CHAPTER

23 Stereotactic Irradiation: CNS Tumors

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The term *radio-surgery* was possibly first used in a medical context more than 90 years ago, when Dr. Francis Hernaman-Johnson described in a lecture to the Royal Society of Medicine an assortment of indications where x-ray therapy might be combined with surgery for benign and malignant indications. From the modern perspective, Dr. Hernaman-Johnson's oration is quaint but wonderfully lyrical, at times invoking Biblical metaphors and Greek fables.[1] Prophetically, though, he concluded with the message that "no human mind can compass the whole field of medicine. Hence the hope of the future lies in specialism [*sic*] tempered by co-operation."

Fast-forward to the mid-20th century, and with the loss of a hyphen along the way, the term *radiosurgery* was repurposed to describe the procedure now widely used as treatment for a variety of benign and malignant intracranial neoplasms as well as a few selected functional disorders. Applying principles of stereotactic surgery and harnessing the tissue- and tumor-ablative potential of ionizing radiation, the Swedish neurosurgeon Lars Leksell designed the first prototype unit for stereotactic radiosurgery (SRS), opening up new clinical opportunities and launching a Hernaman-Johnsonian interspecialty cooperation between neurosurgeons and radiation oncologists that continues to provide valuable clinical service to patients and new insights into tumor and normal tissue biology.

In this chapter we review the distinct technical aspects of SRS, the current understanding of SRS radiobiology, and clinical outcomes after SRS for common indications.

DEFINITION AND TECHNICAL PRINCIPLES OF STEREOTACTIC RADIOSURGERY

In the half-century following Leksell's pioneering work in SRS, numerous other investigators around the world made important contributions to the technical development of SRS. Whereas Leksell eventually settled on a design involving a hemispherical pattern of multiple cobalt-60 sources shielded and arranged so that their output gamma rays would converge on the target, in the 1980s and 1990s various linear accelerator-based SRS platforms were also developed.[2,3] Many of these newer commercially available systems are also capable of delivering other forms of radiotherapy, and there came a period of time when the commonly used terminology describing SRS and non-SRS forms of radiotherapy were somewhat loosely interchanged. Ultimately, the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS), and the American Society for Radiation Oncology (ASTRO) agreed that a uniform description of SRS was required to avoid confusion, and the consensus definition is as follows[4]:

> *Stereotactic Radiosurgery is a distinct discipline that utilizes externally generated ionizing radiation in certain cases to inactivate or eradicate (a) defined target(s) in the head or spine without the need to make an incision. The target is defined by high-resolution stereotactic imaging. To assure quality of patient care the procedure involves a multidisciplinary team consisting of a neurosurgeon, radiation oncologist, and medical physicist.*
>
> *Stereotactic Radiosurgery (SRS) typically is performed in a single session, using a rigidly attached stereotactic guiding device, other immobilization technology and/or a stereotactic image-guidance system, but can be performed in a limited number of sessions, up to a maximum of five.*
>
> *Technologies that are used to perform SRS include linear accelerators, particle beam accelerators and multisource Cobalt 60 units. In order to enhance precision, various devices may incorporate robotics and real time imaging.*

Contained within this definition are references to several essential ingredients of SRS. The treatment is noninvasive and involves external radiation sources or beams. As it is also elaborated in other ASTRO statements concerning SRS,[5] the adjective *stereotactic* implies that the target lesion is localized relative to a fixed three-dimensional spatial coordinate system, using either a rigid head frame or reliable internal fiducial markers (bony landmarks or implanted markers). And, most importantly, SRS is a multidisciplinary endeavor in which the quality of patient care is of paramount importance.

Regarding the issue of patient safety, in 2011 ASTRO issued a white paper concerning quality and safety considerations for SRS and the extracranial application of high dose-per-fraction irradiation, stereotactic body radiation therapy (SBRT).[6] This report highlights structure and process elements that are essential for establishing and operating a clinical program with the proper recognition of the risks involved and attention to detail that maximizes the chance for successful treatment while minimizing the chance of error.

As for any clinical activity involving radiation therapy, developing a culture of safety is crucial.[7] Collegiality and a nonjudgmental atmosphere can contribute to an environment that fosters proactive recognition of ways to avoid systematic problems that might produce potentially harmful errors. In the context of SRS, mistakes can be magnified beyond what might be seen in conventionally fractionated radiotherapy treatments. The fact that an entire treatment course is delivered in only a single or perhaps a few fractions means that a targeting inaccuracy greatly increases the odds of tumor progression via geographic miss. Furthermore, the fact that each individual treatment involves a large amount of ionizing radiation dose deposition means that the risk of injury to normal tissue may be escalated beyond an acceptable range if the delivered dose hotspots drift into adjacent normal brain parenchyma rather than remain in the target volume. A thorough discussion of quality assurance methods in SRS is outside the scope of the present chapter. Among the high-priority tasks are accurate initial commissioning and periodic calibration of the treatment delivery technology, proper personnel training, and various patient-specific preparation routines.[6]

Common to all delivery technology for SRS is the use of multiple nonopposed radiation beams that converge on a

