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The biology of radiosurgery and its clinical applications for brain tumors

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Stereotactic radiosurgery (SRS) was developed decades ago but only began to impact brain tumor care when it was coupled with high-resolution brain imaging techniques such as computed tomography and magnetic resonance imaging. The technique has played a key role in the management of virtually all forms of brain tumor. We reviewed the radiobiological principles of SRS on tissue and how they pertain to different brain tumor disorders. We reviewed the clinical outcomes on the most common indications. This review found that outcomes are well documented for safety and efficacy and show increasing long-term outcomes for benign tumors. Brain metastases SRS is common, and its clinical utility remains in evolution. The role of SRS in brain tumor care is established. Together with surgical resection, conventional radiotherapy, and medical therapies, patients have an expanding list of options for their care. Clinicians should be familiar with radiosurgical principles and expected outcomes that may pertain to different brain tumor scenarios.

Keywords: brain tumor, metastases, radiobiology, radiosurgery, schwannoma.

Biological Effects of Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) uses stereotaxis, image guidance, and beams from multiple vantage points to deliver a precise and high dose of radiation to a chosen target volume.[1] Use of this technique allows high-dose radiation to be delivered to a target volume containing healthy or pathological tissue while minimizing significant acute or late radiation damage to adjacent tissues.

In addition to differences in target volume size between SRS and conventional radiotherapy, there are differences in biological effects between these 2 modalities. Well known are the 5 principles described by Withers and Peacock regarding radiation of tumors[2,3] including:

- Repair of sublethal damage
- Reoxygenation of the tumor
- Reassortment or redistribution within the cell cycle
- Repopulation or regeneration of surviving normal and malignant cells
- Radiosensitivity

The effectiveness of conventional radiotherapy is based on an interplay of these principles in which repair and repopulation increase tumor cell survival, while reassortment, reoxygenation, and radiosensitivity increase tumor cell kill. One can envision advantages and disadvantages in the case of brain tumors based on how radiation might be utilized. Some of these may be real and some only potential. One potential radiobiological disadvantage of SRS, or even any hypofractionated regimen, is inability to exploit cell cycle redistribution. Single-fraction SRS may not result in improved cell kill compared with a protracted conventional radiotherapy regimen because cells do not have time to redistribute into more radiosensitive phases (G2 and M) of the cell cycle. A second potential radiobiological disadvantage of single-fraction SRS is inability to exploit reoxygenation in hypoxic tumor cells, which is another potential advantage of conventional radiotherapy. However, a potential radiobiological advantage of SRS is its ability to limit tumor cell repopulation, a disadvantage seen in conventional radiotherapy. Another potential radiobiological advantage of single-fraction SRS is enhanced antitumor immunity after tumor irradiation, commonly known as the abscopal effect. Based on clinical evidence for melanoma, irradiation with hypofractionated radiation, and potentially SRS, to a tumor at one site can contribute to antitumor immunological rejection of a metastatic lesion at a distant site.[4] In this case of the observed abscopal effect, radiation was given concurrently with

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ipilimumab. This phenomenon was also demonstrated with a hypofractionated regimen of 30 Gy in 5 fractions, concurrent with ipilimumab, to a patient with metastatic lung adenocarcinoma who demonstrated complete response at the initial site and at all distant sites of disease.[5] Of course, for any specific tumor, the relative importance of any of these concepts is unclear. Actual clinical outcomes are more important than theoretical considerations and have helped to modify some established tenets of biology. Based on clinical outcomes, SRS is an effective treatment modality for functional disorders, arteriovenous malformations, benign brain tumors, and malignant brain tumors.[6]

The linear-quadratic (LQ) model has been used to calculate the effects of ionization radiation to normal and neoplastic cells, calculate isoeffect doses between different therapeutic regimens, and describe tumor cell kill (through 1 or 2 tracks resulting in chromosome breaks) with these 5 principles in mind. Although these principles are often applied to conventional radiotherapy, the main difference between conventional radiotherapy and SRS is the size of the dose delivered and the target volume. More importantly, the technology used in SRS allows delivery of high doses of precise and accurate radiation, with a steep dose fall-off to a defined target during one procedure to provide a powerful radiobiological effect. This is accomplished while sparing more normal tissue such as surrounding brain.[7]

The alpha beta ratio (α/β ratio) is based on preclinical and clinical data and is $\sim$2 for tissue in the CNS, 3 for late-responding tissues, and 10 for early responding tissues. The α/β ratio is also necessary when calculating the LQ equation to determine the dose equivalent to a conventional radiotherapy regimen[8]. These ratios can then be used to help determine the dose for tumor control while minimizing normal tissue toxicity. In general, malignant tumors such as brain metastases and malignant brain tumors have higher α/β ratios, estimated to be closer to 10 and representative of early responding tissues, while slow-growing benign brain tumors such as pituitary adenomas, arteriovenous malformations (AVMs), and benign meningiomas have lower α/β ratios, estimated to be closer to 3 and representative of late responding tissues.[8,9] Regardless of the uncertainties of the true α/β ratios of all tumors, especially in the brain, the overall goal of SRS is to provide highly conformal treatment with radiation to the tumor while sparing normal CNS tissue surrounding the target volume.

The radiobiology and application of the LQ model to SRS continues to be a matter of investigation and debate because clinical results have validated application of the LQ model to radiation doses within the dose range of 1 Gy to 5 Gy per fraction.[10] Using this dose range, the LQ model has been used to approximate in vitro clonogenic survival. Single doses $>$5 Gy, which are commonly used in SRS, are considered by some to affect the validity of the LQ model.[11,12] The use of the LQ model is theorized to underestimate tumor control at the high doses commonly used in SRS and do not reflect other mechanisms involved in tumor cell kill. In addition to mechanisms of DNA strand breaks and chromosome aberrations by conventional radiotherapy, SRS with doses $>$10 Gy per fraction are hypothesized to cause vascular damage resulting in decreased blood perfusion and leading to indirect tumor cell death.[13] This was observed in experimental tumors using human tumor xenografts and rodent tumor models. Likewise, others have considered application of the LQ model to SRS to be inappropriate due to the LQ model not representing observed clinical data, with data extracted from in vitro rather than in vivo observations and not accounting for the impact of radioresistant cancer stem cells.[11]

Others have proposed use of alternate models such as the lethal-potentially lethal (LPL) model that may be used for large fraction/acute doses. However, the LPL model is limited by its general applicability to clinical data. Modification of the LQ model, otherwise known as the modified LQ (MLQ) model, introduces a parameter characterized not only by in vitro cell survival data of human tumor cell lines but also by in vivo animal isoeffect curves, which results in closer fitting of isoeffect data than the original LQ model. This has resulted in better approximation of the radiobiological effects of high single doses of irradiation, as used in SRS. The use of this model is not only consistent with the LPL model but also retains the generalizable characteristics of the LQ model.[14,15] Although there continues to be much debate regarding the application of the LQ model to SRS, it is clear that use of this modality induces DNA damage (double and single stranded breaks). In addition, as seen in Gamma Knife radiosurgery (GK), dose heterogeneity from higher central doses provides a radiobiological advantage not seen in conventional radiotherapy therapy for small to moderately sized target intracranial target volumes.[16] Other radiosurgery platforms also have dose heterogeneity, but doses are prescribed to the 80%–90% isodose line and result in reduced dose heterogeneity. Even within conventional radiotherapy, small volume "hot spots" are noted that are 5%–10% above the prescription dose. These are quite small compared with the 100% increase in GK plans prescribed to the 50% isodose line.

