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"Personalizing Isodoses, Curing Lives"
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Stereotactic Radiosurgery for Gliomas

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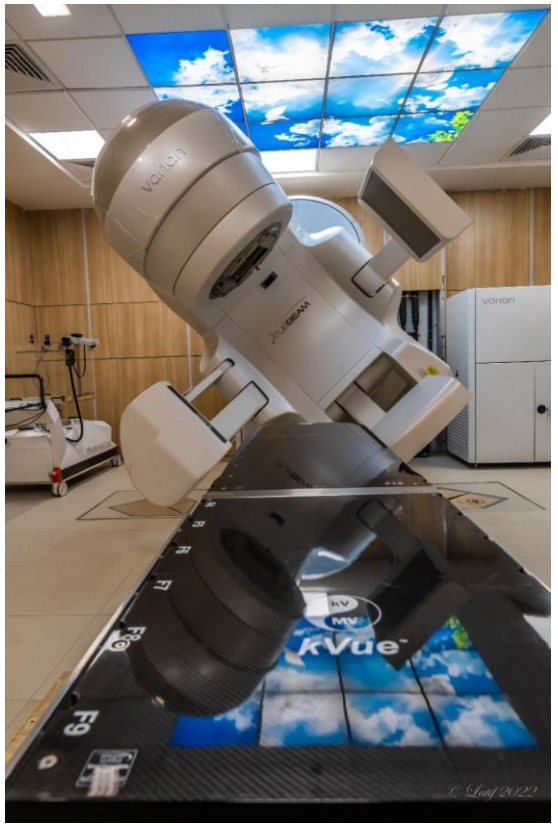


Disclosures

- None

Learning points

- SRS – Basics & Radiobiology
- Glioma classification -2021
- SRS in circumscribed gliomas
- SRS in Low grade gliomas
- SRS in high grade gliomas
- SRS in recurrent gliomas
- Conclusion

SRS – Basics & Radiobiology

Radiosurgery – As defined by Leksell

A single high dose fraction of radiation, stereotactically directed to an intracranial region of interest through intact skull

One versus > 1 fraction

2007 – AANS , CNS, ASTRO – suggested that SRS be used for upto 5 fractions

Gamma Knife

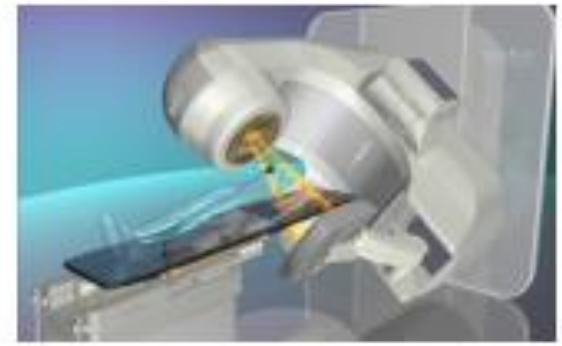
Proton Therapy

Radiosurgery Machines

Cyberknife

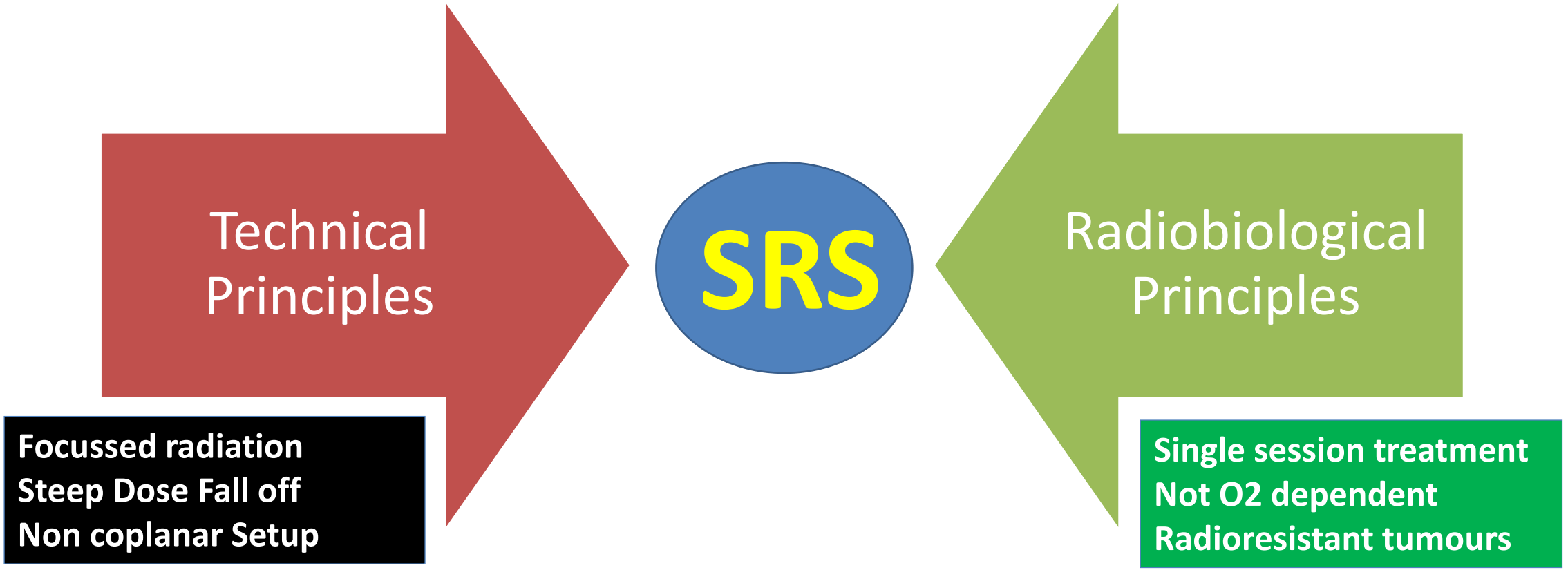
Tomotherapy

Brainlab Vero



Varian-Truebeam

Definition - Elaborated



Hallmarks of Radiosurgery

Minimizes dose to normal tissues

Maximum Dose to Target

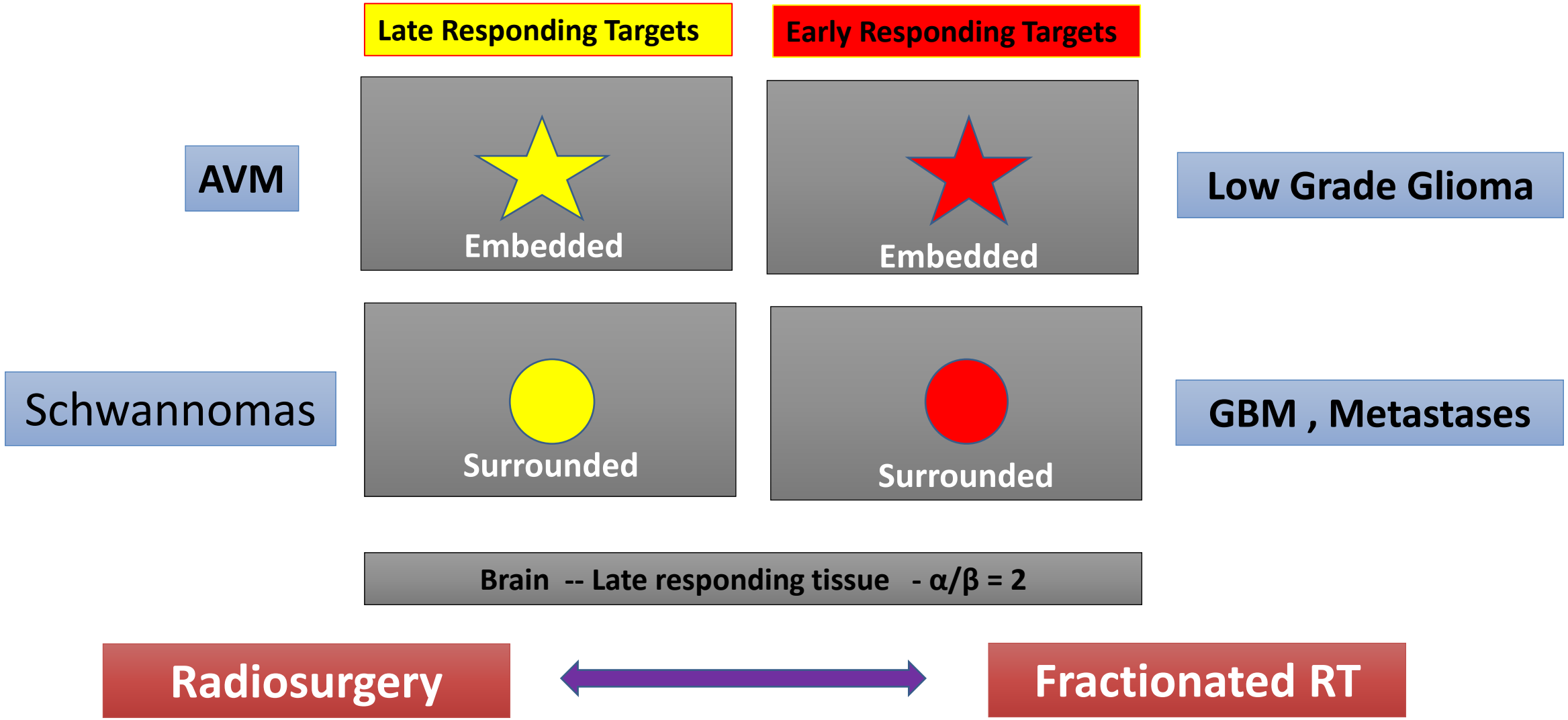
Radiobiology -- SRS

Radiobiological Effect of Single Fraction (> 10 Gy):

1. Endothelial cell Damage → Cytotoxicity & Apoptosis. (Ceramide Pathway)
2. Vascular Damage at High Doses → ++ 2^{nd} Cell Killing.
3. Enhanced Anti-Tumor Immunity after Tumor Irradiation.
4. Tumor Hypoxia is of Less Importance.

Fuks Z, Kolesnick R. Cancer Cell 2005;8:89-91.
Clement JJ, Radiology 1978;127:799-803.

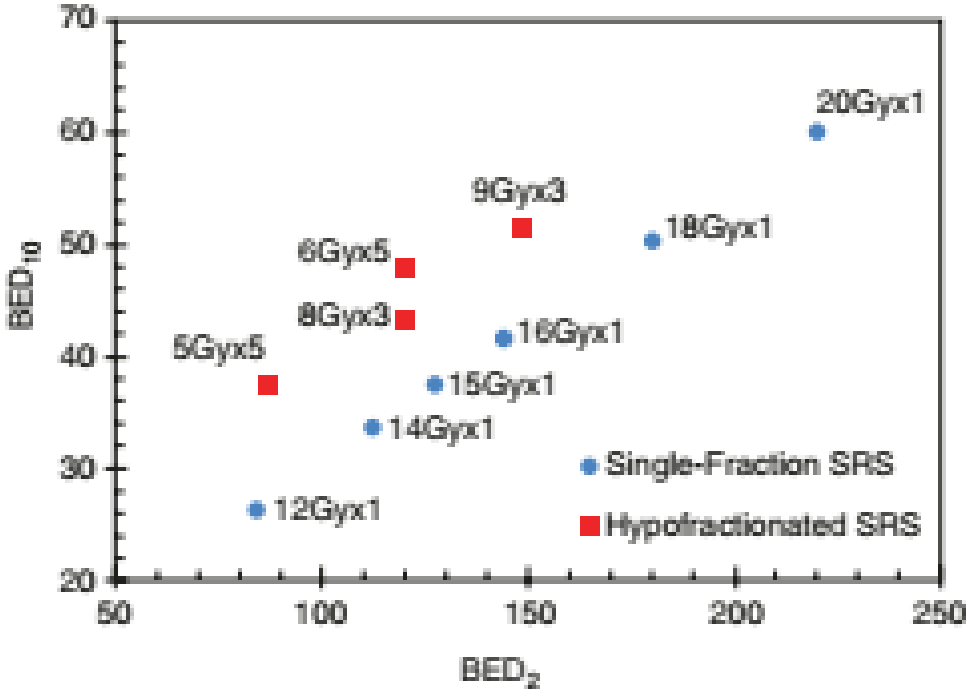
Radiobiological Complexity of Cranial Targets



SRS – Typical Indications

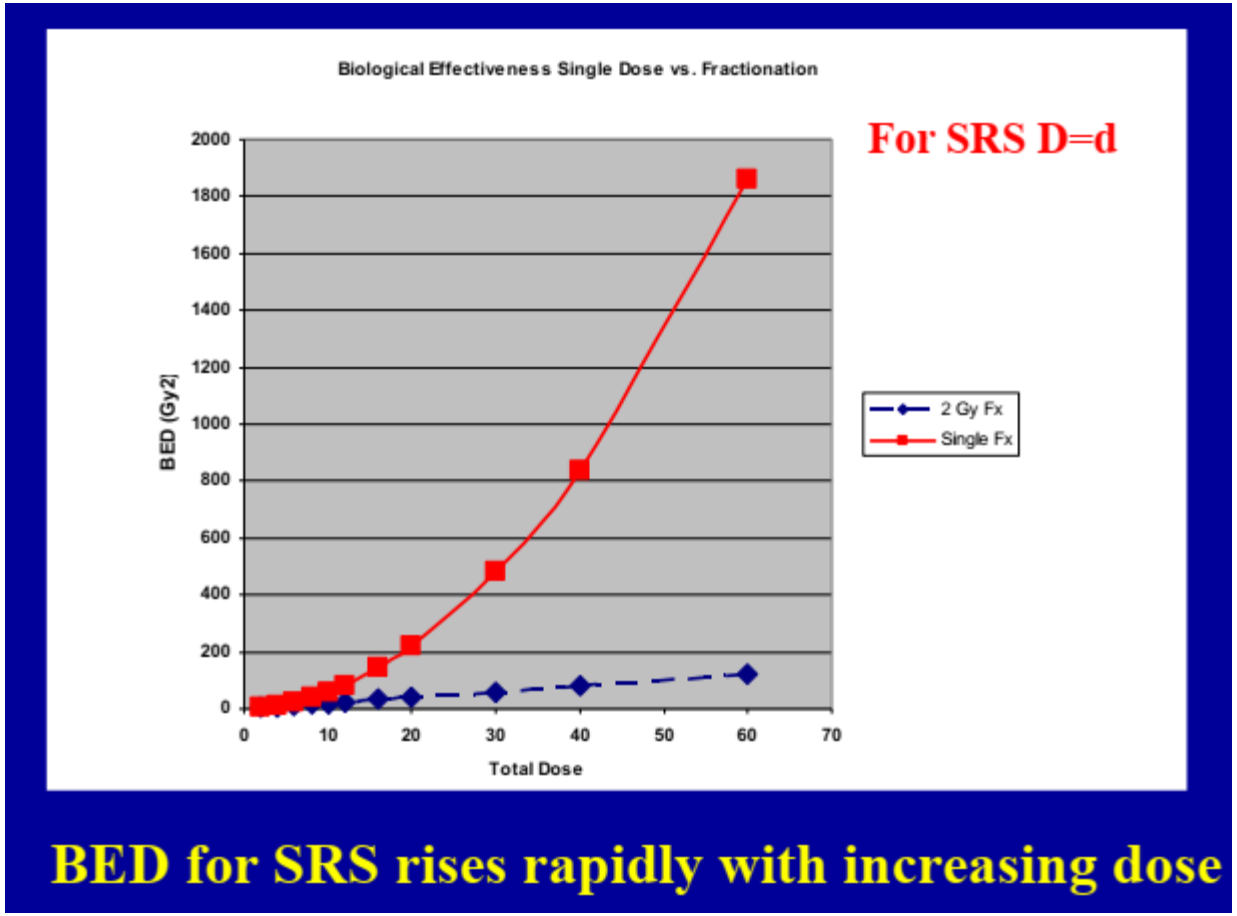
Benign	Malignant	Functional
• AV malformations • Schwannomas • Meningioma (<3cm) • Pituitary Adenoma • Craniopharyngioma • Glomus tumor • Paraganglioma	• Brain Metastases • Recurrent Glioma • Small residual LGG	• Trigeminal neuralgia • Temporal lobe epilepsy