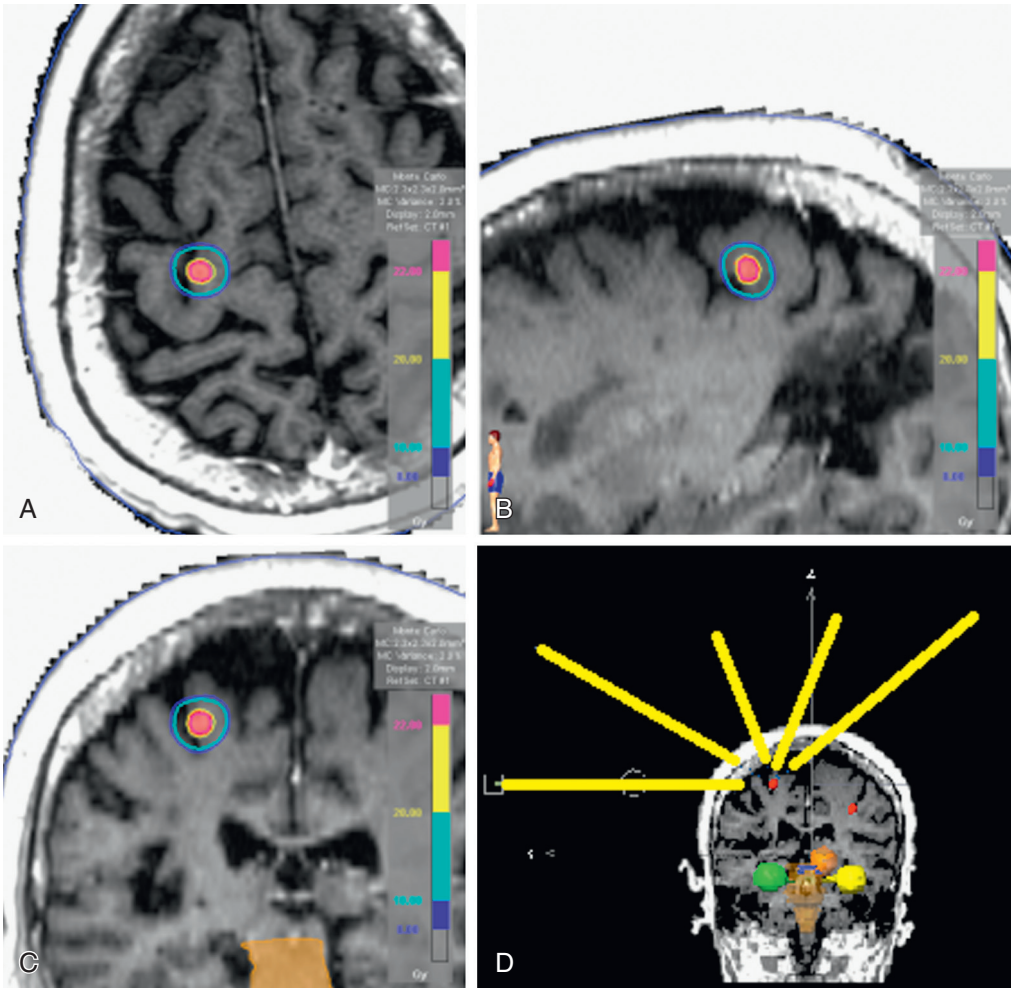

Figure 23-1 Example of an SRS treatment of a right parietal lesion to a prescription dose of 20 Gy, illustrating good conformality. The target is outlined in red and shaded in pink. The 20-Gy prescription isodose volume is outlined in yellow and is shown on axial **(A)**, sagittal **(B)**, and coronal **(C)** planes through the center of the lesion, in all views tightly surrounding the target. The treatment was delivered on a linear accelerator, and panel D is a coronal view showing the angles through which the arcs passed *(yellow lines)*. The beam angles were achieved by table rotations. A separately treated left-sided lesion is also seen in red in that panel, and several normal tissue structures are also outlined.

target in the brain, thus avoiding a high dose to normal tissues in the entrance and exit paths of the beams while depositing an ablative dose within the target volume. The ideal treatment delivery plan achieves a high level of conformality, implying that the volume receiving the prescription dose closely approximates the target volume, thus minimizing the volume of normal tissue exposed to a high dose (Figure 23-1). Unlike the case in some applications of conventionally fractionated radiation therapy, wherein dose homogeneity within the target volume is clinically valuable for cosmetic or other endpoints,[8] for SRS it is generally advantageous to allow for a dose hotspot to be present within the target volume, both for the purpose of increasing the intensity of therapeutic effect and also steepening the gradient of dose falloff into surrounding normal tissues in the brain. This latter goal in particular is often best achieved under the conditions whereby the beam's eye view of the tumor nearly surrounds the contour of the target itself, perhaps with even a "negative margin" where the beam is slightly smaller than the target in cross section—effectively exploiting the fact that the maximum slope of dose falloff outside the beam is generally at the midpoint of the lateral penumbra, a consideration also applicable in SBRT.[9]

THE RADIOBIOLOGY OF STEREOTACTIC RADIOSURGERY

Upon recall of the classic "4 R's" of radiobiology, it is readily apparent that SRS involves considerations that depart from the traditional views of conventionally fractionated radiotherapy. For a single treatment course, the interfraction processes of repair, repopulation, redistribution, and reoxygenation are not relevant realities. Furthermore, for single or extremely hypofractionated regimens, the utility of the popular linear-quadratic model of radiobiological potency has been challenged given the lack of agreement with some preclinical observations and emerging awareness of dose threshold effects that impact tumor and normal tissue responses via vasculature-related events.

