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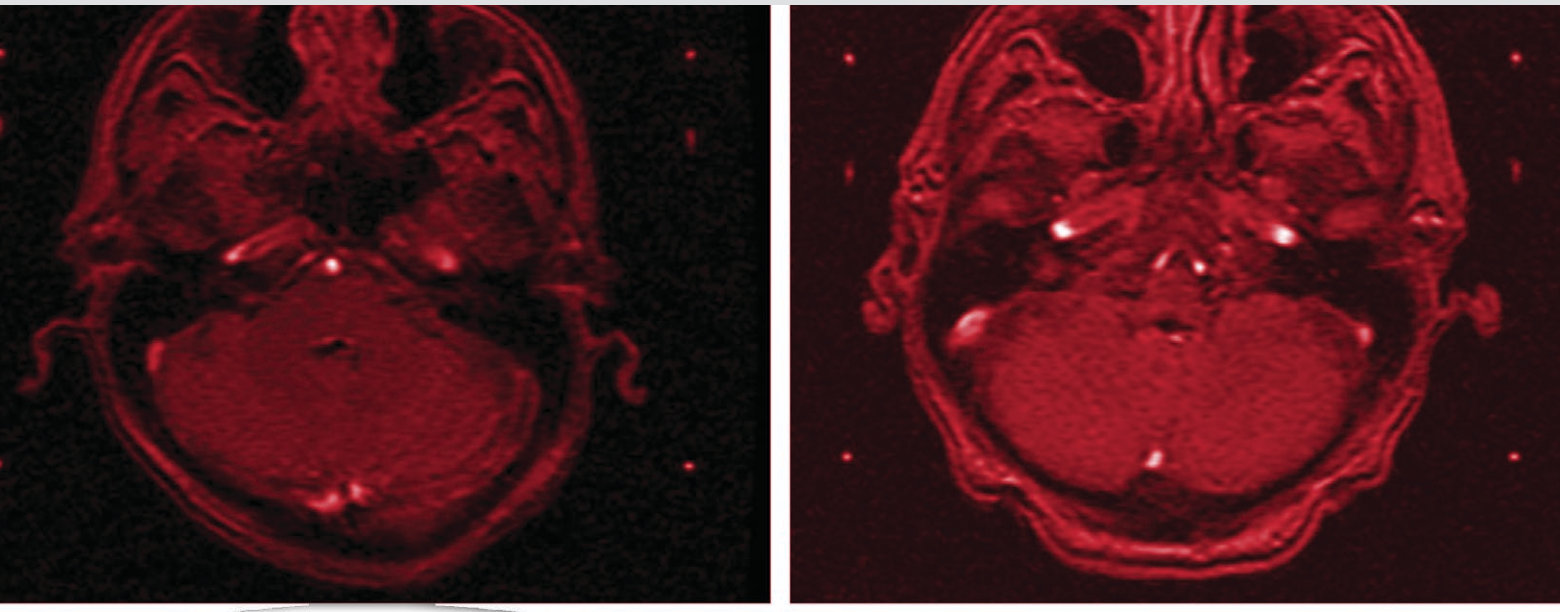

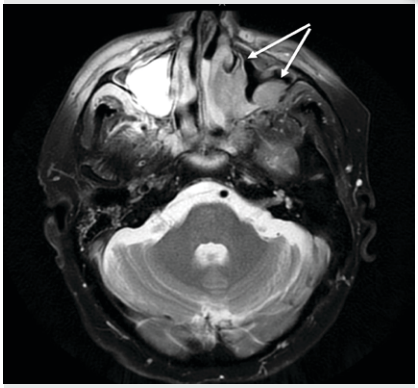

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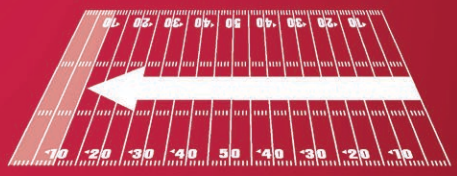