Radiosurgery and BED



BED 2 – Response of normal tissue to RT Greater
Greater BED2 → Greater Toxicity Risk

BED 10 – Response of tumor tissue to RT
Greater BED10 → Higher tumor control probability



Steps of Radiosurgery

Create Stereotactic Space

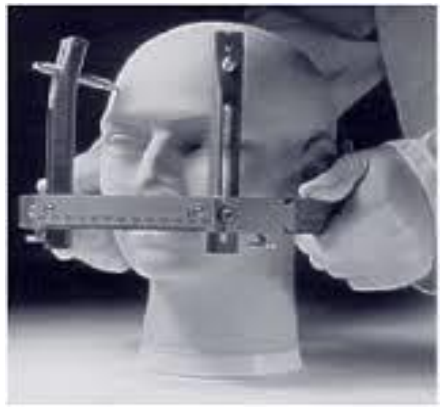
Identify Target in Stereotactic Space

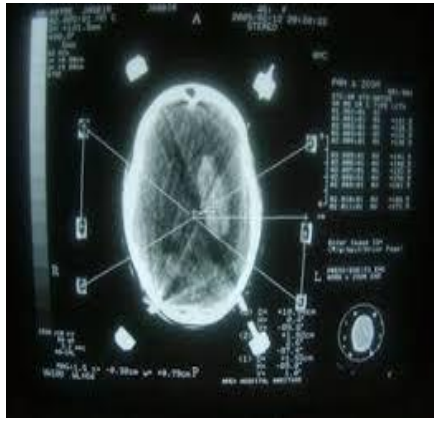
Place target at isocentre of radiation delivery system

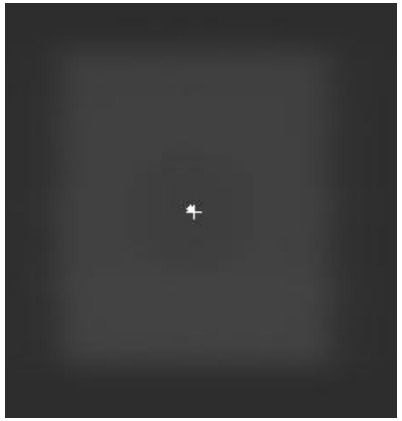
Treat with non coplanar beams

Quality Assurance

SRS







Pros of Radiosurgery in Gliomas

Technology

- High Precision techniques
- Allows Dose escalation
- Minimal collateral normal tissue damage
- Short treatment time can allow access to specialized centres

Radiobiology

- High dose rate to target and low dose rate to surrounding normal tissues
- Threshold dose rates of 1Gy /min intensify this effect
- Rapid dose fall off
- Neuromodulation
- Immunomodulation

Others

- Gliomas fail within 1-2 cm of tumor margins
- Shorter overall Treatment time
- Well suited for children under anaesthesia
- Short course minimize lymphopenia and the immunosuppressive effect of prolonged treatment courses

Cons of Radiosurgery in Gliomas

01

Infiltrative pattern

- Gliomas are infiltrative in nature
- Ill defined margins
- Unsuitable for radiosurgel

02

Alp

- h
- ve
- h a/b ratio and
- defined – poor
- argets

03

Toxicity

- Narrow therapeutic window between tumor control and toxicity
- SRS for gliomas associated with high rates of radiation necrosis

No Level 1 Evidence showing SRS has superior outcome in Gliomas

Glioma –Classification 2021

Gliomas according to WHO 2021 classification

Adult type diffuse gliomas
- Astrocytoma IDH mutant
- Oligodendroglioma, IDH mutant and 1p19 q codeleted
- Glioblastoma , IDH wild type

Paediatric type diffuse low grade gliomas

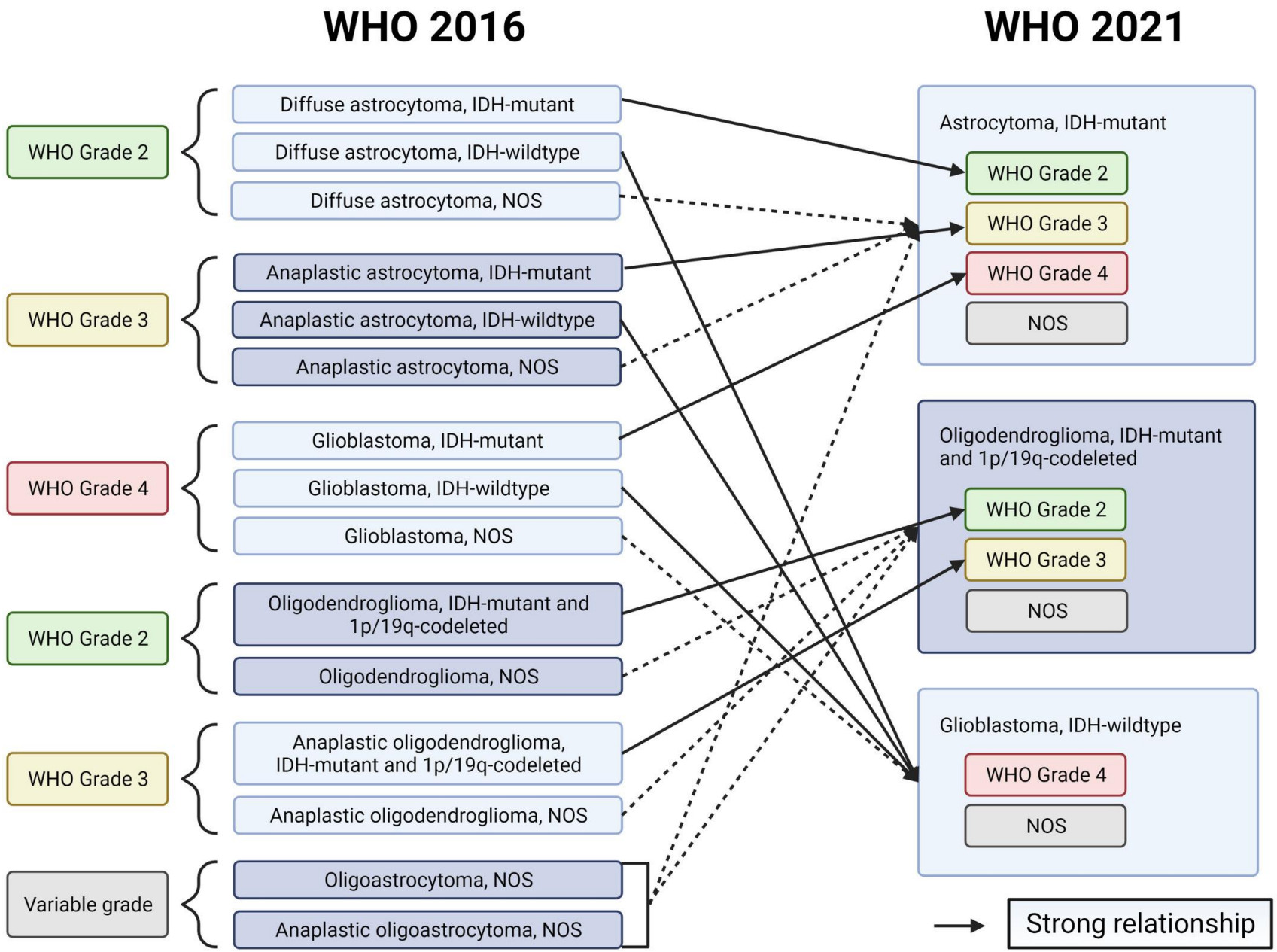
Paediatric type diffuse high grade gliomas

Circumscribed gliomas
- Pilocytic astrocytoma
- High grade Astro with piloid
- Pleomorphic xanthoastrocytoma
- SEGA
- Choroid glioma

Ependymal tumors

Table I. Gliomas according to WHO 2021 classification of CNS tumours

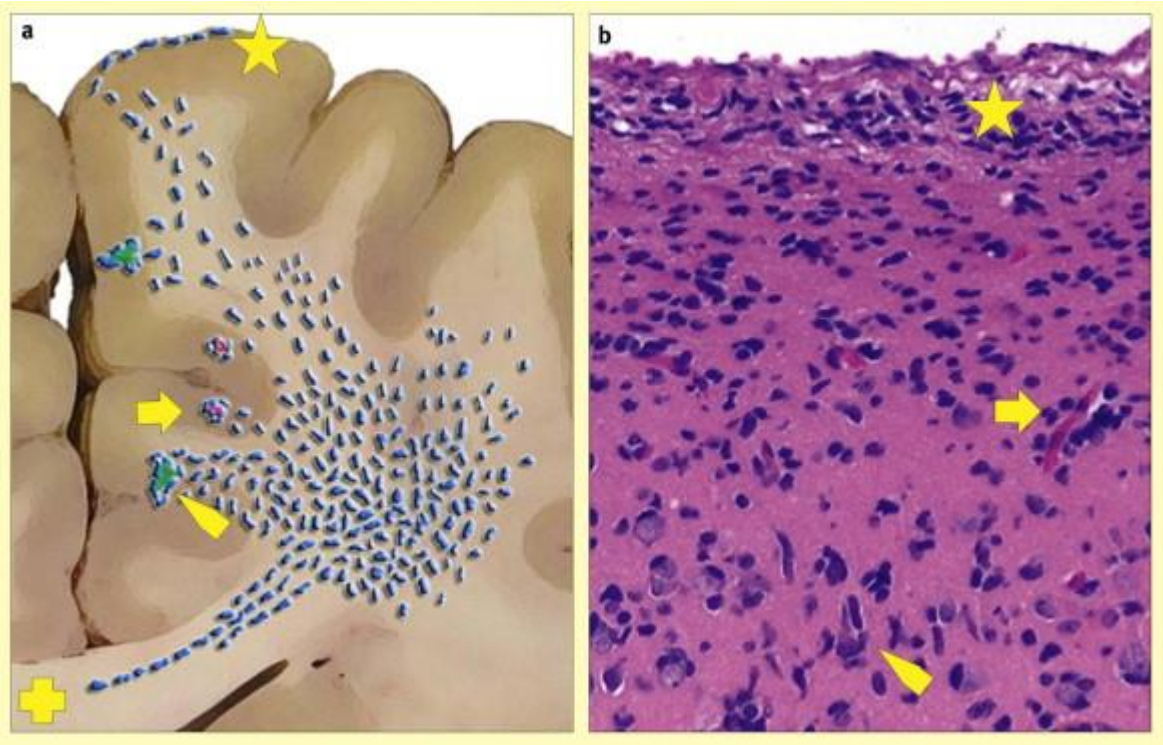
Adult-type diffuse gliomas
Astrocytoma, IDH-mutant
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
Glioblastoma, IDH-wildtype
Paediatric-type diffuse low-grade gliomas
Diffuse astrocytoma, MYB- or MYBL1-altered
Angiocentric glioma
Polymorphous low-grade neuroepithelial tumour of the young
Diffuse low-grade glioma, MAPK pathway-altered
Paediatric-type diffuse high-grade gliomas
Diffuse midline glioma, H3 K27-altered
Diffuse hemispheric glioma, H3 G34-mutant
Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
Infant-type hemispheric glioma
Circumscribed astrocytic gliomas
Pilocytic astrocytoma
High-grade astrocytoma with piloid features
Pleomorphic xanthoastrocytoma
Subependymal giant cell astrocytoma
Chordoid glioma
Astroblastoma, MN1-altered
Ependymal tumours
Supratentorial ependymoma
Supratentorial ependymoma, ZFTA fusion-positive
Supratentorial ependymoma, YAP1 fusion-positive
Posterior fossa ependymoma
Posterior fossa group A (PFA) ependymoma
Posterior fossa group B (PFB) ependymoma
Spinal ependymoma
Spinal ependymoma, MYCN-amplified
Myxopapillary ependymoma
Subependymoma


WHO 2016
WHO 2021
WHO Grade 2
Diffuse astrocytoma, IDH-mutant
Diffuse astrocytoma, IDH-wildtype
Diffuse astrocytoma, NOS
WHO Grade 3
Anaplastic astrocytoma, IDH-mutant
Anaplastic astrocytoma, IDH-wildtype
Anaplastic astrocytoma, NOS
WHO Grade 4
Glioblastoma, IDH-mutant
Glioblastoma, IDH-wildtype
Glioblastoma, NOS
WHO Grade 2
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
Oligodendroglioma, NOS
WHO Grade 3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted
Anaplastic oligodendroglioma, NOS
Variable grade
Oligoastrocytoma, NOS
Anaplastic oligoastrocytoma, NOS
Astrocytoma, IDH-mutant
WHO Grade 2
WHO Grade 3
WHO Grade 4
NOS
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
WHO Grade 2
WHO Grade 3
NOS
Glioblastoma, IDH-wildtype
WHO Grade 4
NOS
Strong relationship

2021 – WHO classification of gliomas

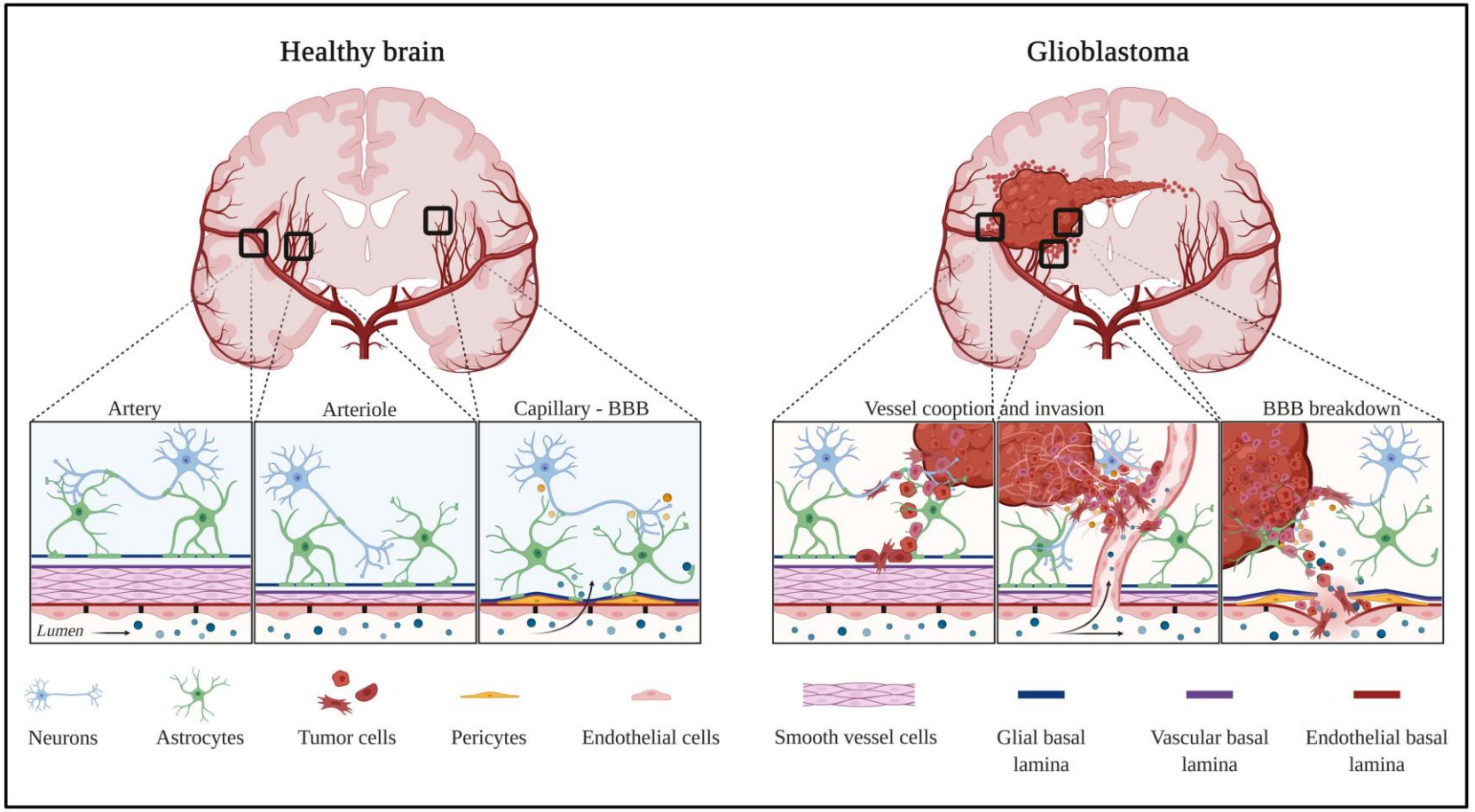
Grade / Type	WHO grade 1	WHO grade 2	WHO grade 3	WHO grade 4
	Circumscribed type		Diffuse type	
		Low Grade	High Grade	
Astrocytoma	Pilocytic astrocytoma	Grade 2 Astrocytoma	Grade 3 Astrocytoma	Grade 4 Astrocytoma Glioblastoma
Oligodendroglioma		Grade 2 Oligodendroglioma	Grade 3 Oligodendroglioma	

