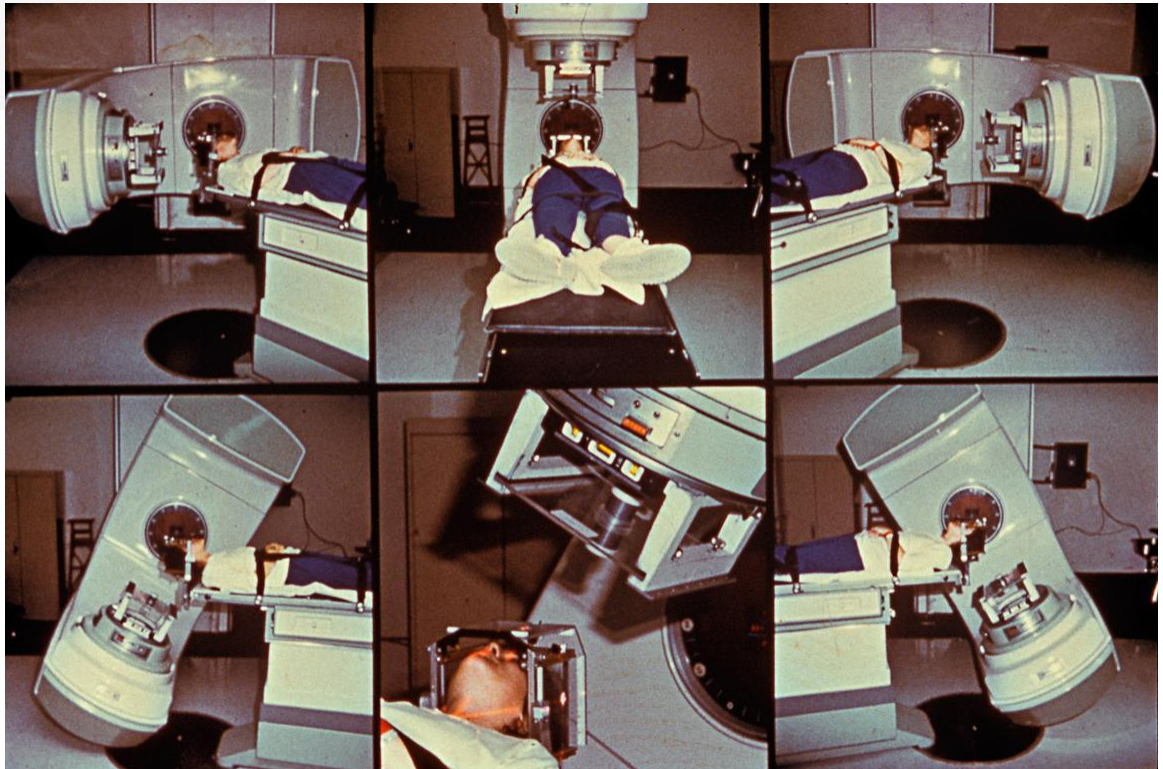






Rotación dinámica



CyberKnife

NovalisTx

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

0360-3016/00/$–see front matter

ELSEVIER

PII S0360-3016(99)00507-6

CLINICAL INVESTIGATION **Brain**

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.†

*Department of Radiation Oncology, Wake Forest University School of Medicine, Winston Salem, NC; †Radiation Therapy Oncology Group, Philadelphia, PA; ‡Department of Radiation Oncology, McGill University, Montreal, Quebec, Canada; §Department of Neurology and ‖Division of Radiation Oncology, Mayo Clinic, Rochester, MN; and ¶ Joint Center for Radiation Therapy, Boston, MA

Purpose: To determine the maximum tolerated dose of single fraction radiosurgery in patients with recurrent previously irradiated primary brain tumors and brain metastases.

Methods and Materials: Adults with cerebral or cerebellar solitary non-brainstem tumors ≤ 40 mm in maximum

Conclusions: The maximum tolerated doses of single fraction radiosurgery were defined for this population of patients as 24 Gy, 18 Gy, and 15 Gy for tumors ≤ 20 mm, 21–30 mm, and 31–40 mm in maximum diameter. Unacceptable CNS toxicity was more likely in patients with larger tumors, whereas local tumor control was most dependent on the type of recurrent tumor and the treatment unit.

Trastornos tratados con radiocirugía estereotáctica

Trastornos Funcionales	Lesiones vasculares
Neuralgia trigeminal	Malformación arteriovenosa
Psiconeurosis	Angioma cavernoso
Dolor intratable	Fístula Carótida-Cavernosa
Enfermedad de Parkinson	Angioma venoso
Epilepsia	

Trastornos tratados con radiocirugía estereotáctica

Tumores benignos	Tumores malignos
Neuroma acústico	Metástasis
Meningioma	Gliomas
Adenoma pituitario	Meduloblastoma
Craneofaringioma	Linfoma
Cordoma	Tumores Pineales
Hemangioblastoma	Nasofaringe (refuerzo)

Neuralgia trigeminal

- Trastorno del quinto par craneal (V)
- Intensa sensación de choque eléctrico
- ¿Compresión vascular?
- ¿Desmielinización del nervio trigémino?

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Tratamiento

- Médico
- No ablativo
  - Descompresión neurovascular
- Ablativo
  - Radiofrecuencia
  - Rizolisis de glicerol
  - Compresión con balón
  - Rizotomía sensorial parcial de la fosa posterior
  - Radiocirugía

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Adquisicion de imagenes

- Imágenes de alta resolución.
- Cortes de 1 mm
- Nervio identificado desde el tronco cerebral hasta la cueva de Meckel
- Objetivo 2-4 mm anterior a la unión del nervio V y la protuberancia

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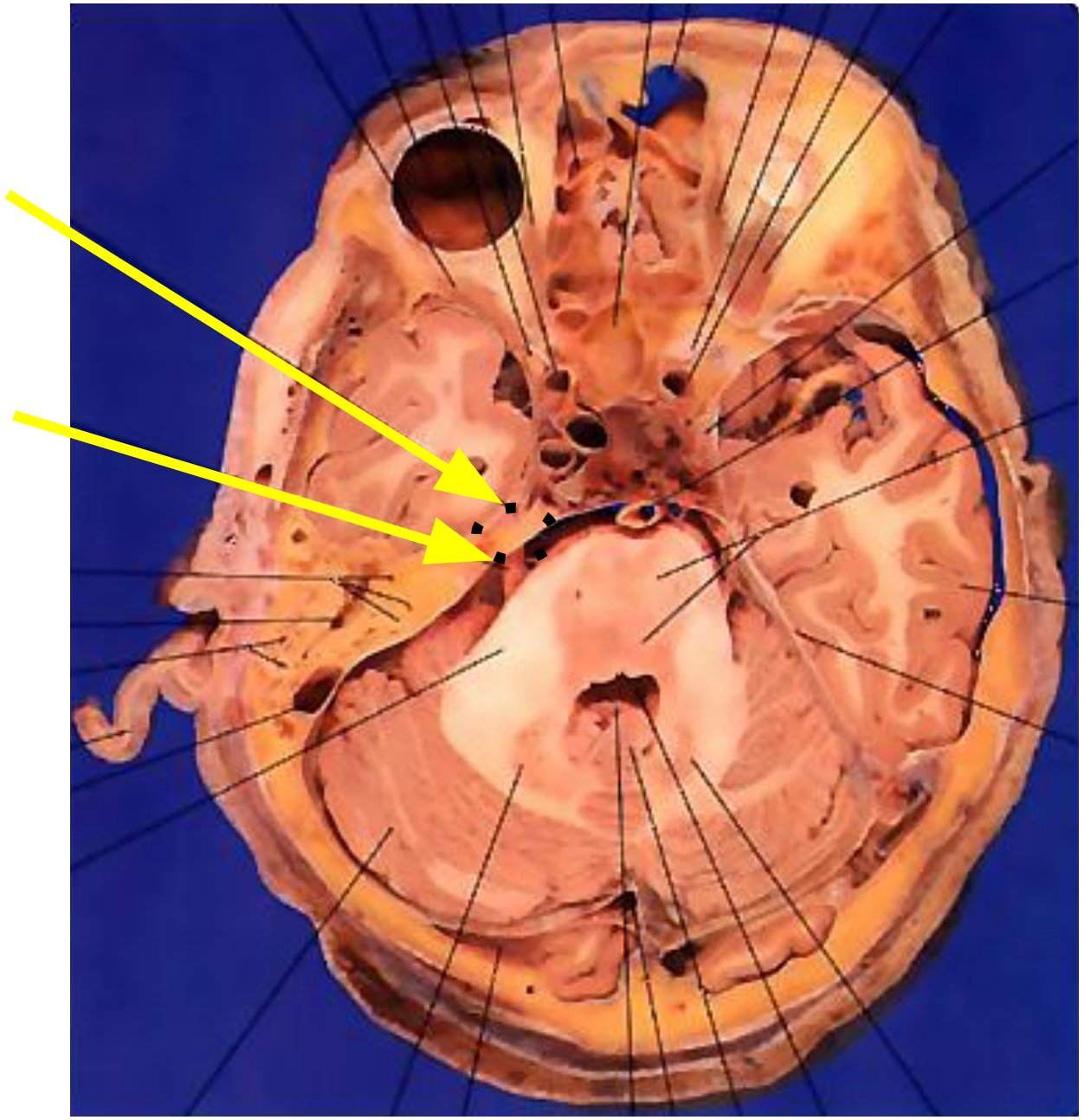

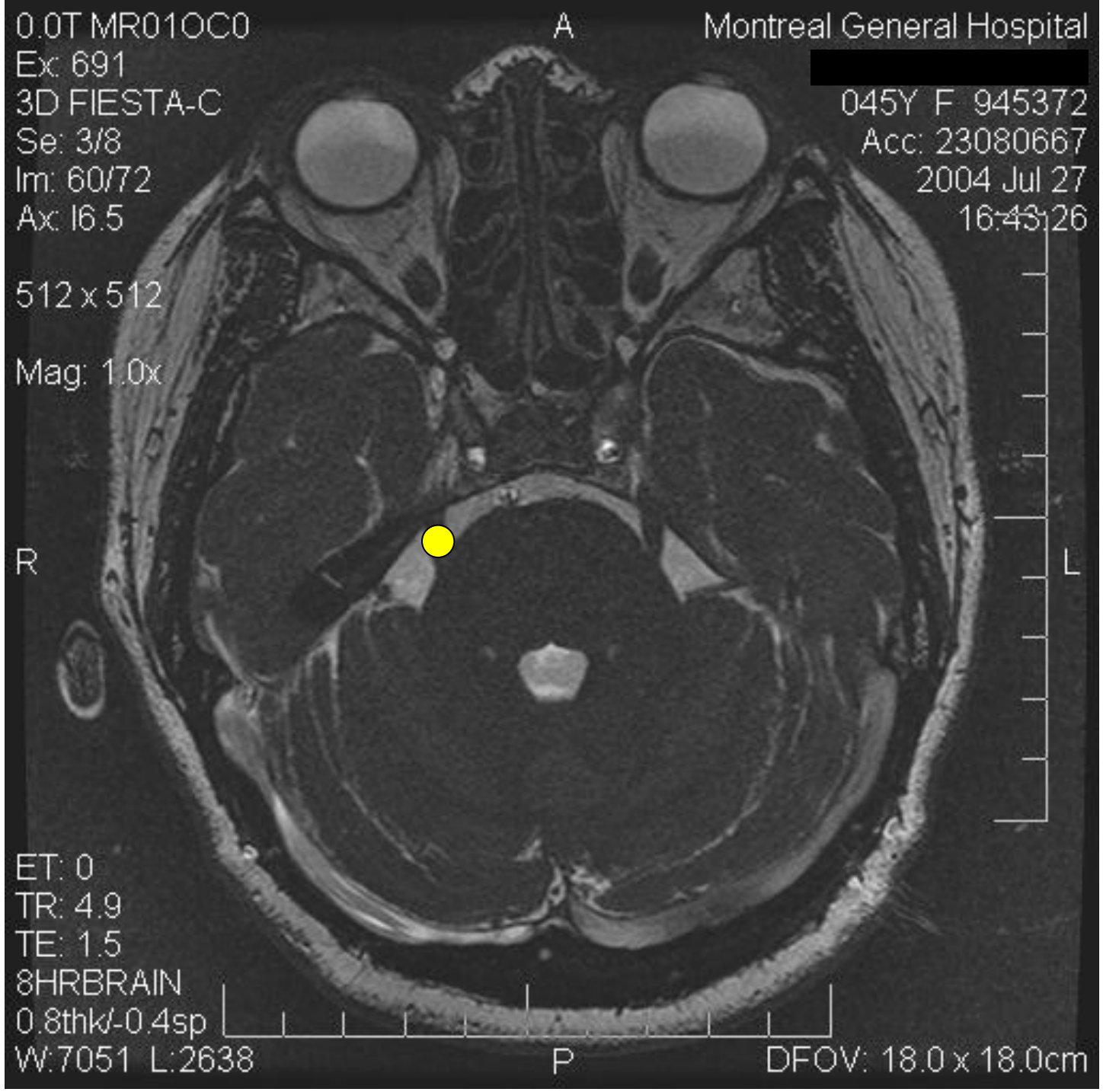
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Ex: 691
3D FIESTA-C
Se: 3/8
Im: 60/72
Ax: I6.5
512 x 512
Mag: 1.0x
A
Montreal General Hospital
[redacted]
045Y F 945372
Acc: 23080667
2004 Jul 27
16:43:26
R
L
ET: 0
TR: 4.9
TE: 1.5
8HRBRAIN
0.8thk/-0.4sp
W:7051 L:2638
P
DFOV: 18.0 x 18.0cm

Resultados del tratamiento

Author	# pts	Follow-up (months)	Complete pain relief (%)					
			6mo	1 yr	2 yr	3 yr	4 yr	5 yr
Kanpolat 2001 (radiofreq.)	1216	60		90	62	62	59	56
North 1990 (glycerol rhyz)	85	36	78	68	60	54		
Brown 1993 (ballon comp)	50	36	91	86	79	69		
Maesawa 2001 (radiosurgery)	220	22	68	63	59	56		
Pollock 2002 (radiosurgery)	117	26	66	65	58	55		

Lopez et al Neurosurgery 2004

Neuromas acústicos

- Se originan en las células de Schwann que rodean el nervio vestibular (VIII)
- Poco común 1:100 000
- Edad Media 45-47 años
- NF-2 en 2-4%

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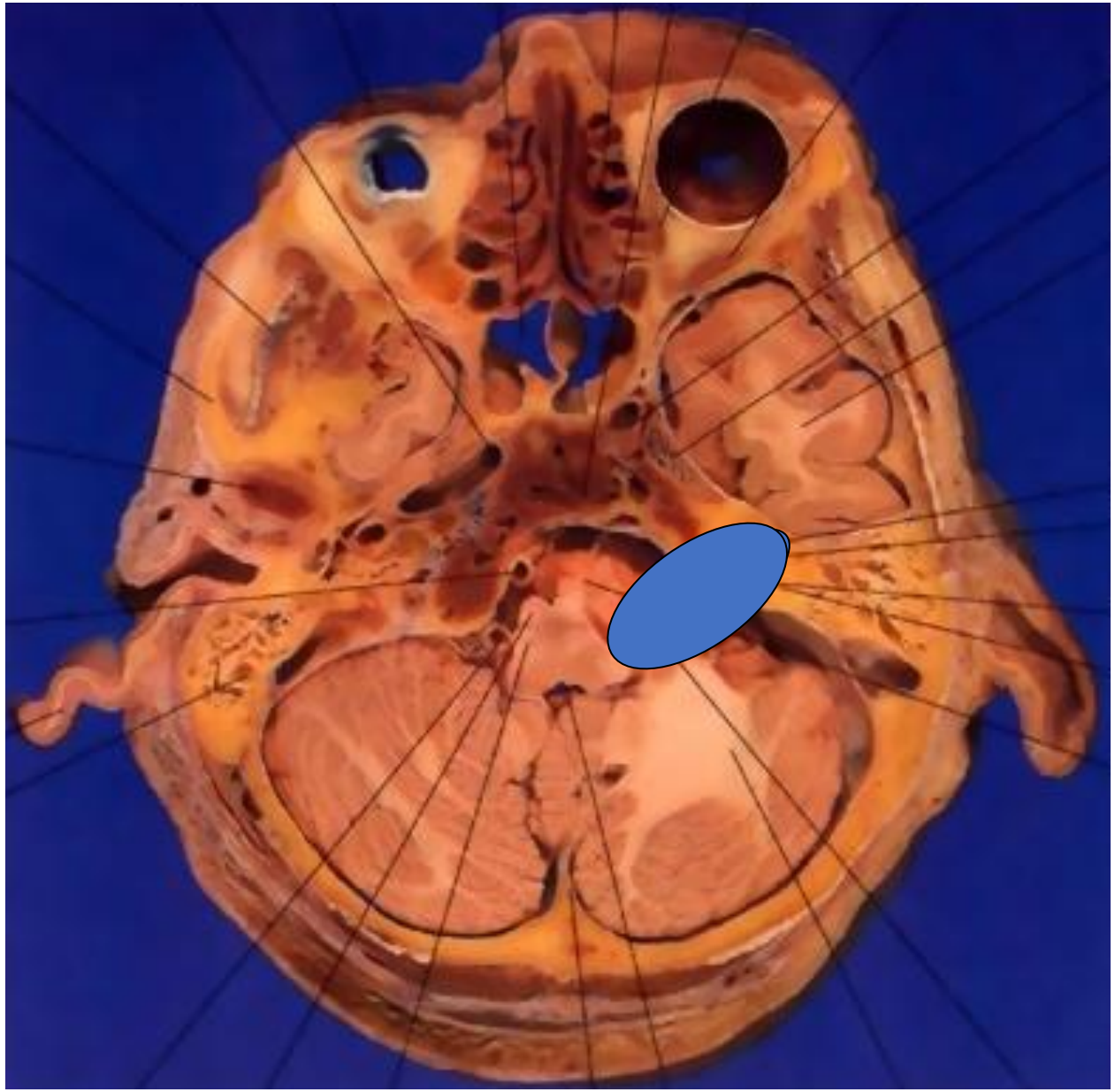