By the 1980s SRS had become appreciated as a safe and effective therapy for arteriovenous malformations (AVMs),[10,11] and efforts were initiated to understand the nature of the therapeutic histologic effect on blood vessels in particular. Interestingly, a wide variety of animal models of SRS have been employed to study normal tissue effects including a goat, baboon, and cat, among others.[12-14] Some of these early reports

included experimental single fraction doses on the order of 150 Gy to 200 Gy, and thus their relevance to modern clinical practice, which frequently uses doses an order of magnitude smaller, is uncertain. However, using a dose more closely in line with current human clinical practice, Acker et al at Duke University studied the pial vasculature in a rat using a window chamber model that allowed for repeated direct visual inspection of the in vivo microcirculation.[15]

The experimental setup at Duke included a 4-MV linac fitted with a 2.2-mm diameter collimator. Doses in the range of 15 Gy to 30 Gy were administered in a single exposure, and serial observations were made to characterize the effect on blood flow, vessel density, and leukocyte-endothelial cell interactions. Acute reductions in vessel length density and blood flow were observed at 24 hours postirradiation and continued to become more pronounced 30 days after exposure, without a suggestion of dose-dependence above the level of a 15-Gy dose. Notably foreshadowing a future area of intense focus by others, morphologic changes that included extensive sections of endothelial cell loss were also observed within weeks after irradiation. The authors found this apparently apoptotic effect to be somewhat curious, speculating on its relationship to changes observed in white blood cell interactions with the vessel walls and hypothesizing that platelet-activating factor might play an important role.

This possibility that the tumor vasculature is an important target of radiotherapy is not an especially modern concept and was suggested at least as long ago as 1930, when James Ewing commented that with regard to certain tumors whose cells were thought to be relatively radioresistant, "it seems to me highly probable that the influence is mainly upon the blood vessels, which eventually shrink and cut off the blood supply."[16] However, there was rather limited investigation into this topic specifically between that statement and the SRS-inspired work of the late 20th and early 21st centuries. Many of these studies are cataloged in a recent review by Park et al, who concluded that there appears to be a suggestion of a threshold effect occurring at a fraction size on the order of 10 Gy, above which there appears to be substantial vascular damage that contributes indirectly to a tumoricidal effect.[17]

Perhaps best exemplifying these studies, while also adding fundamental mechanistic insights, is the work of Garcia-Barros et al from Memorial Sloan-Kettering Cancer Center.[18] In the experiments reported in 2003, these investigators implanted MCA/129 fibrosarcomas and B16F1 melanomas into mice that were either genetically wild type or deficient in acid sphingomyelinase (asmase), an enzyme needed for endothelial cell apoptosis. For both tumor cell types, host asmase deficiency was associated with radioresistance as evidenced by significantly enhanced tumor growth delay after a single dose of 15 Gy. Confirmatory assays of endothelial apoptosis reported in the same paper demonstrated that the effect occurs acutely, peaking within 3 to 6 hours after exposure. Additionally, there is an apparent threshold dose for inducing endothelial apoptosis between 7 Gy, where essentially zero apoptosis was seen, and 11 Gy, where the percentage of apoptotic cells in asmase wild type jumped up to approximately 20%. There was a continued increase in percentage of apoptotic endothelial cells up to approximately 60% with a dose of 25 Gy, the upper limit of dose evaluated in this study. As will be discussed, the profound vascular effects of SRS are also well illustrated clinically by the frequently successful obliteration of complex intracranial AVMs when using single fraction doses in the upper range of what was tested here preclinically.

For fractionated radiotherapy the most frequently applied mathematical model to relate radiation dose to expected tumor cell kill is the linear-quadratic (LQ) model, based on a formula that first appeared in Lea and Catcheside's description of the relationship between radiation dose and incidence of chromosomal translocations, using a plant model.[19] Although this model has been the most popular in recent decades and is discussed elsewhere in this book, sometimes overlooked in the original publication by Lea and Catcheside is recognition that for high dose exposure, there would in principle need to be a correction applied to the LQ model that accounted for a decaying effect when the dose is delivered over a prolonged interval, presumably related to what amounts to intrafractional repair as some radiation-induced single-stranded breaks recombine without translocation. Experimental data supporting this possibility in mammalian cells may be found in the work of Eley et al, who used a glioma cell line and modeled SRS-type dose effects, comparing radiosensitivity when the same 12-Gy dose was given either in a single brief exposure or else in a series of smaller exposures spread out over 1 hour.[20] The intent was to simulate SRS treatments that might be delivered clinically using multiple beam angle and table position changes, thus effectively prolonging the time of dose delivery. The results revealed that the cells underwent detectable cell cycle arrest at the G2/M after the first subfraction in intermittent exposure conditions and that this effect was associated with relative radioresistance, consistent with the Lea-Catcheside predictions.

