



# NSI Handbook of Stereotactic Radiosurgery

## Clinical Perspectives through Case- Based Practice

Compilations of the NSI CME on  
Radiosurgery and Pain, Vizag 2024

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Dr Deepak Agrawal



FIRST EDITION

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Case-Based Practice

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**DR DEEPAK AGRAWAL**

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Dr Deepak Agrawal

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Dr Deepak Agrawal asserts the moral right to be identified as author of this work.

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## DEDICATION

To my parents, whose guidance and support have been the foundation of my academic pursuits.

To our patients, whose experiences continue to inspire our commitment to research and discovery.



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# CONTRIBUTORS

**Deepak Agrawal, MBBS, MS, MCh**

Professor, Department of  
Neurosurgery & Gamma-Knife,  
JPN Apex Trauma Centre, AIIMS,  
New Delhi

**Kshitij Agarwal, MBBS**

Junior Resident, Department of  
Neurosurgery & Gamma-Knife,  
AIIMS, New Delhi

**Chirag Bansal, MBBS**

Junior Resident, Department of  
Neurosurgery & Gamma-Knife,  
AIIMS, New Delhi

**Harsh Deora, MBBS, MCh**

Assistant Professor, Department  
of Neurosurgery, NIMHANS,  
Bangalore

**Debnarayan Dutta, MD**

Professor & Head, Department  
of Radiation Oncology, Amrita  
Institute of Medical Science, Kochi

**Syed Yasin Shahtaz Emanee, Ph.D**

Postdoctoral Fellow, Sree Chitra  
Tirunal Institute for Medical  
Sciences and Technology  
(SCTIMST), Trivandrum

**Kanwaljeet Garg, MBBS, MCh**

Associate Professor, Department of  
Neurosurgery & Gamma-Knife,  
AIIMS, New Delhi

**Pawan Goyal, MBBS, MS**

Senior Consultant, Department of  
Neurosurgery, Artemis Hospital,  
Gurgaon

**Sarvesh Goyal, MBBS, MS**

Senior Resident, Department of  
Neurosurgery & Gamma-Knife,  
AIIMS, New Delhi

**Aditya Gupta, MBBS, MCh**

Director, Neurosurgery and  
CyberKnife Centre, Artemis  
Hospital, Gurgaon

**Shashank Sharad Kale, MBBS, MS, MCh**

Professor & Head, Department of  
Neurosurgery & Gamma-Knife,  
AIIMS, New Delhi

**Rakshay Kaul, MBBS**

Junior Resident, Department of  
Neurosurgery & Gamma-Knife,  
AIIMS, New Delhi

**Shweta Kedia, MBBS, MS, MCh**

Additional Professor, Department of  
Neurosurgery & Gamma-Knife,  
AIIMS, New Delhi

**Shiva Krishna, MBBS**

Junior Resident, Department of  
Neurosurgery & Gamma-Knife,  
AIIMS, New Delhi

**Chandra Kiran A, MBBS, MCh**

Senior Resident, Department of  
Neurosurgery & Gamma-Knife,  
AIIMS, New Delhi

**Sandeep Mishra, MBBS, MS**

Senior Resident, Department of  
Neurosurgery & Gamma-Knife,  
AIIMS, New Delhi

**Ranjith K. Moorthy, MCh**

Professor & Head, Department of  
Neurological Sciences, Christian  
Medical College, Vellore

**Gopishankar Natanasabapathi, PhD**

Associate Professor, Department of Radiation Oncology (Medical Physics), IRCH, AIIMS, New Delhi

**Abhilash Reddy, MBBS, MS, MCh**

Senior Resident, Department of Neurosurgery & Gamma-Knife, AIIMS, New Delhi

**Keyur Gopal Bhai Shah, MCh**

Chief Resident, Department of Neurosurgery, NIMHANS, Bangalore

**Prachi Singh, MBBS**

Junior Resident, Department of Neurosurgery & Gamma-Knife, AIIMS, New Delhi

**Dattaraj P Sawarkar, MBBS, MS, MCh**

Associate Professor, Department of Neurosurgery & Gamma-Knife, AIIMS, New Delhi

**Hanok Srithej, MBBS**

Junior Resident, Department of Neurosurgery & Gamma-Knife, AIIMS, New Delhi

**Sanjeev Srivastava, MBBS, MCh**

Senior Consultant, Department of Neurosurgery, Artemis Hospital, Gurgaon

**Mahnaaz Sultana, MBBS, MS**

Senior Resident, Department of Neurosurgery & Gamma-Knife, AIIMS, New Delhi

**Manjul Tripathi, MCh**

Additional Professor, Department of Neurosurgery & Gamma-Knife, PGIMER, Chandigarh

**Onam Verma, MBBS**

Research Fellow, University of Virginia, USA

**Satish Verma, MBBS, MCh**

Additional Professor, Department of Neurosurgery, AIIMS, New Delhi

## PREFACE

Stereotactic radiosurgery, particularly with the Gamma Knife, has significantly changed the way neurosurgeons treat a wide range of conditions. It offers high precision, safety, and long-term effectiveness. Today, it plays a role in nearly half of all neurosurgical cases, and its use continues to grow as diagnostic tools become more advanced. What sets Gamma Knife apart is that it was developed specifically for neurosurgeons and is operated by them, making it a uniquely tailored platform in neurosurgical care.

This handbook was created to support that growing shift. As stereotactic radiosurgery becomes more central to patient management, it is important for all neurosurgeons to understand when and how to use it. Even those who do not practice it directly will find value in knowing how to guide referrals and make informed decisions about treatment options.

The content in this book is based on lectures delivered during workshops conducted by the Neurological Society of India. Each chapter presents a real case to illustrate the clinical process. This case-based format helps bridge the gap between theory and practice. It brings clarity to planning, execution, and follow-up in radiosurgical care.

Whether you are just starting out or have years of experience, we hope this book provides useful guidance and strengthens your ability to care for patients with confidence and precision.





It is a matter of profound professional fulfilment and academic pride to present the NSI Handbook of Stereotactic Radiosurgery: Clinical Perspectives through Case-Based Practice. Spearheaded by Dr. Deepak Agrawal, this publication stands as a testament to the Neurological Society of India's commitment to advancing neurosurgical knowledge and promoting best practices in contemporary care.

Stereotactic radiosurgery (SRS) has redefined neurosurgical treatment paradigms, offering precision-based interventions across a spectrum of intracranial conditions. Despite its wide-ranging applications from tumors to vascular and functional disorders—its intricacies often remain underexplored beyond specialized circles. This handbook bridges that gap, transforming complex theory into applied wisdom through compelling, case-driven narratives.

Organized into focused sections, the volume navigates core principles, evolving technologies, and clinical strategies with clarity and depth. Its case-based approach makes it especially valuable connecting evidence to patient outcomes, and demonstrating how thoughtful planning and multidisciplinary expertise lead to effective care.

A notable strength lies in its diverse authorship. Contributors from across India's leading institutions bring a wealth of experience and varied perspectives, showcasing the maturity and versatility of SRS practice nationally. Their insights imbue the handbook with relevance both locally and globally.

Dr. Agrawal's editorial leadership deserves high praise. His vision, precision, and academic rigor have shaped this work into a resource that will serve learners and seasoned practitioners alike. I am confident it will become a reference of choice in neurosurgical settings across the country.

On behalf of the Neurological Society of India, I proudly endorse this publication. It exemplifies our shared mission to foster excellence, support innovation, and advance clinical neuroscience for the benefit of patients everywhere.

**Dr. Manas Panigrahi**

President, Neurological Society of India  
Senior Consultant Neurosurgeon,  
KIMS Hospitals, Hyderabad





Radiosurgery is an inseparable and important subspecialty of Neurosurgery. It is a non-invasive technique designed to deliver high-dose radiation to precise intracranial targets while sparing surrounding healthy tissue. Originally conceptualized by Professor Lars Leksell, this subspecialty has become immensely popular in the treatment of benign tumors, vascular malformations, a few malignant diseases, and has emerging indications. The concept of radiosurgery has also expanded from a single-session treatment to a treatment with limited fractionations. Using volume and dose fractionations, larger volumes are being treated. At the same time, many different technologies have been designed to deliver this treatment.

The Neurological Society of India organized a 2 day CME at Vizag in 2024 to discuss the present role of Radiosurgery in the treatment of various diseases. It was attended by seventy delegates from over the country, and was an immensely successful program. I congratulate and thank Prof Deepak Agrawal for collating the proceedings of the conference into a book. This will be of invaluable benefit to the postgraduates and neurosurgeons alike, and will help as a reference guide for years to come.

**Dr. Paritosh Pandey**

Honorary Secretary,  
Neurological Society of India  
Consultant,  
Department of Neurosurgery and Neurointervention,  
Manipal Hospital,  
Old Airport Road, Bangalore



# LIST OF ABBREVIATIONS

<b>Abbreviation</b>	<b>Full Form</b>
AIIMS	All India Institute of Medical Sciences
BPNST	Benign Peripheral Nerve Sheath Tumor
CNS	Central Nervous System
CT	Computed Tomography
CTV	Clinical Target Volume
DIBH	Deep Inspiratory Breath Hold
ETV	Endoscopic Third Ventriculostomy
FLAIR	Fluid-Attenuated Inversion Recovery
FOV	Field of View
GK	Gamma Knife
GTV	Gross Tumor Volume
HSRT	Hypofractionated Stereotactic Radiotherapy
ICC	Intracranial Compartmental Cavity
IJNT	Indian Journal of Neurotrauma
JPN	Journal of Pediatric Neurosciences
JPNS	Journal of Peripheral Nerve Surgery
LINAC	Linear Accelerator
MPR	Multi-Planar Reconstruction
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NIH	National Institutes of Health
NSI	Neurological Society of India
PET	Positron Emission Tomography
PNS	Peripheral Nervous System
PTV	Planning Target Volume
QOL	Quality of Life
RF	Radiofrequency
ROI	Region of Interest
RT	Radiotherapy
SBRT	Stereotactic Body Radiation Therapy
SRS	Stereotactic Radiosurgery
T1W	T1-Weighted Imaging
T2W	T2-Weighted Imaging
TRUS	Transrectal Ultrasound
WBRT	Whole Brain Radiotherapy
WHO	World Health Organization



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The editors gratefully acknowledge the Neurological Society of India (NSI) for its continued encouragement and support. The content of this volume draws upon the lectures and discussions presented at the 7th Super Specialty CME on Radiosurgery and Pain, Vizag 2024, convened under the auspices of the NSI. The Society has provided a valuable platform for advancing clinical exchange and education in stereotactic radiosurgery.

We extend our sincere appreciation to the contributors whose scholarly insights, case presentations, and commentaries have enriched this work. Their collective efforts reflect the breadth and depth of radiosurgical practice across the country.

We also record our gratitude to the patients whose clinical journeys form the basis of many of the cases and perspectives included herein. Their experiences continue to inform our understanding and guide progress in the field.

**Deepak Agrawal**



SECTION I

# Foundations of Radiosurgery



# Introduction of Radiosurgery to Neurosurgeons

Onam Verma ■ Manjul Tripathi

## INTRODUCTION

Stereotactic radiosurgery (SRS) unites the principles of stereotaxy (3D target localization) with high-dose focused radiotherapy to ablate or biologically modify intracranial targets without open surgery. By delivering a concentrated ionizing radiation dose to a small volume, SRS achieves an effect akin to a surgical lesion while minimizing damage to adjacent brain structures. The term was coined by Swedish neurosurgeon Lars Leksell, who, together with physicist Börje Larsson, developed the first dedicated SRS device (the Gamma Knife) in the 1950s–1960s.<sup>1</sup> The Leksell Gamma Knife, first used clinically in 1967, utilized multiple Cobalt-60 sources arrayed in a hemisphere to converge gamma rays on a target point. This invention provided neurosurgeons a “scalpel made of rays,” enabling treatment of deep or surgically inaccessible lesions with unprecedented precision. Over the ensuing decades, SRS has evolved with imaging and technological advances, but Leksell’s core concept endures as an indispensable tool in neurosurgery.

### **Radiosurgery vs. Conventional Radiotherapy (Table 1.1)**

Unlike conventional fractionated radiotherapy (which delivers 1.8–2 Gy per session over several weeks), SRS delivers a very high dose (often  $\geq 12$ –25 Gy) in a single session (or a few sessions, in hypofractionated SRS). This high dose per fraction causes direct DNA double-strand breaks and disrupts tumor microvasculature, leading to secondary ischemic and immunogenic effects, in contrast to the gradual accumulation of sublethal damage in fractionation. Classic radiobiological principles (“5 R’s” of repair, redistribution, reoxygenation, repopulation, radiosensitivity) apply differently: in single-dose SRS, there is minimal opportunity for tumor cell repair or regrowth between fractions, and hypoxic radioresistance is partly overcome by the intense dose delivery. Endothelial apoptosis and vascular occlusion are prominent at doses  $>8$ –10 Gy, causing tumor angiogenic shut-down, while high-dose radiation may also stimulate anti-tumor immune responses (including occasional abscopal effects where untreated lesions regress). These unique radiobiological effects underlie

TABLE 1.1 ■ Radiosurgery vs Conventional Radiotherapy

Parameter	Radiosurgery (SRS)	Conventional Radiotherapy
Dose per session	12–25 Gy	1.8–2 Gy
Number of sessions	1–5	20–30
Precision	Sub-millimeter	Millimeter
Mechanism	Direct DNA damage, vascular shutdown	Sublethal DNA damage accumulation
Treatment duration	Single day	Several weeks

SRS's capacity to control certain tumors and AVMs that might tolerate lower-dose fractionated radiation. On the other hand, single-fraction treatment demands stringent precision to avoid normal tissue injury, achieved through rigid immobilization and sophisticated treatment planning.<sup>2</sup>

### Radiosurgical Technologies

Multiple platforms deliver SRS, all aiming for sub-millimeter targeting accuracy but with differing mechanisms (Table 1.2)

#### Indications

Initially limited by crude imaging and device constraints, SRS now has a broad range of accepted indications in neurosurgery, expanding dramatically from its initial use in functional disorders. Today, its indications span four major categories:

1. Benign Tumors: This is the most common category.
  - Vestibular Schwannomas (VS): SRS is a primary treatment option for small- to medium-sized VS, offering excellent tumor control rates (>95%) with high rates of facial nerve and useful hearing preservation.<sup>3</sup>
  - Meningiomas: Particularly effective for skull base meningiomas where complete surgical resection carries high morbidity. SRS provides durable tumor control and is an excellent option for residual or recurrent tumors.<sup>4</sup>
  - Pituitary Adenomas: For both secreting and non-secreting adenomas, SRS can provide tumor control and, in functional adenomas, biochemical remission, especially for Cushing's and acromegaly.<sup>5</sup>
2. Malignant Tumors:
  - Brain Metastases: This is now one of the most common indications for SRS worldwide. For patients with a limited number of metastases, SRS offers high rates of local control, often obviating the need for whole-brain radiation therapy (WBRT) and its associated cognitive decline.<sup>6</sup>
  - Glioblastoma: SRS is used as a boost therapy for recurrent tumors or as part of the initial treatment in select cases.
3. Vascular Malformations:
  - Arteriovenous Malformations (AVMs): SRS is the treatment of choice for deep-seated, eloquent, or surgically inaccessible AVMs. It induces

TABLE 1.2 ■ Comparison of Stereotactic Radiosurgery Platforms

Platform	Radiation Source & Delivery	Targeting Method	Typical Uses	Accuracy
Gamma Knife <sup>1</sup>	192 Co-60 gamma ray sources in hemispheric array (fixed installation) – spherical dose focus via collimator helmets (4–16 mm sizes).	Rigid stereotactic frame (or mask in Icon) with MRI/CT targeting. Automated sector collimators in latest models.	Intracranial lesions exclusively. Gold standard for brain mets, AVMs, small tumors, functional targets.	~0.3 mm (very high precision, steep dose fall-off).
LINAC (Novalis, etc.)	High-energy X-ray photon beam from linear accelerator, shaped by cones or multileaf collimators. Gantry rotation/arcs for dose convergence.	Frameless (mask) or frame-based; image-guided positioning (X-ray/CBCT) before each treatment arc. Often one isocenter with multiple arc arrangements.	Intracranial and also body SRS/SBRT. Versatile (brain tumors, spine mets, etc.) in centers without dedicated GK.	~1 mm (depends on imaging and delivery; modern systems highly accurate).
CyberKnife	Mini 6 MV LINAC on a six-axis robotic arm; delivers many non-coplanar beams with real-time image guidance.	Frameless; uses skull-based image tracking or fiducials. The robot adjusts beam aim continuously for any movement.	Intracranial and spinal tumors, can also treat lung/liver, etc. Excellent for patients who cannot tolerate frame fixation; allows multi-fraction SRS.	~0.5 mm (very high, with continual motion correction).
ZapX	Self-shielded 3 MV gyroscopic LINAC	Frameless thermoplastic mask with integrated stereoscopic kV X-rays + cone-beam CT; 6-DOF robotic couch and automatic intra-fraction position monitoring	Dedicated cranial/upper cervical SRS; attractive where a shielded bunker or cobalt source is impractical	Sub-millimetric ( $\leq 0.5$ mm) isocentre targeting accuracy demonstrated in commissioning and clinical QA

progressive thrombosis, leading to obliteration in approximately 80% of cases within 2–3 years.<sup>7</sup>

#### 4. Functional Disorders:

- **Trigeminal Neuralgia:** SRS targeting the trigeminal nerve root provides pain relief in over 80% of patients and remains a primary option for those who are not candidates for or have failed microvascular decompression.<sup>8</sup>
- **Movement Disorders & Epilepsy:** Radiosurgical thalamotomy for essential tremor and corpus callosotomy for drop attacks are established procedures. Its use in mesial temporal lobe epilepsy is also a valuable alternative to open surgery in select patients.<sup>9,10</sup>

In summary, SRS (especially Gamma Knife) has become an integral modality in neurosurgery, enabling treatment of a spectrum of intracranial pathologies with proven efficacy and an expanding clinical evidence base.<sup>11,4</sup> However, its optimal

integration with microsurgery and other therapies requires nuanced decision-making, as discussed below.

## CONTROVERSIES

Despite the maturation of radiosurgery, several management controversies persist in neurosurgical practice. Key debates revolve around “*Radiosurgery versus Microsurgery*” and “*Radiosurgery versus Observation*” in specific conditions. Some common scenarios are discussed below -

### Vestibular Schwannoma

For small tumors (<2 cm), SRS offers ~95% tumor control with 98–100% facial nerve preservation and 60–70% hearing preservation when performed early. Microsurgery carries a 10–20% risk of facial nerve palsy and greater hearing loss. Observation risks delayed growth in ~50% over 5 years. SRS is increasingly preferred for Koos I–II tumors in younger/fit patients; surgery reserved for larger (>3–4 cm) or cystic lesions<sup>3</sup>.

### Incidental Meningioma

SRS achieves >90% control with low risk in skull base or eloquent regions. Observation is often sufficient in elderly with static tumors. Treatment decisions hinge on growth, location, and potential impact. No Class I evidence exists for timing, making multidisciplinary discussion crucial<sup>4</sup>.

### Trigeminal Neuralgia (TN)

GKRS (70–90% pain relief) is non-invasive with low risk, ideal for elderly or unfit patients. MVD offers 80–95% immediate relief but is invasive. TN secondary to MS/tumors often responds better to SRS. Repeat GKRS is feasible; repeat MVD riskier<sup>5</sup>.

### Movement Disorders

GK thalamotomy offers >80% tremor reduction in essential tremor but is limited to unilateral use. DBS allows bilateral, adjustable therapy. Radiosurgery has delayed effects and irreversible lesions but is suitable for elderly or high-risk patients. MRg-FUS now adds to the non-invasive lesioning arsenal<sup>6</sup>.

### Epilepsy

In MTL, resection offers ~60–80% seizure freedom. SRS has delayed effects (~24% at 1 year, possibly higher over time) and better cognitive preservation. In HH and deep lesions, SRS is favored. ROSE trial supports surgery first-line, SRS for select or high-risk patients<sup>7</sup>

Each of the above scenarios underscores a common theme: patient selection and multidisciplinary evaluation are critical. The “turf” battle that once existed – radiosurgery vs surgery as competing approaches – is gradually giving way to a more nuanced understanding of when each modality is optimal. For example, an experienced neurosurgical team will weigh tumor size, location, patient age, medical comorbidities, and patient preferences when deciding between SRS and open surgery. Sometimes combined approaches are used (resection of a large tumor followed by SRS to residual tumor or tumor bed). The controversies continue to be studied, but increasing evidence and longer follow-up are helping to clarify best practices. Neurosurgeons must stay abreast of current outcome data to make informed recommendations rather than defaulting to one approach based on training bias. In summary, while SRS has firmly established its role, its proper integration with traditional neurosurgery in certain cases remains an area of healthy debate and research.

## CURRENT PRACTICE

Modern radiosurgery practice reflects over half a century of accumulated experience, yielding refined protocols and expanding indications. Gamma Knife radiosurgery (GKRS) in particular has set benchmarks for clinical efficacy and safety in many conditions, supported by large series and long-term follow-ups.<sup>11</sup>

### Standard of Care for Many Lesions

SRS is no longer experimental – it is an accepted standard option for many intracranial pathologies. For instance, small vestibular schwannomas are now commonly managed with upfront radiosurgery in suitable patients, with outcomes that have made it a first-line therapy at many centers.<sup>12</sup> Similarly, SRS is an established definitive treatment for many skull base meningiomas that are difficult to completely resect; tumor control rates ~90% at 5–10 years have been consistently reported for such benign tumors after radiosurgery.<sup>11</sup> For residual or recurrent tumor after microsurgery (e.g. a subtotally resected meningioma or pituitary adenoma), adjunctive radiosurgery is routinely employed to prevent further growth. In vascular neurosurgery, SRS for AVMs is standard for unresectable lesions <3 cm, and even larger AVMs are being tackled with volume-staged SRS or hypo-fractionated schedules to improve safety.<sup>3</sup> Multiple brain metastases are now frequently treated with radiosurgery alone, deferring or avoiding whole-brain radiotherapy – a major shift supported by clinical trials showing preservation of cognitive function without compromising survival.

### Technological Advancements

The precision and practicality of radiosurgery have improved with each generation of technology. The Gamma Knife Perfexion (2006) and Icon (2015) models introduced fully automated collimation, expandable cranial reach, and integrated imaging for setup, dramatically reducing treatment times and enabling single-session

treatment of dozens of lesions. The Icon's mask system and optical tracking allow fractionated SRS when needed (e.g. for larger tumors close to sensitive structures), blending the radiobiological advantages of SRS with fractionation's safety – for example, hypofractionated GK treatments (3–5 fractions) are being used for sizable metastases or skull base tumors near the optic chiasm.<sup>7</sup> LINAC systems, with image-guidance and beam-shaping, now achieve similar dosimetric precision for intracranial targets, making high-quality SRS more accessible in centers without Gamma Knife. CyberKnife systems are treating an increasing volume of intracranial cases, especially when frameless convenience or extra-cranial reach is desired. As a result, more patients than ever have access to radiosurgery, and referral patterns have changed – it is not unusual for a patient with a newly diagnosed small brain tumor to be referred to a radiosurgery center as the preferred initial management. This widespread adoption has been facilitated by improved training and awareness among neurosurgeons.

*Outcomes and Follow up:* Accumulated data have reinforced that when applied to appropriate indications, SRS yields outcomes on par with surgery for tumor control, with generally lower risk of serious complications. Long-term tumor control rates ~90–95% are observed in benign tumors like vestibular schwannoma and meningioma,<sup>11</sup> while 1-year local control for metastases is ~85% or higher in modern series. Even functional outcomes, such as pain relief in trigeminal neuralgia or tremor reduction, are very favorable in properly selected patients. The flip side is that radiosurgery outcomes are highly operator-dependent – meticulous treatment planning by an experienced team is essential to maximize efficacy and minimize adverse effects. Radiation-induced complications do occur, but their rates are low. Examples include peritumoral edema or radiation necrosis (most often in large metastases or meningiomas, incidence ~5–10% depending on size/dose), cranial neuropathies (e.g. a small risk to hearing in vestibular schwannoma treatments, which is correlated with cochlear dose<sup>5</sup>), or pituitary hormone deficits after pituitary adenoma SRS. These risks are well-characterized and generally acceptable compared to surgical risks, but they require careful patient counseling and monitoring. Follow-up protocols typically involve MRI at intervals (e.g. 6 months, 12 months, then yearly) to track lesion response. It's worth noting that the radiographic response to SRS can be variable – some tumors shrink, many remain stable in size, and some initially enlarge due to benign radiation effect (“pseudoprogession”) before later stabilizing. Neurosurgeons must recognize these patterns to avoid premature surgical intervention on a tumor that is actually responding to treatment.

## Training and Education

One practical aspect of current practice is that neurosurgical training is gradually incorporating radiosurgery. In some regions (including India), formal fellowships in SRS are still limited, and many neurosurgeons learn on the job or via short courses and workshops. The Neurosurgery community, through societies like the International Stereotactic Radiosurgery Society (ISRS) and Leksell Gamma Knife Society, has increased focus on training opportunities, recognizing that familiarity with ra-

diosurgery is now expected of contemporary neurosurgeons. The NSI (Neurological Society of India) has also integrated basic radiosurgery concepts into neurosurgery curricula. This chapter itself is an example of educational efforts to introduce radiosurgery principles to neurosurgeons who may not have had extensive exposure during residency.

In summary, the current practice of radiosurgery is characterized by its mainstream status in neurosurgical care, refined techniques that maximize therapeutic ratio, and a rich evidence base demonstrating effective outcomes. As technology and techniques continue to advance (e.g. incorporation of imaging advances like diffusion tractography to avoid critical white matter tracts, use of radiogenomic markers to predict response, etc.), one can expect the indications for radiosurgery to further widen. The challenge for neurosurgeons is to stay current with these developments and to judiciously integrate radiosurgery into patient management algorithms alongside microsurgery, rather than viewing it as a competitor. When used appropriately, SRS is a powerful complement that extends the therapeutic reach of neurosurgery beyond the limits of the scalpel.

## LEARNING POINTS

- **Patient Selection is Paramount:** SRS is a powerful tool, not a panacea. The key to success lies in meticulous patient selection and understanding when SRS is superior, equivalent, or inferior to microsurgery or other alternatives.
- **Latency of Effect:** Unlike surgery, the effects of SRS are not immediate. Tumor control and AVM obliteration occur over months to years. This latency period must be clearly communicated to patients.
- **Unique set of Complications:** Be prepared to manage post-SRS complications. Radiation-induced edema is common and usually managed with steroids. Radiation necrosis is a more serious, albeit rarer, complication that may require medical management or even surgical resection.
- **Multidisciplinary Collaboration:** Optimal SRS practice requires seamless collaboration between neurosurgeons, radiation oncologists, medical physicists, and neuroradiologists.
- **Rapidly Evolving Technology:** The field is constantly evolving with advances in imaging, planning software, and delivery systems. Continuous learning is essential to providing the best care.
- **Future Perspectives:** SRS continues to evolve, with ongoing research into dose optimization, combination therapies (e.g. SRS plus immunotherapy for metastases), and new indications. The neurosurgeon's role is expanding from just operative care to *radiosurgical care* of patients. By understanding and utilizing radiosurgery, neurosurgeons can offer truly comprehensive treatment options – ranging from open surgery to radiation – tailoring the approach to each patient's condition. In modern neurosurgical practice, competence in SRS is increasingly important, ensuring that patients receive the least invasive yet effective therapy for their illness.

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# Radiobiology of Radiosurgery

Debnarayan Dutta

## INTRODUCTION

### Basic Principles of Radiobiology

In early days of radiation therapy practice, physicians experienced that larger dose (time of treatment) in one day (fraction) causes high skin reactions.<sup>1-2</sup> However, smaller doses (time of treatment) for multiple days don't cause skin reactions, but the mass (tumour) shrinks in size (response to treatment). Hence, the concept of fractionation and radiobiology of fractionated radiation therapy was developed based on clinical observations. Radiobiology evolved as a mathematical model to evaluate different dosage schedules (dose per fraction and number of fractions), calculate equivalent dose schedule with different dose fractions and predict response to treatment as well as toxicity.<sup>3-4</sup> Radiobiology models are not only a mathematical model, but a clinical predictor model for response and toxicity.<sup>5</sup> Hence, radiobiology models are challenged with clinical outcome data and modifications of the models are considered based on clinical observations. Radiobiology for fractionated radiation therapy and radiosurgery are classic examples that clinical outcome dictates radiobiology models and dose equivalent calculations, not the radiobiology models restricted in prediction of the clinical outcome. Radiobiology calculation models are derivatives of clinical observations.<sup>6</sup> The impact of radiation and pathway is explained in Figure 2.1.

Radiobiology principles are based on '4 pillars of radiobiology', called the four "R"s of radiobiology.

The four "R"s (further detailed) are represented by

- Repair of sublethal damage
- Redistribution through parts of the cell cycle (with different sensitivities)
- Re-population of cells between successive radiation treatments
- Re-oxygenation of hypoxic cells.

### Repair of Sublethal Damage

Radiation-induced DNA damage is the most important cellular effect of the radiation, causing significant chromosomal alteration<sup>7</sup>. Although double-stranded DNA breaks are the most common cause of lethal cell injury, single-stranded breaks may

## How Radiation therapy works ?

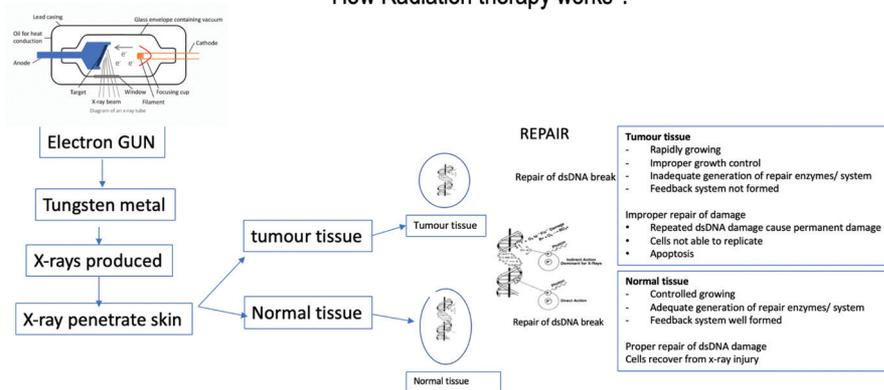


Figure 2.1 Pathway of radiation therapy.

accumulate and eventually cause lethal cell injury. The repair of sublethal damage is tissue-dependent (early versus late-responding) and mostly complete between 4-6 hours of RT (maximum of 24 hours). The terms '*sublethal damage*' and '*potentially lethal damage*' have been employed as designating repair of both the preceding cellular and molecular responses. Many incomplete DNA repairs occur within and after longer irradiation treatments.

### Redistribution Through Parts of the Cell Cycle (with Different Sensitivities)

Cells in different phases of cell cycle have different radiation sensitivity to radiation therapy, late S being more resistant, whereas G1 and early S being most sensitive.<sup>8</sup> Cells in the G1M phase are more sensitive to radiation therapy. Redistribution of cells to G1 phase during the long course of radiation therapy makes radiation therapy effective.

### Re-Population of Cells Appears Between Successive Radiation Treatments

Radiotherapy treatments are given in fractionated doses allowing the recovery of normal tissues between treatments. Nevertheless, surviving cancer cells will also proliferate during the intervals between the treatment itself and this process is called re-population, which means recovery from sublethal damage. Repopulation is an important cause of treatment failure.<sup>8</sup>

### Re-Oxygenation of Hypoxic Cells

Fractionated radiation therapy allows shrinkage of the tumour and allows the central necrotic part of the tumour to have better vascularization and oxygenation supply (re-oxygenation). Oxygen ( $O_2$ ) is a potent radio-sensitizer through free radicals

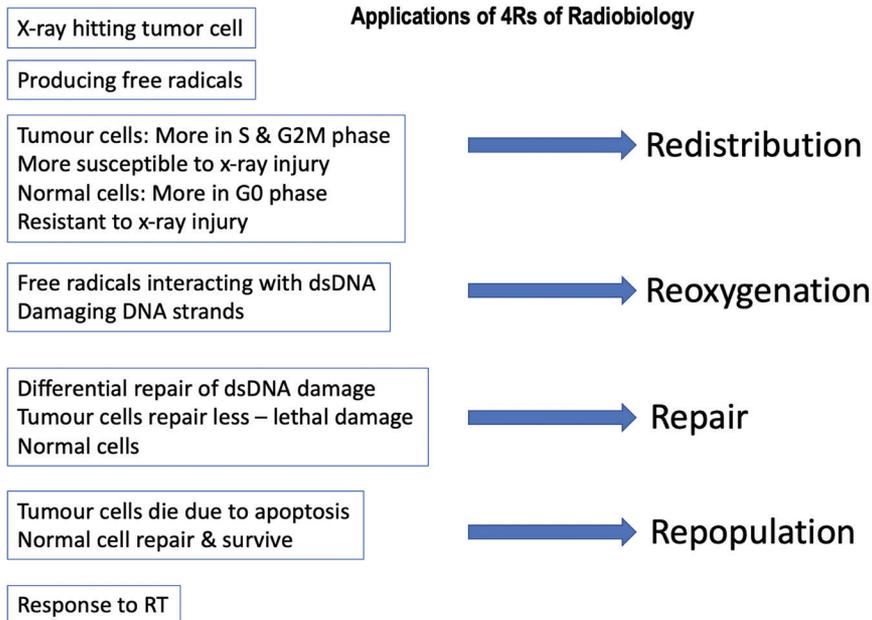
and its electron-affinity. Oxygen produces free radicals that cause DNA damage and improve the efficacy of radiation.<sup>9-10</sup>

**Tissue Radio-Sensitivity (the 5th R)**

Radio-sensitivity is classically defined as a relative susceptibility of cells, tissues, and organs to the effect of radiation<sup>11</sup>. Radio-sensitivity is different for different cell types. Radio-sensitive cells have high division rate (proliferation), high metabolic rate, and are well nourished (oxygenated). Higher radio-sensitive tissues respond to radiation therapy better (Figure 2.2).

**TYPES OF DAMAGE**

There are two types of radiation damage- 1) alpha-type damage and 2) beta-type damage<sup>12</sup>. The alpha/beta measures sensitivity of an endpoint to the effect of fractionating (capacity for repair). Alpha is the cell kill rate by a single hit mechanism, whereas beta-type damage is the rate of cell kill by a multiple hit mechanism.<sup>13</sup> Radiation can directly ionize an atom in the DNA molecule or indirectly affect the DNA by forming hydroxyl radicals. Cell death occurs due to apoptosis, autophagy, necrosis, senescence, and mitotic catastrophe. Alpha cell killing (direct kill) is the component that is less affected by fractionation. Hence, the high alpha/beta ratio would mean that alpha cell killing predominates. Cells with lower alpha/beta ratio will have better response with SABR (radiosurgery), whereas cells with higher



**Figure 2.2** Radiobiology for fractionated radiation and radiosurgery.

alpha/beta ratio will have better response with a fractionated schedule.<sup>14</sup> Increase in fractionation will improve therapeutic ratio if the surrounding tissue has a lower alpha/beta ratio than the target or tumor tissue. High alpha/beta (range 8–12) is for early responding tissues (tumor), which are rapidly proliferating and might further potentially benefit from fractionation. Late responding tissue has an alpha/beta of 2–4.<sup>15</sup> Benefit of fractionation is reduced for benign tumors because the alpha/beta ratio is similar for the target and the adjacent tissue.

## RADIOSURGERY AND RADIOBIOLOGY

Standard '4 Rs' of radiobiology applicable for radiosurgery as well. The '4 Rs' are – 1) Repair of sublethal damage, 2) Reassortment of cells within the cycle, 3) Repopulation, 4) Reoxygenation.

Radiobiological models are to establish the effect of radiation on tumour tissue & normal cells and calculation of equivalent radiation dose with different schedules. Radiobiology is to 1) Calculate dose schedules, 2) Response to different dose schedules & toxicity, 3) Effect on cells. Radiobiology is not only a mathematical model. Radiobiology is a clinical outcome prediction model. Conventional fractionation radiation therapy models are well established for comparing the response to treatment and toxicity.<sup>16-17</sup> However, radiobiology may not be completely understood in radiosurgery (Table 2.1).

### SABR and Repair

Tumor cells with lethal damage will lead to DNA breakage and cell death<sup>18</sup>. After sublethal radiation induced injury to both normal tissue and tumour tissue, both the tissue lineage undergo 'repair'. Normal cells with intact repair mechanisms have the potential for complete recovery and hence have minimal toxicity. However, tumour cells with impaired repair mechanism, cell repair after radiation is mostly incomplete and hence cells undergo apoptosis. There is a potential for tumour cells to repair after radiation (low dose or resistant disease) and hence have recurrence or failure of radiation therapy. Sublethal damage or potentially lethal damage repair after radiation therapy due to 'repair' mechanism continue to proliferate owing to

TABLE 2.1 Comparison of impact of 4Rs in Conv RT & SABR

	Conventional RT	SABR
Repair	Detrimental for cell kill	Short treatment time. Hence not applicable
Redistribution	Useful to increase radio sensitivity	Short treatment time. Hence not applicable
Reoxygenation	Useful to increase radio sensitivity	Short treatment time. Hence not applicable
Repopulation	Detrimental for cell kill	Short treatment time. Hence not applicable

the inadequate doses of radiation (or resistant disease), which results in tumor recurrence and metastasis. Repair compromises efficiency of radiation and reduces radio-sensitivity of tumors. In SABR, high-dose radiation per fraction is applied and total doses are delivered in 2–5 times fractions within a relatively short period, inducing more necrosis than apoptosis. Repair of tumor cells is almost impossible or very low incidence in shorter fractionation schedules. Majority of tumor cells will suffer from lethal damage leading to cell death. Hence, ‘repair’ does not work as a radiobiology model in radiosurgery (short course radiation).

### **SABR and Redistribution**

During long course (fractionated) radiation therapy sessions, tumor cells at G<sub>0</sub> stage of cell cycle accelerate into G<sub>2</sub>/M stage for replenishment or rebalancing (radiation-induced G<sub>2</sub>/M arrest). Tumor cells at G<sub>2</sub>/M stage are highly sensitive to radiation therapy. During conventional EBRT, sensitivity of radiation is potentially enhanced, as the proportion of tumor cells at G<sub>2</sub>/M stage increases. Redistribution of the cell cycle improves the killing ability of conventional multi-fractionated EBRT. In SABR (radiosurgery), the cell cycle is completely blocked at all stages after single higher-dose ablation radiation (e.g., >20Gy). Therefore, it is impossible for tumor cells’ redistribution since both sensitive and insensitive tumor cells are directly killed. Hence, ‘redistribution’ does not work as a radiobiology model in radiosurgery (short course radiation).

### **SABR and Reoxygenation**

Oxygenated tumor cells are sensitive to radiation therapy. In conventional EBRT with a fractionated schedule, as the tumor shrinks during the radiation course, tumor cells in hypoxic state re-oxygenate and are better killed by radiation therapy. Reoxygenation enhanced the killing effects in the setting of conventional fractionated EBRT. In SABR (Radiosurgery), owing to the relatively short duration the effect of re-oxygenation is significantly reduced. On the contrary, tumor hypoxia may persist after vascular injury (less oxygen supply) caused by SABR. In SABR, as direct cell kill is more predominant instead of free radical induced killing, the impact of oxygenation is minimal. Both oxygenated and hypoxic cells are ablated by high-dose radiation under SABR, resulting in highly efficient tumor killing. Hence, ‘reoxygenation’ does not work as a radiobiology model in radiosurgery (short course radiation).

### **SABR and Repopulation**

Sensitive tumor cells quickly enter the apoptosis state under conventional EBRT, leading to cell populations’ unbalance. In the beginning of homeostasis, tumor cells at the stationary stage proliferate to compensate for the loss of cell populations. Repopulation of tumor cells usually occurs in 2–3 weeks after conventional fractionated EBRT, depending on the fractionated radiation doses, total doses, pathological

types with increase of radiation resistance and decrease of killing effects. The SABR treatment scheme is usually within 2–5 fractions and completed within 1 week with no time to spare the tumor cells to start the repopulation process. Hence, repopulation may not be a useful model to explain the effectiveness of radiosurgery.

Relationship between biological effects of high dose per fraction radiation (Radiosurgery) and the actual clinical efficacy with SABR (Radiosurgery) could not be explained by the conventional LQ model.<sup>19</sup>

## **OTHER METHODS OF RADIOBIOLOGY IN RADIOSURGERY**

Explanations with conventional radiobiology concepts do not explain the efficacy of high dose per fraction (radiosurgery) radiation therapy. Hence, it is assumed that there are more methodologies involved in radiobiology of radiosurgery.<sup>18-19</sup>

### **Vascular Endothelial Injury theory**

Endothelial apoptosis regulates angiogenesis-dependent tumor growth, which only occurs at RT dose more than 8 Gy per fraction. Vascular injury occurs with dose more than 10 Gy per fraction, which induces hypoxia, acidification of tumor microenvironment, indirect death of tumor cells. High-dose RT delivered by SABR increased vascular permeability and apoptosis through the ceramide pathway, exacerbated platelet aggregation and thrombosis formation. High dose RT induced blood vessel injury and ischemia cause tumor necrosis (direct cell kill). Consequently, anti-tumor effects increase with radiosurgery through vascular injury and direct cell death.

### **Immune Activation theory**

Radiation therapy stimulates responses not only at the treatment site but also at the non-irradiated and remote tumor deposits, which is called “abscopal effect”. RT directly or indirectly activates inflammatory cytokine, e.g., IL-1 and TNF, and recruits immune cells, resulting in an intense CD8(+) T-cell tumor infiltrate and a loss of myeloid-derived suppressor cells. Tumor cells are ablated and tumor antigens are substantially released under high dose radiation, leading to immunogenic cell death and further release of tumor necrosis antigens and adenosine triphosphatase (ATP). Activation and release of these substances enhance the human immune responses and immune cells recruitment to the microenvironment. Radiosurgery through immune response increases the efficacy and clinical response.<sup>20</sup>

### **Dose-Effect Relationship Models in SABR**

LQ Model applicable for iso-effect dose calculation with conventional radiation therapy. Prerequisite of LQ model application is complete oxygenation of tumor cells during radiation and dose per fraction of 1 to 6Gy. In a fractional dose of more

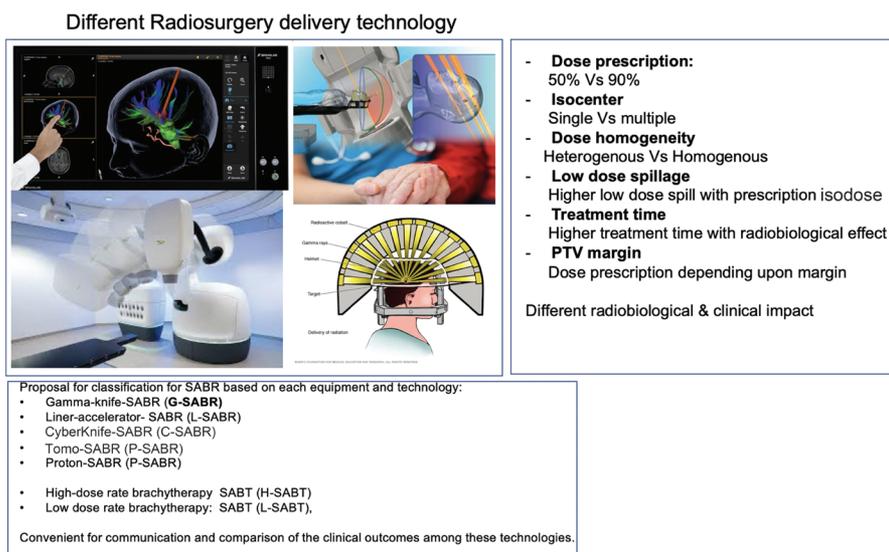
than 8–10Gy per fraction, the LQ model is inappropriate to predict the effects induced by RT. Some clinical studies find that the LQ model actually underestimates tumor control by SABR. In 2004, Guerrero and Li et al suggested a modified LQ model (MLQ) taking dose fraction size in consideration. In 2008, Park et al, introduced Universal Survival Curve model (USC model), which integrated LQ model with multi-target model, and incorporated effects by both low dose and high dose RT. In 2010, Wang et al, introduced the general LQ model (gLQ model), which used in all dose range indirect effects such as radiation-induced injury of blood vessels. However, all these proposed models are investigational and not yet used routinely in clinical practice.<sup>19</sup>

### Proposed Classification for SABR

There are different technologies for delivery of radiosurgery, such as gamma-knife, cyberknife, linac based SRS systems etc. All these technologies may have different radiobiological impact as there is variation in – 1) prescription isodose, 2) PTV margin, 3) low and high dose region, 4) treatment time, 5) fractionation schedule. Clinical efficacy and its side effects are quite variant based on the radiobiological effect in these technologies (Figure 2.3).<sup>20-21</sup>

*Proposal for classification for SABR based on each equipment and technology:*

- Gamma-knife-SABR (G-SABR)
- Liner-accelerator- SABR (L-SABR)
- CyberKnife-SABR (C-SABR)
- Tomo-SABR (T-SABR)



**Figure 2.3** Radiobiology implications of different radiosurgery technology.

- Proton-SABR (P-SABR)
- High-dose rate brachytherapy SABT (H-SABT)
- Low dose rate brachytherapy: SABT (L-SABT)

The classification may be convenient for communication and comparison of the clinical outcomes among these technologies.

In conclusion, the LQ model is still the basis for iso-effective dose calculation in SABR. However, the LQ model may under-estimate the effect of radiation in SABR. Newer models may be useful after validation in clinical trials. Dose prescription and distribution parameters may be different with different planning systems. There is a need for validation with clinical outcome data.

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# Gamma Knife: A Multisource Co-60 Irradiation-Based Radiosurgery Tool

Gopishankar Natanasabapathi ■ Shashank Sharad Kale ■ Deepak Agrawal

## INTRODUCTION

The term radiation applies to emission and propagation of energy through space or material medium. The radiation exists in the form particles or electromagnetic radiation (EM) or both. The type of radiation useful in health sector is available in the form of radioactive source e.g. Co-60 (e.g. gamma rays), Bremsstrahlung X-rays (e.g. high energy X-rays used in linear accelerator) and charged particle beams (e.g. P+, C-ion used for proton therapy or Carbon Ion Therapy). Stereotactic radiosurgery (SRS) or also known as radiosurgery (RS) was a concept envisioned by a team of neurosurgeons and physicists in Sweden about 75 years ago. Prof Leksell and his colleagues in Sweden in 1950s, pioneered the use of SRS, applying it mostly to gammathalamotomy in parkinsonism and cancer pain, vestibular schwannomas, arteriovenous malformations (AVM), Cushing's disease and craniopharyngiomas.<sup>1</sup> The SRS principle was to deliver highly focused radiation to precise targets in the brain while minimizing injury to adjacent areas. This chapter discusses how multiple sources of Co-60 gamma rays are used for SRS purposes.

## RADIATION PRINCIPLE

According to the radiation principle when X or Gamma ray beams pass through a medium, interaction between photons and matter can take place resulting in transfer of energy to the medium. Initial process in interaction is ejection of electrons from the atoms. These high-speed electrons transfer their energy by producing ionization and excitation of atoms along their paths.<sup>2</sup> If the absorbing medium consists of body tissues, enough energy may be deposited within its cells, destroying their reproductive capacity. In this interaction most of the absorbed energy is converted into heat, producing no biological effect. The radiation interaction of X or Gamma ray beam through medium is in general classified as:

- Interaction through medium is classified as:
  - Inelastic collisions with atomic electrons.
  - Ionization & Excitation

- Inelastic collisions with nuclei.
  - Bremsstrahlung
- Elastic collisions with atomic electrons
  - Rutherford scattering
- Elastic collisions with nuclei
  - Neutron Scattering - Billiard Ball Collision

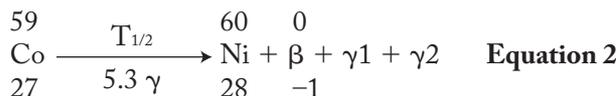
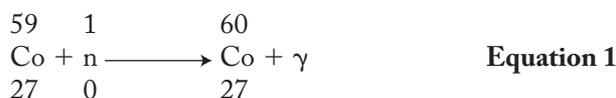
## IMPORTANCE OF CO-60 SOURCE AS A RADIATION TOOL

The photons used in radiosurgery are produced either by radioactive decay or by bremsstrahlung of accelerated photons. The use of Co-60 source for radiotherapy purpose is not a new concept. The history dates back to the 1950s when first Co-60 was used in external beam radiotherapy (teletherapy) machines that produced a beam of gamma rays which was directed into the patient's body to destroy tumor tissue.

The major difference between the cobalt source used in a telecobalt unit and a Gamma Knife (GK) is the number of sources used and the treatment area. A GK uses multiple sources (192 Co-60 sources in latest model) to treat brain lesions, while a telecobalt unit uses a single source to treat cancerous tumours.

The GK equipment is designed to use the gamma rays of 1.17 and 1.33 MeV emitted by the isotope Co-60 as it decays to Ni-60. The Co-60 radiation is essentially monochromatic and has fixed energy. The difference between photons produced by linear accelerator is that the radiation consists of a broad spectrum, the mean energy which can be varied. For photon energies above several hundred keV, the dose is low at the surface, rises to a maximum at some depth.

### Decay Process of Co-60 isotope



The  $\beta$  particles are absorbed in the cobalt metal and the stainless steel capsules result in emission of bremsstrahlung x-rays and small amount of characteristic x-rays in 0.1 MeV range which are strongly attenuated by source material and the capsule. There are other "contaminants" such as lower energy  $\gamma$  rays produced by the interaction of the primary  $\gamma$  radiation with the source itself, the surrounding capsule, the source housing and the collimation system.<sup>2</sup> Thus, the scattered components of the beam contribute significantly (~10 %) to the total beam intensity. The secondary interactions result in beam heterogeneity to some extent. In addition,

electrons are also produced by these interactions and constitute electron contamination of the photon beam.<sup>2</sup>

## STEREOTACTIC RADIOSURGERY (SRS)

Stereotactic radiosurgery (SRS) or also known as radiosurgery (RS) was a concept envisioned by a team of neurosurgeons and physicists in Sweden about 55 years ago. The SRS principle was to deliver highly focused radiation to precise targets in the brain while minimizing injury to adjacent areas. There are numerous stereotactic systems and frames for use in stereotactic radiosurgery. Few were intended to be used for stereotactic neurosurgery and applied directly to radiosurgery. Some required some degree of modification before applying to radiosurgery.<sup>1</sup> Some were developed solely for a particular radiosurgical situation. The Gamma Knife (GK) is a dedicated radiation delivery unit which uses a dedicated SRS frame.

The basic requirements for stereotactic systems are:

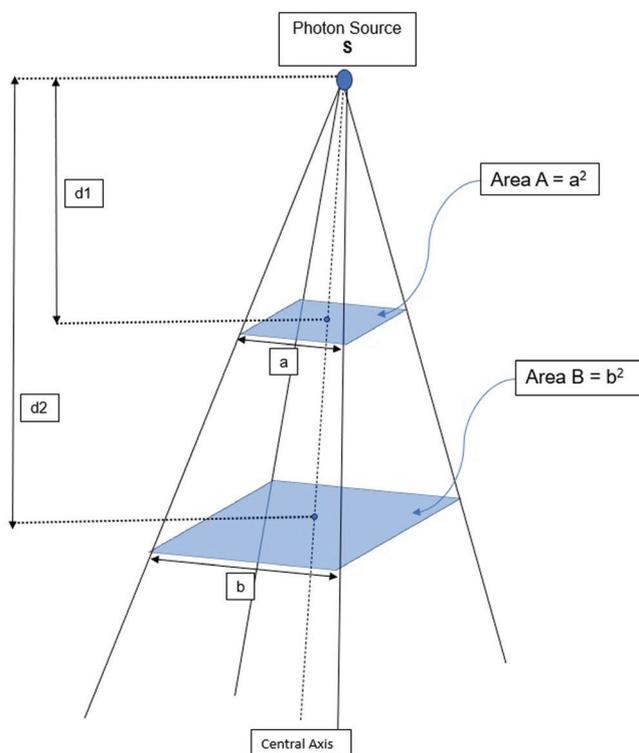
- To provide a unique and fixed reference frame relative to the brain.
- To provide the means by which the reference frame can be applied to radiological images of the brain and surrounding structures.
- To provide precise and accurate positioning for as many diagnostics and treatment procedures as necessary.

## WHY ARE MULTIPLE CO-60 SOURCES REQUIRED IN SRS?

The photons used in RS are produced either by radioactive decay or by bremsstrahlung of accelerated photons. The GK is designed to use the gamma rays of 1.17 and 1.33 MeV emitted by the isotope Co-60 as it decays to Ni60. The Co-60 radiation is essentially monochromatic and has fixed energy. The difference between photons produced by a linear accelerator (LINAC) is that the radiation consists of a broad spectrum, the mean energy which can be varied. For photon energies above several hundred keV, the dose is low at the surface, rises to a maximum at some depth.

The major difference between the SRS performed with GK and LINAC radiosurgery is the radiation source used in each technique and how the beams are delivered. With GK using multiple fixed cobalt source beams radiation converges from various angles to create a very focused beam, while a LINAC uses a single moving radiation source (X-Ray beam or electron beam) to target the tumour from different positions (i.e. LINAC rotate around the patient to target tumor from different directions), allowing for greater flexibility in treating larger or more complex lesions; both are used for highly precise radiation therapy, but GK is typically preferred for smaller brain tumours due to its sharper dose fall-off, minimizing damage to surrounding tissue.

Irrespective of the delivery technique the radiation beam emitted from a single photon source is divergent by nature. As the depth increases the beam expands. Figure 3.1 demonstrates the divergent photon beam originating from a photon point source (S). The square field area with side  $a$  (area  $A = a^2$ ) defined at distance  $d_1$  from the source



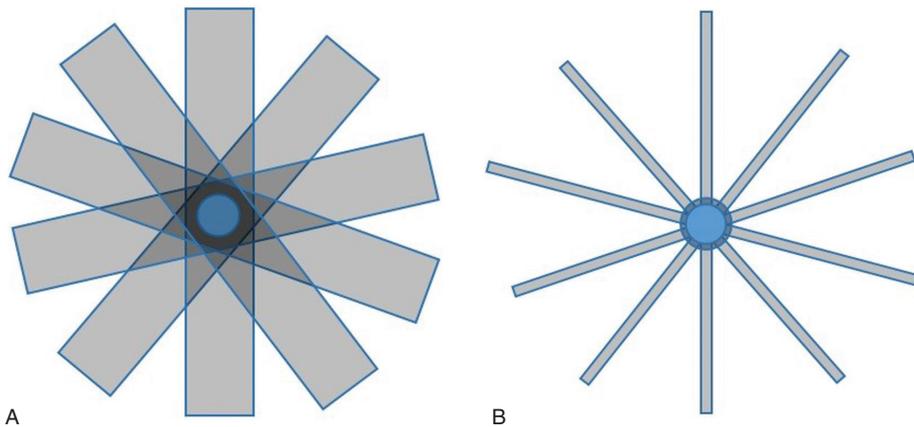
**Figure 3.1** Single point source and its divergence principle.

and square field area with side  $b$  (area  $B = b^2$ ) defined at distance  $d_2$  from the source. This concept is applicable in telecobalt unit. The typical Co-60 source used in teletherapy is a cylinder of diameter ranging from 1.0 cm to 2.0 cm<sup>3</sup>.