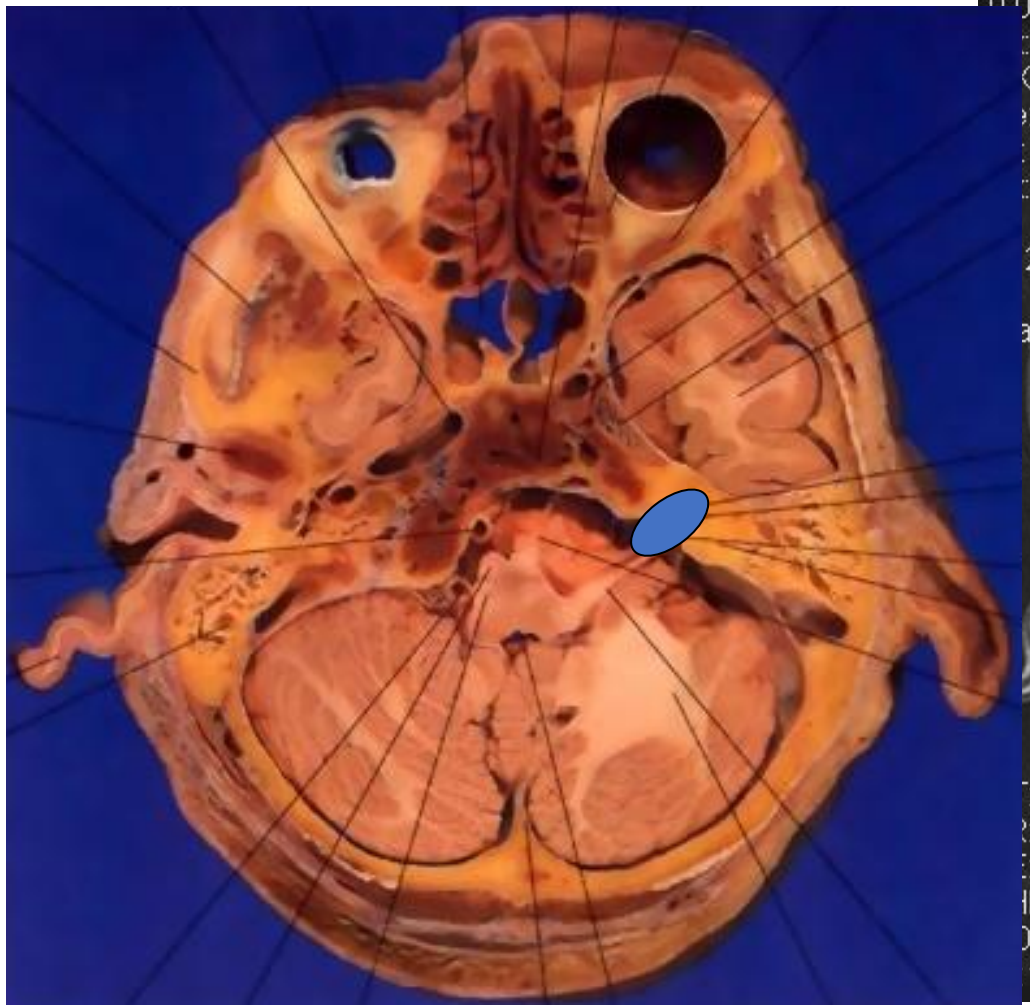

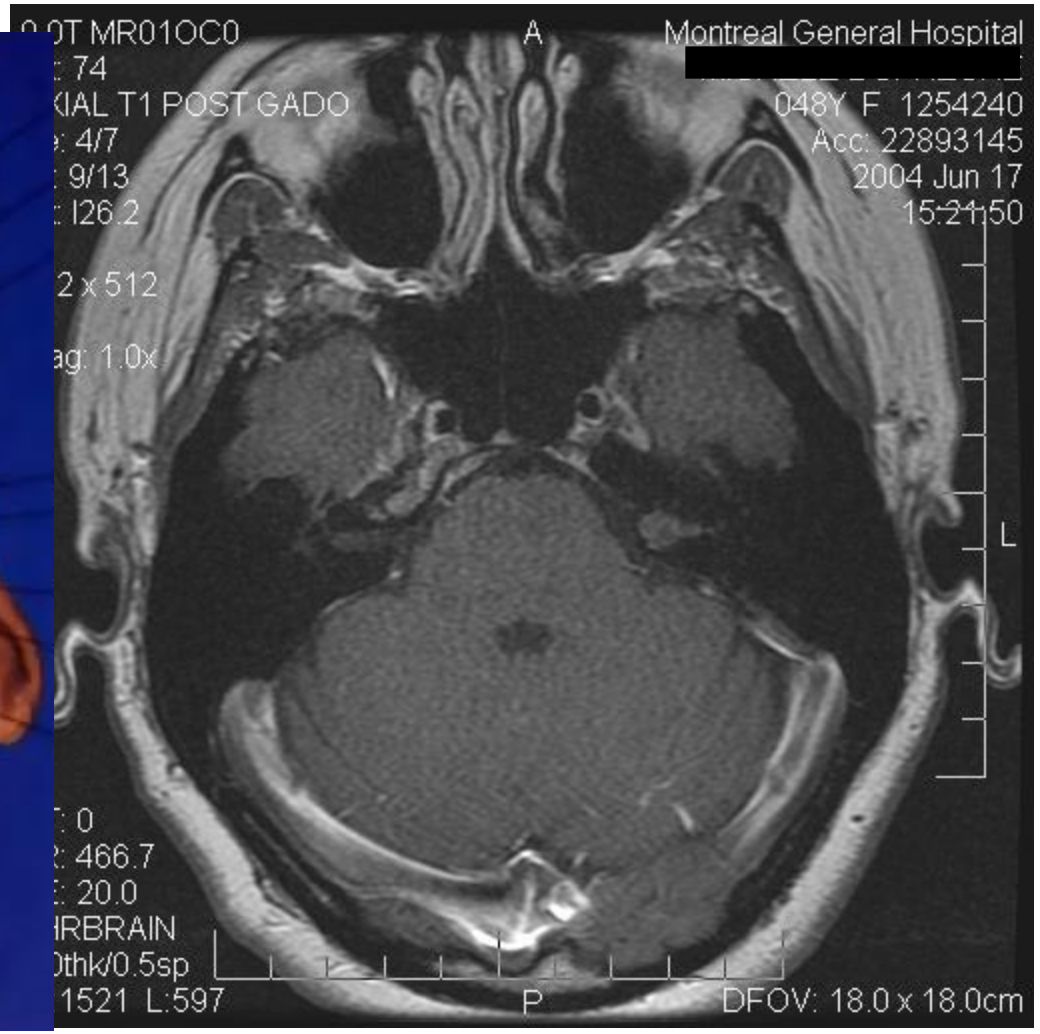
A
Montreal General Hospital
74
IAL T1 POST GADO
4/7
9/13
I26.2
2 x 512
ag: 1.0x
048Y F 1254240
Acc: 22893145
2004 Jun 17
15:21:50
L
0
466.7
20.0
RBRAIN
0thk/0.5sp
1521 L:597
P
DFOV: 18.0 x 18.0cm

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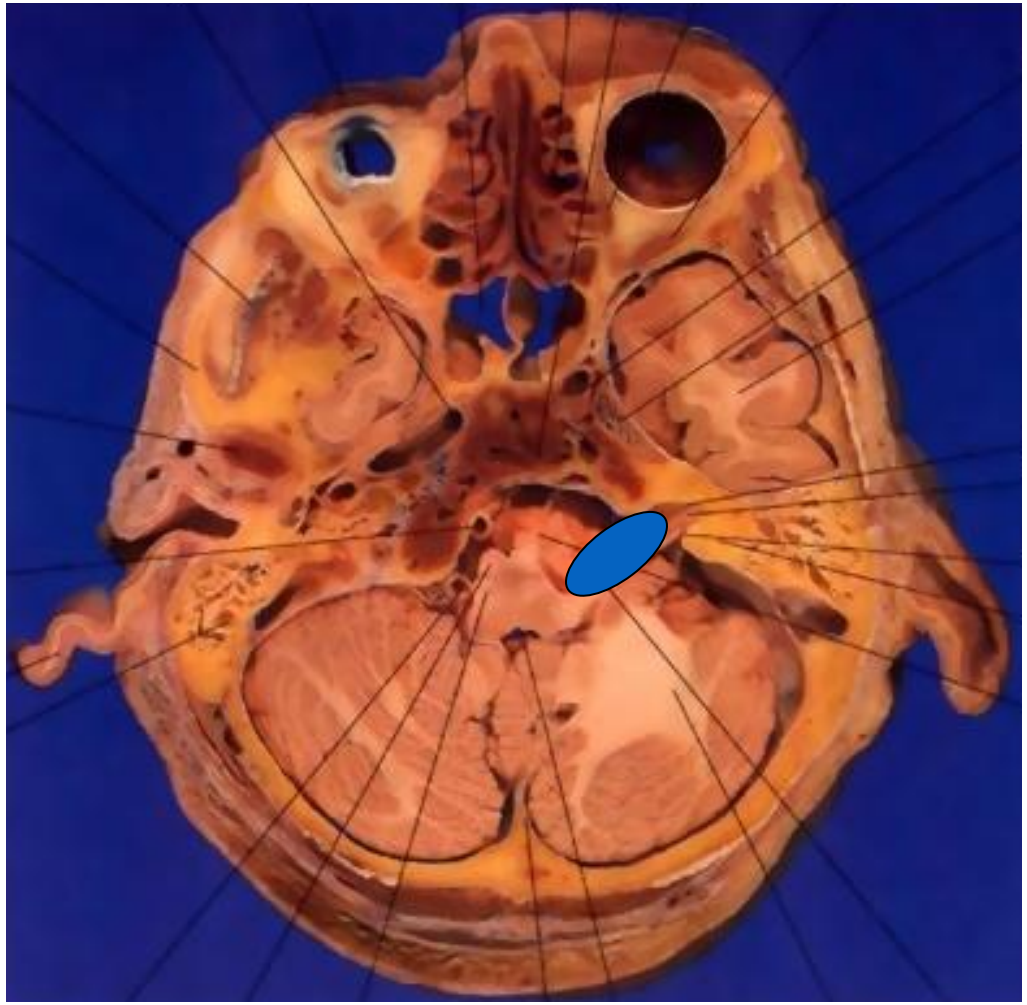
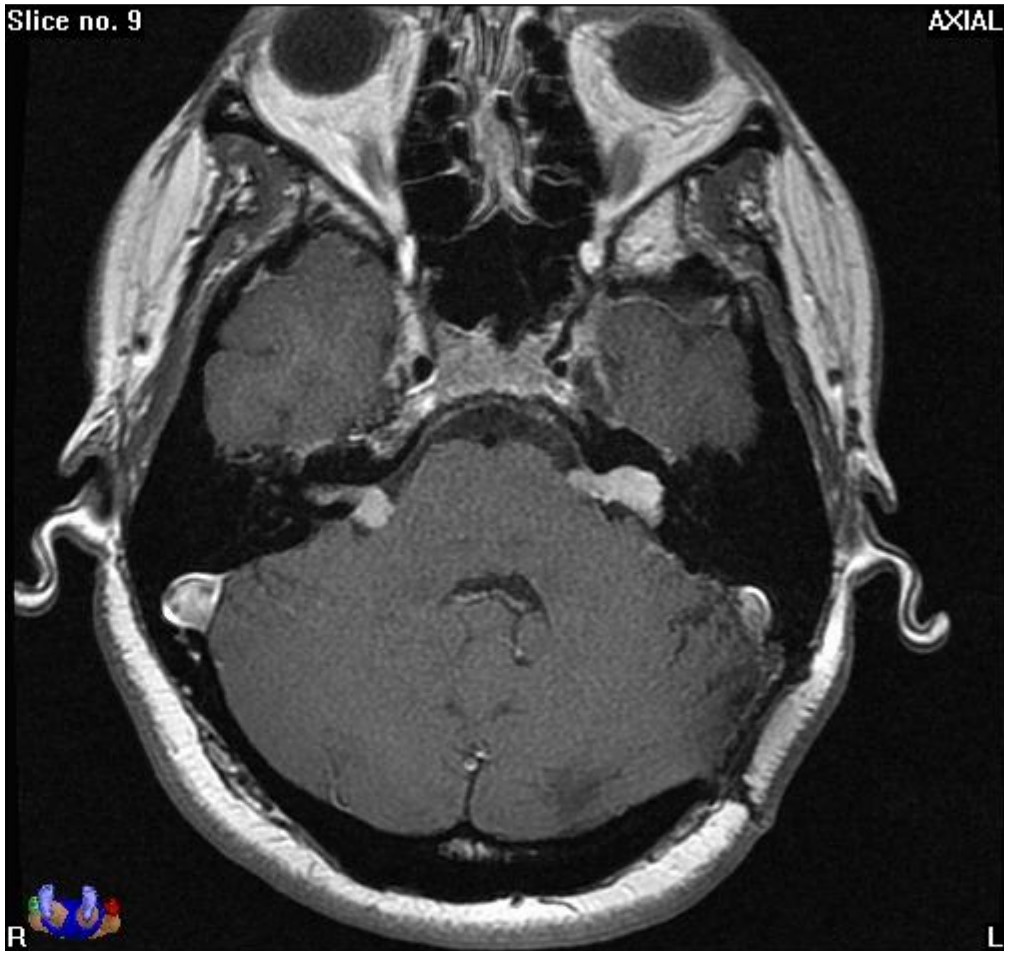
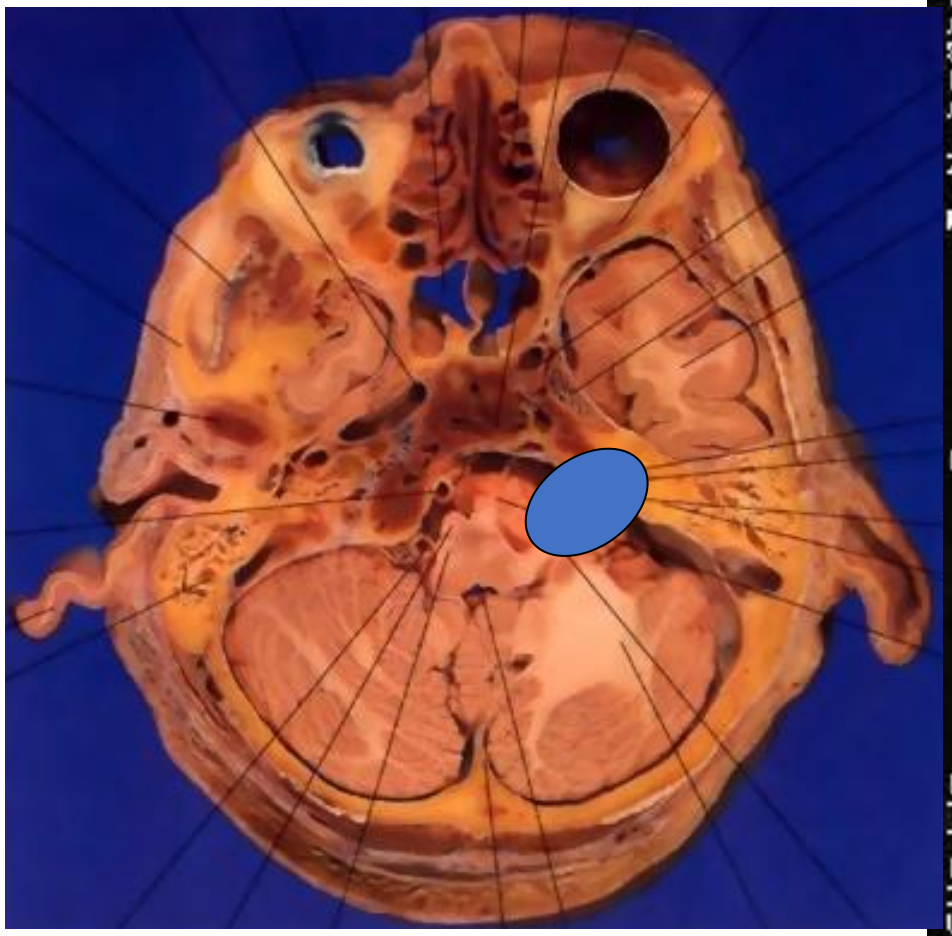
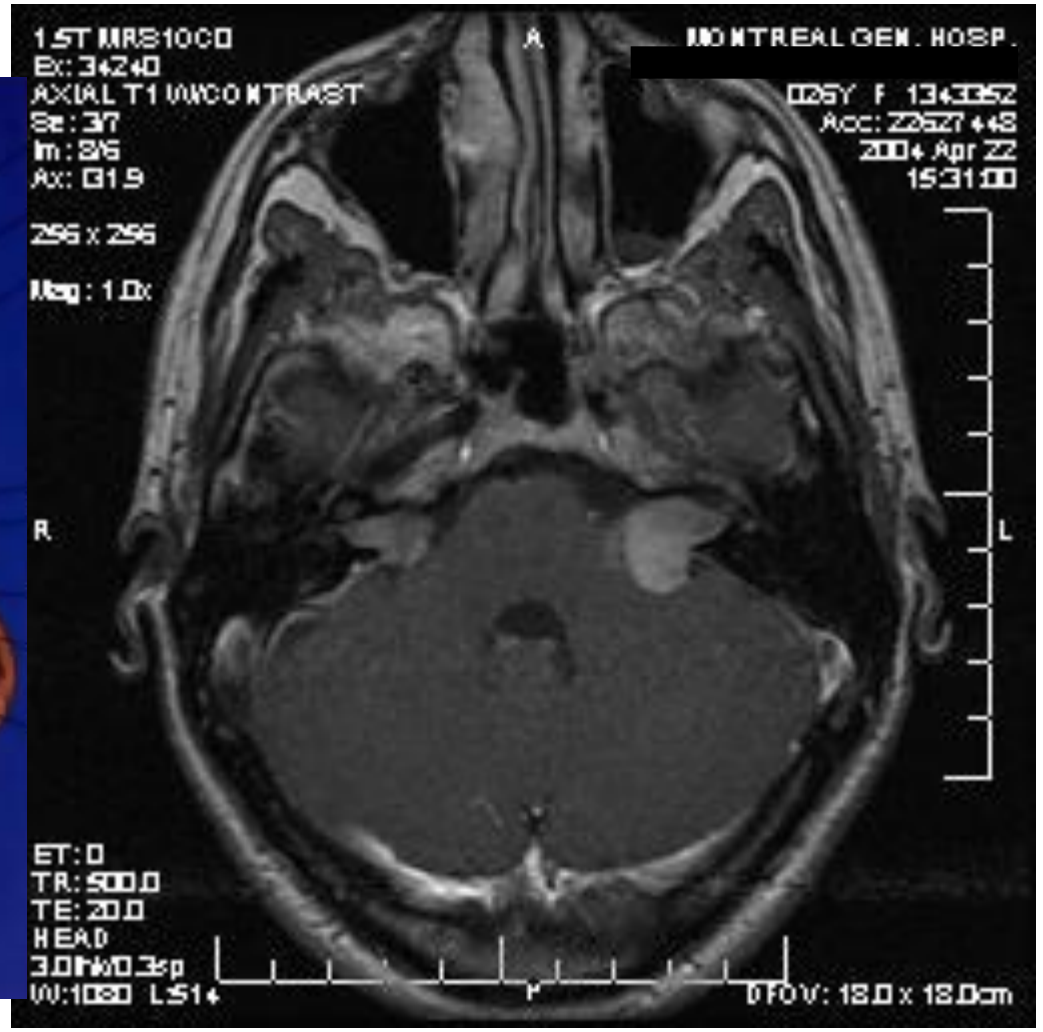
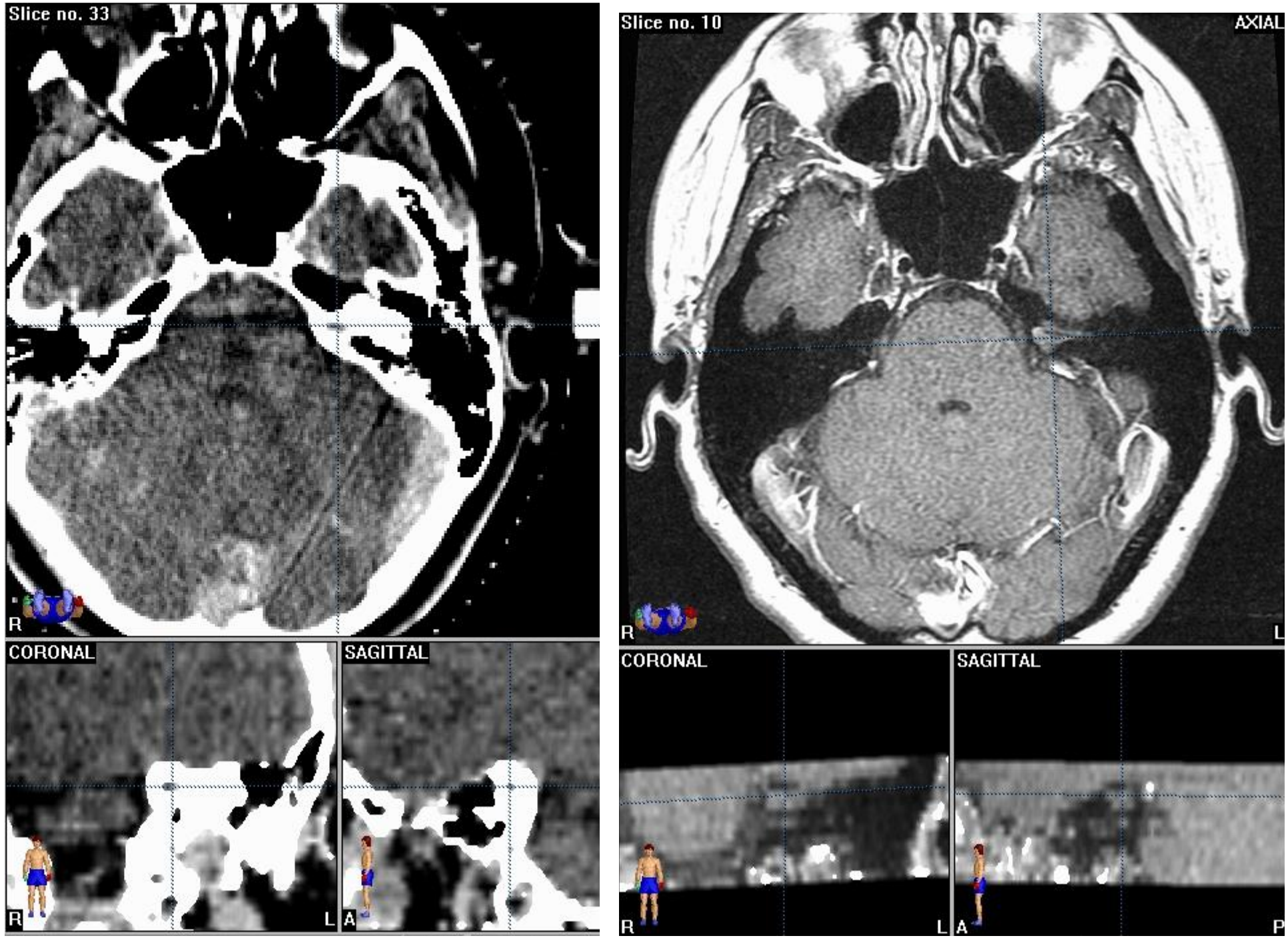