Diffuse Gliomas



- Accumulation of tumour cells around neurons (perineuronal satellitosis, arrowhead)
- Around blood vessels (arrow)
- Under the pia (asterisk)
- Tumour cells migrating along white matter tracts (intrafascicular growth; + in **a**)

Glioblastoma – Brain Vascular Architecture



GBM is a highly angiogenic and infiltrative tumor.
Cells invade along blood vessels to support tumor growth (co-option).
GBM displaces astrocytes end-feet and alters pericyte stability, leading to perivascular niches and cell evasion

SRS in circumscribed gliomas

Type \ Grade	WHO grade 1	WHO grade 2	WHO grade 3	WHO grade 4
	Circumscribed type	Low Grade	Diffuse type	High Grade
Astrocytoma	Pilocytic astrocytoma	Grade 2 Astrocytoma	Grade 3 Astrocytoma	Grade 4 Astrocytoma Glioblastoma
Oligodendroglioma		Grade 2 Oligodendroglioma	Grade 3 Oligodendroglioma	

SRS for PA in recurrent or unresectable pts

37 patients
GTV : 4.7 cc
Margin dose : median 15 Gy (9.6 – 22.5 Gy)
Tumor control : 93 %
Overall survival : 89 %

Grade 1 Glioma
Solid, cystic or mixed
Well circumscribed
1st option : Radical resection when feasible
RT avoided due to young age

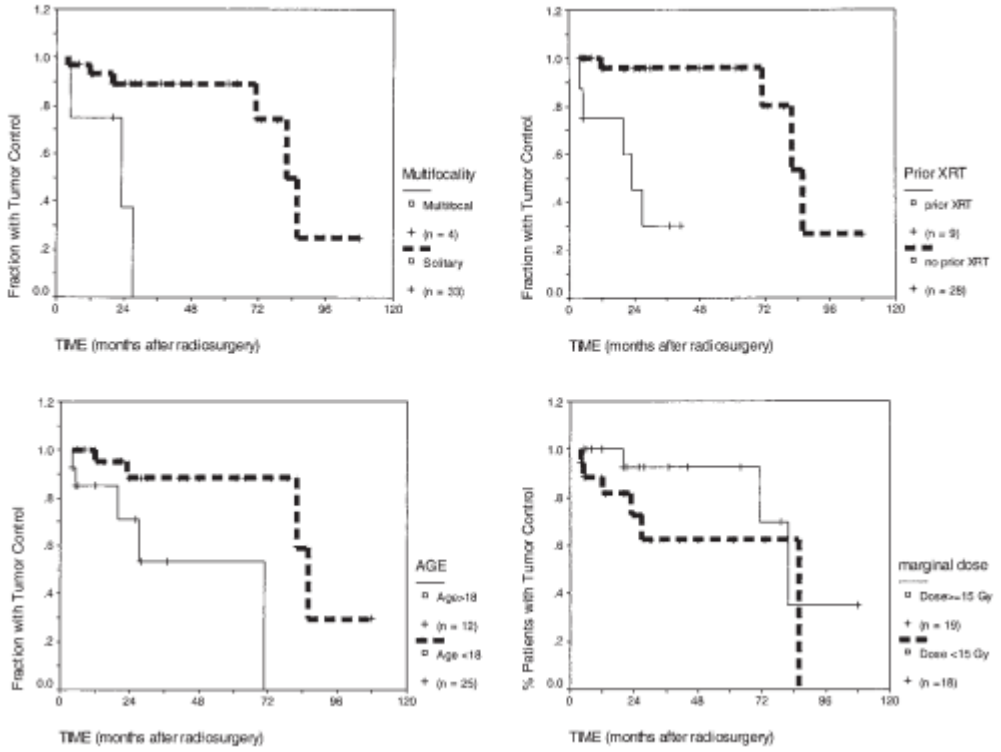
Poor prognostic factors:
Age > 18 yrs
Marginal dose < 15 Gy
Multifocal disease
Prior RT

J Neurosurg 97:56–64, 2002

2002

Stereotactic radiosurgery for pilocytic astrocytomas when multimodal therapy is necessary

Constantinos G. Hadjipanayis, M.D., Douglas Kondziolka, M.D., M.Sc., Paul Gardner, M.D., Ajay Niranjan, M.Ch., Shekhar Dagam, M.D., John C. Flickinger, M.D., and L. Dade Lunsford, M.D.



SRS for Pilocytics in paediatric population

J Neurooncol (2009) 95:219–229
DOI 10.1007/s11060-009-9912-6

CLINICAL STUDY - PATIENT STUDY

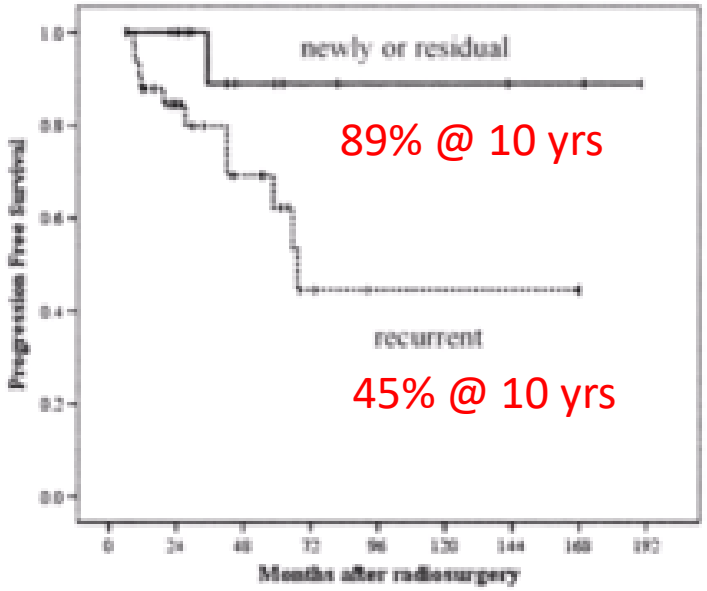
2009

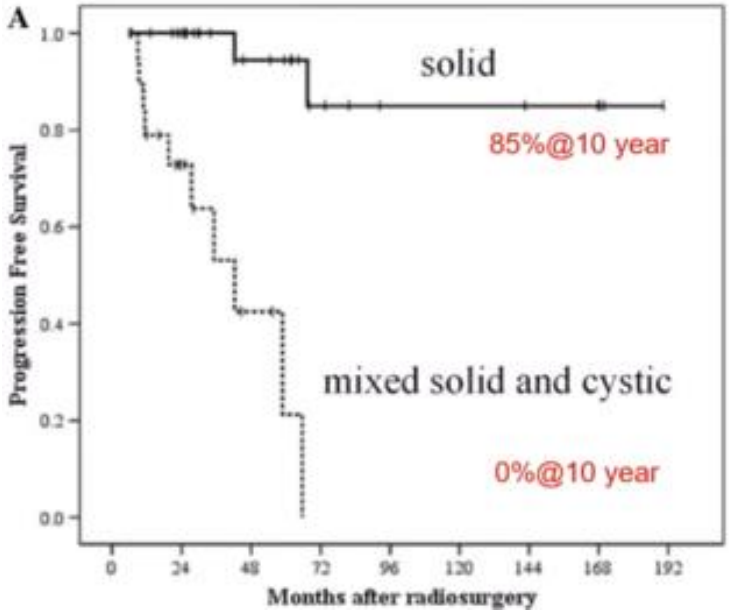
Stereotactic radiosurgery for pilocytic astrocytomas part 2: outcomes in pediatric patients

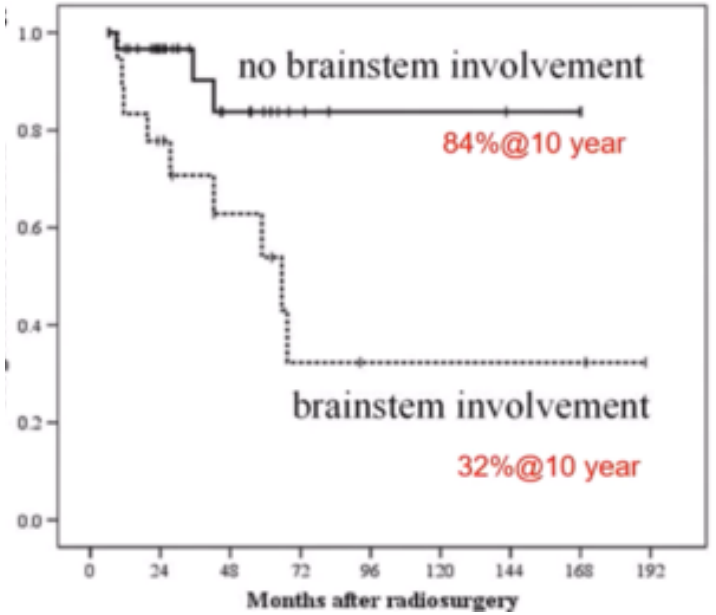
Hideyuki Kano · Ajay Niranjan · Douglas Kondziolka · John C. Flickinger · Ian F. Pollack · Regina I. Jakacki · L. Dade Lunsford

50 patients
GTV : 2.1 cc
Margin dose : 14.5 Gy (11-22.4 Gy)

Tumor control (5yr PFS) : 71 %
Overall survival (10yr) : 98 %
ARE : 10 %







SRS for PA in recurrent or unresectable pts

2012

Clinical Investigation: Central Nervous System Tumor

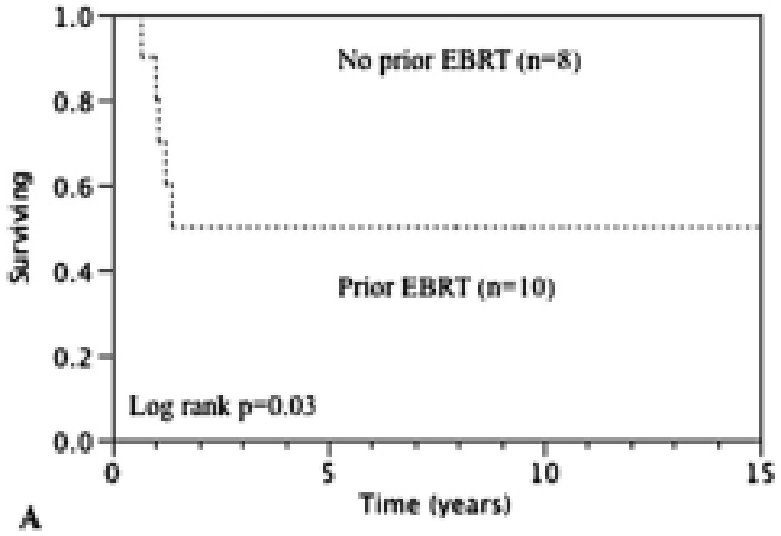
Stereotactic Radiosurgery for Recurrent or Unresectable Pilocytic Astrocytoma

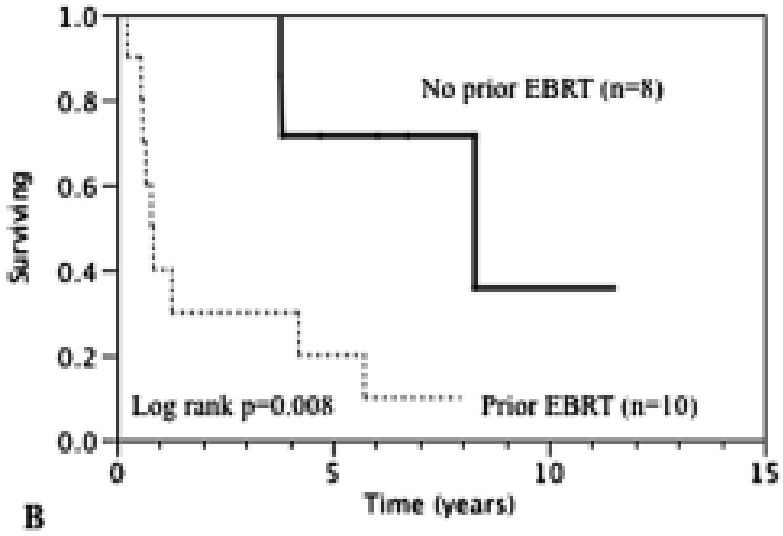
Christopher L. Hallemeier, M.D.,* Bruce E. Pollock, M.D.,*,† Paula J. Schomberg, M.D.,* Michael J. Link, M.D.,† Paul D. Brown, M.D.,‡ and Scott L. Stafford, M.D.*

*Departments of *Radiation Oncology and †Neurological Surgery, Mayo Clinic, Rochester, MN; and ‡Department of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX*

18 patients	
GTV	: 9.1 cc
Margin dose	: 15 Gy (12-20 Gy)

Tumor control (5yr PFS) : 41 % 10 yr PFS : 17 %
Overall survival (5 yr) : 71 % 10 yr OS : 71 %
ARE : 10 %
Poor prognostic factors : Prior EBRT





SRS for small PA

J Neurooncol (2017) 134:297–302
DOI 10.1007/s11060-017-2521-x

CLINICAL STUDY

2017

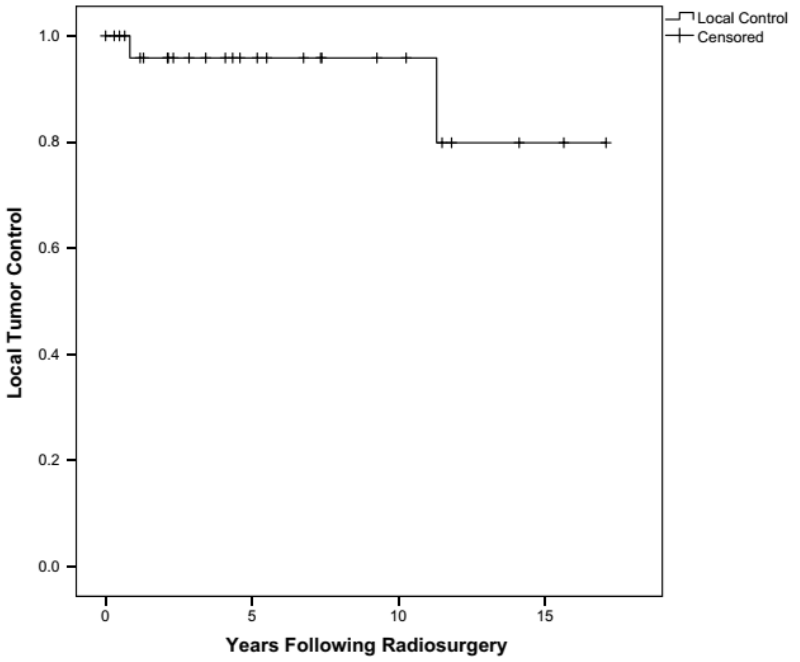
Evaluation of outcomes after stereotactic radiosurgery for pilocytic astrocytoma

Daniel M. Trifiletti[1,3] · M. Sean Peach[1] · Zhiyuan Xu[2] · Ronald Kersh[1] · Timothy N. Showalter[1] · Jason P. Sheehan[1,2]

28 patients
GTV : 1.84 cc (0.19 – 15.9cc)
Margin dose : 16 Gy (4 – 20 Gy)
Tumor control : 93 %
Overall survival : 100 %

6 yr PFS 96 %,
12 yr PFS 80 %
ARE - None

Fig. 2 Radiographic evidence of pilocytic astrocytoma progression following stereotactic radiosurgery among 28 patients



Pooled Data Analysis for SRS in PAs.