As far as the radiation defining field sizes (FS) used in SRS are concerned they are smaller in dimensions in comparison with FS used in conventional radiotherapy technologies such as in 3DCRT, IMRT or VMAT.

The figure 3.2A explains the multiple broader radiation beams irradiating a target (blue circle) from various angles. Due to broader beam width in each field, there is overlap of beams beyond the intended target. The main reason for radiation dose spillage to adjacent critical organs. Whereas figure 3.2B illustrates the multiple narrow beams irradiating the same target from various angles yet contributing significantly lesser dose to adjacent critical organs.

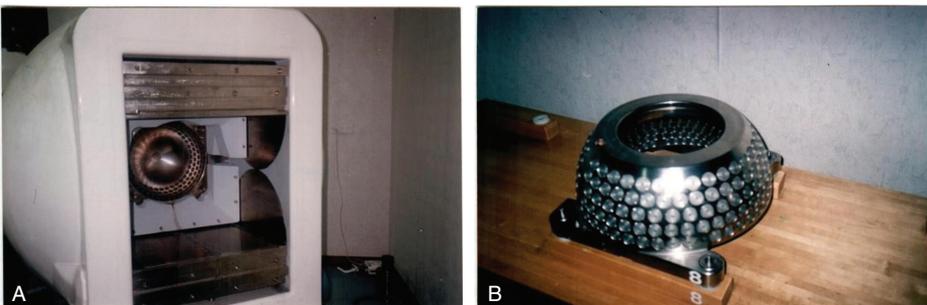
In order to make smaller radiation beams and at the same time having more penetration Co-60 beams are of the best choice. High specific activity of some radionuclides has several advantageous for a numerous application.<sup>2</sup> The activity per unit mass of a radionuclide is known as specific activity. The reason for Co-60 has a radiation source is due to its higher specific activity. The total activity of the GK is specified to 6000 Ci + 10 % ( $2.22 \times 10^{14}$  Bq + 10%).



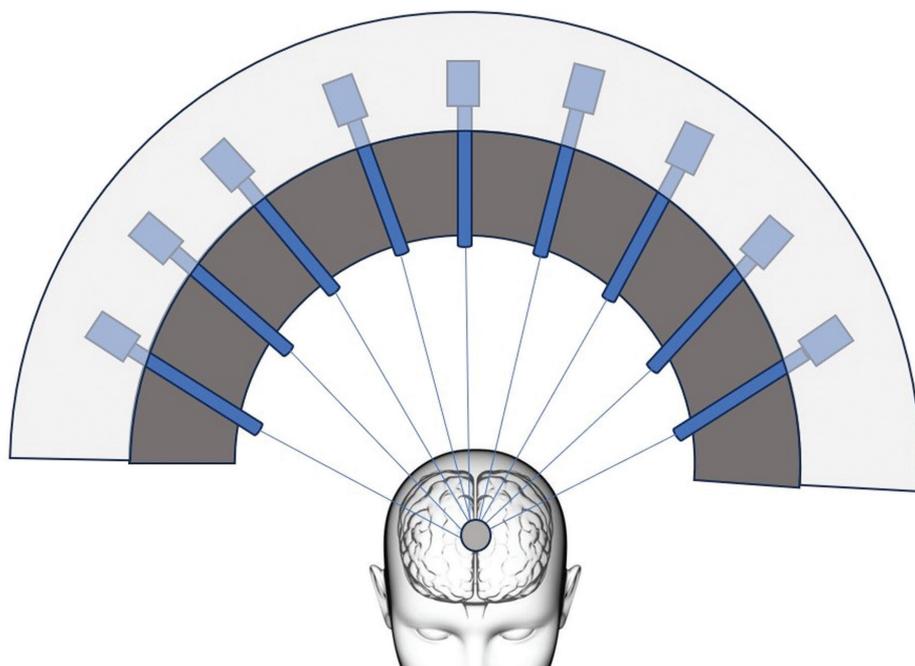
**Figure 3.2** (A) Multiple broad beams irradiating a target (Blue Circle). Additional radiation (shadow regions) extending beyond the target. Reason for dose spillage to adjacent critical organs. (B) Multiple narrow beams irradiating a target (Blue Circle). Significantly lesser shadow region in comparison with broad beams as shown in figure 3.1.

In the case of GK, smaller intracranial lesions are targeted by multiple gamma rays emitting Co-60 sources from various angles similar to the analogy shown in Figure 3.2A.

Figure 3.3A shows the internal central body region of the GK Model B unit. Within the central body, 201 Co-60 sources are positioned in a specific angle and orientation to focus the radiation at the isocentre which coincides with the mechanical unit centre point (UCP) of the GK. The shielding door in the front region closes after the treatment is delivered for the patient. In the latest GK Model ICON the central body holds 192 Co-60 sources. The multiple sources are further directed towards the UCP through secondary and tertiary collimator assembly made of tungsten material. Figure 3.3B represents a tertiary collimator helmet which is generally set on the treatment couch and moves towards the central body of the GK unit during treatment delivery in GK Model B Figure 3.4. There are four collimator helmets, 4, 8, 14 and 18 mm in Model B unit.



**Figure 3.3** (A) GK model B unit displaying central core of the unit. (B) 8 mm tertiary collimator helmet with 201 collimators.



**Figure 3.4** Illustration of the radiation focusing delivery technique of multiple Co-60 beams.

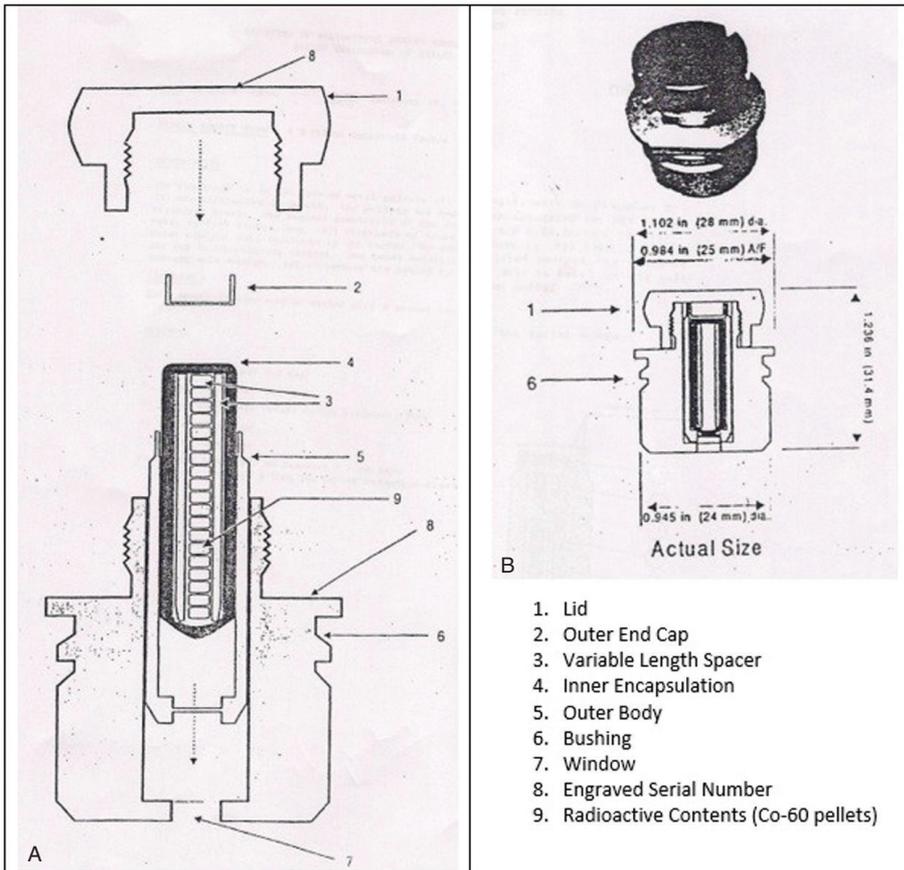
## HOW ARE THE MULTI-SOURCE OF CO-60 LOADED IN GK?

### Radiation Source of GK

The figure 5 represents a single source of GK and its various parts. There are 192 such sources arranged hemi spherically in the central body of the present GK model. A sketch of a single source of GK is shown in figure 3.5. The source consists of 12 to 20 Co-60 pellets stacked inside a cylindrical source capsule made of stainless steel. Each pellet is 1 mm long and has a diameter of 1 mm. The source capsule is further enclosed in a second stainless steel capsule. Further this assembly is arranged in an outer body made of aluminium which is the source casing with a lid. It has a bushing mechanism to position inside the GK central body.<sup>1</sup>

When the source is positioned in the GK, the common axis of the pellet is exactly aligned with the axis of the beam channel. Figure 3.5A shows the pellet arrangement in a single source container. The radiation in GK is emitted in the axial direction of the cylindrical source. The radiation emitted by a source pellet is attenuated when it penetrates through other pellets.<sup>1</sup> The source pellet arrangement (19 pellets) is seen in figure 3.5A-B. The radiation emitted by the first topmost pellet is attenuated by 18 pellets before exiting the window.

Hence the dose rate measured at UCP depends upon the number and position of Co-60 pellets in each source in addition to the total activity. Each source is specified



**Figure 3.5** (A–B) Sketch of a single Co-60 source and source housing used in GK.

to contain an average of the total activity in the GK + 10% i.e. total activity divided by 201 or 192 depending on the GK model. The sources are positioned such that the activity is distributed evenly in GK.

The radiation emitted by each source is collimated by the three different collimators. The radiation field in GK is shaped as a conical beam with circular cross section which diverges from the source towards the UCP. In old GK models the collimator closest to the patient and one closest to the source are made of tungsten (density = 17.8 g/cc). The intermediate collimator is made of lead. The collimator is incorporated in an exchangeable collimator helmet. The lateral extension of the beam is defined by the collimator closest to the patient. In the latest GK ICON model the collimator is an inbuilt collimator system. The size of the collimator in GK is defined as the diameter of its circular aperture as projected on a surface placed perpendicular to the beam axis at the UCP.<sup>1</sup>

### Source Loading and Reloading in GK

The prefabricated Co-60 sources are loaded into the GK system at the radiation site facility during installation. The sources are transported in a radiation-shielded source transport container. A custom designed, shielded loading machine (Hot cell) encloses the container and is attached to the narrow slot in the shielding shell of the GK (Figure 3.6A). Five source positions can be reached through this slot. The sources are transferred from the transport container into their position in the central body of GK, using manipulators in the loading machine. Empty source positions are moved to the slot by rotating the central body inside the GK by degrees around the horizontal axis. All the decayed sources are replaced by new ones in the same way. When all sources are in position, rotation of the central body is rigidly locked in its stationary position and a shielding block is pushed into the narrow slot.

Generally, the radiation source of the GK unit is replaced after the first half life of 5.27 years. The Figure 3.6B represents the source casing of Co-60 sources removed from the GK unit ready for export to its original destination from where it was shipped to our hospital for clinical use.

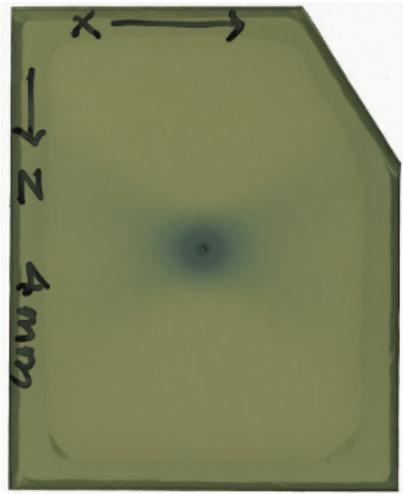
The figure 3.7 represents one of the Gamma Knife quality assurance tests done periodically to test the radiation delivery accuracy of the equipment. The radiological focus accuracy check tool has an option to place a radiochromic film in its slot. The radiochromic film is the preferred detector for medical applications which involve small (less than 1 cm) radiation fields, high-dose gradients, and high-dose rates.<sup>4,5</sup> The film test is done to predict the focus precision accuracy of the GK unit. The black circular pattern in the middle with a pinprick shown in the EBT3 film centre represents the radiation pattern created by 192 Co-60 sources (Figure 3.7).

### CLINICAL CASES TREATED WITH MULTI SOURCE CO-60 BEAMS OF GK

The GK system is in general used to treat small brain tumours, functional disorders, arteriovenous malformations, acoustic neuromas, pituitary adenomas, meningiomas,

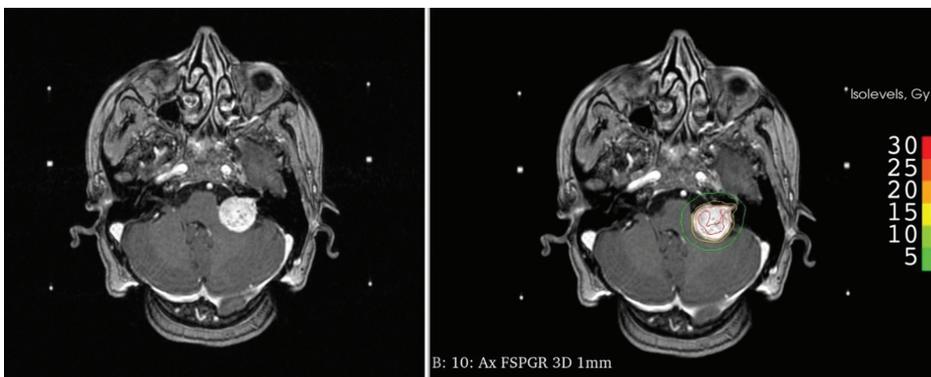


**Figure 3.6** (A) Illustration of multiple Co-60 sources loading and unloading mechanism in GK. (B). The multiple Co-60 sources were removed from Gamma Knife SRS unit for disposal.



**Figure 3.7** A radiological focus accuracy test performed for 4 mm collimator in Gamma Knife Unit.

multiple metastatic tumours etc. The usual tumour volume suitable to be treated with GK is of 25 cc to 30 cc and 3 cm in diameter. The GK is suitable when focused irradiation with a highly escalated dose is needed. It can target specific areas in the brain without damaging the surrounding organs at risk. Figure 3.8 depicts a case of acoustic neuroma adjacent to the brainstem and left cochlea region. The radiation dose distribution after treatment planning is seen on the tumour [Figure 3.8B]. The green line represents the 5 Gy isodose line and the yellow line represents the 15 Gy isodose line. Various other isodose lines are seen as well. The radiation lines seen on the tumour region is the radiation contribution from 192 Co-60 beams.



**Figure 3.8** The figure shows a brain tumour compressing brainstem and cochlea organ in MR image. A multigamma Co-60 source radiation dose pattern created around the brain tumour. Various isolevels (Gy) are displayed as well.

## VARIOUS OTHER MULTIPLE CO-60 SOURCE SYSTEMS IN RADIOTHERAPY

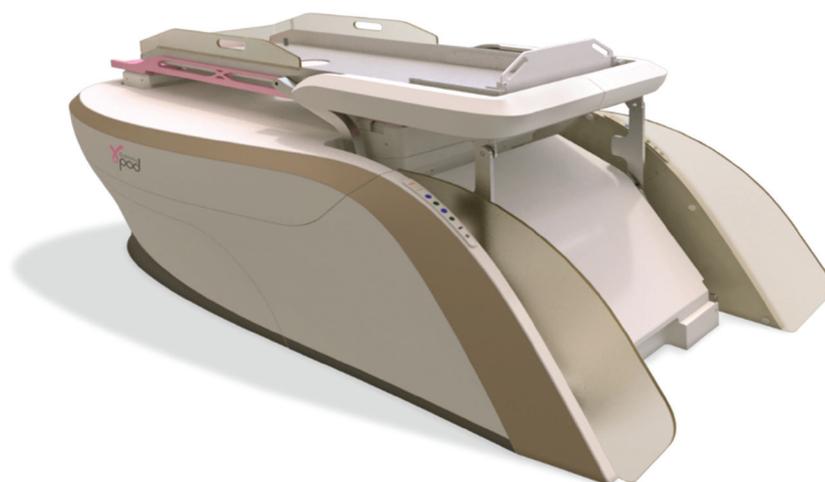
There are various other multisource Co-60 systems available as well. Let us see a few of multisource Co-60 units commercially available.

### Rotating Gamma Knife System

A novel rotating gamma stereotactic radiosurgery (RGSRS) system (Galaxy® RTi) with real-time image guidance technology is available for high-precision SRS and frameless fractionated stereotactic radiotherapy (SRT) as well.<sup>6</sup> The RGSRS system uses 30 cobalt-60 sources on a rotating gantry to deliver non-coplanar, non-overlapping arcs simultaneously, while the LGK ICON (Elekta AB, Stockholm, Sweden) uses sector driven 192 cobalt-60 sources to deliver non coplanar beams.<sup>7</sup> One of the major drawbacks of this LGK ICON system is the relatively large number of Co-60 sources which may cause security concerns and higher costs for source replacement. In turn, this may make GK unaffordable to clinics with limited budgets and/or lower-income regions. Further, due to the large number of sources, source loading (or reloading) procedure typically results in several weeks of downtime, disrupting the SRS program and patient treatment.<sup>7</sup>

### GammaPod – An SRS Tool for Breast Irradiation

GammaPod is a stereotactic solution for breast cancer care [Figure 3.9]. The equipment consists of 25 Co-60 sources arranged in a source housing which continuously rotates to deliver gamma radiation to the breast region. Similar to GK it delivers focal radiation to the target. The technology exhibits uniform target coverage, lower dose to whole breast volume, significantly lower dose to the heart.



**Figure 3.9** GammaPod stereotactic partial breast irradiation using multiple Co-60 sources.

The equipment delivers ultrahigh accelerated courses of adjuvant and neo adjuvant stereotactic partial breast irradiation. The GammaPod system has two collimators 15 mm and 25 mm of the GammaPod system. The immobilization and stereotactic localization are provided by a breast cup system (BCS). It is a two-cup design which evacuates air by suction pump to create a vacuum seal.<sup>8</sup> The potential benefits of the system are it is a non-invasive method, minimizes dose to the whole breast volume, heart and lungs and superior targeting accuracy.

## SUMMARY

For radiosurgery a single beam of photons does not provide the dose localization characteristics needed due to the inherent limitation in its properties such as the depth-dose curve and lateral beam spreading. Hence, a large number of narrow beams directed from various angles but intersecting at one point “focal point” provide very good dose localization. The chapter summarizes how multiple Co-60 sources emitting gamma rays are used in radiation treatment for treating various tumours.

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# Workflow and Introduction to Planning in Gamma Knife Radiosurgery

Kshitij Agarwal ■ Shweta Kedia

## INTRODUCTION

Stereo-tactic Radiosurgery is essentially a day care procedure. By definition, the treatment is delivered within a day or may be fractionated over 1- 5 days depending on the lesion and treatment plan. Radiosurgery can be delivered either with the use of photons, charged particles or gamma rays. The Gamma Knife Radiosurgery has stood the test of time and still considered the gold standard platform for radiation delivery. There has been a lot of advancement over the last decades in the construction of the Gamma Knife machine and the planning softwares. Addition of newer frames, frame-less methodology and faster planning software in the armamentarium of the treating surgeons have made the system more patient and user friendly. In India, there is limited availability of Gamma Knife facility and therefore the routine working of the Gamma Knife is unknown to most of the neurosurgeons. It is essential to understand the basic workflow of Gamma Knife even as a non radio- surgeon.

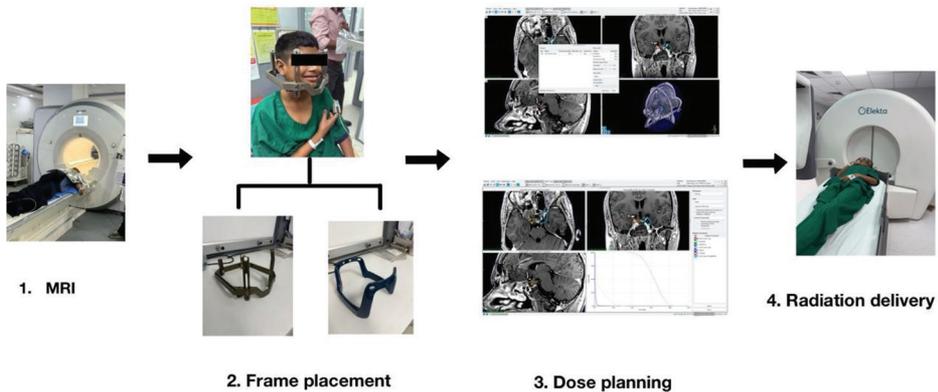
The workflow depends on the case type and planning strategy for the individual patient. This chapter shall focus on the workflow and planning protocol involved in Gamma Knife radiosurgery.

The workflow for GKRS can be divided into two: Frame based and Frameless. The frame based can again be divided as with and without frame MRI.

The oldest and the time tested workflow of Gamma Knife was based on with frame application. The Leksell G frame and the Vantage frame are the two commonly used frames in Gamma Knife at present. The workflow is independent of the frame used.

The steps include: (Figure 4.1)

1. **Frame application** under local anaesthesia. Before applying the frame, the site should be thoroughly cleaned and the four points are locally anesthetized. The frame is held in place over the patient's head and the pins tightened over the posts so that it is adequately fit and immobilized. If tightened very hard, there is a possibility of fracture of the outer calvaria and if too loose, the frame may slip off during the treatment. The vitals are closely monitored while applying the frame. It is essential to ensure that the patient has taken their routine scheduled medications and has an intravenous access in place.

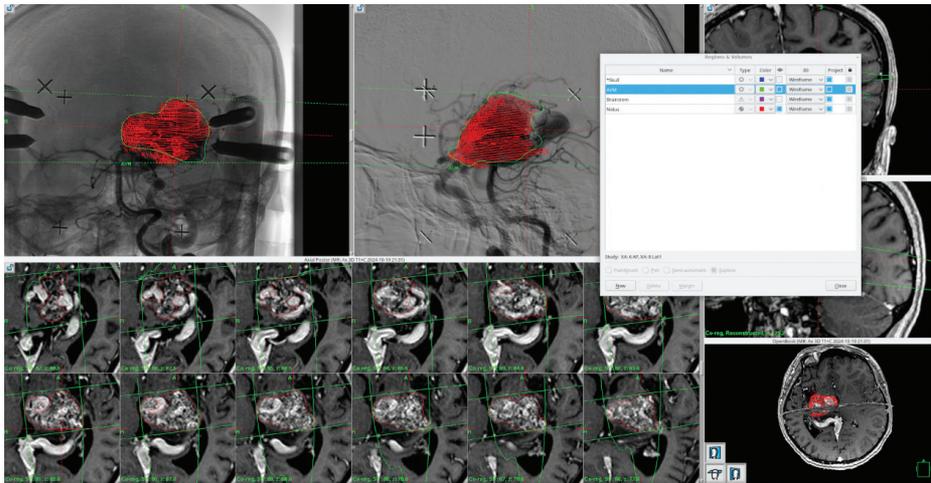


**Figure 4.1** The workflow for frame based GKRS.

- The patient is then shifted to the **Magnetic Resonance Imaging** Room where the 1mm thin cuts contrast MRI (Minimum voxel size 1mmx1mmx1mm in x,y,z coordinate system) is done. Other sequences obtained as per the requirement of the case. The specific Gamma knife protocol images are obtained which can be transferred to the Gamma Plan and then used for planning purposes.

**Deviation:** Alternately, the new ICON model of Gamma Machine is equipped with Cone beam CT which allows to obtain the CT scan under stereo-tactic guidance while the patient is lying down in the couch.<sup>1</sup> Therefore the patient may undergo MRI before the frame application and the desired plan made on the image thus obtained with a virtual skull and fused with the stereotactic CT image obtained after frame application. This allows for better preparedness with the plan, rules out possibilities of collisions at the planning level and reduces the time with frame on for the patient. However, this requires the surgeon to ensure that the fusion of the MRI image and the CT obtained from CBCT be accurate in order to obtain accurate delivery of the dose.

- If it is a case requiring **Digital Subtraction Imaging**, the patient is then wheeled into the angio suite for DSA. (Figure 4.2) The indicator box for DSA is different from that of the MR indicator box and marked with Cross and multiply sign. These signs help in lateralization of the image and act as stereotactic reference points. The image from DSA is transferred to the gamma plan but in a 2D format.
- Planning time:** Once the images have been obtained and transferred to the gamma plan the station is ready for the radiosurgeon for planning. The planning process involves contouring of the skull, the target and the organs at risk. The skull image gets generated automatically in the current system from the MRI images. If the contour is not correct or collision observed, the measurement based on posts used in the frame or the bubble cap is used to obtain the skull contour.



**Figure 4.2** The frame based protocol for AVM radiosurgery. The angio image and the CEMRI Brain image is obtained with frame.

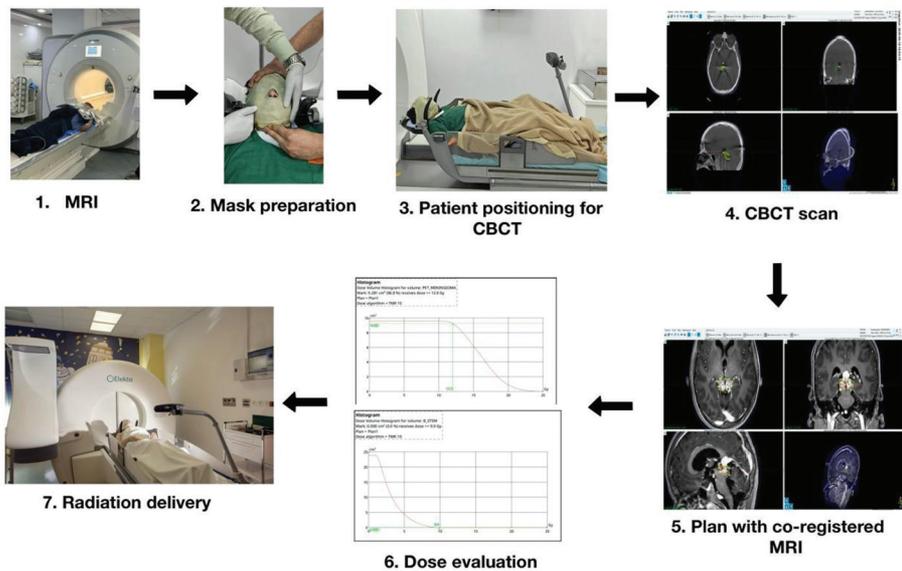
5. The **target lesion** can be single or multiple. Each has to be contoured as per the shape. There are three tools available for contouring. The pen, semi-automatic and the paint brush. The computer is trained to treat the target that is marked and therefore it is crucial to include all of the lesions and exclude the normal brain from the target.
6. The **organ at risk** is usually marked based on the target and is going to be the area that need to be protected from the radiation. So, if the lesion is located in the Cerebello pontine angle, brainstem is the organ at risk and for a sellar pathology chiasm and optic apparatus are the organs at risk.
7. The **dose to be prescribed** to the target is well defined and is based on the radiosensitivity of the pathology. Benign pathologies are treated with a dose of 12-14 Gy and a higher grade lesion is treated with 18-22 Gy at the margin. The isodose line to which this dose is prescribed is usually kept at 50 -56 % when attempting to plan manually. This is chosen based on how homogeneous or heterogeneous the dose distribution and creating a hot spot within the target. Higher the isodose line at the margin, more heterogeneous is going to be the dose distribution and this is used for aggressive small sized lesions. The need for choosing the prescription isodose line is now obviated because of the availability of Lightning software. It requires placing of target dose and allowable max dose limit to organs at risk and titrating the beam on time.
8. **Plan approval and execution** : Requires involvement of physicists and radiation oncologist along with the treating neurosurgeon. Before approval of the plan the Gamma angle, selection of the right frame / mask and all collisions need to be excluded, clearance analysis is done. The plan which offers best conformality along with good coverage is considered the best plan. The treatment depends on the interplay of the shots and the age of the gamma source. Shorter the time with adequate coverage and selectivity, better is the plan.

9. The treatment is delivered in the single sitting in an uninterrupted manner. However, there have been occasions where patients have thrown seizures during the treatment delivery or for other unforeseen circumstances, the delivery has to be interrupted. The system has the built-in system to remember the dose that has been delivered. So, if the patient has moved, the cone beam CT needs to be repeated, the images re-registered and the treatment resumed from the point where it was interrupted.
10. After the delivery of the radiation, the frame is taken off the patient. Patient is kept under observation for a few hours and then sent home on the same day. There are usually no complications that happen on the table or while applying and taking off the frame. There is a possibility of vagal syncope in an anxious or hypertensive patient and the emergency trolley with the provision of monitoring the patient. Rarely the patient may bleed from the pin site.
11. Follow up in our scenario is usually after 1 year in benign cases with the contrast MRI. The aggressive pathologies like metastases, grade 2, 3 meningiomas are kept under close watch and are called at an interval of 3 months for the 1<sup>st</sup> year. Imaging is done early in case of new onset neurological symptoms and signs.

**Workflow for the frameless treatment Stereotactic Radiosurgery** with Gamma Knife: The ICON model has the provision of a patient tracking system and integrated with high definition motion management system. Therefore this and the newer Esprit model are equipped for frameless radiosurgery.<sup>2</sup>

Once the patient is identified and planned for dose fractionated radiation over 3–5 days based on the pathology location/ volume, he is scheduled for mask based treatment. (Figure 4.3)

1. The appropriate MRI imaging is done for the patient either on the same day or a day or two prior.
2. Contouring and treatment planning was carried out the same way as in a frame based system with the virtual stereotactic reference in the pre-planning mode. The dose is generally delivered in the per fraction manner and the standard dosing is 5Gy in 5# or 8 Gy in 3 #. However this may be delivered on a daily basis (preferred) or an alternate day basis.
3. The patient is then taken on the couch. The head cushion is placed on which the patient is made to lie down and then the thermoplastic mask is heated either in the hot water bath or hot air oven. The mask thus moulded is placed on the patient's face and fixed at three points. In 2-3 minutes, it hardens to take the patient's facial contour and is ready to be reused. The mask though less invasive than the frame, is less rigid.
4. With a mask and cushion in situ, the Cone beam CT (CBCT) is done to get the patient specific stereotactic reference. The CT is then fused with MRI and now the treatment mode is enabled. The planning is fine tuned based on new reference points if required and is now ready to be approved and transferred.
5. The physicist looks into various parameters and a CBCT is repeated again, this time to mark the baseline threshold for the patient. The plan is re-calculated



**Figure 4.3** Workflow for frameless Mask based treatment.

after “shot” position translation based on the co-registration and the new dose distribution is compared to the original plan. The treatment plan is corrected to an updated stereotactic coordinate system. The treatment is then initiated.

6. The system has a High Definition Motion Management Camera with an infrared tracker to monitor any micro movement of the patient. The Infrared markers are placed on the nose tip and are monitored throughout the treatment in relation to the four stationary reflectors present on the mask frame adaptor. HDMM camera sets its baseline for tracking and from that moment, the fiducial marker is tracked to stay within a threshold distance in any direction set by the treatment provider (i.e., 1.5 mm) of its original position or else treatment is paused. The delivery of the dose stops automatically if the movement beyond threshold is detected. The CBCT may have to be repeated on occasions to re-register the image if the patient has moved significantly.
7. For the subsequent delivery, the mask and the cushion are reused. Before the delivery of the dose the next day, the CBCT is repeated and the image co-registered with the baseline imaging. Once the readings are verified and zeroing reconfirmed, the subsequent fraction of the treatment is delivered.

The mask immobilization, cone beam CT immobilisation and the intrafraction motion management in ICON machine has well been validated in the various studies in literature.<sup>3</sup> The limitations of the mask based system in the current era is that the freedom of gamma angle is not there. The Gamma Knife machine has a provision of placing the head frame at an angle, either 90 degrees or 70 or 110. The 70 degree and 110 degree would mean the head is in the flexion or extended

position respectively. This helps protect the organ at risk. However, in the mask based algorithm, the frame is kept at 90 degree only and therefore lesions close to orbit may not be treated with a mask. Also, since there is no frame, angio images under stereotactic localization are not available and so the plan of AVM is essentially MR based in the frameless system.

The plan quality is not affected by any modification in the workflow.

Introduction to the planning station.<sup>4</sup>

The second part of the chapter involves understanding the basic steps of planning in Gamma Plan.

The workstation of gamma plan is very user friendly and is directly linked with the imaging system of the hospital. The required MRI sequences done under Gamma Protocol are retrieved on the patient' page and then worked upon.

1. The planning can be done in the pre-planning mode or the treatment mode as described above.
2. The MRI obtained after frame fixation already has three localizers on the three axes, which are registered and then forms the working image for the patient.
3. The target organ, organ at risk and skull marked as described above with the help of the available tools.
4. The most crucial part is the placement of shots in order to obtain the desired parameters of coverage, selectivity index, gradient index and the beam on time.
5. The Gamma Machine has 4, 8, 16 mm collimators arranged in the sectoral manner and each shot can either be uniform having a single collimator or composite having a mix of different collimators in the single shot.
6. There are three ways to plan the treatment in the current gamma plan.

The oldest being the manual method of forward planning. Here the surgeon places the shots in a methodical manner allowing for the interplay of shots and then titrates the sectors to get the desired parameters. The prescription isodose line is chosen based on the nature of the tumor and the collimators in each shot are manually adjusted.

The later versions of Gamma Plan allowed for inverse planning. Here, we could ask the computer to place the shots first to get a good plan. However, this plan needs to be manually redefined as few of the shots carry low weights and will not allow for plan approval. Moreover, these shots placed by inverse planning may not always be the best ones.

At present, there is a lightning software available with the Gamma Plan that allows the shots to be placed automatically based on the dose that is prescribed to the target organ and organ at risk.

Each shot represents the couch position for the radiation focal point. The good plan should have a coverage of more than 95% with good conformality ranging above 0.8 and gradient index of 2-3 and short beam on time. However, for smaller targets and for targets with irregular contours like in residual pituitary tumors for secondary GKRS, to achieve both the coverage and selectivity may not be feasible.

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SECTION II

**Skull Base and Cranial  
Tumors**



# Primary Gamma Knife Radiosurgery for Craniopharyngioma

Satish Verma ■ Deepak Agrawal

## INTRODUCTION

Craniopharyngiomas are WHO grade 1 tumors believed to be arising from the embryonic remnants of epithelium of Rathke's pouch. Their strategic location near the hypothalamic-pituitary axis and visual apparatus pose inherent challenges in attaining complete surgical resection. In addition, their potential for recurrence and rapid growth warrants adjuvant modalities for longer progression-free and overall survival. Radiation has proved as a reliable adjunct for local tumor control. Stereotactic radiosurgery using Gamma Knife is a non-invasive modality with extreme precision due to high dose conformality and rapid dose fall-off.

## REPRESENTATIVE CASE

### History & Examination

A 54 year old female was referred after 3 months of trans-cranial decompression of craniopharyngioma done at some other centre. She presented to that centre with progressive painless bilateral visual diminution for 6 months. She started developing a holocranial headache for the last 15 days before presentation. On examination, as per medical records, she was conscious and oriented to time, place and person. Visual acuity as per Snellen's chart was 6/60 in right eye and 6/24 in left eye with bitemporal hemianopia. No other positive neurological findings were elicited. She reported improvement in vision after surgery. Prior to Gamma Knife radiosurgery, her visual acuity was 6/36 in right eye and 6/18 in left eye with marked improvement in bitemporal hemianopia. She was on corticosteroid and thyroxine replacement.

### Imaging

At presentation, Contrast enhanced magnetic resonance imaging (CEMRI) of the brain suggested a suprasellar lesion with solid-cystic areas, solid areas were T1 and T2 hypointense and cystic areas were T1 hypo- and T2-hyperintense. Solid areas showed post-gadolinium enhancement. Pituitary gland could be seen separately. These findings were consistent with craniopharyngioma. Post-operative MRI

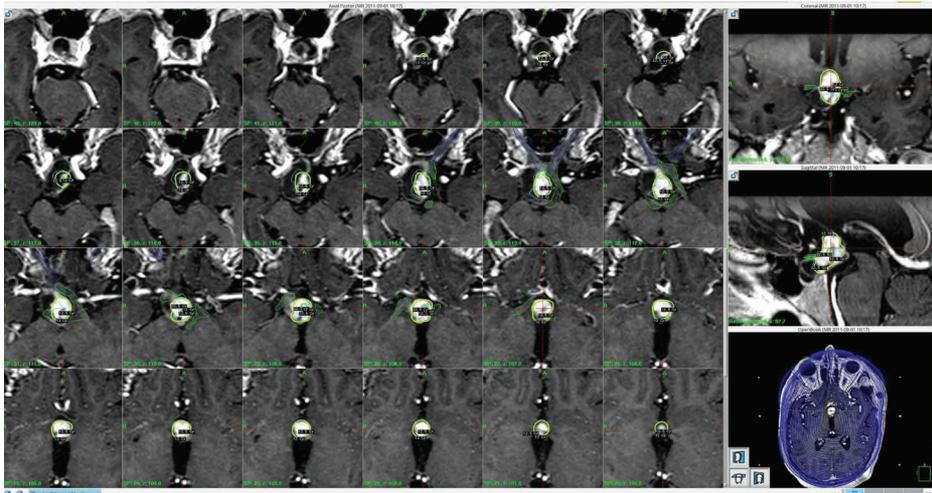
showed an enhancing residual lesion in the suprasellar area of size 2.1 cm × 1.3 cm × 1.2 cm. For the purpose of Gamma Knife planning, after fixation of Leksell-G frame, post-gadolinium 3-dimensional (3D) Magnetization -prepared Rapid Gradient Echo (MPRAGE) sequence was acquired in axial plane with voxel size 1.0 × 1.0 × 1.0, slab 1, slice per slab 176 and Field of View (FoV) 256 mm.

### GK Protocol

Gamma knife was performed on a Leksell Gamma Knife Perfexion unit (Elekta AB, Stockholm, Sweden) with Leksell GammaPlan. Manual tumor segmentation was done for the tumor and Organs-at-risk (OAR) (optic apparatus and brainstem). Total tumor volume was 1.343 cubic centimetre (cc). Inverse planning with optimization of six iso-centres (combinations of 4 and 8 mm collimators) was performed with prescription dose of 12 Gy at 50% isodose line to the tumor margin (Figure 5.1). Further optimization was done manually to exclude OARs out of the prescribed dose constraints achieving following parameters - coverage -93%, selectivity - 80%, Gradient Index - 3.01. Beam-on time (BOT) was 45.1 minutes with a treatment dose rate of 3.530 Gy/min. Maximum dose to the segmented volumes were : tumor - 24.1 Gy, left optic nerve - 4.0 Gy, right optic nerve - 7.9 Gy, optic chiasma - 12.4 Gy, brainstem - 7.0 Gy (Figure 5.2). Although selectivity was sub-optimal, the majority of radiation spillage was into the CSF space in the suprasellar and interpeduncular cisterns.

### Follow Up

Patient tolerated the procedure well. Follow up clinical visit after 3 months was done with a visual examination, that was same as pre-GKRS status. Follow up CEMRI was done annually for the first three years and then after 2 years which showed



**Figure 5.1** Gamma Knife planning for the index case. Tumor margin (Blue), 12 Gy (prescription dose) isodose line (yellow).

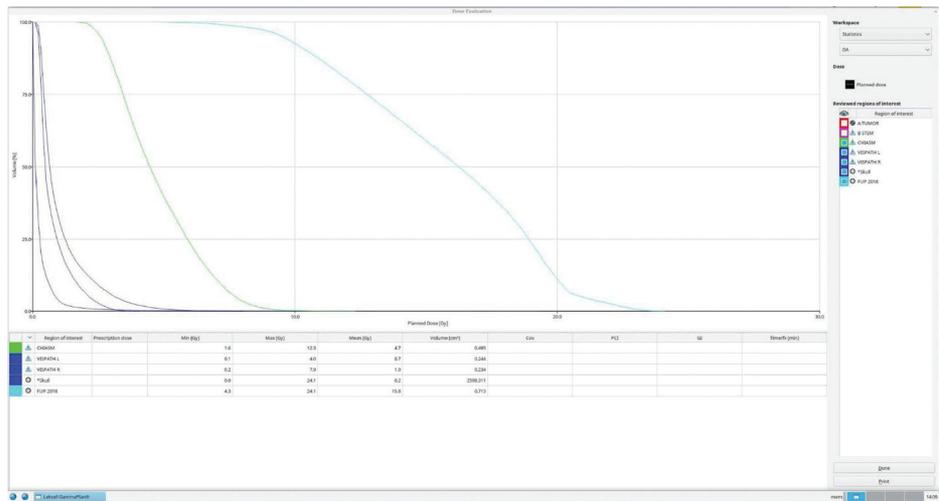


Figure 5.2 Dose volume histogram (DVH) for the tumor and optic apparatus.

gradual reduction in tumor volume. At the last follow up available, at 79 months, the residual tumor volume was 0.713 cc (Figure 5.3). She was on corticosteroid and thyroxine replacement. Visual acuity remained the same as pre-GKRS.

## DISCUSSION

Craniopharyngioma are benign but locally aggressive tumors with bimodal age distribution. There are two different histological varieties -adamantinomatous and papillary.<sup>1,2</sup> Due to its close proximity to the hypothalamus-pituitary axis and visual

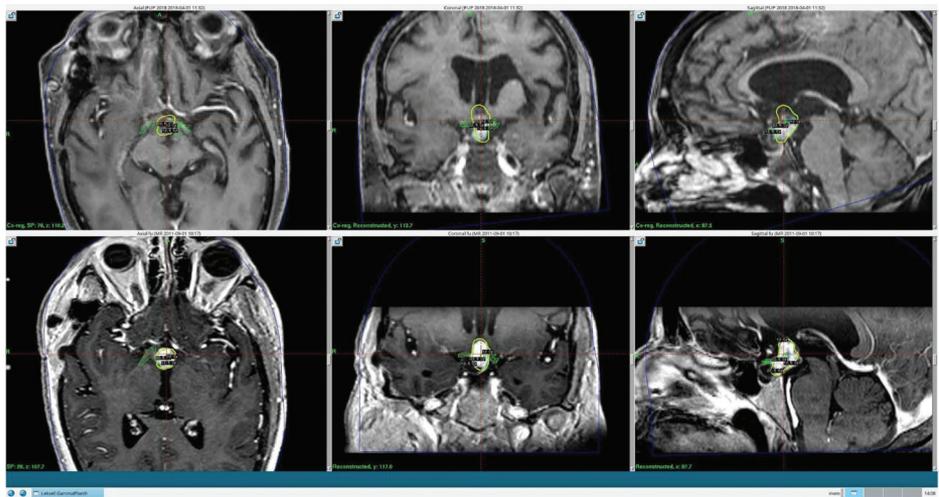


Figure 5.3 Follow-up MRI done after 79 months (upper panel) compared to the baseline MRI at the time of GKRS (lower panel).

apparatus, complete microsurgical resection, although considered as the treatment of choice, is difficult to achieve and not feasible most of the time. Goal of surgery is maximal safe resection, as either direct mechanical injury or vascular insult to hypothalamus or visual apparatus results in devastating complications. Even after gross total clearance of the tumor, 10% - 25% recur. And about all residual lesions progress after a subtotal resection.<sup>3,4</sup> Residual craniopharyngiomas usually grow in size at a variable pace and if not sizeable enough to cause compression over optic apparatus may be managed with radiation as a salvage treatment. Many centres offer GKRS for recurrent craniopharyngiomas even with compression over the optic apparatus considering high complication rates associated with repeat resection.

Radiation as an effective treatment for craniopharyngiomas was initially established by Kramer et al.<sup>5</sup> Gamma knife radiosurgery is a non-invasive modality for delivering high dose radiation with extreme precision due to superior dose conformity as compared to conventional radiotherapy. Backlund and Leksell treated the first case of craniopharyngioma with Gamma Knife radiosurgery at Stockholm, Sweden in 1968.<sup>6</sup> Initially, it was presumed as a cystic lesion, and planned for stereotactic aspiration, but it turned out to be a solid tumor and no significant tumor decompression was attempted, rather two radio-opaque clips were placed at the anterior and superior tumor margins. That case was planned on plain radiographs, utilising radio-opaque clips as surrogate for tumor margins. A single 4 mm isocentre was used in a single session with a cumulative dose of 50 Gy. After GKRS, the case underwent 4 more interventions, spanning over a 55-year follow-up period, to manage recurrences. Since then, there has been significant developments in GKRS units and MRI techniques and image quality that has led to precise dose delivery with exclusion of OARs from the radiation field.

## CONTROVERSIES

Although GKRS has a well-established role in treating residual or recurrent craniopharyngiomas, its use as a primary modality remains debated. Surgical resection remains the preferred first-line intervention due to the need for decompression and histological diagnosis. However, given the high morbidity associated with repeat surgery and incomplete resections, radiosurgery is gaining traction as a frontline option in selected cases. Critics question long-term control rates and the potential for radiation-induced endocrine dysfunction or optic neuropathy, especially in tumors closely abutting the optic chiasm.<sup>1,4,8</sup>

## CURRENT PRACTICE

Most centers reserve GKRS for salvage treatment post-surgery. Marginal doses of 12–14 Gy in single fractions are typically employed, with hypofractionated schedules being used for larger lesions or those near critical structures. BED2 >80 Gy has shown better progression-free survival. Image-guided planning with modern MRI sequences and dosimetric modeling has enhanced target accuracy and safety. Hypofractionation, enabled by newer mask-based platforms like Gamma Knife ICON,

allows safer treatment of tumors near the optic apparatus while maintaining therapeutic efficacy.<sup>13,19,21</sup>

## LEARNING POINTS

- Craniopharyngiomas are benign but locally aggressive tumors that frequently recur despite surgery.
- GKRS offers a precise, non-invasive treatment alternative, particularly for small residual or recurrent tumors.
- BED2 >80 Gy correlates with improved outcomes.
- Strict adherence to optic dose constraints (<10 Gy in 1 fraction, <20 Gy in 3 fractions) reduces risk of RION.
- Hypofractionated GKRS may expand indications for treating larger or critically located lesions.

## CONCLUSION

Gamma Knife radiosurgery offers a safe and effective treatment for craniopharyngiomas, particularly in patients unsuitable for reoperation. While primary GKRS is not yet standard, emerging evidence—including this case—suggests it may be viable in selected scenarios with favorable tumor size, anatomy, and visual function. Long-term follow-up supports its efficacy, with acceptable safety profiles when modern planning protocols and dose limits are applied.

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# Gamma Knife Radiosurgery for Functional Pituitary Tumors

Hanok Srithej ■ Shweta Kedia

## INTRODUCTION

Pituitary tumors comprise of 10-12 % of all brain tumors.<sup>1</sup> 90% of these are adenomas, may be benign or malignant. These may present because of compression of the optic apparatus or due to over or under secretion of hormones. Functional pituitary adenomas are notorious in presenting with sellar dysfunction features due to over-secretion of hormones and also the visual symptoms. The primary line of treatment for functional adenomas is surgery, the exception being prolactinomas which respond very well to medical management. The primary goal of treatment is to obtain sustained hormone remission through radical excision of tumor. However, some of these may not be amenable to complete surgical resection and present with residual lesions with raised hormone levels. In the past they were subjected to conventional radiation. However, now the Gamma Knife Radiosurgery (GKRS) is an established mode of treatment for residual functional pituitary adenomas.

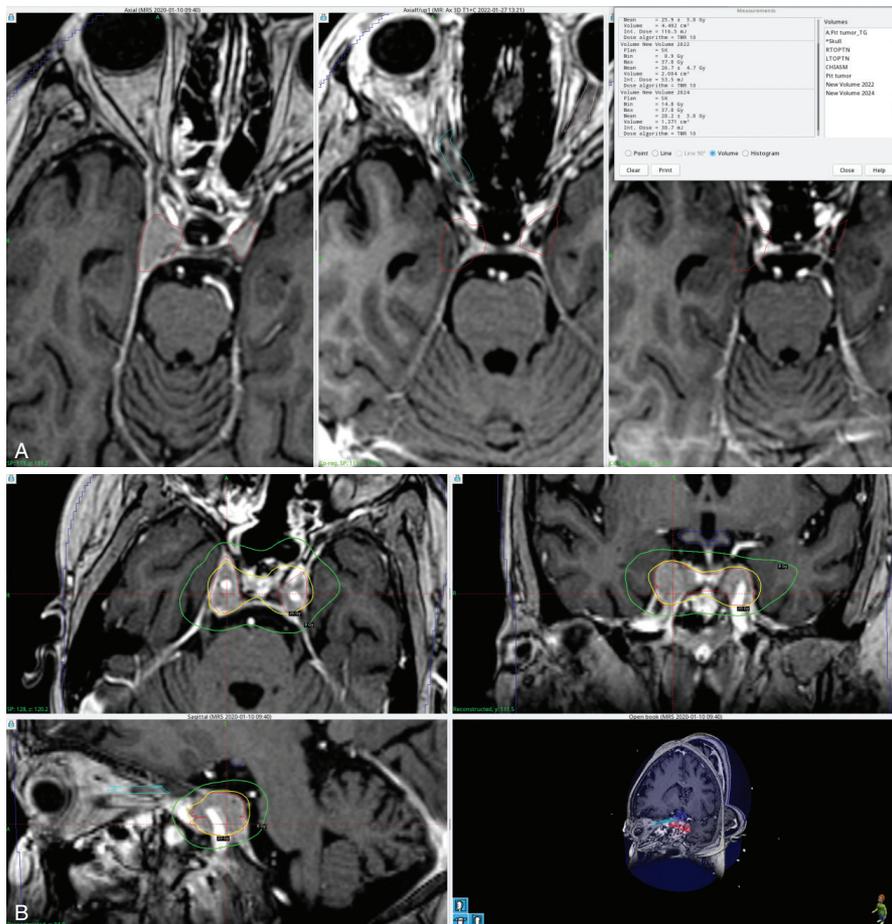
This chapter will discuss the case selection, technique of GKRS, the outcome and adverse radiation effects of GKRS in functional pituitary adenomas.

## THE INDEX CASE

Young unmarried female of age 20, presented with Cushingoid features for over the last 2-3 years. The patient was referred by the endocrinologist after appropriate workup and then taken up for surgery. The patient was operated twice through a trans nasal endoscopic approach, the last surgery done 6 months before GKRS. She had significant residual in the para sellar area. This patient was started on medical therapy and referred for radiosurgery. Post operative ACTH was 66.12 and Serum cortisol was 35.28. She was on drugs for her Diabetes and Hypertension.

A dose of 20Gy to the margin of the tumor was prescribed at 50% isodose line. Optic pathway (covering right and left optic nerve and chiasm were marked as organs at risk with Max permissible dose allowed as 10Gy.

For the initial 4 years of GKRS, the biochemical control was not good and the patient was taken up for bilateral adrenalectomy following which she was in complete hormonal remission.



**Figure 6.1** (A) The tumor is marked as two different targets in the right and left parasellar area. The tumor volume reduced to 1.37cc at the end of 4 years following a volume of 4.492cc. (B) Shows the planning strategy 20Gy at 53% isodose line is delivered with 95% coverage. See the 8Gy line marked in Light green well away from the optic apparatus.

6 years later, the patient presented with Right side third nerve dysfunction, which progressed to complete palsy in a month's time. The hormone evaluation at this time was normal. Her latest Cortisol is 0.74ug/dl and ACTH is 706.4

The MRI showed almost complete reduction in tumor volume.

The contrast MRI did show radiation induced changes in the third nerve. The patient was started on high dose dexamethasone and showed significant resolution in symptoms in a week's time.

## DISCUSSION

All the functional adenomas including, Cushing', Acromegaly, TSHoma and also Prolactinomas are amenable to radiosurgery as an adjuvant mode of treatment. The bulk of the cases in functional tumors is constituted by Acromegaly and Cushings.



**Figure 6.2** Radiation induced Rt third nerve neuritis which responded well to high dose steroid therapy. (A) Pre Dexamethasone. (B) Post Dexamethasone.

As suggested earlier in the text, GKRS is the second or the third line of treatment. Case selection plays a significant role in determining the outcome post GKRS.

The first line of treatment for any patient with Cushing's with pituitary lesion is trans-sphenoidal excision of tumor. The patients present with cushingoid habitus with Micro-adenomas in a young patient with no visual symptoms. Post surgery, most of them respond and become eucortisolic or require hormone replacement. They are closely followed up for biochemical remittance and in our practice CEMR sella is repeated three months post surgery. These patients may come back with residual or have biochemical recurrence. In case of residual lesion that is surgically amenable to resection, patient is offered repeat surgery. In case surgery is not feasible, the severity of disease determines the course of action. Depending on the hormone levels, Mild to moderate recurrence, the patient may be sent for GKRS with or without medical therapy. In case of severe disease, the patient is subjected to bilateral adrenalectomy and hormone remittance is checked for. In case of persistent disease, these patients are then referred for GKRS.

Acromegaly usually presents with Giant adenomas, and therefore these patients may also have visual symptoms along with the effect of raised circulating growth hormone. Again, these patients are first offered surgical excision. In case of residual lesion and where surgery is not feasible, the patients are offered medical therapy in the form of Somatostatin analogues. These medications are expensive and need to be taken life long and therefore in these cases radiosurgery as an alternative is a feasible option.

Prolactinomas are primarily treated with Dopamine Agonists. Residual or resistant diseases are offered surgery. The patients who have tumors which are not resectable are occasionally referred for radiosurgery. Likewise TSHomas are very rare tumors and surgery forms the first line of treatment.

While offering GKRS as the treatment option the primary consideration is given to the volume of the tumor that has to be treated. The proximity to the optic apparatus is another important factor that has to be looked at. In contrast to the non functional tumors that are treated with 12-15Gy, the functional tumors require a higher dose( 22-25Gy). Therefore, the volume and the distance of the optic apparatus becomes relatively difficult to titrate.

The workflow and the planning technique is similar to any other cases being subjected to GKRS. The target organ in this case is usually very irregular and may not always be in continuity as a single target. The Surgeon may choose to mark it as two or multiple different targets if the residual lesion is widely separated or mark it as one depending on the desired coverage and specificity. Some of the patients like in Cushing may not have any definite tumor volume on the MRI. The number of patients with no clear lesions may be very high around 30-40%. There is no lateralization on inferior petrosal vein sampling. In these cases the whole of sella may be marked as target organ and radiated with the appropriate dose. This is referred to as “Radiosurgical hypophysectomy”. The organ at risk is the Chiasm and right and left optic nerves and are to be marked separately for the correct volumetric assessment for the computer. The preferred sequence for marking the optic apparatus is Fiesta/ T2 weighted sequence and coronal cuts show the pathway best. For a long standing lesion with significant compression of the optic apparatus, it may not be feasible to trace down the pathway correctly on the MRI. The newer softwares which have AI based algorithms are available that could help to anatomically draw the pathway. The optic apparatus may be engulfed by the tumor or lie in very close proximity to the tumor(< 3mm distance). In these circumstances, if the vision is intact, it is best to fractionate. The standard fractionation protocol that is being followed is 5Gy in 5 # over 5 days.