Slice no. 9
AXIAL
R
L




1.5T MRS10CD
Ex: 34240
AXIAL T1 W/CONTRAST
Se: 37
Im: 8/6
Ax: 01.9
256 x 256
Mag: 1.0x
A
MONTREAL GEN. HOSP.
L
R
ET: 0
TR: 500.0
TE: 20.0
HEAD
FOV: 18.0 x 18.0cm


Slice no. 33
R
CORONAL
R
L
SAGITTAL
A
Slice no. 10
AXIAL
R
L
CORONAL
R
L
SAGITTAL
A
P

Objetivos del tratamiento

- Control local
- Preservación de la audición
- Evitar complicaciones

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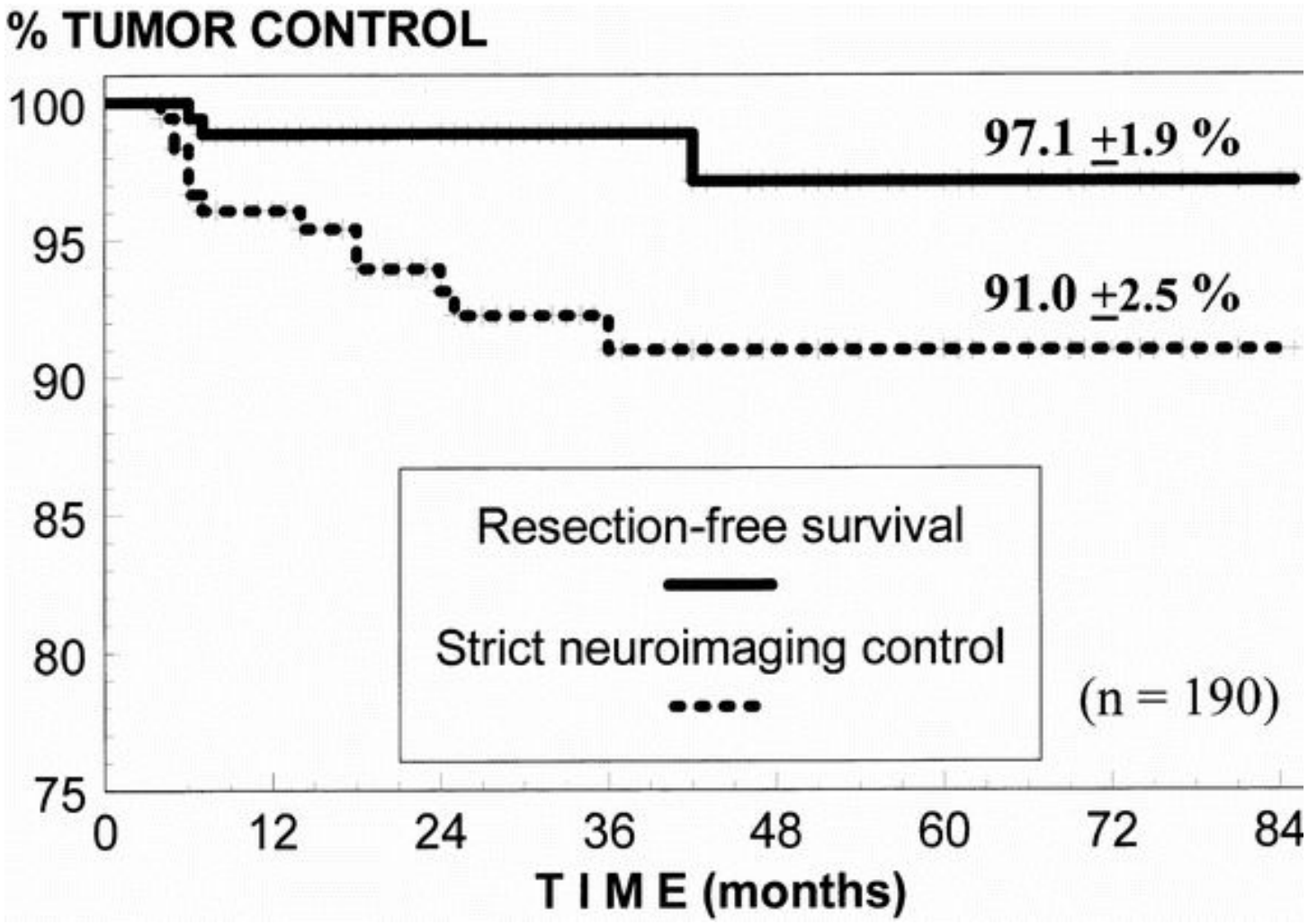
Control tumoral



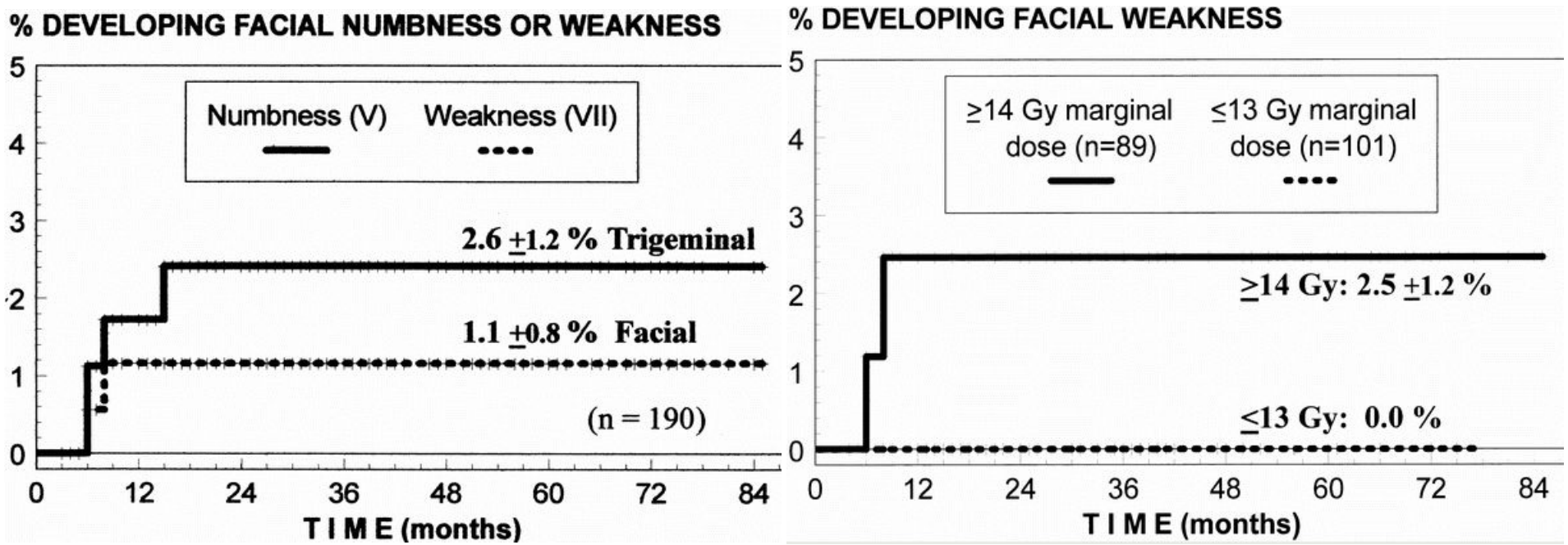
Tamaño del tumor

35%

Flinckinger et al J Neurosurg 2001

Complicaciones

Debilidad facial y neuropatía trigémina



Neuromas acústicos: Neuropatía

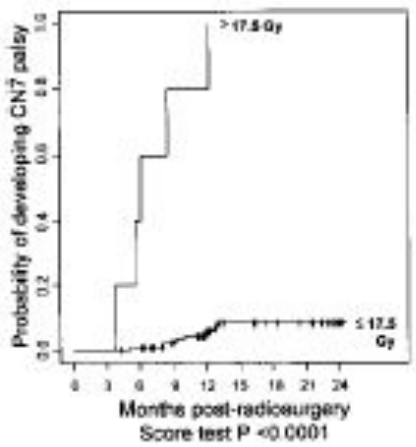
- University of Florida

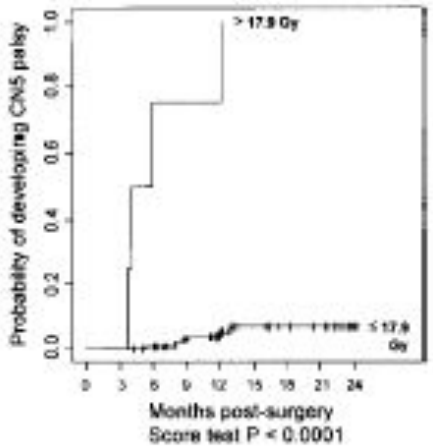
	Antes de 1994	Después de 1994
Facial	29%	5%
Trigeminal	29%	2%