Biological Effects on Cranial Nerves

SRS is also used in functional disorders such as trigeminal neuralgia, and its effects have been studied in primate models. A single 4 mm isocenter with a maximal dose of 80 Gy or 100 Gy was targeted to each proximal trigeminal nerve anterior to the pons. Compared with a control group, the histological effects of treatment were studied using light and electron microscopy. Nerves irradiated to 80 Gy demonstrated focal axonal degeneration and mild edema, while nerve necrosis was identified in nerves irradiated to 100 Gy.[17] These findings were confirmed in rhesus monkey models with little impact on the structure of the trigeminal nerve at 60 and 70 Gy and with axonal degeneration and demyelination at 80 Gy and neuronal necrosis at 100 Gy.[18] These histological changes provide a better understanding of trigeminal neuralgia treated with SRS and it clinical effects and also of normal brainstem effects from doses used to manage brain tumors.

Blood Vessels

SRS is believed to cause a proliferative vasculopathy within the blood vessels of an AVM, and similar effects can be seen in benign tumors. The process of vasculopathy begins with endothelial cell injury secondary to exposure to high doses of ionizing radiation.[19,20] Following endothelial cell injury, vessels

become hyalinized and thickened, leading to luminal closure. When this response becomes chronic, gliotic scarring or fibroblasts replace much of the AVM. Myofibroblasts lead to wall contraction and subsequent obliteration of the AVM.[21] In addition to induced thrombosis, 75% of AVM vessels are completely obliterated by 2–3 years.[22,23,24]

Recent preclinical studies in rat models hypothesized correlation with Notch1 and 4 signaling pathways and development of AVMs. Use of SRS to 25 Gy demonstrated enhanced apoptotic activity and inhibited expression of Notch receptors. This resulted in reduction of size and thrombotic occlusion of nidus vessels in a rat model of AVMs.[25] The clinical effects in targeting blood vessel malformations are well published.[26,27]

In the clinical setting, SRS is a widely accepted management option for patients with AVMs. The use of SRS in patients with high-grade or Spetzler-Martin grades IV and V AVMs can result in high and unacceptable rates of morbidity and mortality when addressed with microsurgery. Use of median prescription dose of 19 Gy to a median AVM volume of 5.7 cc has demonstrated cumulative obliteration in 44% of treated patients, with a median time to obliteration measured at 43 months.[26] SRS in patients with low-grade or Spetzler-Martin grades I and II AVMs has demonstrated a cumulative obliteration rate of 76%, with median time to obliteration measured at 40 months. Predictors of obliteration included no prior embolization, decreased AVM volume, single draining vein, and lower AVM scale score.[27]

Benign Tumor Stereotactic Radiosurgery

SRS is performed frequently on benign tumors, and published outcomes are now available for virtually all intracranial tumor types. However, since the majority of treated patients remain alive and few have had their tumors removed, little tissue has been available for histological study to evaluate the effects of SRS. In one series, the goal was to study the histopathological changes associated with imaging-defined enhancing versus nonenhancing regions of after irradiation. When assessing the pathological specimens patients with WHO grade I meningioma, biopsies of enhancing areas correlated with inflammation, demyelination, and cystic changes.[28] Biopsies of areas with lack of enhancement demonstrated coagulative necrosis, edema, vasculopathy, and reactive astrocytosis. These pathological changes, including radiobiological changes of cytotoxic and delayed vascular effects, are also noted in resections of schwannomas, pituitary tumors, and other benign neoplasms.

Evaluation of this effect on benign tumors such as schwannomas was demonstrated with an experimental xenograft model of human vestibular schwannomas transplanted onto the subrenal capsule of nude mice. Following SRS with single doses of 10, 20, or 40 Gy, tumor size and vascularity were assessed. Histological review of mice treated with SRS demonstrated significantly decreased tumor size due to proposed cytotoxic effects at 20 and 40 Gy as well as vascular changes with higher incidence of hemosiderin deposits and mural hyalinization. The use of a subrenal capsule xenograft in nude mice was an excellent model for studying the in vivo radiobiology of acoustic schwannomas after SRS.[29] The results of these preclinical studies provide insight regarding the effects of SRS on benign tumor cell death.

In the clinical setting, the use of MRI-based stereotactic planning provides detailed imaging of the tumor and regional neural structures. As a result, use of multiple small irradiation isocenters allows for conformal SRS to cranial base tumors while decreasing side effects of treatment including cranial nerve neuropathy or brainstem effects.[30] The SRS plan should be conformal and highly selective to the target. Limitation of cochlear dose appears to be important and will be discussed below.

Malignant Tumor Stereotactic Radiosurgery

Malignant tumor SRS, including primary and metastatic brain tumors, has been the subject of many studies. Brain metastasis SRS is the most common indication at many centers, although more experimental studies have utilized glioma models. The response of glioma cell lines to varying radiation doses has also provided a platform for response to SRS.[31–35] Preclinical studies using in vivo rat malignant glioma model have demonstrated tumoricidal and cytotoxic effects of single-fraction, focused radiation.[36] Preclinical studies of these rat models with implanted C6 glioma cells in the right frontal brain region compared histological changes and effects of SRS with conventional radiotherapy regimens. Rats were randomized to control groups or treatment groups with different radiation regimens. Treatment groups included rats treated with SRS to 35 Gy to the tumor site ($n = 22$), whole-brain radiation with 20 Gy in 5 fractions ($n = 18$), SRS plus whole-brain radiation ($n = 13$), partial-brain radiation with 85 Gy in 10 fractions ($n = 16$), or single-fraction partial-brain radiation with 35 Gy in 1 fraction ($n = 10$). When compared with the control group (median survival of 22 days), there was a statistically significant increase in overall survival (OS) in all rats treated with different radiation regimens. In addition to increased survival, all treatment group, except animals treated with whole-brain radiation, demonstrated reduced tumor size. Reduced tumor cell density and increased intratumoral edema were identified in rats that underwent SRS and SRS plus whole-brain radiation therapy (WBRT) when compared with rats in the control group, a finding not observed in other treatment regimens. We found that the histological responses after SRS were generally greater than those achieved with biologically equivalent doses of conventional radiotherapy therapy, which were likely due to increased tumor cytotoxicity.[37] From a biological perspective, interesting concepts include radiosurgical targeting of white matter tumor cell invasion and potential synergistic effects of bevacizumab.[38]

Benign Tumors

Vestibular Schwannomas

Management approaches for vestibular schwannomas (VSs) have been significantly altered by the evolution of SRS. Microsurgery was the standard option for all patients who could tolerate surgery. The role of SRS was initially limited to those who were poor surgical candidates (advanced age, multiple comorbidities), who had failed previous surgical interventions, or who had neurofibromatosis type II.[39–41] Recent reviews indicate that practice patterns have changed significantly, and

one analysis found a 41% decrease in surgery rates for VSs from 2000 to 2007 alone.[42,43]