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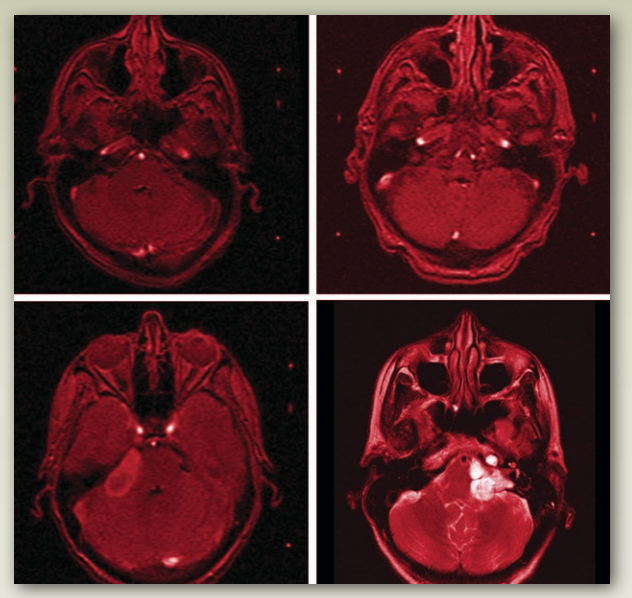

CENTRAL NERVOUS SYSTEM FOCUS

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EDITORIAL

John Suh, MD, Editor-in-Chief

Thinking about CNS Tumors

As part of this month's focus on cancers of the central nervous system (CNS), we are pleased to provide a comprehensive review of one of the most common types of benign brain tumors: acoustic neuroma (AN), which is also known as a vestibular schwannoma or neurilemmoma. AN affects approximately 2 in 10,000 people and often manifests as irreversible hearing loss. Although about 20% to 40% of ANs either shrink or stop growing if left untreated, early intervention is crucial to preserving as much hearing as possible in those affected, as discussed in our lead article, *Interdisciplinary management of acoustic neuromas*. Heva Jasmine Saadatmand, MPH, and colleagues from New York's Columbia University Medical Center, provide an excellent assessment of treatment options, expected response, and side effects in AN management.

The second CNS review article, *Glioblastoma: Multidisciplinary treatment approaches*, examines the most prevalent and most malignant primary tumor of the CNS. Unfortunately, overall survival of GBM patients has improved little over time, despite advances in molecular diagnostics, neurosurgery, radiation oncology, medical oncology, imaging, and immunotherapy, and remains a difficult challenge for all involved. Luis Moreno Sánchez, MD, who practices at several facilities in the Dominican Republic, describes treatment approaches for GBM, toxicities from treatment, diagnosis of recurrence, options for tumor recurrence, and extracranial metastatic disease.

In addition, our winning case report this quarter focuses on GBM. *Metastases from glioblastoma disguised as a new primary malignancy* discusses the use of surgical intervention and focal radiation therapy for a patient whose quality of life is affected by disease burden. Congratulations to Joshua L. Rodriguez-Lopez, BS, of Ponce Health Sciences University School of Medicine in Ponce, Puerto Rico!

A second case report, *Pain flare and vertebral fracture following spine stereotactic radiosurgery for metastatic renal cell carcinoma,* describes several key considerations associated with the use of spine stereotactic radiosurgery for a patient with lower extremity radicular pain, numbness and weakness and a medical history significant for renal cell carcinoma.

Finally, we help update you on volumetric-modulated arc therapy for prostate cancer in this month's Technology Trends article. VMAT pioneer Cedric X. Yu, DSc, FAAPM, and other specialists weigh in on key issues, including constant-dose-rate VMAT compared to variable-dose-rate VMAT, single arc and double arc treatments, patient motion issues, and the use of pre-treatment imaging among other areas.

As you anticipate spring, we hope you enjoy our March issue and benefit from the insight and practical applications our articles provide. As always, thank you for your continued support of *Applied Radiation Oncology* in print and online at *appliedradiationoncology.com*!