141 patients
GTV : 3.45 cc
Margin dose : 14.0 Gy (11-22.4 Gy)
Primary SRS : 39 %
Secondary SRS : 61 %

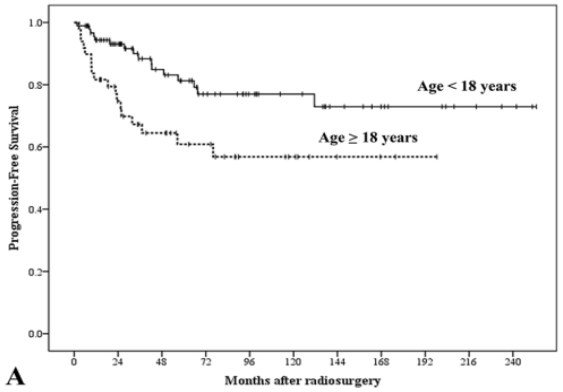
10 yr OS 92.5 %,
10 yr PFS 70 %
ARE - 10 %

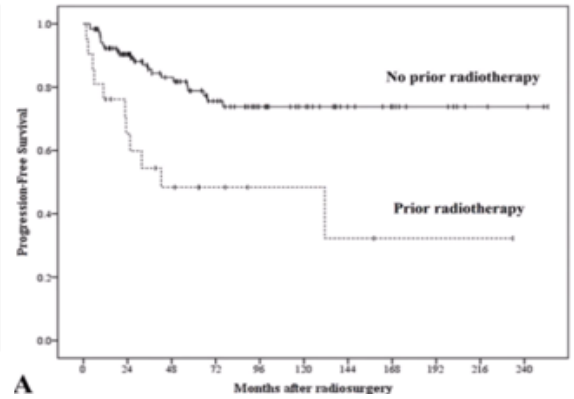
JNS CLINICAL ARTICLE
J Neurosurg 134:162–170, 2021

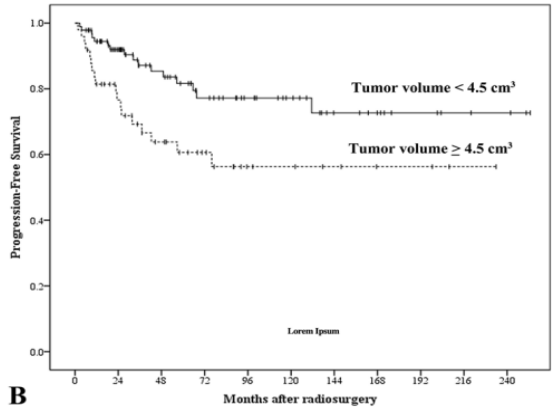
2021

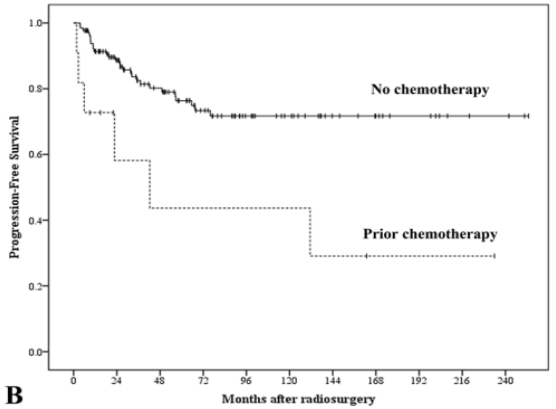
Outcomes of stereotactic radiosurgery for pilocytic astrocytoma: an international multiinstitutional study

Erin S. Murphy, MD,[1,13] Shireen Parsai, MD,[1] Hideyuki Kano, MD, PhD,[2] Jason P. Sheehan, MD,[3] Roberto Martinez-Alvarez, MD, PhD,[4] Nuria Martinez-Moreno, MD, PhD,[4]









SRS for Pilocytic Astrocytoma's

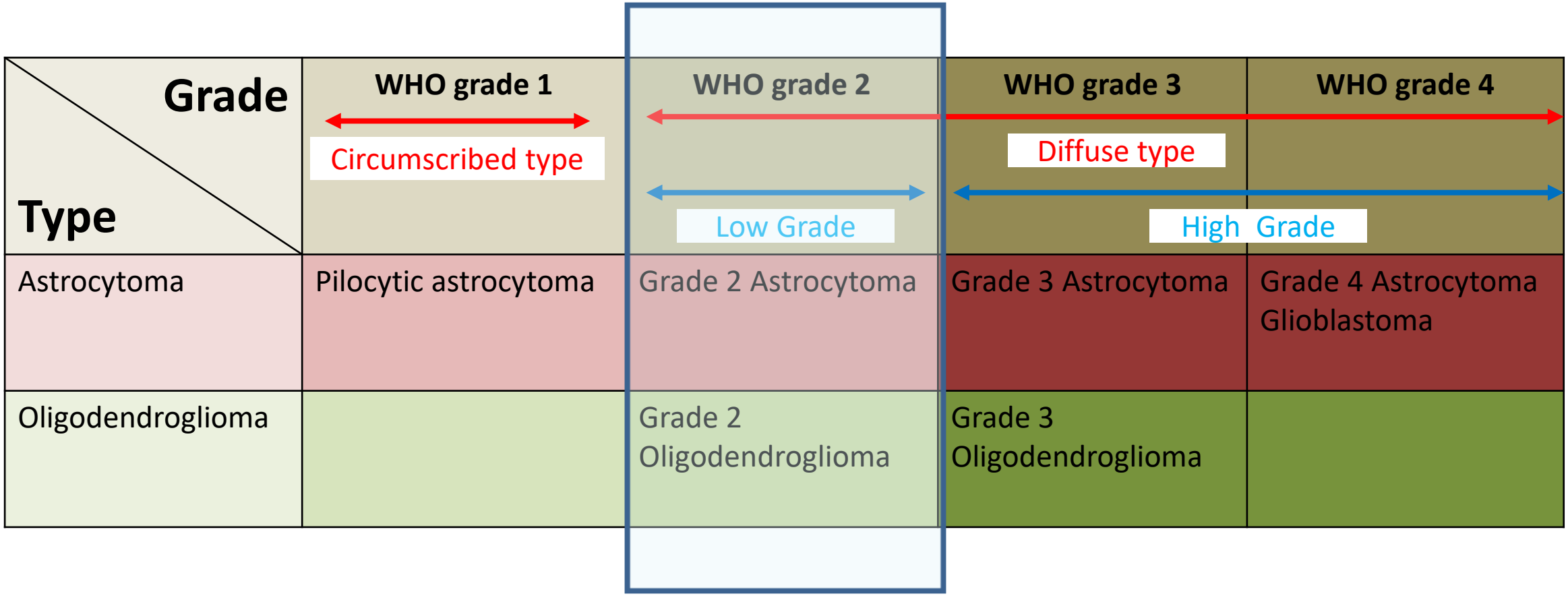
First author	Patients, n	Pediatric, %	Median age, years	Local tumor control, %	5-year PFS, %	Tumor volume, cc	Median margin dose, Gy	Median follow-up, years	Complications, %
Somaza , 1996	9	100	–	100	–	–	15 (mean)	1.6 (mean)	0
Kano , 2009	50	100	10.5	76	70.8	2.1	14.5	4.6	10
Kano , 2009	14	0	32.3	50	31.5	4.7	13.3	3	0
Hallemeier , 2012	18	33	23	75	41	9.1	15	8	44
Simonova , 2016	25	100	13	84	–	2.7	16^{a}	–	16
Trifiletti , 2017	28	50	17.4	93	96	1.84	16	5.4	0

2.1 cm Diameter sphere has 5 cc volume

Conclusion- SRS in Pilocytic astrocytoma's

- SRS can minimise potential long term ARE by targeting tumor with sharp borders and can achieve radiobiological effect by accurate focused RT.
- SRS should be considered
  - When re-resection is not feasible or there is an early recurrence
  - Prior to EBRT or chemotherapy
  - Solitary, small solid residual tumors (< 5 cc)
  - Age < 18 yrs
- SRS is less effective for cystic tumors

SRS in Low Grade gliomas



Early Vs Delayed SRS Grade 2 Astrocytomas

J Neurooncol (2011) 103:523–532
DOI 10.1007/s11060-010-0409-0

2011

CLINICAL STUDY – PATIENT STUDY

Early or delayed radiosurgery for WHO grade II astrocytomas

Kyung-Jae Park · Hideyuki Kano · Douglas Kondziolka · Ajay Niranjan · John C. Flickinger · L. Dade Lunsford

25 patients - Median age 30 yrs
GTV : 3.7 cc
Margin dose : 14 Gy
Followup : 65 months

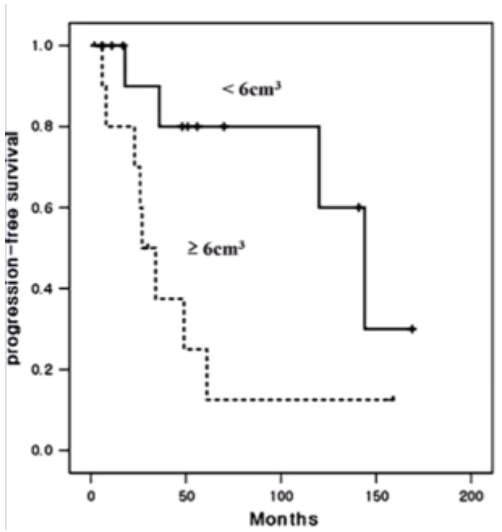
Tumor control : 52 %
5 yr PFS : 54 %
10 yr PFS : 37 %

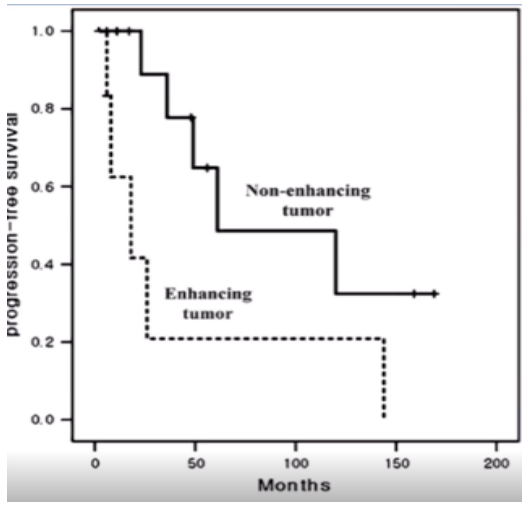
Good prognostic factors

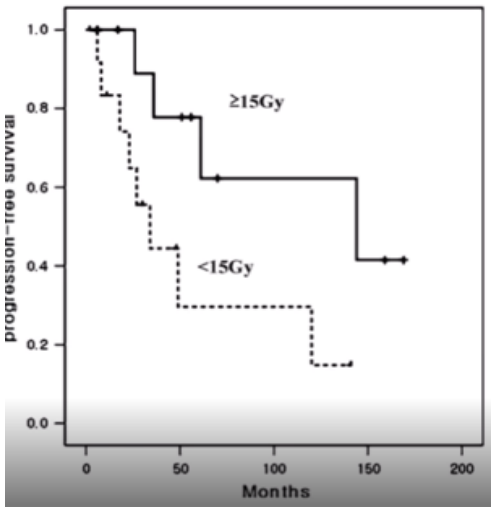
Tumor volume < 6cc
SRS Dose ≥ 15 Gy
Non contrast enhancing tumor

2.26 cm Diameter sphere has 6 cc volume

Early SRS : 16
Delayed SRS : 9







Primary Vs Adjuvant SRS Oligodendrogliomas

J Neurosurg 110:564–

2009

Does radiosurgery have a role in the management of oligodendrogliomas?

Clinical article

Hideyuki Kano, M.D.,[1] Ajay Niranjan, M.Ch.,[1] Aftab Khan, M.D.,[1] John C. Flickinger, M.D.,[2] Douglas Kondziolka, M.D.,[1] Frank Lieberman, M.D.,[1] and L. Dade Lunsford, M.D.[1]

Departments of [1]Neurological Surgery and [2]Radiation Oncology, University of Pittsburgh School of Medicine and the University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

30 patients - Median age 41 yrs

GTV : 15.4 cc
Margin dose : 14.5 Gy
Followup : 65 months

Median OS : 33 months

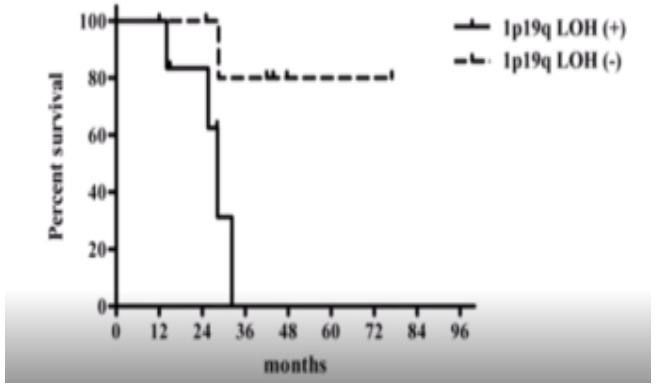
5 yr OS : 91 %
10 yr O S : 68 %

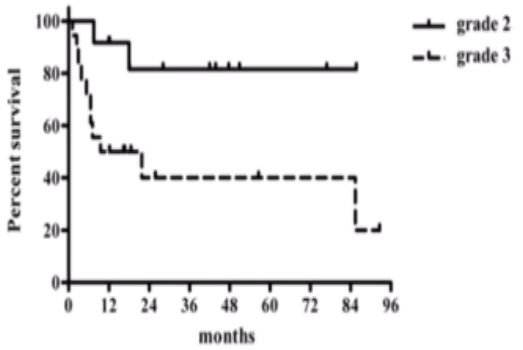
Good prognostic factors

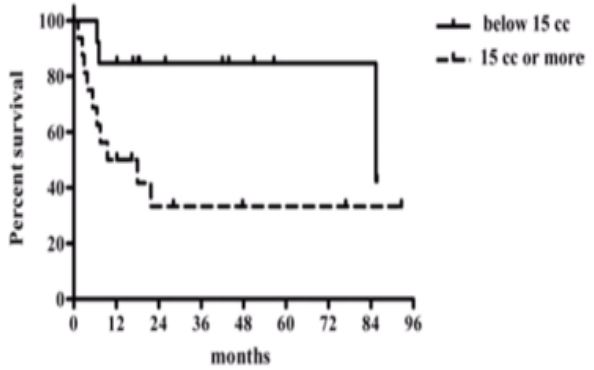
Tumor volume < 15 cc
Better PFS for Grade 2 tumors
Better PFS for 1p19q LOH

3.1 cm Diameter sphere has 15 cc volume

Primary SRS
5 (Biopsy)
Adjuvant SRS
25







SRS for Grade 2 or Fibrillary Astrocytomas

First author	Patients , n	Median age, years	Local tumor control %	5-year PFS %	Tumor Volume in CC	Median margin dose, Gy	Median Follow up , years	Complications, %
Kida , 2000	39	30.9 (mean)	87.2	–	2.37 (diameter)	15.7 (mean)	2.2 (mean)	41
Hadjipanayis , 2002	12	25	67	–	4.6	16	4.3	–
Wang , 2006	Grade 1: 8 Grade 2: 13	20	67	–	2.4	16.5	4.1	40
Szeifert , 2007	17	29.4 (mean)	71	–	3.4	13.4 (mean)	2.8 (mean)	23.5
Park , 2011	25	30	52	54	3.7	14	5.4	4

SRS for Grade 1 and 2 Gliomas

Authors & Year	Year	No. of Patients	Tumor Grade	No. of Patients w/ Prior RT	Tumor Size*	Marginal Dose (Gy)	FU (mos)	% Patients w/ Tumor Control
Barcia et al.	1994	16	I, II, UK	12	NA	21.7	NA	81
Somaza et al.	1996	9	I	2	1.6 cc	15	19	100
Kida et al.	2000	12	I	null	2.5 cm	12.5	27.6	91.7
Boëthius et al	2002	16	I	2	3.3 cc	11.3	102	100
Hadjipanayis et al	2002	37	I	10	3.4 cc	15	28	92
Kano et al	2009	50	I	5	2.1 cc	14.5	55.5	70
Henderson et al	2009	8	I	NA	4.4 cc	13	48.2	75
Mansur et al	2011	6	I	1	NA	15.5	60	80
Weintraub et al	2012	24	I, II, III	NA	2.4 cc	15	144	96
Simonova et al	2016	25	I	6	2.7 cc	16 Gy/1 fx, 25 Gy/5 fxs	181	80
Trifiletti et al	2017	28	I	4	1.8 cc	16	62.4	93

Conclusion- SRS in LGGs

- Why SRS for LGG:
  - EBRT is not shown to improve Survival
  - Young patients could avoid chemotherapy
  - Tumor near critical organs.