Considerations for managing VS include controlling tumor growth, avoiding facial nerve and trigeminal nerve dysfunction, preserving serviceable hearing, maintaining or improving overall neurologic status, and minimizing comorbidities such as infection, hydrocephalus, hemorrhage, and others. SRS techniques have been modified over time in order to better strike the balance between tumor control and avoidance of comorbidities. There have been significant modifications in the technique of SRS between 1987 and 1992, including a change from CT to MRI-based planning, improvements in computer workstations and conformal dose planning, the use of more isocenters of radiation, and the use of smaller irradiation beams. Beginning in 1992, we reduced the average dose to the tumor margin to 12–14 Gy, with the 50% isodose line used in 90% of our patients. By the late 1990s, the tumor margin dose of 12–13 Gy was the most common. This dose can be adjusted and tailored to the individual patient depending on cranial nerve function, tumor volume, and clinical history. These adjustments have resulted in a significant reduction in the morbidity of SRS.[44,45]

Hearing preservation is an important goal for some patients. It has recently been recognized that the radiation dose to the cochlea plays a significant role in hearing outcomes for patients receiving SRS. Techniques that reduce the cochlear dose below 4 Gy appear to have higher rates of serviceable hearing preservation.[44,46] Methods for achieving hearing preservation include beam blocking and use of the smallest collimators. Limiting the dose to the cochlea is particularly challenging in patients whose tumors extend into the internal auditory canal. Two methods include reducing the marginal dose and limiting treatment to the lateral aspect of the tumor, but long-term effects on tumor control rates are not known.[47] Another option may be conventional radiotherapy, which theoretically should be effective in limiting maximal cochlear dosage, but studies have failed to show improved hearing rates with this approach.[48–51] Not all studies, however, even agree that the radiation dose to the cochlea matters.[52] Other authors make the point that tumor arrest should take precedence and that dose planning should not be modified to spare the cochlea at the expense of tumor control until lower doses are shown to control tumor growth.[53] Another metric that may influence hearing outcomes is the patient's total cochlear volume. Patients with larger volumes may have more hearing reserve, and this may allow the clinician to be more aggressive with treatment plans.[54–56] Patients with useful hearing before SRS continue to report an ~60%–85% overall rate for maintenance of useful hearing in studies with short-term follow-up, depending on tumor size.[57] For patients with intracanalicular tumors, the short-term rate of hearing preservation is above 80%.[30,45]

Recently, there have been studies in the literature with longer-term results showing that serviceable hearing rates may continue to decline linearly as far as 10 years post SRS. One study of 44 patients receiving a median dose of 12 Gy found 57% hearing preservation at 5 years but only 24% at 10 years.[58] Another study of 44 patients also found a steady decline in serviceable hearing, with 1, 3, 5, 7, and 10-year hearing rates of 80%, 55%, 48%, 38%, and 23%, respectively.[59] The most important predictive factors for hearing loss appear to be pretreatment hearing level and tumor size. An important question to ask is whether SRS is improving or worsening the natural history of the disease itself. Recently, a large study compared the rate of hearing loss post SRS to the natural history of hearing loss for VS. The study found an annual hearing reduction of 3.77 dB/year following SRS compared with 5.39 dB/year before SRS. Again, a cochlear dose <4 Gy was found to be important. Additionally, the authors pointed out that aging alone leads to an average annual hearing loss of 1 dB/year.[60] This fact is highlighted by a study of SRS for VS in patients <40 years of age. In this age group, 93% of patients with serviceable hearing in the preoperative period maintained serviceable hearing 10 years post SRS.[61] By comparison, the microsurgical literature suggests that serviceable hearing can initially be maintained in ~30%–60% of patients. In a long-term follow-up of microsurgical hearing results (mean follow up, 113 months), <25% of patients were shown to retain serviceable hearing following retrosigmoid microsurgical resection.[62]

Another major goal of VS treatment is preservation of facial nerve function. The advantages of SRS for this goal are clearly demonstrated in the literature. The risk for any grade of delayed facial nerve dysfunction in patients receiving <13 Gy has consistently been shown to be <1%.[44,45,63] At least one study found that a small percentage of patients even experienced markedly improved facial nerve function following SRS, although this is clearly not the norm.[60–65]

Transient complications of SRS are relatively common, but the risk of permanent complications is extremely low. Other complications can include trigeminal nerve dysfunction, shunt-dependent hydrocephalus, radiation-associated inflammatory effects, or malignant transformation. Studies have shown rates of trigeminal dysfunction from 1% to 3%.[66] Malignant transformation of VS following SRS is exceedingly rare, and there have been only 6 confirmed cases reported as of 2013.[67,68] In our experience, we have not seen a single case develop.

Patients may opt for conservative management of VS if they are poor surgical candidates or simply due to patient preference for avoiding or delaying interventions. One large series shows that 70% and 95% of patients who choose this approach will experience measurable growth at 5 and 10 years, respectively.[69] By contrast, tumor control rates in patients opting for SRS range from 93%–100%.[39,41,57,61,63,64,66,69–84] Serviceable hearing preservation using observation has been found to decline to 78%, 43%, and 14% of patients at 1, 2, and 5 years, respectively.[85] This can be contrasted with SRS, in which serviceable hearing rates range from ~50%–70% at the 5-year follow-up. Compared with SRS, observation typically leads to subsequent tumor growth and deterioration of serviceable hearing function.

Most patients choose SRS over microsurgery because of its ability to provide equivalent tumor control rates and better preservation of facial nerve function and hearing without the comorbidities of a large, invasive procedure. Many authors now argue that SRS should be the standard of care for most patients with small and mediumsized VSs. Although there has not been a randomized trial providing level 1 evidence to compare SRS to resection (and one is not likely to be performed), there have been several matched cohort studies. The cohort studies reported on

patients with similar-sized tumors and evaluated clinical, imaging, and quality of life outcomes. These reports have shown improved hearing outcomes and facial and trigeminal function; decreased hospital stay, time away from work, and total cost; and increased patient satisfaction with SRS compared with surgical resection. They have also shown similar results for the preoperative symptoms of tinnitus and imbalance as well as similar freedom from tumor progression rates.[48,49,59,60,62,66,69,75,80,82,83,86,87] In some patients, there can be transient expansion of the tumor capsule after irradiation due to the expected intratumoral injury that is to the goal of the procedure. Such changes are usually observed without further treatment.[88,89] Based on these data, we believe that the remaining indications for surgical resection in a patient with a small-to-moderate sized tumor are brainstem compression causing disabling imbalance, intractable trigeminal neuralgia or headache, hydrocephalus, an unclear diagnosis and, of course, patient choice.