It is a day care procedure and the patient is called on the day of treatment. Treatment could be either frame based or frameless if being fractionated. 1 mm cuts of contrast MRI brain with fat suppressed images and T2 sequences are obtained to delineate both the organs at risk and target organs. Cone Beam CT acquired to co register with MRI of the patient and treatment mode is enabled. The shots are placed so as to attain maximum coverage with the dose constraints to organs at risk.

The patients are continued on the hormone replacements post GKRS in the same dosage as prior to GKRS. The medical therapy like any Somatostatin Analogues for the specific hormones is with-held for at least four weeks around the GKRS as it interferes with the efficiency of radiosurgery.

Most of these patients will need medical therapy support for a year or two. The hormone remission happens in around 3-4 years. MRI is done to look at the tumor size on an annual basis for the first two years. Then they are followed up every two years for 10-15 years. The response is good if the tumor is stable or reduces in size. If there is an increase in volume by 20% or the hormone levels remain persistently high at the end of two years, the treatment is said to have failed and alternative medical or surgical therapy need to be initiated.

The response rates of Cushing are better than acromegaly. The criteria for cure in acromegaly is age appropriate normalization of Insulin like Growth Factor 1 and

Growth hormone. To confirm the remission in ACTH secreting tumors, we look at the 24 hours Urine free cortisol concentration, it should normalise while the patient is not on cortisol lowering medications. The basal ACTH level and suppression of cortisol during low dose Dexamethasone test are other markers for assessing remission. The remission rate in Cushing is more than 50% in most of the cases versus 50-65% in acromegaly.<sup>2</sup> The 5-year recurrence free survival in Cushing is around 73%. However recurrence may happen after apparent remission in 15-20% of the cases. The usual presentation in such a situation is presence of a new lesion at a site outside the then treated site. The remission usually happens after 3-4 years of GKRS treatment. The tumor control rate in acromegaly is good in the order of 70-80% at the end of two years. Overall remission is seen in 46% and 5-year recurrence free survival is seen in 52% in acromegaly.<sup>3</sup> The remission probability increases with increasing time lapse from the time of treatment in acromegaly and reaches 70% at the end of 10 years.

The remission rate for prolactinomas also is around the same range of 50%.<sup>4</sup> Recurrence after remission in prolactinomas is rare and happens in around 5-8% of the patients. The remission rate reaches 70% when the patients are offered Dopamine agonists after GKRS. Large tumor volume of more than 5cc and history of previous multiple surgeries are associated with poor outcome. The failure of treatment is usually because of the tumor relapse outside the field of radiation, which was probably not visible during the treatment time.

These patients, irrespective of the functionality of the tumor may have pituitary insufficiency in the long period and therefore need to be closely evaluated for the hormone levels. Studies have shown that at least one of the hormone functions will be affected post radiosurgery in 0-40% of cases.<sup>5</sup> We initially do the hormone assessment every 6 months and then annually. Some of the patients may present with visual deterioration following GKRS. The radiation induced optic neuropathy occurs in 0-5% cases. The shrinkage of the tumor in the sella, leads to traction on chiasm, causing visual field loss. Very rarely patients may present with radiation induced cranial neuropathies. These respond to very high doses of steroid and are treated as adverse radiation effects. There are few case reports to suggest ICA infarcts following GKRS due to radiation induced vasculitis. However, the adventitia is very resistant to radiation and therefore such occurrences are not seen very often.

## CONCLUSION

Gamma Knife radiosurgery is a safe adjuvant modality for treating functional pituitary adenomas with a remission rate of around 50-65%. The Endocrinopathies post GKRS may happen in 40% of the cases, necessitating hormone replacement therapy. The optic and other cranial neuropathies are rare occurring 0-5% of the cases

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# Primary Gamma Knife Radiosurgery in Pituitary Adenomas

Chandra Kiran A ■ Deepak Agrawal ■ Satish Verma

## INTRODUCTION

Pituitary adenomas represent a heterogeneous group of tumours that arise from the pituitary gland. Giant pituitary adenomas present unique challenges in diagnosis, management, and treatment. These tumours account for a very small fraction (8%) of pituitary adenomas. These tumours account for a very small fraction (8%) of pituitary adenomas(2). These tumours often cause significant neuroendocrine dysfunction, neuro-ophthalmic dysfunction or compression of adjacent structures and may present with neurologic deficits. Gamma Knife radiosurgery (GKRS) has emerged as an effective non-invasive modality for treating pituitary adenomas, offering both tumour control and symptom relief, particularly in patients for whom surgical resection is not feasible or carries substantial risk. Preliminary data suggest that resolution of pituitary hypersecretion is faster with high durable rates of tumour control in gamma knife therapy. We present here a case report of successful single fraction Gamma Knife radiosurgery in a case of GPA (Giant Pituitary Adenoma) and the noteworthy functional recovery of the patient.

## CASE PRESENTATION

A 55-year-old male patient presented with a 6-month history of progressive visual disturbance in the right eye, and 3-day acute onset headache, dizziness, diplopia and fatigue. His past medical history was significant for hypothyroidism and type 2 diabetes mellitus both being treated adequately. On examination, he was vitally stable and had a corrected visual acuity of FC @ 6 feet in the right eye and 6/18 in the left eye. He was found to have a bilateral temporal visual field defect consistent with bitemporal hemianopia. He also had a right eye lateral rectus palsy. Hormonal evaluation revealed subnormal levels of serum PROLACTIN (0.3mcg/L, reference-2.1-17.7), and elevated serum cortisol levels (49mcg/dl,reference range 5-23). The patient was asked to get a visual field charting done which confirmed the presence of bitemporal homonymous hemianopia (Fig. 7.1, 7.2)

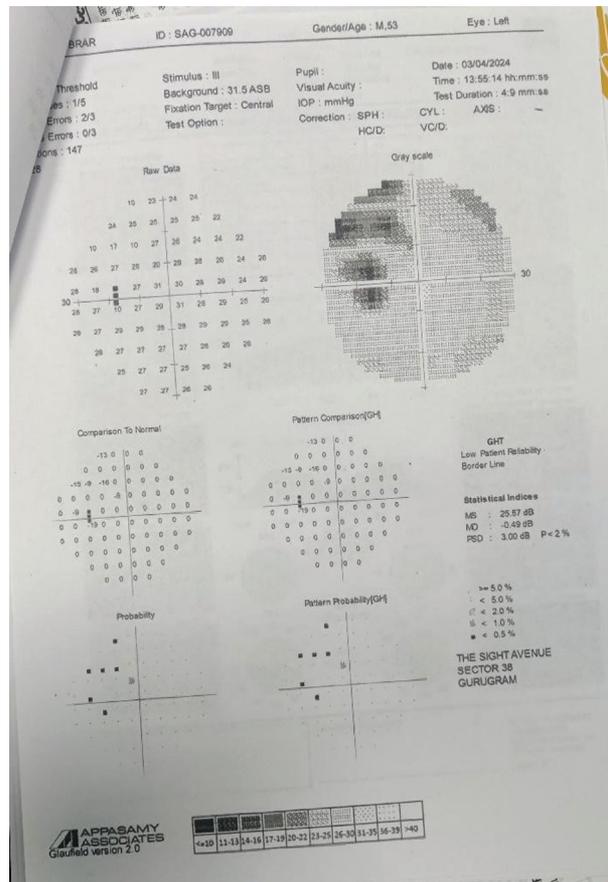


Figure 7.1

## Imaging

Magnetic resonance imaging (MRI) revealed a giant pituitary adenoma measuring  $31 \times 34 \times 25$  mm (approx.  $27 \text{ cm}^3$  in volume), with non-visualisation of anterior pituitary and causing significant compression and splaying of the optic chiasm (Fig. 7.3). Due to the tumour's size and its intimate involvement with critical neurovascular structures, and the patient's persistent refusal to undergo surgical intervention, the decision was made to proceed with Gamma Knife radiosurgery after a detailed informed written consent was taken from the patient with proper risks and benefits explained.

## GK Protocol

Given the size and location of the tumour, a treatment plan was carefully designed to minimize radiation exposure to surrounding healthy tissues, particularly the optic pathways and hypothalamus. The patient underwent a high-precision stereotactic

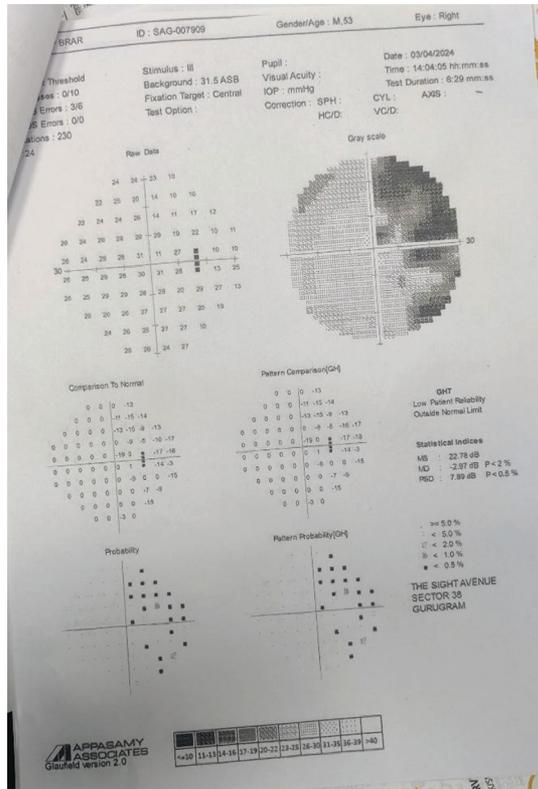


Figure 7.2

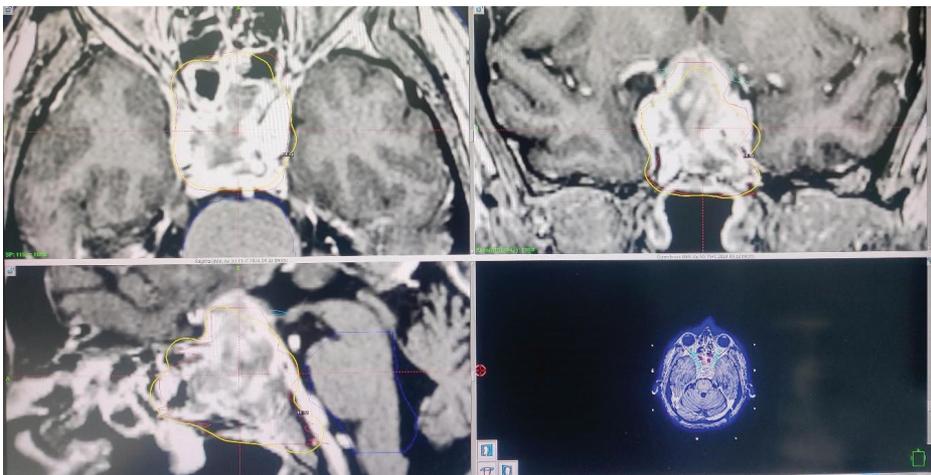


Figure 7.3

MRI scan, followed by the placement of a stereotactic frame under local anaesthesia. The tumour was delineated with high accuracy on the imaging, and a total dose of 14 Gy was prescribed to the tumour with a volume of 28.195 cm<sup>3</sup> and a coverage of 92.6%, delivered in a single fraction. Left and right optic nerve along with optic chiasma were strategically spared, effectively receiving almost nil radiation. Patient was discharged on the same day of irradiation with a set of supportive medication.

### Follow Up

Post-treatment immediate 2 week and 1 month follow-up showed no evidence of acute complications such as radiation-induced oedema or haemorrhage. The patient was followed up with clinical evaluation and serial imaging. At 12 months, MRI demonstrated a significant shrinkage of tumour size (Fig. 7.4A, 7.4B), and the patient reported significant improvement in visual acuity, with near normalization of his visual field. (Fig. 7.5, 7.6)

Endocrine follow-up at 12 months showed adequate control of hormonal values under medication, though not entirely within the normal reference range. More significantly, the patient's symptoms of fatigue and headache had improved dramatically, and his quality of life was markedly better.

## DISCUSSION

### Controversies

The use of Gamma Knife as a primary treatment for GPAs is debated. Surgery is often considered the first-line option, particularly for patients with severe visual symptoms or those with tumors causing obstructive hydrocephalus. However,

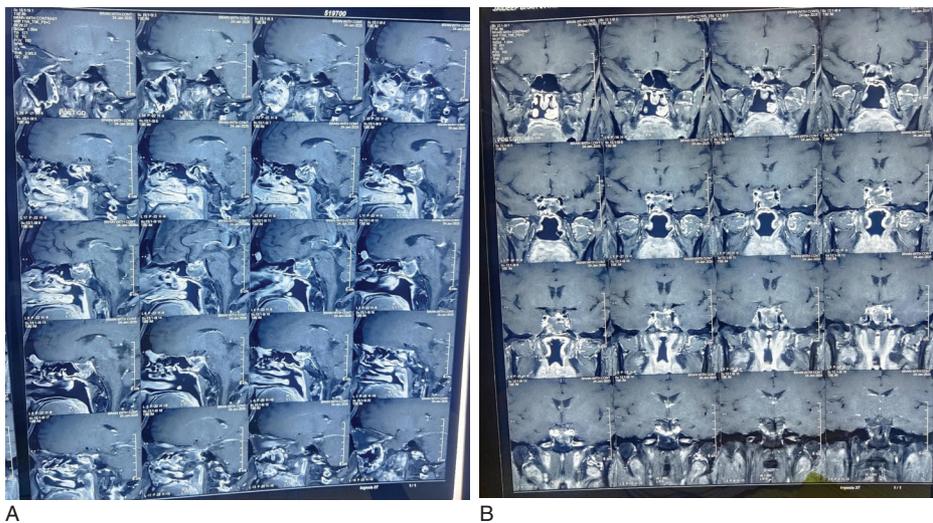


Figure 7.4

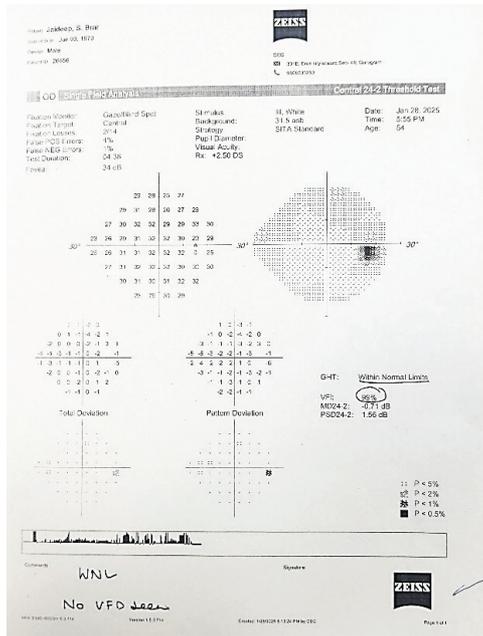


Figure 7.5

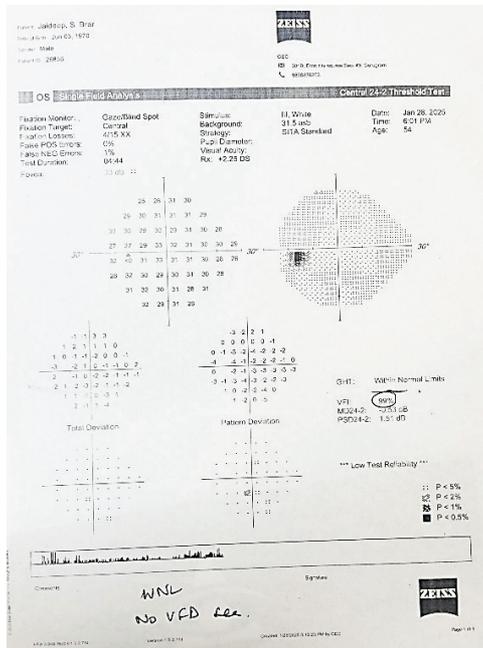


Figure 7.6

complete resection of large tumors is often difficult and may involve significant risk, particularly when the tumor invades the cavernous sinus or encases neurovascular structures. Critics argue that GKRS, while non-invasive, may not immediately relieve mass effect or restore pituitary function. Additionally, the response to radiosurgery is often delayed, with full radiological and clinical benefits seen over months to years, which may not be suitable for rapidly progressive cases.<sup>3-4</sup>

### Current Practice

Surgical resection remains the standard for most GPAs. Endoscopic endonasal approaches have improved resection rates but still pose risks when tumors extend laterally or superiorly. In patients who are poor surgical candidates or when the tumor involves critical areas, GKRS serves as a valuable alternative. Studies have demonstrated favorable outcomes with primary radiosurgery, including durable tumor control and functional improvement.<sup>6-8</sup> The integration of radiosurgery into multimodal treatment plans is becoming increasingly common, especially for residual or recurrent tumors post-surgery.<sup>3,10</sup>

### Learning Points

- GKRS can offer effective tumor control and symptom relief in selected cases of GPA where surgery is not possible or is high risk.
- The technique provides precise, high-dose radiation delivery while sparing surrounding critical structures, such as the optic chiasm and hypothalamus.
- Long-term monitoring of endocrine function is crucial, as hormonal normalization may be incomplete despite tumor shrinkage.
- Optimal patient selection and individualized treatment planning are critical for success.

## CONCLUSION

Primary Gamma Knife radiosurgery represents a promising option for patients with giant pituitary adenomas who cannot undergo surgery or where tumor location makes resection unsafe. The present case illustrates significant tumor reduction, improved vision, and enhanced quality of life within a year of treatment. While not a replacement for surgery in all cases, GKRS plays an increasingly central role in the multidisciplinary management of these complex tumors. Future studies with long-term follow-up are necessary to better define its role as a standalone treatment.

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# Gamma Knife Radiosurgery for Glomus Jugulare

Dattaraj P Sawarkar ■ Abhishek Kumar ■ Deepak Agrawal

## INTRODUCTION

Glomus Jugulare tumors (GJTs) are uncommon neuroendocrine tumors that tend to occur more frequently in females.<sup>1</sup> Patients often present with symptoms such as hearing loss, pulsatile tinnitus, ear pain, a feeling of fullness in the ear, vertigo, and dysfunction of the lower cranial nerves.<sup>2</sup> About 1% to 3% of GJTs are secretory and may exhibit clinical signs indicative of catecholamine overproduction.<sup>3</sup> Despite being benign, these tumors are difficult to treat owing to their hypervascularity and proximity to critical neurovascular structures near jugular foramen. Due to its indolent nature, it grows slowly at a rate of 1 mm/year, therefore treatment is typically recommended to symptomatic patients.<sup>4</sup> In the past, microsurgery, with or without preoperative embolization, was the primary method of treatment.<sup>5</sup> However, surgical excision of the tumor is associated with considerable post operative morbidity including cerebrospinal fluid leaks (3.7%-17.6%) and lower cranial nerve deficits (6.6%-61%).<sup>6</sup> Due to a better side effect profile, conventional stereotactic radiosurgery has emerged as a preferred option, either alone or in combination with surgery.<sup>5</sup> Tumor control rates of 90% to 100%, along with fewer side effects and improved quality of life, have been reported, making GKRS the preferred treatment option.<sup>7,8</sup> Drawbacks of conventional RT include the exposure of healthy tissue to high doses of radiation, as well as long-term complications such as temporal bone necrosis, cerebral necrosis, and radiation-induced malignancies.<sup>9,10</sup> Stereotactic radiosurgery (SRS), with its capacity to deliver radiation precisely and its steep dose decline at the tumor margins (Bragg peak effect), provides a better safety profile and has emerged as a primary treatment option for GJTs.<sup>11-13</sup>

## REPRESENTATIVE CASE

### History & Examination

*A 30 year old gentleman presented to our Outpatient department with complaints of gradually progressive visual deterioration in both eyes for 6 months associated with insidious onset diplopia on left lateral gaze. On neurological examination, he was found to*

have left lateral rectus palsy.

### Imaging

His CMRI brain showed an intensely enhancing 24cc mass in the Left temporal bone suggestive of left Glomus jugulare with extra cranial extension.

### GKRS Protocol

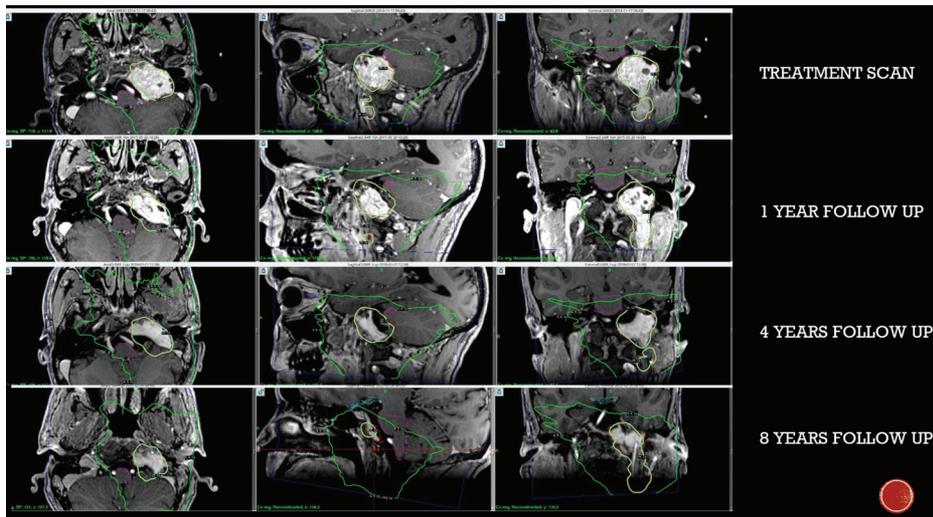
He was scheduled for GKRS at our institute. A dose of 25Gy was given at 50% isodose line. Rt Optic nerve received <7.5 Gy, while Lt optic nerve received <5.4 Gy. Chiasm received <5.5. Gy

### Follow Up

His post GKRS MRI, done after an interval of 1,4 and 8 years after GKRS showed significant reduction in size of tumor (Fig. 8.1).

## DISCUSSION

Given the biphasic and slow growth pattern of these benign tumors, it is crucial to customize treatment strategies to minimize post-treatment complications and preserve the quality of life in patients with GJTs.<sup>4</sup> Also, Radiosurgery uses a single high-dose radiation fraction targeted at a small area, whereas conventional radiotherapy delivers multiple fractions to a larger volume. SRS has become a primary treatment modality for this condition, offering a superior safety profile compared to surgery, while achieving similar tumor control rates (tumor recurrence rate of 3.1% for micro-neurosurgery versus 2.1% for SRS).<sup>14</sup> While tumor cells are known



**Figure 8.1** Patient with Lt Glomus showing significant decrease in tumor size over a follow up of 8 years.

to persist after radiation therapy, the primary theory supporting the use of RT for these tumors is its effect on the vasculature, causing fibrosis which leads to growth stabilization or inhibition.<sup>15</sup>

## CURRENT PRACTICE

GKRS is now considered a primary treatment option for GJTs, especially in patients with high surgical risk or residual tumors post-surgery. Tumor control rates across studies range from 80% to 100% with median doses of 13.5 to 20 Gy.<sup>13,16,18</sup>

Sheehan et al., in the largest multi-institutional series published to date (n = 132 patients, 134 procedures), reported an actuarial tumor control rate of 90% at 3 years and 88% at 5 years, respectively.<sup>16</sup> In line with this study, we observed a comparable 5-year tumor control rate of 87% ± 6%.<sup>17</sup> In their study, Ibrahim et al. reported a 5-year tumor control rate of 92.2% in 75 patients (76 tumors) using a median prescription dose of 18 Gy (range 12-25 Gy).<sup>18</sup>

## CLINICAL RESPONSE

In the literature, transient and permanent clinical worsening has been reported in up to 16% of patients following SRS for glomus tumors.<sup>16,18</sup> In contrast, Sharma et al. did not observe any new cases of cranial nerve paresis in their study.<sup>17</sup> This could be attributed to the lower median prescribed dose used in our study (15 Gy compared to 18 Gy in the other study)<sup>18</sup>. In their study, Sheehan et al. reported that 15% of patients experienced worsening of pre-SRS cranial nerve deficits, while 11% showed improvement following SRS.<sup>16</sup> In the same study by Sheehan et al., pre-existing tinnitus improved in 49% of patients following SRS.<sup>16</sup> Another study found that pulsatile tinnitus resolved in 8% of patients, while hearing improved in 4% of patients.<sup>18</sup> Progressive reduction in tumor blood flow is proposed to cause improvement in tinnitus post GKRS. Sheehan et al. attributed the worsening of cranial nerve deficits to the adverse effects of radiation, even though good radiographic tumor control was achieved.<sup>16</sup>

## PREDICTORS OF OUTCOME

Sheehan et al. identified preoperative trigeminal nerve dysfunction (hazard ratio [HR]: 11.109, P = .001), a higher number of isocenters (HR: 0.767, P = .005), and stable or improved cranial nerve dysfunction at the last follow-up (HR: 7.618, P = .002) as independent predictors of tumor-progression-free survival in their cohort.<sup>16</sup> However, none of the patient, tumor, or treatment-related variables were found to be significantly associated with the tumor control rate in Sharma et al.'s study.<sup>17</sup>

## CONTROVERSIES

In a recent recent meta-analysis, which compared various SRS platforms, tumor control rate was reported to be 97%, with either GK (95% confidence interval: 94%-99%) or linear accelerator (LINAC) (Novalis, Brainlab Inc)/Cyber Knife® (CK,

Accuray Inc, Sunnyvale, California; 95% confidence interval: 92%-100%).<sup>19</sup> In a similar vein, clinical control rates of 94% and 97% were reported with GK and Cyber Knife® (CK), respectively, in this study.<sup>19</sup> This meta-analysis analyzed 19 studies (14 involving GK, n = 278, and 5 involving LINAC/CK, n = 57), with 10 of the studies having a mean or median follow-up duration greater than 36 months. Overall, no differences in tumor or clinical control rates have been observed based on the type of SRS platform. In their study, Dupin et al. reported 5-year and 10-year actuarial tumor control rates of 100% and 98.7%, respectively, in 66 patients with 81 head and neck paragangliomas treated with conventional external beam RT, at a median follow-up of 4.1 years (range: 0.1-21.2 years).<sup>7</sup> The recent introduction of the stereotactic frameless GK Icon™ system (Elekta AB) has made it possible to treat large GJTs using fractionated GK radiosurgery with a margin. This approach helps avoid complications linked to treating large tumors in a single session while still achieving effective tumor control.<sup>20</sup>

## CONCLUSION

GKRS is a safe and effective treatment for patients with GJTs, providing durable long-term control. GKRS should be considered for healthy young patients as the risk of long-term significant neurological complications is greater following surgery than after GKRS. Additionally, GKRS can be utilized as either an initial or salvage treatment after surgical resection, with favorable long-term outcomes.

## LEARNING POINTS

- GJTs are best managed with individualized treatment planning given their benign nature and slow growth.
- GKRS offers high tumor control with minimal morbidity, especially in anatomically complex cases.
- Radiation-induced vascular fibrosis is the likely mechanism for tumor stabilization.
- Clinical outcomes are generally independent of SRS platform, with comparable results reported across GK and LINAC-based systems.
- Fractionated GKRS using newer platforms enables safe treatment of larger lesions.

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SECTION III

**Vascular Malformations**

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# Gamma Knife Surgery in Intracranial Dural Arteriovenous Fistulas

Prachi Singh ■ Deepak Agrawal

## INTRODUCTION

The management of intracranial dural arteriovenous fistulas (dAVFs) has evolved to include multimodal approaches, with stereotactic radiosurgery (SRS) emerging as a viable treatment. Initially reserved for non-aggressive dAVFs, SRS is now used for aggressive cases, offering comparable outcomes to embolisation and surgery. SRS achieves complete obliteration in 50–93% of cases, with an average latency of 23 months. While embolisation provides immediate relief, SRS is less invasive and preferred by patients due to lower risks of infection and complications. Factors influencing SRS success include location, absence of cortical venous drainage, and smaller target volumes. SRS is increasingly considered a first-line treatment.

## HISTORY AND EXAMINATION

A 14-year-old male presented with complaints of headache, pulsatile tinnitus and two episodes of generalised tonic-clonic seizure. On examination, no neurological deficits were present. He underwent an MRI followed by DSA and was diagnosed with right petrous Dural AVF with Cortical Venous Drainage (CVD). The patient and his guardians were apprised of the disease and offered the option of GKRS, embolisation or surgery along with all the pros and cons of the different procedures. They decided to go ahead with GKRS.

### Imaging

Cerebral angiography, complemented by high-resolution stereotactic MR images, is essential for dose planning. Although most small dAVFs are not fully visualised on MR images, MRI remains valuable for assessing the 3-dimensional conformity of the dose plan and identifying critical brain structures at risk. Additionally, MRI aids in selecting the optimal dose, as the margin dose is determined based on the risk to nearby critical structures. High-quality digital subtraction angiography is crucial for accurate radiosurgery dose planning for dAVFs. We need to ensure that the dAVF is visible in both AP and lateral views, all fiducial markers are identifiable,

and adequate subtraction views are obtained. The images that best depict the dAVF should then be selected and uploaded to the dose planning system and co-registered with the MRI.

### **GK Protocol**

The patient underwent an MRI the day before treatment delivery. On the day of treatment, the Leksell stereotactic G frame was first secured with anterior posts fixed above the supraorbital ridge and posterior posts fixed to the occipital bone. The patient was then taken for digital subtraction angiography which was fused with the MRI.

Planning was done on the co-registered MRI and DSA which involved demarcating the target lesion and at-risk area, i.e., the brainstem and the right cochlea. The dose prescription is determined by the location and volume of the dAVF. The margin dose for the dAVF typically ranges from 18 to 25 Gy in a single session. The doses are determined by the location and volume of the dAVF. The margin dose for the dAVF typically ranges from 18 to 25 Gy in a single session. We used lightning software for planning the dose delivery after setting the prescription dose of 25 Gy at 50% isodose line. Dural AVF with a total volume of 3.9cc receives a mean dose of  $33.2 \pm 5.6$  Gy.

### **Follow Up**

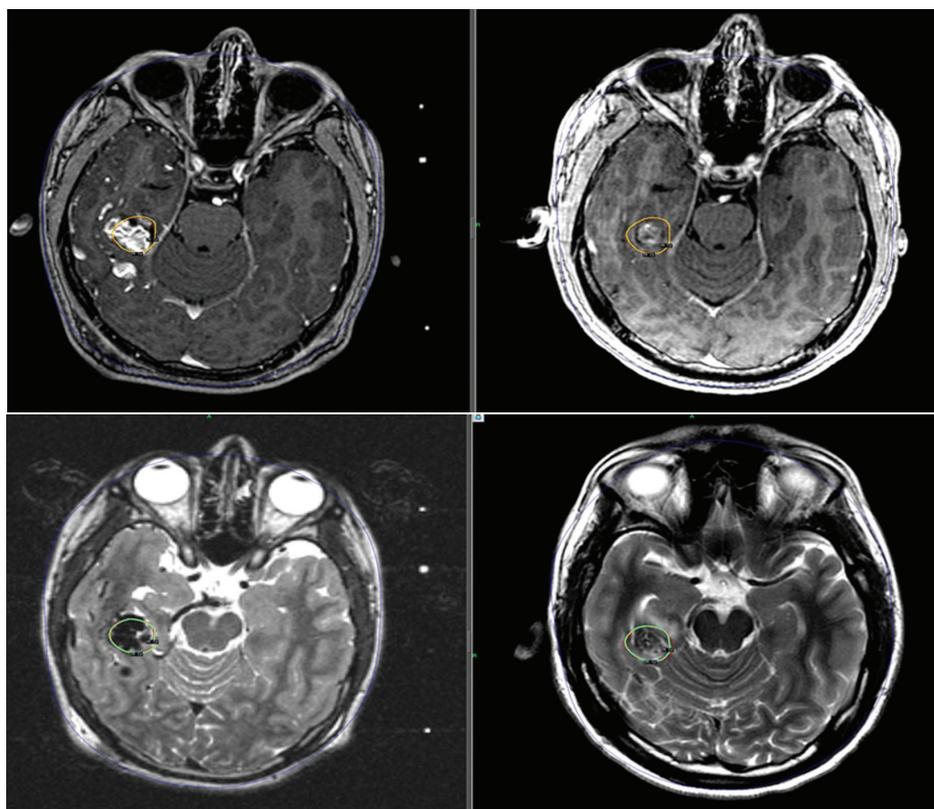
The patient underwent follow-up contrast MRI and DSA after 3 years. (Fig. 9.1 and Fig. 9.2 depict 3 years of follow-up MRI and DSA respectively). The follow-up MRI shows a significant reduction in volume, from a treatment volume of 3.9cc to 0.6cc residual volume. The follow-up DSA showed no residual AVF. The patient reported improvement in symptoms and no episodes of seizure 3 years post-GKRS. As a result, anti-epileptics were gradually tapered off.

## **DISCUSSION**

The management of dural arteriovenous fistulas (dAVFs) has evolved significantly over the decades, transitioning from observational approaches to advanced multimodal therapies that integrate embolisation, surgery, and radiosurgery, all tailored to dAVF characteristics. Stereotactic radiosurgery was first utilised for treating arteriovenous malformations (AVMs) in 1970 and later extended to the management of dural arteriovenous fistulas (dAVFs) in the late 1970s.

## **CURRENT PRACTICE**

For achievement of successful treatment outcome of intracranial dAVFs, treatment strategies should be decided according to the angiographic characteristics of the dural AVF- based on the location, venous ectasia and drainage pattern as well as clinical characteristics such as the severity of the symptoms and perceived risk for intracranial haemorrhage. While Endovascular embolisation and surgery have long



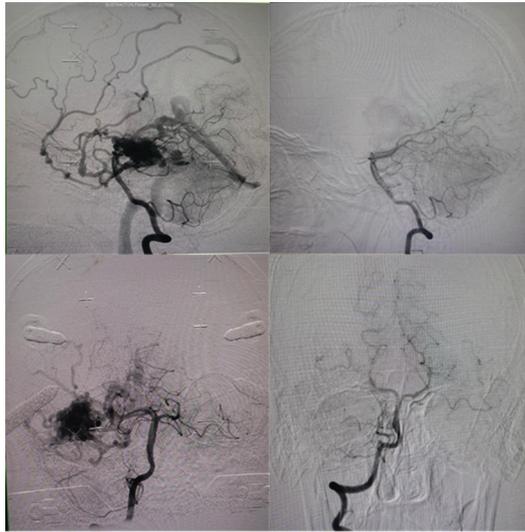
**Figure 9.1** Right side- treatment MRI :T1+C (above) and T2 (below) sequences, Left side- follow up MRI at 3 year: T1+C and T2 sequences. Red line marks the target and the yellow line shows the 25 Gy isodose line. The follow up MRI shows significant reduction in volume from 3.9 cm<sup>3</sup> treatment volume to 0.6 cm<sup>3</sup> residual volume.

been regarded as the preferred treatment modalities due to the achievement of immediate obliteration, emerging evidence has established GKRS as a desirable treatment option. Despite its delayed obliteration time (at least 6 months),<sup>1,2</sup> GKRS is effective for both aggressive (high rates of intracranial haemorrhage- ICH, neurological deficits and with cortical venous drainage- CVD) and benign/non-aggressive groups (lack of CVD, Cognard type I and IIa, low rates of ICH and transient or mild neurological symptoms).

Complete obliteration is reported in 50%–93% of dAVF, treated by GKRS with the average latency period of dAVF closure reported as 23 months (minimum 6 months).<sup>1,2,5</sup>

## CONTROVERSIES

Initially, Gamma Knife Radiosurgery (GKRS) was reserved as a treatment option for dAVFs for non-aggressive dAVFs, as these are less likely to cause immediate



**Figure 9.2** Right side- treatment DSA: Lateral (above) and PA (below) sequences, Left side- follow up DSA at 3 year Lateral(above) and PA(below). The follow up DSA shows no residual AVF.

complications. GKRS was also considered for residual or recurrent dAVFs as an adjunct to embolisation and surgery, as well as inaccessible dAVFs located in areas that are surgically challenging, or inaccessible arterial feeder during angiography. Dural AVFs with CVD are well-known to carry a significantly higher risk of haemorrhage compared to those without CVD, with an annual risk of haemorrhage of 1.4%-3% in patients with unruptured DAVFs with CVD vs 7.4%-46% of rebleed in patients with ruptured dAVFs.<sup>1</sup>

Recent studies<sup>1,3,7</sup> have compared the efficacy of GKRS as a stand-alone treatment option in aggressive dAVFs to endovascular embolisation in terms of clinical improvement, radiological obliteration and risk of haemorrhage in the latency period of around six months before obliteration of the fistula. A study at our institute<sup>1</sup> has shown clinical improvement in 77.78% of the patients who received GKS for DAVF with CVD, and 57.7% in the patients who underwent embolisation ( $p = 0.431$ ) and complete obliteration of DAVF was seen in 55.56% of the patients in the GKS group and 57.7% of the patients in the embolisation group ( $p = 1$ ). Still, a controversy exists in terms of its effectiveness as a monotherapy in cases with CVD with studies at different institutes showing contradictory results in terms of risk of subsequent haemorrhage or radiation-related complications. However, none of the studies have reported a drastic increase in the risk of post-GKRS haemorrhage or poor obliteration rate compared to the endovascular group.<sup>1,7</sup> Some studies have advocated for SRS followed by embolisation where embolisation can provide early symptom relief and SRS offers the potential for delayed complete fistula closure.<sup>6</sup>

Factors that have a positive impact on the obliteration rates of DAVF following SRS are the location of DAVF with the cavernous sinus DAVF having much better obliteration rates than DAVF located at other locations, Borden Type I or Cognard

Types III or IV DAVFs, absence of CVD, haemorrhage at the time of initial presentation, and target volume lesser than 1.5 mL.<sup>3,4,7</sup>

The most important factor that is to be considered is the growing patients' preference for GKRS as the choice of dAVF treatment owing to the absence of surgical incisions or catheter insertions and lower risk of infection or procedural complications. Latency period haemorrhage and radiation-induced changes to the perinidal parenchyma though not abundantly reported are the potential complications post-GKRS. In contrast, embolisation or surgery, being an invasive procedure, carries a higher risk of serious complications, occurring in up to 25% of cases- Onyx migration, intraparenchymal hematoma, and delayed cerebral venous infarction.<sup>8</sup> Additionally, multiple reports have documented the recurrence of dAVFs that appeared to be cured after embolisation.<sup>6</sup>

## LEARNING POINTS

- GKRS achieves 50%–93% obliteration in dAVFs with an average latency of 23 months.
- Comparable clinical and radiological outcomes to embolisation are observed, especially in CVD-positive cases.
- Favorable predictors include small target volume (<1.5 mL), absence of CVD, and cavernous sinus location.
- Patient selection and precise dose planning are critical for success.
- GKRS should be strongly considered in dAVFs with CVD, particularly when surgical or endovascular risks are high.

## CONCLUSION

Gamma Knife Radiosurgery is a safe and effective modality for treating intracranial dural AVFs, including those with cortical venous drainage. Given its comparable outcomes to embolisation and a better safety profile, GKRS should be considered a first-line treatment in appropriately selected cases. Advances in imaging, dose planning, and increasing clinical experience are likely to further expand its indications in the coming years.

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# Gamma Knife Radiosurgery for Spetzler-Martin Grade III Cerebral Arterio-Venous Malformations

Satish Verma ■ Deepak Agrawal

## INTRODUCTION

Cerebral arterio-venous malformations (AVMs) are an important cause of morbidity and mortality. Spetzler-Martin (SM) grading categorizes AVMs into 5-tiers depending on the size of nidus, eloquence of the area involved and type of venous drainage. SM grade III (SM III) AVMs are peculiar, as they comprise of the most heterogeneous groups as far as angioarchitecture, drainage and eloquence are concerned. This category is a borderline zone where few expert neurosurgeons will still offer microsurgical excision to subset of these AVMs. But the majority of centers offer non-invasive or minimally invasive options like Gamma Knife Radiosurgery (GKRS) or endovascular embolization. An unruptured SM III AVM can be managed effectively with upfront GKRS with complete obliteration in the majority of cases.

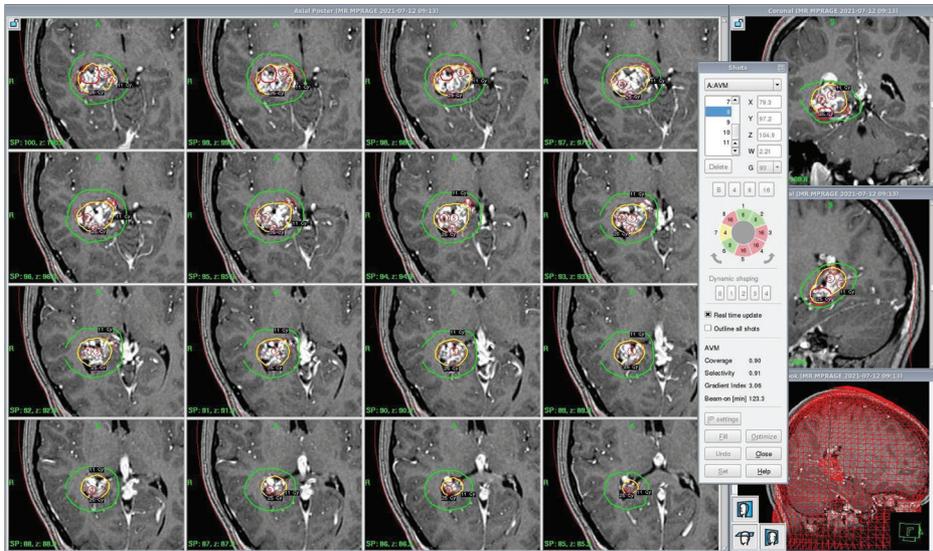
## REPRESENTATIVE CASE

### History & Examination

A 20 year old female, housewife presented with progressive headaches for 6 months. Headache was occipital in distribution, not associated with nausea, vomiting or visual obscuration. No history of seizures, loss of consciousness or sudden onset severe headache or motor weakness. Her neurological examination was within normal limits.

### Imaging

A screening brain computed tomography scan showed a hyperdense lesion in the atrium of right lateral ventricle with extension to right thalamus. Contrast enhanced MRI of brain showed multiple flow voids on T2WI with contrast enhancement. Train-of-flight (TOF) magnetic resonance angiography (MRA) confirmed AVM (Spetzler-Martin Grade III, type IIIB (S1E1V1)). Digital subtraction angiography



**Figure 10.1** Gamma Knife planning for the index case. AVM nidus margin (red), 12 Gy (prescription dose) isodose line (yellow).

(DSA) with 6 vessel catheterisation revealed a right sided AVM with feeders primarily from the posterior choroidal branches of right posterior cerebral artery and early venous drainage into the deep venous system. In view of the unruptured status of AVM and multiple small feeders from posterior choroidal arteries, she was offered GKRS.

### GK Protocol

For the purpose of Gamma Knife planning, after fixation of Leksell-G stereotactic frame, post-gadolinium 3-dimensional (3D) Magnetization -Prepared Rapid Gradient Echo (MPRAGE) sequence and 3-D TOF MRA were acquired in axial plane with voxel size  $1.0 \times 1.0 \times 1.0$ , slab 1, slice per slab 176 and Field of View (FoV) 256 mm. Images were transferred to the treatment planning system (TPS) in Digital Imaging and Communications in Medicine (DICOM) format.

Gamma knife was performed on a Leksell Gamma Knife Perfexion unit (Elekta AB, Stockholm, Sweden) with Leksell GammaPlan. Manual AVM segmentation was done for the tumor and Organ-at-risk (OAR) (brainstem). Total tumor volume was 6.96 cubic centimetre (cc). Inverse planning with optimization of 19 iso-centres (combinations of 4, 8 and 16 mm collimators) was performed with prescription dose of 25 Gy at 50% isodose line to the AVM nidus margin (Figure 10.1). Further optimization was done manually to exclude OAR out of the prescribed dose constraints achieving following parameters - coverage -90%, selectivity - 91%, Gradient Index - 3.06. Beam-on time (BOT) was 123.3 minutes with a treatment dose rate of 0.963 Gy/min. Maximum dose to the segmented volumes were : AVM nidus - 50.1 Gy and brainstem - 10.5 Gy (Figure 10.2).

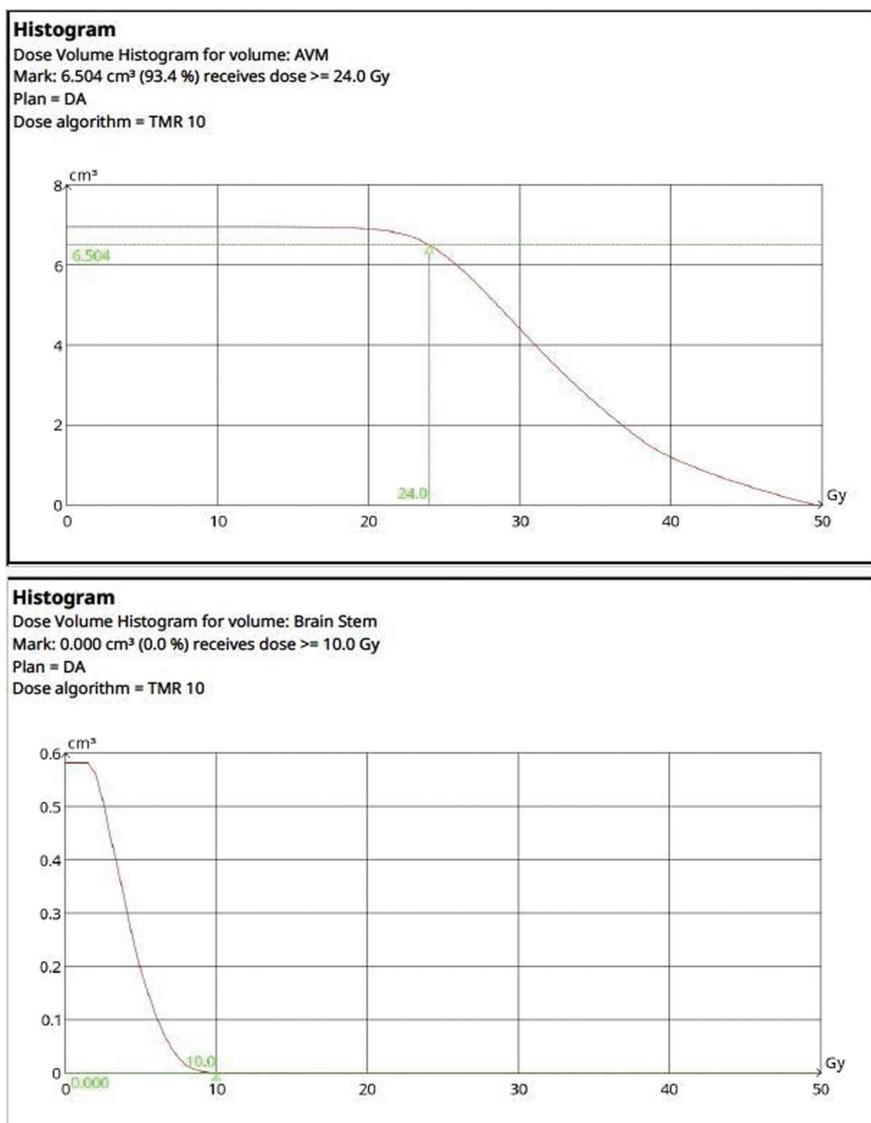
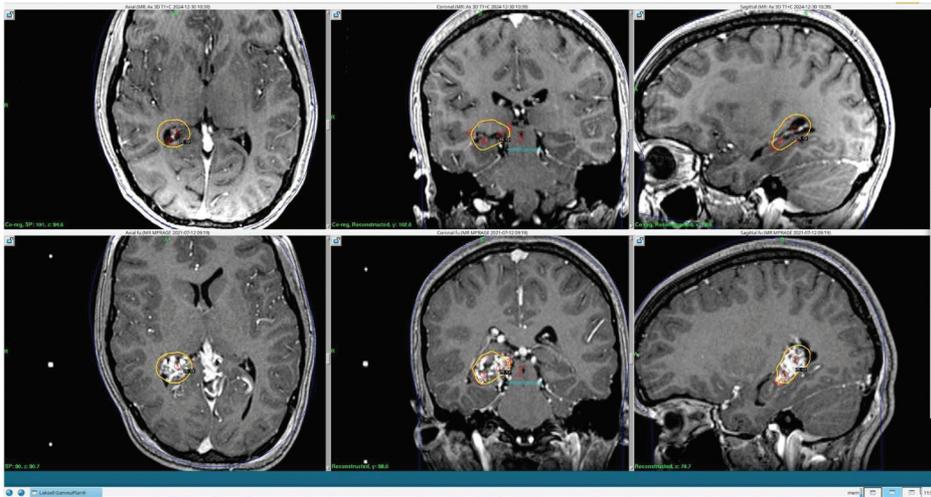


Figure 10.2 Dose volume histogram (DVH) for the AVM and brainstem.

## Follow Up

Patient tolerated the procedure well. Follow up clinical visit after 6 months was done and no significant complaints were reported. Follow up CEMRI was done annually which showed gradual reduction in AVM volume. At the last follow up available, at 39 months, AVM was obliterated completely (Figure 10.2). No post-radiation imaging changes were appreciated on MRI. She is planned for digital subtraction angiography after 1 year.



**Figure 10.3** Follow-up MRI done after 39 months (upper panel) compared to the baseline MRI at the time of GKRS (lower panel) showing complete obliteration of the nidus and decrease in the number and size of draining veins.

## DISCUSSION

Brain AVMs are the most common vascular malformations with the prevalence of symptomatic brain AVMs of about 1.2 per 100,000 population.<sup>1</sup> In general, the annualized risk of future hemorrhage is roughly 1.8% when the brain AVM are unruptured at presentation and 4.7% when they are ruptured.<sup>2</sup> The cumulative risk of future hemorrhage is 16% and 19% at 10 and 20 years respectively when the AVM is unruptured at presentation, and 35% and 45% at 10 and 20 years when they present with a hemorrhage.<sup>2</sup> The chances of significant permanent neurologic deficit or death from a hemorrhagic event is about <50% and <10% respectively. Ding et al suggested a 3 – tier classification (Class A, B and C) of AVMs based on the original 5–tier gradings (Spetzler-Martin grades I–V) for management recommendations.<sup>3</sup> Management of Class A (SM grades I–II) and Class C (SM grades IV–V) AVMs is relatively straightforward. Class B (SM III) AVMs are different as they comprise of the most heterogenous groups as far as angioarchitecture, drainage and eloquence are concerned. SM grade III AVMs can be classified further into 4 types as follows: IIIA – S1E1V1, IIIB – S2E0V1, IIIC – S2E1V0, IIID – S3E0V0.<sup>4</sup>

## CONTROVERSIES

The management of SM Grade III AVMs remains a topic of debate. Some centers advocate surgical resection in selected patients, particularly those with accessible lesions and favorable angioarchitecture. Others favor GKRS for unruptured AVMs due to its minimally invasive profile. The latency period following GKRS poses a hemorrhage risk, prompting discussions on the necessity and timing of adjunctive

embolization. Moreover, the use of staged radiosurgery—either volume-staged or dose-staged—is not universally standardized and raises questions regarding optimal timing and fractionation protocols.

Clinical presentation with or without intracranial hematoma (ICH) is an important point for deciding management. AVMs presenting with ICH are at a greater risk of rebleed. If feasible, at least partial embolization is recommended to secure the fragile substrate of AVM. Unruptured SM grade III AVMs can be managed effectively with primary GKRS. Nguyen et al reported their experience with GRS for 307 SM grade III AVMs. They achieved 68.7% complete obliteration rate at a median follow-up of 53.3 months with a latency of about 24 months. Interestingly, the complete obliteration rates had linear correlation with the subtypes – type III A had highest obliteration rates (80.8%) and type III D had the lowest obliteration rate (25.0%).

AVM nidus obliteration ranges from 70%–90% when the prescribed dose to the nidus margin is  $>18$  Gy.<sup>5</sup> Radiation induces endothelial cell proliferation that results in progressive luminal closure and gradual obliteration of the nidus. There is an inherent latent period before the AVM obliterates completely, exposing the subject to the risk of AVM hemorrhage during the latent period. Most important factors predicting AVM obliteration are AVM volume<sup>6–8</sup> and marginal dose.<sup>5,8</sup> *AVM volume* is the strongest predictor of obliteration after GKRS. However, complete in-field obliteration has positive correlation with margin dose rather than AVM volume.<sup>8</sup> In principle, margin dose needs to be reduced for a larger volume AVM, to avoid adverse radiation effects and that is the reason for lower obliteration rates for large volume AVMs. In addition, incidence of untargeted residual AVM nidus (residual AVM volume which was not included in target at the time of GKRS) increases with AVM volume. Most important factor contributing to this is post-embolization status. *Marginal dose*, in general, is a very important factor determining AVM obliteration rates. Flickinger et al analyzed dose-response of AVM radiosurgery and concluded that AVMs demonstrate highest obliteration rates of 88% with a marginal dose of 25 Gy. Importantly, there was no additional benefit if marginal dose was increased  $>25$  Gy. In addition, marginal dose  $<18$  Gy predicted inferior obliteration rates.<sup>5,9</sup> *Cobalt-60 dose-rate* is also reported as an important factor for AVM obliteration. Dose rates  $>2.9$  Gy/min were associated with significantly higher rates of obliteration as compared to dose rates  $<2.1$  Gy/min.<sup>10</sup> *Age of the patient* was proposed as an important factor, increasing age considered as negatively correlated with obliteration rates. Pollock and Flickinger incorporated age as a negative predictor in their radiosurgery-based AVM score. However, recent studies find no statistically significant difference in obliteration rates based on age.<sup>11,12</sup>

Type III B, III C and III D grade AVMs have an inherent component of a large nidus size of  $>3$  cm. Conceptually, radiosurgery was developed by Leksell as a focused and accurate delivery of radiation to a particular target in a single stage.<sup>13</sup> Single stage radiosurgery is still the norm for the majority of indications. Factors that limit a single stage dose delivery to achieve treatment goal are larger target volume and larger prescribed marginal dose, as the dose spillage over the surrounding

normal neural tissue has to be taken into consideration to avoid long term adverse radiation effects (AREs), specifically radiation necrosis. Usual standards consider that the  $V_{12}$  (Volume of normal brain minus gross target volume) should not exceed 10 cubic centimeters (cc), as the risk of radiation necrosis exceeds 10% if the  $V_{12}$  exceeds 10 cc.<sup>14</sup> With these strict dose constraints to the normal brain tissue, the risk of radiation necrosis can be kept at a predictably low rates. However, it limits the volume of AVM that can be treated or the radiation dose that can be prescribed to the target margin in a single stage. Large AVMs were defined differently by different authors. The size of nidus - either maximum dimension >3 centimeters (cm) or volume >10-15 cubic centimeters (cc) were considered large by most of the authors performing staged SRS, as the  $V_{12}$  exceeds beyond the recommended limits over and above these dimensions.<sup>15,16</sup> Another important way of preventing radiosurgery related complications is to keep the draining vein out of the radiation field. Shielding the draining vein resulted in lesser new post-GKRS neurological deficits, less incidence of AVM bleed and adverse radiation effects.<sup>17</sup>

Considering the above limitations, the concept of staged radiosurgery evolved to optimize the obliteration rates with acceptable long-term complications. There are two distinct strategies to stage AVM radiosurgery – Volume staged SRS (VS-SRS) and Dose staged SRS (DS-SRS). Pollock et al conceptualized volume-staged radiosurgery for AVMs. They published their experience with 10 patients where they compared the radiation dosimetry of VS-SRS to hypothetical single session SRS (SS-SRS).<sup>18</sup> They found that VS-SRS decreased the  $V_{12}$  by an average of 27.2% as compared to SS-SRS and this difference was statistically significant without compromising the AVM obliteration rates. The ideal duration between two stages of SRS is debatable. The duration between stages with VS-SRS varies from 2-9 months and for DS-SRS ranges from 1 day to a few weeks.<sup>15</sup> The criteria are not well defined, due to limited understanding of the underlying radiobiological principles. Considering the low  $\alpha/\beta$  (3.5) for AVMs with respect to the linear quadratic equation used to estimate the radiobiological response after radiation, fractionation, conceptually, should increase the therapeutic index.