Early SRS for poor prognosis LGG

Age > 40

Tumor > 5cm

Not a candidate for Near total excision

Delayed SRS for good prognosis LGG

(At recurrence)

Age < 40

Tumor < 5cm

Near total excision

SRS in high grade gliomas

Type \ Grade	WHO grade 1	WHO grade 2	WHO grade 3	WHO grade 4
	Circumscribed type	Low Grade	Diffuse type / High Grade	
Astrocytoma	Pilocytic astrocytoma	Grade 2 Astrocytoma	Grade 3 Astrocytoma	Grade 4 Astrocytoma Glioblastoma
Oligodendroglioma		Grade 2 Oligodendroglioma	Grade 3 Oligodendroglioma	

SRS in high grade gliomas

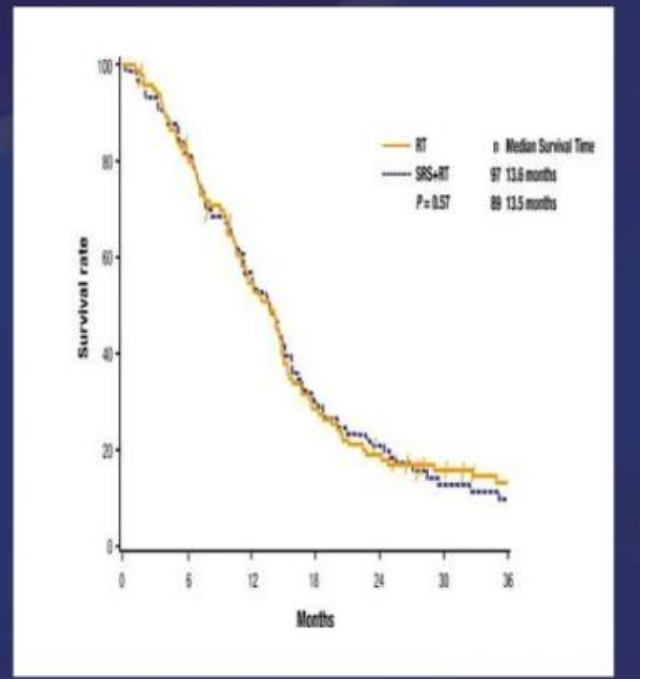
- As a Boost to chemoRT
- As a primary treatment
- In recurrent scenario

RTOG 9305 – Newly diagnosed glioblastoma SRS Boost →Standard RT

Arm 1
RT – 60Gy / 30 #
BCNU 80mg/m2 D1-3 of RT then
Q8weeks for 6 cycles

Arm 2
SRS followed by
RT – 60Gy / 30 #
BCNU 80mg/m2 D1-3 of RT then
Q8weeks for 6 cycles

SRS Dose
24Gy – Lesion < 2cm
18 Gy- Lesion 2.1 -3 cm
15 Gy – Lesion 3.1-4 cm



Median survival
14.1 mths vs 13.7 mths +/- SRS

>90 % failures in each arm accounted for local failures

RTOG 0023
Weekly SRS Boost

EBRT – 50 Gy in 25 fractions
Week 3-56 → 4 fractions of 5-7 Gy

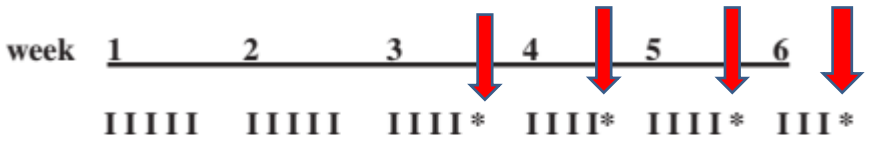


Fig. 1. Treatment schema. **I** = external beam radiation therapy (EBXRT; preoperative tumor volume plus edema), 2 Gy × 25 fractions. * = Stereotactic radiotherapy (SRT) boost, 5–7 Gy × 4 fractions.

A PHASE II TRIAL OF ACCELERATED RADIOTHERAPY USING WEEKLY STEREOTACTIC CONFORMAL BOOST FOR SUPRATENTORIAL GLIOBLASTOMA MULTIFORME: RTOG 0023

Robert Cardinale, M.D.,* Minhee Won, M.A.,† Ali Choucair, M.D.,‡ Michael Gillin, Ph.D.,§ Arnab Chakravarti, M.D., Ph.D.,‖ Christopher Schultz, M.D.,¶ Luis Souhami, M.D.,** Allan Chen, M.D., Ph.D.,†† Huong Pham, M.D.,‡‡ and Minesh Mehta, M.D.,§§

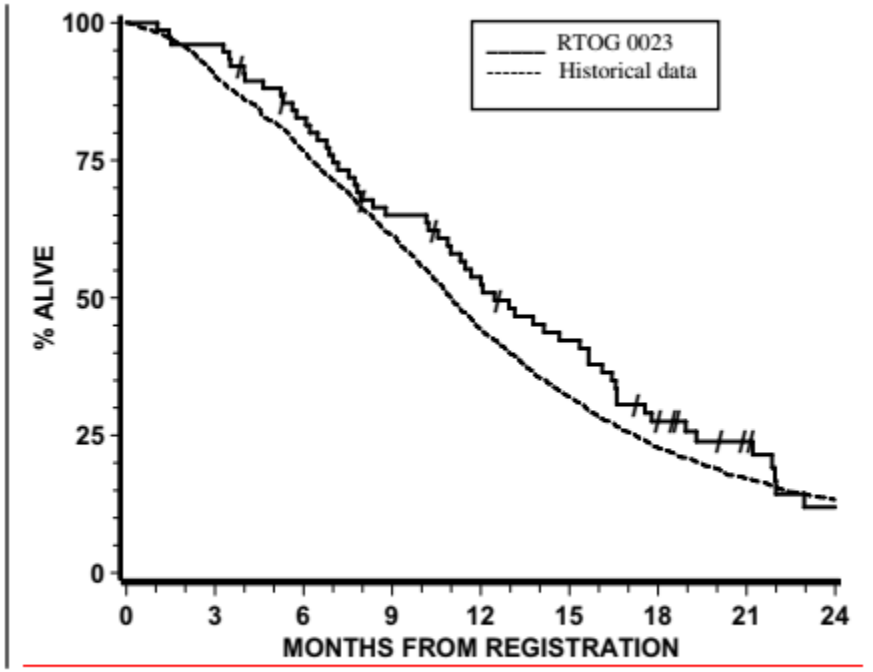


Fig. 2. Overall survival for Radiation Therapy Oncology Group (RTOG) 0023 patient group vs. historical controls from the RTOG database ($p = 0.24$).

Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 1, pp. 47–55, 2005

0360-3016/05/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2005.05.024

2005

ASTRO REPORT

THE AMERICAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY (ASTRO) EVIDENCE-BASED REVIEW OF THE ROLE OF RADIOSURGERY FOR MALIGNANT GLIOMA

MAY N. TSAO, M.D., MINESH P. MEHTA, M.D., TIMOTHY J. WHELAN, M.D., DAVID E. MORRIS, M.D., JAMES A. HAYMAN, M.D., JOHN C. FLICKINGER, M.D., MICHAEL MILLS, PH.D., C. LELAND ROGERS, M.D., AND LUIS SOUHAMI, M.D.

- **For patients with malignant glioma, there is Level I-III evidence that the use of radiosurgery boost followed by external beam radiotherapy and BCNU does not confer benefit in terms of overall survival, local brain control, or quality of life as compared with external beam radiotherapy and BCNU.**
- **The use of radiosurgery boost is associated with increased toxicity.**
- **For patients with malignant glioma, there is insufficient evidence regarding benefits / harm of using**
  - radiosurgery at the time progression or recurrence.
  - stereotactic fractionated radiation therapy in patients with newly diagnosed or progressive/recurrent malignant glioma

SRS vs fSRS

Fractionated stereotactic radiosurgery for malignant gliomas: comparison with single session stereotactic radiosurgery

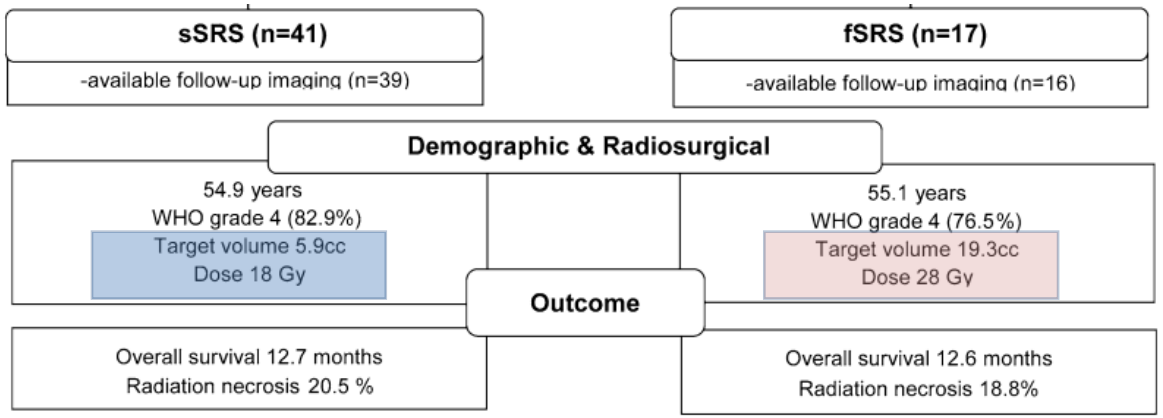
2019

Seung Won Choi[1] · Kyung Rae Cho[1] · Jung Won Choi[1] · Doo-Sik Kong[1] · Ho Jun Seol[1] · Do-Hyun Nam[1] · Jung-Il Lee[1]

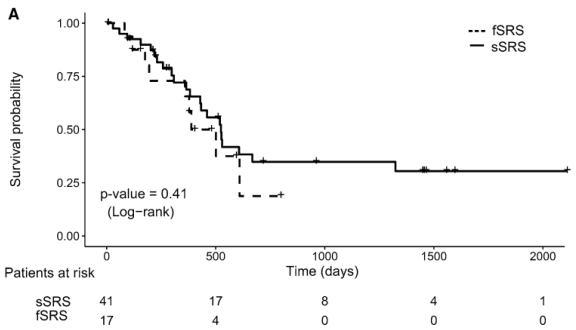
Korea

2.26 cm Diameter sphere has 6 cc volume

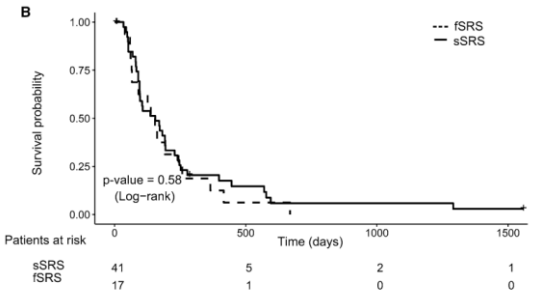
3.3 cm Diameter sphere has 19 cc volume



Variable		sSRS	fSRS	p value
No. of patients		41	17	
Age (years) (mean ± SD)		54.9 ± 13.1	55.1 ± 12.9	0.95*
Sex (Female:Male)		23:18	6:11	0.25*
Pathologic diagnosis (%) (no. of case)		AA 4.9% (2/41) AOA 2.4% (1/41) AODG 9.8% (4/41) GBM 78.0% (32/41) Gliosarcoma 4.9% (2/41)	AA 11.8% (2/17) AODG 11.8% (2/17) DMG 5.9% (1/17) GBM 70.6% (12/17)	0.55**
WHO grade (%) (no. of case)		Gr 3 17.1% (7/41) Gr 4 82.9% (34/41)	Gr 3 23.5% (4/17) Gr 4 76.5% (13/17)	0.71**
Prior therapy (%) (no. of case)	CTx	85.4% (35/41)	76.5% (13/17)	0.46**
	RTx	100% (41/41)	88.2% (15/17)	0.08**
	None	41.5% (17/41)	29.4% (5/17)	0.56**
Concomitant therapy (%) (no. of case)	TMZ	48.8% (20/41)	47.1% (8/17)	1**
	BEZ	0% (0/41)	5.9% (1/17)	0.29**
	others	9.8% (4/41)	17.6% (3/17)	0.34**
Target volume (mm^3) (mean ± SD)		5.9 ± 6.67	19.3 ± 13.0	< 0.001*
Dose (Gy) (median) (range)		18 (11–25)	28 (24–35)	
Isodose (%) (median) (range)		50% (50–50)	50% (50–65)	



OS



PFS

Journal of Neuro-Oncology (2019) 145:571–579
https://doi.org/10.1007/s11060-019-03328-3

SRS treatment of newly diagnosed glioblastoma

Author	N	Treatment Schema	Survival Rate	Median OS (…ths)
Sarkaria	115	54-60 Gy RT + 6-20 Gy SRS	2-yr OS: 45% 2-yr OS for KPS ≥ 70 2-yr OS for KPS	
Gannett	30	44-62 Gy RT + 0.5-18 Gy SRS	1-yr DSS: 2-yr	13.9
Masciopinto	31	RT + 15-35 Gy SRS		9.5
Mehta	31	54 Gy RT + 15-30 Gy SRS		42 weeks
Nwokedi	33 RT alone; 31 RT + SRS	28-80 (median 59 (median 7.1	…ents: …S: 67% 2-yr OS: 40% 3 yr OS: 26%	RT alone: 13 RT + SRS: 25
Balducci	41 (36 GBM, 5 A…	59 …Gy) + …19 Gy	2-yr OS: 63%	All pts: 30 GBM: 28
Cardinale	8	36 Gy SRS	NR	GBM: 16 AA: 33
Shrieve		…T + SRS	1-yr OS: 88.5% 2-yr OS: 35.9%	19.9
Flo…		40 Gy RT + 24 Gy SRS, temozolomide	NR	13
Lar…	23	Estramustine + SRS	2-yr OS: 38%	16
Omur…	40	6 x 6 Gy or 6 x 4 Gy SRS + temozolomide + bevacizumab	1-yr OS: 93%	19

CAUTION --- These patients were not classified on basis of IDH mutations - Wildtype vs mutant

Leading Edge Radiosurgery Glioblastoma

Microscopic infiltrative growth up to 4 cm from visible tumor location along white matter tracts in normal brain tissue

- “leading-edge” is defined by FLAIR MRI
- LERS a median of 18 days from diagnosis
- Median target volume of 48.5 cm3 (range 2.5-222.0 cm3)
- Median dose of 8 Gy (range, 6-14 Gy) at 50% isodose line
- As a boost to standard therapy

Glial cells express genes that produce membrane type 1 MMP2
Enables breakdown of the extracellular matrix of white matter
Leads to migration along white matter tracts.
Contralateral spead via corpus callosum and corona radiatia
Lead to diffuse incurable disease.