In view of the vascular threshold dose effects and possible intrafraction repair effects, among other differences from fractionated radiotherapy, an argument can be made that alternatives to the LQ model are needed.[21] Indeed, numerous groups have proposed alternative models to characterize the relationship between radiation dose and tumor cell kill when doses in the realm used for SRS or SBRT are employed. For example, Guerrero and Li proposed a modified LQ (MLQ) model based largely on the lethal-potentially lethal model of Curtis,[22] except they proposed a new term, δ, to account for repair kinetics related to dose rate. In a model that combines elements of LQ formalism and a multitarget model, Park et al at the University of Texas–Southwestern Medical Center have described a "universal survival curve" (USC) that involves a step function: LQ estimates apply below a certain dose per fraction, but above a transition dose, D_T, there is a correction that effectively straightens the curve to maintain a linear relationship between dose and log cell kill above D_T.[23] The purpose of this construct is to match the true relationship between high dose exposure and log cell kill, which tends to be overestimated by the LQ model. The USC model may be used to derive a convenient index of radiobiological potency, the single fraction equivalent dose (SFED), by which different SRS or SBRT regimens might be compared. When the dose per fraction, d, exceeds D_T, SFED is calculated as follows:

$$SFED = D - (n-1)D_q$$

where D is the total dose, D_0 is the dose required to reduce the surviving fraction of cells to 37%, n is the total number of fractions, and D_q is the quasi-threshold dose of the multitarget model. The SFED metric has been demonstrated to describe a dose-control relationship for a variety of tumor types treated with SBRT.[24,25]

To gauge the true dose-related normal tissue toxicity risk in clinical settings, even the best predictive mathematical models are not a substitute for careful analyses of actual clinical data. The QUAntitative estimates of Normal Tissue Effects in the Clinic (QUANTEC) project was sponsored jointly by the American Association of Physicists in Medicine (AAPM) and ASTRO. Medical physicists, radiobiologists, and radiation oncologists from across North America, Europe, and Asia participated. The group's charge was to catalog, review, analyze,

and summarize all published literature concerning the quantitative relationship between dose of ionizing radiation and injury to normal tissues, with the intent of identifying practical guidelines for normal tissue dose constraints based not on models but on actual patient observations. Of direct relevance to SRS are the QUANTEC reports on radiation effects in the brain, brainstem, and optic nerves and chiasm.[26-28]

In each case there are acknowledged limitations concerning the quantitative data available for analysis; nevertheless the QUANTEC papers do offer dose-volume parameters that are clinically useful in the design and evaluation of SRS treatment plans for individual patients. Largely influenced by the synthesis of numerous reports involving the treatment of AVMs and subsequent risk of radionecrosis, the authors of the QUANTEC brain paper concluded that toxicity increases rapidly once the volume of the brain exposed to >12 Gy is >5 cm^3 to 10 cm^3.[26] An added caveat is that eloquent areas of the brain such as the brainstem or corpus callosum require extra caution.

The QUANTEC brainstem summary is mainly concerned with tolerance to fractionated radiotherapy, given the larger number of studies available for that setting relative to the setting of brainstem SRS and, in particular, the paucity of long-term reports after SRS to brainstem metastases.[27] One clinical indication for SRS in which long-term follow-up is typically available is for the treatment of acoustic schwannomas, a benign condition with negligible risk of mortality to the patient. Here, the dose to the brainstem is primarily just a glancing focus of scattered dose away from the actual target; a maximum point dose of less than 12.5 Gy is associated with a low risk of new cranial neuropathy in that setting. Regarding injury to the optic nerves or chiasm, the QUANTEC reviewers found that the risk of radiation-induced optic neuropathy in the more modern context of MRI-aided planning is low, with a maximum point dose of ≤12 Gy to the optic apparatus.[28] Figure 23-2 provides an illustration of a patient treated with SRS where the tumor approached the chiasm, necessitating caution with the optic chiasm dose.

CLINICAL OUTCOMES

In Leksell's report describing the first 762 cases treated with SRS at the Karolinska Institute, the three most common diagnoses were AVMs, Cushing disease, and acoustic neuromas.[29] No brain metastases were treated, and a large percentage of the cases were functional disorders such as trigeminal neuralgia, intractable pain elsewhere in the body, or pituitary tumors. Nowadays, the most common indication for SRS is brain metastases. Although many of the diagnoses treated in the early years by Leksell are still managed by SRS today, others such as Parkinsonism or anxiety or obsessive-compulsive disorder are managed with other interventions.

Pituitary Tumors

It is difficult to summarize the full spectrum of literature on SRS, primarily because there have been so many papers involving so many patients. In an encyclopedic review of recent series, Sheehan et al identified 25 separate reports published between 2002 and 2013 concerning SRS for nonfunctioning pituitary tumors alone.[30]

A representative series, that is also the largest published experience, would be the multicenter retrospective study of the North American Gamma Knife Consortium.[31] Among 512 patients with nonfunctional pituitary adenomas, 94% had prior resection and 7% had prior fractionated radiotherapy, the median age at the time of SRS was 53 years. Most patients had some degree of baseline pre-SRS hypopituitarism. The median SRS dose to the tumor margin was 16 Gy. The actuarial rate of tumor control, assessed radiographically, was 95% and 85% at 5 and 10 years post-SRS, respectively. New or worsened hypopituitarism after SRS was noted in 21% of patients, most commonly manifest as thyroid or cortisol deficiencies. Prior fractionated radiotherapy and higher tumor dose were associated with a higher risk of endocrinopathy. New or progressive cranial nerve deficits occurred in <10% of patients. In multivariate analysis, decreasing age, increasing volume, prior fractionated radiotherapy, and prior pituitary axis deficiency were predictive of new or worsening cranial nerve dysfunction. No patient died as a result of tumor progression. The authors concluded that SRS is effective and well-tolerated for recurrent or residual nonfunctional pituitary adenomas. A marginal dose of 16 Gy to 18 Gy, lower if needed to constrain the maximum point dose to the optic pathway structures below 10 Gy to 12 Gy, appears a reasonable consideration in this setting.