Dose fractionated SRS for AVMs was first described by Kirkeby et al.<sup>19</sup> Over the last two decades, many centers have published their experience with this technique, also termed as hypo-fractionated SRS (2-5 fractions). Proponents of DS-SRS argue that this technique is straightforward in the sense that the radiosurgical planning is similar to single stage SRS (SS-SRS) as the volume subset segmentation is not required. Also, the chances of post-SRS latency hemorrhage are lesser when compared to VS-SRS as there is no differential irradiation which can lead to flow redirection within AVM and altered flow dynamics theoretically leading to lower bleed rates in DS-SRS technique.

## LEARNING POINTS

- Spetzler-Martin Grade III AVMs are a heterogenous group of AVMs
- Unruptured AVMs can be managed with primary GKRS.

- AVM nidus volume and marginal dose are strong predictors of AVM obliteration rate.
- Type III A have the highest obliteration rates due to small nidus volume that allows a higher marginal dose.
- Type III D are large volume AVMs and may be offered a staged treatment to avoid adverse radiation effects.

## CONCLUSION

Spetzler-Martin grade III cerebral AVMs are a heterogeneous group of AVMs. Primary GKRS for unruptured AVMs is recommended treatment modality considering good obliteration rates and low rates of complications. Small nidus volume and higher marginal dose predict good obliteration rates. Volume of normal brain receiving  $>12$  Gy ( $V_{12}$ ) of radiation should not exceed 10 cc to keep rates of adverse radiation effects less than 10%. Staged GKRS is an effective method to reduce  $V_{12}$  and thus complications. Type III A AVMs have best obliteration rates. Type III A AVMs are mostly treated in single session, unless in brainstem. Type III D may require a staged GKRS depending on the volume of nidus. For ruptured AVMs, it is recommended to secure high-risk substrate of AVM, if feasible with endovascular approach, to prevent rebleed.

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# Draining Vein Shielding During Gamma Knife Radiosurgery in Intracranial Arteriovenous Malformations

Deepak Agrawal ■ Mahnaaz Sultana

## INTRODUCTION

Gamma Knife radiosurgery (GKRS) has emerged as a pivotal tool in the management of intracranial arteriovenous malformations (AVMs), particularly for deep-seated or surgically inaccessible lesions. By delivering highly focused radiation, GKRS promotes gradual endothelial proliferation, leading to nidus obliteration over time. However, the presence of a major draining vein within or adjacent to the radiation target presents a significant challenge. Shielding the draining vein is often necessary to prevent radiation-induced venous thrombosis, which can lead to venous infarction, increased intracranial pressure, and hemorrhagic complications. Nevertheless, shielding the vein may compromise the effectiveness of the treatment by leaving portions of the nidus untreated, necessitating a staged approach.

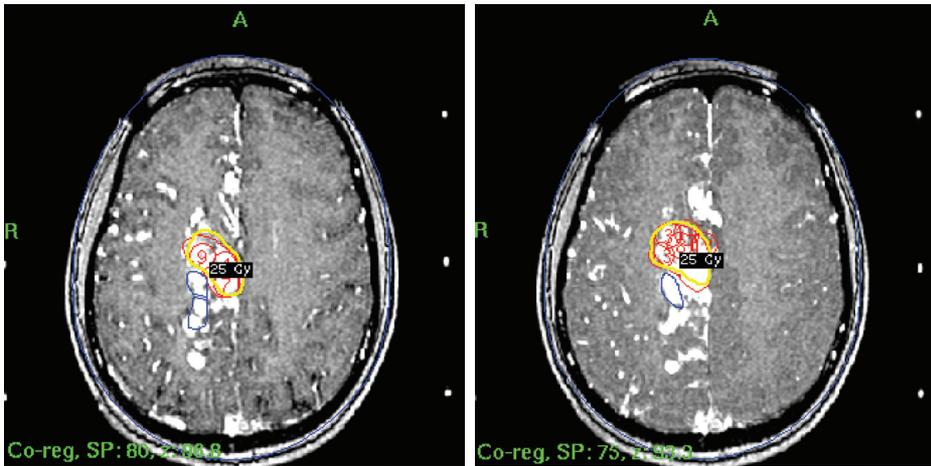
In this chapter, we present a case of a right striatal AVM treated with GKRS, where the treatment plan required partial shielding of the draining vein. We discuss the rationale, planning strategies, outcomes, and future considerations for improving AVM radiosurgery outcomes while mitigating risks associated with draining vein involvement.

## CASE PRESENTATION

### History and Examination

A 24-year-old female presented with a 10-month history of progressive left-sided weakness. She denied any history of seizures, headaches, or previous cerebrovascular events. Her past medical history was unremarkable, with no history of prior neurosurgical interventions or systemic illnesses.

Neurological examination revealed left-sided motor weakness (4/5) without sensory deficits. Fundoscopic examination showed no signs of papilledema. The

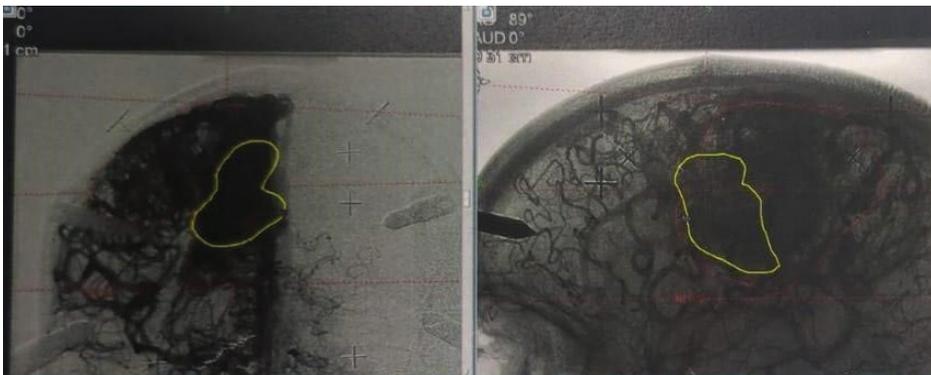


**Figure 11.1** Gamma knife radio-surgery planning for right striatal AV malformation draining into internal cerebral vein.

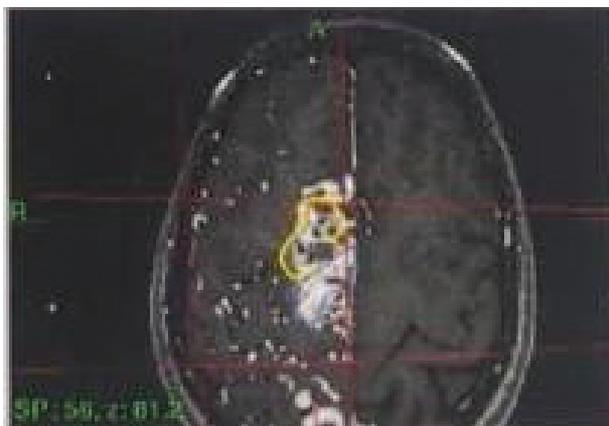
patient's cognitive function remained intact, and cranial nerve assessment was unremarkable.

### Imaging

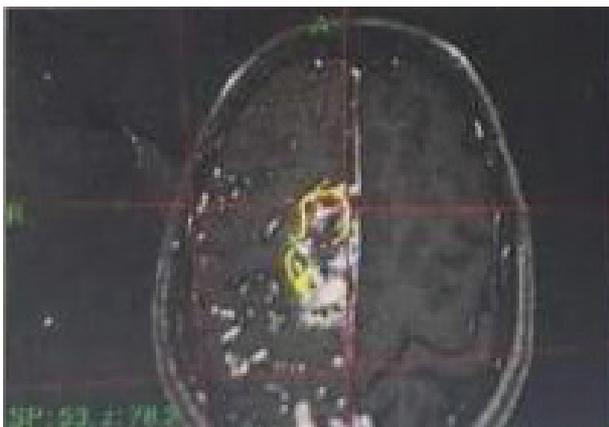
Magnetic resonance imaging (MRI) with contrast demonstrated a right striatal AVM with deep venous drainage into the internal cerebral vein. Digital subtraction angiography (DSA) confirmed a Spetzler-Martin Grade III AVM with a compact nidus measuring 3.2 cm. The deep location and venous drainage pattern increased the risk of hemorrhage, making microsurgical resection less favorable. Given the complexity of the lesion, GKRS was selected as the primary treatment modality.



**Figure 11.2** Digital subtraction angiography (DSA) confirming the AVM nidus and venous outflow, highlighting the risk associated with treating the draining vein.



**Figure 11.3** Post-GKRS follow-up MRI at six months showing partial nidus regression with preserved venous drainage.



**Figure 11.4** Final MRI at two years post-treatment demonstrating near-complete nidus obliteration and an intact draining vein.

### Follow-Up

The patient underwent the first stage of GKRS without immediate complications. At the six-month follow-up, MRI showed partial reduction in AVM size with persistent draining vein patency. A second GKRS session was performed to address the residual nidus, following the same dosimetric principles. Over the next two years, serial imaging demonstrated progressive nidus obliteration with no new neurological deficits or hemorrhagic events.

## DISCUSSION

One of the fundamental challenges in GKRS for AVMs is balancing effective nidus obliteration with the preservation of normal vascular structures. Draining veins play a crucial role in maintaining cerebral hemodynamics, and their inadvertent occlusion can lead to catastrophic consequences such as venous infarction and post-radiosurgical hemorrhage. Shielding these veins from excessive radiation is essential, but it introduces a trade-off: a portion of the AVM nidus may remain untreated, necessitating repeat GKRS later. However, risks of re-hemorrhage become greatly reduced with draining vein shielding.

## CONTROVERSIES

The balance between nidus obliteration and preserving normal venous drainage remains contentious. While effective radiosurgical dosing typically requires high conformity, excessive radiation to draining veins has been linked to complications such as hemorrhage and edema. Critics argue that shielding these veins may lead to partial nidus treatment, increasing the likelihood of recurrence. However, Bose et al demonstrated a significant reduction in edema ( $P = .002$ ) and hemorrhage ( $P = .03$ ) when the draining vein was shielded<sup>1</sup>. As AVMs vary widely in architecture, individualized treatment plans are essential. There remains no standardized threshold dose universally accepted for draining vein safety.

## CURRENT PRACTICE

GKRS is widely accepted for AVM management, particularly in lesions that are deep, inaccessible, or surgically high-risk. For AVMs with critical draining veins, shielding during planning is increasingly being adopted. Dose constraints of  $<40$  Gy to draining veins have been recommended<sup>1</sup>, although many centers prefer even stricter limits. Staged radiosurgery is gaining traction as a solution for treating residual nidus after shielding. Yen et al have shown that sequential GKRS can safely improve obliteration rates<sup>6</sup>. The use of high-resolution imaging, such as 3D MPRAGE MRI and DSA, allows precise planning of dose distributions.

## LEARNING POINTS

- GKRS is effective in managing deep AVMs but carries risks when draining veins are irradiated.
- Shielding draining veins reduces the risk of post-radiosurgical edema and hemorrhage<sup>1</sup>.
- Staging the radiosurgical dose allows safe nidus targeting over time without compromising outcomes<sup>6</sup>.
- Advanced imaging and individualized planning are essential for identifying vein-nidus relationships.
- Future protocols should include draining vein shielding and staged treatment as standard considerations in complex AVMs.

## CONCLUSION

Draining vein shielding during Gamma Knife radiosurgery significantly mitigates the risks of post-treatment edema and hemorrhage. Though this approach may require repeat radiosurgery, it does not compromise the ultimate efficacy of nidus obliteration. Staged radiosurgery, when planned meticulously, is a viable strategy for complex AVMs with critical venous outflow. As radiosurgical planning evolves, integrating these practices will improve patient safety and long-term outcomes.

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# Gamma Knife Radiosurgery in Hypothalamic Hamartomas

Deepak Agrawal ■ Chirag Bansal

## INTRODUCTION

Hypothalamic hamartoma is a developmental lesion and can present with symptoms like Gelastic seizures, precocious puberty, and neuropsychiatric.<sup>1</sup> Hypothalamic Hamartoma is often associated with refractory epilepsy.<sup>2-4</sup> In such cases, Gamma Knife radiosurgery (GKRS) has emerged as one of the most effective techniques in the management of hypothalamic hamartomas (HH).<sup>5</sup> The Gamma Knife delivers targeted radiation to the hamartoma, providing a safer outcome as compared to other surgical procedures. Here, we summarise key findings from a representative case of Hypothalamic Hamartoma that was treated with GKRS at our institute.

## REPRESENTATIVE CASE

### History & Examination

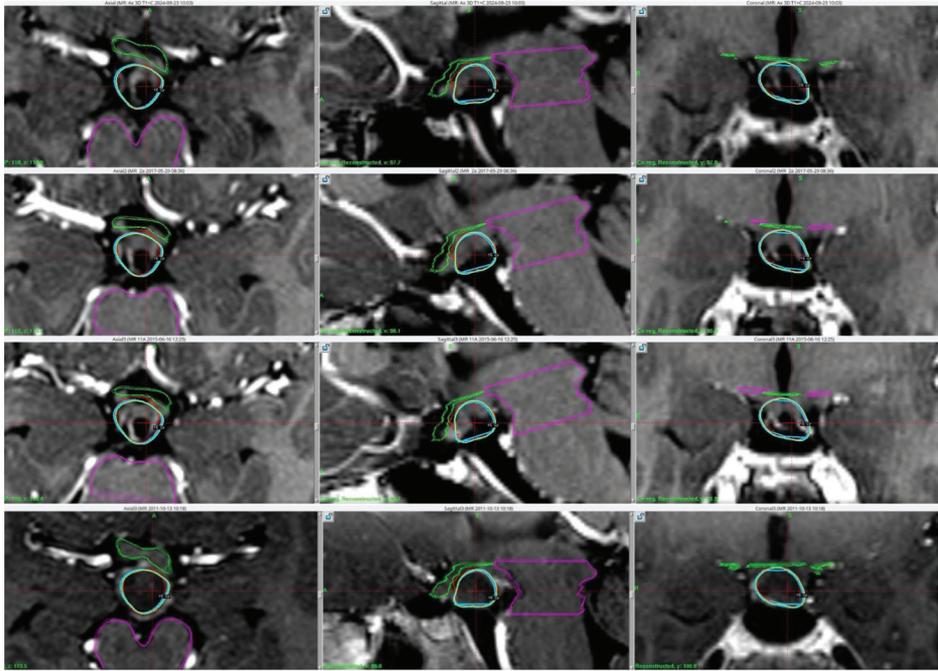
A 5-year-old child presented with rapid height growth and precocious puberty for 6 months, with Gelastic seizures occurring once every month. On examination, there were no motor, sensory or cranial nerve deficits. Cerebellar signs were absent and higher mental functions were within normal limits with a MMSE of 30/30. The patient was followed up for over 13 years.

### Imaging (Figure 12.1)

CEMRI brain was suggestive of T1 isointense, T2 hyperintense rounded mass in the hypothalamus region, projecting inferiorly behind the infundibulum of pituitary gland mildly enhancing on post-contrast images.

### GK Protocol

Primary GKRS therapy was given for Hypothalamic Hamartoma in the year 2011 using a Gamma Knife model B machine. Leksell Coordinate Frame G was used for fixation Configuration, and planning was done on Gamma plan version 11.3.2.



**Figure 12.1** Contrast MRI axial, sagittal and coronal sections of a patient with Hypothalamic hamartoma at baseline (2011) (bottom row), at 4 years (2015) (3<sup>rd</sup> row), 6 years (2017) (2<sup>nd</sup> row) and at 13 years (2024) (top row) follow-up.

15 Gy at 50% isodose line was planned with a coverage of 0.9, selectivity of 0.92, Gradient Index of 2.83, and beam on time of 38.7 minutes. The tumor volume was 0.861 cc and optic chiasm and brainstem shielding was done.

### Follow-Up & Seizure Control

As shown in the imaging above, there was a progressive decrease in the tumour volume on serial imaging. The lesion volume was assessed during the follow-ups in 2015, 2017, and 2024. Clinically, a reduction in seizure frequency was observed within 3 months of GKRS with Agnel score of 1 (Seizure free), six months following GKRS. Anti-seizure medication could be stopped one year after GKRS and the patient remains off medication till date. Precocious puberty progression also halted with a reduction of secondary sexual character's progression. No hormonal dysfunction was noticed on the last follow-up.

## DISCUSSION

GKRS is effective for treating several conditions responsible for epilepsy in humans, including Pituitary adenomas, arteriovenous malformations,<sup>1</sup> Vestibular schwann-

nomas, mesial temporal lobe epilepsy,<sup>2</sup> and hypothalamic hamartomas (HH).<sup>5-7</sup> In cases of Hypothalamic Hamartoma, GKRS has proven effective in reducing seizure frequency and controlling gelastic seizures.<sup>5</sup> Although the Hypothalamus is a surgically challenging area, the precision of GKRS minimises damage to surrounding brain structures.<sup>8</sup> GKRS has good safety and efficacy in seizure reduction and in managing refractory epilepsy due to hypothalamic hamartomas.<sup>9</sup> It has been shown that GKRS results in HH tissue injury characterised by total cell loss without necrosis.<sup>10</sup> Reactive gliosis and microglial infiltration are significantly increased in the post-GK cohort, whereas microvascular changes are relatively mild, and degenerative changes are inconsistent. These findings support the premise that cell death contributes to the efficacy of GK for managing chronic epilepsy.<sup>10</sup> Following this radiosurgery, adequate symptomatic control is normally achieved, with a notable decrease or even disappearance of the seizures.<sup>9</sup> Additional reported changes are Radiological, such as a decrease in the size of the tumour or adjacent edema secondary to non-necrotising radiotherapy-induced inflammatory reaction.<sup>10</sup> Side effects and neurological complications are also rare occurrences.

## CONTROVERSIES

The management of hypothalamic hamartomas continues to spark debate, particularly concerning the optimal modality for seizure control and hormonal preservation. While microsurgical resection remains the traditional standard, it carries substantial risks of hypothalamic damage, endocrine dysfunction, and cognitive impairment. Endoscopic disconnection and thermocoagulation offer minimally invasive alternatives but are technically demanding and not universally available. GKRS, while promising, has been criticized for its delayed therapeutic effect, necessitating prolonged follow-up. There are also concerns regarding optimal dosing, especially in larger or giant hamartomas, and potential radiation exposure to adjacent critical structures.

## CURRENT PRACTICE

GKRS has increasingly become an accepted modality for treating HH, especially in patients with refractory epilepsy. The high precision of Gamma Knife systems enables targeted radiation to the lesion with minimal collateral damage. The current standard marginal dose ranges between 16–20 Gy, adjusted based on lesion size and proximity to the optic chiasm or hypothalamus. Small-volume HHs (<3 cc) are ideal candidates, although emerging studies support hypofractionated GKRS for larger lesions. Fractionated regimens (2–3 sessions) have demonstrated safety and efficacy, particularly in preserving endocrine function while achieving seizure control. MRI and angiography aid in accurate planning and post-treatment surveillance.

In a study, Manjul Tripathi et al.<sup>16</sup> tried to maintain a low peripheral isodose to the lesion margin (18–26 Gy at 50% isodose) in a 2–3 fractionation scheme to minimise the chances of radiation exposure to the radiosensitive organs at risk (mamillary bodies 10 Gy, optic apparatus 6 Gy, brain stem 10 Gy). The purpose of the dose

**TABLE 12.1 ■ Summary of the Main Endocrinologic Effects of the Different Techniques Used for Treating Hypothalamic Hamartoma**

Author, year	Technique	Pituitary Deficiency	Weight Gain	Hypothalamic Syndrome/ Dysnatremia
Freeman, 2003 <sup>11</sup>	Transcallosal intra forniceal surgery	38%	45%	41%
Drees, 2012 <sup>12</sup>	Endoscopic surgery	24%	59%	17%
Drees, 2012 <sup>12</sup>	Combined surgical approaches	57%	71%	17%
Schulze-Bonanghe, 2008 <sup>13</sup>	Brachytherapy	No	20%	No
Abla, 2010 <sup>14</sup>	Gamma Knife radiosurgery	No	20%	10%
Frederic Castinetti, 2017 <sup>15</sup>	Gamma Knife radiosurgery	3%	3%	No

fractionation was to deliver the adequate dose to these patients without creating counter effects. The usual dose of radiation to be given is 8.1–9.2 Gy per fraction at 50% isodose in 2–3 fractions, targeting the entire giant hamartoma volume (4.45 cc to 7.39 cc). Traditionally, ideal candidates for GKRS are HH that are small in size (< 3 cc), at a safe distance from the optic apparatus, and in a stable neurological status. As per David Mathieu et al.,<sup>8</sup> between March 1999 and January 2003, 4 patients (Case No 2–5 in Table 12.2) with hypothalamic hamartomas had Gamma Knife radiosurgery. The hamartoma volumes ranged from 0.20 to 0.55 ml (mean 0.37). The 50% isodose line was used to deliver a mean of 17.5 Gy (range 16–20) to the margin of the lesion. The mean maximum dose was 35 Gy (range 32–40). No plugging pattern was used, and the radiation dose received by the optic pathways was kept below 8 Gy for every patient. The results from the above study have been compared to the index case (Case No. 1 in Table 12.2) in the following table:-

It can be concluded that early administration of GKRS (at the onset of the disease), followed by a prolonged follow-up, may lead to better seizure control post-GKRS.

## LEARNING POINTS

- GKRS significantly reduces seizure frequency and intensity, particularly in gelastic seizures commonly linked to Hypothalamic Hamartoma.
- Studies indicate minimal adverse effects, preserving endocrine functions and avoiding major neurological deficits.
- Consistent seizure control and improved quality of life are reported in long-term follow-ups.
- GKRS is particularly advantageous for deep-seated lesions, reducing risks associated with open surgery.
- Gamma Knife radiosurgery is an effective and minimally invasive alternative for treating hypothalamic hamartomas, especially in medically refractory epilepsy, with emerging long-term evidence supporting its use.

TABLE 12.2

Case No.	Age Years at Treatment	Seizure Duration, Years	Seizure Types	Lesion Volume, ml	Marginal Dose, Gy	Follow-Up Months	Time to Improvement, Months	Engel Class Attained
1*	5	0.5	Gelastric	0.861	15	156	3	I
2	29	28	gelastic, GTCS	0.51	16	77	3	II
3	6	4	gelastic, GTCS, CPS	0.22	18	22	2	III
4	14	13	gelastic, GTCS, Atonic tonic	0.20	20	22	NA	IV
5	5	4	gelastic, CPS	0.55	16	6	3	II

CPS = Complex partial seizures; GTCS = generalized tonic-clonic seizures; NA = not assessed.

\*INDEX CASE

## CONCLUSION

GKRS can be an effective and non-invasive solution to many surgically challenging tumours like Hypothalamic Hamartoma. Due to its efficacy in reducing gelastic seizures and improving quality of life with negligible morbidity, GKRS should be considered the gold standard for hypothalamic Hamartomas.

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# Stereotactic Radiotherapy/ Radiosurgery Paradigms for Complex Arteriovenous Malformations (AVM): Dose/Volume Fractionation

Ranjith K Moorthy

## INTRODUCTION

Complex AVMs include Spetzler-Martin (SM) grade III deep seated and eloquent region AVMs and SM grade IV-V AVMs. While incidentally detected Spetzler-Martin (SM) grade IV-V AVMs may not require treatment, AVMs presenting with hemorrhage or steal phenomenon require treatment.<sup>1</sup> It has been estimated that large AVMs have a cumulative risk of hemorrhage of 1% per year with 40% risk of hemorrhage in cases with prior bleed.<sup>1,2</sup> Large and complex AVMs presenting with seizures only without hemorrhage may be managed with antiepileptic medications alone in select cases. Complex AVMs require multimodality treatment approaches in the form of a combination of embolization, surgery or radiosurgery. While embolization as a sole modality is non-curative in large AVMs, surgery can be challenging and associated with morbidity due the large volume as well as deep venous drainage that these AVMs are often associated with. Hence, stereotactic radiosurgery (SRS) has been used as a sole modality or as an adjunct with surgery/embolization in management of these lesions.<sup>1-3</sup>

## CASE ILLUSTRATION (FIGURE 13.1)

### History and Physical Examination

A 15 year old male with no previous co-morbidity presented with sudden onset headache with altered sensorium to another institution. He had no focal neurological deficits. He was managed conservatively for intraventricular hemorrhage involving the right lateral ventricle (Fig. 13.1A). He was managed conservatively for the same elsewhere and presented to our centre three months later. A four vessel digital subtraction angiogram (Figures 13.1B-H) showed a SM grade III AVM in the corpus callosum measuring 17 cc in volume fed by the anterior cerebral artery on either side and the posterior pericallosal artery with venous drainage into the deep venous system.

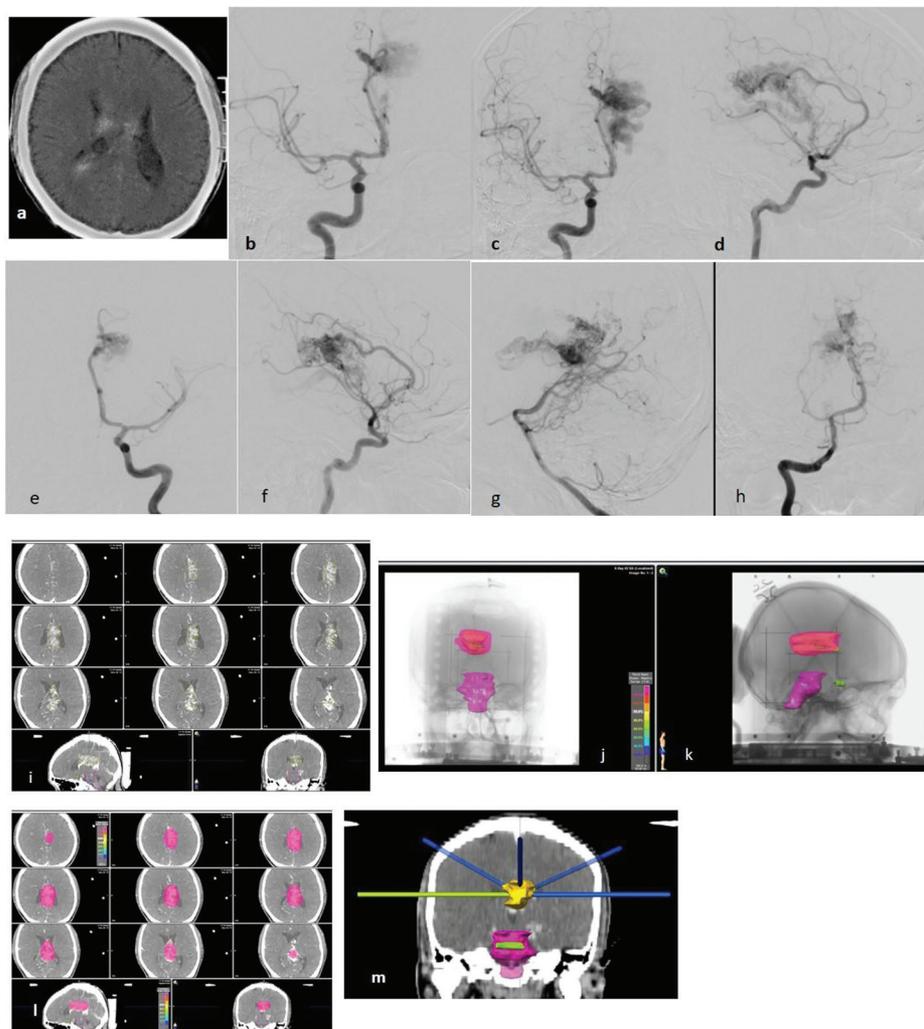


Figure 13.1 A–M

### Linear Accelerator Based Dose Fractionated Radiotherapy (HSRT)

He underwent dose HSRT receiving 6Gy per fraction for 6 fractions. The immobilization was done using a thermoplastic mask while delivering the radiation. Stereotactic contrast CT brain (Figure 1i shows the relevant axial, sagittal and coronal slices showing the corpus callosal AVM) obtained was fused with stereotactic angiography (Figure 131J-K showing AP and lateral views of angiogram with the AVM marked in red, optic chiasm in green and the brain stem in pink colours) and the AVM was contoured on the workstation. Brain stem and optic chiasm were considered as organs at risk and an appropriate plan created with multiple collinear beams were placed to deliver the radiation to the lesion (seen contoured with a golden hue

in Figure 13.1M). The dose volume histogram was constructed on the planning software and dose of radiation delivered to the AVM, optic chiasm, brain stem and other specific organ at risks checked before finalizing the radiation plan. The radiation plan was then exported to the linear accelerator for delivery of radiation after calculating the appropriate monitor units. The marginal dose of radiation along the periphery of the lesion was 6 Gy per fraction and this was along the 80% isodose line as shown in Figure 13.11.

### Follow Up

He had an uneventful course post radiation therapy. Serial T2W MRI done at 2 years post HSRT (Figure 13.2A) and 4 years post HSRT (Figure 13.2B) showed progressive reduction in the size of the nidus with the latter MRI showing near complete disappearance of the early draining vein. He underwent DSA at 9 years post HSRT (Figure 13.2C) that demonstrated absence of nidus or early draining vein on the internal carotid artery (right half of panel) and vertebral artery injection (left half of panel). He had no new symptoms and had completed college education.

## CURRENT PRACTICE

### Rationale for SRS and Need for Hypofractionation

Stereotactic radiosurgery (SRS) is a modality to deliver a precise dose of high dose of radiation to the AVM nidus with minimal dose being delivered to the adjacent normal brain tissue due to steep gradient of dose fall-off.<sup>1-3</sup> Based on reaction to radiation delivered, body tissues have been classified into early or late responding tissues. In radiation oncology parlance,  $\alpha$  refers to rate of killing of cells with a single

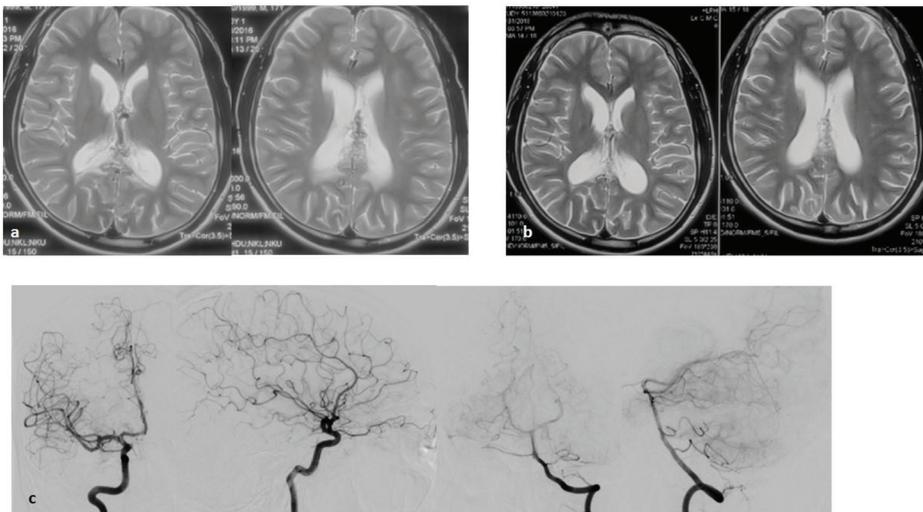


Figure 13.2 (A-C)

hit while  $\beta$  refers to the cell killing rate with a double hit mechanism.<sup>4</sup> The  $\alpha/\beta$  ratio refers to the ability of tissue to recover from the effects of radiation. Based on this principle, central nervous system tissues are late responding tissues with a low  $\alpha/\beta$  ratio of around 2 and they would be spared if fractionation is used. AVMs also have a similar  $\alpha/\beta$  ratio of 2 to 3 ( $2.2 \pm 1.6$ ).<sup>5</sup> To treat an AVM with radiation, a large dose of radiation in a single fraction or limited number of fractions would be hence required as it is a late responding tissue. Conventional fractionation hence may not be effective while treating brain AVM.<sup>1,5,6</sup> The practice of delivering moderate doses of radiation in successive or alternate days (3 to 6 fractions) treats the lesion but spares radiation induced side effects for the normal brain tissue and this is termed as hypofractionated stereotactic radiation therapy (HSRT) or Dose fractionated radiosurgery.<sup>6</sup>

Radiosurgery results in obliteration of AVMs (particularly those that are  $<3\text{cm}$ ) in up to 70% of patients as a result of endothelial proliferation and thrombosis.<sup>1-3,7</sup> The dose of single fraction recommended ranges from 16-17Gy in linear accelerator (LINAC) based series and over 20Gy in Gamma Knife radiosurgery(GKRS).<sup>1-3</sup> However, administering a high dose of radiation to larger AVM volume will result in changes to the adjacent brain that will tend to receive a higher than tolerated dose in a single fraction. Receiving this high dose can result in radiation induced damage to the adjacent normal structures and neurological deficits. For instance, the dose limit tolerated by optic chiasm with a single fraction is 8Gy while it is 23Gy with five fractions. Thus, while only  $<8\text{Gy}$  can be administered to a lesion abutting the optic chiasm in a single fraction SRS, the same lesion can be administered up to 23Gy if the dose is divided into five fractions. While 8Gy will be ineffective in achieving obliteration of AVM, it is possible that administering a higher dose in a limited number of fractions (termed as hypofractionation) will aid in achieving obliteration.<sup>5,6,8,9</sup>

As a high dosage of radiation is administered during SRS, up to a 40% proportion of patients develop radiation induced changes and perinidal hyperintensity on T2W MRI at follow up. This may be symptomatic in about 10% of individuals who develop this change.<sup>2,7</sup> The development of radiation induced changes has been correlated with higher AVM volume as well as dose. Hence, there is increased risk of developing these changes in patients with AVM with larger volumes.<sup>7</sup> If the dose of radiation is proportionately decreased to avoid this complication, the AVM may not be obliterated. To overcome this issue, radiation dose can be reduced in each fraction and the entire treatment can be performed using 3 to 6 fractions; i.e. hypofractionated stereotactic radiotherapy (HSRT), which is also termed hypofractionated stereotactic radiosurgery by some authors. The American Association of Neurological Surgeons, Congress of Neurological Surgeons and American Society for Therapeutic Radiology and Oncology has defined SRS as radiation delivered up to 5 fractions.<sup>1</sup>

While performing HSRT, it is important that when dose fractionation is planned, the total dose delivered is equivalent to the biologically effective dose achieved through a single fraction SRS. This biologically effective dose can be increased by

increasing the dose per fraction while limiting the number of fractions to 5 or less. The dosing parameters are decided by the volume of AVM as well keeping in mind the constraint or maximal dose that the adjacent critical organs can receive. This calculation of the constraint doses for each organ at risk is based on the linear quadratic equation model as well as the universal model developed by the Texas Southwestern University group and standard dosing parameters have been established in radio-surgical literature.<sup>5</sup>

### **Dose Fractionated Radiosurgery (HSRT)**

In dose fractionated radiosurgery (HSRT), the total dose delivered to the AVM is divided into 5 or 6 fractions of 5-6Gy per dose. This will provide a biologically effective dose of approximately 58Gy for a tissue with  $\alpha/\beta$  ratio of 2.2. The radiation is delivered on successive days or on alternate days with a thermoplastic face mask being used to achieve immobilization during radiation delivery.<sup>8-14</sup> While a dose of 6Gy per fraction for 5-6 fractions provides AVM obliteration or diminution in volume, increasing dose per fraction to >7Gy does not improve obliteration rate but increases the rate of radiation related complications.<sup>9,13</sup>

Unpublished data from the author's centre showed complete obliteration in 2/14 (14.3%) of large AVMs, >50% decrease in volume with 7(50%) and <50% decrease in volume in the remaining 5(35.3%) at median follow up of 18 months post dose staged HSRT. Most of the AVMs received 6Gy per fraction for 6 fractions in this series. Other authors have also reported similar complete obliteration rates of 20% or less with HSRT for large AVMs. The literature reporting HSRT for large AVMs is difficult to interpret as those reporting larger obliteration rates usually include smaller AVMs <10cc also that would result in higher obliteration rates being observed. Table 13.1 summarizes the relevant literature reporting obliteration rates of dose staged AVM.<sup>8-14</sup>

### **Volume Fractionated Radiosurgery**

Volume fractionated radiosurgery is an alternative to HSRT in management of large AVMs. In this treatment paradigm, the AVM is divided into 2 or 3 sectors, such as the volume of each sector can receive at least 16-17Gy radiation as a single fraction without the risk of side effects.<sup>2,9</sup> The sectors may be divided based on the arterial blood supply received by the AVM (For example, an AVM with supply from anterior circulation and posterior circulation may be treated as two separate lesions, one being supplied by the anterior circulation feeders and another being supplied by the posterior circulation feeders only). In a large AVM being fed by a single vessel, the superficial and deep components may be treated separately.<sup>15</sup> It has also been suggested that the part of the AVM drained by the major vein (when there are multiple veins) be targeted last.<sup>16</sup>

The suggested interval between delivery of radiation to one sector and the other is at least 3 months, though authors have reported intervals as late as 15 months.<sup>2,15,16-20</sup> This will allow adjacent brain tissue to recover from any radiation induced damage.

TABLE 13.1 ■ Summary of Literature Reporting Dose Staged Radiation Therapy (HSRT) for Large AVMs

Author	Number of Patients	Total Dose/ Fractions(#)	Volume (cc)	Complete Obliteration Rate	Haemorrhage Post SRS	Radiation Necrosis	Mode of SRS
Veznedaroglu <sup>8</sup> (2004)	24	42Gy in 6# 30Gy in 5#	23.8 14.5	83% 22%	Not reported	14% 8.7%	LINAC
Silander <sup>10</sup> (2004)	19	20-25Gy in 2 or 4 #	24	36%	Not reported	26%	Proton beam
Chang <sup>11</sup> (2004)	33	20-28/4#	>10cc or eloquent area	71% (at 6 years)	22%	3%	Proton beam/ LINAC
Zabel-du Bois <sup>12</sup> (2006)	15	25-30/5 or 6#	27	33% at 4 years	20%	0	LINAC
Xiao <sup>13</sup> (2010)	20	25-30/5 or 6#	46.8	0	2%	Not reported	LINAC
Blamek <sup>14</sup> (2012)	49	12-28Gy/2-4#	25.1	21%	4%	12%	LINAC
Sparks <sup>9</sup> (2019)	37	25-30Gy/5-6#	29.6	11.3%	4.8%	11.9%	LINAC

The complete obliteration rates following volume staged radiosurgery is reported to range between 20 to 50% in most series.<sup>2,15-20</sup> However, several series reporting data on volume fractionated radiosurgery include smaller AVMs and also report data following surgery after AVM reduction after radiosurgery that confounds the results. The data on volume fractionated radiosurgery is summarized in Table 13.2.<sup>15-20</sup>

## CONTROVERSIES

A meta-analysis quoted in a recent review has suggested that complete obliteration rates following dose fractionated HSRT and volume fractionated SRS is 40.7% and 32.7% respectively.<sup>2</sup> It is also not certain as to whether partial obliteration results reported in literature actually offer benefit to the patient. However, partial obliteration or shrinkage of the AVM to a smaller size may result in the residual smaller AVM becoming amenable to single session SRS or microsurgical excision.<sup>2</sup>

Results reporting volume or dose fractionated SRS are difficult to interpret as several authors have included smaller sized AVMs along with the larger AVMs.<sup>2,17</sup> Some series reporting results have also combined patients who have undergone repeat radiosurgery as well as surgery after radiosurgery which also make interpretation of results difficult. Both volume fractionated and dose fractionated paradigms seem to have similar results. One of the advantages of the dose fractionated paradigm would be that the entire treatment will be completed over a period of 1-2 weeks. As interval between two sessions of radiation is longer in volume fractionated paradigm, ensuring patient compliance may be challenging in some situations, particularly in a country like India.

**TABLE 13.2 ■ Summary of Literature on Volume Staged Radiosurgery for Large AVMs Following GKRS**

Author	Number of Patients	Volume (cc)	Number of Sessions (Interval in Months)	Dose Per Volume (Gy)	Obliteration Rate (%)	Haemorrhage Rate Post SRS	Complications
Sirin <sup>18</sup> (2006)	37	>15	2-3 (3-8)	16	50	14%	8.1%
Kano <sup>17</sup> (2012)	47	>10	2 (3-15)	16	28	4.3%	13%
Huang <sup>19</sup> (2012)	18	>15	2 to 4 (3-9)	15	89 at 10 years	27.8%	NA
Pollock <sup>16</sup> (2017)	34	22.2	2 to 4 (3-6)	16	53	12%	6%
Seymour <sup>20</sup> (2016)	31 38	27.3 18	2 2-4 (3-6)	15.7 17	21 at 5 years 68 at 5 years	31% 24%	16% 3%
Hanakita <sup>15</sup> (2016)	18	38	2-3(6)	16	33.3 at 4.5 years	33%	33%

It has been reported that volume fractionated radiosurgery may have higher risk of hemorrhage while awaiting obliteration or second stage treatment due to the long interval between the doses.<sup>9</sup> As several of these large AVMs undergo partial embolization prior to SRS, it is not certain whether the embolization related artefacts contribute to difficulties in contouring the residual AVM.<sup>13</sup> This may contribute to the lower obliteration rates with dose or volume fractionated regimes.

## LEARNING POINTS

- Stereotactic radiosurgery delivered in a single session is the best suited modality of radiation therapy for treatment of smaller AVMs <3cm in size.
- To limit the radiation induced damage to the normal nervous tissue, large AVMs will require dose fractionation (HSRT) or volume fractionation to ensure adequate dose delivery.
- While both volume fractionated and dose fractionated radiosurgical paradigms will not achieve complete obliteration of large AVMs, the reduction in volume achieved may make it feasible for further management with single staged SRS or microsurgery.

## CONCLUSIONS

Management of large intracranial AVMs is challenging and often requires multi-modality management with embolization, radiation therapy and surgery often in combination. While single session SRS will result in almost 80% obliteration of small AVMs, dose or volume fractionated SRS results in complete obliteration of less than a third of large AVMs. However, the reduction in size achieved with these

hypofractionated radiotherapy paradigms may aid in the residual AVM being amenable to single session SRS or microsurgery.

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# Radiosurgery in the Management of Brain Arteriovenous Malformations

Dwarakanath Srinivas ■ Keyur Gopal Bhai Shah

## INTRODUCTION

There have been a myriad of possibilities in the management strategies for arteriovenous malformations (AVMs) of the brain. The ideal management has remained a matter of debate over the years, partly because of the variable natural history and the risk of rupture being around 2%–4 % per annum<sup>1</sup>. The therapeutic options range from microsurgical resection to embolization and radiosurgery. However, the risk of the curse of Maslow's hammer looms large over the management options offered to the patient.<sup>2,3</sup> There has been a general agreement on the management of a ruptured Arteriovenous malformation of the Brain (BAVM), with all clinicians agreeing that some form of intervention is needed as the rebleed rate is high. However, when it comes to the management of unruptured BAVMs (uBAVMs), the value of intervention is not so well accepted. The ARUBA and SIVMS have reinstated the debate regarding the role of conservative management and any form of intervention regarding uBAVMs.<sup>3,4</sup>

The current management option for intracranial AVMs ranges from watchful conservative follow-up to using microsurgery, radiosurgery, embolisation or a combination of any of the above treatment options. In this chapter we will discuss the role of Gamma Knife Radiosurgery (GKRS)/stereotactic radiosurgery (SRS) for the management of brain AVMs alongwith review of relevant literature.

## HISTORY OF GKRS

In the 1950s, Leksell and, later, Larsson conceived the idea of using stereotactically guided external radiation to produce a predictable irradiation effect at an accurately defined intracranial target.<sup>5,6</sup> After extensive experimentation, he developed the first-generation cobalt gamma unit in 1968. He called the technique "Radiosurgery". One of the early reports on the use of stereotactic radiosurgery (SRS) for an AVM with the gamma knife was that of Steiner.<sup>7</sup> Around the same time, Lunsford et al first reported a large series of 227 patients with AVM successfully treated with cobalt-60 gamma knife at the University of Pittsburgh.<sup>8</sup> Over the past three decades, multiple studies have consistently demonstrated the efficacy of GKRS in the treatment of arteriovenous malformations (AVMs).

## PRINCIPLES AND RADIOBIOLOGY OF RADIOSURGERY

Stereotactic radiosurgery is the accurate delivery of high doses of precisely focused radiation to a targeted area while minimizing the irradiation toward healthy tissues due to the steep gradient of dose distribution. In radiosurgery, the planning is done to obtain a sharp dose fall off with the normal tissue receiving a very small, non-toxic dose of radiation compared to the target that receives a high therapeutic dose.<sup>9-11</sup> Stereotaxy aids in precise target localization while radio-surgical planning and delivery platforms help in achieving conformality. Though the exact mechanisms of action are unclear, SRS induces vessel obliteration by thrombotic endothelial proliferation.<sup>12</sup>

In GK radiosurgery (GKRS), the target is usually localized with the Leksell stereotactic frame. The Gamma Knife (GK) is currently in its sixth generation of evolution, the Gamma Knife ICON™ and Gamma Knife Espreo™. (Elekta, Stockholm, Sweden) The latest Leksell Gamma Knife ICON/Espreo has 192 Co-60 sources with approximately 30 curies (1.11TBq) each, placed in a heavily shielded assembly that emits photon radiation (gamma rays) via radioactive decay. Co-60 sources are arranged in a spherical array via collimators to focus all the radiation beams on a center point. In ICON, 192 cobalt-60 sources are arranged in a conical shell, distributed within eight sectors, allowing for a nearly  $2\pi$  geometry. Each sector has 24 sources, which can be blocked or positioned to 4, 8, or 16-mm diameter collimators, resulting in converging gamma beams of corresponding diameters at the isocenter. Frameless radiosurgery can also be offered with the mask-based treatment using high high-definition motion management system, during dose delivery.<sup>13</sup> as happens with LINAC delivery systems. Included is the Cone beam CT which allows fractionation and an overlap in which both frame based and mask based radiation delivery can be performed.

Positional accuracy in the radiation delivery is the key to success in SRS. The volume of the brain tissue receiving a specific dose (e.g., 12-Gy or 10Gy volume) correlates with the risk of radiation necrosis and each plan attempts to keep this to minimum and hence the dose gradient or dose fall off around the lesion is considered important.<sup>14</sup>

## PRINCIPLES OF RADIOSURGERY PLANNING

In all SRS planning systems for AVMs, three-dimensional Contrast Magnetic resonance imaging (MRI) or MR angiography, computed tomography (CT) along with stereotactic digital subtraction angiography or CT angiography images are transferred into the planning software. After reconstruction of the volumetric acquisition images, the various imaging modalities are stereotactically defined or fused to one another so that a target delineated in one imaging modality can be viewed in the other modality too. The target (nidus of the AVM) is drawn slice by slice on the cross-sectional images or on the DSA images. The target is chosen on the DSA in the image just prior to where contrast filling of the early draining vein is seen to avoid delivery of radiation to the draining vein and avoids missing out part of the

nidus.<sup>15</sup> Once the target is delineated, the organs at risk are also contoured on the software. Typically, the brainstem and optic nerve and chiasm along with any other organ at risk may also be defined (Figure 14.1).

The physicist, radiation oncologist and the neurosurgeon work as a team to place the radiation beams/ shots or isocenters on the software to deliver radiation to the target. A typical Gamma knife plan is often multi-isocentric and comprised of multiple superimposed dose clouds, each with its own isocenter called a 'shot'. The goal is to create a confluence dose cloud that conformally encloses the target. This fundamental aspect of the gamma plan makes it inherently conformal but also prone to heterogeneity. The planning may be done through the forward planning algorithm or the inverse planning algorithm.

In the forward planning algorithm, the Dose plan is constructed by placing individual shots of varying collimator size and or composite shots in the target. An efficient dose plan includes large collimators used away from critical structures and smaller collimators closer to critical structures. To achieve the coverage of more than 95% with high conformality and to achieve a high gradient sector, blocking may be deployed. These isocenters are placed and adjusted to the three-dimensional volume of the lesion, and then the dose to the organs at risk is checked in forward planning. In an inverse planning algorithm, the dose is preset to the organs at risk at the beginning and then the isocenters are placed by the software. The latest iteration of the Leksell gamma plan software called lightning (Fast Inverse planning) has the capability of producing very fast plans with quality equivalent to an experienced forward planner.<sup>16</sup>

During the planning session, the radiation delivery to the AVM is studied based on the isodose lines. Isodose refers to the curve or the line that will cover the area that will receive a particular dose of radiation. It is expressed as a percentage of the prescribed dose. For example, if the prescription dose is 20 Gy at 50% in a single

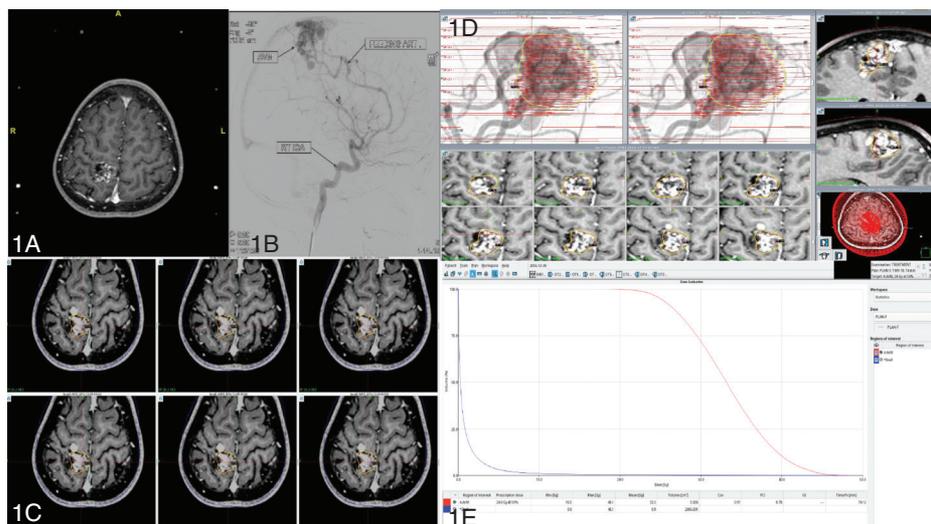


Figure 14.1

isocenter, the margins of the nidus will receive 20 Gy and the centre of the nidus will be getting 40 Gy. The isodose received along the margin or periphery of the AVM nidus is what is reported to be the dose administered.<sup>17</sup>

Gamma knife has a more flexible work plan with an efficient dosimetry, but the treatment time is longer when compared with LINAC and cyber knife systems. The quality of a treatment plan in a forward planning system such as Gamma knife is affected by not only the target location, target shape, and target size, but also the planning technique used and the experience of the planner. Gevert et al compared SRS modalities and concluded that GK-Perfexion planning system produced high conformity with minimal low-dose spread to adjacent tissues when compared to dynamic arc therapy or non-isocentric fixed beams.<sup>18</sup> The dose fall-off rate is also superior with the GK planning systems compared to Cyberknife. In similar studies in the past, it has been shown that protection of organ at risk is best with GKRS.<sup>19</sup>

## HEMODYNAMICS OF AVM AFTER SRS

Radiosurgery works by inducing fibro-intimal damage of the endothelium of the arteries supplying the AVM, leading to inflammatory changes, formation of granulation tissue and radiation induced vasculopathy resulting in eventual obliteration of the nidus. This process takes 1 to 3 years.<sup>20</sup> The risk of hemorrhage in this latency period is at the same rate as pre-treatment. Hemodynamic changes are observed as early as 2 months post SRS. These hemodynamic changes are seen as decreased flow within the feeding artery. Structural changes in the draining veins happen early and are a structural biomarker. For patients with large AVMs ( $\geq 27 \text{ cm}^3$ ), structural changes in nidus volume are subtle and gradual with minimal changes even at 16 months post-SRS<sup>21</sup> (Figure 14.2).

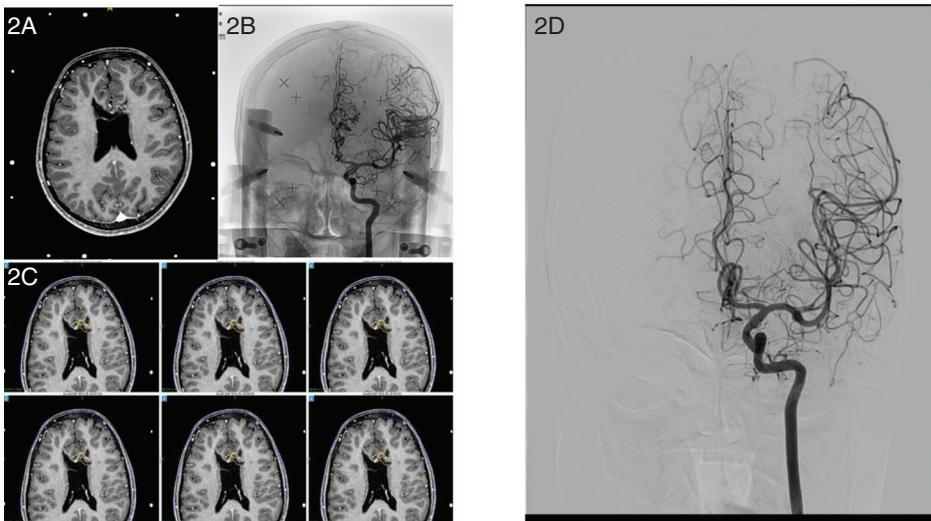


Figure 14.2

## WHEN TO IRRADIATE? - THE ROLE OF ANGIOARCHITECTURE

### Obliteration Rate Based on Spetzler-Martin(SM) Grading<sup>22</sup>

International Stereotactic Radiosurgery Society Practice Guidelines were published in two articles discussing the effect of SM grade on outcomes of AVMs treated with SRS. Among these, the first article was a systematic review by Graffeo et al, including all the publications between 1986 and 2018, 1102 AVMs were analysed. The overall obliteration rate was 80%. The literature for SM grade I-II AVM was of low quality due to selection bias introduced with favourable AVMs undergoing resection and those at increased risk of complications and non-obliteration being referred disproportionately for SRS.<sup>23</sup> In another systematic review by Graffeo et al, the obliteration rate for SM grade III AVMs was 72% while that for SM grade IV and V AVMs was less than 50%.<sup>24</sup> Overall obliteration rate in the author's institute (unpublished data) was 75.5%, with predominantly SM grade 2 and SM grade 3 AVMs.