Risk Factors: Dose to brain stem

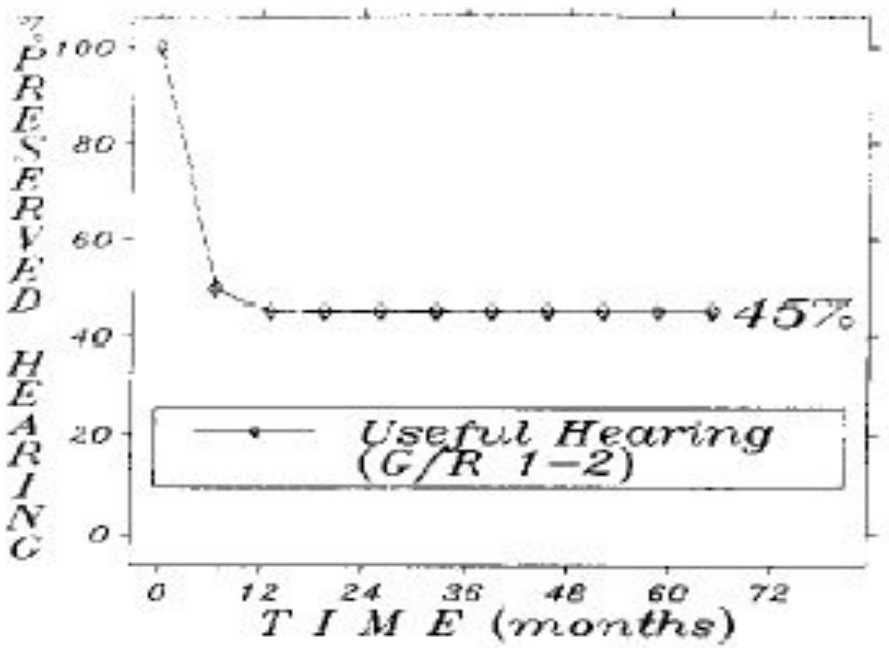
Prior surgery

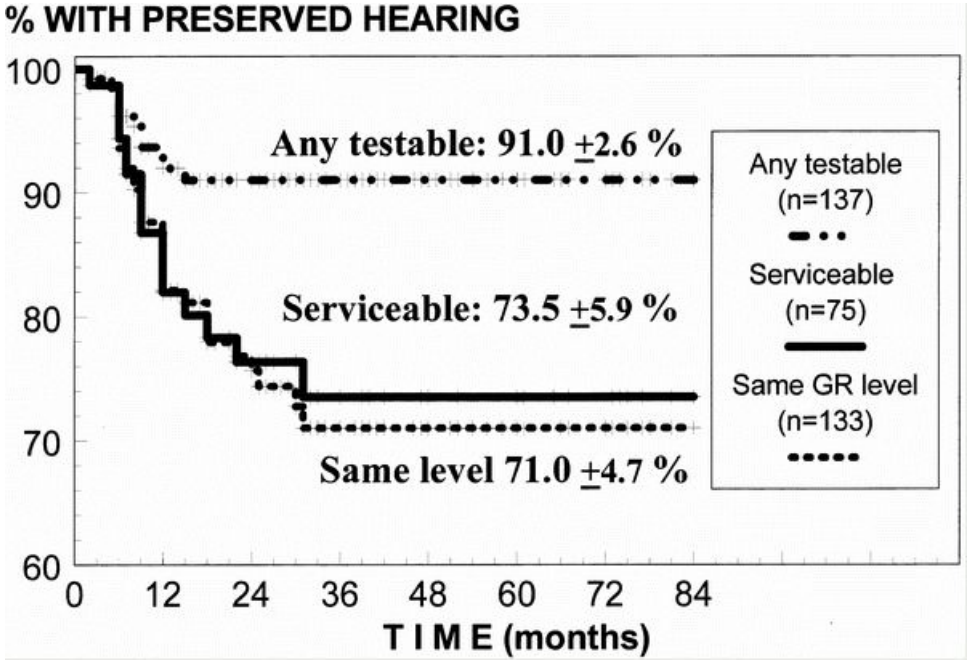
Nerve length





Preservación de la audición





Cambios en las complicaciones.

	Dosis mediana	
Complicacion	**16 Gy**	**13 Gy**
Neuropatia facial	21%	1.1%
Neuropatia trigeminal	27%	2.6%
audición	49%	29%

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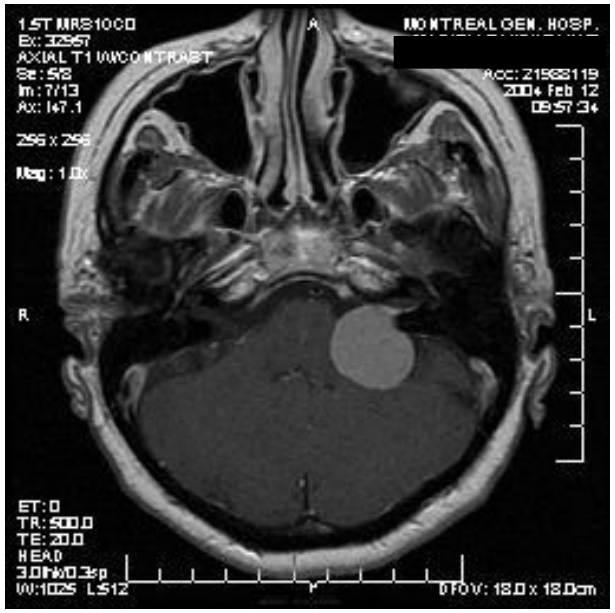

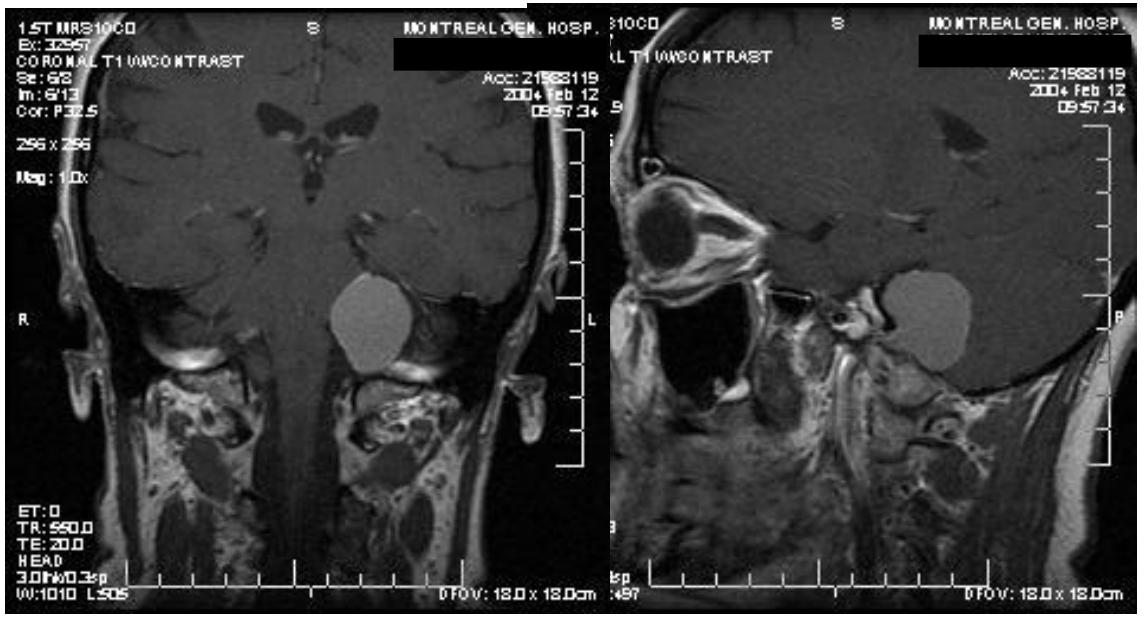

[redacted]

- Evitar tumores > 3 cm
- Planificación detallada necesaria
- Limitar la dosis a las estructuras vitales

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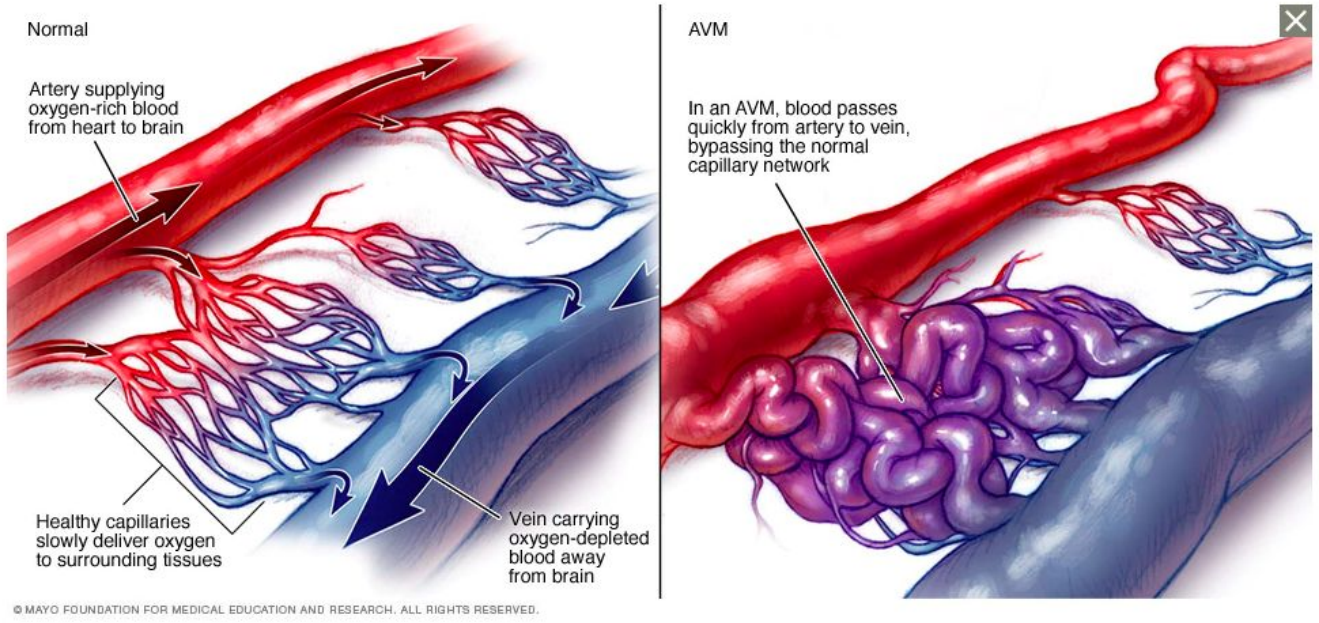
Neuromas acústicos

- La radiocirugía es un tratamiento efectivo para NA pequeños (≤ 3 cm)
- La dosis de 12-13 Gy parece ser segura y eficaz
- Una resonancia magnética es esencial para la planificación

Malformación arteriovenosa (MAV)

- Hemorragia intracraneal: 30-50%
- Riesgo de hemorragia: 2.2%/yr
- Riesgo de muerte por ruptura: 10-29%
- Morbilidad a largo plazo: 20-60%



Flujo sanguíneo en la malformación arteriovenosa

En una malformación arteriovenosa (MAV), la sangre pasa con rapidez desde la arteria hasta la vena, lo que interrumpe el flujo sanguíneo normal y priva a los tejidos circundantes de oxígeno.

Terapia para MAV

- Observación
- Resección quirúrgica
- Embolización endovascular
- Radioterapia (SRS)

Objetivos de la terapia

- Obliteración completa
  - La terapia subtotal no confiere protección contra la hemorragia
- Evitar complicaciones

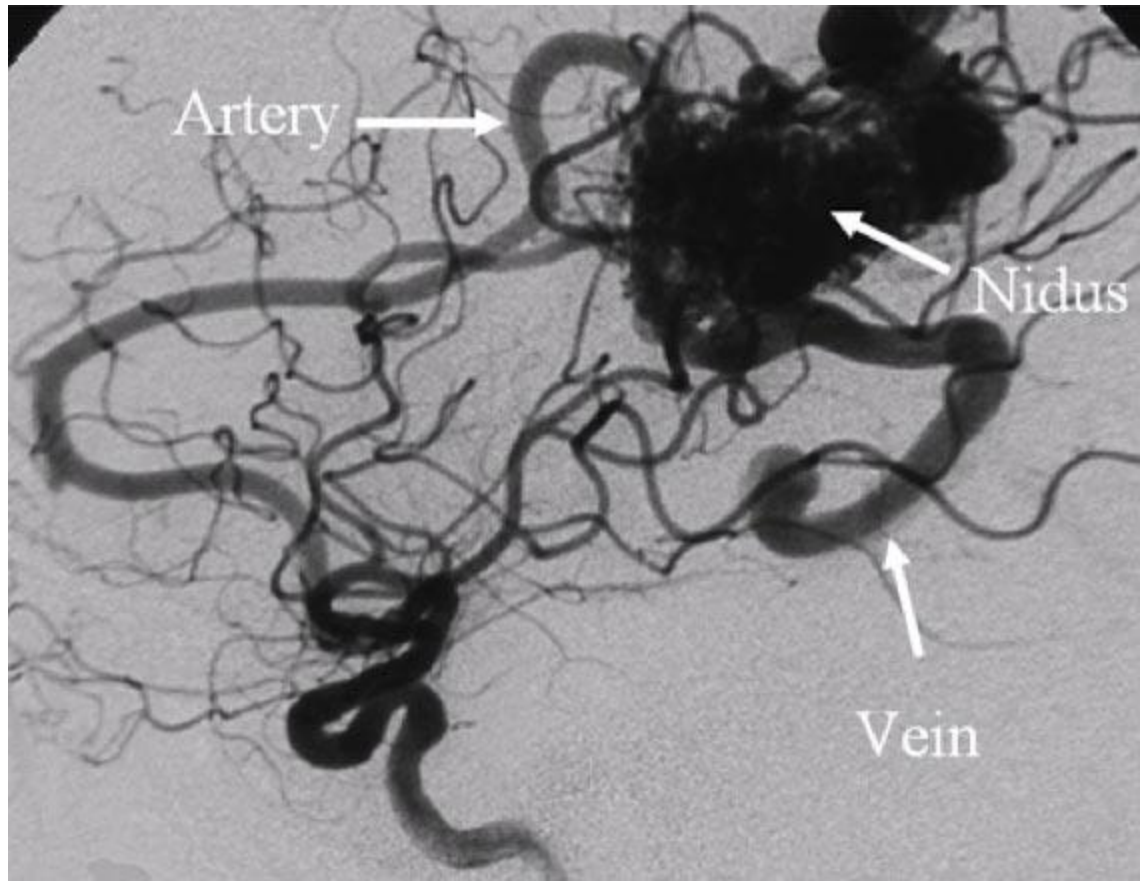
Riesgo de hemorragia

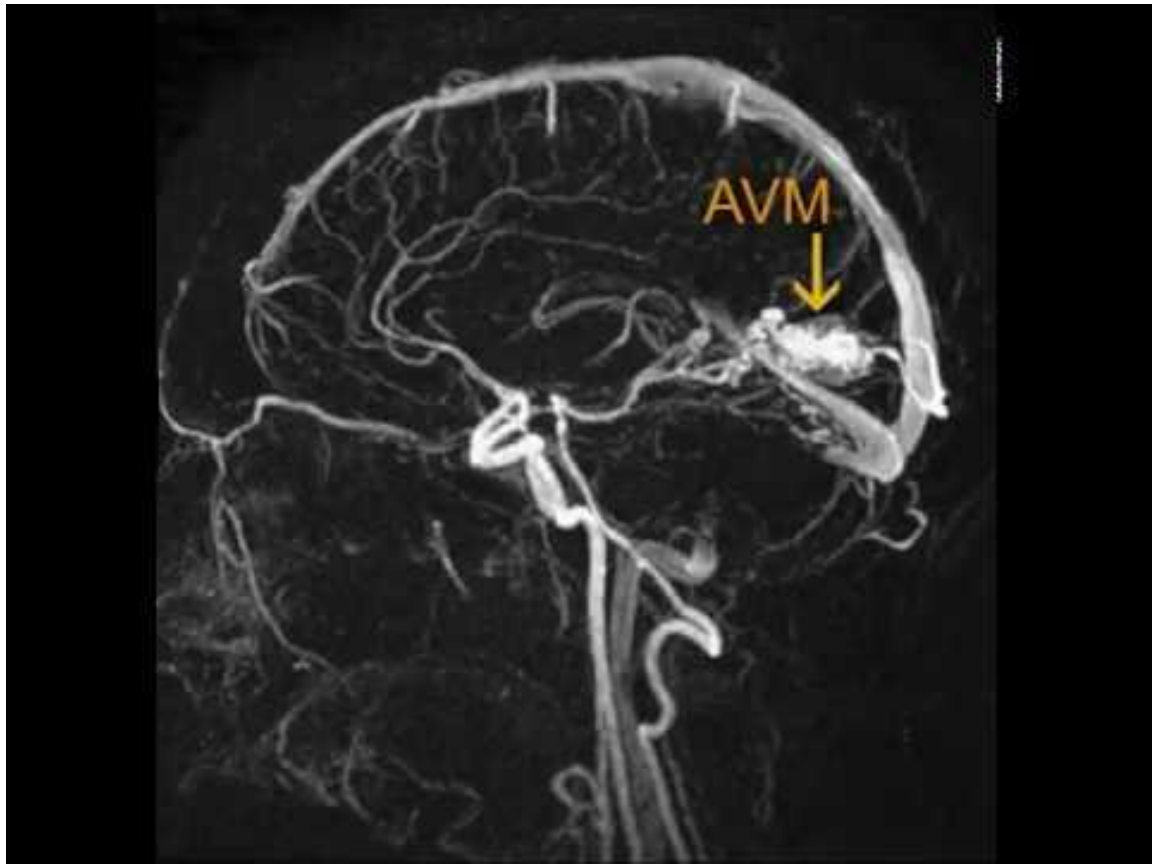
Lifetime risk (%) = 105 – edad del paciente (años)