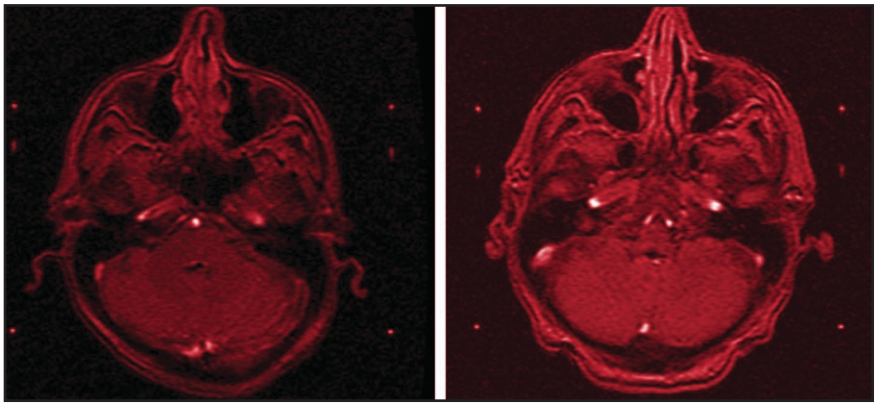
Dr. Suh *is the editor-in-chief of* Applied Radiation Oncology, *and professor and chairman, Department of Radiation Oncology at the Taussig Cancer Institute, Rose Ella Burkhardt Brain Tumor and Neuro-oncology Center, Cleveland Clinic, Cleveland, OH.*

Interdisciplinary management of acoustic neuromas

Heva Jasmine Saadatmand, MPH; Cheng-Chia Wu, MD, PhD; and Tony J. C. Wang, MD

Acoustic neuromas (ANs), histologically described as vestibular schwannomas, are benign tumors of Schwann cells. They originate most frequently from the intracanalicular portion of the vestibular nerve, typically in the medial part of the internal auditory canal (IAC).[1] The incidence of clinically recognized AN is 1-2 in 100,000 person-years in the U.S. population,[2,3] and the prevalence is estimated at 2 in 10,000 people.[4] These tumors comprise 5% to 8% of all intracranial tumors[5] and 80% to 90% of cerebellopontine angle (CPA) tumors,[6] occurring with about equal frequency in men and women.[2] The majority of these (> 90%) are sporadic and unilateral, with the bilateral, hereditary variant limited to neurofibromatosis-2 (NF-2).[7] Risk factors for AN include exposure to ionizing radiation, NF-2, and acoustic trauma.[8]

***Miss Saadatmand** is a fourth-year medical student, **Dr. Wu** is a resident physician in radiation oncology, and **Dr. Wang** is assistant professor of radiation oncology, all in the Department of Radiation Oncology, College of Physicians and Surgeons, Columbia University Medical Center, New York, NY. Miss Saadatmand and Dr. Wu are co-first authors.*



Acoustic neuromas are slow-growing (average growth rate 1.9 mm/year), presenting at a median age of 50. Patients can present between ages 30 to 50 depending on severity of symptoms.[9] Presenting symptoms typically involve dysfunction of cranial nerves V, VII, and VIII, most commonly hearing loss (95%) and tinnitus (63%).[9] Despite being the most common presenting symptom, progressive hearing loss is noticed in only 66% of patients who ultimately have hearing deficit.[10] This is reflective of the indolent nature of this tumor, often manifesting as irreversible hearing loss in many patients.

If left untreated, about 20% to 40% of ANs are stable, either shrinking or ceasing to grow.[2] There has been no shown predictive relationship between growth rate and size of tumor at presentation.[11] However, patients with a tumor growth rate of 2.5 mm per year have higher hearing preservation than those with faster tumor growth.[11] Non-incidental diagnosis depends on patient symptoms, such as hearing loss, which, in turn, is related to the size and location of the tumor. Of note, tumor location is more predictive of hearing loss than tumor size.[11] As such, studies have emphasized the importance of early intervention to preserve as much useful hearing as possible.[12,13] Treatment options for newly diagnosed acoustic neuroma include observation with serial imaging, surgical management, and radiation therapy. The goal of this review is to discuss the treatment options, expected response, and associated side