Functioning pituitary adenomas are also commonly treated with SRS, and likewise there have been dozens of studies published since 2000.[30] A key difference in both clinical goal and follow-up evaluation is that the intent is to achieve endocrine normalization that is evaluable by serum or other assay. Table 23-1 includes a summary of the five largest series of SRS for Cushing disease or acromegaly published since 2007. Note that the doses employed are typically higher than for nonfunctioning tumors; prescription doses on the order of 20 Gy to 25 Gy are considered reasonable. Also, there is typically a delay of 1 to 2 years after SRS before the endocrine remission is achieved. Limited data suggest that it might be advantageous to discontinue pharmacological suppression of pituitary hormonal secretion at the time of SRS, possibly because the octreotide reduces the metabolic activity and proliferative activity within tumor cells, allowing opportunity for repair of radiation damage.[40]

AVM

Steiner et al at the Karolinska Institute are credited with the first use of SRS in the management of an AVM.[41] A dose of 25 Gy was prescribed in an effort to obliterate the fistulous point of a sizeable AVM. Success was achieved, and since then. SRS has emerged as an important modality in the treatment of AVM. Numerous centers have reported clinical outcomes in large series, not infrequently including 500 or more patients.[30] Representative series from the University of Pittsburgh and the University of Virginia document an obliteration rate in the range of 70% or higher with a low risk of serious toxicity, with doses in the range of 20 Gy to 25 Gy for small lesions (<4 cc), and somewhat lower doses for larger lesions.[42,43] In the latter analysis, factors associated with a favorable outcome included no prior hemorrhage, AVM in a noneloquent location, and AVMs with a volume of less than 4 cc. When the target volume exceeds 10 cc to 12 cc, consideration is given to a staged treatment regimen, whereby portions of the lesion are treated to a dose of 16 Gy to 18 Gy, followed by a break of 4 to 6 months, and then SRS to another portion.[44]

Meningiomas and Other CNS Tumors

SRS can play an important role in the management of intracranial and skull-based meningiomas. Although most are benign low-grade tumors, these neoplasms may develop in locations that can cause symptoms indirectly via mass effect on eloquent areas such as the brainstem or motor cortex or can directly cause pain and threaten cranial nerve functional compromise if located along the skull base. Numerous single-institutional experiences have been published on this