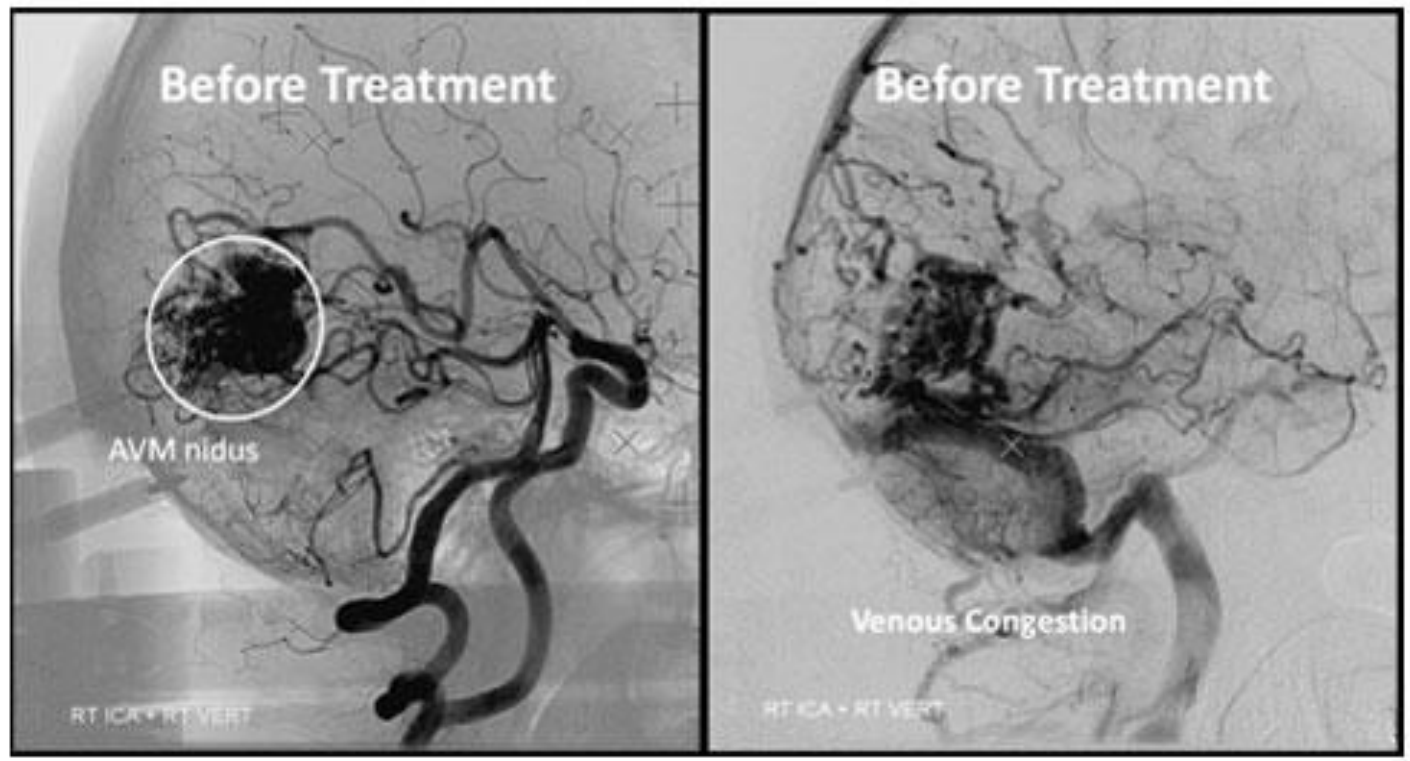
Kondziolkla et al. Neurosurgery 1995
Brown Neurosurgery 2000

Indicaciones para radiocirugía

- MAV pequeñas (<10 cm^3 o <3 cm)
- Lesiones profundas
- Alto riesgo quirúrgico


Artery
Nidus
Vein


AVM


Before Treatment
AVM nidus
Before Treatment
Venous Congestion

Radiocirugía para MAV

Centro	Técnico	# Pts	Cura	Hemorr.	Complic.	Seguimiento
Karolinska	γ knife	310	85%	4%	3%	9-22
Pittsburgh	γ knife	111	70%	16%	4%	1-6
Sheffield	γ knife	96	59%	4%	4%	1-6
Vicenza	Linac	153	80%	10%	NA	1-2
Gainesville	Linac	60	80%	4%	2%	1-6
Heidelberg	Linac	148	55%	8%	4%	2-9
McGill	Linac	102	65%	4%	4%	>2

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Radiocirugía para MAV

- La obliteración se correlaciona con:
  - Dosis de radiación
  - Volumen de tratamiento
  - Ubicación de la MAV
  - Embolización previa

Obliteración de MAV y dosis

Autor	# Pts	Dosis (Gy)	Tasa de obliteración
Souhami (1990)	33	≥ 25	62%
		< 25	0%
Flickinger (1996)	197	≥ 18	60%
		≤ 14	20%
Miyawaki (1999)	73	> 16	80%
		≤ 14	0%
Karlsson (1999)	938	> 20	78%
		≤ 20	45%

Obliteración de MAV y volumen

Center	Volumen de MAV	Tasa de obliteración
Vicenza	< 15 mm	97%
	15-25 mm	74%
	> 25 mm	34%
Pittsburgh	< 4 cm^3	67%
	4-14 cm^3	58%
	> 14 cm^3	23%

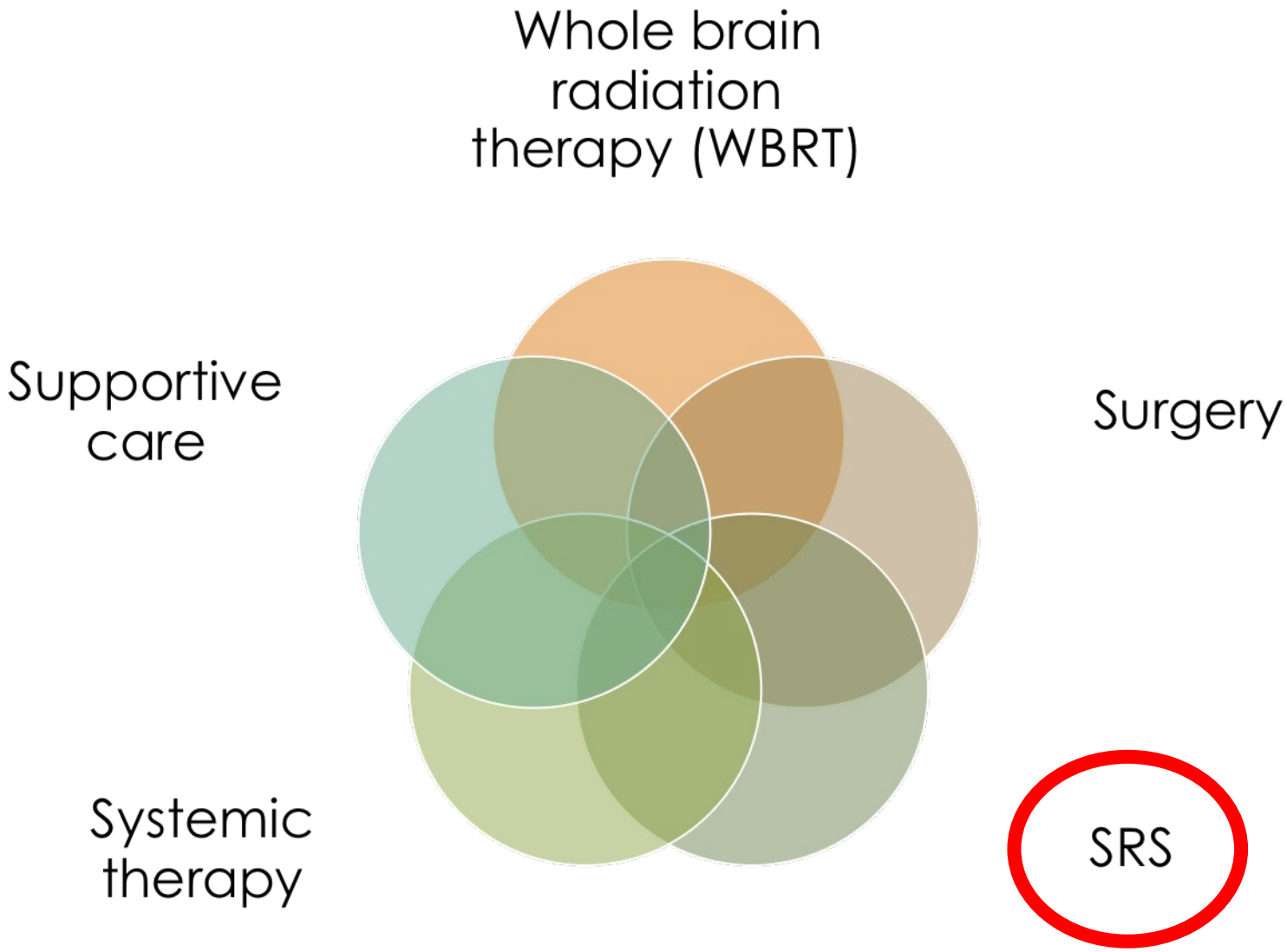
MAV: complicaciones de la radiocirugía

- Las complicaciones agudas son poco frecuentes:
  - Cambios en las imágenes en pacientes asintomáticos: 10%
  - Mejora en 50%
  - Radionecrosis: 2%

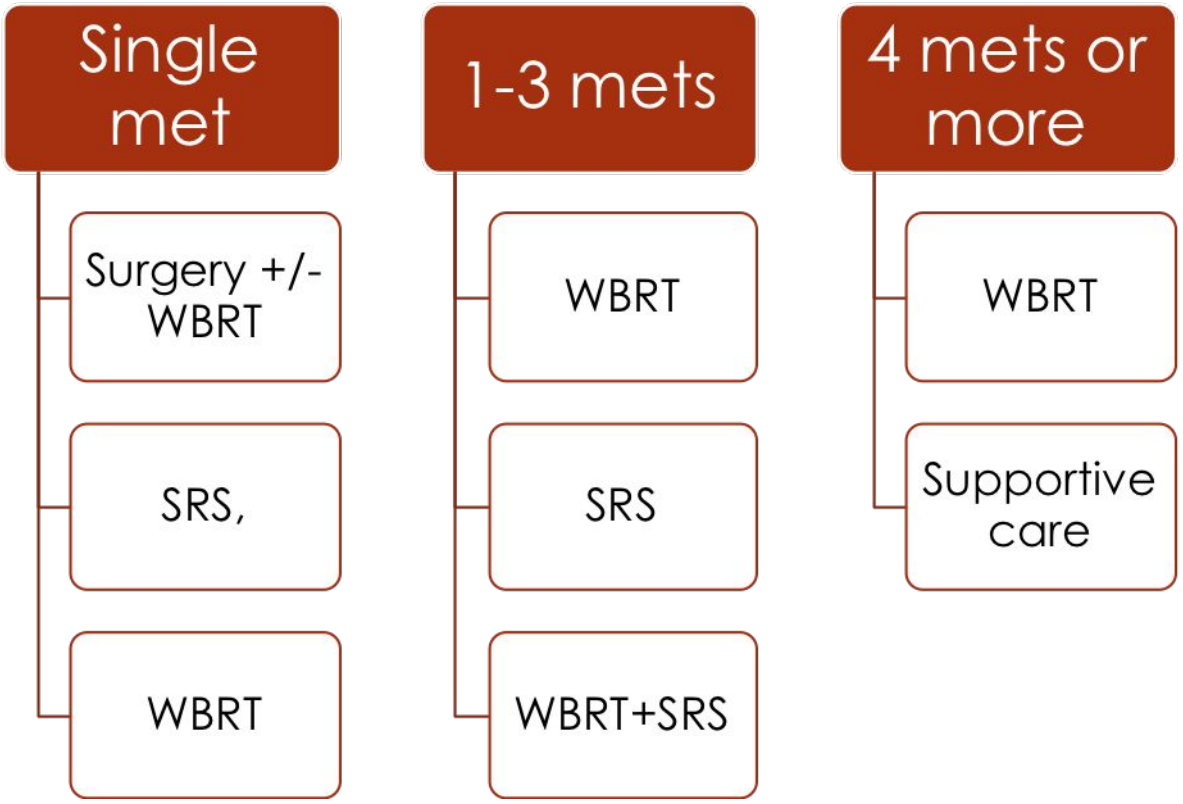
Conclusiones

- SRS es una excelente modalidad de tratamiento para MVA seleccionadas
- Si es posible, dosis a la periferia = 25 Gy
- Evitar dosis altas a la vena de drenaje

Manejo de metástasis cerebrales



Algoritmo de tratamiento del pasado (reciente) ...



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NCCN Guidelines Version 1.2019
Limited Brain Metastases

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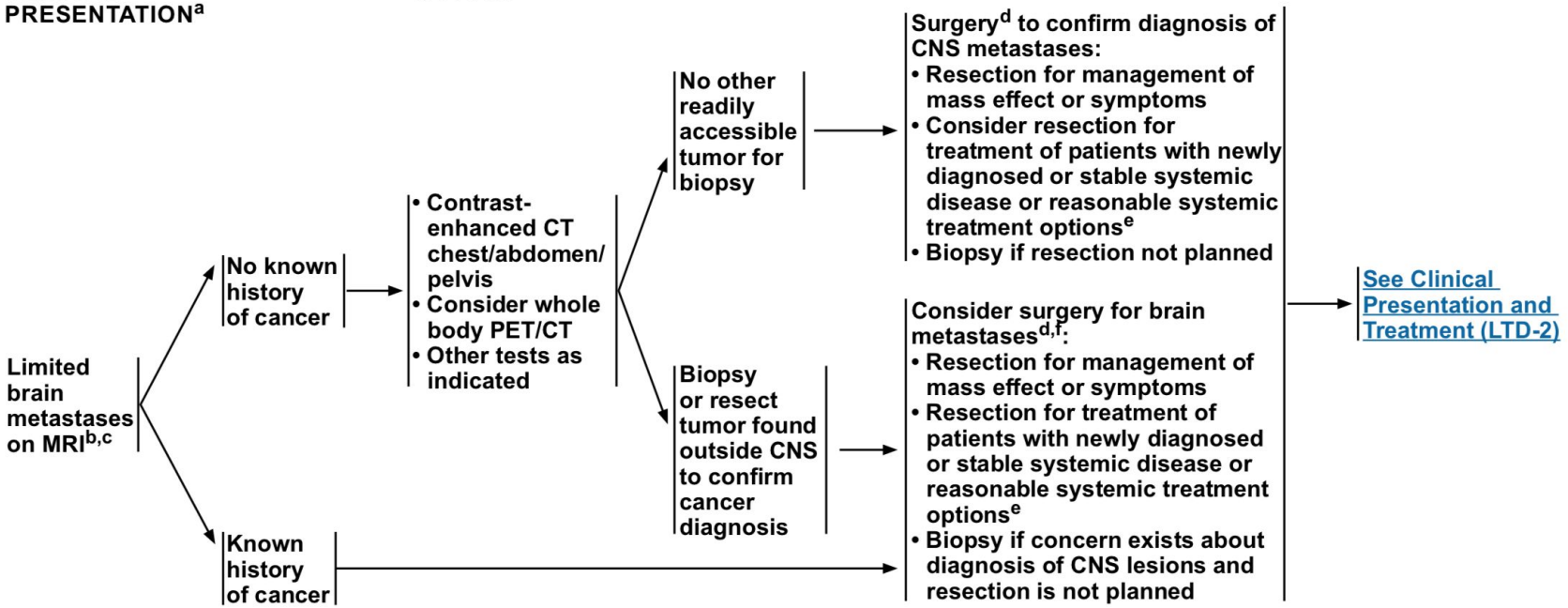
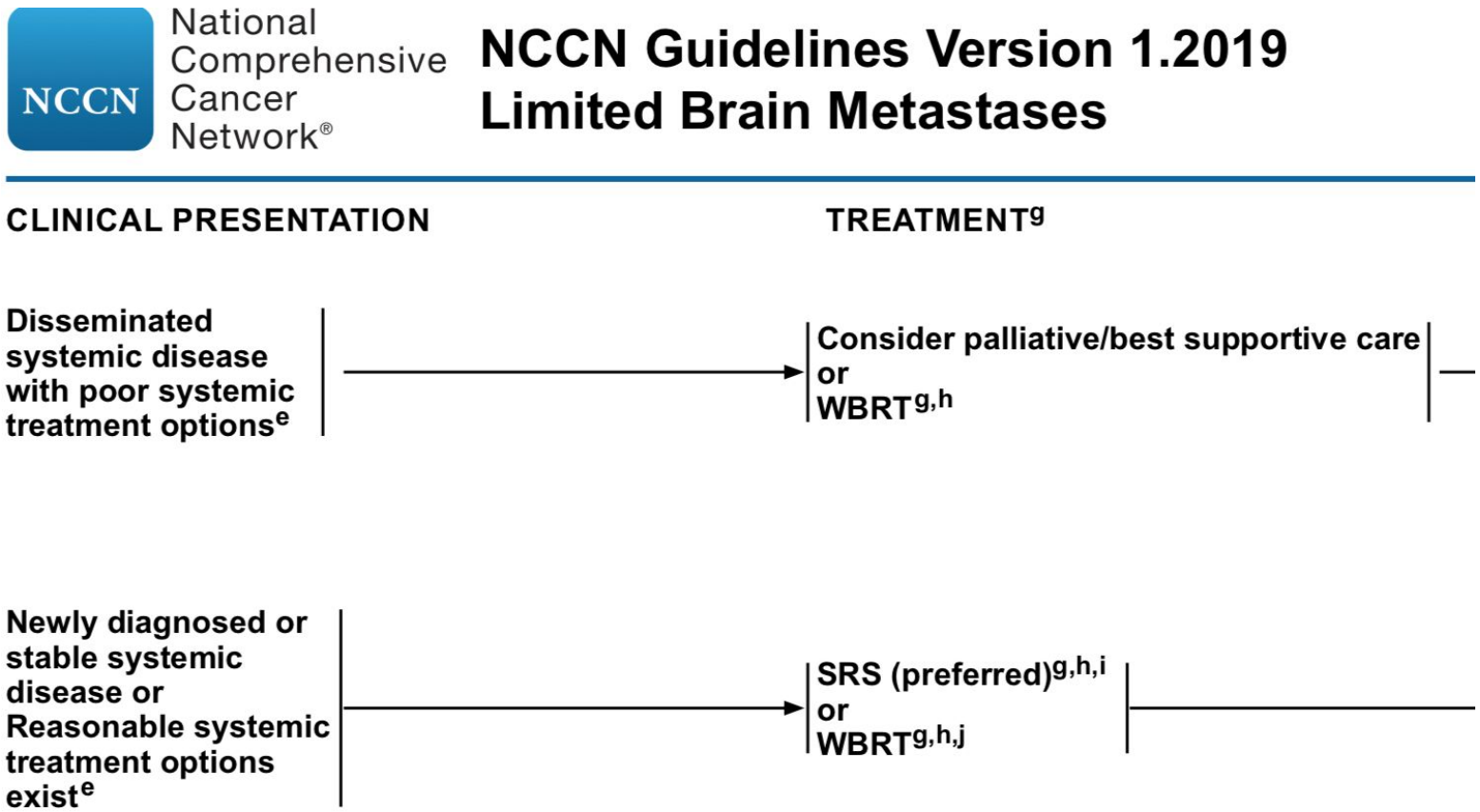
Table of Contents
Discussion