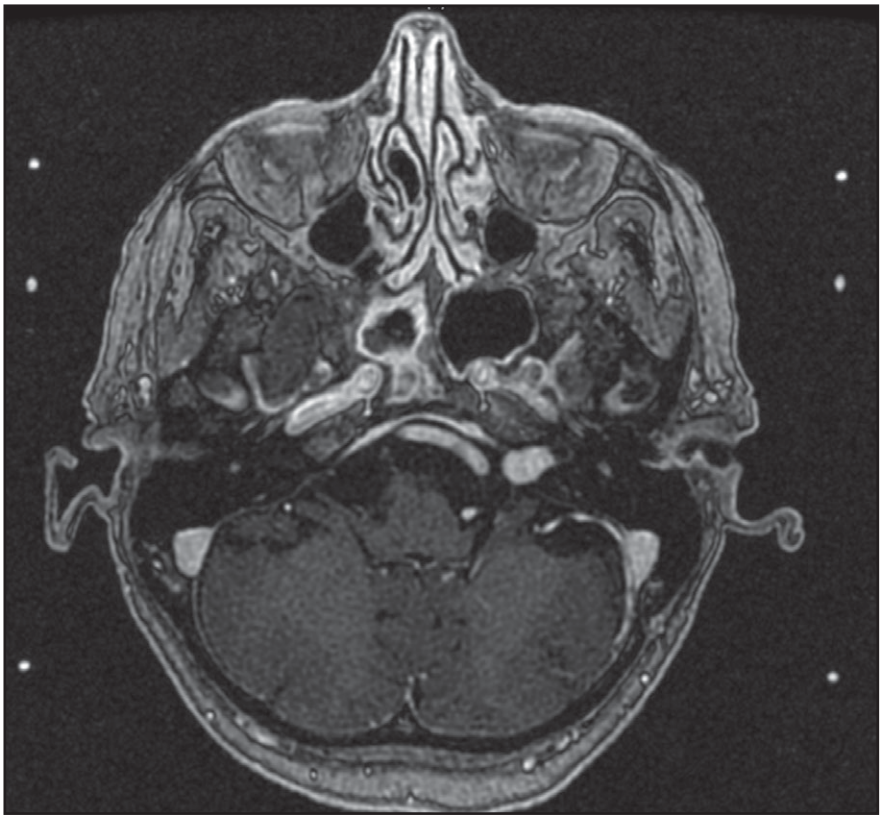


FIGURE 1. *Axial MRI demonstrating an "ice cream cone" lesion in the left cerebellopontine angle and the internal acoustic canal.*

effects in the management of acoustic neuromas.

Initial Workup

For patients presenting with hearing loss due to acoustic nerve dysfunction, initial workup includes audiometry to establish a new baseline. These evaluations typically show asymmetric sensorineural hearing loss, usually more prominent in the higher frequencies. Functional hearing is typically described as < 50 dB and > 50% speech discrimination.[14] The preferred method for the diagnosis and follow-up of AN is MRI.[15] Specifically, diffusion tensor imaging (DTI) is used to assess the auditory tract in the brainstem in those who have sensorineural hearing loss.[16-18] Structures to be aware of in treatment planning include the trigeminal nerve, facial nerve, vestibulocochlear nerve, cochlea, modiolus, and brainstem. Thin-slice (1.0-1.5 mm) MRI with gadolinium is recommended to detect tumors as small as 1-2 mm in diameter, revealing an enhancing lesion typically described as "ice cream cone" in the region of the internal acoustic canal (Figure 1) or a "dumbbell" extending into the foramen magnum.[19] High-resolution CT scan (with or without contrast) can be used if the patient cannot undergo MRI evaluation.

Overview of Management Strategy for Acoustic Neuroma

Overview of Treatment Strategies

The goals of treatment for these benign tumors are long-term tumor control and maintenance of existing neurologic function. Treatment options include surgery, stereotactic radiotherapy, and conservative management with observation.[20,21]

In the event of small tumors (< 2.0 cm) or tumors with no or slow growth without symptom progression — typically either asymptomatic tumors or tumors causing mild, stable symptoms — observation as conservative management is recommended. This includes follow-up with audiometry and MRI every 6-12 months.[2] This strategy is also indicated for older patients or those who may not be able to tolerate stereotactic radiosurgery (SRS) or surgical resection.[1] The problem with this approach includes ongoing hearing loss during the observation period as well as possible mass effect if the tumor is large or grows during follow-up. With symptomatic tumors, intervention becomes key.