### Pollock Scoring as Prediction

A radiosurgery-based arteriovenous malformation (AVM) grading scale was developed by Pollock B.E. and John C. Flickinger<sup>25</sup> and further modified to predict patient outcomes after radiosurgery.<sup>26</sup>

Modified Pollock Flickinger(PF) score /AVM score = (0.1) (volume, mL) + (0.02) (age, yr) + (0.5) (location, hemispheric/corpus callosum/cerebellar = 0; basal ganglia/thalamus/brainstem = 1).

This score takes into account the AVM volume, location of the AVM and age of the patient, which can be known beforehand while counselling the patient for the outcome of radiosurgery for AVMs. Modified PF score correlated with the percentage of patients with AVM obliteration without new deficits ( $\leq 1.00$ , 89%; 1.01–1.50, 70%; 1.51–2.00, 64%;  $\geq 2.00$ , 46%) ( $P < 0.01$ ) and a decline in Modified Rankin Scale ( $\leq 1.00$ , 0%; 1.01–1.50, 13%; 1.51–2.00, 20%;  $> 2.00$ , 36%) ( $P < 0.01$ ).<sup>26</sup>

### Overall AVM Obliteration Rates

The overall obliteration rate in a study of 313 patients by the authors' institution for single-session gamma knife radiosurgery is 77.5% (unpublished data). This rate is similar to several other large studies by Ding et al. (2014) (76%)<sup>27</sup>, Graffeo et al. (2019) (83%)<sup>28</sup>, Nataf et al. (2007) (78%)<sup>29</sup> and Koltz et al. (2013) (91%)<sup>30</sup>. However, these studies are retrospective in nature and introduce selection bias due to the inherent limitations in retrospective studies. These rates decrease further in systematic review and meta-analysis.

In a meta-analysis studying pooled estimates of outcomes post-GKRS for AVMs, the obliteration rate was 60.47% and 69.48% on DSA and DSA or MRI, respectively.<sup>31</sup> In a recent meta-analysis by Essibayi et al., the pooled obliteration rate was 63%.<sup>32</sup> The variability in obliteration rates can be attributed to differences

**TABLE 14.1 ■ Comparing AVM Characteristics, Treatment Plan, Obliteration Rates, Haemorrhage Rates, Clinical Outcomes, Radiation-Induced Changes and Follow-up Duration in Published Large Series**

Author	Year	n	AVM Volume (cu.mm)	Eloquent Location	Deep Drainage	RBAS (Median [Range])	Margin Dose Max Dose (Median [Range])	Total Obliteration (n)	Total Obliteration (%)	Haemorrhage (n)	Haemorrhage (%)	Time-to-Obit. (m, Median)	RIC (n)	RIC (%)	Excellent Outcome (n)	Excellent Outcome (%)	Death (n)	Death (%)	Follow-up (m, Median)
Yamamoto <sup>33</sup>	1996	19	-	-	-	-	-	12	63	1	5	-	-	-	-	0	0	0	97 (54-205)
Friedman <sup>34</sup>	2003	107	-	-	-	-	-	80	75	11	10	-	1	1	-	-	0	0	36 (-)
Nataf <sup>35</sup>	2007	27	-	4	9	-	25	21	78	1	4	-	0	0	21	78	0	0	25 (11-168)
Kano <sup>35</sup>	2012	217	2.3 (0.1-14.1)	52	34	-	22 (15-27)	202	93	13	6	30(25-35)	7	3	202	93	7	3	64 (6-247)
Fokas <sup>36</sup>	2013	24	-	-	-	-	-	15	63	1	4	-	-	-	-	-	-	-	93 (12-140)
Koltz <sup>40</sup>	2013	33	-	-	-	-	-	30	91	3	9	-	4	12	29	88	0	-	102 (5-16)
Ding <sup>27</sup>	2014	502	2.8 (0.1-22.5)	236	111	1.03 (0.21-2.96)	23 (-)	382	76	30	6	40 (6-193)	30	6	354-382	71-76	-	-	62 (7-239)
Grafico <sup>48</sup>	2019	173	2.9 (0.1-13.6)	85	24	1.20 (0.34-2.19)	20 (16-25)	143	83	6	4	37 (6-194)	5	3	137	79	1	<1	68 (24-275)

in patient selection and AVM characteristics such as size, location, drainage patterns, and treatment protocols, including margin dose and radiosurgical techniques.

## UNIQUE SITUATIONS

### Deep-Seated AVM

Deep-seated arteriovenous malformations (AVMs) comprise 3–13 % of intracranial AVMs.<sup>37</sup> The risk of haemorrhage among this subset of AVMs appears to be 2–11 % higher than in other locations.<sup>38,39</sup> Even in the absence of antecedent haemorrhage, intervention is often warranted due to the severe morbidity and mortality associated with the potential rupture of deep-seated AVMs.<sup>40</sup> Hence, the primary goal of the treatment of deep-seated AVMs is complete obliteration. While surgical resection is challenging due to deep location and proximity to eloquent areas of the brain, GKRS is an important minimally invasive alternative providing high precision treatment with steep dose gradients.<sup>41</sup> Among deep-seated AVMs, GKRS has been demonstrated to result in obliteration among 49–67 % of patients.<sup>42–44</sup> At the same time, the reported incidence of radiation-related complications ranges between 2.4 and 9.4 %.<sup>45</sup> Overall obliteration rate for deep-seated AVMs in the authors' institute is 48.2%, with associated complications in 5.8%. Nidus volume was the most significant predictor of successful obliteration.<sup>44</sup> Despite the challenges posed by the complex anatomy of deep AVMs, including variable venous drainage and the potential for radiation-induced oedema, GKRS is equally effective in AVMs located in the thalamus, basal ganglia, and brainstem.

TABLE 14.2 ■ Studies Summarizing Results of GKRS for Deep Seated AVMs

Study	Year	Type of Study	n	Location Wise	Obliteration (%)
Ohadi <sup>43</sup>	2023	Systematic review and meta-analysis (N=34 studies)	2508	Brainstem	67%
				Basal-ganglia/Thalamus	65%
Patel <sup>42</sup>	2021	Prospective study	54	–	–
Nadeem et al <sup>44</sup>	2025	Retrospective Single centre	137	Thalamus	50.60%
				Basal-ganglia	42.50%
				Brainstem	57.10%
Chen <sup>40</sup>	2020	Retrospective multicentre	363	Basal-ganglia/Thalamus	64.80%
Cohen-Inbar O <sup>38</sup>	2017	Retrospective multicentre	205	Brainstem	65.40%
Kano <sup>46</sup>	2012	Retrospective Single centre	133	Brainstem and thalamus	72%

**TABLE 14.3 ■ Studies Comparing Obliteration Rate of AVM After Single Session GKRS Based on Nidus Type**

Author	Year	Type of Study	n	Nidus Types	Obliteration Rate	p-value
Choi <sup>48</sup>	2012	Retrospective	24	Compact	75%	0.048
				Diffuse	66.70%	
Paul <sup>49</sup>	2014	Retrospective	532	Compact	87%	< 0.001
				Non compact	57.40%	
Koo <sup>47</sup>	2023	retrospective	154	Compact	48.10%	0.434
				Diffuse	39.10%	

## COMPACT VS DIFFUSE NIDUS

In a study by Koo et al, where AVMs were divided in to diffuse vs compact nidi, it was found that there was no significant difference between the two groups in terms of obliteration rates as well as radiation induced changes. Several other studied reported that diffuse-nidus was associated factor in complete obliteration, whereas others, have not found statistically significant differences.<sup>47</sup>

However, in the case of diffuse-type nidus AVM, GKRS is usually used with a low radiation dose, and this often comes into effect slowly; hence, it can be generally inferred that complete obliteration can be measured to be low in practice. Considering that the primary purpose of AVM treatment is to minimize complications and reduce the risk of bleeding, GKRS is clearly effective and feasible for the treatment of diffuse-type AVM.

It can be anticipated that the smaller size of the nidal vessels in the diffuse-type AVM compared to the compact group may allow for effective nidus obliteration through radiation effects even with a low radiation dose. Due to the characteristic of smaller nidal size, diffuse-type AVMs often have limitations in endovascular embolization, and there are limited alternative treatments besides GKRS. Many cases also pose challenges in selecting the appropriate Gamma plan.

GKRS is a safe and feasible treatment for brain AVMs characterised by both diffuse- and compact-type niduses. The optimal treatment plan and radiation dose identified by accurate angioarchitectural classification may minimise GKRS complications in AVM.<sup>47</sup>

## RADIOSURGERY FOR EMBOLIZED AVMS

Combination of SRS after embolisation is being used frequently for SM grade III and above AVMs. There are theoretical advantages of doing embolisation of AVM before radiosurgery, like it provides potential benefit of improving vascular steal, reducing the volume of the nidus, hemorrhagic risk reduction in the latency period, and eliminating radioresistant features like the presence of fistulas. However, there are numerous reports of reduced efficacy of gamma knife radiosurgery after embolisation of AVMs.<sup>50,51</sup>

In a single centre retrospective study from the author's institute, GKRS after embolization was done in 46 cases with mean nidus volume of 19.4 ml and complete

TABLE 14.4 ■ Outcomes of Radiosurgery for Embolized AVM

Author	No of Patients	Pre-embolisation Nidus Volume	Pre-GKRS Nidus Volume	Obliteration Rates
Dawson <sup>56</sup>	7	NA	NA	29
Mathis <sup>57</sup>	56	41.8	14.1	50
Gobin <sup>58</sup>	125	18.6	6.2	65
Mizoi <sup>59</sup>	54	NA	10.9	37
Andrade-Souza <sup>51</sup>	61	NA	7.42	47
Izawa <sup>60</sup>	16	16.7	9.9	67
Schwyzler <sup>60</sup>	215	NA	4.7	33
Nadeem <sup>52</sup>	46	19.4	4.7	60

obliteration was achieved in 60% of the cases and 6% had morbidity. While, the literature reports reduced efficacy of GKRS after embolization of AVMs, the complex nature and higher grade of AVMs, makes embolization as an attractive adjunct. The nidus volume and SM grade did not affect the obliteration rates in authors' study, but the interval of less than 12 months between embolization and GKRS lead to better obliteration rates.<sup>52</sup> With the advent of fractionation in GKRS in the current Gamma knife machine models (ICON and further models), the GKRS after embolisation is being gradually replaced by volume-staged GKRS<sup>53,54</sup> and hypo-fractionated GKRS (dose fractionation).<sup>55</sup> The long term results of these are still awaited.

## AVM IN PEDIATRIC AGE GROUP

The paediatric population presents unique challenges in the management of intracranial arteriovenous malformations (AVMs) that are associated with a greatly enhanced cumulative lifetime risk of haemorrhage compared to adults. Radiosur-

TABLE 14.5 ■ Outcomes of GKRS for Pediatric AVMs

Author (s)	Year	Number of Patients	Obliteration Rate (%)	Hemorrhage(%)	Complications (%)	Follow-Up (Months)
Dinca <sup>63</sup>	2012	363	82.7%	2.2	3.6	24
Potts <sup>64</sup>	2014	80	52%	20	48	50
Nicolato <sup>65</sup>	2015	100	88.1%	9	11	82.2
Starke <sup>66</sup>	2017	357	63%	Unruptured 0.8; ruptured 1.6	8	92
Hasegawa <sup>61</sup>	2019	201	–	–	6.1	136
Hasegawa <sup>67</sup>	2019	189	5 yr 64%, 10 yr 81%	2.8	–	136
McDowell <sup>68</sup>	2020	212	79.4%	6	–	79.7
Goyal-Honawar <sup>62</sup>	2025	101	77.8%	1	11.8	41.4

gery presents a promising approach to manage paediatric AVMs; however, the risks of haemorrhage during the interval to obliteration and radiation-related complications present important considerations. Gamma Knife radiosurgery (GKRS) in paediatric patients appears to produce AVM nidus obliteration rates in excess of 80%.<sup>61</sup>

In a retrospective study from the authors' institution, reporting long-term outcomes in 101 paediatric patients treated with GKRS for brain AVMs, 77.8% of AVMs were obliterated. Mean dose delivered was  $22.7 \pm 2.4$  Gy. Factors predicting poor outcomes were Dose  $>22$  Gy and volume  $\geq 3$  cc. Higher SM grade and higher PF score predicted residual nidus at follow-up.<sup>62</sup>

## OUTCOME ANALYSIS

### Assessing Imaging

The obliteration rates were considered based on the absence of flow voids on MRA, and as DSA is an invasive method of investigation, it was not performed routinely. The study by Lee et al.,<sup>69</sup> including 136 patients treated with SRS, concluded that MRI with MRA predicted AVM obliteration in most patients and can be used for their follow-up. However, the fact remains that DSA is the gold standard investigation to prove the complete obliteration of AVM. Furthermore, the MRI with MRA had sensitivity as high as 84.9 % and specificity as high as 95.2%.

In a recent meta-analysis by Kolahi et al.(2025)<sup>70</sup>, studying the diagnostic performance of MRI in post-radiosurgery monitoring of Brain AVMs, advanced MRI sequences such as 4D MRA and ASL (arterial spin labelling) show acceptable diagnostic accuracy (AUC 0.97 and 0.96 respectively) compared to DSA. This study indicates that MRA can be a feasible alternative to DSA, but further studies are pending.<sup>70</sup>

## ADVERSE EFFECTS OF RADIOSURGERY

### Radiation-Induced Side Effects

A systematic analysis done by Ilyas et al. concluded that, approximately 1 in 3 patients with AVMs treated with SRS develop radiologically evident RIC (radiation induced changes), and of those with radiologic RIC, 1 in 4 develop neurological symptoms. Lack of prior AVM hemorrhage and repeat SRS are risk factors for radiologic RIC, and deep nidus location is a risk factor for symptomatic RIC. Several studies on radiation-induced changes in AVMs have shown that higher marginal dose, greater Spetzler -Martin (SM) grade, greater radiosurgery-based score, and deep location in the brainstem and thalamus have a higher likelihood of developing radiation-induced changes. Radiation-induced changes in the vascular wall and intimal hyperplasia are a well-known phenomenon and are the reason for its therapeutic intent in AVMs. AVM volume increases the radiation given to the surrounding brain, which can cause RIC. Similarly, the cyst formation is a known RIC in large AVMs with prior bleed.<sup>71</sup>

## CYST FORMATION POST SRS

Post-SRS cysts typically develop within or adjacent to the site of the original AVM nidus, several years after treatment, and are believed to be related to the formation of telangiectatic perinidal vessels. fragile vessels are prone to rupture, which promotes serum and protein exudation, edema, cyst formation, and encapsulating hematoma formation.

A pooled analysis of all the studies who reported cyst formation after radiosurgery for AVMs included 22 studies that showed an overall incidence of post-SRS cyst formation to be 3% (78/2619 patients). Cyst formation was associated with nidus obliteration in 76.9%. 32.8% were symptomatic among them one third were treated with surgical intervention, whereas the remaining two-thirds were managed conservatively. The mean latency period to post-SRS cyst formation was 78 months. Higher SRS maximal dose, larger nidus volume, lobar AVM location, and obliteration to be predictors of cyst formation.<sup>72</sup> Pan et al. found RIC and prior nidus embolization to be significantly associated with cyst formation.<sup>73</sup>

## CHRONIC ENCAPSULATED INTRACEREBRAL HEMATOMA (CEIH)

Chronic encapsulated intracerebral hematoma is a very rare complication of radiosurgery for cerebral AVM, the reported incidence ranging from 0.6 to 4%. CEIHs are made

of a thickened hematoma capsule with abundant microvasculature and the hematoma which itself is serious. Radiation-induced inflammation triggers neoangiogenesis of fragile new vessels, breakdown of the blood brain barrier, fluid exudation in the nearby brain, edema and potential cyst formation. CEIHs were associated with cysts in 62.1% of cases pointing to a possible common pathophysiologic mechanism. The latency time from radiosurgery to CEIHs diagnosis is about 7.7 years. Symptoms, the most common being from headache, hemiparesis, nausea/ vomiting mostly related to the mass effect. The most efficient treatment is complete excision, which will lead to clinical and/or radiological improvement. Conservative management consisting of follow-up or steroid administration can be tried but may be unsuccessful in most cases and had to be complemented by total excision of the hematoma and the capsule to achieve good clinical outcome.<sup>74</sup>

## HEMORRHAGE RISK DURING THE LATENCY PERIOD

In a pooled meta-analysis annual haemorrhage rate following GKRS was 1.4% while waiting for obliteration<sup>31</sup>. This suggests that radiosurgical intervention may afford partial protection from AVM rupture during the latency interval before nidus obliteration. In a cohort of 1204 AVMs treated with GKRS, annual AVM haemorrhage risk was 2.0% for the entire cohort and it was 3.7% for AVMs with prior haemorrhage.<sup>75</sup> Kano et al. reported a reduction in annual haemorrhage rate from 3.4% (based on natural history) to 1.3% following radiosurgical intervention in a

cohort of 407 ruptured AVMs.<sup>76</sup> The range of rebleeding while waiting for AVM obliteration after SRS has been reported to range between 1.3 to 9%. Low marginal dose of radiation, periventricular location of the AVM and presence of multiple draining veins have been reported to be risk factors for haemorrhage during the latency period between SRS and AVM obliteration.<sup>77</sup>

## SEIZURE REDUCTION AFTER SRS

According to a systematic review and meta-analysis of 27 studies, one or more seizures occurred in 1,456 of 4,826 patients (34.7%, [26.0-43.9%]), and the mean follow-up was  $48 \pm 7$  months. Seizure control (seizure freedom or seizure improvement) was achieved in 910 of 1,312 patients (73.1% [66.9-78.9%]). AVM obliteration (OR = 4.61;  $p < 0.001$ ), shorter seizure duration (OR = 6.80;  $p < 0.001$ ), generalized seizure type (OR = 2.27;  $p = 0.007$ ), and prior AVM haemorrhage (OR = 5.10;  $p < 0.001$ ) were significantly associated with seizure freedom.<sup>78</sup> In the author's experience of treated AVMs presenting with seizures using single session GKRS, 69% patients were seizure-free, and 29.6% had well-controlled seizures on anti-epileptics.

## MANAGEMENT OF RESIDUAL AVM AFTER GKRS

There are several options for the residual AVM after GKRS. The first being observation. Observation with serial MRI should be the first option after single-session GKRS. We suggest waiting for at least 4 years for AVM to undergo obliteration, as the risk of repeat GKRS in this period can cause higher AREs, whereas the interval risk of bleeding after GKRS is minor. The option of repeat single-session GKRS can be given after 4 years if there is subtotal obliteration in a small volume AVM. While for larger volume AVMs, we suggest repeat hypo-fractionated GKRS. The volume reduction over time could be a reliable parameter to predict success with repeat GKRS.<sup>79</sup> The option of embolization is not feasible due to the heterogeneity of nidus obliteration after GKRS and can lead to lower obliteration rates. The final option for incomplete obliteration remains microsurgical excision. However, the risk of permanent neurological deficit is higher for residual AVMs in eloquent or deep-seated AVMs. So, for such cases, multimodality treatment starting with GKRS should aim at eliminating the deep areas or nidus near eloquent areas to make AVM more feasible for subsequent microsurgical resection of the residual nidus.<sup>80</sup>

## REPEAT RADIOSURGERY FOR AVM

In a study by Pikiş et al, for repeat SRS for residual AVM after prior SRS, 170 patients underwent repeat SRS. After repeat SRS, the actuarial 3-, 5-, 10- year AVM obliteration rates were 37.6%, 57.3% and 80.9% respectively. Repeat SRS was more favourable for adult patients and those with residual AVMs smaller than 20 mm in maximum diameter. The authors advised that to increase the rate of residual AVM obliteration, a prescription dose  $\geq 19$  Gy should be used for repeat SRS.<sup>81</sup> In a

recent study by Shaaban et al., a Systematic review and meta-analysis reporting 630 patients in 4 studies concluded that overall obliteration rate after repeat SRS was 59%(51-67%) with median follow-up between 21 and 50 months. Median prescription dose ranged from 15 to 25 Gy. Haemorrhage rate was 5% and RIC was 12%.<sup>82</sup>

## **THE ARUBA EFFECT: ROLE OF GKRS IN UNRUPTURED/ARUBA-ELIGIBLE AVMS.**

After the publication of ARUBA, there have been many prospective and retrospective studies involving “ARUBA eligible patients” managed either by microsurgery or SRS. Well-designed studies by Yen et al and Pollock et al report better outcomes in ARUBA-eligible patients when treated with SRS than those obtained in the conservatively treated group from ARUBA. Both the studies demonstrated GKRS as a reasonably safe modality for uBAVMs with low procedure-related morbidity.

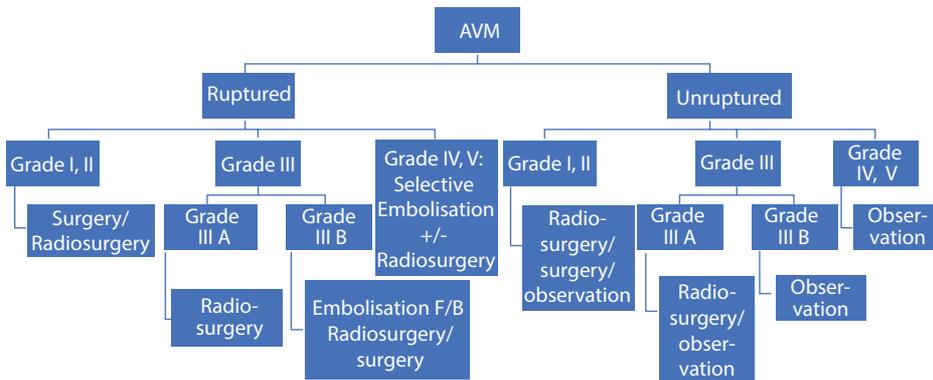
In a recent meta-analysis by Ilyas et al.<sup>83</sup>, studying stereotactic radiosurgery for ARUBA-eligible patients, 1620 ARUBA-eligible patients in 8 studies were analysed, and obliteration rate was 68% with a mean follow-up duration of 80 months (6.6 years). In our experience the obliteration rate in ARUBA.-eligible AVMs is 74% (unpublished data). Hence, SRS carries favourable risk-to-benefit for small-volume ARUBA-eligible patients.

In simple terms, ARUBA has not changed the management practice in the world but has made us all aware of the need for better assessment of treatment options. Based on the volume of evidence, we suggest that the management of uBAVMs should be case-by-case basis. A ‘one size fits all’ policy is clearly undesirable.<sup>84</sup> We believe that management options need to be tailored, after a thorough discussion with the patient, based on the expertise available at a particular centre, as this will go a long way in providing optimal care.

## **CONCLUSIONS**

We prefer the following management algorithm as elucidated by the lead author.<sup>2</sup> (Figure 14.3) According to the above algorithm, the role of radiosurgery is prescribed in the following clinical settings- In case of ruptured brain AVMs, radiosurgery is an alternative to surgery in SM grade I/II AVMs. While for SM grade IIIA AVMs, radiosurgery is preferred. Radiosurgery is an alternative to surgery after embolization in SM grade IIIB AVMs. SM grade IV/V requires an individualised approach to the patient with selective embolisation with or without radiosurgery.

In case of unruptured AVMs, radiosurgery is an alternative to surgery or observation in SM grade I/II uBAVMs. While for SM grade IIIA uBAVMs, radiosurgery is an alternative to observation. Radiosurgery is not a preferred option in unruptured SM grade IIIB, IV and V uBAVMs, as observation is considered more advisable. However, with the advent of volume or dose fractionation on the new GKRS systems, we have started using dose fractionation. This algorithm is practical, though debatable, based on individual patient preferences. So, the current consensus in management of brain AVMs is to have a multidisciplinary team approach in large



**Figure 14.3** Management algorithm.

volume centres with availability of all the treatment modalities for a patient-centred individualised treatment plan based on the current evidence.

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SECTION IV

# Schwannomas

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# Gamma-Knife Stereotactic Radiosurgery for Large Vestibular Schwannoma

Satish Verma ■ Deepak Agrawal

## INTRODUCTION

Management of large vestibular schwannoma remains a significant challenge. Microsurgical maximal safe resection preserving the facial nerve is the standard treatment. However, many patients even with large vestibular schwannomas (VS) are not symptomatic for the mass effect on brainstem and few of them still have a serviceable hearing. Many of them present at an advanced age, may have poor functional status, may be on mandatory anticoagulation or have other comorbidities. Very few cases peculiarly present with a large residual lesion after a failed micro-surgical resection due to various reasons and refuse any further surgery. Because of these practical concerns, many authors have evaluated the role of GKRS in large vestibular schwannoma. There is no clear definition of 'large' vestibular schwannomas, with almost all studies defining large tumors being those with volumes  $>8-10 \text{ cm}^3$ . Conventionally, tumors more than 2.5 cm in diameter (equivalent to a volume of about 8 cubic centimeters ( $\text{cm}^3$ )) were not considered suitable for stereotactic radiosurgery (SRS) because of poor tumor control and significant long-term radiation induced toxicity.<sup>1-3</sup> Recent studies suggest that GKRS for lesions more than 3 cm or volume  $\geq 14 \text{ cm}^3$  is a feasible option with acceptable tumor control and adverse radiation effects.<sup>4-7</sup> Hypo-fractionated GKRS has shown similar results for large vestibular schwannoma.

## REPRESENTATIVE CASE

### History & Examination

A 55-year-old male, an engineer by profession, presented with progressive hearing loss on right side for 9 months, which was later on associated with tinnitus and vertigo for 3 months. It was not associated with facial sensory loss or paresthesia or neuralgia, facial deviation, gait ataxia, headache, or vomiting. On examination, he had reduced hearing on the right side. Rinne's test was positive bilaterally and Weber's test was lateralizing towards the right side. Audiometric evaluation with

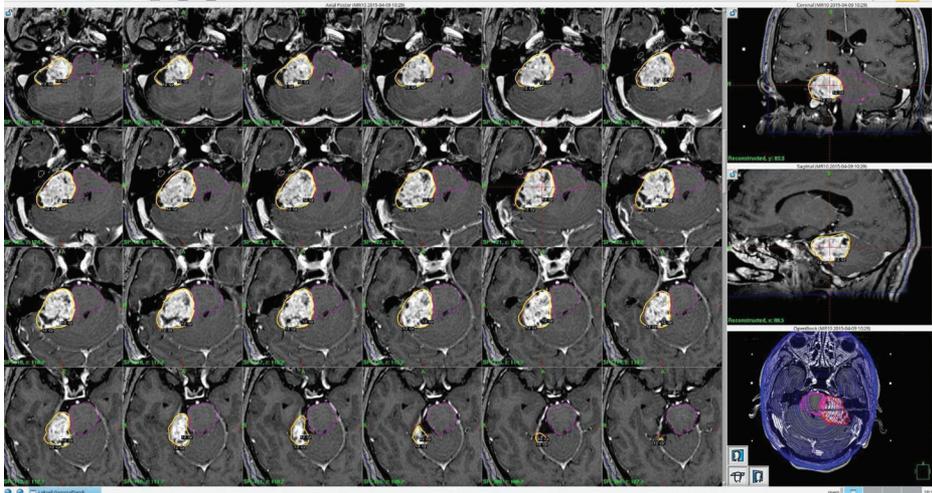
pure tone audiometry (PTA) was consistent with profound sensory-neural hearing loss on the right side of >70 decibels at 2 kiloHertz (kHz) frequency. Rest of the neurological examination was within normal limits.

## Imaging

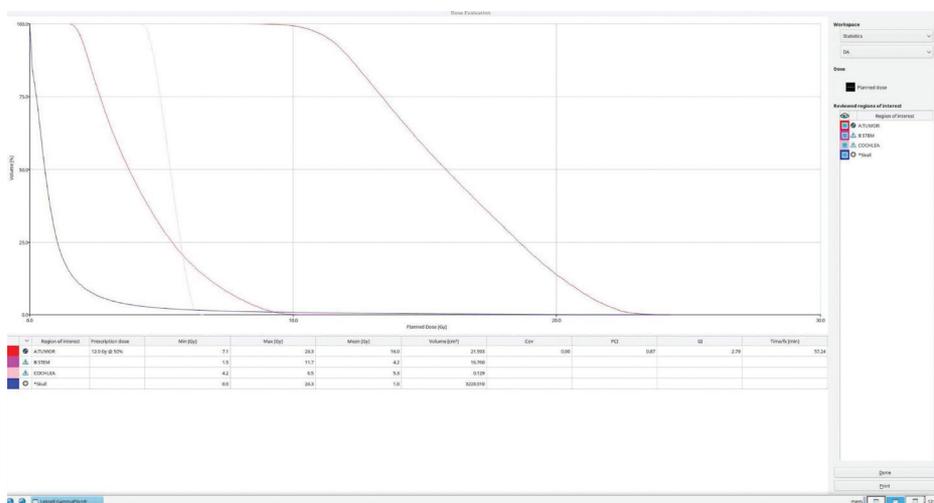
Contrast enhanced MRI of the brain showed a large heterogeneously enhancing lesion in the right cerebello-pontine angle extending into the internal auditory meatus and causing mass effect on cerebellar peduncle and brainstem without obliterating the fourth ventricle. Hydrocephalus was absent. He was offered GKRS as there were no disabling symptoms attributable to brainstem compression. Hearing was non-serviceable, and prognosis was explained to the patient.

## GK Protocol

Gamma knife was performed on a Leksell Gamma Knife Perfexion unit (Elekta AB, Stockholm, Sweden) with Leksell GammaPlan. Manual AVM segmentation was done for the tumor and Organ-at-risk (OAR) (brainstem and cochlear/modiolus). Total tumor volume was 21.59 cubic centimetre (cc). Inverse planning with optimization of 19 iso-centres (combinations of 4-, 8- and 16-mm collimators) was performed with prescription dose of 12 Gy at 50% isodose line to the tumor margin (Figure 15.1). Further optimization was done manually to exclude OARs out of the prescribed dose constraints achieving following parameters - coverage -90%, selectivity - 98%, Gradient Index - 2.80. Beam-on time (BOT) was 57.2 minutes with a treatment dose rate of 2.196 Gy/min. Maximum dose to the segmented volumes were: tumor - 24.3 Gy, brainstem - 11.7 Gy and Cochlea - 6.5 Gy (Figure 15.2). The coverage of the tumor was intentionally kept at 90% to limit the dose to brain-



**Figure 15.1** Gamma Knife planning for the index case. Tumor margin (red), 12 Gy (prescription dose) isodose line (yellow).



**Figure 15.2** Dose volume histogram (DVH) for the tumor, brainstem and cochlea.

stem. Still the marginal dose to >94% of tumor volume was >11.5 Gy. This strategy ensured that not more than 0.1 cc of brainstem received >10 Gy.

### Follow Up

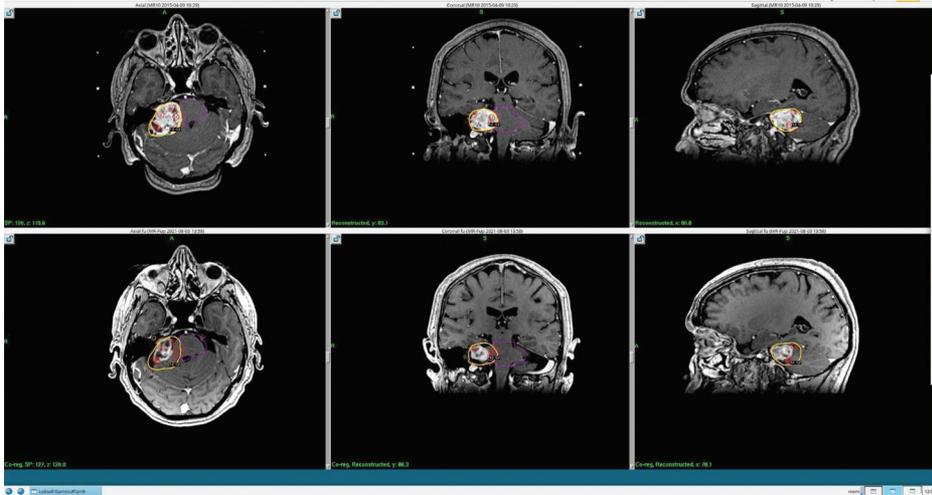
Patient tolerated the procedure well. Follow up clinical visit after 3 months was done and no features of gait ataxia or raised intracranial pressure were observed. Follow up CEMRI was done annually for the first three years and then after 2 years which showed gradual reduction in tumor volume. At the last follow up available, at 75 months, the residual tumor volume was 7.8 cc (Figure 15.3). Tinnitus persisted for 6 months post operatively. Post- GKRS PTA was done after 1 year which showed further impairment to >80 dB loss. This worsening was expected and explained to the patient as the hearing was not serviceable and no attempt was made to preserve hearing.

## DISCUSSION

For large vestibular schwannoma, microsurgery is generally considered as the treatment of choice, primarily to reduce the mass effect on the brain stem. However, for various reasons, surgery may not be feasible or refused by the patient. In such cases, GKRS is a very useful non-invasive modality for good long-term tumor control. Primary GKRS is a standard treatment modality for small vestibular schwannoma presenting without any mass effect on the brainstem or cerebellar peduncles.<sup>6-11</sup>

## CONTROVERSIES

The role of GKRS in managing large vestibular schwannomas remains debated. Conventionally, GKRS has been reserved for tumors with volume <8-10 cm<sup>3</sup> or



**Figure 15.3** Follow-up MRI done after 75 months (lower panel) compared to the baseline MRI at the time of GKRS (upper panel) showing marked reduction in tumor size.

diameter  $\leq 2.5 \text{ cm}^3$  due to concerns regarding poor tumor control rates, acute or subacute tumor swelling leading to increase in brainstem compression and risk of radiation induced brain stem injury.<sup>12-14</sup> Microsurgery has its own limitations. The reported rates of preservation serviceable hearing are extremely low with microsurgery. Post-operative facial nerve outcomes are mostly sub-optimal.

Over the last three decades, the role of radiosurgery for large vestibular schwannoma has been assessed by many centers with encouraging results.<sup>15,16</sup> For large VS, the need for microsurgical decompression should be considered depending upon pre-treatment symptom burden specifically attributable to brainstem compression rather than the tumor size. Recommended ideal candidates are those without symptomatic mass effect and disabling symptoms like ataxia or hemiparesis, with serviceable hearing and with comorbidities that increase the peri-operative procedure and anesthesia-related risks. Patient's wish to avoid microsurgical resection may be evaluated on an individual case basis considering the above-mentioned recommendations. Most of the studies are based on single-fraction GKRS. Hypofractionation (2-5 fractions) regimens are recently proposed by many centres due to its potential for treating relatively larger tumor volumes while reducing adverse radiation effects. No well-controlled studies are yet available to compare these two methods of GKRS.

Tumor control rates of 57%-100% are reported at a follow up ranging from 21 – 156 months.<sup>17</sup> A recent study reported tumor control rates of 91% at a mean follow-up of 78.5 months.<sup>18</sup> Cranial nerve preservation rates are high. Reported rates of preservation of serviceable hearing are up to 56.5% at 2-year follow-up, ranging from 37%-75.1%. Similarly, excellent facial nerve preservation rates are reported, reaching nearly 100% (range 99.9%-100%). Trigeminal nerve related complications are very low, <6% (range 2.9% - 9.2%). However, new-onset vestibular symptoms

(tinnitus and vertigo) are reported upto 9%.<sup>18</sup> Radiosurgery offers an acceptable tumor control rate of 89% at 6-year and 84.5% at 10-year follow-up.

## CURRENT PRACTICE

GKRS is now increasingly considered in patients with large VS who lack disabling mass effect symptoms or are unfit for surgery due to age or comorbidities. Marginal dose of 12-13 Gy is recommended for good tumor control. For avoiding adverse radiation effects on brainstem, maximum point dose of <12 Gy and maximum dose of <10 Gy to a volume of 0.1 cc is practiced. Maximum point dose up to 15 Gy is accepted at many centres. Marginal dose <13 Gy and early pseudo-progression predicts deterioration of facial nerve function. Tumor volume less than 10 cc and non-cystic schwannoma predict good facial nerve function. For hearing preservation, recommended mean dose/point dose to the cochlea and modiolus is <4 Gy. Better hearing (Gardner-Robertson grade 1) at the time of GKRS and age less than 60 years predict better hearing preservation. Salvage resection may still be required in cases who fail to respond to GKRS and this possibility must be clearly conveyed to the patient. Few cases required further surgical intervention in the form of either ventriculo-peritoneal shunt (VP shunt) to manage hydrocephalus or microsurgical resection to salvage symptomatic brainstem compression. Shunting may be needed in up to 5% cases and salvage resection may be required in up to 8% in most of the series.

Cystic VS are a particular entity where the role of GKRS is not clear, more so in large cystic VS. Due to their unique characteristics like unpredictable biologic behavior due to rapid cyst expansion or hemorrhage and adherence to brainstem and cranial nerves. Complete microsurgical resection is difficult and associated with poor facial nerve function and hearing preservation rates as compared to solid VS. Initially considered as poorly-responsive to radiosurgery, recent studies have proved beyond any doubt that cystic VS respond well to radiosurgery with tumor shrinkage rates up to 92%.<sup>19</sup>

Upfront GKRS for large VS is effective for elderly patients. The incidence of comorbidities and frailty increases with age. Many of the patients in this age group are on mandatory anticoagulation or antiplatelet medications for various reasons. A recent study assessed the role of GKRS in large VS in elderly patients > 65 years. Tumor control rates were 96% at 5 years and 86.2% at 10 years. Actuarial serviceable hearing preservation rate was 51% and facial nerve function preservation or improvement rate of 91% at 10 yr.

## LEARNING POINTS

- Large VS (> 8 cc) can be effectively managed with GKRS in carefully selected cases.
- Large VS presenting without disabling symptoms may be offered upfront GKRS. Less than 10% cases require a surgical intervention later on.
- Elderly patients with multiple co-morbidities and high anesthesia risk may be suitable should be offered GKRS

- GKRS provides better cranial nerve function preservation
- Serviceable hearing at treatment is likely to be preserved longer than microsurgical controls

## CONCLUSION

Gamma knife radiosurgery for large VS – either upfront or post-resection, is an effective treatment option in carefully selected cases without any disabling symptoms due to brainstem compression. Patient related factors like advanced age, co-morbidities and patient refusal may be important in decision making. Serviceable hearing rates are much better with GKRS even for large VS. Facial nerve and trigeminal nerve outcomes are better with GKRS. Presentations with trigeminal neuralgia or hemifacial spasm are ideally managed with microsurgical decompression. Patients should be properly conveyed that GKRS may aggravate symptoms and may require a surgical intervention.

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# Pseudoproggression in Vestibular Schwannoma following Gamma-Knife Radiosurgery

Kanwaljeet Garg ■ Abhilash Reddy ■ Deepak Agrawal

## INTRODUCTION

Vestibular schwannomas (VS) are histologically benign tumours that usually arise from the Schwann cells of the vestibular nerve. It is one of the most common intracranial tumors, representing approximately 6-8% of all intracranial tumors with a reported annual incidence of 1 in every 100,000 people.<sup>1</sup> SRS is a commonly used treatment modality for VS. Pseudoproggression, defined as a significant volume increase at any time following treatment, which resolves/stabilizes on subsequent imaging, may be observed after radiotherapy/radiosurgery for VS.<sup>5</sup> Although tumor growth with increasing symptoms or neurological deficit may herald treatment failure, the concept of pseudoproggression, or a transient increase in size followed by stability or regression, has been increasingly recognized following radio surgical treatment of VS.<sup>6</sup> The reported incidence of pseudoproggression following radiosurgery for VS has varied widely from 6-74%, using different methods of measurement. We will present a patient who experienced pseudoproggression following GKRS for VS.

## REPRESENTATIVE CASES

### Case 2

#### *History & Examination*

A 39-year-old female was operated on for left vestibular schwannoma in February 2015 at another hospital. On examination, the patient had left-sided profound SNHL, grade 4 facial palsy, and cerebellar signs were absent.

#### *Imaging*

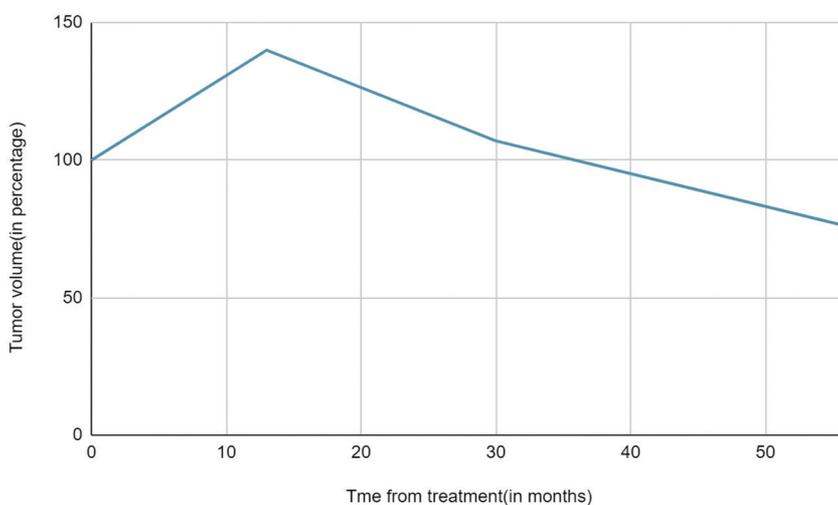
Post-operative MRI showed a residual lesion for which she was planned for secondary GKRS. Contrast-enhanced MRI brain showed a tumour in the left-right cerebellopontine angle with extension into the internal acoustic meatus and abutting the brainstem without significant brain stem compression. There was no evidence of hydrocephalus.

### **GK Protocol**

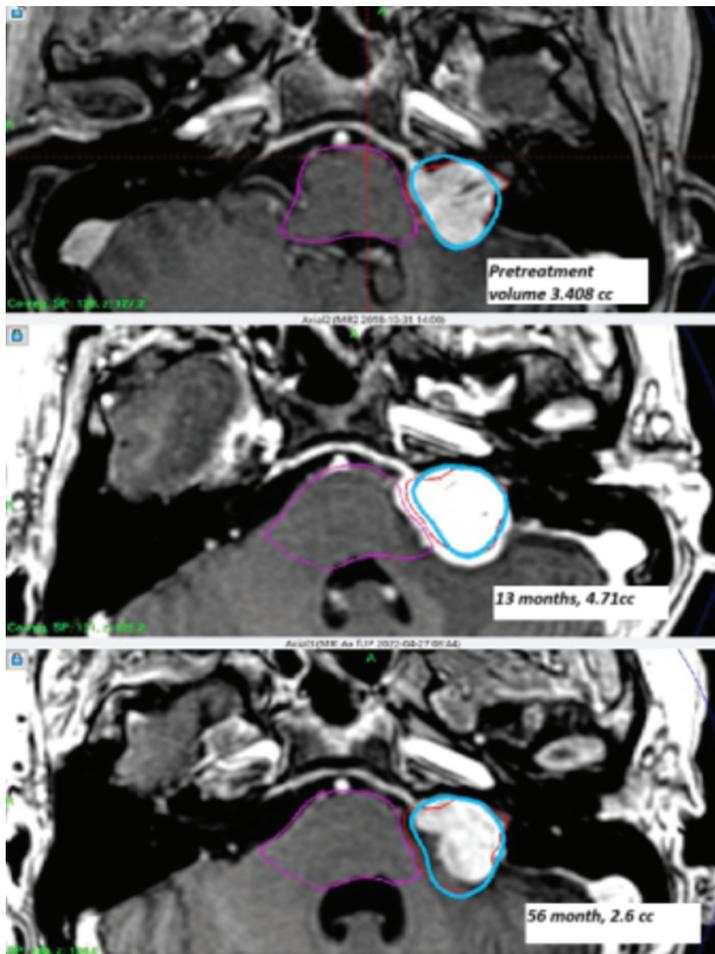
The patient opted for GKRS after being explained all the possible options, including watchful waiting with serial MRI scans, surgery and GKRS. MRI brain was done following fixation of stereotactic frame (Leksell Model G) MRI brain included T1-weighted high-resolution magnetization-prepared 180 degrees radio-frequency pulses and rapid gradient-echo (MPRAGE) sequences with 192 slices with a slice-thickness of 1 mm without intersectional gaps were acquired. These images were imported to the treatment planning station, and GKRS planning was done using GammaPlan® v11.3 (Elekta AB, Sweden) software. Tumor volume (by volumetric method) was found to be 3.408cc. The treatment plan was made, and GKRS was administered using Leksell Gamma Knife Perfexion™. A dose of 12 Gy to the 50% isodose line was administered. The procedure was uneventful, and the patient was discharged in stable condition.

### **Follow Up**

A follow-up MRI of the brain done 13 months post-procedure showed an interval increase in the tumour size from 3.408 cc to 4.715 cc. Differentials included a non-response to GKRS or pseudoprogression. Treatment options considered were observation, surgery, and repeat radiation. The patient was clinically stable, with no signs of brainstem compression, and had no radiation-related adverse effects. After a discussion with the patient, it was decided that the patient should be followed up with interval imaging. Further MRI of the brain done at 30 months post-procedure showed an interval reduction in tumour volume from 4.71cc to 3.654 ccs, and at 56 months post-procedure showed further reduction in tumour volume to 2.6cc (Figures 16.1 and 16.2). The patient is under regular follow-up and clinically stable with new symptoms, no signs of brainstem compression, and no new radiation-induced adverse effects.



**Figure 161** Line graph showing the change in the size of the lesion over time following GKRS



**Figure 16.2** Serial MRIs of representative case 1 showing pseudoprogression with transient increase followed by regression

## Case 2

### *History & Examination*

A 34-year-old female presented with complaints of vertigo and tinnitus. On evaluation, the patient had no facial sensory loss, facial palsy, no cerebellar signs, and no signs of raised ICP. She has mild right-sided SNHL.

### *Imaging*

MRI of the brain was suggestive of a contrast-enhancing lesion in the right cerebellopontine angle extending to the internal acoustic meatus.

### *GK Protocol*

Treatment options, including GKRS, surgery and observation, were discussed with the patient, and the patient opted for primary GKRS. An MRI brain was done at

the Gamma Knife MRI centre using the Gamma Knife protocol. Tumor volume (by volumetric method) was found to be 0.378cc. These images were imported to the treatment planning station, and planning was done using GammaPlan® v11.3 (Elekta AB, Sweden) software.

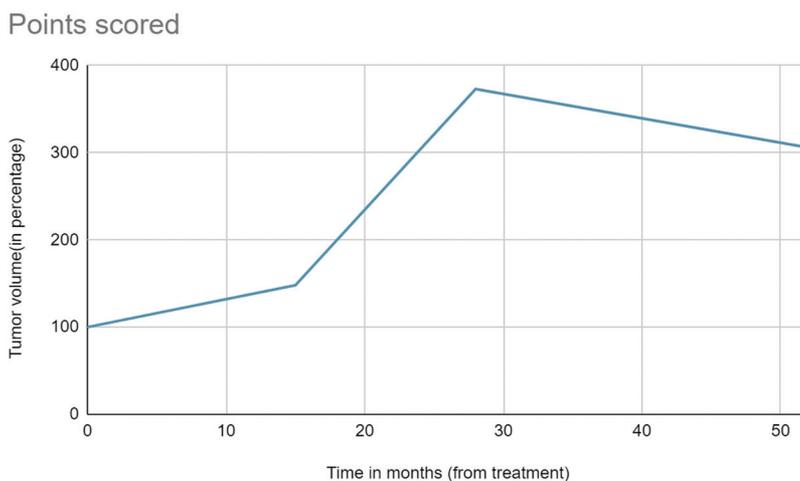
Treatment plan was made and GKRS was administered using Leksell GammaKnife Perfexion™. Dose of 12 Gy to the 50% isodose line was administered. The procedure was uneventful, and the patient was discharged the same day in a stable condition.

### Follow Up

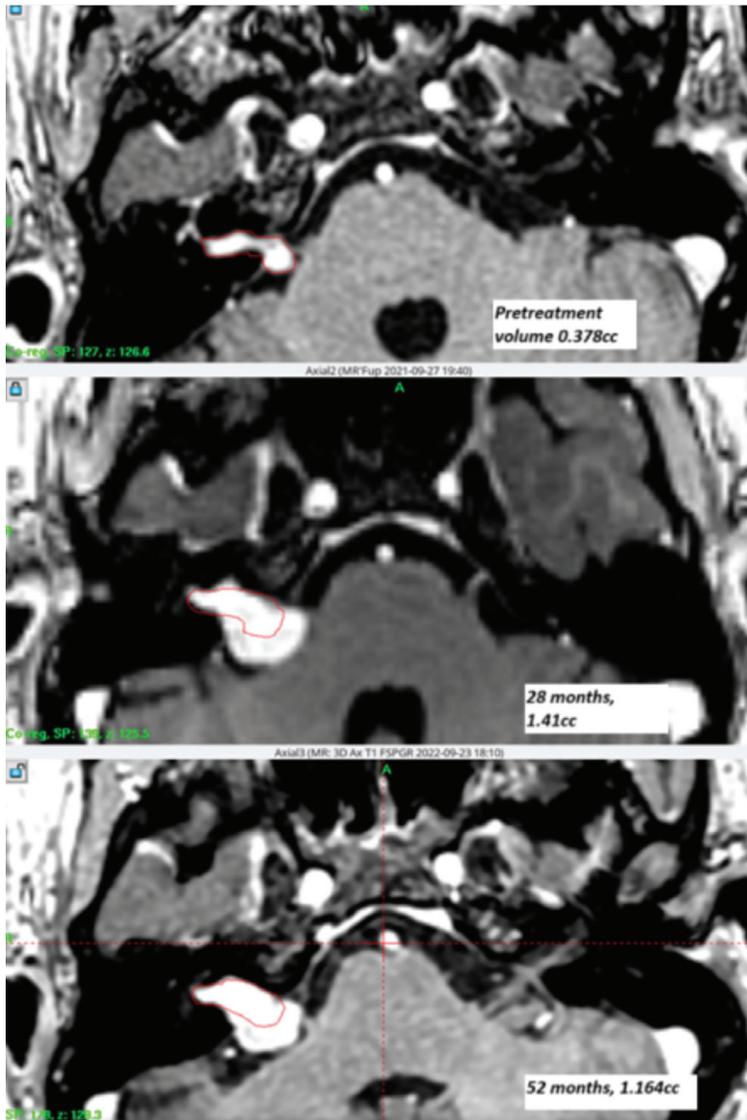
A Follow-up MRI done at an interval of 15 months revealed an increase in tumour size to 0.563 ccs. The patient was clinically stable and had no radiation-related adverse effects. Treatment options considered were observation, surgery, and repeat radiation. After a discussion with the patient, it was decided that the patient should be followed up with interval imaging. Further imaging revealed an increase in tumour volume to 1.41cc at an interval of 28 months post-procedure. The patient was clinically stable and opted for follow-up with imaging. A follow-up MRI done at 52 months post-procedure showed regression in tumour volume to 1.164 cc (Figure 16.3 and 16.4)

## DISCUSSION

GKRS has become the primary treatment choice for small and medium-sized tumours in view of improved facial nerve outcomes, hearing preservation rates, and lower overall morbidity. Post-radiosurgery surveillance of the patients is done using regular imaging, with MRI being the most used modality. Pseudoprogession, defined as a significant volume increase at any time following treatment, which resolves on subsequent imaging, may be observed after radiotherapy for VS.



**Figure 163** Line graph showing the change in the size of the lesion over time following GKRS.



**Figure 16.4** Serial MRIs of representative case 2 showing pseudoprogression with a transient increase followed by regression.

## CONTROVERSIES

The primary controversy surrounding pseudoprogression lies in differentiating it from true tumor progression. Post-GKRS volume increases are often interpreted as treatment failure, leading to premature or unnecessary surgical interventions. Current diagnostic markers are largely radiological, with no universally accepted criteria for pseudoprogression. The lack of consensus on threshold volume increases, time to

peak, and duration until regression complicates clinical decision-making. Further, the variability in reporting incidence (6% to 74%) reflects inconsistent measurement methodologies across studies.<sup>1-8</sup> Some clinicians remain skeptical of observation beyond 12 months of progressive growth, especially in patients with borderline neurological symptoms.

Here, we presented two cases of pseudoprogression in vestibular schwannoma to understand the temporal dynamics of tumour response post-GKRS. One case was upfront treated with GKRS, and another treated with adjuvant GKRS for residual tumor post subtotal resection.

The published literature on pseudoprogression reports the incidence, time to onset, time to peak volume, maximum volume change, and the percentage of volume change per year as aids for diagnosis and subsequent decision-making. The timing of tumour regression is highly variable. The onset of pseudoprogression can occur from 3 to 69 months following treatment, and resolution can occur from 6 months to 110 months<sup>1,9,10</sup>. Few studies show that about 1/3rd of the tumours regress between the 4th and 6th years after treatment.<sup>1</sup>

## CURRENT PRACTICE

GKRS is currently favored for small to medium VS due to its high tumor control rates and excellent cranial nerve preservation. In our cases, an increase in tumour size was noted at 13 months and 15 months, and regression was noted at 30 months and 52 months, respectively. Previous studies have reported a 20 to 88 % increase in tumour volume as compared to tumour volume, with one study reporting a 167% increase in tumour volume from pretreatment volume 8 cc to 20 cc before the onset of regression. Our cases show an increase in volume up to 40% and 248% before the onset of regression. Our cases demonstrate that observation remains an option despite the percentage increase in the tumour volume if the patient remains asymptomatic despite alarming radiological findings. The tumour removal remains associated with difficulty in preserving cranial nerve function with a risk of hearing loss, facial palsy, facial numbness, and other surgical morbidity. In the absence of new symptoms, patients with this finding can be observed with serial MRI and clinical examination and not undergo unnecessary and potentially morbidity-producing surgery.

## LEARNING POINTS

- Pseudoprogression is a common post-GKRS phenomenon in VS, with up to 248% volume increase documented.
- It usually occurs within 1–2 years post-treatment and may take 3–5 years to regress.
- Patients are often asymptomatic despite significant radiological enlargement.
- Observation with periodic imaging is safe and effective in clinically stable patients.
- Differentiating pseudoprogression from true progression prevents unnecessary surgical morbidity.

## CONCLUSION

Pseudoprogession following GKRS for vestibular schwannoma is a critical diagnostic consideration during post-treatment surveillance. Recognizing the temporal and volumetric characteristics of pseudoprogession enables clinicians to avoid premature interventions and focus on functional preservation. Management should be individualized, emphasizing clinical stability over radiological alarm. The phenomenon underscores the importance of longitudinal follow-up and patient education, reinforcing that radiological changes do not always necessitate therapeutic escalation.