National Comprehensive Cancer Network®

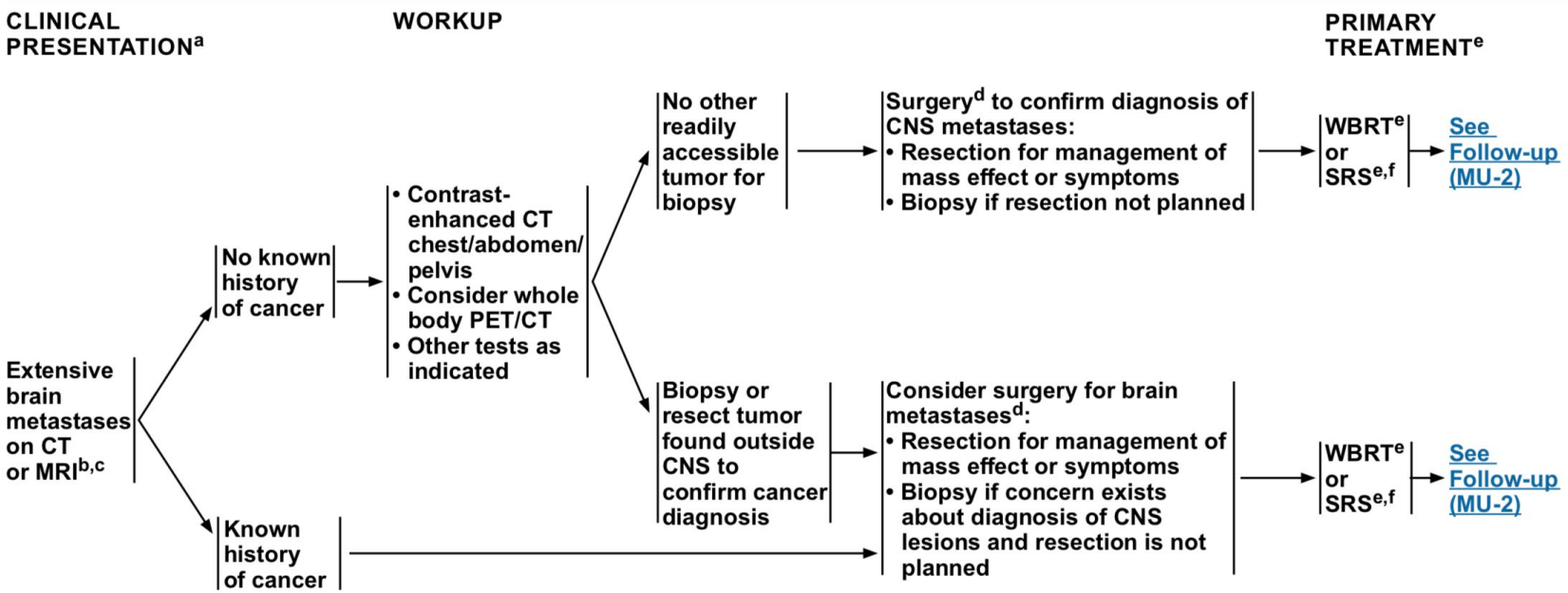
NCCN Guidelines Version 1.2019
Limited Brain Metastases



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Extensive Brain Metastases

NCCN Guidelines Index
Table of Contents
Discussion



¿Qué son los mets cerebrales "limitados"?

"Limited" brain metastases defines a group of patients for whom SRS is equally effective and offers significant cognitive protection compared with WBRT. The definition of "limited" brain metastases in terms of number of metastases or total intracranial disease volume is evolving and may depend on the specific clinical situation. (Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol 2014;15:387-395.)

¿Cuándo debe llamar a la neurocirugía para resecar?

[f]The decision to resect a tumor may depend on the need to establish histologic diagnosis, the size of the lesion, its location, and institutional expertise. For example, smaller (<2 cm), deep, asymptomatic lesions may be considered for treatment with SRS versus larger (>2 cm), symptomatic lesions that may be more appropriate for surgery. (Ewend MG, Morris DE, Carey LA, Ladha AM, Brem S: Guidelines for the initial management of metastatic brain tumors: role of surgery, radiosurgery, and radiation therapy. J Natl Compr Cancer Netw 2008; 6:505-513.)

- Grande (> 2 cm)
- Solo una metastasis
- Aumento de presión intracraneal
- Sintomas importantes
- Necesidad de confirmar la patología
- Buen pronóstico
- Región no elocuente / resecable

¿Por qué estamos usando menos radioterapia cerebral?

- Sin ventaja de supervivencia
- Impacto neurocognitivo nocivo que se entiende mejor a medida que mejora el pronóstico de los pacientes con cáncer
- Alternativas de tratamiento mejores

Estudios aleatorizados SRS vs. WBRT+SRS

Autor	Tratamiento	Sobrevida global Media (mes)	Sobrevida global 1-año	Recurrencia cerebral (1 año)
Aoyama[1]	SRS WB+SRS	8.0 7.5	28.4% 38.5%	76.4% 46.8%*
Roos[2]	SRS/S WB+SRS/S	6.2 9.2		78% 30%
Chang[3]	SRS WB+SRS	15.2* 5.7	63%* 21%	73% 27%*
Kocher[4]	SRS/S WB+SRS	10.9 10.7	48% 48%	78% 48%*
Brown[5]	SRS WB+SRS	10.4 7.4	38% 38.5%	49.5% 17%*

1- JAMA 2006; 2-Radioth Oncol 2006; Lancet Oncol 2009; 4- J Clin Oncol 2011; 5- ASCO 2015

JAMA. 2016 Jul 26;316(4):401-9. doi: 10.1001/jama.2016.9839.

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.

Brown PD[1], Jaeckle K[2], Ballman KV[3], Farace E[4], Cerhan JH[5], Anderson SK[3], Carrero XW[3], Barker FG 2nd[6], Deming R[7], Burri SH[8], Ménard C[9], Chung C[10], Stieber VW[11], Pollock BE[5], Galanis E[5], Buckner JC[5], Asher AL[12].

Author information

Abstract

IMPORTANCE: Whole brain radiotherapy (WBRT) significantly improves tumor control in the brain after stereotactic radiosurgery (SRS), yet because of its association with cognitive decline, its role in the treatment of patients with brain metastases remains controversial.

OBJECTIVE: To determine whether there is less cognitive deterioration at 3 months after SRS alone vs SRS plus WBRT.

DESIGN, SETTING, AND PARTICIPANTS: At 34 institutions in North America, patients with 1 to 3 brain metastases were randomized to receive SRS or SRS plus WBRT between February 2002 and December 2013.

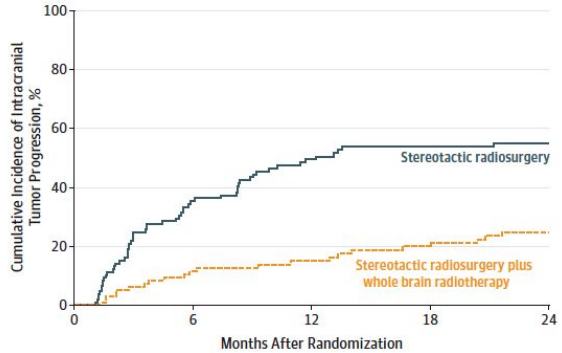
INTERVENTIONS: The WBRT dose schedule was 30 Gy in 12 fractions; the SRS dose was 18 to 22 Gy in the SRS plus WBRT group and 20 to 24 Gy for SRS alone.

MAIN OUTCOMES AND MEASURES: The primary end point was cognitive deterioration (decline >1 SD from baseline on at least 1 cognitive test at 3 months) in participants who completed the baseline and 3-month assessments. Secondary end points included time to intracranial failure, quality of life, functional independence, long-term cognitive status, and overall survival.

Table 2. Patients Who Experienced Cognitive Deterioration by 3 Months and Difference Between Groups

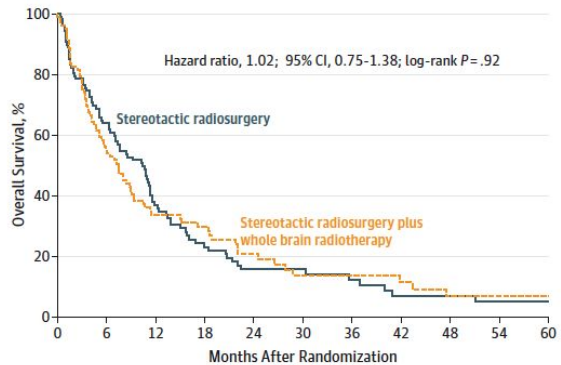
	No. (%) of Participants			
	SRS Alone (n = 63)	SRS Plus WBRT (n = 48)	Mean Difference, % (95% CI)	*P* Value[a]
Change from baseline[b]				
HVLT-R				
Immediate recall				
Deterioration	5 (8.2)	14 (30.4)	22.2 (5.4 to 39.1)	.004
No deterioration	56 (91.8)	32 (69.6)		
Delayed recall				
Deterioration	12 (19.7)	24 (51.1)	31.4 (12.1 to 50.7)	<.001
No deterioration	49 (80.3)	23 (48.9)		
Recognition				
Deterioration	14 (22.6)	19 (40.4)	17.8 (−1.5 to 37.2)	.06
No deterioration	48 (77.4)	28 (59.6)		
TMT-A time to complete				
Deterioration	10 (16.7)	14 (30.4)	13.8 (−4.4 to 32.0)	.11
No deterioration	50 (83.3)	32 (69.6)		
TMT-B time to complete				
Deterioration	11 (19.0)	16 (37.2)	18.2 (−1.4 to 37.9)	.07
No deterioration	47 (81.0)	27 (62.8)		
COWAT total				
Deterioration	1 (1.9)	8 (18.6)	16.7 (2.4 to 31.0)	.01
No deterioration	52 (98.1)	35 (81.4)		
GPS total seconds				
Deterioration	17 (29.3)	21 (47.7)	18.4 (−2.4 to 39.3)	.07
No deterioration	41 (70.7)	23 (52.3)		
Outcome for cognitive progression at 3 mo				
Stable	23 (36.5)	4 (8.3)	−28.2 (−44.2 to −12.2)	<.001
Progression	40 (63.5)	44 (91.7)		

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



No. at risk					
Stereotactic radiosurgery	111	35	12	5	1
Stereotactic radiosurgery plus whole brain radiotherapy	102	43	24	16	9

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



No. at risk											
Stereotactic radiosurgery	111	64	35	19	13	10	7	4	4	2	2
Stereotactic radiosurgery plus whole brain radiotherapy	102	50	28	22	13	8	8	5	3	1	1

Key Points

Question What is the effect of whole brain radiotherapy in addition to stereotactic radiosurgery on cognitive function of patients with 1 to 3 brain metastases?

Findings In this randomized clinical trial that included 213 adults with metastases amenable to radiosurgery, there was less cognitive deterioration at 3 months after stereotactic radiosurgery alone (64%) than after stereotactic radiosurgery plus whole brain radiotherapy (92%), a significant difference.

Meaning In patients with 1 to 3 brain metastases, stereotactic radiosurgery alone may be the preferred strategy.

American Society for Radiation Oncology

10

Don't routinely add adjuvant whole brain radiation therapy to stereotactic radiosurgery for limited brain metastases.

Primary analyses of randomized studies have demonstrated no overall survival benefit from the addition of adjuvant whole brain radiation therapy (WBRT) to stereotactic radiosurgery (SRS) in the management of selected patients with good performance status and brain metastases from solid tumors.

The addition of WBRT to SRS is associated with diminished cognitive function and worse patient-reported fatigue and quality of life. These results are consistent with the worsened self-reported cognitive function and diminished verbal skills observed in randomized studies of prophylactic cranial irradiation for small cell or non-small-cell lung cancer.

Patients treated with radiosurgery for brain metastases can develop metastases elsewhere in the brain. Careful surveillance and the judicious use of salvage therapy at the time of brain relapse allow appropriate patients to enjoy the highest quality of life without a detriment in overall survival. Patients should discuss these options with their radiation oncologist.

Original Article

Patient preference for stereotactic radiosurgery plus or minus whole brain radiotherapy for the treatment of brain metastases

K. Liang Zeng[1], Srinivas Raman[1], Arjun Sahgal[1], Hany Soliman[1], May Tsao[1], Carole Wendzicki[2], Edward Chow[1], Simon S. Lo[2*]

[1]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; [2]Department of Radiation Oncology, University Hospitals Seidman Cancer Center, Cleveland, OH, USA

Table 2 Patient reported important considerations as part of treatment decision making

Consideration	Score (out of 10; 10 is extremely important to consider, 0 is not at all important to consider)
Quality of life	9.4
Maintaining functional independence	9.3
Survival	9.2
Neurocognition	9.0
Side effects	8.4
Ability of treatment to prevent existing brain metastases from growing	8.1
Ability of treatment to prevent both existing brain metastases from growing and new brain metastases from growing in other areas of the brain at 1-year following treatment	7.3
Risk of you developing new brain metastases in other areas of the brain at 1-year following treatment	7.3
Ability of treatment to prevent new brain metastases growing in other areas of the brain	7.0
Number of trips to the hospital for treatment	5.0

¿Podemos minimizar el impacto neurocognitivo de la radioterapia cerebral?