One of the traditional criteria for resection has been for control of large a VS. GK has even shown to be suitable for some patients in this group. One study evaluated 246 patients with brainstem compression over 17 years and found a tumor control rate of 97% for VS along with preservation of serviceable hearing in 72% of patients at 65 months. Only 5% required an additional procedure such as a ventriculoperitoneal shunt.[90] Another study described 65 patients with VS ranging from 3–4 cm and found that at 2 years 89% of VSs were either stable in size or smaller at 2 years. Only 12% required a subsequent procedure: either resection or ventriculoperitoneal shunt placement.[91] Another study looked at 28 patients with VSs measuring 3–4 cm and found a 2-year tumor control rate of 86% with facial nerve and hearing levels maintained in all patients. There was an 80% transient complication rate, but only 1 patient experienced a permanent complication (worsening of pre-existing hemifacial spasm).[87] Yet another study looked at 24 patients with VS >3 cm and found 3 and 5-year progression-free survivals of 95% and 82%, respectively. That report concluded that SRS is still a reasonable option for some larger VSs (at least up to 4 cm in diameter), especially in patients who are poor surgical candidates.[92]

SRS for VS attempts to utilize the concept of normal tissue to repair itself in between fractions, which may provide a different set of biological effects on target and adjacent tissue. This was thought to be particularly useful for larger, asymptomatic lesions in close proximity to the vestibular or trigeminal systems. Regimens have varied widely and have included those as long as 30 fractions and as short as 18 Gy in 3 fractions. The Stanford group has reported their results with a 5-year tumor control rate of 96%, a crude rate of serviceable hearing preservation of 76%, and no facial weakness.[93] Multiple other studies have shown tumor control rates ranging from 94%–95%.[75,82] Hearing preservation rates in major studies have included 57% at 2 years, 71% at 5 years, and 61% at 5 years.[51,94,95] A recent study described the use of conventional radiotherapy (46.8 Gy in 1.8 Gy fractions) and showed that 54% hearing preservation at 5 years could be achieved without sacrificing tumor control rates.[96] Still, one of the major rationales for fractionated dosing is to improved hearing outcomes, but hearing outcomes following fractionated SRS are not superior to single-fraction SRS as a whole.

Meningiomas

SRS has proven to be highly effective for patients with benign (WHO grade I) meningiomas, which are usually well demarcated and rarely infiltrative. As a result, with sophisticated planning, one can create a steep radiation fall-off that may limit the radiation dose to surrounding critical tissues. Historically, SRS was initially considered only for residual or recurrent meningiomas following surgical management.[97] The problems of delayed tumor recurrence after surgery, surgical morbidity, and surgical mortality (especially in the elderly), have increasingly led to consideration of SRS as the primary tumor management, particularly when a potentially curative grade 1 resection is not feasible.[76,98]

For benign meningiomas, the long-term control rate exceeds 90% in most studies. In the University of Pittsburgh comprehensive analysis, there were 972 patients with 1045 intracranial meningiomas. The series included 70% who were women, 49% who had undergone a prior resection, and 5% who received prior conventional radiotherapy. The mean age was 57 years. Tumor locations included middle fossa ($n = 351$), posterior fossa ($n = 307$), convexity ($n = 126$), anterior fossa ($n = 88$), parasagittal region ($n = 113$), or other sites ($n = 115$). The mean tumor volume was 7.4 mL. Follow-up past 5, 7, 10, and 12 years was obtained in 327, 190, 90, and 41 patients, respectively.

The overall control rate for patients who had adjuvant SRS for known WHO grade I (benign) meningiomas (prior resection) was 93%.[97] Primary SRS patients (no prior histological confirmation; $n = 482$) had a tumor control rate of 97%. The results were poorer for adjuvant SRS used in patients with WHO grades II and III tumors. Tumor control rates were 50% and 17% in those 2 groups, respectively. Recent studies indicate that there may be a dose-response relationship for these more aggressive tumors, with better control rates being obtained using tumor margin doses above 15 Gy. At 10 years or more, adjuvant grade I tumors were controlled in 91% ($n = 53$) of patients and primary tumors in 95% ($n = 22$) of patients. No patient in this series developed a radiation-induced tumor, despite the existence of case reports about a radiation-associated glioblastoma multiforme or chondrosarcoma.[99,100] Primary patients had an unchanged or improved neurological condition in 93% of cases, whereas those with adjuvant-managed tumors were unchanged or improved in 91% of cases. The overall morbidity rate was 7.7%, and symptomatic imaging changes developed in 4% of cases at an average of 8 months. Such changes were more common in parasagittal or convexity meningiomas. For ~20 years, there has been a protocol that restricted the optic apparatus dose to ≤ 8–9 Gy using MRI to identify the optic nerve. By doing so, the risk of delayed radiation-related optic neuropathy is minimal.

Recent studies have attempted to stratify results by type and location of meningioma. An analysis of 115 patients with convexity meningiomas irradiated with a mean tumor margin dose of 14.2 Gy showed a 3-year and 5-year actuarial tumor control rate of 95% and 86%, respectively, for patients with benign meningiomas without prior surgery. There was an overall morbidity rate of 10%, with symptomatic peritumoral imaging changes being consistent with edema or adverse radiation effects in 5%.[101] A study of 168 patients with petroclival

meningiomas (median tumor volume, 6.1 cm^3) showed overall 5-year and 10-year progression-free rates of 91% and 86%, respectively. Tumor volume was observed to decrease in nearly half (46%) of patients.[102] An analysis of 21 patients with foramen magnum meningiomas at a median follow-up of 47 months showed that 10 patients had an overall tumor reduction of >25% and that the other 11 patients had arrested tumor growth. Ten out of 17 symptomatic patients had improvements in their symptoms, and no patients suffered adverse radiation effects.[103] A study of 65 patients with 90 parafalcine or parasaggital meningiomas showed 3-year and 5-year tumor control rates of 85% and 70%, respectively. The authors hypothesized that these lower control rates may be due to longer dural tails leading to higher recurrence rates.[104] Many of these meningiomas would have had significant risks of morbidity via microsurgical resection. SRS should be considered as a primary management strategy for patients with small meningiomas in areas that are surgically challenging to access.

SRS has changed the way many neurosurgeons and radiation oncologists manage patients with meningiomas. Rather than performing a subtotal resection and following the patient, we now advocate postoperative SRS to the residual gross tumor to reduce the risk of delayed progression.[105] We believe that this strategy is particularly valuable for patients less than 75 years old. Several longitudinal studies have shown that untreated meningiomas under observation continue to grow over time. We also believe that SRS is the preferred option for a young patient with a critically located small meningioma. Observation is no longer the best choice for such patients, especially if they are symptomatic.

Anaplastic/malignant meningiomas (WHO grade III) are best managed with complete resection, if feasible, followed by conventional radiotherapy to 55–60 Gy because of their tendency to extend beyond the borders seen on imaging.[106] Recommendations for grade II tumors are less clear, and either SRS or radiotherapy can be considered for residual disease after resection. We favor SRS for nodular residual tumors and radiotherapy for more extensive tumor resection beds. The estimated risk of local recurrence following surgery alone is high, particularly for grade III tumors in which survival beyond 10 years is uncommon.[107] As a result, external beam radiotherapy is often recommended for improving local control. Radiotherapy planning is based on preoperative and postoperative MRI with irradiation of the gross tumor volume plus a margin of 1–2 cm.[108] Despite local control with resection alone, local and regional progression is still significant. This strategy requires consideration of a multimodal approach incorporating maximum surgical resection, conventional radiotherapy, and possible SRS boost to residual gross disease.