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# Meningiomas and Other Indications

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# Stereotactic Radiosurgery For Asymptomatic Meningiomas: Prudence vs Overkill

Harsh Deora

## INTRODUCTION

Meningiomas are the most common benign primary CNS neoplasm with a reported incidence in the general population of 1.85 in 100,000(1) with a female predominance of 2:1. They are most commonly located in convexities (35%) followed by parasagittal angle (20%) and sphenoid ridge (20%). More than 90 % of meningiomas are benign histology. (2) Owing to better healthcare, an ageing population, easy availability of diagnostic imaging and increased use of radiological screening for brain injuries(3) more and more asymptomatic meningiomas are being diagnosed. A better understanding of natural history and appropriate management protocols are necessary to avoid unnecessary interventions and their resultant morbidity. Though SRS has emerged as a safer alternative in comparison to microsurgery, it is not without complications.<sup>1-10</sup>

In this chapter, we will discuss the rationale involved in the decision-making when it comes to the management of asymptomatic meningiomas. Meningiomas are usually brought to notice when symptomatic due to mass effect on the adjoining neural structures or resultant raised ICP due to large size.<sup>11-20</sup> However, when small asymptomatic meningiomas are detected incidentally, whether to treat or observe precedes the decision of which treatment modality. When the conservative approach is chosen, patient compliance with radiological follow-up becomes mandatory to prevent permanent neuropathies. This becomes a major limitation in our country along with the added cost of repeated imaging.

## NATURAL HISTORY

Meningiomas are benign slow-growing tumors except for WHO grade 2 and 3 tumors.<sup>20-27</sup> The major drawback of non-operative management of asymptomatic meningiomas is that it precludes histopathological diagnosis. A meta-analysis of the natural history of untreated meningiomas showed that 51% of untreated meningiomas  $\leq 2.5$  cm demonstrated no growth over a follow-up period of 4.6 years, and

an additional 26% grew  $\leq 10\%$  per year. Approximately 2% of patients with initial tumour diameters  $< 2$  cm developed symptoms at follow-up.<sup>4</sup> The highest risk for developing progressive symptoms were those with tumours between 2 and 2.5 cm in initial diameter and tumours demonstrating a linear growth rate  $> 10\%$  per year.

## HIGH RISK FEATURES

### Tumor Size and Location

The larger the tumour, the higher the growth potential. This has been a consistent finding in several studies.<sup>5</sup> Skull base tumours are known to be slower in growth when compared to convexity meningiomas.<sup>6</sup>

### Tumor Characteristics on MRI

T2 and FLAIR hyperintensity correlate with high vascularity, rapid tumour growth and progression. Evidence of calcification in meningiomas correlates with slower growth, hence non-progression and tumour stability. Peritumoral oedema denotes pial invasion and is the strongest predictor of tumour progression explained by its strong correlation with a higher MIB-1 labelling index.<sup>3</sup>

### Size

$> 10$  CC meningiomas are generally surgically managed. Volumetric changes of  $\geq 20\%$  from baseline (at GKRS) were defined as tumour progression, while  $\leq 20\%$  changes in volume as tumour regression. Volumetric changes within  $\pm 20\%$  of the original tumour volume were stable.

## REPRESENTATIVE CASE

- History & Examination
- 4.2 Imaging
- GK protocol
- Follow up

## DISCUSSION

### Controversies

#### *SRS vs Active Surveillance for Asymptomatic Meningiomas*

Uncertain long-term outcomes, proximity to critical neurovascular structures, location, chance of volume exceeding the SRS limits and patient preference lead to upfront treatment for incidental meningioma. Most of the incidentally detected meningiomas are small in size and are amenable to SRS and it remains the most agreeable choice due to excellent local control rates (98%–99%), and the low risk of permanent side effects (2.5%–3%) (Table 17.1).<sup>10</sup>

TABLE 17.1 ■ Studies Before IMPASSE<sup>27</sup> on Asymptomatic Meningiomas

Study (Year)	N	Female/ Male	Age (Mean/ Median)	Tumor Size (Median)	Follow up (Months)	Modality	Tumor Control	Symptomatic Progression	Complications
Jo et al (2011) <sup>14</sup>	154	121/33	59.2yrs	17mm	61.2m	Obs, Surgery, Gkrs	100% (Gkrs)/66.8% (Obs)	31.2% (Obs) required treatment	39.1% transient (GKS), none permanent
Salvetti et al (2013) <sup>15</sup>	42	33/9	53 years	4.0ml	59 mo (imaging), 76 mo (clinical)	GKRS	95.7% (5 & 10 yr)	4.8%	2.4% radiation injury
Kim et al (2018) <sup>16</sup>	354	277/77	57.6 years	1.7 cm (obs), 2.5 cm (GKS)	57 months	Gkrs vs Obs	94.4% (GKS, 5 yr), 88.5% (GKS, 10 yr) / 38.5% (Obs, 5 yr), 7.9% (Obs, 10 yr)	2.6% (GKS) / 36.3% (Obs)	13.3% adverse events (GKS)
Gupta et al (2019) <sup>17</sup>	117 (122 tm)	85/32	60yrs	3.6ml	53 months	Gkrs	97% (5 yr), 94.4% (10 yr)	14% (5 yr), 9% (10 yr)	18%, more in post-op
Fu et al (2020) <sup>18</sup>	59	44/15	56years	22mm	66.8months	Gkrs	97% (5 & 10 yr)	15.3%	25.4% edema, 1 surgery

## IMPASSE

Since the current guidelines were more in favour of expectant management, SRS is still less often chosen as the first line of management. To address the same issue, Sheehan et al (27) in the IMPASSE (International Multi-center Matched Cohort Analysis of Incidental Meningioma Progression During Active Surveillance or After Stereotactic Radiosurgery) study investigated the progression of incidentally detected meningioma during active surveillance and after SRS. It was a multicentre age matched cohort analysis investigating the safety and efficacy of SRS. The SRS cohort included patients with incidentally detected asymptomatic lesions who underwent SRS recruited through the International Radiosurgery Research Foundation and observation cohorts enrolled by study investigators. Patients older than 16yrs or with multiple meningiomas were excluded.

SRS was delivered in a single session using a Gamma knife. The technique and dose selection were as per local clinician team and radiosurgical technology available at the centre. Mean follow up duration was 4 years. Tumor control was defined as per RANO criteria. Total of 727 SRS patients and 388 conservatively managed patients were recruited in the study. The mean age was 56.9 and 62.6 ( $p < .001$ ) respectively. The mean tumor volume in each group was 4.3 and 3.7 cc, respectively ( $P = .055$ ). The mean dose to the tumor was 13.0 Gy in the SRS-treated cohort.

Among the unmatched cohorts, tumor control (ie, stability or regression) was observed in 99.0% of SRS-treated patients and 64.2% of patients in the observation cohort. PFS was significantly different over time in between the 2 study cohorts and favoured SRS. No patients in the SRS cohort showed evidence of radiation associated intracranial malignancy. New deficits attributable to the meningioma were noted in 2.3% of SRS and 3.2% of the observation cohort in matched cohorts. Tumor control in the SRS and observation cohorts was observed in 99.4% and 62.1%, respectively.

The results of this study demonstrate the long-term durability of tumor control with SRS without increasing risk of neurological deficits while avoiding the risks of resection in incidental asymptomatic meningiomas. Participation of various countries has ensured the generalizability of results. Retrospective nature of the study along with non-protocolized treatment assignment to each patient fails to exclude biases in recruitment. Surveillance protocols for radiologic and clinical assessment were dependent on institutional practices which decreases the reliability. Lastly, conclusions of overall outcome are lacking in the study as details of neurological deficit which may have led to initiation of steroid treatment or surgical treatment are not revealed.

Focused analysis of asymptomatic petroclival meningioma patients undergoing SRS from IMPASSE study showed that SRS is a safe management option for these patients and can be offered as a treatment option at diagnosis or at the time of documented growth during radiological follow up.(10) The mean radiological follow up in these patients was 52.5 months and tumor control was achieved in all 72 patients

only 6 (8.33%) developed SRS related complications and 3(4.17%) of them showed new neurological deficits.

Similarly, subgroup analysis performed for the parasagittal and parafalcine meningioma patients from the IMPASSE study showed tumor control in all patients treated with SRS vs only 61.2 % patients in the active surveillance cohort. SRS related neurologic deficits were noted in 3.1% patients and were transient. Tumor progression leading to neurological deficit was documented in 2% and death in 1%.<sup>11</sup>

Another similarly designed study exploring the role of SRS vs active surveillance in skull base meningiomas showed that tumor control was achieved in 98.2% and 61.8% of the SRS and active surveillance cohorts, respectively. SRS was associated with superior local tumor control compared to active surveillance. Three patients (2.7%) in the SRS cohort and six (5.5%) in the active surveillance cohort exhibited neurological deterioration. One (0.9%) patient in the SRS-treated and 11 (10%) patients in the active surveillance cohort required surgical management of their meningioma during follow-up. This again reinstated that SRS can be offered as the first line of management for skull base meningiomas at diagnosis or at first documented growth.<sup>12</sup> Similar results were demonstrated in several other studies with decrease in mean tumor volume from 4.04cc to 2.73cc post SRS. Permanent neurologic morbidity was reported only in 2.75% patients (Table 17.2).<sup>13</sup>

### Is GKRS for Meningiomas Completely safe?

While the rates of growth rates after GKS for asymptomatic meningiomas are generally low (1.5–2.9%). Peritumoral edema is the most common adverse effect (15–23%), but most cases are asymptomatic or transient. Symptomatic complications like seizures, headaches occur in ~8–10% of asymptomatic patients. Risk factors include tumor size (>4.2 cc), hemispheric location, and pre-existing edema. Malignant transformation is extremely rare but highlights the need for cautious patient selection (Table 17.3).

## CURRENT PRACTICE

When an incidentally diagnosed meningioma does not qualify for upfront intervention, periodic imaging and clinical evaluation remains the first line of management as recommended by EANO, NCCN and NICE. The monitoring interval and follow-up duration in stable or regressing meningioma vary in each guideline. To have a personalised follow-up plan few prognostics models have been formulated such as Asan Intracranial Meningioma Scoring System (AIMSS) and Incidental Meningioma: Prognostic Analysis Using Patient Comorbidity and MRI Tests (IMPACT) calculator which can guide in decision making.<sup>7</sup>

AIMSS is a weighted scoring system that predicts the specific probability of rapid tumour growth for patients with untreated IM thereby helping in identifying and screening out patients with high risk of rapid tumour growth. The authors defined rapid growth rate as an absolute growth rate of  $\geq 2$  cm<sup>3</sup> per year. Tumor size, calcification, peritumoral edema, and Signal intensity on T2 weighted MRI were found

TABLE 17.2 ■ Analysis of Various Subsets of Impasse Trials with SRS as a Treatment Modality for Meningiomas

Study	Sample Size	Mean Age (Years)	Tumor Location	Treatment Groups	Tumor Control Rate	New Neurological Deficits	Complications
Cavernous Sinus Meningiomas <sup>19</sup>	37	55.05 ± 11.56	Cavernous Sinus	SRS	100%	2.7%	5.4%
Convexity Meningiomas <sup>20</sup>	198 (Matched)	56.52 ± 12.56	Convexity	SRS vs Active Surveillance	99% (SRS) vs 69.4% (AS)	2.0% (both groups)	Not specified
Frontobasal Meningiomas <sup>21</sup>	112	Not specified	Frontobasal	SRS vs Active Surveillance	100% (SRS) vs 52% (AS)	0%	Not specified
Parasagittal Meningiomas <sup>11</sup>	196 (Matched)	Not specified	Parasagittal	SRS vs Active Surveillance	100% (SRS) vs 61.2% (AS)	3.1% (SRS) vs 2% (AS)	1 death (AS)
Petrocival Meningiomas <sup>10</sup>	72	59.53 ± 11.9	Petrocival	SRS	100%	4.17%	8.33%
Skull-Based Meningiomas <sup>12</sup>	220 (Matched)	62.9 ± 12.3	Skull Base	SRS vs Active Surveillance	98.2% (SRS) vs 61.8% (AS)	2.7% (SRS) vs 5.5% (AS)	0.9% (SRS) vs 10% (AS, surgery needed)

TABLE 17.3 ■ Incidences of Post GKRS Complications for Asymptomatic Meningiomas

Study (Year)	N	Growth Post GKRS	Adverse EFFECTS	Key Risk Factors
Chang et al (2003) <sup>22</sup>	140	2.9%	Peritumoral imaging changes: 23.6% Transient cranial nerve dysfunction: 1.4%	Convexity/ parasagittal/falx location
Kunert et al. (2009) <sup>23</sup>	1	Rapid Growth	Malignant Transformation	Radiosurgery
Hoe et al (2015) <sup>24</sup>	320	1.5%	New/increased edema: 15.3% Symptomatic edema: 8.8%	Tumor >4.2 cc, hemispheric location
Islim et al (2019)- systematic review <sup>25</sup>	389	1.5%	Pooled morbidity: 32.0% (headaches, seizures) Symptom development during monitoring: 8.1%	Tumor size, location, pre-existing edema

to be significant predictors of the rapidity of growth. The score classifies tumors into low, intermediate and high risk based on scores assigned as per above parameters.<sup>8</sup>

IMPACT risk calculator guides active monitoring strategies for patients with incidental asymptomatic meningiomas within the first 10 years of diagnosis. It stratifies patients based on MRI parameters: meningioma volume, meningioma signal intensity on T2/ FLAIR, peri-tumoral signal change and location in addition to clinical features such as comorbidity and functional status.<sup>9</sup>

## LEARNING POINTS<sup>26</sup>

- Growth Kinetics and Risk Stratification: Absolute Growth Rate (AGR) >2 cm<sup>3</sup>/year or Relative Growth Rate (RGR) ≥30%/year defines “rapid growth,” occurring in ~7% of cases. These thresholds correlate with higher symptomatic progression risk, warranting intervention (IMPASSE study, Table 17.2). Hyperintense T2-WI MRI signal and peri-tumoral edema are the strongest imaging predictors of growth (sensitivity: 82–94%). Calcification absence on CT/MRI further supports aggressive biology
- IMPACT and AIMSS Prognostic Models: IMPACT Calculator integrates MRI parameters (volume, T2 signal, edema) and clinical factors (comorbidity, age) to stratify 5-year progression risk. High-risk patients (e.g., volume >10 cm<sup>3</sup> + T2 hyperintensity) may benefit from early SRS. AIMSS Score focuses on calcification and T2 signal but requires external validation. Both tools aim to personalize imaging intervals (e.g., 6–12 months for high-risk vs. 3–5 years for low-risk).
- SRS Outcomes vs. Observation: SRS achieves 98–99% local control at 5 years but does not reduce symptomatic progression risk (~3% in both SRS and observation cohorts). Adverse events post-SRS (2.5–3%) correlate with pre-existing edema or volumes >4 cm<sup>3</sup>.<sup>16, 27</sup> Tumor volume >10 cm<sup>3</sup> disqualifies SRS eligibility, emphasizing the need for early intervention in rapidly growing tumors to preserve SRS as an option.

- **Surgical Morbidity in Asymptomatic Cases:** Asymptomatic meningioma resection carries a 4.9% risk of permanent neurological deficits (e.g., cranial nerve injury) and a 7% seizure risk, comparable to symptomatic tumors (Table 17.3). Surgery is reserved for symptomatic/growing lesions or critical locations.
- **Skull Base vs. Non-Skull Base Dynamics:** Skull base meningiomas exhibit slower AGR (0.23 cm<sup>3</sup>/year vs. 0.68 cm<sup>3</sup>/year in non-skull base) but may cause symptoms (e.g., visual deficits) without volumetric progression due to neurovascular compression. Volumetric accuracy is limited in skull base tumors due to irregular morphology (Table 17.2).
- **Hormonal Influences:** High-dose cyproterone acetate (CPA) accelerates growth, necessitating intervention. Estrogen-based HRT does not correlate with growth, and progesterone receptors (PR) may indicate indolent behavior.
- **Core Outcome Sets (COSMIC Initiative):** Standardized endpoints (e.g., clinical progression, loss of SRS eligibility) are critical for future trials. Current studies inconsistently report outcomes, complicating comparative efficacy analyses.
- **Psychosocial and Cognitive Impact:** 42% of monitored patients develop anxiety (“scanxiety”), and 25% exhibit depression. Neurocognitive decline post-SRS remains unstudied, while post-surgical fatigue and sleep disorders are documented.
- **Economic and Workflow Considerations:** Active monitoring incurs ~\$2,500/patient/year in incidental finding costs. SRS costs vs. long-term imaging surveillance lack health economic models, particularly for high-risk cohorts.
- **Emerging Biomarkers and Trials:** DNA methylation profiling (e.g., *\_HOXA/OTX2\_* loci) and Fibulin-2 expression may predict growth but require validation in untreated cohorts. Risk-stratified trials (e.g., SRS vs. observation for T2-hyperintense + edematous tumors) are prioritized over broad population studies due to low progression rates.

## CONCLUSION

Active monitoring should be considered the first-line management strategy in patients with an incidental meningioma. Tailored management using validated prognostic models (IMPACT/AIMSS) prioritizes SRS for high-risk anatomy/imaging features and addresses psychosocial burdens through multidisciplinary care. These remain to be externally validated. Early intervention for patients at high risk of progression may be considered. Features that would suggest a high risk include a hyperintense meningioma signal on T2-WI MRI, volume >10 cm<sup>3</sup> and peri-tumoral edema. First line therapeutic intervention may be SRS or surgery in case of incidental meningioma; the majority are eligible for SRS (<10 cm<sup>3</sup>). In cases of progression despite SRS (1% risk) or when SRS is contra-indicated (volume > 10 cm<sup>3</sup>), surgery may be considered. There should be shared decision-making with the pros and cons discussed such that informed patient preference for treatment can be achieved for all 3 management options. COSMIC and IMPACT external validation results may refine protocols further.

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# Stereotactic Radiosurgery for Convexity and Parafalcine Meningiomas

Sandeep Mishra ■ Kanwaljeet Garg

## INTRODUCTION

Meningiomas, arising from arachnoid cap cells of the dura mater, account for 13–26% of primary intracranial tumors in adults.<sup>1</sup> The majority are benign (WHO grade I) meningiomas, while few others show atypical (grade II) or malignant (grade III) features. Common locations include the convexity, parasagittal region, frontobasal area, sphenoid ridge, posterior fossa, and, less frequently, intraventricular or orbital spaces. Among these, convexity and parafalcine meningiomas are notable due to their location and potential to cause neurological symptoms by compressing adjacent structures.

Current treatment options for meningiomas include microsurgical excision, fractionated radiotherapy, and stereotactic radiosurgery (SRS). Surgical excision remains the standard approach, aiming for maximal safe tumor removal. However, factors such as large size, deep-seated location, and proximity to vital neurovascular structures can limit surgical feasibility and increase risks of neurological deficits, recurrence, and postoperative complications. SRS has emerged as a widely accepted alternative or adjunctive therapy for intracranial meningiomas. While it is less commonly employed for convexity and parafalcine meningiomas compared to skull base tumors, SRS has significantly broadened management options. It offers a non-invasive solution, allowing patients to avoid the binary choice between craniotomy and observation, particularly in cases where surgery poses substantial risks or is contraindicated.

## CONTROVERSIES

### Role of SRS versus Surgery

The role of SRS in treating convexity and parafalcine meningiomas remains a subject of debate. The standard approach for symptomatic cerebral convexity meningiomas is craniotomy with tumor and dural attachment resection. However, surgery may not always be viable, especially in elderly or frail patients or when tumors are near critical cortical veins or eloquent brain regions, limiting the use of SRS in such cases.

Parasagittal meningiomas, often located near vascular structures like the superior sagittal sinus and bridging veins, present significant challenges for complete resection. Even when a Simpson grade I resection is accomplished, the risk of recurrence remains significant after a decade of surgery. In these scenarios, SRS, whether in single or multisession formats, and stereotactic radiotherapy (SRT) have proven effective as adjuvant treatments, achieving favourable outcomes with minimal toxicity. For patients at high surgical risk, SRS alone offers a safe and effective alternative, enhancing quality of life and reducing treatment-related complications.

### **Primary versus Adjuvant SRS**

The use of SRS as either a primary or adjuvant treatment for meningiomas is context-dependent. Studies show standalone SRS achieves outcomes comparable to Simpson Grade I resection and better than Grades II–IV, with Kondziolka et al. reporting 97% 4-year tumor control for small tumors (<3.5 cm).<sup>2</sup> Prior surgery is associated with poor tumour control, especially in older patients and tumours in parasagittal or cavernous sinus locations. Ding et al. found 5-year progression-free survival (PFS) rates of 93% for primary SRS versus 70% for post-surgical cases.<sup>3</sup> At the same time, Park et al. highlighted better outcomes and improved cranial nerve function with primary SRS.<sup>4</sup> The ISRS Practice Guidelines attribute primary SRS advantages to planning challenges after surgery or tumor aggressiveness requiring subtotal resection. The decision remains institution- and patient-specific.<sup>5</sup>

### **Efficacy of SRS versus Surgery**

SRS is highly effective in achieving tumor control, with reported PFS rates exceeding 90% at 5 years for smaller meningiomas. In their study of 198 benign meningiomas, Pollock et al. compared the outcomes of surgical resection (n=136) with those of Gamma Knife radiosurgery (GKRS; n=62). Over a mean follow-up of 64 months, tumor recurrence or progression was higher in the surgical group (12%) compared to the GKRS group (2%, p=0.04). PFS rates for Simpson grade 1 resection (3- and 7-year: 100% and 96%) were similar to GKRS (100% and 95%, p=0.94), but GKRS outperformed Simpson grades 2 (91% and 82%) and grades 3–4 (68% and 34%, p<0.001). Subsequent treatments were required more frequently after surgery (15% vs. 3%, p=0.02), and complications were higher in the surgical group (22% vs. 10%, p=0.06). The authors noted that GKRS offers excellent tumour control and minimal morbidity, making it a preferred option for small-to-moderate meningiomas without significant mass effects.<sup>6</sup>

### **Long-Term Outcomes**

A key debate centres on the long-term outcomes of SRS. While surgery offers immediate and often permanent tumor removal, concerns persist regarding the potential recurrence of meningiomas following SRS, especially in higher-grade lesions. SRS achieves excellent long-term tumor control for convexity and parafalcine

meningiomas, with 5-year PFS rates exceeding 90% for benign (WHO grade I) lesions. However, for higher-grade meningiomas (WHO grades II and III), PFS rates are lower, reflecting an increased risk of recurrence. A study by Kondziolka et al. involving 115 patients with benign convexity meningiomas treated with a mean dose of 14.2 Gy reported 3- and 5-year tumor control rates of 95% and 86%, respectively. Morbidity was 10%, with 5% experiencing symptomatic edema or radiation-related effects.<sup>7</sup> Similarly, for parafalcine meningiomas, a study of 65 patients treated with a median dose of 15 Gy reported 3- and 5-year control rates of 85% and 70%, respectively, with lower rates linked to longer dural tails. Symptomatic peritumoral edema occurred in 8.2% of cases, with temporary symptoms in 6.1% and permanent effects in 2%.<sup>3</sup> GKRS is an effective option for long-term control of small to medium-sized tumors in non-surgical cases, with minimal toxicity risks.

## CURRENT PRACTICE

The use of SRS for convexity and parafalcine meningiomas has evolved significantly over the past two decades. Treatment approaches are tailored to individual patient factors, such as tumor size, location, growth rate, health status, and personal preferences.

### Patient Selection

SRS can serve as a definitive treatment option for patients with small meningiomas who are either unsuitable for safe surgical resection, unwilling to undergo surgery, or have asymptomatic tumors that do not require surgical resection. It is also a suitable option when curative resection is not feasible or when surgical risks outweigh potential benefits. SRS may additionally be employed as adjuvant therapy for high-grade meningiomas or residual tumors following surgery. Suitable candidates for SRS must have an adequate life expectancy, the ability to tolerate stereotactic frame placement, and the capacity to undergo the procedure.

### Technical Aspects

Patients are assessed using high-resolution MRI, with contrast-enhanced CT as an alternative for those unable to undergo MRI. CT is also valuable in specific cases to evaluate bone involvement. The procedure starts with the placement of an MRI-compatible stereotactic frame under local anaesthesia and mild sedation if required. High-resolution imaging is acquired using a fiducial system, including a 3D volume-acquisition MRI (T1-weighted with contrast, T2-weighted, and fat-saturation sequences) with thin axial slices (1 mm) to visualise the tumor and adjacent structures. A T2-weighted scan visualizes brain parenchyma, edema, and cranial nerves, with planning carried out using axial images and coronal or sagittal reconstructions.

### Dose Planning

Dose planning in GKRS focuses on complete tumor coverage while protecting brain and cranial nerve function. Key principles include dose conformity (matching

the dose to the tumor's 3D geometry) and selectivity (ensuring rapid dose fall-off beyond the tumor margin) to minimize exposure to critical structures. Techniques such as precise volume definition, multi-isocenter planning, beam weighting, and plug patterns enhance safety. Small collimators (4–8 mm) are used for precision, while larger collimators (14–18 mm) target larger tumors, with 4-mm isocenters safeguarding sensitive areas like the optic nerves and chiasm.

### ***Dose Selection***

After plan optimization, the target maximum dose and tumor margin dose are determined collaboratively. In Gamma Knife radiosurgery (GKRS), 11–16 Gy is commonly delivered to the 50% isodose line, with 12–13 Gy being common for grade I meningiomas, achieving over 90% long-term control. Higher doses (16–20 Gy) may benefit grade II or III tumors, though the optimal dose is unclear. Fractionated SRS typically involves administering 25 Gy over 5 fractions or 30 Gy over 3 fractions, adjusted based on tumor size and its proximity to vital structures.

### **Importance of Tumor Characteristics**

Meningiomas, often well-circumscribed and slow-growing (WHO grade I or benign), are ideal for SRS. Their gradual progression allows time for radiation-induced vascular occlusion to take effect.<sup>8</sup> Single-session SRS is preferred for tumors <3 cm in diameter, with careful dose adjustments near sensitive structures like the optic chiasm.

### ***Tumor Grade***

Kondziolka et al. reported a median 4-year tumor control rate of 93% for Grade I, 50% for Grade II, and 17% for Grade III meningiomas in 972 patients (mean SRS dose: 14 Gy), half of whom had prior surgery.<sup>2</sup> Pollock et al. reviewed 416 WHO Grade I cases treated with a median 16 Gy dose, showing 5- and 10-year local control (LC) rates of 96% and 89%. For Grade II and III tumors (median dose: 18 Gy), LC rates were significantly lower, at 65% and 45% after 1 and 5 years, respectively.<sup>9</sup>

### ***Tumor Size***

Some studies found no link between tumor size and LC or progression-free survival (PFS),<sup>3,10,11</sup> others reported that larger tumors were associated with poorer control and increased adverse effects.<sup>12</sup>

### ***Tumor Location***

Parasagittal, parafalcine, and convexity meningiomas exhibit lower tumor control rates compared to skull base lesions. Santacrose et al. and Pollock et al. identified these locations as negative predictors for LC rates.<sup>9,11</sup> Contributing factors include proximity to the superior sagittal sinus, risks of radiation-induced thrombosis, venous infarcts, and cerebral edema. Parafalcine lesions, with deeper draining veins, pose challenges for complete obliteration, while longer dural tails in parasagittal and parafalcine tumors often fall outside treatment areas, leading to higher recurrence rates.

## **Radiation-Induced Complications**

Radiation effects from SRS for meningiomas are similar to those in other intracranial treatments, influenced by dose, tumor location, prior therapy, and individual sensitivity. Parafalcine meningiomas pose higher risks due to their proximity to the sagittal sinus. Delayed effects, such as edema or radionecrosis, can cause headaches, seizures, or neurological deficits, while long-term complications may include cysts or vascular malformations. Rarely, severe or persistent issues require surgical intervention.

### ***Optic Neuropathy***

Damage to the optic apparatus from radiation may cause reduced visual acuity, visual field deficits, or loss of vision, usually appearing within first three years of treatment.

### ***Peritumoral Edema***

Peritumoral edema is common in parasagittal and parafalcine meningiomas and may be temporary or persistent.<sup>13</sup> Temporary edema often lasts several months and require corticosteroids for resolution. Persistent edema is often difficult to treat due to the risks of long-term steroid use, sometimes necessitating surgical tumor resection.

### ***Vascular Complications***

Vascular complications after radiosurgical treatment of meningiomas are very rare and include hemorrhage or vessel occlusion leading to ischemia. Vessel occlusion, occurring in 1–2% of cases, typically arises in a delayed timeframe, ranging from 14 to 60 months post-GKRS.<sup>14</sup>

## **Risk Mitigation Strategies**

Toxicities from SRS for meningiomas are generally mild and self-limiting. According to some authors, prophylactic corticosteroids can lower the risk of acute edema on treatment days, with additional steroid therapy managing delayed symptoms like radionecrosis. Tumor size and location, particularly in parasagittal regions, increase edema risk, and pre-treatment with corticosteroids may help mitigate this. Fractionated SRS offers a better toxicity profile for larger or critically located tumors but lacks the long-term data available for single-session SRS.

## **Management of Venous Sinus Invasion**

Surgical resection is the standard treatment for PSPF meningiomas, but the complex venous anatomy, especially near the posterior sagittal sinus, complicates safe gross-total resection and risks venous infarction. Tumor invasion into dural sinuses and bridging veins adds to the challenge. While sinus sacrifice or reconstruction may improve resection rates, complications remain common. For parafalcine meningiomas involving the superior sagittal sinus (SSS), SRS offers a non-invasive alternative for tumor control but is limited in addressing venous invasion, highlighting ongoing management challenges.

## Follow-Up and Monitoring

Monitoring involves gadolinium-enhanced T1- and T2-weighted MRI with fat suppression:

- Grade I Meningiomas: Imaging is recommended every six months for the first two years, then annually for 2–3 years, and subsequently biennially thereafter.
- Grade II and III Meningiomas: Imaging is recommended every three months for the initial 2–3 years, transitioning to intervals of 6–12 months thereafter.

## Future Directions

SRS, in both single session and fractionated formats (FSRT), is a practical and effective option for primary or adjuvant treatment of challenging cases. Studies also suggest the role of fractionated therapy in larger lesions and cavernous sinus meningiomas. Novel techniques like molecular and genetic profiling of meningiomas may allow for better risk stratification and tailored therapeutic strategies. Advances in meningioma biology, including next-generation sequencing and epigenetic research, are uncovering potential molecular targets for therapy, particularly for high-grade tumors.<sup>15</sup> Immunotherapy, such as targeting PD-L1, shows promise for aggressive meningiomas.<sup>16</sup> Ongoing clinical trials aim to integrate molecular therapies with traditional treatments, potentially transforming meningioma management in the future.

## LEARNING POINTS

- Patient-Centered Treatment Decisions
  - SRS is suitable for patients unfit for surgery or with small, asymptomatic tumors, while surgery is necessary for larger lesions or symptomatic cases requiring decompression.
- Efficacy of SRS
  - SRS provides high PFS rates, comparable to or better than surgery for certain tumor grades.
- Risks and Mitigation
  - Radiation-induced edema and toxicity, though generally mild, can occur. Pretreatment with corticosteroids or using fractionated SRS can mitigate risks for large or critically located tumors.
- Combination Therapy
  - SRS is often used as an adjuvant to surgery for residual or recurrent tumors, improving outcomes in challenging cases where complete resection is not feasible.
- Challenges with Venous Sinus Invasion
  - Tumors invading venous sinuses pose challenges for safe gross-total resection. SRS offers a non-invasive alternative.
- Future Directions in Meningioma Management
  - Advances in molecular and genetic profiling are uncovering therapeutic targets, especially for high-grade meningiomas.

- Integration of SRS with molecular therapies and immunotherapy (e.g., targeting PD-L1) holds potential to transform meningioma treatment.
- Newer Techniques
  - Fractionated SRS and newer imaging technologies are improving treatment precision and reducing toxicity, offering hope for better outcomes in complex cases.

## CONCLUSION

SRS offers a non-invasive alternative or adjunct for managing convexity and parafalcine meningiomas. Treatment decisions should consider age, tumor location, comorbidities, and patient preferences. Surgery is preferred for large tumors causing mass effect, while SRS is ideal for challenging locations or patients unfit for surgery. SRS aims to control tumor growth, preserve neurological function, and minimize surgical risks and is particularly beneficial for older patients. Long-term studies are required to confirm SRS durability, especially for higher-grade tumors, and to compare its efficacy and quality of life with surgical approaches.

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SECTION VI

**Gliomas**

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# Gamma Knife Radiosurgery in Gliomas and Glioblastomas

Chirag Bansal ■ Rakshay Kaul ■ Deepak Agrawal

## INTRODUCTION

Gliomas are the most common primary brain tumours in adults. They range from slow-growing low-grade lesions to aggressive glioblastomas. While surgery and chemoradiation are the standard treatments, these approaches have limits, especially for tumours located deep in the brain or near critical areas. Gamma Knife Radiosurgery (GKRS) offers a non-invasive alternative with high precision. It targets tumors effectively while minimizing damage to healthy brain tissue, leading to improved functional outcomes and quality of life.<sup>1</sup>

High grade gliomas incorporate grade III, grade IV Astrocytomas and Glioblastomas which have now been designated as the most common primary brain tumour in adults. Primary CNS malignant tumours account for 2% of all cancers but cause a disproportionate amount of cancer related morbidity and mortality. Despite the medical advances in today's time, the outcome of high-grade glioma is abysmal. The median length of survival is less than 2 years for patients with glioblastoma and 2 to 5 years for patients with anaplastic glioma.<sup>2-5</sup>

While traditionally used as a complementary or alternative option for malignant or managing high-grade gliomas (HGGs) such as glioblastoma multiforme (GBM) and anaplastic astrocytoma, high-grade gliomas, especially inoperable tumours, eloquent brain regions, recent evidence suggests its efficacy in managing specific cases of LGGs, after conventional treatments like surgery and chemotherapy.<sup>1</sup>

This chapter presents three patient cases and explains how timing, patient health, and tumour features shape outcomes.

## REPRESENTATIVE CASE

### History & Examination

A 21-year-old Female patient presented with h/o Headache and seizures (GTCS) for 6 months (Frequency: 1-2 per month). Imaging findings were suggestive of right medial temporal glioma. The patient underwent surgery for the same and the Biopsy report was suggestive of Pilocytic astrocytoma, WHO grade 1. Postoperative

imaging was suggestive of some residual for which the patient underwent secondary Gamma Knife therapy 4 months after surgery. The examination showed no motor, sensory or cranial nerve deficits in the patient. Cerebellar signs are absent and higher mental functions are within normal limits. MMSE- 30/30. The patient is followed up over 4 years.

## Imaging

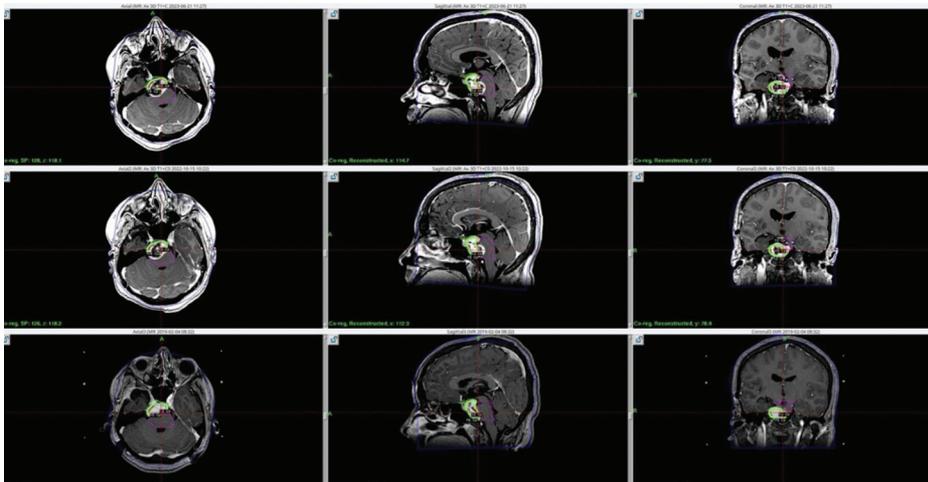
CEMRI brain was suggestive of T1 isointense, T2 hyperintense rounded mass in the region of hypothalamus, projecting inferiorly behind the infundibulum of pituitary gland mildly enhancing on post-contrast images.

## GK Protocol

Primary GKRS therapy was performed for the right medial temporal glioma in the year 2019 using the Gamma Knife model B machine. Leksell Coordinate Frame G was used for fixation Configuration and planning was done on Gamma plan version 11.3.2. 15 Gy at 50% isodose line was planned with a coverage of 0.9, selectivity of 0.83, Gradient Index of 2.96 and beam on time of 129.9 minutes. The tumour volume was 5.215 cc and shielding of the optic chiasm and brainstem was done.

## Follow Up

Repeated CMRI brain scans were done in 2019, 2022 and 2023 to assess the volume of lesions. Follow-up imaging showed approx. 20% and 30% reduction in volume at 3 and 4 years of follow-up. Clinically also, a reduction in Headache and



**Figure 19.1** Contrast MRI axial, sagittal and coronal sections of a patient with Right Medial Temporal Glioma at baseline (2019) (bottom row), at 3 years (2022) (2<sup>nd</sup> row), at 4 years (2023) (top row) follow up.

seizure frequency was noticed within 6 months of GKRS, with an Engel score of 1 (seizure-free). Anti-seizure medication could be stopped 2 years after GKRS and the patient remains off medication till date.

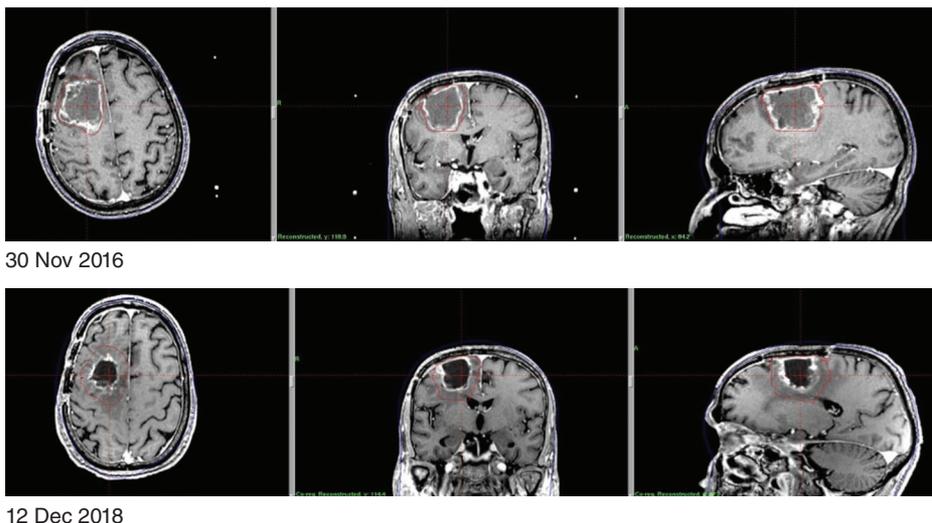
## CASE II

### History & Examination

A 56-year-old Male patient presented with h/o Left side spastic hemiparesis for 2 years with Kernofsky's performance score of 90. Imaging findings were suggestive of Right frontal high grade glioma. The patient underwent surgery for the same with biopsy suggestive of Glioblastoma, WHO grade 4. Postoperative imaging was suggestive of some residual for which the patient was started on Temozolomide and the patient underwent secondary Gamma knife therapy after 2 months of surgery. On examination, the patient had left sided hemiparesis with power 3/5 at most joints. Left side Ashforth grade 3 Hypertonia / Spasticity present. Cerebellar signs are absent and higher mental functions within normal limits. Post operatively, Kernofsky's Performance score of patient was 50, Requires considerable assistance and frequent medical care. Neurologically similar to preop.

### Imaging (Figure 19.2)

CEMRI brain suggestive of T1 isointense, T2 hyperintense rounded mass in region of Right frontal region enhancing on post contrast images.



**Figure 19.2** Contrast MRI axial, sagittal and coronal sections of a patient with Right Frontal High Grade Glioma at baseline (2016) (top row), at 2 years follow up (2018) (bottom row) showing progressive reduction in size of tumour size.

## GK Protocol

Primary GKRS therapy was given for Right Frontal High grade glioma in the year 2016 on gamma knife model B machine. Leksell Coordinate Frame G was used for fixation Configuration and planning was done on Gamma plan version 11.3.2. 20 Gy at 50% isodose line was planned with a coverage of 0.88, selectivity of 0.95, Gradient Index of 2.82 and beam on time of 116.1 minutes. The tumour volume was 47.246 cm<sup>3</sup> and optic chiasm and brainstem shielding was done.

## Follow Up

Follow up MRI was done in 2018 and volume of lesion was assessed. On follow-up over 2 years, progressive decrease in volume (approximately 20%) was noticed as shown in imaging above. Clinically also, reduction in headache and spasticity was noticed within 6 months of GKRS. Power on the left side also improved to 4/5 at many joints within 2 years of GKRS. The patient was lost to follow up later on and further imaging studies couldn't be done, However, on telephonic follow up In Jan 2025, the patient was alive though bedridden, even 9 years after surgery and GKRS.

## CASE III

### History & Examination

A 60-year-old male presented with a generalised tonic clonic seizure on 25<sup>th</sup> December 2022. The seizures were associated with loss of consciousness. He had undergone left Fronto Temporal craniotomy and gross total excision of tumour on 21<sup>st</sup> March 2023. Histopathology was Glioblastoma, IDH wild type.

On examination, the patient was alert with a Karnofsky score of 100. There were no cranial nerve/ motor/ sensory deficits.

### Imaging

#### *CEMRI Brain (2016)*

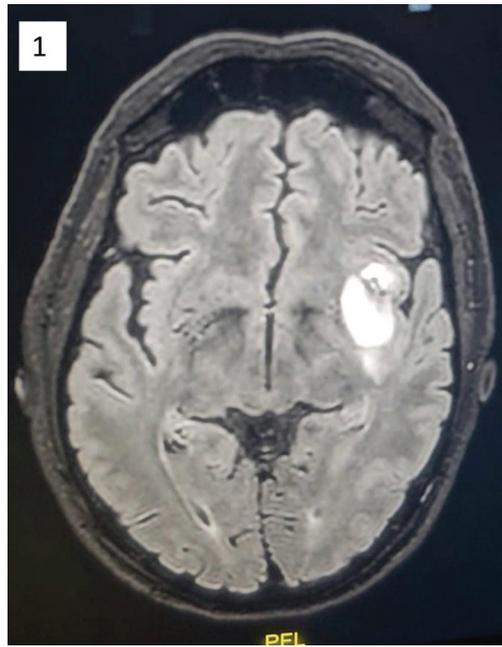
Well-defined solid cystic T2/Flair hyperintense, T1 hypointense subcortical lesion with peripheral nodularity (along antero-superior aspect) measuring 2.8 × 1.9 × 2.8 cm left insula, extending up to external capsule medially. Raised perfusion on T2\* perfusion and ASL map. Minimal perilesional oedema extending into the left parieto-temporal lobe(Figure 19.3).

#### *NCCT Head (Post op)*

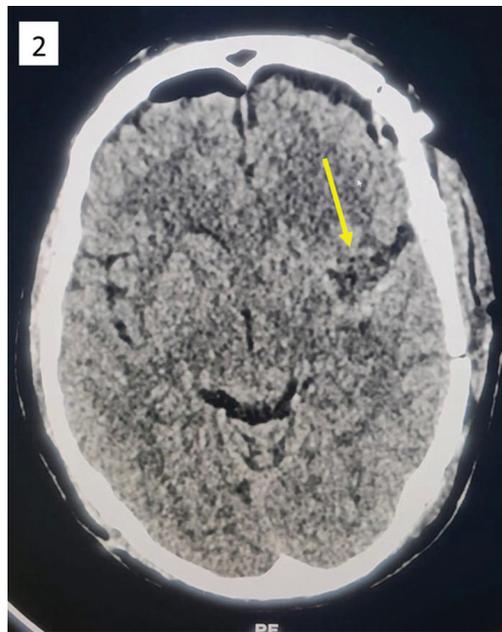
Post operative cavity can be seen with gross tumour free cavity with minimal hyper-density suggestive of postoperative blood collection (Figure 19.4).

#### *MRI Brain (During GKRS)*

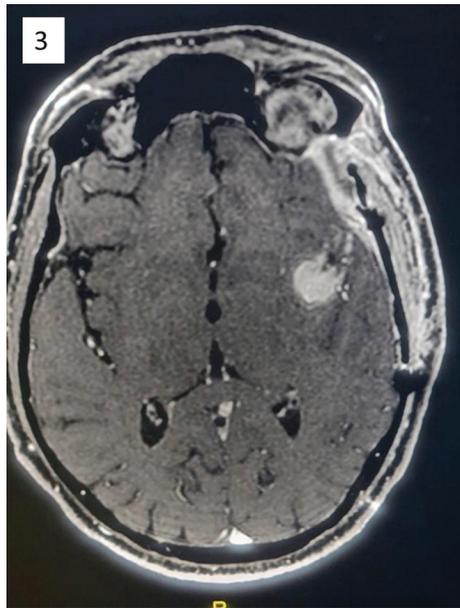
Post operative resection cavity is seen in the left insula showing T1 hyperintensity. Ill defined Flair hyperintensity seen medial and anterior left temporal lobe suggestive of residual tumour (Figure 19.5).



**Figure 19.3** Showing preoperative MRI scan of the left insular high-grade tumour with almost homogeneous contrast enhancement on T1 weighted imaging with contrast.



**Figure 19.4** Shows a postoperative non-contrast CT scan of the head with the tumour cavity appearing hypodense (yellow arrow) with mild peripheral hyperdensity suggestive of collected blood or residual tumour tissue. Anteriorly pneumocephalus is present.



**Figure 19.5** Shows an MRI scan after 1 month of surgery at the time just prior to GKRS. We can see a contrast enhancing lesion along the distal end of post-operative cavity.

### **MRI Brain (Post GKRS)**

A relative reduction in tumour size can be seen with non-homogeneous contrast enhancement of residual tumour lesion (Figure 19.6).

## **GK PROTOCOL COURSE**

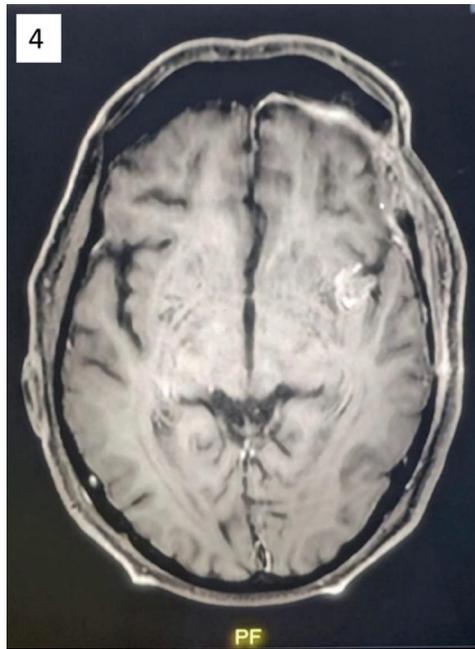
Secondary GKT was given to the tumour cavity. 3.99 cc of the tumour received 18 Gy at 50% isodose line (Figure 19.7)

## **FOLLOW UP**

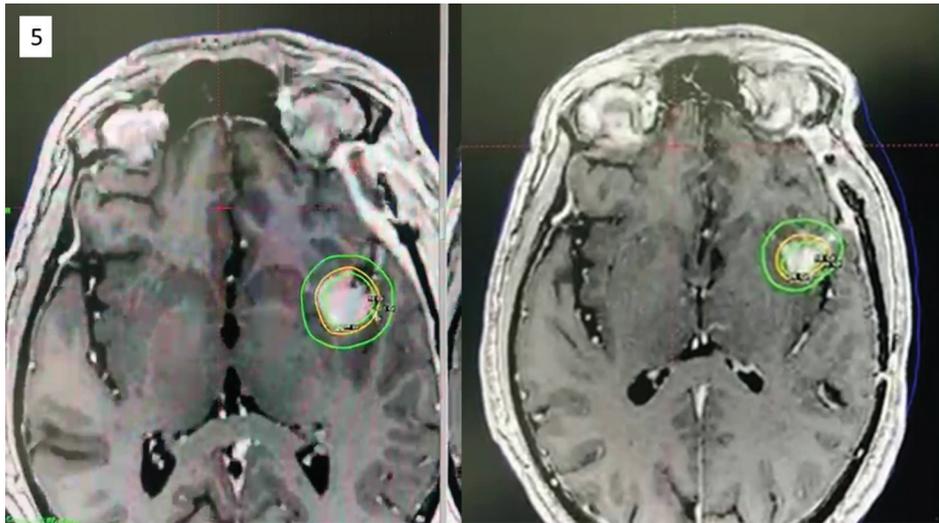
The patient has been doing well post GKRS. At 25 months follow up, the patient was reviewed and has been advised for re-surgery in view of recent increase in size of the tumour.

## **DISCUSSION**

GKRS is typically used as an adjunct to the standard treatment regimen for HGGs, which includes surgical resection, radiation therapy, and chemotherapy (e.g., temozolomide).<sup>10</sup> It may be used in specific clinical scenarios where conventional radiation therapy and systemic treatments are insufficient or impractical. GKRS is particularly valuable for targeting small, localized residual tumour tissue or recurrent tumour nodules after initial treatment.<sup>11</sup>



**Figure 19.6** A T1 weighted axial scan of Brain done few months after GKRS revealing a small heterogeneously hyperintense residual tumour with a reduction in the size as compared to the previous MRI.



**Figure 19.7** Shows the Gamma Knife dose protocol with focus on the target lesion.

GKRS is a very effective treatment option for Residual Low-grade gliomas post-surgery.<sup>12</sup> With its excellent GKRS precision, it aids in controlling tumour growth while preserving surrounding eloquent tissues. Clinical guidelines also emphasize its use as *primary therapy* in cases which are unfit for conventional surgeries due to their proximity to eloquent areas.<sup>12</sup>

In a study conducted by Filippo Gigliardo et al.,<sup>13</sup> LGGs near eloquent brain regions demonstrated lower symptomatic control with GKRS compared to conventional radiosurgery. It has also been observed to improve cognitive and neurological outcomes post-gamma knife radiosurgery.<sup>7</sup>

#### Comparative Protocols for Managing Low-Grade Gliomas<sup>13</sup>:

Here is a detailed comparison of Gamma Knife Radiosurgery (GKRS) with surgical resection and conventional radiotherapy:

Treatment Modalities	Indications	Advantages	Limitations	Survival Outcomes (PFS)
Gamma Knife Radiosurgery (GKRS)	Residual or recurrent low-grade gliomas, tumours in eloquent brain regions, small tumour volumes ( $\leq 3 \text{ cm}^3$ )	Minimally invasive, precise tumour targeting, preservation of surrounding healthy tissue	Not suitable for larger tumours ( $>3 \text{ cm}^3$ ), potential risk of radiation necrosis and edema	5–10 years (depends on size, location, and subtype)
Surgical Resection	Primary approach for accessible gliomas, especially in non-eloquent areas or larger tumours ( $>3 \text{ cm}^3$ )	Complete tumour debulking, immediate pathological confirmation.	Involves surgical risks, may not be viable for tumours in critical areas	Varies based on resection extent; gross total resections achieve $>10$ years for pilocytic astrocytomas
Conventional Radiotherapy	Adjuvant treatment post-surgery or for larger lesions not amenable to GKRS	Coverage of larger areas, systemic treatment for infiltrative growth.	Increased risk of long-term neurocognitive side effects and radiation-induced damage.	3–5 years as stand-alone, improved when combined with other modalities

Using GKRS in conjunction with other modalities like chemotherapy and fractionated radiation can improve progression-free survival.<sup>12</sup>

Similar studies in the literature have shown that tumor progression-free survival (PFS) after GKRS in low-grade gliomas (LGGs) ranges between 5 to 10 years, with patients having low-risk pilocytic astrocytomas showing longer survival intervals. GKRS also reduces side effects such as neurotoxicity and white matter changes compared to traditional radiotherapy. Moreover, long-term assessments indicate that patients treated with GKRS maintain better cognitive and emotional quality of life over time.<sup>14</sup>

### Progression-free Survival (PFS) following GKRS by Subtype<sup>15</sup>:

Histological Subtype	5-Year PFS	10-Year PFS	Recurrence Risks
Pilocytic Astrocytomas	85–90%	75–80%	Low (<10%)
Oligodendrogliomas	70–80%	60–70%	Moderate (~15%)
Gangliogliomas	90–95%	85–90%	Low (~5%)
Optic Pathway Gliomas	60–70%	50–60%	High (>20%)

### Summary of Molecular marker-based Management as per literature<sup>16-17</sup>:

Marker	Implication	Recommended Strategy
IDH Mutation	Low recurrence, better radiosensitivity	GKRS as monotherapy in IDH-mutant gliomas
1p/19q Co-deletion	High radiosensitivity, low aggressiveness	Lower radiation dose protocols
MGMT Methylation	Reduced radio-resistance	Combine GKRS with adjuvant chemotherapy
High Ki-67	Faster tumor progression	Intensify treatment with adjuvant therapies

Considering that High Grade gliomas are incurable due to their malignant nature, a treatment strategy must be formulated to at least manage this disease and its progression with the hopes of increasing the survival time while maintaining a good quality of life. Although the standard of treatment in these remains cytoreductive surgeries followed by a regimen of concomitant chemoradiotherapy yet despite the aggressive measures taken the yield of the treatment is far from satisfactory most of the time. Gamma knife Radiosurgery has been debated as one of the treatment measures but mostly as an adjunct to the main treatment protocol as its efficacy in improving the outcome has yet not been proven substantially.<sup>11</sup>

High-grade gliomas often have infiltrative growth patterns, making them less ideal for GKRS as it is best suited for discrete, well-defined lesions.<sup>18</sup> There is also a small risk of Radiation Necrosis, particularly with high cumulative doses or in previously irradiated brain tissue. Although some studies suggest benefits, the role of GKRS for high-grade gliomas is less well-established compared to its use for benign tumours and brain metastases and close follow-up with MRI is necessary to monitor for tumour progression, treatment response, and potential complications. Using GKRS in conjunction with other modalities like chemotherapy and fractionated radiation can improve progression-free survival.<sup>19-21</sup> As per study conducted by Zjiwar H A Sadik et al<sup>9</sup> 92 patients (52 males and 40 females) underwent GKRS for recurrent glioma. The median age at time of GKRS was 50 years (range 7–76). Eighty-five patients had undergone at least one operation before GKRS. Seven patients underwent biopsy followed by adjuvant treatment in the form of chemotherapy, EBRT or a combination of both, before GKRS.

The Radiation Therapy Oncology Group (RTOG) published a trial conducted by Souhami and colleagues which was the first of its kind on the evaluation of adding stereotactic radiosurgery (SRS) to the treatment of high-grade gliomas. It was a multicentre randomized controlled trial to analyse the inclusion of SRS (both Gamma Knife Radiosurgery and LINAC (linear accelerator)-based radio surgical techniques) in comparison to the standard external beam radiation therapy (EBRT) for the treatment of GBM.<sup>4</sup> As a part of the primary treatment, SRS was used for the management of GBM rather than considering it later as a means of palliative therapy. Around 203 patients were assigned randomly in such a way that supratentorial GBM would receive either adjuvant SRS (prescription dose 15–24 Gy) followed by EBRT and carmustine, or EBRT and carmustine without giving SRS beforehand. It was observed that there was no difference between the two groups of patients as far as the primary endpoint of survival was concerned: the SRS group had a mean survival time of 13.5 months, whereas the control group had a mean survival time of 13.6 months. The lack of a definitive comparative result propelled further investigative efforts by different researchers around the globe to validate these results separately.