Disminuyendo la toxicidad de la radioterapia cerebral

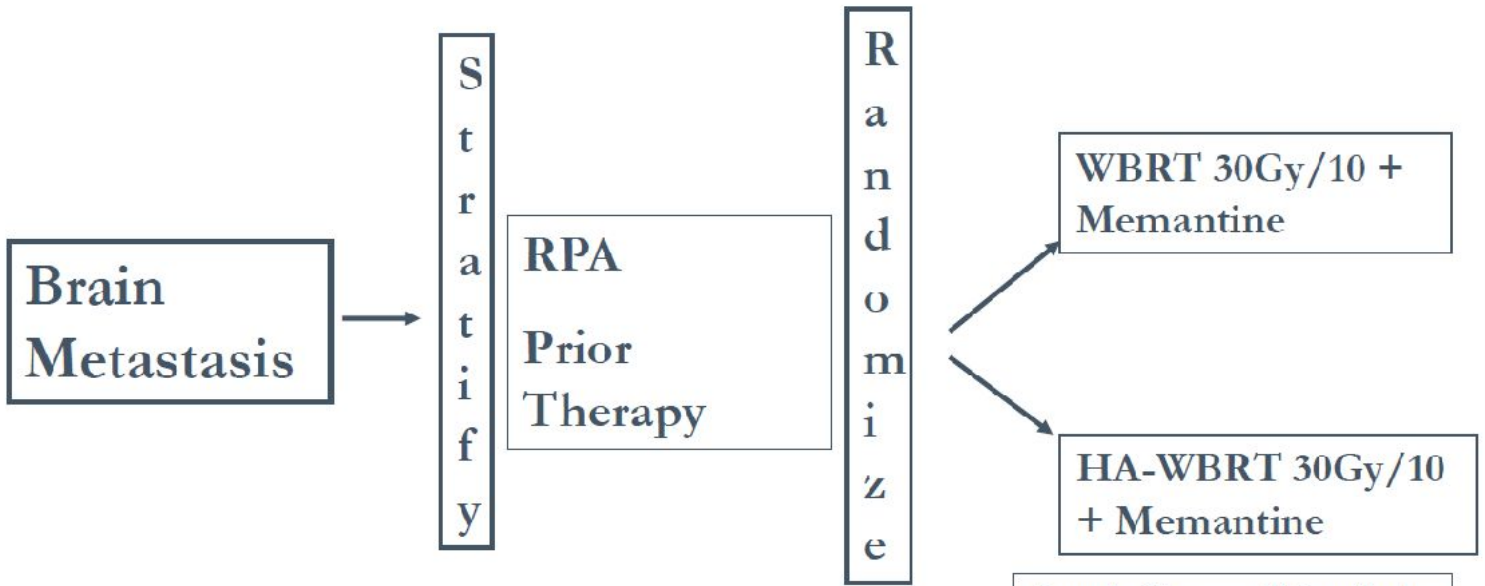
- Memantina: medicamento eficaz y bien tolerado para la demencia vascular

- En un ensayo aleatorizado RTOG, 554 pacientes que recibieron radioterapia cerebral fueron aleatorizados a memantina o placebo:
  - Pacientes tratados con memantina:
    - Mayor tiempo de deterioro cognitivo (HR 0,78, p <0,01)
    - Menos falla cognitiva a las 24 semanas (54 vs 65%)
  - No hay diferencia en la calidad de vida en comparación con el placebo

NRG-CC001: Phase III Trial Memantine and WBRT with or without Hippocampal Avoidance in Patients with Brain Metastases

PIs: Paul Brown (MDACC) + Vinai Gondi (Cadence)

Basic Eligibility: Brain Mets 5mm outside hippocampus; KPS≥70; MRI scan



Sample Size: 518 patients

Primary endpt: Time to cognitive failure--HVLT-R, COWA, and TMT A and B

Basic Statistical Design:
Cognitive fxn failure 53.8% at 6 months with WBRT vs. 42.8% with HA-WBRT. 388 analyzable pts.

Protocol approved by NCI, **to be activated soon**

NRG ONCOLOGY™

Radioterapia cerebral: Conclusiones

- Hay un cambio de paradigma contre la RT cerebral completa debido a:
  - Ausencia de una ventaja de supervivencia
  - Otras opciones efectivas
  - Secuelas neurocognitivas importantes

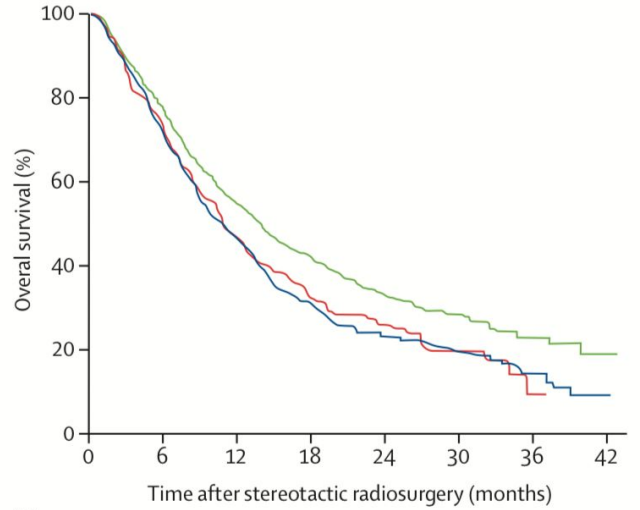
- No obstante, la RT cerebral completa puede y debe ofrecerse en situaciones clínicas seleccionadas
- Se están estudiando estrategias de reducción de toxicidad

Radiocirugía sola para múltiples metástasis cerebrales

- JLKG 0901 fue un ensayo observacional prospectivo para pacientes con 1-10 metástasis cerebrales nuevas tratadas solo con radiocirugía inicial
- 1194 pacientes
- Ninguna diferencia en sobrevida global entre 2-4 mets cerebrales y 5-10 mets cerebrales
- Ninguna diferencia en los eventos adversos
- Conclusión: SRS puede ser una alternativa adecuada para hasta 10 mets cerebrales

Yamamoto, M, Lancet oncol 2014

Group	Median overall survival, months (95% CI)	HR (95% CI)	p value
1 tumour	13·9 (12·0–15·6)	0·76 (0·66–0·88)	0·0004
2–4 tumours	10·8 (9·4–12·4)	Reference	
5–10 tumours	10·8 (9·1–12·7)	0·97 (0·81–1·18)	0·78



Number at risk				
1 tumour	455	234	97	22
2–4 tumours	531	215	61	16
5–10 tumours	208	84	31	1

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

CE7 (CCTG CE.7)	A Phase III Trial of Stereotactic Radiosurgery compared with Whole Brain Radiotherapy (WBRT) for 5-15 Brain Metastases	Open to Accrual

− Read More

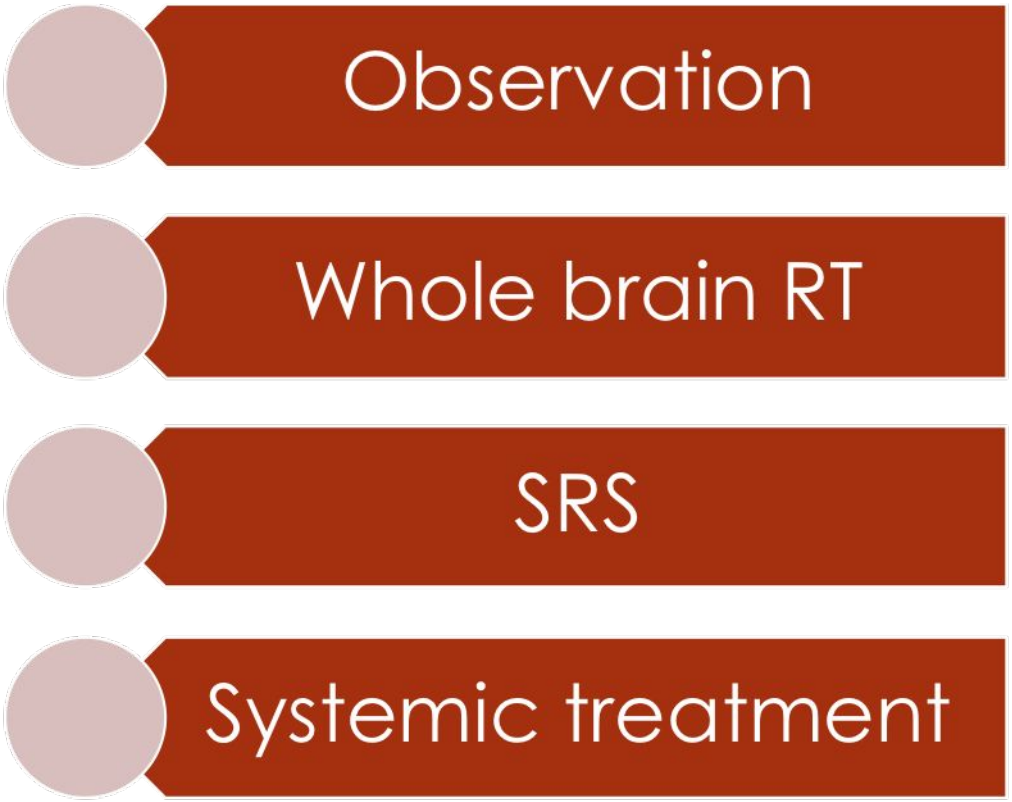
A Phase III Trial of Stereotactic Radiosurgery compared with Whole Brain Radiotherapy (WBRT) for 5-15 Brain Metastases

Complexity Level: 2

Eligibility: - Patient must have 5 or more brain metastases by MRI obtained within 30 days of registration. Largest brain metastasis must be <2.5cm, and total tumour volume must be 30cm3 or less - Patient must be willing and able to complete QoL questionnaires, neurocognitive assessments, and must agree to use effective contraception if of child bearing potential - Centre must be IROC credentialied and able to treat patients using an SRS system - Patient must have a pathological diagnosis of a non-hematopoietic malignancy - Patient must be >18 years old, ECOG 0-2, and creatinine clearance of 30ml/min or more

Objectives: Primary Endpoints: - Overall Survival and neurocognitive PFS Secondary Endpoints: - time to CNS failure; difference in CNS failure patterns;number of salvage procedures following SRS; cognitive tests; adverse events; time delay to re-initiation of systemic therapy post treatment; validate nomogram; Health Economics; Quality of Life; Correlative Studies; Imaging data collection and evaluation

Opciones después de la resección quirúrgica

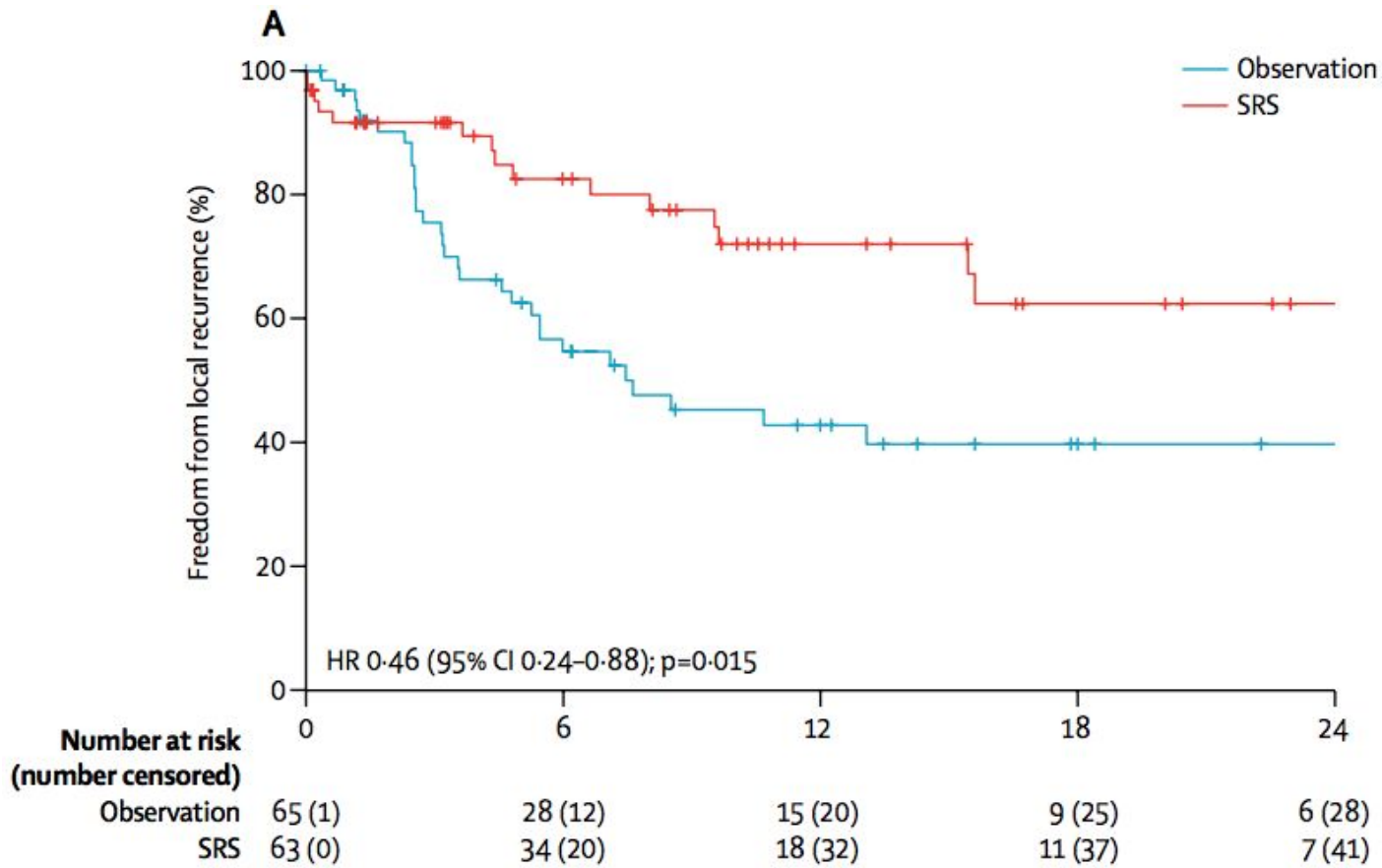


Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial

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

- Pacientes con 1-3 metástasis con una metástasis completamente resecada
- Observación vs SRS al sitio de la resección local

Sobrevida libre de progresión local a 1 año: 72% vs 43%



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

Summary

Background **Whole brain radiotherapy (WBRT) is the standard of care to improve intracranial control following resection of brain metastasis. However, stereotactic radiosurgery (SRS) to the surgical cavity is widely used in an attempt to reduce cognitive toxicity, despite the absence of high-level comparative data substantiating efficacy in the postoperative setting. We aimed to establish the effect of SRS on survival and cognitive outcomes compared with WBRT in patients with resected brain metastasis.**

Lancet Oncol 2017
Published Online
July 4, 2017
http://dx.doi.org/10.1016/S1470-2045(17)30441-2
See Online/Comment

	SRS (n=98)	WBRT (n=96)
Resection cavity diameter		
≤3 cm	59 (60%)	58 (60%)
>3 cm	39 (40%)	38 (40%)
Extent of resection		
Subtotal	8 (8%)	13 (14%)
Total (gross)	90 (92%)	83 (86%)
Surgical approach		
En bloc	54 (55%)	61 (64%)
Piecemeal	43 (44%)	35 (36%)
Data missing	1 (1%)	0
Number of brain metastases		
One	75 (77%)	74 (77%)
Two to four	23 (23%)	22 (23%)

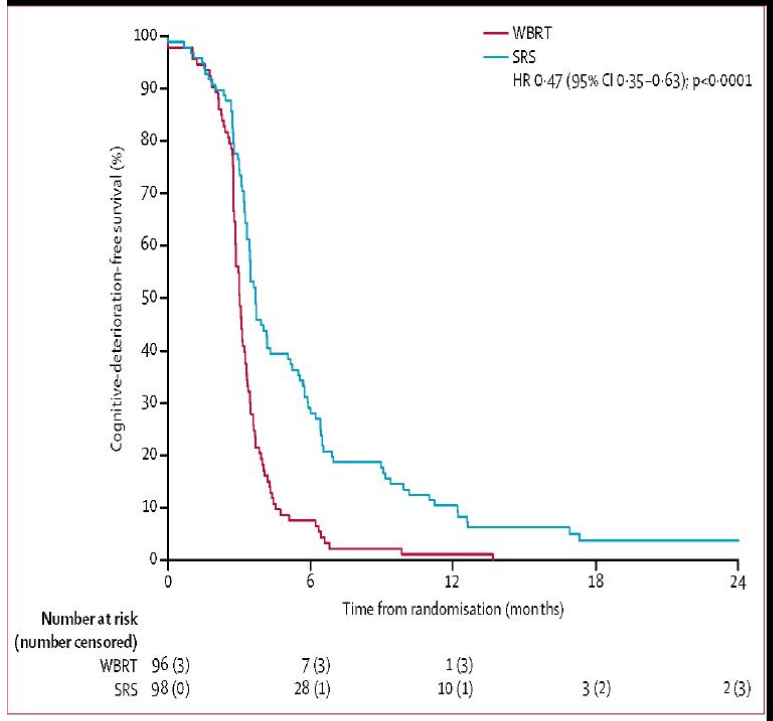


Figure 2: Cognitive-deterioration-free survival
WBRT=whole brain radiotherapy. SRS=stereotactic radiosurgery.