JNS CLINICAL ARTICLE
J Neurosurg (Suppl 1) 125:40–49, 2016

Upfront boost Gamma Knife “leading-edge” radiosurgery to FLAIR MRI–defined tumor migration pathways in 174 patients with glioblastoma multiforme: a 15-year assessment of a novel therapy

Christopher M. Duma, MD,[1,2] Brian S. Kim, MD,[2,3] Peter V. Chen, MD,[2,3] Marianne E. Plunkett, MS,[2,3]

2000 -2016

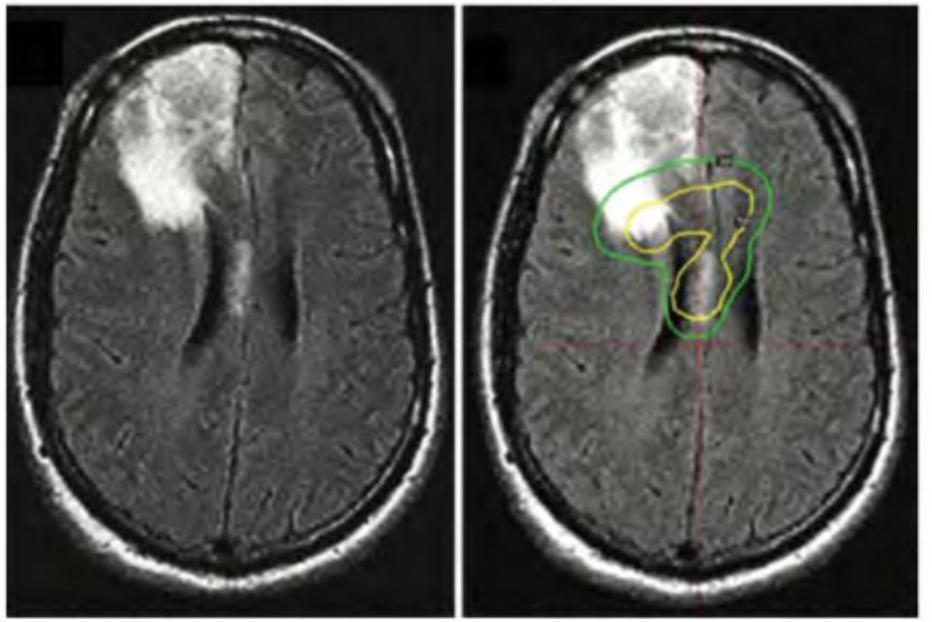


FIG. 2. Left: Distant “invisible” tumor spread into the corpus callosum as revealed on FLAIR sequence seen in Fig. 1. **Right:** Gamma Knife LERS plan used to arrest migration. A 10-Gy dose at the 50% isodose line was prescribed.

4.5 - 7.5 cm Diameter sphere
has 48 - 222cc volume

Leading Edge Radiosurgery Glioblastoma

JNS
CLINICAL ARTICLE
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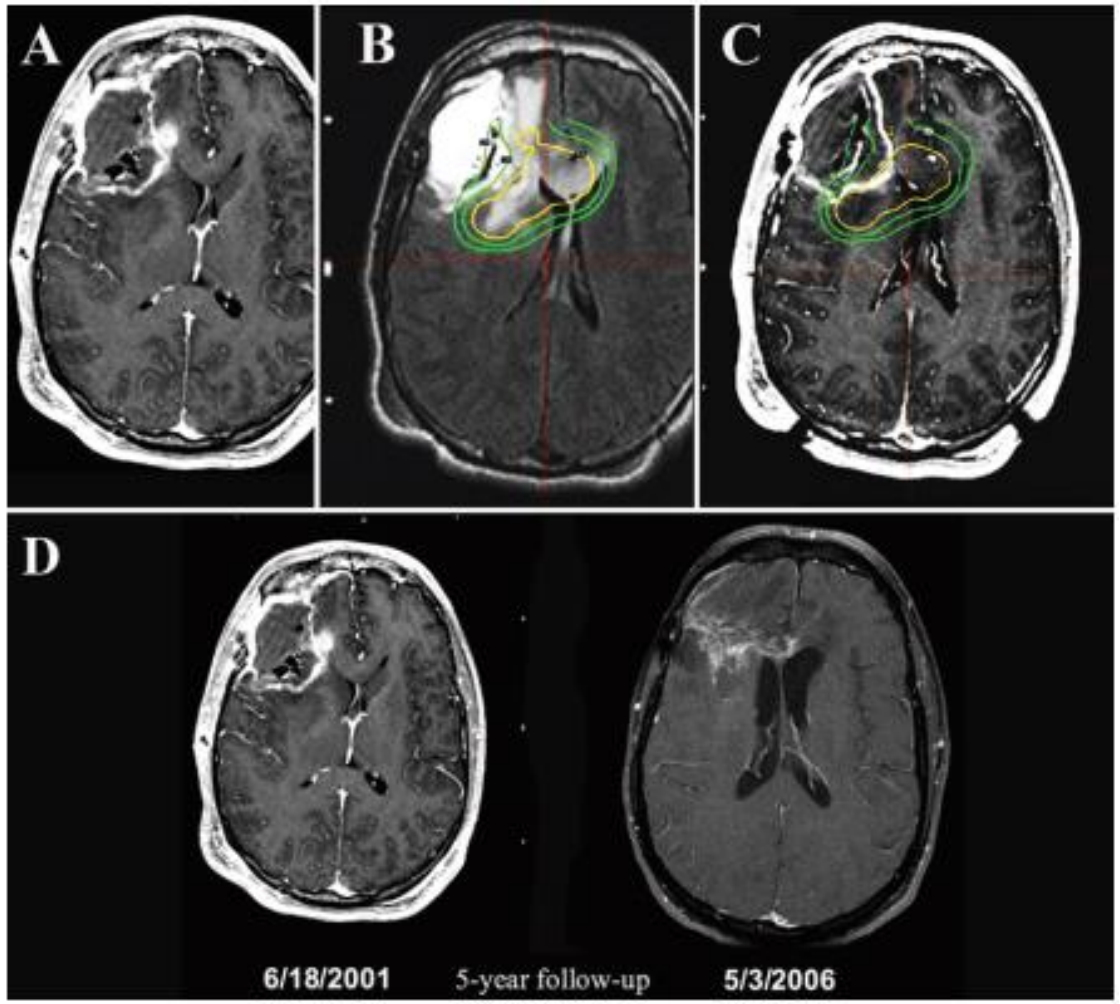

FIG. 4. A: T1-weighted Gd-enhanced MR image obtained the day of Gamma Knife LERS showing postoperative 95% resection of the tumor bed. B: An LERS FLAIR sequence from the same day, showing "invisible" dramatic migration of tumor across midline and posteriorly down the corona radiata. The LERS plan is overlaid. The patient received 12 Gy at the 50% isodose line (*yellow*). C: The same LERS plan is overlaid on the T1-weighted post-Gd MR image, showing "invisible" tumor spread apparently treating normal brain. D: T1-weighted contrast-enhanced MR images, from the day of LERS and at 5 years later, respectively, showing residual scar tissue. This patient lived 8 years after treatment and ultimately died as a result of GBM progression.

Leading Edge Radiosurgery Glioblastoma

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J Neurosurg (Suppl 1) 125:40–49, 2016

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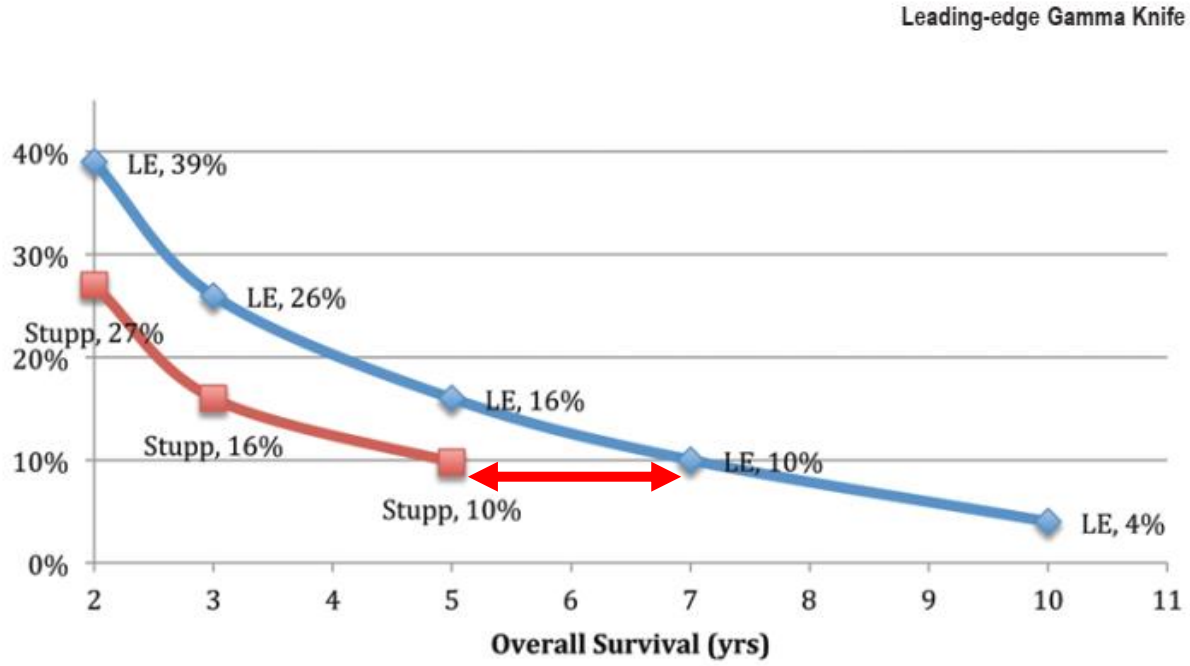

FIG. 5. The percentage of LERS-treated patients alive versus time, compared with data from Stupp et al.[45,46]

The median overall survival from diagnosis was 23 months (standard error 0.78 months, mean 43 months).

At the time of analysis, 149 patients (86%) were dead.

The 2-,3-, 5-, 7-, and 10-year actual overall survival rates using LERS were 39%, 26%, 16%, 10%, and 4%, respectively

Leading Edge Radiosurgery Glioblastoma

Day -1 - To do 1.5- or 3.0-T MRI 2-mm-thick FLAIR

Contour the The FLAIR abnormality

Check the volume - Exclude those with TV > 80 cc

Doses will be administered to this target volume as follows:
0–20 cm^3, 10 Gy;
21–40 cm^3, 9 Gy;
41–60 cm^3, 8 Gy; and
61–80 cm^3, 7 Gy

After this proceed with Concurrent ChemoRT and Adj Temozolomide as per stupps protocol.

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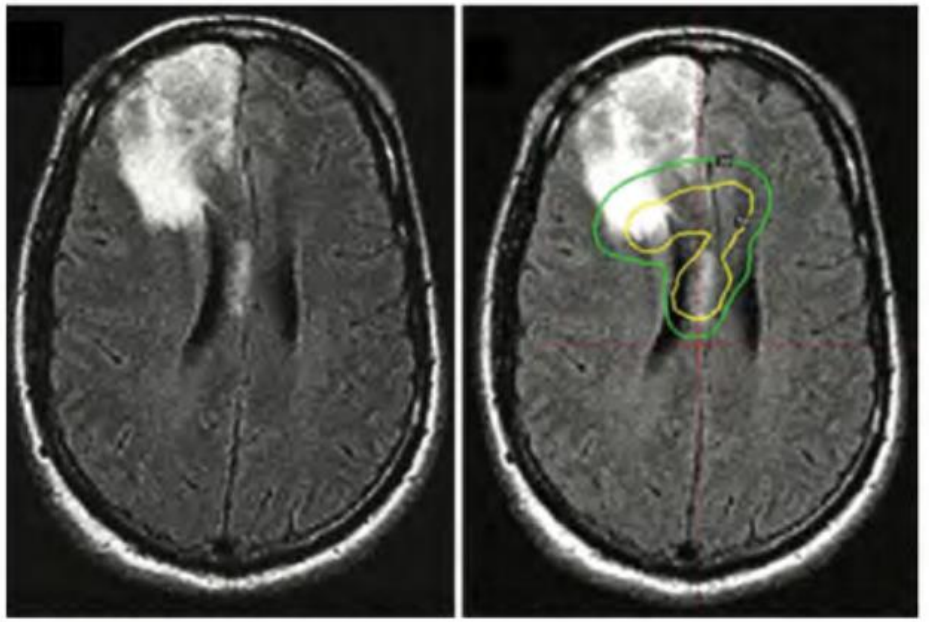


FIG. 2. Left: Distant "invisible" tumor spread into the corpus callosum as revealed on FLAIR sequence seen in Fig. 1. **Right:** Gamma Knife LERS plan used to arrest migration. A 10-Gy dose at the 50% isodose line was prescribed.

2015

IAEA Trial

International Atomic Energy Agency Randomized Phase III Study of Radiation Therapy in Elderly and/or Frail Patients With Newly Diagnosed Glioblastoma Multiforme

Wilson Roa, Lucyna Kepka, Narendra Kumar, Valery Sinaika, Juliana Matiello, Darejan Lomidze, Dalenda Hentati, Douglas Guedes de Castro, Katarzyna Dyttus-Cebulok, Suzanne Drodge, Sunita Ghosh, Branislav Jeremić, Eduardo Rosenblatt, and Elena Fidarova

Frail → Age > 50 years and KPS 50 -70
Elderly and frail → age >65 years and KPS 50 -70
Elderly Age→ > 65 years and KPS 80 -100

- Arm 1 – Short-course radiotherapy

(25 Gy in five daily fractions over 1 week)

- Arm 2 – HFRT

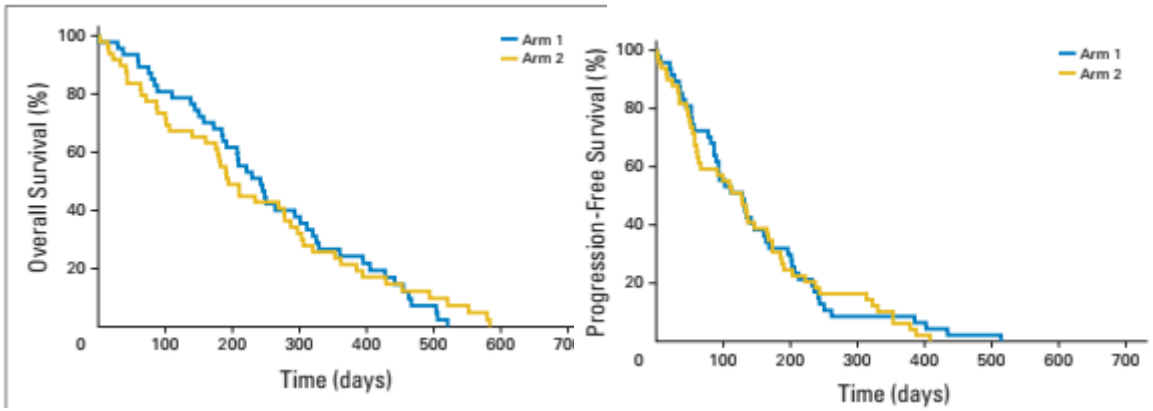
40 Gy in 15 daily fractions over 3 weeks

	Arm 1 25 Gy in 5 Fr	Arm 2 40 Gy in 15 Fr
Median OS	7.9m	6.4m
Median PFS	4.2 m	4.2 m
QOL at median follow up of 6.3 months was similar with both arms		

Gross tumor volume was defined as the entire postoperative enhancing tumor and surgical cavity.