It was Emmanuel C. Nwokedi<sup>22</sup> and his team who evaluated 64 follow ups among the 82 patients with confirmed pathological GBM having received EBRT between August 1993 and December 1998. These patients were divided into those who were treated with EBRT alone vs those who received GKRS within 6 weeks of completion of EBRT. The median EBRT dose was 59.7 Gy (range, 28–070.2 Gy), and the median GK-SRS dose to the prescription volume was 17.1 Gy (range, 10–28 Gy). The median age of the cohort was 50.4 years, and the median pre-GKRS Karnofsky performance status was 80. The median overall survival for the entire cohort was 16 months. It was interestingly observed that with regards to the overall survival of the group which received GKRS, there was an increase in the median survival up to 25 months in contrast to 13 months in the group receiving only EBRT ( $P = 0.034$ ). This result was in contrast to the previous study and laid an important basis for conducting GKRS as a valuable asset to be used for high grade glioma management.

The two studies discussed above have both considered the utility of GKRS however the timing of applying GKRS in the treatment protocol seems to have resulted in contradictory results. The study by Souhami et al<sup>4</sup> used GKRS followed by EBRT whereas the later study used GKRS after the EBRT was given hence giving a clue into figuring out the optimal timing of using GKRS in these patients.

Realising the potential of giving GKRS in a timed manner for optimal yield led many other studies to follow a pattern of treatment similar to Nwokidi et al., to evaluate the consistency of those results. Loeffler *et al*<sup>23</sup> conducted a prospective study before Nwokidi in 1992 and evaluated 37 patients between 1991 and 1998 to evaluate the role of radiosurgery as a part of the initial management. Patients in one study group received only EBRT while the other group received radiosurgery (dose of 10 - 20 Gy) about 2 to 4 weeks after completion

of conventional radiotherapy with a median tumour volume of 4.3cm<sup>3</sup> at the time of radiosurgery. The study showed an appreciable increase in median time of survival and led to the conclusion that radiosurgery is beneficial as part of initial treatment protocol for small, radiographically well-defined high-grade gliomas.

Kondziolka<sup>24</sup> *et al.*, evaluated the survival benefit of SRS in 107 patients with high grade glioma during an 8-year interval at the University of Pittsburgh. They compared their series of patients with GBM, who were treated by GKRS with historical control groups. They also concluded that an improved survival benefit after radiosurgery was identified for patients with glioblastoma and anaplastic astrocytoma although the selection of patients who underwent SRS had smaller tumour volumes irrespective of the tumour location.

A study by Nagai *et al.*<sup>25</sup> also had a similar conclusion stating that radiosurgery could provide a survival benefit when included as a part of multimodality treatment, however, the study also highlighted the possibility of selection bias as most of the patients responding in a positive manner were those with lower tumour volumes (<3.5cm in average diameter) and a good Karnofsky score. A similar conclusion was derived from the study of Kondziolka<sup>24</sup> as well showing that GKRS particularly benefited patients with a Karnofsky performance scale Score ranking of at least 90 and those patients who have received adjuvant chemotherapy.

An analysis done by us<sup>32</sup> on histologically proven Glioblastomas operated at AIIMS, New Delhi between January 2016 and November 2018 compared the efficacy between two groups: one group who received EBRT plus Temozolomide (6 cycles) postoperatively and another group who received GKRS within 4 weeks of surgery (without EBRT) along with continued Temozolomide. This study evaluated the efficacy of GKRS without conventional EBRT. This study concluded that even without the use of EBRT, GKRS to tumour bed/residual tumour after primary surgery with concurrent chemotherapy yielded a result of overall survival and progression free life similar to the conventional EBRT group.

Despite multiple studies under evaluation the subject of using GKRS in the treatment algorithm remains inconclusive and warrants a larger randomised study (Table 19.1)

## TAKE HOME MESSAGE

Gamma Knife Radiosurgery (GKRS) is a precise, non-invasive option for managing both low- and high-grade gliomas, including glioblastomas. It effectively targets residual or recurrent lesions after surgery, helping reduce tumour size and symptoms with minimal radiation exposure. While well-established in low-grade tumours, its role in high-grade gliomas is supportive, offering focused control when combined with surgery, chemotherapy, or radiotherapy.

**TABLE 19.1 ■ Shows a Comparative of Different Studies Done by Various Authors to Evaluate the Effects of GKRS in Patients with High Grade Glioma**

<b>Authors</b>	Selch et al <sup>1993</sup>	Masciopinto <sup>27</sup> et al 1995	Gannett <sup>28</sup> et al	Buatti <sup>29</sup> et al 1995	Kondziolka <sup>24</sup> et al 1997	Shenouda <sup>30</sup> et al 1997	Shrive <sup>31</sup> et al 1999	Nwokedi <sup>22</sup> et al 2002
<b>Number of Patients</b>	35(18 primary lesions)	31	30	11	107(65 primary lesions)	14	78	31
<b>KPS</b>	100% >70	57% >70	97% >70	all >90%	mean KPS 90	79% >70	median 90	61% >70
<b>Median Tumor Volume (CC)</b>	20	16	24	14	6.5	<34	10	25
<b>Median survival (months)</b>	9	9.5	GBM 13 AA 28	17	GBM 20 AA 56	10	19.9	25
<b>1-Year Survival (%)</b>	GBM 33 AA 100	37	GBM 43 AA 64.5	-	-	43	88.5	-
<b>2-Year Survival (%)</b>	GBM 33 AA 100	-	GBM 8 AA 53	-	GBM 41 AA 88	-	-	-
<b>EBRT</b>	45-60Gy	0-66	median 59.4	mean 60	60	60	73-78	>59
<b>Median Follow Up (Months)</b>	10	9.5	30	6	-	8.8	25	-
<b>Number of Reoperations</b>	0/2	-	0/10	0/4	3//22	1//14	20/39	-
<b>Prognostic Factors on Multivariate Analysis</b>	-	Age, KPS, extent of surgery	KPS	Re operation	Age, KPS	None	Age	SRS

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SECTION VII

**Metastasis**

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# Gamma Knife in Multiple Metastasis

Rakshay Kaul ■ Deepak Agrawal

## INTRODUCTION

Multiple metastasis to the brain is known to be most common malignant neoplasms of the brain and most common brain tumours overall.<sup>1</sup> The proportion of metastasis to brain in comparison to primary intracranial neoplasm is as close to 10:1 and is only progressing with the recent advances in imaging techniques as well as prolonged survival benefits that are a result of better control of disease progression due to anti-cancer medications. In adults, lung cancer is the most common cause (50%–60%), followed by breast cancer (15%–20%) and melanoma (5%–10%).<sup>2,3</sup> Traditionally the treatment of choice for multiple cerebral metastasis has been whole brain radiotherapy (WBRT) and it continues to be used universally still despite the adverse effects that have been associated with it. No randomized trials have yet determined a beneficial effect of WBRT as a primary treatment modality with respect to the best possible palliative care.<sup>4</sup> In terms of a good long-term local control, WBRT is not proving to be worthy enough and with its detrimental effects on the cognitive status of patients. It is not being preferred as an option for patients with good clinical performance status over a longer survival period.<sup>5,6</sup> Considering the beneficial efficacy of GKRS in single metastasis to brain has become valuable enough to make it a part of mainstream tumour management, the evaluation to assess its efficacy in multiple metastasis to brain has become an imperative task at hand.

## CASE REPRESENTATION

### History & Examination

A 63-year-old male patient, with adenocarcinoma of lung controlled on novel anti-chemotherapeutic agent Loratinib 50mg presented with multiple cerebral metastasis who had previously received GKRS in 2020. He was doing well for 1.5 years when he had 2 episodes of focal seizures (in Feb 2023) involving the right upper limb lasting 15 seconds and not associated with any loss of consciousness. Patient was alert with a Karnofsky score of 100. Cerebellar signs were *impaired* Dysdiadochokinesia/Finger nose test/Tandem walking towards the left side.

## Imaging

*MRI Brain* (31-01-2023)- Reduction in previous lesions along with appearance of new lesions in left paracentral, superior frontal and left superior parietal gyrus (Fig. 20.1).

## GK Protocol

Primary GKRS was given for multiple metastasis in August 2020 following which there was reduction in those target lesions. New Lesions were noticed in Repeat MRI in January 2023 for which primary GKRS was given on 21<sup>st</sup> March 2023. All lesions were given an 18Gy prescription dose and planning was done using the 'Lightning plan'.

## Follow Up

The patient was admitted in view of Hemoptysis in July 2023 and was managed conservatively. The patient gradually improved and was discharged with a GCS of E4V5M6 and stable vitals in August 2023. At 5 year follow up (from first GKRS) the patient is symptomatically well with mild deficit in form of needing support while walking.

## DISCUSSION

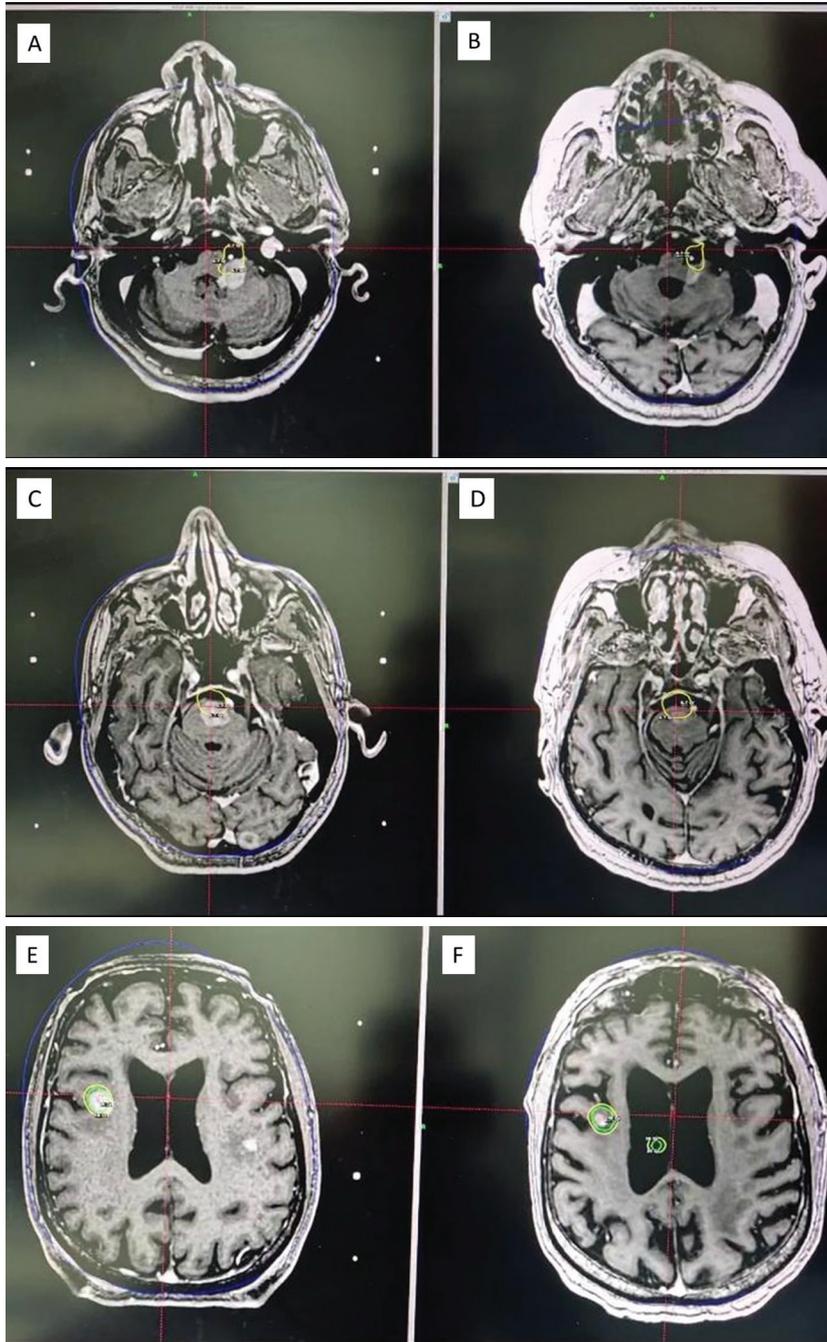
### Evolution of Management Strategies

The management of brain metastases has undergone significant transformation over the past three decades. While WBRT provided global intracranial coverage, its neurocognitive toxicity and limited survival benefit prompted exploration of more targeted modalities. The advent of SRS, particularly GKRS, revolutionized local control by enabling precise high-dose delivery with sharp dose fall-off. The early work of Leksell and Lindquist (1989) established the feasibility of GKRS for solitary metastases.<sup>7</sup> the landmark JLGK0901 trial (Yamamoto et al., 2014)<sup>11</sup> prospectively evaluated 1194 patients treated with SRS alone and demonstrated no significant survival difference between those with 2–4 and 5–10 lesions. This study, along with follow-up analyses, formed the basis for expanding the indication of GKRS beyond limited metastases.

Subsequent reviews and meta-analyses reaffirmed these findings. Tsao et al.<sup>15</sup> and Sahgal et al.<sup>21</sup> demonstrated that SRS offers equivalent survival outcomes compared to WBRT while preserving cognitive function and quality of life. Recent evidence suggests that total tumour volume, rather than the number of lesions, is the dominant prognostic factor influencing outcomes.<sup>17,23</sup>

### Current Evidence and Outcomes

Modern series report 1-year local control rates exceeding 85% and median overall survival of 10–18 months depending on tumor histology and systemic disease



**Figure 20.1** Showing evident reduction in sizes of metastatic lesions as seen in pre-GKRS and post-GKRS MRI scans. Legends (A, C, E, G) show (pre GKRS) metastatic lesions in the brain in the left Middle cerebellar peduncle, left pontine, Right frontoParietal and left insular regions respectively. Corresponding to these are the post GKRS MRI scans of follow up (B, D, F, H) showing the relative reduction of lesions in size over time.

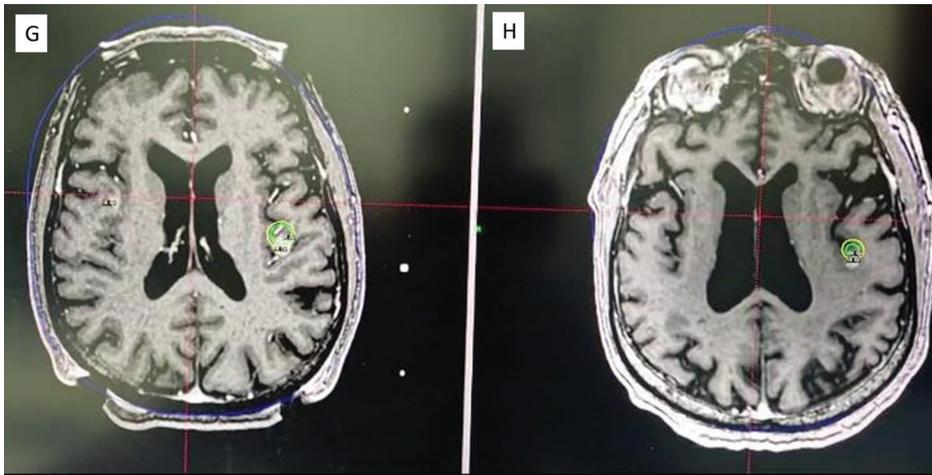


Figure 20.1 Continued

control.<sup>17,23</sup> In a 2024 Korean cohort, patients who underwent multiple ( $\geq 5$ ) GKRS sessions for non-small cell lung carcinoma metastases achieved 5-year survival of approximately 37%, with significantly lower rates of radiation-induced leukoencephalopathy in those without prior WBRT.<sup>23</sup> Similarly, Upadhyay et al.<sup>22</sup> demonstrated that SRS for  $\geq 15$  brain metastases is feasible, safe, and yields cognitive outcomes comparable to those observed in limited-lesion SRS.

### Neurocognitive Preservation and Toxicity

The NCCTG N107C trial (Brown et al., 2016)<sup>8</sup> provided robust evidence that cognitive decline occurs in 52% of SRS patients versus 85% of those treated with WBRT at 3 months, emphasizing GKRS as the preferred option for neurocognitive preservation. The ongoing CAR Study B29 continues to evaluate long-term cognitive outcomes. Recent NTCP modelling by Hsu et al.<sup>24</sup> has shown that tolerance to retreatment diminishes with cumulative dose, reinforcing the importance of individualized adaptive planning to mitigate radio necrosis risk.

### Technological Advances

Innovations in dose planning have substantially improved the efficiency and safety of GKRS for multiple metastases. The *Lightning Plan* algorithm allows automatic optimization across targets, reducing planning time while maintaining conformity. Deep-learning models such as GAN-GK and U-Net-GK have demonstrated  $>84\%$  accuracy compared with clinical dose distributions, streamlining multi-target planning.<sup>25</sup> The introduction of isocentre partitioning algorithms for VMAT-based SRS systems further refines dose conformity for complex multi-lesion scenarios.<sup>26</sup> Radiomic-based approaches are now being explored to identify high-risk lesions based on peritumoral texture, allowing personalized adaptive dose escalation.<sup>27</sup>

## Prognostic Factors and Patient Selection

Prognostic indices such as the Recursive Partitioning Analysis (RPA)<sup>13</sup> and Graded Prognostic Assessment (GPA) have been validated as key determinants of survival. Younger age, KPS  $\geq 70$ , controlled primary disease, and absence of extracranial metastases predict better outcomes.<sup>13,23</sup> Recent literature emphasizes cumulative tumour volume ( $< 15$  cc) over lesion count as the more relevant criterion for GKRS suitability.<sup>11,23</sup> Patients with limited total volume and good systemic control benefit most from repeated radiosurgery while avoiding the neurocognitive drawbacks of WBRT.<sup>5-6,21</sup>

## CONTROVERSIES AND LIMITATIONS

While the role of GKRS in multiple metastases continues to expand, several questions persist. There are no randomized controlled trials comparing GKRS and WBRT in patients with  $> 10$  metastases. Additionally, meta-analytic data indicate a slightly increased risk of leptomeningeal disease following SRS alone (HR  $\approx 3.0$ ),<sup>2</sup> suggesting vigilance in follow-up imaging. Cost-effectiveness analyses generally favor GKRS in high-resource settings but remain under evaluation in lower-income regions.<sup>21,22</sup> Long-term monitoring is essential to detect new lesions early, allowing for salvage GKRS while deferring WBRT.<sup>23,28</sup> This adaptive management strategy aligns with contemporary oncologic principles of balancing disease control and neurocognitive preservation.

## CONCLUSION

Gamma Knife radiosurgery provides an effective, minimally invasive, and durable treatment for patients with multiple brain metastases.<sup>11,21</sup> It achieves high local control rates and preserves neurocognitive function better than WBRT, especially in patients with good performance status and controlled systemic disease. Repeated GKRS is both feasible and safe, delaying or eliminating the need for WBRT. Continuous technological evolution and refined prognostic modeling are expected to further optimize outcomes. GKRS now stands as a standard of care for carefully selected patients with multiple intracranial metastases.

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# SRS vs WBRT in Multiple Metastasis

Debnarayan Dutta

## INTRODUCTION

Brain metastases have become increasingly relevant to oncologic management as advances in systemic therapy promote extracranial disease control. Lung, breast, kidney, colorectal cancers, melanoma are the most common primary tumours which metastasize to the brain in adults while in children it is the sarcomas, neuroblastoma and germ cell tumours. In India, lung and breast cancers were the most common primaries in men and women. MRI scan brain with contrast is the gold standard imaging modality for brain metastases. Number of lesions, size, site of lesions, mass effect, leptomeningeal involvement and tumoral bleed are the most important radiological features devalued with imaging. Brain metastases management poses unique challenges because of the blood brain barrier thus limiting the effect of chemotherapeutic medications. Radiation therapy plays an important role in the treatment of brain metastases. Management of brain metastases depends on various factors like performance status of the patient, pathology of the primary tumour, status of systemic disease, number of brain metastases, site of disease and intracranial pressure status (mass effect). Advancements in pathology, immunohistochemistry and molecular biology have significant implications in the management and prognosis of brain metastases patients. Prognosis in brain metastases patients has been given by various scores like Recursive partitioning analysis (RPA) classification, Rotterdam Score, Scoring index for radiosurgery (SIR), Graded prognostic assessment (GPA) and several nomograms which help us take a treatment decision. The most commonly used is the RPA classification.

## RPA CLASSIFICATION

RPA classification is based on performance status, age and primary disease control status (Gaspar L et al 1997)<sup>1</sup>. This simple and effective classification in brain metastasis helps in treatment decisions and evaluating expected outcome (Table 21.1).

Patients with RPA class I and II need to be considered for brain metastases directed treatment while RPA class III may be given best supportive care. However, the volume of disease, number of metastasis and molecular markers are not included in the RPA classification.

TABLE 21.1 ■ RPA classification (Gasper et al)<sup>1</sup>

RPA Class	Criteria	Median Survival Time (Months)
I	KPS > 70 < 65 years age Controlled primary tumour No systemic metastases	7.1
	Single metastasis	13.5
	Multiple metastases	6.0
II	KPS ≥ 70 and at least one of the following: ≥ 65 years of age Uncontrolled primary tumor Presence of systemic metastases	4.2
	Single metastases	8.1
	Multiple metastases	4.1
III	KPS < 70	2.3

## RADIATION THERAPY IN BRAIN METASTASIS

The common treatment modalities in brain metastasis are whole brain radiation therapy (WBRT), surgery and radiosurgery (SRS) (Figure 21.1 & 21.2) (Table 21.2).

*Standard treatment options for brain metastasis are given in Table 21.2.*

## RADIATION THERAPY MODALITY-EVIDENCES

There are multi-centric randomized studies with different radiation schedules in brain metastasis.

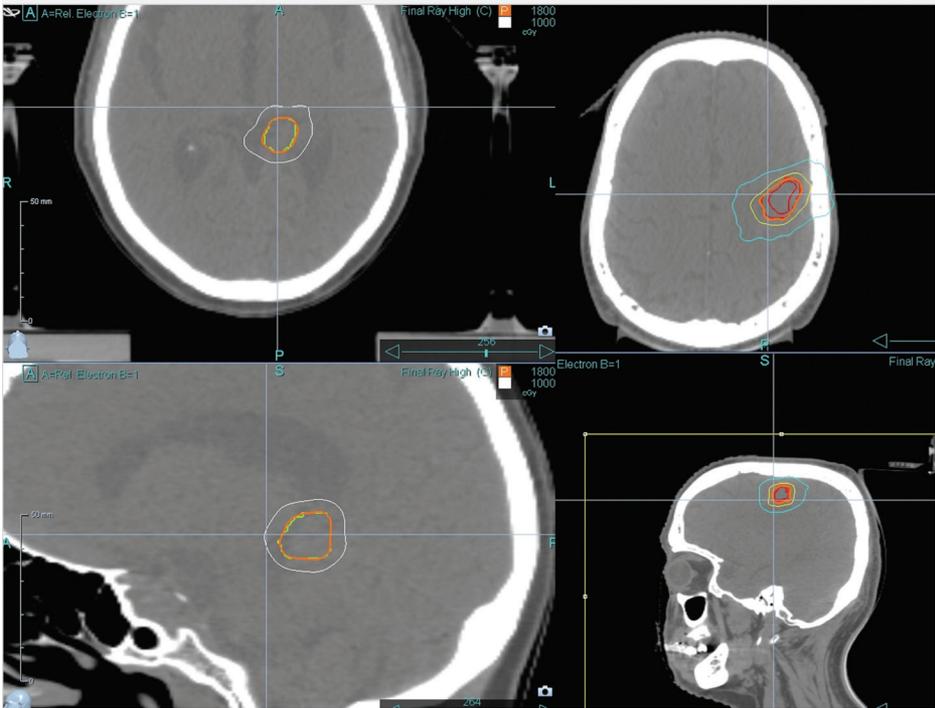
There is level I evidence for the role of SRS in 1-4 brain metastasis (Figure 21.1) and in post-operative SRS (Table 21.3).

## HIPPOCAMPAL AVOIDANCE WBRT (HA-WBRT)

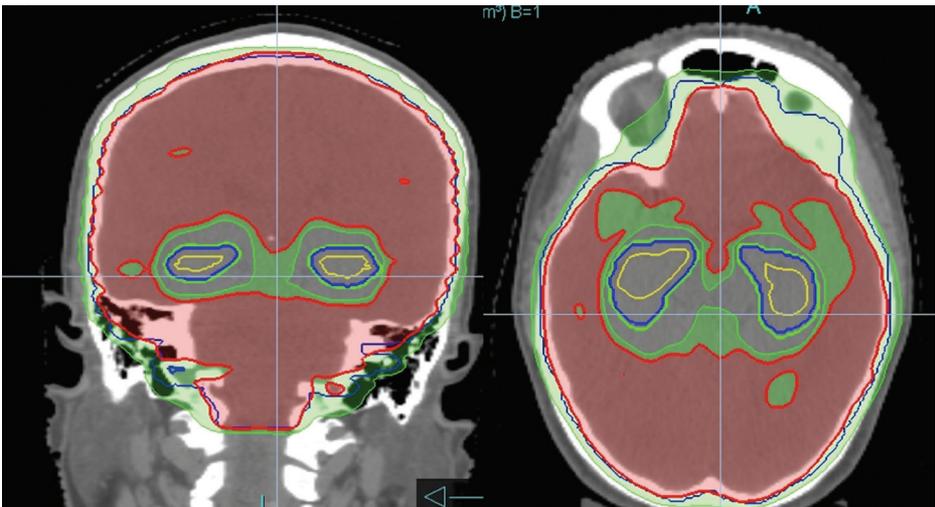
HA-WBRT protected the hippocampal neural stem cells from injury in WBRT thus helping in memory preservation. In a Phase III trial, HA WBRT plus Memantine has lower risk of deterioration in executive functions at 4 months and learning memory at 6 months. There was no significant difference in OS, toxicity or intracranial PFS (Brown, JCO, 2020) (Figure 21.2).

*Indication for HA-WBRT*

- >4 brain lesions
- Oligo brain mets with extra-cranial progression and good PS
- Oligo brain mets with poor PS
- SRS in special histology – SCLC, Melanoma, SCC, adenocarcinoma
- SRS in molecular subtypes



**Figure 21.1** Hippocampal avoidance whole brain radiation therapy (HA-WBRT) in multiple brain metastasis.



**Figure 21.2** SRS for multiple brain metastasis

**TABLE 21.2 ■ Treatment Options in Brain Metastasis**

Multiple brain metastases <ul style="list-style-type: none"> <li>• Good PS with 4–10 metastasis</li> <li>• Good PS with &gt;10 metastasis</li> <li>• Poor PS</li> </ul>	SRS/ HA-WBRT HA-WBRT WBRT/Palliative Care
Oligo-brain metastases <ul style="list-style-type: none"> <li>• 1-3 metastasis with controlled/ low volume primary</li> <li>• 1-3 metastasis with Poor PS / large volume primary</li> </ul>	SRS/SRT WBRT
If large brain mets causing raised intracranial pressure with midline shift	Surgery followed by adjuvant RT (Cavity SRS)
Progressive systemic disease and poor performance status	Best supportive care

**TABLE 21.3 ■ Evidences with SRS in Brain Metastasis**

Author	Study	Design	Results
Patchell et al NEJM 1990(Ref)	Phase III RCT 54 patients	Surgery plus WBRT vs WBRT alone in solitary brain met	Surgery reduced local recurrence( 52 % vs 20 %) and improved median survival (40 vs 15wks)
EORTC 22952-26001 Kocher et al JCO 2011(Ref)	Phase III study 359 patients	Adjuvant WBRT vs Observation after Surgery/SRS in 1-3 brain mets	WBRT decreased 2 yr distant brain failure (27% vs 59%) No difference in OS (WBRT vs Obs) 10.7 vs 10.9 mon Median time to PS>2 9.5 vs 10 mon
Patchell et al JAMA,1998(Ref)	Phase III RCT 95 patients	Surgery followed by WBRT vs Surgery alone in single brain mets	WBRT reduced in brain failure(anywhere 18% vs 70%; local 10% vs 46%); likelihood of neurological death(14% vs 44%) No effect on OS (48 vs 43 weeks)
QUARTZ study Mulvenna et al Lancet 2016(Ref)	Phase III non inferiority study 538 patients NSCLC with brain mets unsuitable for resection or SRS	Optimal supportive care vs WBRT(20Gy/5fr)	No difference in MS(8.5 vs 9.2 wks) OS( 48 vs 43 wks)
Brown et al Lancet,2017(Ref)	Phase III RCT 194 patients with 1-4 mets and resection of one brain lesion	Post op SRS vs WBRT	No difference in OS(MS 11.8 m vs 11.5m) Less neurocognitive decline with SRS (54% vs 86%) and better QOL . Less time to intracranial failure with SRS(6.4 m vs 27.5 m)
Aoyama et al JAMA,2006(Ref)	Phase III RCT 132 patients with 1-4 brain mets	SRS + WBRT vs SRS alone	No difference in OS( SRS alone 8m vs 7.5 in SRS+ WBRT) Distant brain control( 24% in SRS alone and 53% in SRS+ WBRT)
Mahajan et al Lancet, 2017(Ref)	Phase III RCT 132 patients with complete resection of 1-3 brain mets	Post op SRS vs Observation	One year local control (72% in SRS group vs 43% in Observation group) Similar median OS

TABLE 4 ■ Evidences of Cognitive Function Preservation with High Precision RT

Author	Study	Design	Results
Eric Chang et al Lancet, 2009	Phase III RCT 58 patients 1-3 brain mets	SRS+ WBRT vs SRS alone	Memory decline at 4 months (24% in SRS vs 52% in SRS+WBRT)
Brown et al JAMA, 2016	RCT 213 patients 1-3 brain mets	SRS vs SRS + WBRT	Cognitive deterioration at 3 months (63.5% in SRS vs 91.7% in SRS + WBRT)
Gondi et al JCO 2014	RTOG 0933 Phase II trial 100 patients	HA-WBRT for brain mets 5 mm away from hippocampus	Mean relative decline of HVLTR from baseline to 4 months was 7% for HA WBRT vs 30% for WBRT.

Cognitive function preservation is one of the major end-points of SRS and hippocampal sparing RT treatment. There are randomized studies comparing WBRT and SRS / hippo sparing WBRT in brain metastasis.

## BRAIN METASTASIS

SRS is considered to be an effective treatment option for patients with 4 to 10 brain metastases as WBRT. However, there are only a few phase II studies evaluating outcome of SRS in 4-10 lesions. No published randomized studies comparing WBRT and SRS in >4 brain metastasis. SRS alone may be an option for patients with multiple metastases and preserved performance status, deferring the potential side effects of WBRT and allowing WBRT for salvage therapy if needed. SRS has become a standard treatment for patients with 1-4 brain metastases, and use of SRS is expanding in 5-10 metastases patients as well. A Dutch phase III trial (GJ Kim et al 2021) showed that SRS alone led to 1-year survival for 57% of patients with 4-10 brain metastases and maintained QOL parameters. SRS is considered safe, can be repeated, and is less likely to cause acute and delayed side effects compared to WBRT in multiple brain metastasis. While SRS alone is often sufficient for 1-4 metastases, its use for more than 4 is still debated, and some studies suggest that overall survival is not as strongly linked to the number of metastases, rather survival function depends upon volume of intracranial metastasis. Younger age, primary tumor control, favorable tumor histology and good PS are better predictors of overall survival than the number of brain metastases.

## SRS FOR POST-OPERATIVE BRAIN METASTASIS

Radiation therapy is recommended for all patients following resection of brain metastases to improve intracranial control. For patients with limited brain metastases after resection, post-operative SRS is recommended over WBRT to preserve the patient's neurocognitive function and quality of life (Patchell RA, JAMA, 1998).

## **Radiation Dosage Schedule**

### ***Whole Brain Radiation Therapy***

Though multiple dose schedules have been tried for WBRT, a dose of 30 Gy in 10 daily fractions or 20 Gy in five fractions is usually the standard protocol. There are few studies with 40Gy in 15 fractions. There has been no benefit with hyper-fractionation or dose escalation.

### ***Radiosurgery***

Dose schedules in SRS/SRT are dependent on size of the lesion and location. Dose schedules vary from 15–30Gy in 1–5 fractions. Shaw et al in the RTOG 9005 study done to determine the maximum tolerated dose for pts with previously treated primary brain tumors and recurrent brain metastases showed that doses for tumors with diameter 0–2 cm, 2.1–3 cm, and 3.1–4 cm were 24 Gy, 18 Gy, and 15 Gy, respectively (Shaw et al, *Int J Radiat*, 2000). Risk of radionecrosis was 11% at 2 years and rate was higher with larger tumours

### ***Techniques of Radiosurgery***

SRS was primarily done with Gamma Knife system and majority of the published outcome data in brain metastasis with SRS is with Gamma Knife system. Recent publications with linac based radiosurgery, Robotic Radiosurgery also have shown similar outcome compared with Gamma Knife system. However, there are differences in dose prescription, low dose spill and high dose region, fractionation schedule and may be in radiobiology as well between different SRS equipment. Though there is no randomized study comparing different SRS equipment, it seems that the outcome of SRS mostly depends upon the dose delivered, number of lesions, volume of disease and performance status rather than the SRS delivery equipment.

## **COMPLICATIONS**

Most common complication of SRS in brain metastasis is post radiation oedema and radiation necrosis. Higher marginal doses delivered have higher radiation necrosis possibilities. In marginal doses less than 15Gy, there is minimal radiation necrosis possibility and local control probability is almost 60%. Whereas, when marginal dose is higher than 24Gy, radiation necrosis possibility is 10% and local control probability is 93%. Single fraction SRS have higher radiation necrosis compared with fractionated SRS. Radiation necrosis probability with 24Gy in a single fraction schedule is about 10%, whereas in 27Gy in three fraction schedules is about 5%. Slow growing tumours have poorer response and higher radiation necrosis. Patients with previous WBRT have higher possibility of radiation necrosis. On the other hand, immunotherapy (VEGF antagonist) along with SRS reduce radiation necrosis. Normal brain dose is considered as a predictor for radiation necrosis. Usually a single fraction regimen, 14Gy whole brain dose and in multiple fraction regimen 18Gy whole brain dose predicts radiation necrosis. Usually the possibility of radiation necrosis is approximately 10–15%. In brain metastasis less than 3cm size with

BED of 90-127 (dose 24-35Gy/3-5fr), the possibility of radiation necrosis ranges from 2-15%. In a fractionation schedule of 25Gy in 5 fractions, local control is only 56% and radiation necrosis probability is 4%.

In larger volume metastasis, if we need to treat with SRS & keep toxicity same (<5%) then there is a need for dose reduction. However, a reduced dose will increase the recurrence possibility. We need to accept higher radiation necrosis probability in larger brain metastasis to have acceptable local control. Majority of the clinical outcome data of radiation necrosis after radiation therapy is from retrospective series. Radiation necrosis is diagnosed in 24% of cases after SRS by radiology (MRI scan & CT scan). However, the majority of the patients (14%) are asymptomatic. Only 10% of cases have a new neurological deficit. Usually median time to symptomatic necrosis is 11 months (range, 2-32 months). Volume and dose were independent risk factors for necrosis. Risk of necrosis is more than 10% when more than 8.5cc normal brain vol receive >12 Gy. Majority (20%) of radiation necrosis are diagnosed radiologically and need only conservative management. Only 5% of the patients need intervention (Surgery, Hyperbaric oxygen therapy, Immunotherapy).

## INDIAN STUDIES

Majority of the brain metastasis patients in India receive whole brain radiation therapy (WBRT). Usual dose schedule is 30Gy in 10 fractions; 20 Gy in 5 fractions or 8Gy single fraction; depending upon the facilities available, performance status of the patients and extra-cranial site disease status. WBRT is practiced as the preferred choice across different parts of India irrespective of North Indian or South Indian states. Retrospective studies from Eastern India (Sammadar D et al), South Indian centre (Ghosh S et al) (Agarwal JP et al), North Indian centre (Naresh G et al) have shown that WBRT is the most common practice in majority of the centres. Dutta et al [Neurol India 2024] from Amrita Institute have audited the trend of radiation treatment in 788 brain metastasis in the last 15 years (2007-2022) at Amrita Institute, Kochi. Till 2017, majority of the brain metastasis patients were treated with WBRT. Since 2018, there has been an increase in the number of brain metastasis patients treated with radiation therapy and also more patients were treated with radiosurgery. In recent years, patients with small volume asymptomatic patients were treated with radiation therapy, mostly with radiosurgery. It seems, with more availability of radiosurgery facilities and mature published data on radiosurgery in brain metastasis, radiosurgery as treatment option in brain metastasis have increased acceptance in the Indian medical community. There are only a few prospective studies evaluating radiation therapy outcome in Indian patients with brain metastasis. Dutta et al (Neurol India 2023) have published a prospective assessment (CTRI: 2022/01/050237) of outcome data in 138 patients with 251 lesions treated with radiosurgery alone. Patients with up to four lesions with good PS and relative small volume or controlled / stable primary disease patients were accrued in the study. 52% of patients were treated with a single fraction (20-24Gy), 15% with three fractions (27Gy) and 33% with five fractions (25-30Gy) schedule. At mean follow up of

15 months, 78% of patients were alive at 6 months, 47% at 12 months and 19% were alive at more than 24 months follow up. 9% of patients had radiological diagnosis of radiation necrosis and only 2 patients required surgical intervention. Survival outcome was similar with breast or lung primary. However, patients with solitary brain metastasis had significantly better survival compared with multiple metastasis ( $p=0.019$ ). Indian brain metastasis patients are younger with targetable mutations (lung cancer with less EGFR/ALK mutation; Breast cancer with lesser ER/PR positive), however the outcome after radiosurgery alone is similar with western patient population. There is a prospective placebo controlled randomized study with or without memantine in Indian brain metastasis patients (CTRI: 2022/01/039599 ; sample size = 130). Study completion 2025) at Amrita Institute, Kochi is comparing cognitive function preservation status at six months after radiation therapy. Cognitive function assessment done with Addenbrooke Cognitive examination (ACE), adherence with MARS questionnaire and quality of life with EORTC (QLQ 30 & BN20) questionnaire. SRS with memantine have shown significant preservation of cognitive function compared with patients receiving SRS alone. Addition of memantine along with SRS preserves cognitive function (Level I evidence).

*In conclusion*, in multiple brain metastasis (4-10 lesions), SRS is an option to preserve cognitive function and consider WBRT as a salvage option. However, there is only phase II evidence and there is a need for mature outcome data from a randomized study. WBRT or HA-WBRT is considered standard of care in more than 4 brain metastasis. Several factors such as age, performance status, volume of disease and primary histology defines the usefulness of SRS in more than 4 brain metastasis.

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# Cavity Stereotactic Radiosurgery after Surgical Resection for Brain Metastasis

Aditya Gupta ■ Pawan Goyal ■ Sanjeev Srivastava

## INTRODUCTION

Cancer becomes more devastating with the occurrence of metastases to the brain. Approximately 20% to 30% of all cancer patients with systemic disease are affected with brain metastases.<sup>1,2</sup> Surgical resection is an effective treatment for brain metastases which are large and cause mass effect and various pressure symptoms. Surgical resection is usually followed by whole brain radiation therapy (WBRT) as it effectively decreases the risk of local recurrence and the incidence of new metastatic lesions.<sup>3</sup> WBRT is an excellent modality for controlling local recurrence. However, it is associated with significant neurocognitive deficits.<sup>4</sup> Moreover, these toxicities increase in severity with time and significantly impacts the quality of life of patients who otherwise have good systemic cancer control. Other side effects of WBRT are increased fatigue, worsening of Karnofsky performance status. Over and above all, it leads to delay in administration of other systemic therapy as patients take time to recover from acute side effects of WBRT.<sup>5</sup> Keeping in view the side effects associated with WBRT, Stereotactic Radiosurgery (SRS) has become the recommended treatment following surgical resection of a brain metastasis. However, there are certain issues or challenges which need to be resolved like the optimal radiation dose, its timing and delineation of the target.<sup>6</sup>

In this chapter, we will be providing an overview of current treatment standards and advances in stereotactic radiosurgery of resection cavity of an operated metastatic brain lesion. Moreover, we will analyse the current recommendations for radiation dose, technique and treatment related toxicity or side effects for patients receiving radiotherapy.

## CONTROVERSIES

### Target Volume Calculation

The postoperative cavity and target volumes are defined by the neurosurgeon and radiation oncologist. The clinical target volume (CTV) is defined as the contrast-enhancing postoperative cavity as seen on contrast enhancement on MRI and planning CT.

The recommendations as per Soliman et al<sup>7</sup> for CTV (Clinical Target Volume) are:

1. Completely cover the contrast-enhancing surgical cavity, excluding any vasogenic edema
2. Completely encompass the surgical tract on postoperative imaging
3. If preop tumor had dural contact, include a 5–10mm margin along the bone flap that extends beyond the contact area before surgery
4. If there was no contact between the tumor and dura, the CTV should include a margin of 1–5mm along the bone flap
5. If there is any tumor contact (pre-operatively) with any of the venous sinuses, add a 1–5mm margin to the CTV in that area

The contouring of further margins beyond the surgical cavity needs to be defined. It may improve target coverage and also compensate for contouring inaccuracy, but SRS can be associated with an increased risk of radiation necrosis especially when there are large treatment volumes.<sup>8</sup> In most studies, margins of 0 to 3 mm for CTV expansion provide equivalent 1-year local tumor control rates with no evidence of a significantly increased risk of radiation necrosis after SRS. Contrastingly, a few studies have found better local control with margins of 2 mm.<sup>9</sup>

Another debate remains on the inclusion of surgical access track. Several studies have not included the surgical tract for deep lesions. In a series of 64 patients with 66 cavities receiving postoperative SRS for a resected brain metastasis with or without inclusion of surgical corridor in the CTV, Shi et al.<sup>10</sup> showed that omitting the surgical corridor was not associated with statistically significant differences in corridor or cavity recurrence or adverse radiation effects.

### Timing of Radiosurgery

As we know that delineation of target of a resected brain metastasis is typically represented by the rim of enhancement at the edge of the resection cavity. The challenge is that the surgical bed is dynamic after surgery and prone to significant changes in resection cavity dimensions before SRS treatment. It subsequently increases the risk of missing the target and delivering unnecessary high radiation doses to surrounding normal brain parenchyma. Several, but not all, studies indicate a postoperative decrease of the cavity volumes and dynamic changes of resection cavity.<sup>11,12</sup> In a series of 57 patients who received postoperative SRS to the resection cavity, Scharl et al.<sup>14</sup> found significantly average cavity- volume reduction of 23.4% occurring between immediate post-resection MRI and planning MRI ( $p < 0.01$ ). Regardless of the initial volume, cavity shrinkage occurred in 79.1%, remained stable in 3.5%, and increased in 17.4% of cases at a median time of 4 weeks after surgery. In another series of 59 patients with 61 cavities treated with postoperative SRS to the resection cavity, Alghamdi et al.<sup>12</sup> found an average cavity volume reduction of 22.5% at a median time of 4 weeks after surgery, with most changes occurring within 3 weeks. Significant predictors of cavity volume reduction were tumor size  $> 3$  cm, dural involvement and longer time from surgery. Overall, an average cavity volume

reduction of 15% to 43% has been reported in several published studies<sup>11,13</sup> with larger tumor cavities (> 3 cm) that are associated with greater reduction. As far as the timing is concerned, cavity volume reduction occurs within the first 3–4 weeks after surgery in 58–90% of resected brain metastases.<sup>11–14</sup>

There is some consensus evolving on the optimal timing for SRS treatment. As indicated in a majority of studies, shrinkage occurs consistently over time in a significant proportion of patients. It is an effective strategy to wait for a few weeks for SRS to treat a smaller cavity volume. It limits the risk of neurological toxicity while maintaining the efficacy of treatment. Intervals of more than 3–4 weeks between surgery and radiation treatment should be avoided as they have been associated with an increased risk of worse local control.<sup>15,16</sup> Surgery-to-SRS delay longer than 3 weeks and lower maximum radiation dose are risk factors for local recurrence. The estimated 12-month control rates dropped from 87 to 61% if SRS was performed more than 3 weeks after resection. Probably a longer delay leads to an increased spread of microscopic disease that is harder to target because it is not yet radiographically evident. Several studies have observed a significant correlation between increasing delay between surgery and SRS and local failure.<sup>17,18</sup> The recommendation is therefore to perform postoperative SRS to the resection cavity within maximum four weeks after surgery.

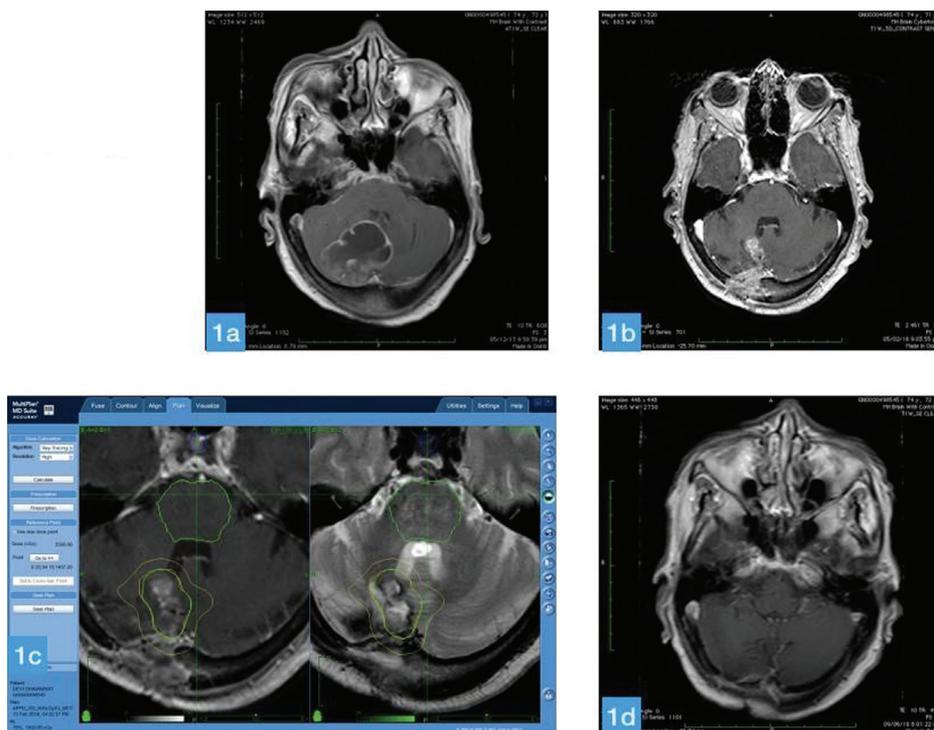
Further, the planning MRI should be acquired < 7 days before treatment to limit negative impact of cavity changes on clinical outcomes.

### **Risk of Radiation Necrosis**

The most significant adverse effect of radiation treatment of brain metastases is radiation necrosis. It presents as a focal enhancing lesion at a variable time of 6–15 months following SRS. It always remains a challenge to differentiate between tumor progression and radiation necrosis. The 12-month estimated risk of radiation necrosis ranges from 1.5% to 28%. Factors correlated with an increased risk of radiation necrosis include higher radiation dose, larger volumes, and combined immunotherapy.<sup>19</sup> Several studies have found a significant correlation between volume of the brain receiving high-dose irradiation and the risk of radiation necrosis after SRS for intact and resected brain metastases.<sup>20,21</sup> During SRS, the volume of the normal brain receiving 12 Gy (brain minus GTV; V12 Gy) >5–10 ml is predictive of a >10% risk of radiation necrosis.<sup>22</sup> In a recent review of single- and multifraction SRS dose/volume tolerances of the brain including 51 studies published from January 1995 through December 2016, Milano et al.<sup>22</sup> reported brain volumes (brain plus target volume) receiving 20 Gy in 3-fractions or V24 Gy in 5-fractions <20 ml were associated with <10% risk of any necrosis or edema in patients with brain metastases.

## OUR EXPERIENCE

### Case 1: Post Ca Lung Cerebellar Metastasis



**Figure 22.1** 1a Pre surgery scan, 1b Post surgery scan, 1c SRS Planning, 1d Post SRS.

## CURRENT PRACTICE DEFINITIONS

Imaging for target delineation	Isotropic post-contrast-enhanced 3D T1-weighted MRI sequences with 1 mm thick slices and T2-weighted images. Additional images include preoperative contrast-enhanced T1-weighted MRI sequences to identify the preoperative tumor extent and dural involvement
Gross Tumor Volume (GTV)	Surgical cavity on postoperative contrast-enhanced T1-weighted MR images (typically represented by the rim of enhancement at the edge of the resection cavity) with inclusion of any residual nodular enhancement
Clinical Tumor Volume (CTV)	The CTV is defined as the GTV plus 0–1 mm margins constrained at anatomical barriers such as the skull. GTV-to-CTV margins up to 5–10 mm are applied along the bone flap/meningeal margin, with larger margins used for tumors in contact with the dura preoperatively. Vasogenic edema and surgical corridor (for deep lesions) are not usually included
Planning Target Volume (PTV)	A margin of up to 3 mm is usually added to the CTV to generate the PTV, depending on the radiation technique. For frame-based SRS, no additional safety margin is necessary; with frameless SRS and SRT, a GTV-to-PTV safety margin of 1–3 mm is usually applied according to Institutional practice

Case 2: Post Ca Breast Right Frontal Metastasis

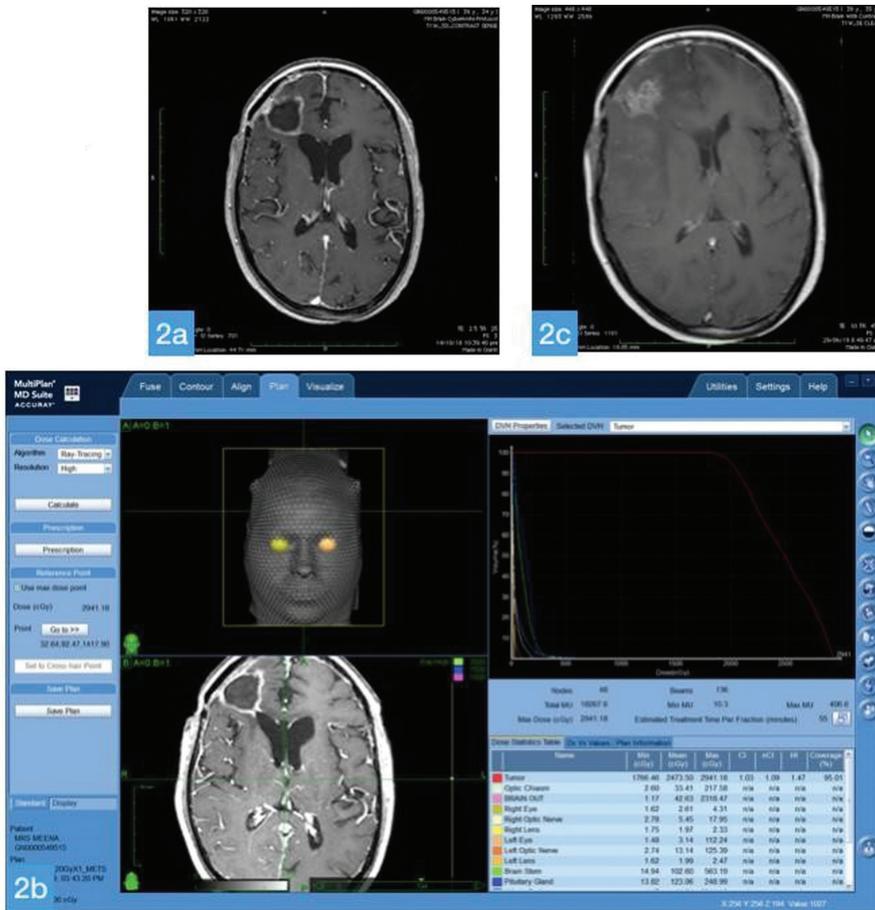


Figure 22.2 2a Post surgery scan, 2b SRS planning, 2c Post SRS.

Timing of treatment	There is a general consensus to perform postoperative SRS/HSRT to the resection cavity within 4 weeks after surgery with planning MRI acquired < 7 days before treatment to limit negative impact of cavity changes on clinical outcomes
Dose and fractionation	12–18 Gy using single-fraction SRS; 24–27 Gy in 3 fractions and 30–35 Gy in 5 fractions using HSRT, typically for larger resection cavity; less commonly 30–40 Gy in 10 fractions

Adapted from Minniti et al<sup>23</sup>

## LEARNING POINTS AND FUTURE DIRECTIONS

The practice has shifted from WBRT to SRS for patients with a limited number of intact brain metastases. Postoperative SRS is replacing WBRT for patients with resected brain metastases as the standard of care. The rationale for delivering focal radiation and not WBRT is to avoid the complications of WBRT while maintaining high local control without negatively impacting survival. MRI at regular intervals of 2–3 months is mandatory to offer appropriate salvage therapy in the event of either local or distant brain progression. Although SRS has shown to improve local control in smaller surgical beds, achieving excellent local control rates still remains a challenge in larger ones. Accurate localization and delineation of the surgical cavity after resection of a brain metastasis is a crucial step in the treatment planning process for improving local control. Future research is needed to answer several questions regarding the optimal treatment timing, target delineation, dose/fractionation, and combination with systemic agents.

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SECTION VIII

**Functional Neurosurgery  
Applications**

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# Gamma Knife Radiosurgery for Trigeminal Neuralgia

Sarvesh Goyal ■ Deepak Agrawal

## INTRODUCTION

Trigeminal neuralgia is characterized by brief, recurrent episodes of intense, electric

shock-like facial pain along the distribution of one or more branches of the fifth cranial nerve. The International Classification of Headache Disorders (ICHD-3) distinguishes classical TN, often due to neurovascular conflict, from secondary TN, which may result from multiple sclerosis or space-occupying lesions. Pharmacologic therapy—typically involving carbamazepine, oxcarbazepine, or other anticonvulsants—is the first-line approach. However, a significant proportion of patients become refractory to medications over time or suffer from side effects such as drowsiness, dizziness, or hepatic dysfunction.

Surgical options for refractory cases include percutaneous techniques (e.g., balloon compression, glycerol rhizotomy, radiofrequency ablation) and microvascular decompression (MVD), the latter being preferred in patients with documented neurovascular compression. However, these procedures carry risks of cranial nerve deficits, anesthesia dolorosa, or cerebrovascular events. In this context, GKRS has emerged as a valuable, minimally invasive modality that delivers targeted radiation to the trigeminal nerve without incisions or general anesthesia.<sup>1</sup> Its safety profile makes it particularly appealing in elderly patients and those with significant comorbidities.

## REPRESENTATIVE CASE

### History & Examination

A 67-year-old male presented with a six-year history of right-sided facial pain. The episodes were sharp, stabbing, and typically lasted a few seconds. The pain was localized to the V2 and V3 distributions of the trigeminal nerve and was triggered by light tactile stimuli, such as brushing teeth, chewing, and speaking. The pain intensity severely impacted the patient's nutrition and psychological well-being. Multiple medication regimens, including high-dose carbamazepine and pregabalin, provided only transient relief and were associated with sedation and ataxia.

Neurological examination revealed no sensory or motor deficits. Corneal reflexes were preserved, and no cranial nerve palsies were observed.