	Control Estimates (95%CI)	
	SRS	WBRT
Surgical Bed Control		
at 3 months	95·9% (92·0, 99·9)	93·5% (88·7, 98·7)
at 6 months	80·4% (72·8, 88·7)	87·1% (80·5, 94·2)
at 12 months	60·5% (51·3, 71·3)	80·6% (73·0, 89·1)
Leptomeningeal Disease Control		
at 3 months	98·0% (95·2, 100)	97·9% (95·0, 100)
at 6 months	93·9% (89·2, 98·7)	96·8% (93·3, 100)
at 12 months	92·8% (87·8, 98·1)	94·6% (90·1, 99·3)

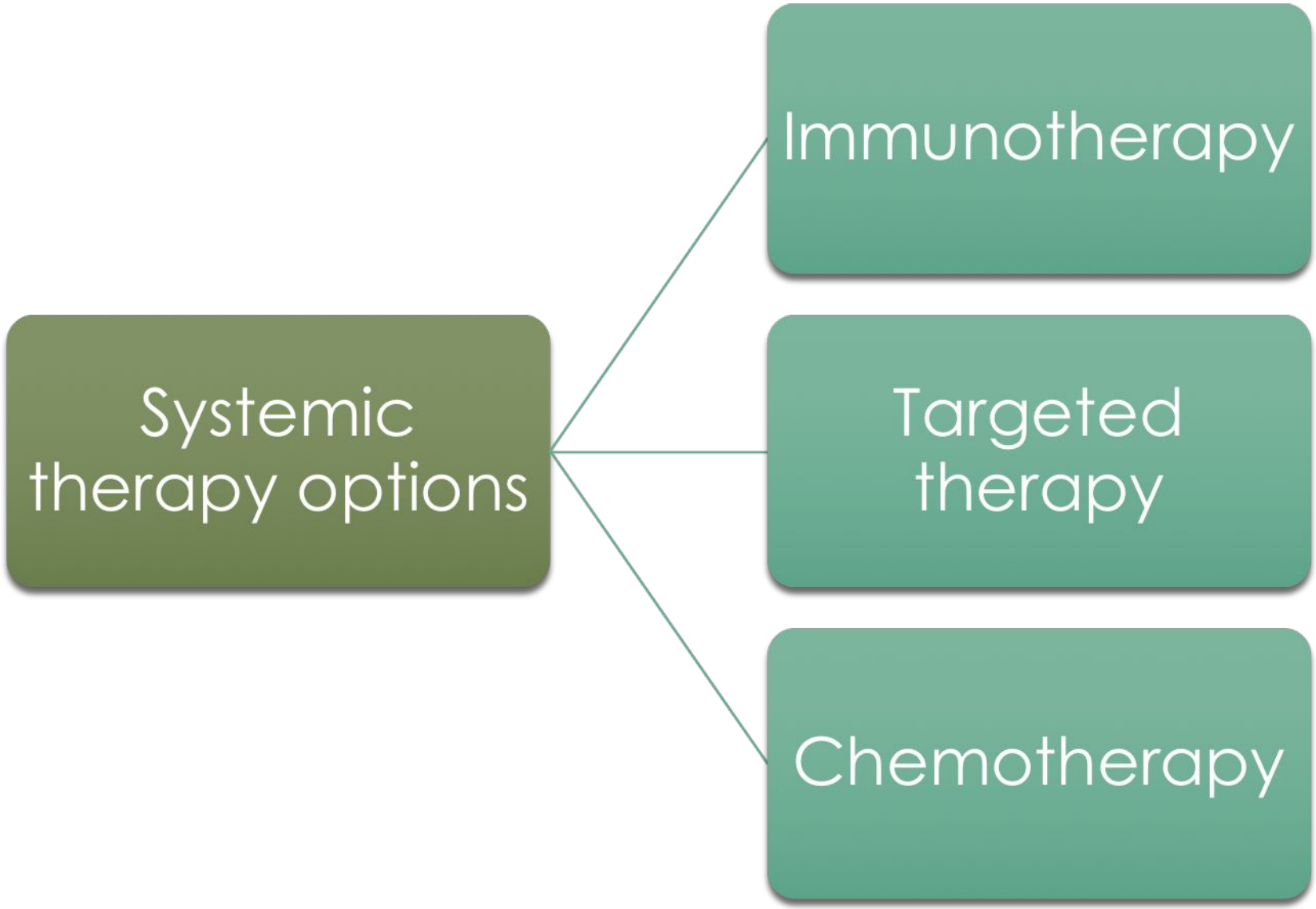
Consensus Contouring Guidelines for Postoperative Completely Resected Cavity Stereotactic Radiosurgery for Brain Metastases

Hany Soliman, MD,* Mark Ruschin, PhD,* Lilyana Angelov, MD,† Paul D. Brown, MD,‡ Veronica L.S. Chiang, MD,§ John P. Kirkpatrick, MD, PhD,‖ Simon S. Lo, MD,¶ Anita Mahajan, MD,‡ Kevin S. Oh, MD,# Jason P. Sheehan, MD, PhD,** Scott G. Soltys, MD,†† and Arjun Sahgal, MD*

Table 2 Recommendations for CTV contouring for postoperative completely resected cavity SRS

Recommendation
CTV should include the entire contrast-enhancing surgical cavity using the T1-weighted gadolinium-enhanced axial MRI scan, excluding edema determined by MRI
CTV should include entire surgical tract seen on postoperative CT or MRI
If the tumor was in contact with the dura preoperatively, CTV should include a 5- to 10-mm margin along the bone flap beyond the initial region of preoperative tumor contact
If the tumor was not in contact with the dura, CTV should include a margin of 1 to 5 mm along the bone flap
If the tumor was in contact with a venous sinus preoperatively, CTV should include a margin of 1 to 5 mm along the sinus

Abbreviations: CT = computed tomography; CTV = clinical target volume; MRI = magnetic resonance imaging; SRS = stereotactic radiosurgery.


Systemic therapy options
Immunotherapy
Targeted therapy
Chemotherapy

Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial

Sarah B Goldberg, Scott N Gettinger, Amit Mahajan, Anne C Chiang, Roy S Herbst, Mario Sznol, Apostolos John Tsiouris, Justine Cohen, Alexander Vortmeyer, Lucia Jilaveanu, James Yu, Upendra Hegde, Stephanie Speaker, Matthew Madura, Amanda Ralabate, Angel Rivera, Elin Rowen, Heather Gerrish, Xiaopan Yao, Veronica Chiang, Harriet M Kluger

Summary

Background Immunotherapy targeting the PD-1 axis has activity in several tumour types. We aimed to establish the activity and safety of the PD-1 inhibitor pembrolizumab in patients with untreated brain metastases from melanoma or non-small-cell lung cancer (NSCLC).

Methods In this non-randomised, open-label, phase 2 trial, we enrolled patients aged 18 years or older with melanoma or NSCLC with untreated brain metastases from the Yale Cancer Center. Patients had at least one untreated or progressive brain metastasis between 5 and 20 mm in diameter without associated neurological symptoms or the need for corticosteroids. Patients with NSCLC had tumour tissue positive for PD-L1 expression; this was not required for patients with melanoma. Patients were given 10 mg/kg pembrolizumab every 2 weeks until progression. The primary endpoint was brain metastasis response assessed in all treated patients. The trial is ongoing and here we present an early analysis. The study is registered with ClinicalTrials.gov, number NCT02085070.

Findings Between March 31, 2014, and May 31, 2015, we screened 52 patients with untreated or progressive brain metastases (18 with melanoma, 34 with NSCLC), and enrolled 36 (18 with melanoma, 18 with NSCLC). A brain metastasis response was achieved in four (22%; 95% CI 7–48) of 18 patients with melanoma and six (33%; 14–59) of 18 patients with NSCLC. Responses were durable, with all but one patient with NSCLC who responded showing an ongoing response at the time of data analysis on June 30, 2015. Treatment-related serious and grade 3–4 adverse events were grade 3 elevated aminotransferases (n=1 [6%]) in the melanoma cohort, and grade 3 colitis (n=1 [6%]), grade 3 pneumonitis (n=1 [6%]), grade 3 fatigue (n=1 [6%]), grade 4 hyperkalemia (n=1 [6%]), and grade 2 acute kidney injury (n=1 [6%]) in the NSCLC cohort. Clinically significant neurological adverse events included transient grade 3 cognitive dysfunction and grade 1–2 seizures (n=3 [17%]) in the melanoma cohort.

Interpretation Pembrolizumab shows activity in brain metastases in patients with melanoma or NSCLC with an acceptable safety profile, which suggests that there might be a role for systemic immunotherapy in patients with untreated or progressive brain metastases.

Tasa de respuesta:
22% en melanoma
33% en CPCNP

N Engl J Med. 2018 Aug 23;379(8):722-730. doi: 10.1056/NEJMoa1805453.

Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain.

Tawbi HA[1], Forsyth PA[1], Algazi A[1], Hamid O[1], Hodi FS[1], Moschos SJ[1], Khushalani NI[1], Lewis K[1], Lao CD[1], Postow MA[1], Atkins MB[1], Ernstoff MS[1], Reardon DA[1], Puzanov I[1], Kudchadkar RR[1], Thomas RP[1], Tarhini A[1], Pavlick AC[1], Jiang J[1], Avila A[1], Demelo S[1], Margolin K[1].

Author information

- Fase 2, 94 pts, 14 meses de seguimiento
- La tasa de beneficio intracraneal fue de 57%: 26% RC, 30% RP
- La respuesta extracraneal fue de 56%

Table 2. Response to Treatment.

Variable	Intracranial (N=94)	Extracranial (N=94)	Global (N=94)
Best overall response — no. (%)*			
Complete response	24 (26)	7 (7)	8 (9)
Partial response	28 (30)	40 (43)	40 (43)
Stable disease for ≥6 mo	2 (2)	6 (6)	5 (5)
Progressive disease	31 (33)	28 (30)	33 (35)
Could not be evaluated†	9 (10)	13 (14)	8 (9)
Objective response‡			
No. of patients	52	47	48
Percent of patients (95% CI)	55 (45–66)	50 (40–60)	51 (40–62)
Clinical benefit§			
No. of patients	54	53	53
Percent of patients (95% CI)	57 (47–68)	56 (46–67)	56 (46–67)

RESEARCH ARTICLE

Efficacy of ALK inhibitors on NSCLC brain metastases: A systematic review and pooled analysis of 21 studies

Fausto Petrelli[1]*, Chiara Lazzari[2], Raffaele Ardito[3], Karen Borgonovo[1], Alessandra Bulotta[2], Barbara Conti[4], Mary Cabiddu[1], Jody Filippo Capitanio[5], Matteo Brighenti[6], Mara Ghilardi[1], Luca Gianni[2], Sandro Barni[1], Vanesa Gregorc[2]

Study name	Effect size	CI Lower limit	CI Upper limit	Weight
Bendaly/2017	70,00	60,33	79,67	6,20%
Costa RT pretreated/2015	33,00	29,52	36,48	6,70%
Costa RT untreated/2015	18,00	12,82	23,18	6,60%
Crino/2016	45,00	35,60	54,40	6,23%
Gadgeel RT pretreated/2016	35,80	31,55	40,05	6,65%
Gadgeel RT untreated/2016	58,50	52,09	64,91	6,50%
Gadgeel/2014	52,00	42,88	61,12	6,26%
Gettinger/2016	41,30	35,28	47,32	6,53%
Kim/2016	23,40	18,55	28,25	6,61%
Kim/2017	52,20	45,75	58,65	6,49%
Lei RT pretreated/2015	63,20	53,20	73,20	6,17%
Lei RT untreated/2015	73,70	62,75	84,65	6,06%
Metro/2016	85,70	59,27	112,13	4,49%
Shaw/2017	35,00	29,85	40,15	6,59%
Xing/2016	15,00	1,90	28,10	5,79%
Yoshida/2016	20,00	9,91	30,09	6,14%
Total (random effect model)	**44,2**	**33,3**	**55,1**	**100,00%**
I^2=0.96; P for heterogenity <0.001; Q=355,97				

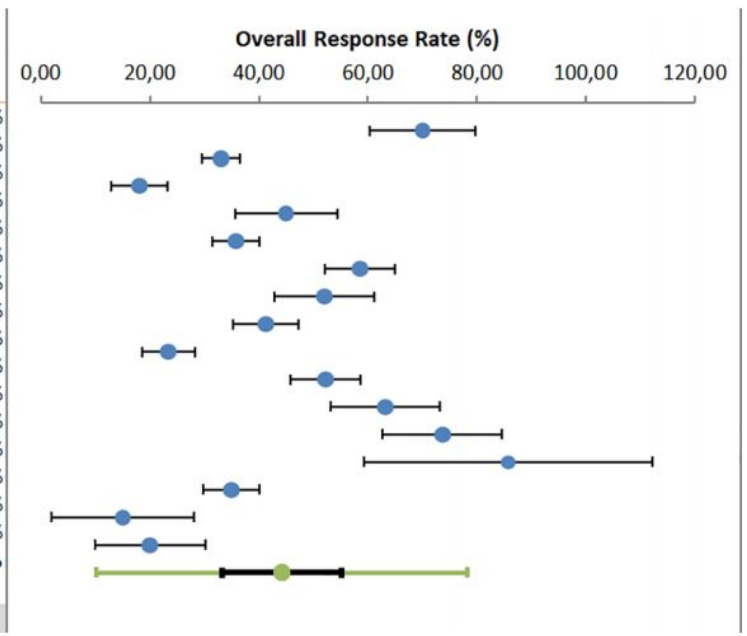


Fig 3. Pooled analysis of intracranial overall response rate (second line or beyond trials).

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ORIGINAL REPORT

Management of Brain Metastases in Tyrosine Kinase Inhibitor–Naïve Epidermal Growth Factor Receptor–Mutant Non–Small-Cell Lung Cancer: A Retrospective Multi-Institutional Analysis

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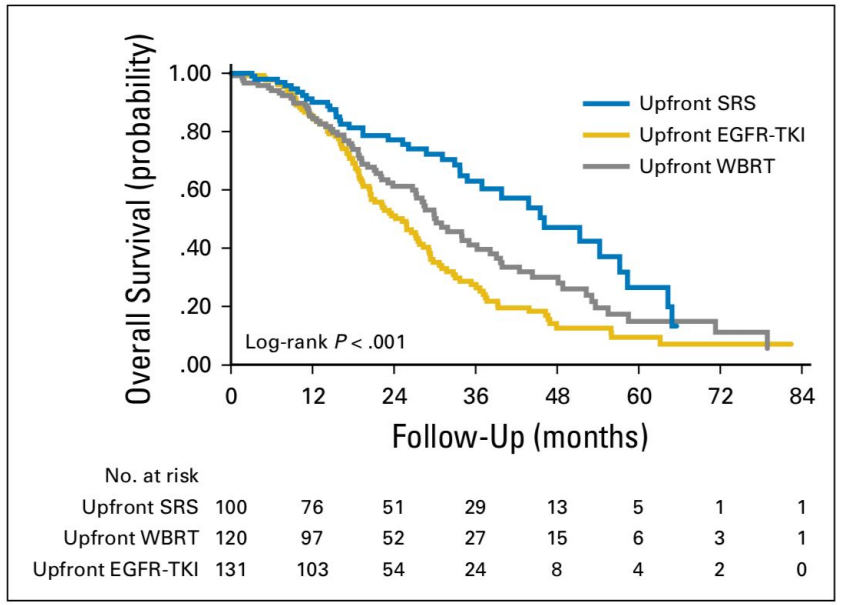

Fig 1. Kaplan-Meier analysis comparing overall survival in patients treated with upfront stereotactic radiosurgery (SRS), upfront whole-brain radiotherapy (WBRT), and upfront epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI).

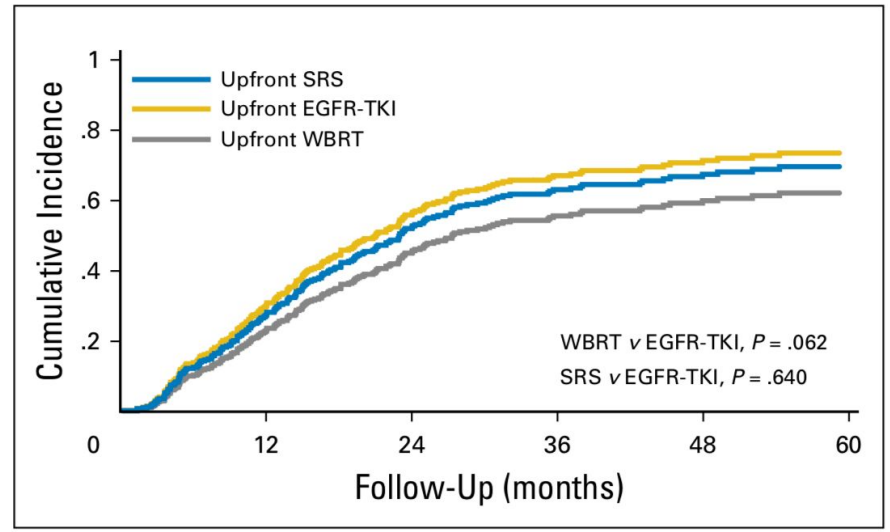

Fig 2. Cumulative incidence of intracranial progression using competing risks regression analysis in patients treated with upfront stereotactic radiosurgery (SRS), upfront whole-brain radiotherapy (WBRT), and upfront epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI).

Conclusiones

- SRS ahora se usa más para pacientes con metástasis múltiples
- Las terapias sistémicas también se investigan y usan más
- Los casos deben ser discutidos en equipos multidisciplinarios para explorar la mejor secuencia de tratamiento para cada paciente
- Se necesitan ensayos que evalúen la secuencia óptima de la radiocirugía y las terapias sistémicas