Surgical resection of AN has been critical in the management of these lesions for more than 100 years, with current microsurgical techniques allowing for potential preservation of CN VIII and its adjacent nerves.[22] For symptomatic or large tumors (> 3.0 cm) exceeding current recommendations for focused radiation therapy,[23] or tumors that recur or progress after prior radiation therapy, surgery is recommended.[24] Recurrence rates after surgical resection are < 1%, and facial nerve preservation is possible in 80% to 90% of patients.[25] However, hearing preservation after surgical resection is about 50%,[26,27] ranging from 35% to 65%.[28] Of note, these numbers are highly dependent on the tumor size or volume, location, and expertise of the surgical team and institution.[28]

The role of radiation therapy in AN treatment depends on whether the patient is a surgical candidate, the experience of the institution with treating AN nonsurgically, and patient preference. Radiation therapy, particularly SRS, is a noninvasive technique that delivers high-dose irradiation to a small, targeted volume of tissue. The use of SRS for AN was first described by Swedish physician Lars Leksell as an alternative to microsurgical resection for small and moderately sized tumors.[29] Studies

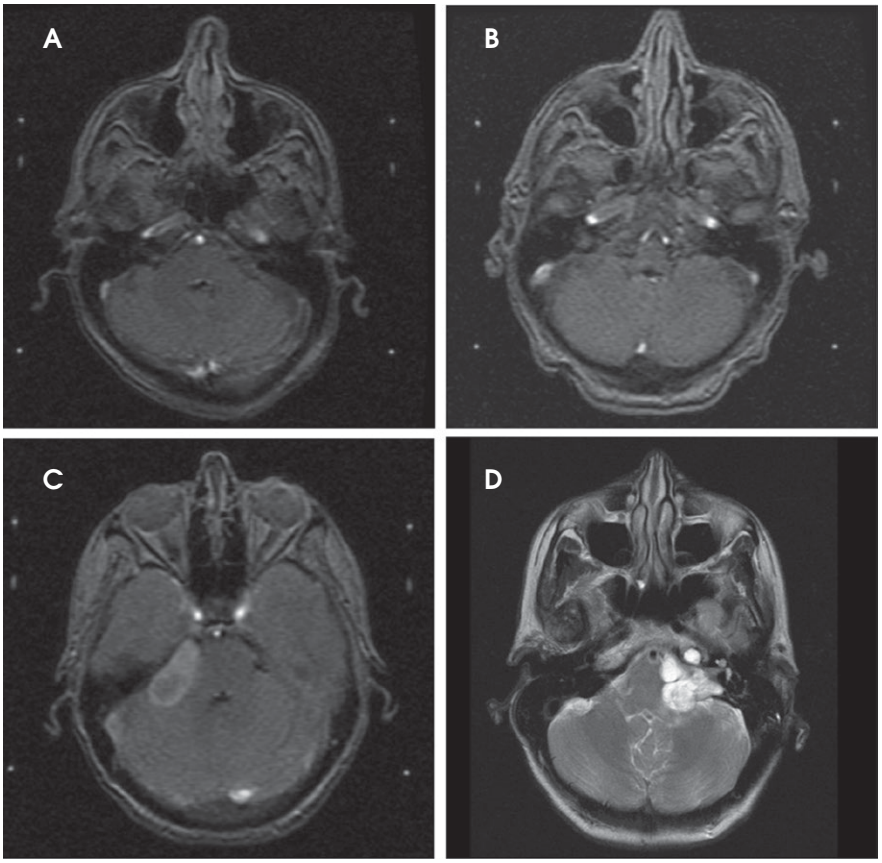


FIGURE 2. *T2-weighted MRI with contrast enhancement showing the 4 stages of AN growth (A-D): (A) Intracanalicular right-sided AN; (B) Cisternal (filling the cerebellopontine angle) right-sided AN; (C) Brainstem compressive right-sided AN; and (D) Hydrocephalic (involving ventricular deviation) left-sided AN*

suggest that SRS can be used to successfully control tumors up to 3 cm in diameter (when including the internal auditory canal in this measurement) in the majority of patients.[30] Two possible modalities exist: single session SRS and fractionated stereotactic radiation therapy (FSR) over multiple sessions. Stereotactic radiosurgery allows facial nerve preservation of > 95%, and hearing preservation in 70% to 90% of patients.[31,32] FSR allows facial nerve preservation of 95% and hearing preservation of 55% to 65%.[33] For both modalities, long-term local tumor control is 90% to 97%.[34,35]