Pituitary Adenomas

The goals of pituitary adenoma SRS are to permanently control tumor growth, maintain pituitary function, normalize hormonal secretion in case of functional adenomas, and preserve neurological function, especially vision.[109] Indications for SRS generally include recurrence or residual growth of pituitary adenomas following resection. Radiosurgery can be used even when tumors come close to the optic apparatus, as long as the tumor targeted is expected to respond to a low dose that allows visual preservation and if the patient does not have a compressive optic neuropathy that would argue for tumor resection and optic decompression. We work to keep the maximum point optic dose to 10 Gy or less. Conventional radiotherapy or fractionated radiotherapy is another option in this setting. For example, one study using Cyberknife fractionated irradiation to a total dose of 25.0 Gy in 5 consecutive fractions demonstrated preservation or improvement of vision and imaging-defined tumor stabilization in 20 of 20 patients at ~30 months follow-up.[110]

Nonfunctioning pituitary adenomas comprise ~30% of all pituitary tumors. Recently, 9 centers pooled their results under the auspices of the North American Gamma Knife Consortium.[111] This review included a total of 512 patients with nonfunctional pituitary adenomas, 479 of whom had undergone prior resection. Patients received a median dose of 16 Gy to the tumor margin, and median follow-up was 36 months. Actuarial tumor control rates were 98%, 95%, 91%, and 85% at 3, 5, 8, and 10 years post SRS, respectively. Approximately 1 in 5 patients experienced new or worsened hypopituitarism after SRS, most commonly involving either the cortisol or thyroid axis. This may be related to the dose received by the pituitary stalk and may be unavoidable. Studies have found that the risk of developing hypopituitarism extends as far as 10 years after SRS. Some have suggested limiting the dose to the pituitary stalk to avoid this effect, but limiting tumor dosage may be more risky to the patient than the risk of delayed hypopituitarism. Nine percent of patients in the cohort had new or worsened cranial nerve deficits, and 7% had new or worsening optic nerve dysfunction. A separate study, with long-term follow-up, showed that most patients tended to demonstrate either tumor shrinkage or tumor growth.[112] For this reason, long-term endocrinological, radiological, and neurological follow-up is recommended to assess clinical status as far as decades after surgery.

In a prior review, our University of Pittsburgh series included 290 patients with pituitary adenomas. We reviewed our results after SRS in patients who had secreting tumors. Endocrinological, ophthalmological, and radiological responses were evaluated. Typically, acromegaly patients respond best, with normalization of growth hormone hypersecretion in > 70% of patients. Approximately 50% of patients with Cushing's disease responded effectively. A recent study of 96 patients with persistent Cushing's disease after resection (irradiated with a mean tumor margin dose of 22 Gy) showed tumor control in 98% of patients and remission of Cushing's disease in 70% of patients at a mean follow-up of 48 months. The study indicated that patients who stop ketoconazole prior to SRS have a significantly shorter mean time to remission.[113] A study of 22 patients with invasive prolactinomas found that 27% achieved endocrine normalization and 55% had endocrine improvement following SRS at a median follow-up of 36 months.[114] We found that all patients with microadenomas and 97% of patients with macroadenomas had tumor control GK was essentially equally effective for control of adenomas with cavernous sinus invasion and suprasellar extension. While endocrine deficits are less common after SRS, recent reports show that 15%–25% of patients may develop some hormone deficiencies over time that may require replacement.

Brain Metastases

The role of SRS in the management of brain metastases has expanded concurrently with a growing body of literature on its clinical use. A common approach to single or multiple brain metastases care for decades has been WBRT. Metastatic brain tumors, which are typically well circumscribed, often provide an ideal target for SRS. The dose fall-off characteristics inherent in SRS serve to minimize toxicity with unnecessary radiation dose delivered to uninvolved brain parenchyma. SRS was initially given in combination with WBRT, whereas it is now increasingly used alone for solid tumors or to irradiate postoperative tumor beds or in combination with systemic biologic, cytotoxic, or immunotherapies with access to the CNS.[81,115–126] The goal of SRS without or with deferred WBRT is to achieve brain control in patients with brain metastases while minimizing the risk of long-term neurotoxic or cognitive side effects associated with WBRT.[115,124–127] Hair loss, fatigue, and both subacute and delayed cognitive deficits (in longer-term survivors) are noted after WBRT and can decrease quality of life.[128] Approaches to mitigate these toxicities include using intensity-modulated radiation therapy to limit scalp dose (ie, hair loss), sparing of dose to the hippocampus as in a recent RTOG study, and using neuroprotectors to decrease late neurotoxicity.[129–133] However, SRS is an attractive alternative or adjunct to WBRT because it is minimally invasive, can be performed on an outpatient basis without hospitalization, involves little recovery or interruption of systemic therapy, provides excellent local control, palliates symptoms, and avoids a craniotomy. Technical advantages in both imaging (typically high-resolution MR imaging) and the delivery platforms for SRS have facilitated the delineation and treatment of multiple tumors in appropriate patients. The toxicity of SRS seems to be limited, even in long-term studies, with the exception of a low-risk of injury to critical structures that can often be managed medically and may not impact patient quality-of-life.

The role of surgery in the management of brain metastases is important and involves providing a tissue diagnosis in unclear clinical situations, prompt alleviation of tumor-related mass effect, and effective cytoreduction for larger tumors. Several randomized studies have established its utility. Patchell, et al in a study that predominantly included patients with lung cancer, demonstrated increased local control in patients who had surgical resection for single metastases plus WBRT compared with WBRT alone.[134] A second randomized study confirmed the importance of postoperative radiotherapy.[135] While this trial utilized WBRT, recent studies have demonstrated a role for either WBRT, partial-brain radiotherapy, or SRS following surgical resection. The question of whether a combination of SRS or surgical resection and WBRT yield superior intracranial disease control is an open one, although separate studies have compared results favorably. To date, the results of combining SRS and WBRT appears to be as effective as surgical resection followed by WBRT for resectable tumors.[120] Patient selection remains important because those with larger tumors causing mass effect and disabling symptoms should be considered for resection if feasible. However, more than 50% of brain metastases in our own experience are now identified in asymptomatic patients using staging imaging, and most are of smaller volume.

The role of SRS has been well characterized in several phase III randomized studies in terms of its benefit in controlling brain metastases. RTOG 9508 was a phase III randomized trial in which 333 patients with 1–3 brain metastases either received WBRT to a dose of 37.5 Gy or a combination of WBRT and SRS. Intracranial control was superior in the combined modality arm. While there was no difference in OS, an unplanned subset analysis suggested a survival difference in patients with a single metastasis.[115] Another randomized trial compared SRS with WBRT and SRS in 132 patients with 1–4 brain metastases. In this study, there was no OS benefit or differences in neurological deaths with the additional of WBRT to SRS alone.[136] Chang, et al reported on a similar trial comparing SRS with and without WBRT. They found that neurocognitive outcomes were worse at 4 months in patients receiving combined WBRT and SRS.[137] The timing of this metric has been criticized.