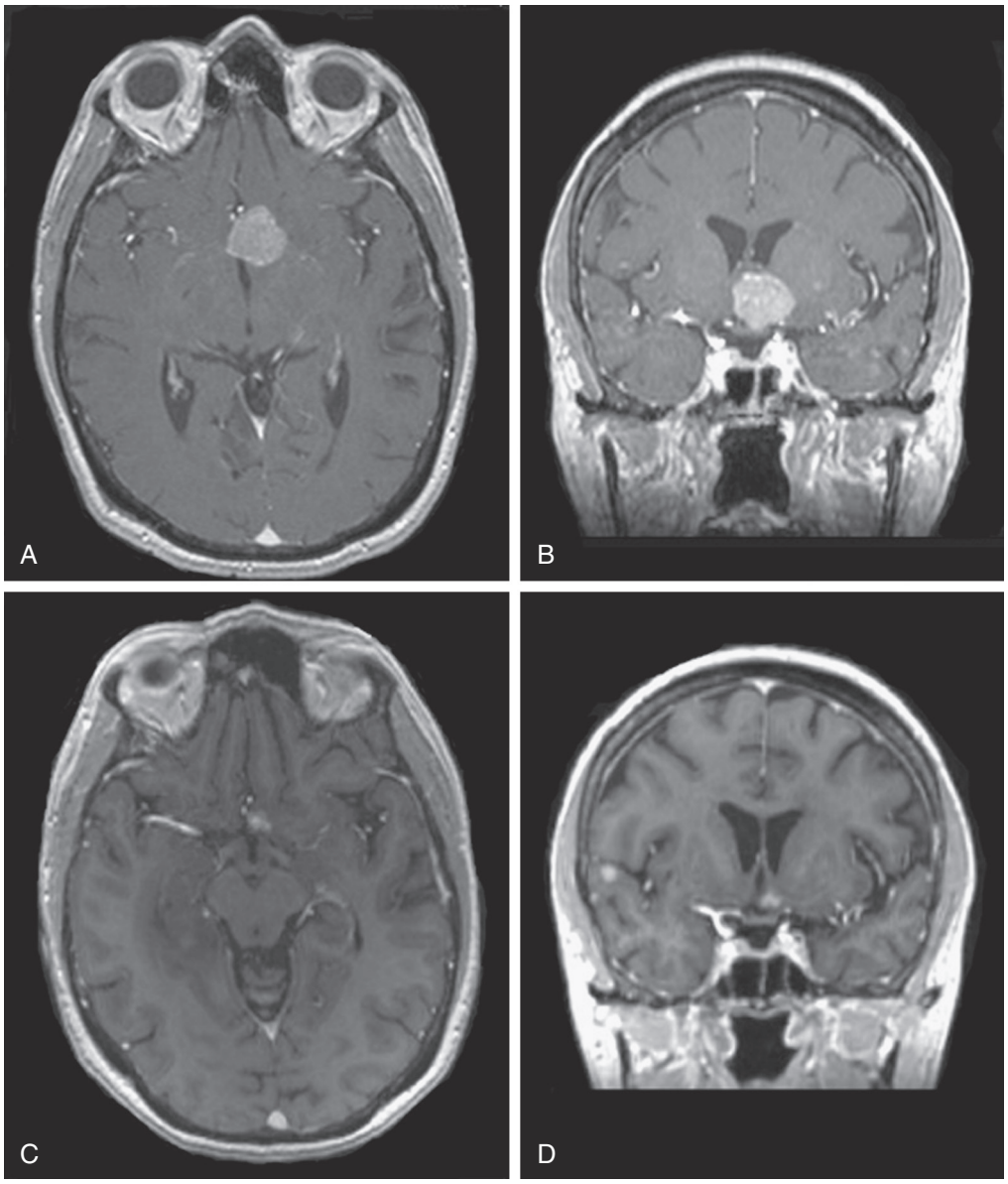

Figure 23-2 The patient is a 54-year-old woman with a history of metastatic non–small cell lung cancer. She underwent stereotactic radiosurgery (SRS) to treat a left perioptic brain metastasis. The tumor was treated in a single session with a margin dose of 16 Gy and a maximum point dose to the optic pathway of 12 Gy. The metastatic lesion is shown on the pre-SRS postcontrast axial **(A)** and coronal **(B)** magnetic resonance imaging (MRI). Six months later, the patient's visual fields and acuity were stable. Her tumor had markedly regressed as demonstrated by the follow up postcontrast axial **(C)** and coronal **(D)** MRIs. Of note, **D** shows a new metastatic lesion in the right Sylvian fissure region that was later treated with SRS.

TABLE 23-1 Summary of Selected Recent Series of Stereotactic Radiosurgery (SRS) for Cushing Disease or Acromegaly

First Author [Reference]	Number of Patients	Mean or Median Follow-Up, Months	Mean or Median Margin Dose, Gy	Endocrine Remission (%)
SRS for Cushing Disease				
Castinetti[32]	40	54.7	29.5	42.5
Jagannathan[33]	90	45	23	54
Petit[34]	33	62	20	52
Wan[35]	68	67.3	23	27.9
Sheehan[36]	82	31	24	54
SRS for Acromegaly				
Jagannathan[37]	95	57	22	53
Losa[38]	83	69	21.5	60.2
Wan[35]	103	67.3	21.4	36.9
Sheehan[36]	130	31	24	53
Franzin[39]	103	71	22.5	60.7

Adapted from Sheehan JP, Yen C-Y, Lee C-C, Loeffler JS: Cranial stereotactic radiosurgery: current status of the initial paradigm shifter. J Clin Oncol 32(26): 2836-2846, 2014.

indication for SRS. A representative example is the most recent update of the Mayo Clinic experience, in which Pollock et al reported on 251 patients treated between 1990 and 2008.[45] The mean patient age was 59 years. Most of the tumors were located in the skull base or tentorium. The mean treatment volume was approximately 8 cc, and the mean tumor margin dose was 16 Gy. After a mean follow-up of more than 5 years, only 3 patients had manifested in-field tumor progression. There was radiographic evidence of tumor size decrease in more than 70% of patients, and no patient died of radiation-related complications. No radiation-induced tumors were observed.

Santacroce et al reported a large European multicenter experience of SRS for meningiomas in 2012.[46] A total of 15 centers contributed data to the retrospective analysis. The median tumor volume was 4.8 cm^3, and median dose to tumor margin was 14 Gy. The median imaging follow-up was 63 months. Similar to the Mayo Clinic experience, the volume of treated lesions was noted to decrease in 58% of cases and remained unchanged in another 34.5%, for a crude local control rate of 92.5%. Tumor control was higher for imaging-defined tumors, female gender, and for skull base compared to convexity tumors.

Prescription dose selection is often influenced by tumor location. For lesions near the cerebellopontine angle, a marginal dose on the order of 13 Gy to 14 Gy is generally advisable,[47] especially considering the need to respect adjacent normal tissue dose constraints. The QUANTEC recommended limit for maximum point dose to the brainstem is 12.5 Gy.[27] For locations where critical structures are not dose-limiting, a marginal dose in the range of 15 Gy to 16 Gy is reasonable.

SRS can also play a role in an assortment of less common indications. This includes recurrent hemangiopericytomas[48-50] and recurrent high-grade glioma,[51,52] among others. Acoustic neuromas (also called vestibular schwannomas) are also commonly treated with SRS[53]; an example case is shown in Figure 23-3.

Brain Metastases

By far the most common current indication of SRS is in the management of brain metastases. In this regard, there are abundant retrospective and also numerous prospective clinical studies.