The clinical target volume added a 2.0-cm margin to the gross tumor volume with no expansion beyond anatomic boundaries (eg, skull).

The planning target volume (PTV) equaled the clinical target volume plus 0.5 cm in all directions



5Fr SRS for Glioblastoma

182 Neuro-Oncology 2020
22(8), 1182–1189, 2020 | doi:10.1093/neuonc/noaa019 | Advance Access date 31 January 2020

A phase I/II trial of 5-fraction stereotactic radiosurgery with 5-mm margins with concurrent temozolomide in newly diagnosed glioblastoma: primary outcomes

- N = 30 , From 2010 to 2015
- The 5-fraction SRS dose was escalated in a standard 3 + 3 design at 4 dose levels: 25 Gy, 30 Gy, 35 Gy, and 40 Gy.
- The median PTV 60 cm3 (range, 14.7–137.3 cm3)
- Contouring
  - CTV - GTV + 5mm (not extending beyond anatomic borders of tumor spread such as the calvarium, falx, and tentorium)
  - Edema was excluded
  - PTV – Same as CTV 0 mm margin.
- Coverage
  - 95 % PTV to be covered by prescription isodose line
  - Optic pathway - 98% of the optic pathways received less than 27.5 Gy
  - Brainstem maximum dose of 30 Gy in 5 fractions
- Treatment Schema:
  - RT - Delivered on 5 consecutive days over 7 elapsed days
  - Concurrent Chemo - TMZ at a dose of 75 mg/m2
  - Standard adjuvant - TMZ at 150–200 mg/m2 daily, 5/28 days x 6 months

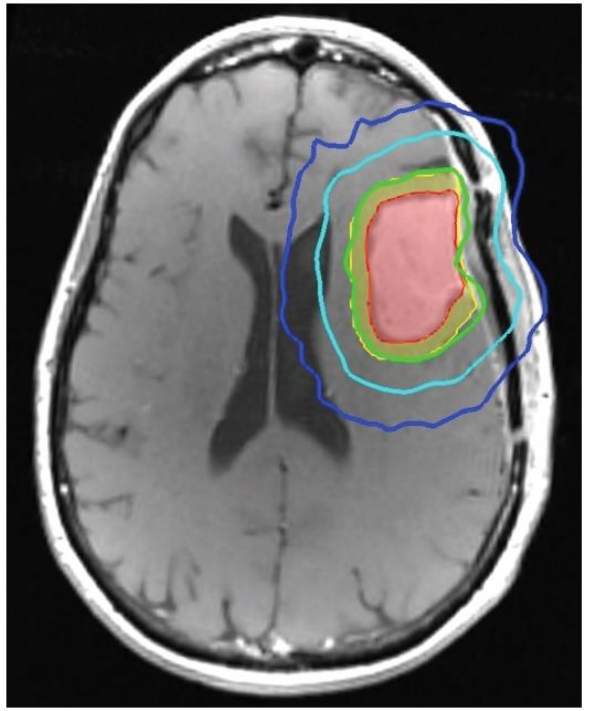
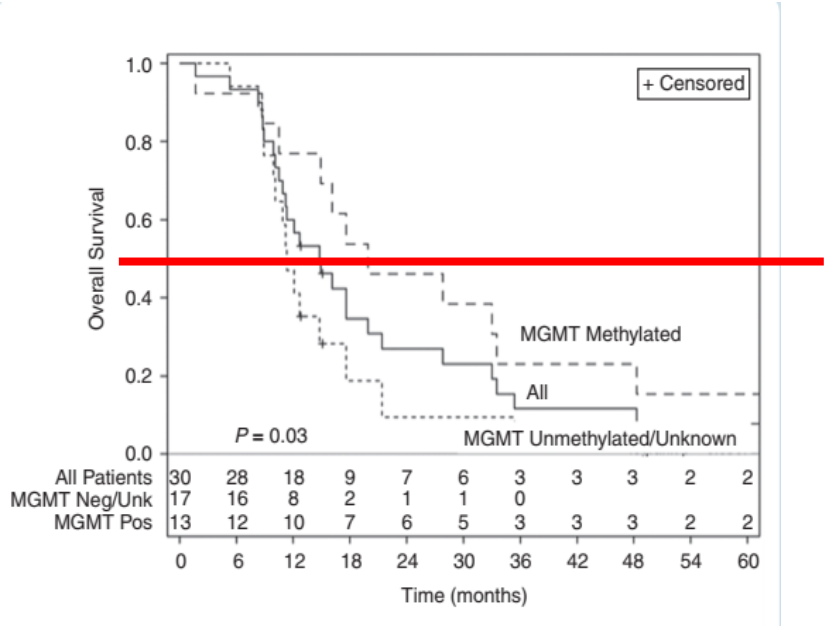
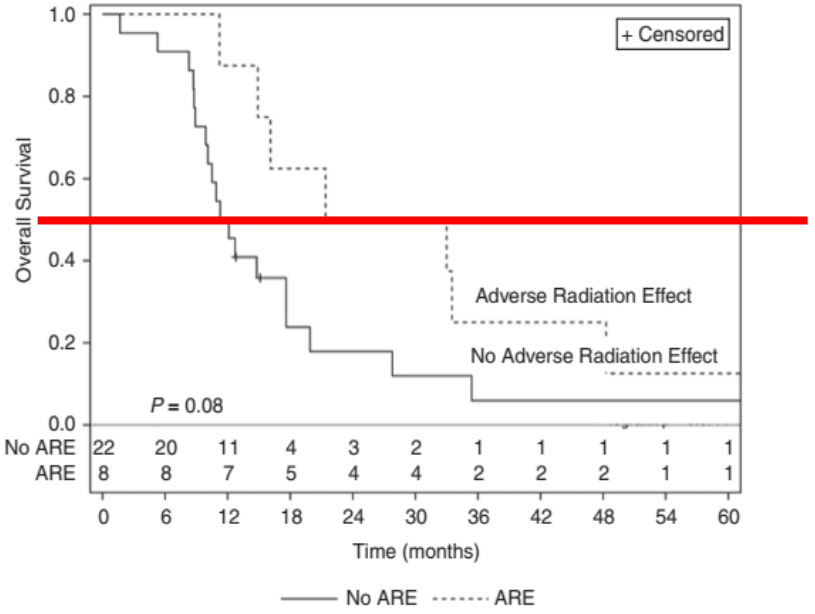


Fig. 1 A representative 5-fraction, 5-mm margin radiotherapy treatment plan. The left frontal resection cavity (red contour) with a 5-mm margin (yellow contour) form the final planning target volume (PTV) which was covered by the 35 Gy prescription isodose line (green). Shown are the 50% dose (cyan) and 25% dose (blue) isodose lines.

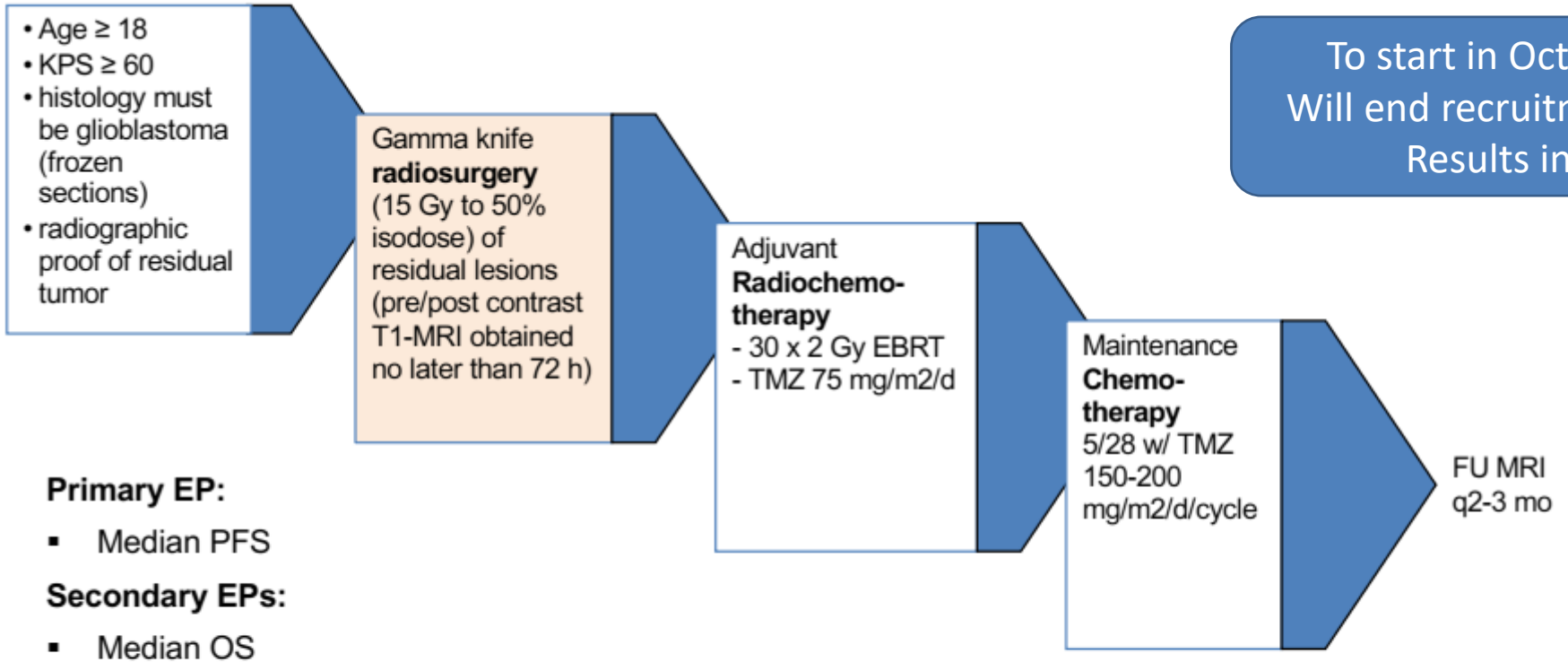
5Fr SRS for Glioblastoma

- Toxicity
  - 2 deaths – while on treatment
  - Late grades 1–2 ARE occurred in 8 patients at a median of 7.6 months (range 3.2–12.6 mo). -- 25 %
  - No grades 3–5 ARE occurred.
- Efficay
  - Follow up period - 13.8 months (range 1.7– 64.4 mo)
  - PFS - 8.2 months (95% CI: 4.6–10.5);
  - OS - 14.8 months (95% CI: 10.9–19.9);
- O6-methylguanine-DNA methyltransferase hypermethylated, 19.9 months (95% CI: 10.5–33.5) versus 11.3 months (95% CI: 8.9–17.6) for no/unknown hypermethylation (*P* = 0.03), and 27.2 months (95% CI: 11.2–48.3)
- if late ARE occurred versus 11.7 months (95% CI: 8.9–17.6) for no ARE (*P* = 0.08).





Early GK SRS to Residual Tumor After Surgery of Newly Diagnosed Glioblastoma (Gamma-GBM) (NCT03055208)



To start in October 2022
Will end recruitment in 2024
Results in 2025

Primary EP:

- Median PFS

Secondary EPs:

- Median OS
- Radiation-related (acute / early delayed / late) neurotoxicity
- Incidence of symptomatic radionecrosis

Preoperative SRS Rationale

2022

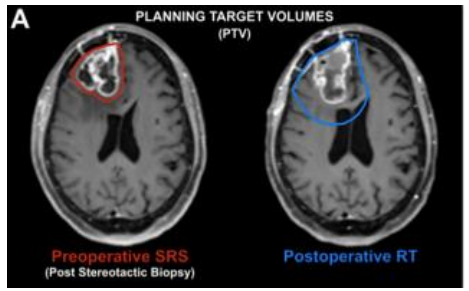
Review

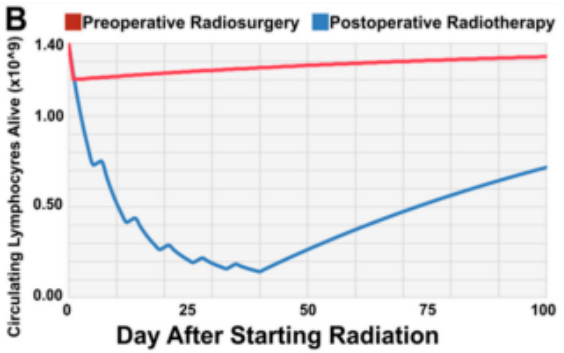
Preoperative Stereotactic Radiosurgery for Glioblastoma

Eric J. Lehrer [1], Henry Ruiz-Garcia [2,3], Anthony D. Nehlsen [1], Kunal K. Sindhu [1], Rachel Sarabia Estrada [2,3], Gerben R. Borst [4,5], Jason P. Sheehan [6], Alfredo Quinones-Hinojosa [3] and Daniel M. Trifiletti [2,3,*]

1. Smaller RT target volumes and more precise target delineation
   - Decreasing dose delivery to nearby NT
   - Lowers treatment-related toxicities (e.g., RN)
2. Intact tissues - high O2 concentrations- more effective RT-induced DNA DSBs
3. Post-irradiation tissue available for analysis – future research
4. Risk of nodular LMD is low

- Ionizing radiation alters the tumor microenvironment and enhances anti-tumor immunity in gliomas
- RT may enhance cytotoxic T-cell activity against GBM
- RT enhances anti-tumor immunity against glioma cells, which may be further amplified by ICI





Preoperative SRS

Preoperative Radiosurgery for the Treatment of High Grade Glioma, The NeoGlioma Study

ClinicalTrials.gov Identifier: NCT05030298

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.