## Imaging

A high-resolution 3T MRI brain with constructive interference in steady-state (CISS) and FIESTA sequences was performed. Imaging revealed a vascular loop of the anterior inferior cerebellar artery (AICA) in contact with the cisternal segment of the right trigeminal nerve near the root entry zone (REZ). No demyelinating plaques, tumors, or ischemic changes were noted. The imaging confirmed a classical neurovascular conflict without evidence of multiple sclerosis or secondary causes.

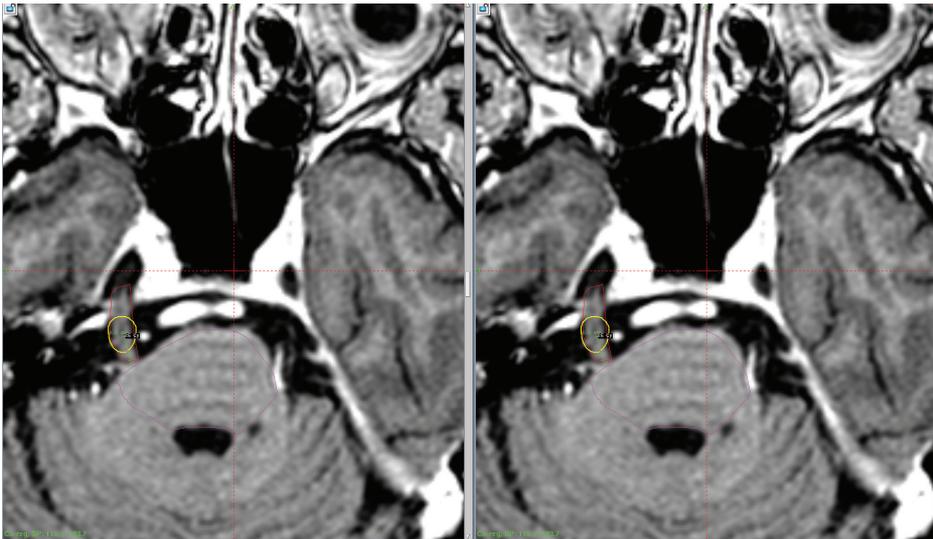
## GK Protocol

The patient was immobilized with a Leksell stereotactic frame under local anesthesia. High-resolution MRI with contrast enhancement was fused with CT imaging to delineate the trigeminal nerve and surrounding structures. A single 4-mm collimator shot was planned to target the retrogasserian zone, approximately 6 mm anterior to the REZ. This location was chosen to minimize the risk of facial hypoesthesia while ensuring effective dose delivery.

A maximum dose of 80 Gy was delivered at the 100% isodose line, with the brainstem exposure limited to <15 Gy.

## Follow-up

The patient reported significant pain reduction within two weeks, with complete pain freedom by one month (BNI pain score: I). He was weaned off medications over three months. At five-year follow-up, the patient remained pain-free without



**Figure 23.1** Trigeminal nerve visualized on T1-weighted MRI. A single 4-mm isocenter was used to target the nerve 6 mm anterior to the REZ. The brainstem received <16 Gy, which is below the critical threshold for radiation toxicity.

any sensory deficits. No new onset hypoesthesia, keratitis, or herpes reactivation was noted. Periodic MRIs confirmed no radiation-induced changes in adjacent brain structures.

## DISCUSSION

### Controversies

#### *Target Site – REZ vs Retrogasserian Zone*

The choice of the optimal target along the trigeminal nerve in Gamma Knife Radiosurgery (GKRS) is a subject of ongoing debate, balancing between treatment efficacy and complication risk. Two principal sites are commonly considered: the root entry zone (REZ) and the retrogasserian zone.<sup>2,3</sup>

The **REZ**, located at the junction between central (oligodendrocyte-rich) and peripheral (Schwann cell-rich) myelination, is historically favored due to its higher radiosensitivity. Targeting the REZ has demonstrated strong initial pain relief, attributed to greater susceptibility of central myelin to radiation. However, this approach carries an elevated risk of **adverse effects**, particularly **facial numbness, keratitis, and dysesthesia**, owing to its proximity to the brainstem.<sup>4</sup>

In contrast, the **retrogasserian zone**, situated 4–9 mm anterior to the REZ, is part of the cisternal segment of the trigeminal nerve. It is now increasingly preferred due to a **lower incidence of sensory complications**, while maintaining comparable efficacy.<sup>5</sup> This site allows precise dose delivery while keeping brainstem radiation exposure below threshold limits (typically <15 Gy). Targeting farther than 8 mm from the nerve's emergence is associated with worse long-term outcomes. Additionally, maintaining a prescription dose  $\geq 80$  Gy and avoiding sector blocking enhances efficacy.<sup>5,6,7</sup>

Targeting both the root entry zone (REZ) and the retrogasserian segment using a two-isocenter strategy provides improved pain relief compared to single-isocenter approaches focused solely on the REZ. Patients undergoing the broader coverage technique more frequently achieve complete pain relief, but this comes with a higher risk of facial numbness.<sup>3</sup>

In practice, **retrogasserian targeting with a single 4-mm isocenter** placed ~6 mm anterior to the REZ strikes a clinically acceptable balance. It is the preferred standard in many centers, as it ensures adequate pain control with minimal morbidity.

Emerging imaging tools, such as **diffusion tensor imaging (DTI)** and high-resolution CISS sequences, further aid in accurate nerve visualization and target delineation, enhancing safety and precision irrespective of the site chosen.<sup>8</sup>

In summary, while the REZ remains a potent target, the retrogasserian zone offers a **safer and equally effective alternative**. The choice should be individualized, taking into account patient factors, anatomy, prior procedures, and institutional expertise.

### ***Dose Protocol and Biologically Effective Dose (BED)***

The prescription dose and radiation delivery technique in Gamma Knife Radiosurgery (GKRS) for trigeminal neuralgia (TN) are pivotal determinants of treatment success and complication risk. Most contemporary protocols prescribe a **maximum dose of 80–90 Gy**, typically using a **single 4-mm collimator** focused on the cisternal segment of the trigeminal nerve. However, beyond the absolute dose, the **Biologically Effective Dose (BED)**—which incorporates the influence of dose rate and tissue repair kinetics—has emerged as a more meaningful metric for outcome prediction.<sup>8,9,10</sup>

Prescription doses below 80 Gy are associated with reduced long-term pain control. Lower dosing results in significantly poorer outcomes, highlighting the importance of maintaining an adequate therapeutic threshold. The calibration dose rate of the Gamma Knife unit also plays a critical role—rates below 2.5 Gy/min, commonly found in older models, correlate with inferior outcomes compared to the higher rates delivered by modern platforms like Perfexion and Icon.

In addition to total dose, the distribution of radiation within the nerve is a key factor. An integral dose (ID50) less than 2.7 mJ and irradiating a smaller portion of the nerve (less than 35%) with more than 80% of the maximum dose are both linked to shorter pain relief duration. These dosimetric parameters are especially predictive of outcome when the isocenter is positioned within 8 mm of the brainstem, underscoring the need for precise anatomical planning.

While higher doses may offer incremental benefit, there is **no consistent evidence** that doses >90 Gy improve pain control, and such regimens carry a **higher risk of complications**, especially brainstem injury and bothersome numbness. Therefore, maintaining a **maximum dose of 80–85 Gy**, ensuring **optimal calibration rate**, and using precise **MRI-based planning** is the current best practice.

In conclusion, the **efficacy and safety of GKRS are not determined solely by dose**, but rather by a careful balance of dosimetric parameters, BED, and individualized anatomical targeting.

### ***Repeat GKRS***

Repeat Gamma Knife Radiosurgery (GKRS) is considered for patients with recurrent or persistent trigeminal neuralgia following an initially favorable response. However, it typically yields lower efficacy and a higher incidence of sensory complications compared to the first treatment.

A substantial number of patients achieve initial pain relief after repeat GKRS, a significant proportion experience new trigeminal dysfunction, and the durability of benefit tends to diminish over time. Salvage GKRS following prior microvascular decompression (MVD) also demonstrates high early response rates, but long-term pain control remains suboptimal. Facial numbness after repeat treatment appears to correlate with longer-lasting relief, suggesting a complex balance between efficacy and adverse effects.

These findings collectively highlight that **repeat GKRS should be reserved for highly selected patients**, preferably those who had a **documented positive re-**

**sponse to initial GKRS** but later relapsed. Detailed imaging reassessment, individualized dosimetric planning, and clear patient counseling regarding **elevated risks and limited durability** are essential before proceeding. In cases with prior destructive procedures or anatomical distortion, **alternative interventions like MVD or percutaneous techniques** may be more appropriate.<sup>11,12</sup>

### ***Gamma Knife Radiosurgery in TN Associated with Tumors and Multiple Sclerosis***

Gamma Knife Radiosurgery (GKRS) is increasingly utilized in managing trigeminal neuralgia (TN) secondary to intracranial tumors and multiple sclerosis (MS), particularly in patients unsuitable for surgery or those with treatment-refractory pain.

In tumor-related TN, the pain typically arises from mass effect or direct compression of the trigeminal nerve by lesions such as meningiomas or schwannomas. While surgical resection remains the primary approach for eligible patients, GKRS offers a safe and non-invasive alternative in cases where surgery is contraindicated or has failed to alleviate pain. Direct targeting of the trigeminal nerve using stereotactic radiosurgery can provide effective pain relief with a low risk of permanent sensory deficits, making it an attractive salvage or adjunctive therapy.

TN in the setting of MS is more complex, often presenting with bilateral or atypical pain patterns due to central demyelination rather than neurovascular compression. These patients tend to have less consistent responses to conventional medical and surgical treatments. GKRS can offer meaningful short-term pain relief, although long-term durability may be limited, with higher recurrence rates compared to idiopathic cases. Sensory disturbances are more common in this subgroup, but typically remain non-bothersome.

In both tumor-associated and MS-associated TN, GKRS serves as a valuable treatment option, particularly in patients with significant comorbidities, prior interventions, or anatomical complexities. Careful case selection, individualized dose planning, and targeted nerve visualization are essential to optimize outcomes in these challenging clinical scenarios.<sup>13,14,15</sup>

## **Current Practice**

### ***Imaging and Targeting***

Modern imaging techniques, including CISS MRI and diffusion tensor imaging (DTI), are pivotal for accurate localization and target selection. DTI, in particular, can be useful in identifying patients likely to benefit from treatment by assessing post-radiation nerve integrity.<sup>16</sup>

### ***Dose Delivery and Isocenter Planning***

Use of a single 4-mm isocenter remains the standard approach. Attempts to increase nerve length irradiated using multiple isocenters or sector blocking have not demonstrated superior outcomes and may reduce the BED. The treatment plan should ensure minimal brainstem exposure without compromising the coverage of the nerve segment.

### **Efficacy and Timing**

Approximately 70–80% of patients experience significant pain relief within the first month of treatment. However, efficacy declines over time, with only 40–45% maintaining pain freedom at 5 years. Early intervention—within three years of symptom onset—has been associated with better outcomes.<sup>17</sup>

## **LEARNING POINTS**

- GKRS is highly effective as a primary treatment in patients who are medically refractory or surgically unfit.
- Retrogasserian targeting offers a better safety profile with comparable pain relief to REZ targeting.
- Post-GKRS facial hypoesthesia, though undesirable, is predictive of better long-term outcomes.
- ANN models can help identify ideal candidates for GKRS by integrating multiple clinical and imaging variables.
- Repeat GKRS has limited utility and should be cautiously considered.

## **CONCLUSION**

Gamma Knife Radiosurgery is a well-established, minimally invasive option for managing classical trigeminal neuralgia. It offers durable pain control with a favorable risk profile, especially in elderly patients and those with medical comorbidities. The success of GKRS hinges on appropriate patient selection, precise imaging and targeting, and adherence to optimal dosimetric parameters. While MVD remains the gold standard in cases with definite neurovascular compression, GKRS provides a compelling alternative with fewer complications.

Advancements in neuroimaging and predictive analytics, particularly the incorporation of artificial intelligence models like ANNs, hold promise in refining patient selection and improving outcomes. Future research should focus on multicentric data pooling to validate predictive models and refine treatment protocols further.

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# Gamma Knife Radiosurgery in Obsessive-Compulsive Disorder (OCD)

Deepak Agrawal ■ Mahnaaz Sultana

## INTRODUCTION

Obsessive-compulsive disorder (OCD) is a chronic, debilitating neuropsychiatric disorder affecting approximately 2–3% of the population. It is characterized by intrusive obsessions (unwanted thoughts, fears, or urges) and compulsions (repetitive behaviors or mental acts performed to reduce anxiety). The disorder disrupts daily functioning, leading to social, occupational, and personal impairment.

While selective serotonin reuptake inhibitors (SSRIs) and Cognitive-behavioral therapy (CBT) are the mainstays of treatment, approximately 10–20% of patients remain refractory despite optimal therapy. In such cases, neurosurgical interventions like deep brain stimulation (DBS) and lesioning procedures (anterior capsulotomy, cingulotomy) are considered.

Gamma Knife Radiosurgery (GKRS) has emerged as a minimally invasive, lesioning-based approach, targeting the anterior limb of the internal capsule (ALIC) and cingulate gyrus. GKRS disrupts the hyperactive cortico-striato-thalamo-cortical (CSTC) loop, which is central to OCD pathophysiology. The gradual nature of radiation-induced lesions allows for controlled modulation of pathological circuits while minimizing side effects.

This chapter presents a case of severe OCD, and the rationale for GKRS, treatment planning, expected outcomes, complications, and clinical insights into managing severe OCD.

## HISTORY

A 29-year-old woman, who suffered from severe OCD since adolescence presented to our department. Her symptoms primarily involve:

- Contamination fears: Excessive washing and avoidance behaviors.
- Repetitive checking rituals: Obsessively verifying locks, stove knobs, and water taps.
- Intrusive thoughts: Persistent fears of harming family members, despite no intent or history of aggression.

Her OCD worsened over the past decade, significantly affecting her quality of life. She lost her job, became socially withdrawn, and required constant family supervision due to her compulsions consuming more than 10 hours per day.

### Previous Treatments Included

1. Pharmacotherapy:
  - SSRI (fluvoxamine, fluoxetine, sertraline) at maximum doses.
  - Clomipramine (TCA) augmentation.
  - Atypical antipsychotics (aripiprazole, risperidone) failed to yield significant improvement.
2. Cognitive-Behavioral Therapy (CBT):
  - Extensive trials of exposure and response prevention (ERP).
  - Initially, there was mild improvement, but relapses occurred repeatedly.
3. Electroconvulsive Therapy (ECT):
  - Given for comorbid depression, with no significant impact on OCD symptoms.

### Examination and Psychiatric Assessment

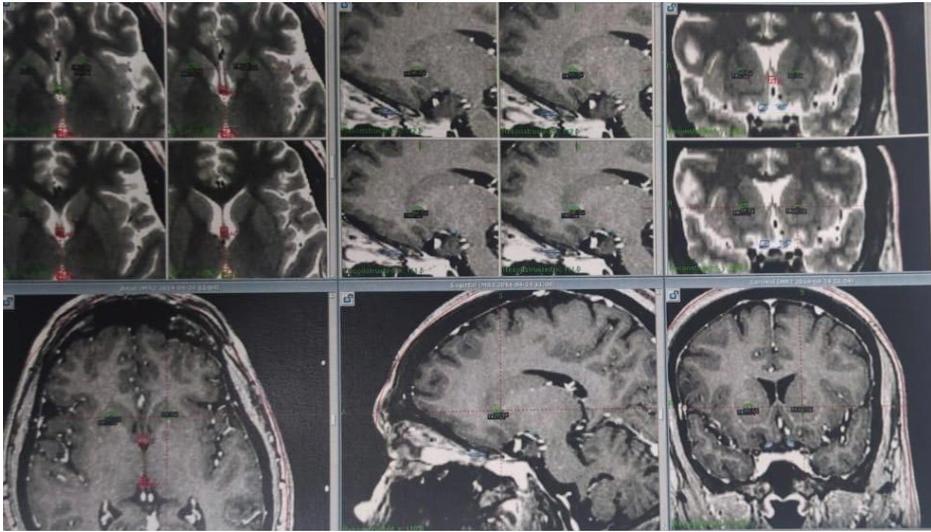
- Mental Status Examination (MSE):
  - Alert, cooperative, but highly anxious and preoccupied with intrusive thoughts.
  - Engaged in ritualistic behaviors during the interview.
  - No delusions or hallucinations.
- Yale-Brown Obsessive-Compulsive Scale (Y-BOCS):
  - Score of 36/40, indicating extreme OCD.

### Investigations

1. Structural MRI:
  - No gross abnormalities, but volumetric analysis showed increased connectivity in the CSTC loop.
2. Functional MRI:
  - Hyperactivity in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and caudate nucleus. (Figure 24.1)
3. Neuropsychological Testing:
  - Preserved cognitive function, with no executive dysfunction.

Given her severe, treatment-refractory OCD, Patient was considered a candidate for Gamma Knife Radiosurgery (GKRS) targeting the anterior limb of the internal capsule (ALIC) bilaterally and 130 Gy given using single 4mm shot on each side. Patient underwent the above procedure and immediate post GKRS period was uneventful. (Figure 24.1)

### Follow Up



**Figure 24.1** (A-F) functional MRI showing hyperactivity in CSTC circuits which helps make a stereotactic MRI-based ALIC targeting plan for GKRS.

Patient was followed up with an MRI, 6 months after completion of GKRS and 6 monthly assessments with Y-BOCS. There was reduction of hyperactive CSTC circuits 6 months after treatment and the Y-BOCS curve improved over a 24 months period. Patient had 80% symptomatic improvement by 18 months and partially resumed her daily activities and the YBOCS decreased to 7/36. She was advised continuation of cognitive behavioural therapy and 6 monthly follow up.

## DISCUSSION

OCD arises due to dysregulation of the cortico-striato-thalamo-cortical (CSTC) loop, primarily due to hyperactivity in the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) 3. Other causes include deficient inhibitory control from the caudate nucleus, leading to repetitive compulsions, as well as dysfunctional serotonin modulation, which explains SSRI efficacy in some cases 1.

## CONTROVERSIES

The role of radiosurgery in psychiatry remains controversial due to ethical, philosophical, and practical concerns. Critics argue that lesioning-based approaches may risk irreversible damage and that patient selection must be stringent. While DBS offers adjustability, GKRS produces permanent lesions, which can complicate treatment if side effects arise. Additionally, variation in response timing (often taking 6–24 months) can challenge treatment monitoring and outcome attribution. Long-term efficacy, optimal targeting, and dose planning remain subjects of ongoing debate.<sup>1,3</sup>

## CURRENT PRACTICE

In severe, treatment-resistant OCD cases, GKRS targeting the ALIC is increasingly accepted. Centers with functional neurosurgery expertise follow stringent inclusion protocols—typically patients with a Y-BOCS >30, functional disability, and documented treatment failure with SSRIs, CBT, and ECT. A dose of 130 Gy with 4 mm collimators is often used bilaterally. Reports from multiple studies confirm improvement in 45–75% of cases, with low rates of major complications.<sup>2,5</sup> Modern imaging like functional MRI helps refine target planning by identifying CSTC circuit hyperactivity.

## LEARNING POINTS

- OCD is linked to dysfunction in CSTC loops, particularly hyperactivity in the OFC and ACC.
- GKRS offers a minimally invasive method to create controlled lesions in the ALIC, reducing pathological connectivity.
- Functional imaging and stereotactic planning enhance treatment precision.
- Symptom improvement is gradual, often taking 6–24 months.
- Cognitive-behavioral therapy remains important post-GKRS to reinforce adaptive patterns.

## CONCLUSION

Gamma Knife radiosurgery is an effective option in managing severe, refractory OCD. While lesion-based interventions raise valid ethical concerns, modern planning techniques and careful patient selection have improved safety. The case presented demonstrates an 80% improvement in symptoms with near-normalization of Y-BOCS scores and functional recovery. GKRS provides hope for patients who have exhausted conventional therapies and is gaining recognition as a credible tool in psychiatric neurosurgery.

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# Stereotactic Radiosurgery for Functional Disorders

Sandeep Mishra ■ Manjul Tripathi

## INTRODUCTION

The concept dates back to 1946, when Spiegel and Wycis used stereotactic guidance to treat Huntington's chorea by injecting alcohol into the globus pallidus and medial thalamus. Lars Leksell introduced radiosurgery in the 1950s as a method for ablative functional neurosurgery targeting psychiatric conditions, pain, and movement disorders. However, its use in functional neurosurgery remained limited due to early imaging constraints and the emergence of deep brain stimulation (DBS). Functional neurosurgery aims to modulate pathological neural circuits to alleviate neurological and psychiatric conditions while preserving normal brain function. Functional neurosurgeries are categorized as neuromodulation (e.g., DBS) or lesioning (e.g., RF, SRS, FUS). While no large trials directly compare Stereotactic Radiosurgery (SRS) with other treatments, its use should be individualized based on patient-specific risks and benefits.

SRS is a precise, non-invasive treatment used for both brain tumors and functional disorders, offering an alternative for patients who are not candidates for surgery or are on anticoagulation. SRS delivers high-dose highly focused radiation with submillimeter accuracy to targeted areas, using technologies like GammaKnife (GKRS), CyberKnife, or LINAC. In functional neurosurgery, it targets either small regions (e.g., VIM, internal capsule, trigeminal nerve) with high doses (80–140 Gy) or larger volumes (e.g., epilepsy) with moderate doses (20–24 Gy). Despite benefits like outpatient delivery, minimal recovery, and repeatability, GKRS has limitations including delayed effects and variable long-term outcomes. This chapter aims to review its role across common functional disorders.

## CONTROVERSIES

### SRS vs Microvascular Decompression (MVD) in Trigeminal Neuralgia (TN)

Classical TN often responds well to anticonvulsants initially, but about half of patients eventually develop medication-refractory pain. Surgical options, especially MVD, offer the best chance for cure by relieving neurovascular compression, with outcomes highly dependent on surgical expertise. GKRS is a non-invasive,

outpatient procedure offering an initial pain relief rate of approximately 70–90%, although the onset is delayed (weeks to months).<sup>1,2</sup> Long-term pain control is maintained in about 50–60% of patients at 5 years.<sup>3</sup> In contrast, MVD is an invasive microsurgical procedure involving craniotomy and direct decompression of the nerve, providing more immediate and durable pain relief, with initial success rates of 80–95% and sustained relief in 70–80% of patients over 5 years.<sup>4,5</sup> MVD is associated with a higher risk of surgical complications including cerebrospinal fluid (CSF) leak, hearing loss, or facial weakness. GKRS has a favorable safety profile and low overall morbidity, with facial numbness or hypesthesia being the most common side effect. Repeat SRS remains a viable option in case of recurrence, whereas revision MVD is less commonly pursued due to increased surgical risks. The optimal treatment strategy depends on careful patient selection: MVD is generally favored for younger, healthier patients with radiologically confirmed neurovascular conflict, while SRS is typically reserved for elderly or high-risk surgical candidates or those seeking a minimally invasive alternative. Radiosurgery is also an effective procedure to treat TN secondary to other causes including multiple sclerosis, tumor related TN, and other craniofacial neuralgias. Centromedian thalamotomy is an upcoming indication for patients with chronic refractory pain. Radiosurgical Hypophysectomy is an underutilized treatment option for cancer related refractory pain.

### **SRS vs DBS in Movement Disorders**

The key advantage of SRS lies in its non-incisional, hardware-free nature, making it preferable for patients reluctant to undergo invasive procedures like DBS. GKRS thalamotomy achieves >80% tremor reduction in essential tremor but is limited to unilateral treatment due to risks associated with bilateral lesions. Frameless SRS allows patients to continue antiplatelet or anticoagulant therapy, unlike DBS, which requires medication interruption. SRS is well-tolerated, with minimal recovery time, enabling patients to resume normal activities almost immediately. A key limitation of SRS versus DBS, RF, or FUS is the absence of neurophysiological feedback, which helps refine targeting and optimize outcomes in movement disorder surgery. Another drawback of SRS is its delayed effect, often taking months to a year, unlike other procedures with quicker symptom relief.

Single session lesional procedures with SRS may cause irreversible brain changes and carry high risks when done bilaterally, including dysarthria, dysphagia, and cognitive deficits. Thus, they are typically limited to unilateral treatment or staged bilateral procedures. For medically fit patients needing bilateral tremor control, DBS is the preferred first-line option.

### **SRS vs Surgery in Mesial Temporal Lobe Epilepsy (MTLE)**

SRS and open surgical—such as anterior temporal lobectomy or selective amygdalohippocampectomy—are established treatment options for drug resistant MTLE, but they differ significantly in approach, efficacy, and safety profile. SRS

is a non-invasive modality, delivering focused radiation to the epileptogenic hippocampus and amygdala, offering long-term seizure freedom rates of 50–65% of patients over 2–3 years.<sup>6,7</sup> Though its therapeutic effect is delayed and outcomes less predictable, SRS better preserves cognitive function and avoids operative risks. In contrast, open surgical resection provides more immediate seizure control, with long-term seizure freedom rates of 60–80%.<sup>8,9</sup> It remains the gold standard for MTLE, particularly in patients with clear MRI findings such as hippocampal sclerosis. However, it is associated with potential risks such as memory impairment, language deficits, and operative complications. SRS is preferred for medically fragile patients, bilateral MTLE, or those unwilling for open surgery. Surgery is favored for maximizing seizure freedom, rapid symptom control, and cases with well-localized lesions.

### **SRS vs Psychosurgery in Obsessive Compulsive Disorder (OCD)**

Traditionally, psychosurgery—such as anterior capsulotomy and cingulotomy—has been used for severe, treatment-resistant OCD. In 1949, Talairach introduced anterior capsulotomy as a less invasive alternative to lobotomy, showing effectiveness in anxiety and OCD but not in psychosis. SRS has since emerged as a non-invasive alternative, targeting the same hyperactive circuits between the orbitofrontal cortex and the thalamic-limbic system with fewer risks. Traditional psychosurgery is invasive and associated with higher rates of complications like hemorrhage, infection, or cognitive side effects. Psychosurgery yields a comparable response rates of 50–75% but often more immediate symptom relief.<sup>10,11</sup> SRS demonstrates comparable efficacy, with studies reporting clinical improvement in 55–75% of patients and a safer profile, with potential complications like radiation-induced edema or necrosis.<sup>12,13</sup> SRS may be preferred for high-risk patients or those seeking a non-invasive option, whereas psychosurgery may be reserved for cases requiring more rapid and robust intervention.

## **CURRENT PRACTICE**

SRS has been utilized in the treatment of a wide range of functional conditions, including trigeminal neuralgia, movement disorders such as Parkinson's disease, essential tremor, and dystonia, as well as epilepsy, psychiatric disorders, and intractable pain syndromes.

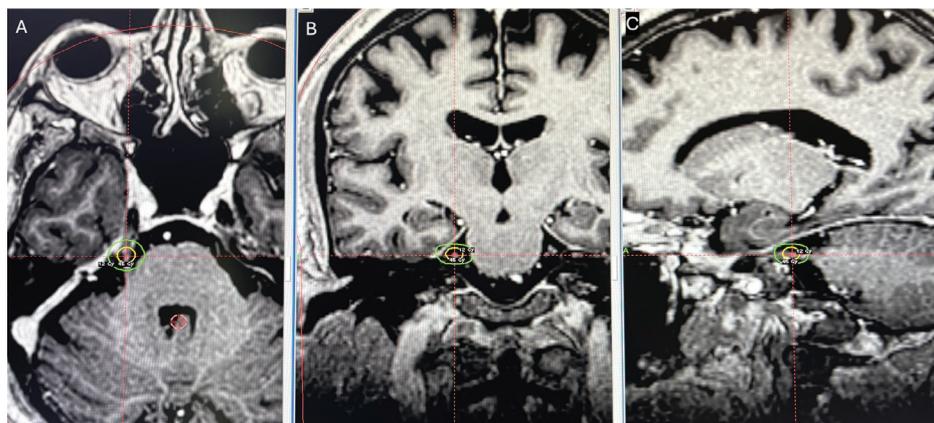
### **Trigeminal Neuralgia (TN)**

TN, the most common facial neuralgia, presents as paroxysmal, lancinating pain along trigeminal nerve branches. While medical therapy is first-line, surgical options like radiofrequency rhizotomy, glycerol rhizolysis, balloon compression, and microvascular decompression are other treatment options when medications fail. SRS is increasingly used, especially in elderly or high-risk patients unsuitable for invasive procedures.

- **Indication:** SRS is increasingly used for medically refractory TN, including as a first-line option in elderly patients, those with comorbidities, or on long-term anticoagulation where invasive procedures are contraindicated.
- **Target:** The cisternal segment of the trigeminal nerve, typically 2–4 mm anterior to the root entry zone (REZ), is the preferred target. Anterior targeting may enhance long-term pain relief, while posterior approaches, though initially effective, may increase complication risk.<sup>2</sup> Some advocate a more anterior, retrogasserian target (7–8 mm from the brainstem) to potentially reduce deafferentation symptoms (Figure 25.1).
- **Dose:** A 70–90 Gy dose is typically delivered using a single 4-mm collimator shot, targeting the trigeminal root entry zone with the 30–40% isodose line tangential to the brainstem.

### Outcomes

- Studies have reported pain relief in 75–92% of trigeminal neuralgia patients at 1 year post-radiosurgery.<sup>1</sup> A systematic review of 120 studies found over 85% achieved pain control, with 52% pain-free without medications.<sup>2</sup>
- Pain relief typically begins ~3 weeks post-GK neuroradiomodulation and may improve for up to 6 months. About 50% achieve complete relief, but recurrence occurs in one-third by 2 years and half by 5 years.<sup>3</sup>
- Efficacy of GK radiosurgery is higher in older patients (>70) and those with purely paroxysmal TN. Outcomes are less favorable in cases with MS or continuous pain. Early treatment improves pain relief and duration. Post-treatment facial numbness strongly predicts success, while prior procedures are associated with reduced long-term benefit, likely reflecting greater disease severity.<sup>2,14</sup>
- Side effects include facial numbness (10–20%), dry eye, deafferentation pain, and keratitis.



**Figure 25.1** Radio surgical targeting of cisternal component of trigeminal nerve with 4 mm single-center shot for trigeminal neuralgia with sharp dose fall out.

## MOVEMENT DISORDERS

### Parkinson's Disease (PD)

Parkinson's disease is a progressive neurodegenerative disorder caused by dopaminergic cell loss in the substantia nigra. Surgical options require prior confirmation of a good response to dopaminergic therapy.

- **Indication:** SRS is suited for tremor-dominant Parkinson's disease in patients unfit for DBS due to age, comorbidities, anticoagulation, or refusal of invasive surgery.
- **Target:** SRS targets for movement disorders include the ventral intermediate nucleus (VIM) of the thalamus (thalamotomy) and the globus pallidus internus (GPi) (pallidotomy). The VIM is typically targeted 2.5 mm above the Anterior Commissure-Posterior Commissure (AC-PC) plane, one-quarter of the AC-PC distance anterior to the PC plus 1 mm, and 11 mm lateral to the third ventricle—avoiding the VPL to reduce sensory side effects.

SRS targeting the GPi can reduce contralateral dyskinesia, bradykinesia, rigidity, and tremor. The isocenter is placed 2–3 mm anterior to the mid-commissural point, within the GPi and above the optic tract using a 4-mm collimator at the 50% isodose line.

- **Dose:** A dose of 130 - 140 Gy with a 4-mm collimator is most often used. These parameters typically produce lesion typically within 3–9 months.

### Outcomes

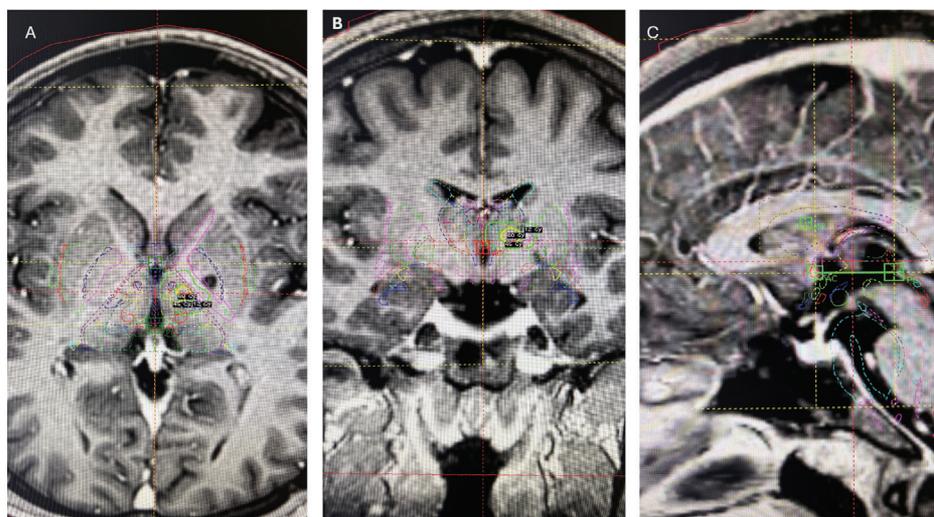
- **SRS Pallidotomy:** Young et al. reported improvement in 64.3% of patients with bradykinesia and rigidity, and in 85.7% of those with dyskinesia. Clinical benefit typically seen in 3–6 months.<sup>15</sup>
- **SRS Thalamotomy:** Régis et al. (99 patients, 60 with >1 year follow-up), found that GKRS (130 Gy, 4-mm collimator) led to 87% tremor improvement and 73% functional gain.<sup>16</sup>
- SRS pallidotomy showed higher complication rates (up to 50%) than thalamotomy, with common adverse events including contralateral hemianopsia and hemiparesis.<sup>17</sup>
- Although the STN is a key DBS target in PD, subthalamotomy is rarely performed due to risks like postoperative hemiballismus, reported in up to 9% of cases.<sup>18</sup>

### Essential Tremor (ET)

ET, the most common movement disorder, causes postural or kinetic tremors, unlike Parkinsonian tremors which occur at rest.

**Indications:** GKRS thalamotomy is suitable for tremor patients refractory to medication who are unfit for invasive surgery due to bleeding risk, anticoagulation, or significant comorbidities making them unfit for general anaesthesia.

- **Target:** VIM of the thalamus (Figure 25.2)
- **Dose:** 130–150 Gy



**Figure 25.2** Radio surgical planning of ventral intermediate nucleus of thalamus on left side with superimposed stereotactic brain atlas.

### Outcomes

- Niranjan et al. reported 93% clinical improvement in ET and tremor-dominant PD following GKRS thalamotomy using 140 Gy, 4-mm collimator, with tremor control in 3–4 months.<sup>19</sup>
- A systematic review by Martínez-Moreno et al. reported 82% clinical improvement after GKRS thalamotomy (130–150 Gy, single 4-mm collimator), with a mean response time of 4.8 months and a 17% complication rate.<sup>20</sup>
- McClelland found SRS to be 40% less costly than unilateral VIM DBS for tremors.<sup>21</sup>

### Dystonia

Dystonia is a movement disorder characterized by sustained muscle contractions that result in involuntary twisting, repetitive motions, or abnormal postures. Dystonia may be hereditary or secondary to factors like birth trauma, infection, toxins, or neuroleptic drugs.

### Indications

- **Target:** GPi is commonly selected as the primary target for treating dystonia. The GPi target for lesioning differs slightly from DBS to avoid damaging eloquent structures. For lesioning, the z-coordinate is at or 1 mm above the AC-PC line, compared to 3–4 mm below in DBS; other coordinates remain similar.
- **Dose:** 130–150 Gy

## Outcomes

Gradual improvement over months, effective in focal dystonias

- Tripathi et al. reported successful GKRS pallidotomy in a 24-year-old with birth asphyxia, with sustained improvement and no motor or visual deficits at 6-year follow-up.<sup>22</sup> Radiosurgical pallidotomy has higher risk of complications because of iron rich zone and radiosensitive lenticulostriate arteries.
- Stancanello et al. reported a favorable outcome after CyberKnife pallidotomy in a dystonia patient with cerebral hypoxia and on anticoagulation.<sup>23</sup>

## Epilepsy

Curative epilepsy treatment was traditionally limited to open microsurgery. Palliative options like Vagal nerve stimulation (VNS), DBS, or disconnection surgeries are used in severe drug-resistant cases unsuitable for resection. Despite promising results, the use of GKRS for epilepsy remains investigational and is typically reserved for highly selected patients. In fact, radio surgical corpus callosotomy is a wonderful palliative procedures for drop attacks and an alternative to conventional disconnection procedures and VNS.<sup>24</sup>

- **Indications:** SRS has been used for medically refractory epilepsy related to cavernous malformations, MTLE, extratemporal foci, and hypothalamic hamartomas (HH).<sup>25</sup>
- **Target:** Hippocampus and amygdala
- **Dose:** 20–25 Gy

## Outcomes

- The ROSE trial demonstrated a 52% seizure freedom rate with SRS, with radiation-induced edema as the primary adverse event.<sup>6</sup> In comparison, Régis reported a 65% seizure freedom rate at two years post-SRS.<sup>7</sup>
- Adverse events reported included transient cerebral edema, new-onset headaches, temporary neurological deficits, and brief seizure exacerbations.<sup>6</sup>
- Slower therapeutic onset compared to open anterior temporal lobectomy
- Preserves cognitive and visual field function better than open surgery

## Psychiatric Disorders

OCD involves distressing obsessions and compulsions that impair daily functioning and are often accompanied by avoidance behaviors. Most patients have persistent symptoms and it significantly decreases the quality of life. OCD is the most commonly treated psychiatric disorder in surgical practice. GKRS treats psychiatric disorders by disrupting specific limbic circuits, relieving symptoms without affecting personality and often improving cognitive function.

- **Indications:** Severe, treatment-resistant OCD and depression who fail all other conventional therapies

### Targets

- Ventral part of the anterior limb of internal capsule (Capsulotomy): most common target
- Cingulate gyrus (Cingulotomy)
- **Dose:** 140–160 Gy

### Outcomes

- Initial studies showed 55–75% improvement in with GKRS anterior capsulotomy.<sup>12,13</sup>
- Sheehan et al. reported 80% clinical improvement and 59–62% Y-BOCS score reduction after a single ventral shot (140–160 Gy) at 24-month median follow-up.<sup>26</sup>
- Higher radiation doses were linked to increased complications, including apathy, memory loss, executive dysfunction, weight gain, incontinence, and sexual disinhibition.<sup>27</sup>
- Use remains restricted due to ethical considerations and the availability of DBS.

### Intractable Pain Syndromes (Nerve Related Pain, Thalamic Pain)

- **Indications:** cancer-related and nonmalignant intractable pain
- **Targets:** posterior medial thalamus or pituitary stalk
- **Dose:** 130–140 Gy

### Outcomes

- SRS provided initial pain relief in 55% of patients, with similar outcomes for cancer-related and nonmalignant pain, though long-term control was limited.<sup>28</sup>
- Adverse effects occurred in 5% of patients, including vertigo, paresthesia, hemiparesis, and radionecrotic cysts.<sup>28</sup>

## LEARNING POINTS

### TN

- GKRS is well-established for TN, offering high efficacy with low complication rates.
- MVD remains the gold standard for refractory TN, but radiosurgery offers similar long-term outcomes with less morbidity.
- Emerging evidence supports GKRS use as a viable primary or salvage treatment option in medically refractory cases.

### Movement Disorders

- SRS thalamotomy offers efficacy comparable to DBS and other lesioning techniques, but lacks neurophysiological feedback and may have variable lesion size, contributing to higher complication rates.

- GKRS thalamotomy is effective, especially for essential tremor, though its use is generally restricted to unilateral procedures.
- GKRS pallidotomy has limited evidence and is associated with a higher risk of visual complications, restricting its use carefully selected cases.
- Despite DBS being the preferred first-line intervention in many centers, SRS remains a valuable non-invasive option in select patients with severe tremor who are not candidates for or decline DBS.

### Seizures

- SRS is an effective treatment for MTLT, with potential cognitive and quality-of-life benefits over open surgery in selected patients.
- It offers a favorable risk-benefit profile for small HH compared to traditional surgical approaches.
- The delayed onset of action is a critical consideration and may prolong seizure activity, increasing the risk of morbidity and mortality.
- SRS is a safe, well-tolerated alternative, particularly valuable in deep-seated or surgically inaccessible lesions like cavernous malformations.

### OCD

- OCD management is complex, and neurosurgical intervention may be considered for carefully selected, treatment-refractory patients.
- GKRS anterior capsulotomy at a dose of 120 Gy is effective and better tolerated than higher-dose protocols.
- GKRS significantly reduces obsessions, compulsions, anxiety, and depression, leading to improved quality of life but patient selection must be meticulous, with ethical oversight.
- As a noninvasive and safe alternative to open neurosurgery, GKRS avoids surgical risks while offering comparable medium- to long-term outcomes.
- It is a suitable option for patients with chronic symptoms seeking a noninvasive and well-tolerated therapeutic solution.

## CONCLUSION

SRS has emerged as a valuable tool in the treatment of various functional neurological disorders, offering a non-invasive, precise alternative to conventional procedures. Its applications span trigeminal neuralgia, movement disorders, epilepsy, psychiatric conditions, and intractable pain, with growing evidence supporting its efficacy and safety. While limitations such as delayed therapeutic onset and variable long-term outcome exist, SRS remains particularly beneficial for patients who are poor surgical candidates or prefer a minimally invasive approach.

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# Management of Intractable Cancer Pain Using Gamma Knife Radiosurgery: A Case Report

Deepak Agrawal ■ Shiva Krishna

## INTRODUCTION

Gamma Knife radiosurgery (GKRS) has been widely adopted for the treatment of various intracranial pathologies, including brain tumors, vascular malformations, and functional disorders such as intractable chronic pain. Historically, surgical or chemical hypophysectomy was employed for managing intractable cancer pain, but these approaches were often associated with significant complications, including panhypopituitarism, diabetes insipidus, and visual dysfunction. In contrast, GKRS offers a non-invasive alternative with a more favorable safety profile. This case report presents a patient with severe cancer-related pain managed with GKRS with pituitary stalk irradiation, providing insights into its clinical application and outcomes.

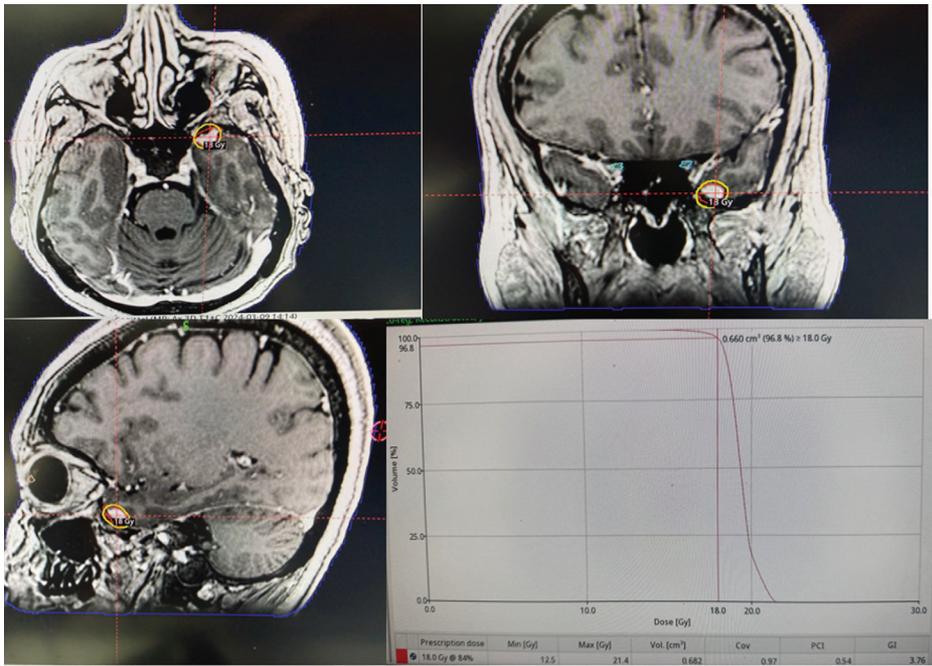
## CASE PRESENTATION

### Patient History

A 43-year-old female with a known history of bronchial carcinoid tumor underwent VATS assisted right lower bilobectomy in 2024. PET-CT showed Tracer avid ill-defined isodense lesion in left temporal lobe treated with Gamma Knife radiosurgery in 2024.

During her first GKRS session, performed for a hypermetabolic lesion in the left temporal pole, imaging revealed a  $7.2 \times 12 \times 11$  mm dural-based lesion abutting the lesser wing of the sphenoid. The lesion was treated with a maximum dose of 18 Gy, while critical structures, including the optic nerve and chiasm, received minimal radiation exposure. Recovery was uneventful, and the patient was discharged on antiepileptics and supportive medications.

Despite initial management, the patient presented with recurrent seizures and debilitating pain—head, neck pain, upper backache and pain in bilateral lower extremities for four months, unresponsive to analgesics.



**Figure 26.1** GKRS to left anterior temporal brain metastasis. 18 GY in single fraction given (in yellow).

### Clinical Examination

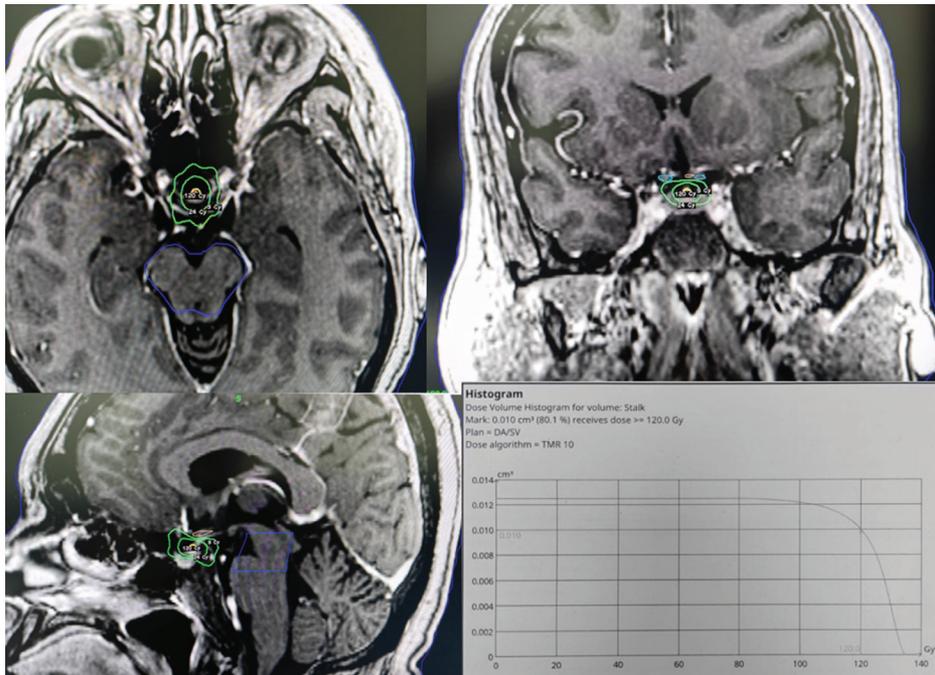
Neurological examination revealed no focal deficits. Contrast enhanced MRI scan and PET-CT scan revealed no new metastases and showed stable disease compared to the prior scan in 2024. Patient reported a VAS score of 8 despite taking Morphine 30mg every 4–6 hours

### Treatment Details

The patient was scheduled for a second Gamma Knife radiosurgery session targeting the pituitary stalk to address her intractable pain. Gamma knife model B machine. Leksell Coordinate Frame G was used for fixation Configuration and planning was done on Gamma plan version 11.3.2. A maximum dose of 120 Gy was delivered, ensuring minimal radiation exposure to adjacent critical structures. 0.012cm<sup>3</sup> of the pituitary stalk was marked for irradiation, 0.010 cm<sup>3</sup> (80.1%) of the pituitary stalk received 120 Gy. Brainstem, bilateral optic nerve and optic chiasma shielding was done. Dose-volume histograms confirmed adequate targeting of the pituitary stalk with protective measures for the brainstem, optic nerves and chiasm.

### Outcome

Post-procedure, the patient reported significant pain relief on day 3, with a VAS score of 4. Morphine dosage was tapered to 30 mg every 12 hourly 3 days after



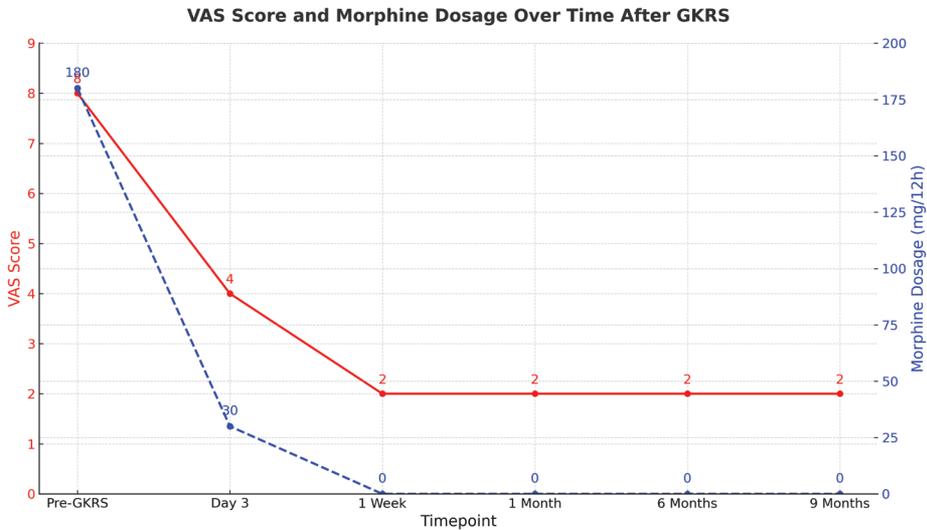
**Figure 26.2** Contrast-enhanced MR axial, sagittal and coronal images of the patient demonstrating pituitary stalk irradiation. 120 Gy in single fraction given (0.01 cc volume, 80.1% receives  $\geq 120$ Gy)

GKRS. On 1 week follow up, patient reported a VAS score of 2, and morphine was completely discontinued, enabling better quality of life and reduced dependency on opioid analgesics, the effect of GKPR showed sustained pain relief on 6 months and 9 months follow up.

## DISCUSSION

Gamma Knife radiosurgery for pituitary stalk irradiation has emerged as a promising modality for managing intractable cancer-related pain.<sup>4</sup> By delivering high-dose targeted radiation, this technique stimulates endorphin release and modulates nociceptive pathways, providing rapid and sustained analgesic effects.<sup>1</sup> Evidence from multicenter studies and case series supports its efficacy in alleviating pain within days of treatment, with minimal complications compared to traditional hypophysectomy.

Historically, surgical and chemical hypophysectomy achieved initial pain relief rates between 75–85% but were limited by serious complications such as diabetes insipidus and hypopituitarism.<sup>6</sup> Modern pituitary radiosurgery maintains comparable or higher efficacy (initial pain relief 95.9%, long-term 73.5%) with markedly reduced morbidity. These findings reinforce the clinical safety and effectiveness observed in our case, in which rapid and sustained analgesia occurred without endocrinological or visual sequelae.



**Figure 26.3** Shows trend in VAS score (in red) and Daily morphine dose (in blue) after GKRS.

The mechanisms of pain relief following pituitary radiosurgery are increasingly understood as multifactorial. Early theories emphasized tumor regression or  $\beta$ -endorphin release, but recent studies propose a broader neuroendocrine modulation hypothesis.<sup>6</sup> High-dose irradiation of the pituitary stalk may induce hypothalamic-pituitary axis modulation, leading to altered release of neuropeptides such as  $\beta$ -endorphins, oxytocin, and vasopressin. Hu et al.<sup>6</sup> introduced the concept of “radio-endocrine modulation,” suggesting that radiosurgery may not simply ablate tissue but instead modulate hypothalamic hormone redistribution, triggering both rapid and long-term analgesia.

High-dose irradiation of the pituitary stalk likely triggers the release of endogenous opioids, including beta-endorphins, which play a key role in pain modulation.<sup>1</sup> Additionally, GKRS may influence hormonal pathways, although the precise mechanisms remain poorly understood. Studies have reported that the analgesic effects often precede noticeable changes in pituitary hormone levels, suggesting a complex interplay of neural and endocrine factors.<sup>3</sup>

In this case, the patient’s pain was refractory to conventional analgesics, including high-dose opioids, underscoring the need for alternative interventions. The rapid pain relief observed post-GKRS aligns with prior studies reporting significant symptom improvement in 80-90% of patients treated for cancer-related pain.<sup>5</sup> The durability of this effect, however, varies among patients, with some experiencing recurrence within months.<sup>2</sup> This variability highlights the importance of patient selection and individualized treatment planning to maximize therapeutic outcomes.

Safety remains a critical consideration in the use of GKRS. Modern dose-planning techniques, as demonstrated in this case, prioritize the protection of critical structures, such as the optic nerves, chiasm, and brainstem, thereby minimizing ad-

verse effects. The absence of hormonal or visual dysfunction in this patient further underscores the potential of GKRS as a safe alternative to traditional hypophysectomy.<sup>1</sup>

The broader implications of this modality extend beyond cancer-related pain to other refractory pain syndromes, such as post-stroke thalamic pain, where similar mechanisms may be leveraged for pain relief. Future directions for research include exploring the long-term efficacy of GKRS in managing cancer-related pain, identifying biomarkers to predict patient response, and optimizing dosimetric parameters to enhance outcomes. Additionally, randomized controlled trials are needed to establish standardized protocols and compare GKRS with other palliative interventions.<sup>5</sup>

## CONCLUSION

This case demonstrates the successful application of Gamma Knife radiosurgery for managing intractable cancer pain. The rapid and sustained pain relief achieved with minimal adverse effects underscores its value as a therapeutic option for patients with advanced malignancies. Future studies should focus on standardizing treatment protocols and exploring its broader applications in pain management.

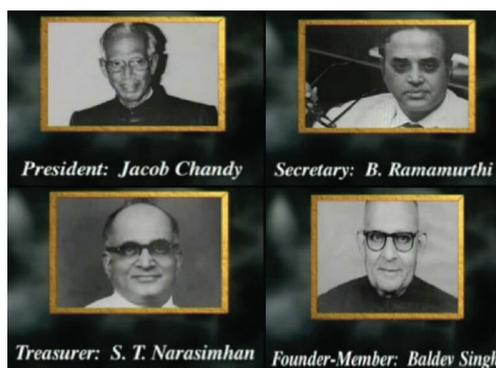
## ACKNOWLEDGMENTS

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# ABOUT THE NEUROLOGICAL SOCIETY OF INDIA (NSI)



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# NSI Handbook of Stereotactic Radiosurgery

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**Deepak Agrawal** is currently a Professor of Neurosurgery and Gamma-Knife at AIIMS, New Delhi. He is a biomedical inventor and holds ten patents to his credit. He has done more than 1200 GK procedures and introduced several innovations in the GK unit at AIIMS. He has also won several national and international awards for his research, including the 'Young Neurosurgeon of the Year' award by the American Congress of Neurosurgeons (CNS). With over 300 indexed publications, he is also the editor of the Journal of Peripheral Nerve Surgery (JPNS), the Indian Journal of Neurotrauma (IJNT), and the Journal of Pediatric Neurosciences (JPN).

Dr. Agrawal's contributions span clinical neurosurgery, device innovation, health systems improvement, and academic publishing, positioning him as a leading figure in Indian neurosurgery.