Because a patient who develops one or more brain metastases is then known to have a risk of manifesting other lesions later, one clinical question that has been asked often asked is whether adjuvant whole brain radiation therapy (WBRT) provides clinical benefit by eradicating occult micrometastases in the brain present at the time of diagnosis with brain metastases. Table 23-2 contains a summary of the four randomized studies performed in the last decade that compared the outcomes of patients who had initial SRS or surgical resection (S) followed by observation or WBRT.[54-57] In addition to the criteria shown in the table, in each study, eligibility typically required good performance status and stable systemic disease. The SRS dose employed was in the range of 18 Gy to 25 Gy. The lack of survival benefit with the addition of WBRT is generally explained by the success of salvage therapy for subsequent brain relapse, which effectively equalizes the chance for durable survival. Additionally, in the study by Chang et al at the M. D. Anderson Cancer Center, the primary endpoint was cognitive decline, and the trial had to be stopped early because of excessive neurocognitive toxicity 4 months after treatment in the WBRT arm. Likewise, in the European Organization for Research and Treatment of Cancer (EORTC) study, a secondary analysis of Health-related Quality of Life (HRQOL) revealed that patients in the observation only arm reported better HRQOL scores than did patients who received WBRT.[58] The differences were statistically significant and clinically relevant, especially during the early follow-up period. Taken together, these studies support a strategy of initial S or SRS for patients with limited brain metastases, followed by close surveillance and salvage therapy later as needed.

Another question commonly asked with regard to SRS for brain metastases is whether there is an upper limit of lesions above which SRS is not appropriate and WBRT should be employed instead. Although the diagnosis-specific graded prognostic assessment index includes number of lesions as a component for certain histologies, it does not address how those patients are ideally managed.[58a] Numerous recent reports have indicated that a patient's prognosis, when treated by SRS, is predominantly driven by performance status and other factors and not the number of lesions. For example, in the M. D. Anderson experience reported by Likhacheva et al, a total of 251 patients underwent SRS for initial treatment of brain metastases.[59] SRS was used as the sole management for most patients but was combined with salvage treatment with SRS, WBRT, or resection on about one third of cases. The median number of brain metastases was 2 (range, 1 to 9). The median overall survival (OS) was 11.1 months. On multivariate analysis, statistically significant predictors of OS were

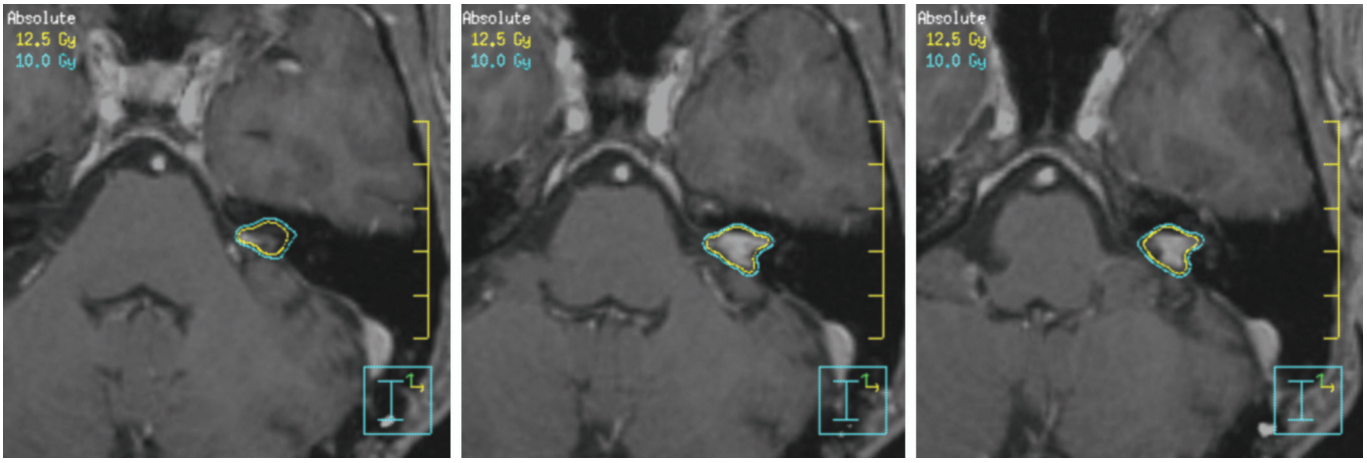

Figure 23-3 Three selected axial cuts through a vestibular schwannoma showing the resulting conformal treatment plan using four different isocenters. The gadolinium contrast enhanced thin slice T1-3D-SPGR MRI data set has been fused to the underlying stereotactic computed tomography (CT) to visualize the vestibular schwannoma. The 12.5-Gy treatment isodose line and the 10-Gy isodose line are shown.