Recruitment Status : Not yet recruiting
First Posted : September 1, 2021
Last Update Posted : August 4, 2022

See **Contacts and Locations**

Sponsor:
Mayo Clinic

Collaborator:
National Cancer Institute (NCI)

Information provided by (Responsible Party):
Mayo Clinic

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Tracking Information	
First Submitted Date ICMJE	August 23, 2021
First Posted Date ICMJE	September 1, 2021
Last Update Posted Date	August 4, 2022
Estimated Study Start Date ICMJE	October 1, 2022
Estimated Primary Completion Date	September 15, 2024 (Final data collection date for primary outcome measure)

https://clinicaltrials.gov/ct2/show/record/NCT05030298

SRS in recurrent gliomas

SRS for recurrent glioblastoma

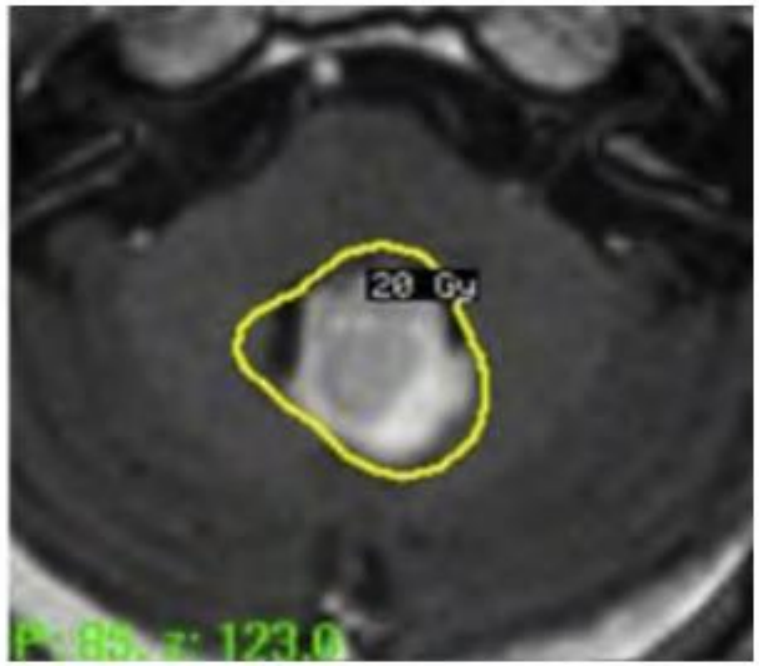
Author	N	Treatment Schema	Median Time to 1st Recurrence (Range) Months	OS Rate After SRS Salvage	Median OS (Range) Months
Shrieve	86 - SRS alone; 32 - Brachytherapy alone	13 Gy (median) SRS	NR	1-yr (SRS pts): 45% 2-yr (SRS pts) : 19%	10.2 for SRS pts
Vordermark	19	20-30 Gy SRS	19 (3-116)	1-yr: 26% 2-yr: 16%	9.3 (1.9-77.6+)
Lederman	9 SRS alone; 14 SRS + Taxol	SRS alone: Mean dose 19.2 Gy in 1# SRS + Taxol: Mean dose of 24 Gy in 4#	11	1-yr SRS alone : 11% 1-yr SRS + Taxol: 50%	SRS alone: 6.3 SRS + Taxol: 14.2
Combs	32	10-20 Gy (median 15 Gy)	10 (1-77)	6 months: 72% 1-yr : 38%	10
Fogh	147	28-80 Gy (median dose 35 Gy in 3.5 Gy fractions)	8 (4-205)	NR	11
Maranzano	22	17 Gy (median) SRS or 30 Gy (median) fractionated SRS	9		11
Greenspoon	31	25 – 30 Gy + temozolomide	NR	NR	9
Hudes	20	24 Gy/3 fx or 30 Gy/3 fx or 35 Gy/3.5 fx	3.1 (0.7-45.5)	1-yr OS: 20%	20
Lederman	88	4 weekly irradiation (median 6 Gy) after Paclitaxel	6.5	1-yr: 17% 2-yr: 3.4%	7
Cuneo	WHO Grade 3: 16 WHO Grade 4: 33	12.5-25 (median 15) Gy SRS 12.5 – 25 Gy SRS + bevacizumab	All pts: 20	Gr3 gliomas : 1-yr: 22% Gr4 gliomas : 1-yr: 50%	Gr 3 glioma: 3.9 Gr 4 glioma: 11.2
Minniti	54	30 Gy/6 fx SRS + temozolomide	Median time between primary RT and reirradiation: 15.5	1-yr: 53% 2-yr: 10%	12.4

1 yr OS ~10 – 50%

Extended field SRS Vs Conventional SRS For recurrent Glioblastoma

Extended Field SRS

- Leksell h
- MRI for
- CTV – G
  no marg
- Margina
- Median
- Vol rece
  <15 cc.



Conventional SRS

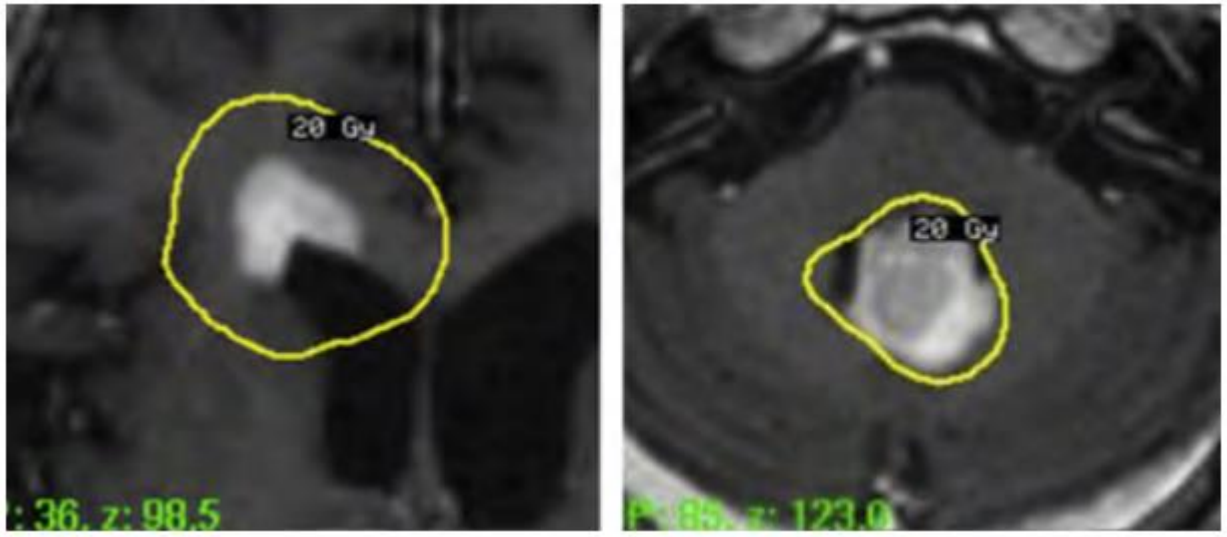
ced lesion with

Gy

c

Koga, Tomoyuki, et al. "Extended field stereotactic radiosurgery for recurrent glioblastoma." *Cancer* 118.17 (2012): 4193-4200.

Extended field SRS Vs Conventional SRS For recurrent Glioblastoma



93% local control vs 47%
28.6% adverse radiation effects

Table 3. Comparison of Characteristics and Outcomes of the Patients Who Received Conventional SRS and Extended Field SRS

Characteristic	Conventional SRS	Extended Field SRS	*P*
Number of patients	9	9	—
Primary glioblastoma	8	7	1.0
Patient age, median y, range	43, 17-64	53, 27-79	.36
KPS at onset, median, range	90, 80-90	90, 80-90	.62
Time from Dx to 1st SRS, median mo, range	14.5, 1-51	12, 6-39	.66
KPS at 1st SRS, median, range	90, 40-90	70, 40-90	.21
Local control	16/34	13/14	.0035
Radiation necrosis	2/34	4/14	.052
Median OS after Dx, mo	24	21	.71
Median OS after 1st SRS, mo	10.5	9	.83
6-month OS after 1st SRS, %	63	89	.83

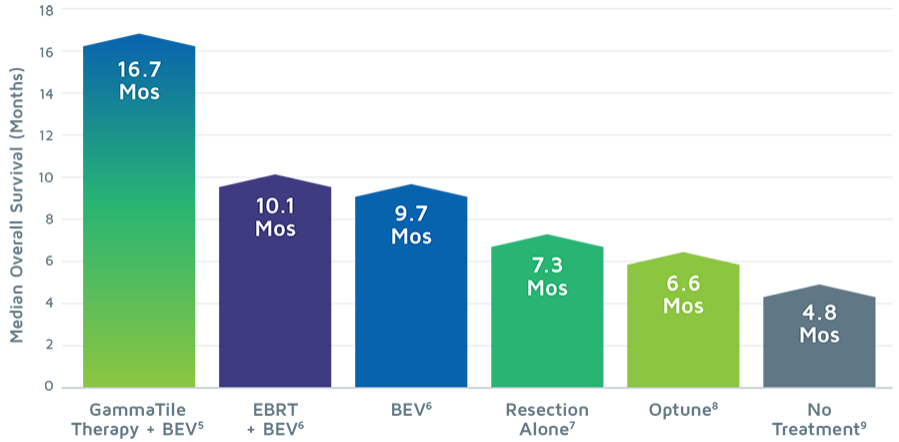
Abbreviations: Dx, diagnosis of glioblastoma; KPS, Karnofsky Performance Scale; OS, overall survival; SRS, stereotactic radiosurgery.

Koga, Tomoyuki, et al. "Extended field stereotactic radiosurgery for recurrent glioblastoma." *Cancer* 118.17 (2012): 4193-4200.

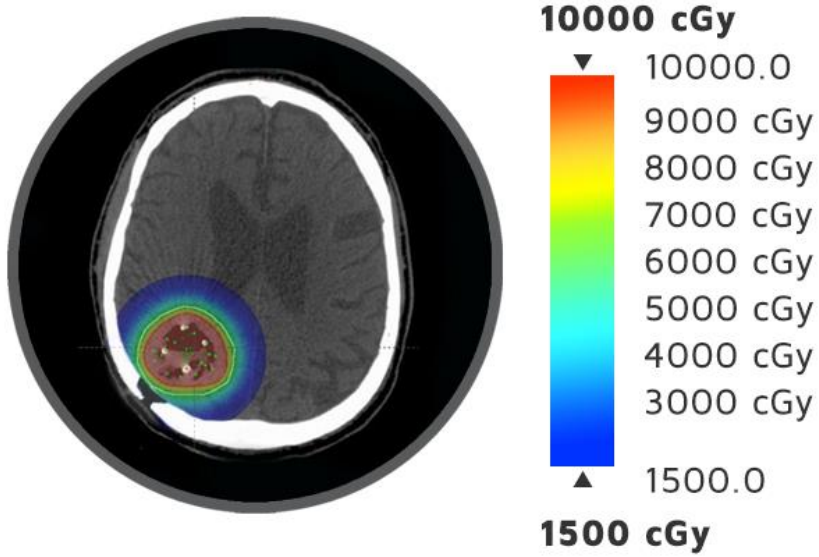
GammaTile® Therapy

Surgically Targeted Radiation Therapy (STaRT) for patients with operable brain tumors

- Gamma-Tile cesium-131 (^{131}Cs)
- Permanent brain implant
- FDA approved for Recurrent Gliomas
- It is a form of brachytherapy where seeds are placed inside a mesh, called a tile



GammaTile Therapy[1]



Isodose depiction modified to illustrate attenuation by the skull

Conclusion- SRS in Recurrent Gliomas

- Reasonable outcome post SRS in many studies
- SRS – GTV based on T1 Contrast enhanced images
  - Any role of functional imaging to delineate target
  - PET imaging to delineate target
- SRS Margins – Studies use 0-2 mm
- Effect of total dose / fractionation / combination with BVZ not understood clearly
- SRS alone unlikely to offer durable control

SRS Treatment related Toxicites - Gliomas

1

Acute

- Is usually self limiting
- Exacerbations of existing symptoms occur

2

Late

- Serious Neurological deficits
- Hemiparesis
- Headache, Somnolence
- Vision loss
- Radiation necrosis (20 %)
- Re surgery (50 %)
- Prolonged steroid requirement

SRS Toxicities

Author	N	Dose	Toxicity	Radiation Necrosis	Defecits	Re-Sur
Sarkaria	115	54 – 60 Gy RT + 10 – 20 Gy SRS	17 patients with radiation necrosis, 1 patient with hemiparesis. 47% required prolonged steroid use. One patient with double vision and hydrocephalus requiring ventricular shunt.	14.80%	1	1
Schrieve	78		50% had reoperation for symptomatic necrosis or recurrent tumor. Rate of reoperation at 24 months after SRS was 54.8%.	50%		54.80%
Fogh	147	Median 35 Gy/3.5 Gy fx	One late Grade 3 CNS toxicity 4 months after hypofractionated SRS.	2%	1	
Cuneo	21 SRS 42 SRS + bevacizumab	12.5to25Gy 12.5 – 25 Gy + bevacizumab	14% Grade 3, 5% Grade 4, 19% radionecrosis, 29% worsening of neurologic symptoms, 19% increase seizures 10% Grade 3, 5% radionecrosis, 24% worsening of neurologic symptoms, 21% increase seizures	19% 5%	29% 24%	
Minniti	54	30 Gy/5 fx + temozolomide	7% Grade 3 neurologic deterioration with radiation-induced necrosis; 7 patients with Grade 3 lymphopenia, 3 patients with Grade 4 lymphocytopenia, 2 patients with Grade 3 thrombocytopenia,	7%	7%	
Park	11	13-18 Gy + bevacizumab	One Grade 3 toxicity and 1 major adverse radiation effect.	9%		
Gutin	25 (20 GBM and 5 AA)	30 Gy/5 fx + bevacizumab	8% Grade 3 leukopenia, 8% Grade 3 neutropenia, 28% Grade 3 lymphopenia, 8% Grade 3 thrombocytopenia, 12% Grade 3 anemia, 4% Grade 3 fatigue, 4% Grade 3 hypertension, 4% Grade 3 CNS hemorrhage, 8% Grade 4 lymphopenia, 4% Grade 4 thrombocytopenia, 4% Grade 4 bowel perforation, 4% Grade 4 wound healing complication, 4% Grade 4 gastrointestinal bleeding			
Niyazi	20 SRS alone 10 SRS + bevacizumab	36 Gy/18 fx +/- bevacizumab	1 Grade 2 fatigue, 1 Grade 2 hypertension, 1 Grade 3 deep vein thrombosis, 1 Grade 4 wound healing complication			
Ogura	30	22.5 – 35 Gy/5 fx	2 patients with Grade 3 radionecrosis	6%		
Cabrera	15	18 or 24 Gy/1 fx or 25/5 fx + bevacizumab	1 Grade 3 severe headache, 2 Grade 2 CNS toxicities. No Grade 4 or 5 events.	0%	3 pat	

OAR Dose Constraints in SRS

Table 8.2 Optic pathway dose constraints for avoidance of ≥ grade 3 optic neuritis

	1 FRACTION	3 FRACTIONS	4 FRACTIONS	5 FRACTIONS
Volume (cc)	<0.2 cc	<0.2 cc	<0.2 cc	<0.2 cc
Volume max (Gy)	8 Gy	15.3 Gy (5.1 Gy/fx)	19.2 Gy (4.8 Gy/fx)	23 Gy (4.6 Gy/fx)
Max point dose (Gy)	10 Gy	17.4 Gy (5.8 Gy/fx)	21.2 Gy (5.3 Gy/fx)	25 Gy (5 Gy/fx)

Table 8.3 Cochlear dose constraints to avoid ≥ grade 3 hearing loss

	1 FRACTION	3 FRACTIONS	4 FRACTIONS	5 FRACTIONS
Max point dose (Gy)	9 Gy	17.1 Gy (5.7 Gy/fx)	21.2 Gy (5.3 Gy/fx)	25 Gy (5 Gy/fx)

Table 8.4 Brain stem (not medulla) dose constraints to avoid ≥ grade 3 cranial neuropathy

	1 FRACTION	3 FRACTIONS	4 FRACTIONS	5 FRACTIONS
Volume (cc)	<0.5 cc	<0.5 cc	<0.5 cc	<0.5 cc
Volume max (Gy)	10 Gy	18 Gy (6 Gy/fx)	20.8 Gy (5.2 Gy/fx)	23 Gy (4.6 Gy/fx)
Max point dose (Gy)	15 Gy	23.1 Gy (7.7 Gy/fx)	27.2 Gy (6.8 Gy/fx)	31 Gy (6.2 Gy/fx)

Source: Reprinted from *Semin Radiat Oncol*, Vol 18(4), R.D. Timmerman, An Overview of Hypofractionation and Introduction to This Issue of Seminars in Radiation Oncology, pp 215–222, Copyright (2008), with permission from Elsevier.

Ideal Candidate for SRS

Ideal Candidate for SRS in gliomas

1	2	3	4
Pilocytic Astrocytoma	LGG	New HGG	Recurrent HGG
1. Age < 18 yrs 2. Tumor Volume < 5 cc 3. No prior EBRT / Chemo 4. Non contrast enhancing tumor 5. SRS Dose > 15 Gy 6. Oligo histology		1. Good KPS 2. Small Volume 3. < 4cm in diameter 4. Atleast 5 mm away from BS / Optic pathway	1. Good KPS 2. Good response to initial ChemoRT 3. Long Interval to recurrence 4. Limited volume 5. Circumsribed recurrence

Fractionated SRS

Gliomas

- Pathology
- Neuro surgery
- Radiation Oncology
- Occupational Therapy
- Dosimetrist
- Medical Physics
- Neurocognition
- Physiotherapy