Across a variety of histologies, the tumor control rate of SRS is high. However, tumor volumes can respond differently, with breast cancers regressing more quickly and more extensively. This can be relevant in decision-making if the clinical goal is to achieve rapid tumor regression and improvement in edema. Naturally, tumor control rates decrease as tumor volume increases. Increased radiation dose will lead to greater control rates, but a dose reduction is common to avoid toxicity. At our own center, we think that tumor margin doses for metastases above 20 Gy are generally unnecessary. More importantly, SRS is likewise effective for tumors traditionally considered resistant to radiation, including melanoma and renal cell carcinoma.[123,124,126,138] Although one may consider increasing SRS doses for brain metastases of radiation-resistant histologies, the dose of 20 Gy is generally determined by the maximum diameter of the metastatic lesion rather than the histology alone, as determined by the RTOG 90–05 (a dose-escalation study in patients with brain metastases that did included radiation-resistant histologies).[139] A phase II study of 36 patients having 1–3 brain metastases and radiation-resistant histologies, including renal cell carcinoma, melanoma, and sarcoma, were treated with SRS alone using doses based on size of metastases consistent with results of the dose-escalation study. However, the authors concluded that intracranial failures were high when WBRT was omitted, even though median survival time of patients in this study was consistent with multiple series of patients treated with SRS combined with WBRT.[140]

A complete mechanistic explanation for improved control rates in radio-resistant histologies has yet to be fully elucidated. Effects on tumor vasculature, predictions based on the LQ model, and additional biological pathways have been associated with benefits from single, large-fraction radiotherapy as given with SRS.[141–143] The combined use of SRS and systemic therapies to treat brain metastases is an important area of current and future study. Biological therapies (eg, tyrosine kinase inhibitors such as those directed against EGFR in non–small cell lung cancer and against Her2 in breast cancer) may have increased utility in conjunction with SRS. Tumor control rates appear similar across histologies, although more volumetric regression is identified in breast cancer. The presence of active extracranial cancer activity has become the most important prognostic indicator for survival, not the presence of CNS disease. In our experience, WBRT has improved local tumor

control in lung cancer patients, which is a finding also noted by others. For other tumor types, it neither affected survival nor local tumor control.

Together with colleagues at the University of Pittsburgh and New York University, we have performed SRS on more than 4000 patients with brain metastases. Only 10% of them had undergone one or more prior resections. Early in our experience, most patients had already failed WBRT. More recently, fewer patients had undergone WBRT before referral, and we seek to avoid WBRT unless leptomeningeal disease or a high numbers of tumors is noted. Given that extended survivals are being seen with more effective care of the extracranial cancer, we work to preserve neurological function and independence so that patients can enjoy their survival. With more frequent use of imaging for screening, the KPS is 100% or 90% in more than 90% of patients at presentation. In this setting, the average tumor volume is small. A common range for the tumor margin dose is 16 to 20 Gy. We use 18–20 Gy in most patients when SRS is the initial approach and lower doses when prior WBRT has been used.

We advocate SRS for patients with multiple brain metastases, including those with >3–4 metastases, who remain in good neurological condition. This strategy paradigm was considered controversial because conventional teaching was that the recognition of more than one metastasis heralded widespread subclinical micrometastases. This concept was proven to be incorrect once high-resolution MRI was able to show whether or not new tumors had developed. An early randomized trial compared SRS plus WBRT to WBRT alone for patients with 2–4 brain metastases. Improved tumor control was observed when patients received both SRS and WBRT.[128] This study and others found that the presence of multiple metastases did not automatically herald the onset of more and more tumors. Thus, patients should continue to be managed aggressively if effective therapies remain for their extracranial cancer.[122] In a recent study, we found that the survival expectation for patients with 5–8 tumors was not significantly different from patients with 2–4 tumors, as long as the total tumor burden was <7.5 mL.[117] Recent work using GK for patients with 10 or more tumors showed that outcomes in specific clinical scenarios could be similar to patients with limited numbers of brain tumors.[144] A prospective, observational study, JLGK0901, concluded that SRS alone for patients with 5–10 brain metastases was noninferior to those with 2–4 metastases.[145] In addition, the toxicity of whole-brain radiation therapy is being further characterized.[146] Randomized trials that evaluate cognitive outcomes have shown the deleterious effects of WBRT, indicating that its use should be careful and judicious.[137] More and better data are needed regarding both subacute and long-term neurotoxicity resulting from the various treatment modalities and whether or not interventions can alleviate these effects.

For patients with large metastatic tumors, SRS delivered to the postoperative cavity represents a recently used strategy to limit radiotherapy doses to normal brain tissue. This involves targeting the postoperative area with a 2–3 mm margin. One recent report demonstrates a local control rate of ~85% in patients receiving resection-bed SRS.[147] A larger review of the literature, which combines many published retrospective publications, supports a control rate of 85% with slightly less than one-third of patients requiring salvage WBRT.[148] Attempts have been made to examine factors that may affect the control rates of SRS following surgery; factors including deep brain metastases smaller than 3 cm and and larger tumors (> 3 cm) with dural or pial involvement lead to higher local failure rates.[149] An additional aspect of SRS is its cost-effectiveness. Several studies have demonstrated that SRS is a cost-effective option for treating patients with brain metastases.[150–152]

Patients who present with recurrent brain metastases following initial treatment with WBRT or SRS can undergo salvage treatment with SRS. A retrospective review of 106 patients who underwent prior radiation (WBRT, SRS) from 2009–2011 reported durable local control after undergoing salvage SRS for recurrent brain metastases. This study demonstrated that salvage SRS may be of particular benefit for young patients with controlled extracranial disease who had durable response to treatment from initial radiation treatment. In the era of improved modern systemic therapies with increased estimated life of expectancy, salvage SRS can be considered for these patients. However, the use of salvage SRS should be balanced against the potential toxicities of retreatment, including radionecrosis.[153]

The ability to determine the prognosis of patients with brain metastases has been an important guide for selecting appropriate therapy. A classic recursive partitioning analysis combined data from several brain metastasis trials and resulted in 3 prognostic stages based on age, KPS, control of the primary lesion, and presence of extracranial metastases.[154] A diagnostic-specific graded prognostic index (GPA) was also determined that takes into account the primary tumor histology in patients with brain metastases. This GPA suggested that different factors are involved in prognosis of differing histologies.[155] Although these criteria are useful for trial design, the ability of physicians to predict OS in patients with brain metastases is difficult. In a prospective evaluation of 150 consecutive brain metastases patients (median age = 62) undergoing SRS, we asked 18 medical, radiation, and surgical oncologists to predict survival from the time of treatment using the factors typically correlated with survival. The actual median patient survival was 10.3 months (95% CI, 6.4–14). The median physician-predicted survival was 9.7 months (neurosurgeons = 11.8, radiation oncologists = 11.0, medical oncologists = 7.2 months). All physicians had individual patient survival predictions that were incorrect by as much as 12–18 months, and 14 of 18 physicians had individual predictions that were in error by >18 months. Of the 2700 predictions, 1226 (45%) were off by >6 months, and 488 (18%) were off by >12 months.[156]

Thus, patient care needs to be individualized. Much has been learned in the creation of the brain metastases management guidelines, but patient care has moved quickly beyond them.[157] Brain metastases patients should not be managed as a homogeneous group. Tumor histologies differ widely, with different responses to treatment. Molecular subcharacterizations of breast cancer, melanoma, and lung cancer have changed treatments and outcomes.[158] The focus on the number of brain tumors, a key inclusion criteria for almost all prior clinical trials, may become less important when the total tumor volume is considered.