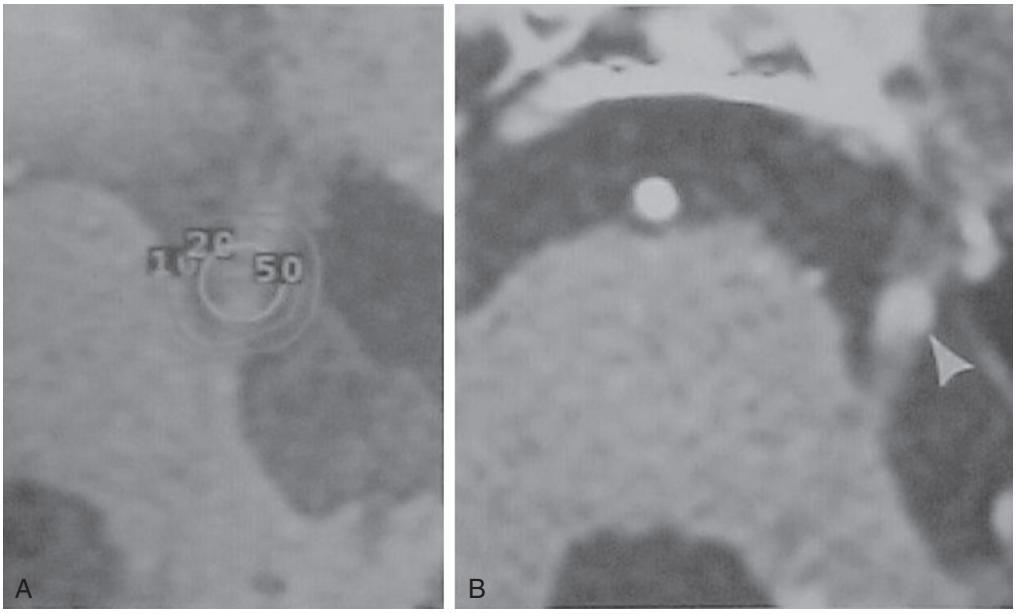

Figure 23-4 **(A)** Typical Gamma Knife radiosurgery dose distribution for trigeminal neuralgia targeted at the root entry zone of cranial nerve V (CN V). The prescription dose is typically 70 Gy to 90 Gy prescribed to the 100% isodose line. **(B)** Magnetic resonance imaging (MRI) 6 months after radiosurgery demonstrating radiographic changes on CN V.

TABLE 23-2 Randomized Studies of Stereotactic Radiosurgery (SRS) versus SRS or Surgery (S) Plus Whole Brain Radiation Therapy (WBRT) for Patients with Brain Metastases

First Author [Reference]	Eligibility	Number of Patients	Median OS (mo.) No WBRT	Median OS (mo.) + WBRT	Comment
Aoyama[51]	1-4 lesions <3 cm diameter	132	8.0	7.5	
Muacevic[52]	1 resectable lesion <3 cm diameter	70	10.3	9.5	SRS vs S + WBRT
Chang,[53] MDACC	1-3 lesions <3 cm diameter	58	15.2	5.7	Trial stopped early because of neurocognitive toxicity in WBRT arm
Kocher,[54] EORTC	1-3 lesions <3.5 cm if 1 <2.5 cm if >1	359	10.9	10.7	SRS or S alone or plus WBRT

EORTC, *European Organization for Research and Treatment of Cancer;* MDACC, *M. D. Anderson Cancer Center;* OS, *overall survival.*

presence of extracranial disease, total tumor volume greater than 2 cc, age ≥60 years, and diagnosis-specific graded prognostic assessment. The number of brain metastases was not predictive of OS or distant brain failure.

Other data indicating that there does not appear to be a number of brain metastases above which SRS is contraindicated are recently reported Japanese experiences. The Japanese Leksell Gamma Knife (JLGK) Society undertook a prospective study of SRS without WBRT (JLGK 0901) to establish evidence that such a treatment strategy is feasible for 5 to 10 brain metastases. A preliminary report showed that the overall survival for patients with 5 to 10 brain metastases was almost the same as that of patients with two to four brain lesions.[60] More recently reported analyzes are confirmatory.[61]

Functional Disorders

Although a variety of functional disorders have been treated with SRS over the years, the currently most common and widely accepted functional indication for SRS is for medically refractory pain from trigeminal neuralgia.[62] The typical dose given is 70 Gy to 90 Gy prescribed to a point located near where the fifth cranial nerve exits the brainstem (Figure 23-4). In a representative study from the University of Maryland, 112 patients were treated with SRS to a median prescription dose of 75 Gy (range, 70 Gy to 80 Gy).[63] Among 95 who were compliant with follow-up surveys, the median follow-up was 5.6 years (range, 1 year to 10 years). Before SRS 88% of patients had inadequate control or severe pain on medication, whereas the remainder described some pain but controlled on medication. After SRS 64% reported no pain and no requirement for medications, 5% had no pain but were still on medication, 12% had some pain controlled on medication, and the rest still had inadequate pain control. The median time to response was 2 weeks (range, 0 weeks to 12 weeks), and the median response duration was nearly 3 years. The actuarial rates of freedom from treatment failure at 1, 3, 5, and 7 years were 60%, 41%, 34%, and 22%, respectively. Response duration was significantly better for those who had no prior invasive treatment versus those in whom a previous surgical intervention had failed (32 versus 21 months, $p < 0.02$).

CONCLUSIONS

SRS is an established method of ablating brain metastases and AVMs as well as treating certain benign intracranial neoplasms and trigeminal neuralgia. Careful patient selection is important and is best done within the context of a multidisciplinary team approach involving the radiation oncologist, neurosurgeon, and other caregivers involved in the patient's management. With proper attention to technique and an especially thoughtful respect for normal tissue dose tolerances, SRS achieves a clinically valuable result in the majority of patients and has a low risk of serious toxicity.

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