Some studies have demonstrated bevacizumab to be associated with AN regression and hearing improvement in patients with NF-2. One study found stable or improved hearing retained in the majority of patients (90%) after 1 year of treatment with tumor shrinkage in > 50% of progressive AN, corroborated by a case report describing tumor regression of 40% in a patient treated for 6 months.[36,37] This treatment option may also be considered in patients with NF-2 preferring medical management, given evidence that it is associated with reduction in volume of most AN while being tolerable to patients.[38]

Despite these promising findings, there is no international consensus regarding the optimal treatment for AN < 3.0 cm.[7] With each treatment option, different risks and benefits are involved, balancing symptom relief with toxicities. Despite the lack of formal guidelines, the literature offers suggestions for optimal management based on various patient and tumor characteristics. Classification systems and scales have been devised and can be helpful in this process.[39,40] As outlined below, a thorough review of this body of data can help delineate select populations that could benefit from one treatment over the other.

Classification and Scales

Samii class for tumor classification. ANs are commonly classified according to size or extension. Four stages of AN growth have been described: intracanalicular, cisternal (filling the cerebellopontine angle), brainstem compressive, and hydrocephalic (involving ventricular deviation) (Figure 2A-D).[32] A classification based on the extent of tumor growth and presence, and severity of brainstem compression was developed by Samii.[41] As tumor location or extension is more predictive of hearing loss than tumor size,[11] classification systems such as the Samii Class[41] are useful in predicting the rate of facial nerve preservation corresponding to tumor size and anatomic extension.[42] The following classes are used to describe tumor location: T1-purely intracanalicular/intrameatal, T2-intra- and extra-canalicular/meatal, T3a-filling the cerebellopontine cistern, T3b-reaching the brainstem, T4a-compressing the brainstem, and T4b-severely dislocating the brainstem and compressing the fourth ventricle.

Samii and Matthies looked at 1000 surgically resected patients with AN, examining both facial nerve[25] and cochlear nerve (hearing)[40] preservation. They found anatomic preservation of the facial nerve was achieved in 93% of patients and of the cochlear nerve in 68%. Hearing preservation for surgical resection was 47%. Despite the opportunity for total or near-total resection with immediate symptom relief, surgical resection comes with a multitude of risks other than hearing loss, including

Table 1. Gardner-Robertson Classification for Hearing Preservation

Class	PTA or SRT (dB)*		Speech discrimination (%)
1	0-30	and	70-100
2	31-50	and	69-50
3	51-90	and	49-5
4	91- max loss	and	4-1
5	No response	and	No response

*Use better score. If PTA/SRT score and speech discrimination scores do not result in placement in the same class, use class appropriate for poorer score. Adapted from Gardner and Robertson paper, 1988.[39]

disequilibrium, particularly imbalance when walking (35%); vertigo (25%) or dizziness (22%); CSF leak/fistulas (9%); trigeminal nerve or facial nerve deficit/palsy (5%); hydrocephalus (2.3%); hematomas (2.2%); bacterial meningitis (1%); wound revisions (1%); hemiparesis (1%); and death (1%).[41] In one microsurgical series, mortality rates ranged from 0% to 6%.[43]

Gardner-Robertson scale for hearing preservation. Given the importance of hearing preservation as a primary outcome, the Gardner-Robertson (GR)[39] scale for hearing preservation after surgical resection was developed by Gardner and Robertson in their survey of the existing AN surgical series in 1988. The authors developed this scale to provide audiometric criteria for the classification of hearing preservation into 5 categories. Patients were graded pre- and postoperatively, and their classification was subsequently correlated to their tumor size. Specifically, this scale distinguishes the various levels of hearing of clinical interest beyond "serviceable" vs. "nonserviceable."[39] Serviceable hearing was defined as pure tone audiogram average (PTA) ≤ 50 dB and/or speech discrimination rate of ≥ 50%, corresponding to either GR Class I or II (Table 1).