Glial Neoplasms

Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults. Unfortunately, the treatment and management of malignant gliomas (WHO grade III and IV) remains

one of the biggest challenges in the field of neuro-oncology. The current standard treatment is maximal surgical resection to the extent that it is safely feasible, followed by conventional radiotherapy in combination with concomitant and adjuvant temozolamide.[159,160] Despite this, nearly all patients develop local recurrence and progression of disease requiring additional treatment, often with other chemotherapeutic agents or SRS.[161–163]

Because most recurrences occur locally at the site of previous radiation, there is an argument to be made for increasing the dose of conventional radiotherapy in an attempt to decrease the rate of local recurrence. However, most are in favor of using SRS to provide a radiation boost to the site of recurrence while minimizing the radiation dose to the surrounding brain parenchyma.[163] There continues to be ongoing debate regarding the optimum dose of the boost and whether SRS is more effective in combination with other therapies.

A multicenter, randomized controlled trial demonstrated no benefit for upfront SRS followed by conventional radiotherapy and carmustine (BCNU) compared with conventional radiotherapy and BCNU alone.[162] It should be noted that this study was performed before temozolamide became the standard chemotherapeutic agent for treatment of malignant gliomas.[163] Interestingly, upfront SRS was never common for this diagnosis. Thus, SRS is used primarily as a boost for smaller residual or recurrent malignant gliomas after completion of conventional radiotherapy with temozolamide. A retrospective analysis of 107 patients demonstrated that GK confers a survival benefit for patients with malignant gliomas when used prior to disease progression as part of the initial treatment plan, in addition to conventional radiotherapy, or when used at the time of disease progression.[161] However, no prospective randomized clinical trial has been performed to evaluate the effect of boost SRS after conventional radiotherapy and temozolamide in malignant gliomas.

More recently, there has been increasing interest in combining SRS with other therapeutic agents, especially bevacizumab, due to evidence that bevacizumab may sensitize tumor endothelium to the effects of radiotherapy by depleting vascular endothelial growth factor.[163–165] A retrospective analysis of 11 patients with recurrent GBM treated with GK followed by bevacizumab combined with chemotherapy demonstrated longer median progression-free survival (PFS) (15 vs 7 months) and median OS (18 vs 12 months) compared with 44 case-matched controls who underwent GK alone without bevacizumab.[165] Another retrospective analysis of 63 patients with recurrent malignant gliomas, 42 of whom were treated with SRS in combination with bevacizumab and 21 of whom were treated with SRS alone, also demonstrated that SRS with bevacizumab was associated with improved outcomes, namely longer median PFS (5.2 vs 2.1 months) as well as longer median OS (11.2 vs 3.9 months).[166] Because of these promising results, a prospective clinical trial was conducted to evaluate the safety of concurrent SRS and bevacizumab for recurrent malignant gliomas, and excessive toxicity was not demonstrated.[38] However, no prospective randomized clinical trial has been performed to evaluate the efficacy of concurrent SRS with bevacizumab.

There are far fewer studies evaluating the role of SRS in low-grade gliomas (WHO grades I and II). These tumors are usually treated with maximal surgical resection and conventional radiotherapy if feasible, given the evidence demonstrating that extent of surgical resection correlates with patient survival.[167,168] SRS is therefore usually reserved for patients with smaller, low-grade gliomas in critical functional cortex, deep brain structures, and the brainstem, or for residual or recurrent tumor.[163,169–171] A retrospective review of 49 patients with low-grade gliomas, treated with GK, demonstrated median imaging PFS of 37 months and median clinical PFS of 44 months, with a 5-year radiological PFS rate of 37% and a 5-year clinical PFS rate of 41%.[169] A retrospective analysis of 25 patients with newly diagnosed or progressive fibrillary astrocytomas (WHO grade II) with GK demonstrated PFS rates of 91.3%, 54.1%, and 37.1% at 1, 5, and 10 years, respectively.[171]

Pilocytic astrocytomas (WHO grade I) are typically found in children and young adults. They are often considered benign tumors because surgical resection can potentially be curative.[163,170,172] However, gross total resection (GTR) is not always possible for tumors located in critical cortex or deep brain structures. Tumors that are unresectable or have recurred after resection require treatment with additional modalities such as SRS. In adults, pilocytic astrocytomas can be cystic, solid, or mixed in nature, with the cystic form occurring the majority of the time. A retrospective analysis of 14 adult patients with pilocytic astrocytomas who underwent SRS as part of multimodality management of their tumors revealed PFS rates of 83.9%, 31.5%, and 31.5% at 1, 3, and 5 years, respectively. They found that delayed cyst progression contributed to loss of long-term tumor control.[170]

Juvenile pilocytic astrocytomas (JPAs) are also well-circumscribed tumors that can be cystic, solid, or mixed in nature, like their adult counterparts.[172] When GTR is not feasible, patients are often treated with chemotherapy or conventional radiotherapy after stereotactic biopsy or subtotal resection (STR). Due to the undesirable long-term toxicities associated with conventional radiotherapy in the pediatric population, especially with respect to neurocognition, chemotherapy is often used as the initial adjuvant treatment in order to delay brain irradiation. However, chemotherapy has a median duration of effect of ~3 years.[172,173] SRS allows for the delivery of high-dose radiation to tumors in critical locations while minimizing the potential long-term toxicities of conventional radiotherapy.[172] In a retrospective analysis of 50 children with unresectable juvenile pilocytic astrocytomas who underwent GK, PFS after GF was 91.7%, 82.8%, and 70.8% at 1, 3, and 5 years, respectively, with the best response seen in patients with small, residual solid tumors that had been treated early.[172]

SRS plays an important role in the treatment of glial neoplasms. In malignant gliomas, it is used primarily to provide a radiation boost after standard chemoradiation to prevent local recurrence or at the time of disease progression. There is also increasing interest in the use of SRS in combination with bevacizumab, although further studies are needed to better evaluate the safety and efficacy of this combination in comparison with other salvage therapies. In low-grade gliomas, SRS is used primarily for tumors in critical locations, where surgical resection is not safely feasible, and for recurrent tumors in adults as well as in children.

Ependymomas

Ependymomas account for 6%–12% of pediatric intracranial tumors and <5% of adult intracranial tumors.[174–176] The

standard treatment for these tumors is surgical resection followed by conventional radiotherapy. Multiple studies have demonstrated that the extent of surgical resection is an important prognostic factor, with the presence of gross residual tumor after surgery indicating a poorer prognosis.[177–180] Unfortunately, GTR is not always feasible.

Management of residual or recurrent ependymomas can be challenging. Repeat surgical resection can be considered if it can be performed safely. Because chemotherapy is generally ineffective in these tumors, repeat radiation therapy in some form is the only other available treatment modality.[181,182] Since patients will have already received a course of radiation, significant consideration must be given to the potential radiation-related toxicities, especially in the pediatric population.[181,182] Because SRS is able to deliver a high dose of radiation to a small volume while limiting the dose to the surrounding tissues, it has become an important therapeutic option for the treatment of residual and recurrent ependymomas.[174,175,181]

There are few published series in the literature regarding SRS in ependymomas. Several small case series have been published and have shown varying results.[173,182–186] In the largest series published to date, Kano et al treated 39 patients with a median age of 22.8 years who had 56 tumors with SRS, all of whom had previously undergone surgical resection followed by conventional radiotherapy.[174] The median marginal dose was 15 Gy, with a median marginal dose of 13 Gy for WHO grade II ependymomas and 16 Gy for WHO grade III ependymomas. The median patient survival was 19.4 months after SRS, with a 73.2% local tumor control rate at a median follow-up of 14.9 months. PFS rates after initial SRS were 81.5% at 1 year and 45.8% at 5 years. Subsequent analyses demonstrated that small SRS target volumes in all patients and homogeneous contrast enhancement on MRI in WHO grade II ependymomas were associated with improved PFS, while spinal dissemination was associated with poor OS. Patient age and histological tumor grade were not significantly associated with PFS.[174] Three of 39 patients (7.7%) developed adverse radiation effects, 2 of which were managed with oral corticosteroids. One patient developed increased contrast enhancement with peritumoral T2 signal changes on MRI but was asymptomatic; subsequent stereotactic biopsy confirmed a combination of necrotic tumor with radiation effects.

Kano et al subsequently published a follow-up report focusing only on their pediatric patients with a longer follow-up after SRS. They treated 21 patients with a median age of 6.9 years who had 32 tumors.[175] The median patient survival was 27.6 months after SRS, with OS rates of 85.2% at 1 year and 23.0% at 3 years. They reported a 72% local tumor control rate. Median PFS was 26.0 months, with PFS rates of 78.4% at 1 year and 41.6% at 3 years. Two of 21 patients (9.5%) developed adverse radiation effects, only one of whom was symptomatic. The patient developed an ipsilateral facial paresis 3 months after SRS to a cerebellopontine angle ependymoma, which was successfully treated with a short course of oral corticosteroids.

SRS is an additional treatment strategy for the management of recurrent or residual ependymomas after maximal safe surgical resection, conventional radiotherapy and, in some cases, chemotherapy.

Craniopharyngiomas

Craniopharyngiomas are benign, slow-growing neuroepithelial tumors that arise from remnants of Rathke's pouch or hypophyseal duct. Due to their location adjacent to many critical structures including the pituitary stalk, optic apparatus, hypothalamus, and vasculature, treatment of these tumors usually requires a multimodal approach that must be tailored to each individual patient. GTR is the optimal treatment strategy, when it can be performed safely. When it is not feasible, STR is usually performed to confirm diagnosis as well as to debulk the tumor and relieve mass effect and is often followed by radiation therapy in some form (eg, conventional radiotherapy, SRS, or intracavitary irradiation).[187,188]

SRS plays an important role in this multimodal treatment strategy for craniopharyngiomas, most often in the treatment of recurrent tumor after GTR or residual tumor after STR. Although GK can be used in the treatment of smaller (<3 cm in diameter) tumors of any type (solid, cystic, or mixed), it is best suited for smaller, predominantly solid tumors that are, ideally, at least a few millimeters away from the optic apparatus.[188–190] The entire enhancing tumor on high-resolution gadolinium-enhanced MR images serves as the target for the procedure. However, many centers report that only the solid component of the tumor is used as the target for certain tumors in which there is a large cystic component, particularly if it is close to the optic apparatus.[187,191–194]

There is currently no definitive consensus on the appropriate treatment dose for craniopharyngiomas, although the mean marginal dose appears to be ~12 Gy in many studies. In the largest series published to date, Kobayashi et al treated 98 patients with a mean tumor margin dose of 11.5 Gy.[192] Chung et al reported a mean margin dose of 12.2 Gy in their series of 31 patients.[195] One review of a 10-case series reported a mean marginal dose of 12.3 Gy, while another review of an 8-case series noted a median marginal dose of 12 Gy.[196,197]

Like meningiomas and pituitary adenomas, the SRS dose is limited in the treatment of craniopharyngiomas primarily because of its proximity to the optic apparatus.[198–200] Craniopharyngiomas are relatively radiosensitive, especially the solid components of these tumors. In their large series, Kobayashi et al reported a 79.6% tumor control rate with complete response in 19.4% of patients at a mean follow-up period of 65.5 months.[192] In a review of a 10-case series, Gopalan et al found the mean tumor control rate to be 75%, with a 90% control rate in solid tumors and a 58.6% control rate in mixed tumors.[196] Another review of an 8-case series by Minniti et al demonstrated similar results with an overall tumor control rate of 69% at a median follow-up of 57 months, with control rates of 90% in solid tumors, 88% in cystic tumors, and 60% in mixed tumors.[197]

SRS for craniopharyngiomas is generally well tolerated by patients. The most common morbidities from SRS are secondary to visual deterioration and endocrine dysfunction, most commonly diabetes insipidus. Gopalan et al reported an overall morbidity rate of 4% and a mortality rate of 0.5% in their review, while Kobayashi et al reported a morbidity rate of 6.1% in their large case series.[192,196] In their series of 46 cases, Niranjan et al reported an overall 5-year survival rate of 97.1%.[187] In terms of morbidities, they reported that 8% of patients with

normal visual fields developed homonymous hemianopsias from tumor progression after SRS. Of patients with visual field defects prior to the procedure, 26.3% had progression of their visual field defects secondary to tumor progression, while 10.5% had resolution of their visual defects in conjunction with their tumor regression. With respect to pituitary function, they reported that all patients with normal pituitary function and all patients with panhypopituitarism prior to SRS remained unchanged after the procedure. Of 15 patients with anterior lobe hypopituitarism, one patient noted improvement, and another patient progressed to panhypopituitarism without tumor progression after GK.[187]

Far fewer studies have been performed using CyberKnife radiosurgery for the treatment of craniopharyngiomas than GK, as with most brain tumors. In one small study of 11 cases, Lee et al reported a 91% tumor control rate at a mean follow-up of 15.4 months.[201] In another series of 43 cases, Iwata et al reported a local control rate of 85% at 3 years and 65% at 5 years.[202]

Summary

SRS has offered new and effective options for patients with brain tumors. Together with surgical resection, external beam radiation therapy, chemotherapy, and immunotherapy, patients and physicians can be managed with new approaches that maximize tumor control, neurological function, and quality of life. Understanding the radiobiological effects of SRS on normal and neoplastic tissue is the key to its proper use.

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