Although this scale was designed to aid in choosing a surgical approach to best preserve hearing postoperatively, it can be applied to patients receiving radiation for AN, as it was a useful tool in measuring and comparing outcomes pre- and post-intervention. It is worth noting that reported hearing preservation rates vary widely based on patient selection criteria and methods of defining hearing preservation.[44] As such, the authors urged that until a universally accepted system of grading hearing status and preservation is established, actual audiometric scores (including information on masking) should be reported for each case in a given study.[39]

Neurosurgical Resection

Microsurgical resection is performed by an otologist and a neurosurgeon. Typically, surgeons must operate on a high volume of patients to obtain the requisite expertise.[13] There are multiple surgical approaches for resection, the selection of which depends on tumor size; extension into the IAC; preoperative hearing level; as well as surgeon experience, preference, and institutional tradition.[1]

Retromastoid approach. The retromastoid approach is an excellent option for facial nerve and hearing preservation, and can be used for any size tumor. However, this approach may not achieve gross total resection if the tumor extends distally into the IAC, and should be reserved for patients with functional hearing and good chances of hearing preservation post-surgery who can be followed for tumor recurrence.[41]

Middle cranial fossa approach. The middle cranial fossa approach allows some hearing preservation, as well as direct access to the lateral end of the IAC to safely remove the most lateral part of the tumor. It has the advantage of gross total resection in addition to facial nerve function preservation (78%),[45,46] and is a good option for small tumors (< 1.5 cm), but at the cost of only moderate hearing preservation. Risk of CSF leak is low; however, depending on tumor location, complete removal may not be feasible.

Translabyrinthine approach. The advantages of the translabyrinthine approach include shorter distance to access the tumor, avoidance of cerebellar retraction, and early identification of the facial nerve at the lateral end of the IAC.[1] This approach is good for anatomic facial nerve preservation while inevitably sacrificing hearing in the process, typically reserved for large tumors (> 3.0 cm) and recommended by some for patients who are deaf or have poor chances of hearing preservation.[47] It also has good results with regard to mortality and morbidity,[48] with the lowest morbidity associated with spinal fluid leaks and postoperative headache.[47] By contrast, this approach has a higher incidence of CSF fistulas and infection, particularly meningitis, in large tumors with hydrocephalus[49] compared to the middle cranial fossa approach.

Suboccipital approach. The suboccipital approach allows excellent visualization of the CPA and, thus, increased safety during dissection from the brainstem and lower cranial nerves while permitting identification of facial and cochlear nerves both proximally and distally, maximizing chances of functional preservation of both. This approach has the advantage of enabling hearing preservation even with larger tumors, with anatomic cochlear nerve preservation at 96% and functional preservation at 44%.[45] Facial nerve preservation with

this technique was noted in 99%, with completely normal function in 78%.[41,45] Evidence shows a lower incidence of temporary facial nerve paresis but higher incidence of headache compared to the middle cranial fossa approach.[50]

Retrolabyrinthine approach. The retrolabyrinthine approach, primarily used for vestibular neurectomy, sacrifices hearing and is less commonly used but performed at some centers for AN.[51]

Desire to preserve hearing, and whether the patient has hearing to spare, can guide decisions regarding surgical approach.[52] Ultimately, it is recommended that in addition to considering specifics of the patient's functional status and anatomic features of the AN, the technique with which the surgical team is most familiar should guide surgical approach.[41]

The population most likely to benefit from surgery as primary treatment includes patients with larger tumors or those who are symptomatic, especially if the patient can tolerate the risks of surgery or requires immediate symptomatic relief. Beyond these indications for surgery, there is some ambiguity and degree of provider and patient preference influencing the decision to perform surgery instead of radiation.

Radiation therapy. Radiation therapy (RT) options include several different types of stereotactic radiotherapy, including FSR applied over multiple sessions, and SRS administered in a single session. Fractionated stereotactic radiation therapy will be discussed in a later section. Cyberknife,[53] (Accuray, Sunnyvale, California) permitting a staged approach with improved tumor dose homogeneity, and proton beam[54] radiosurgery, with its dose distribution advantage, are other options used for patients with nonserviceable hearing and tumors < 2.0 cm, and are used at some centers. The goal of stereotactic radiotherapy in AN management is to prevent further tumor growth; preserve existing function, particularly hearing; and to reduce or avoid the morbidity associated with open surgery.

Stereotactic radiosurgery (SRS) overview. Evidence demonstrates radiosurgery to be a safe, effective management option for small and medium ANs, allowing for treatment in a single, outpatient session.[55,56] SRS allows for accurate targeting techniques for intracranial structures by focusing irradiation onto a stereotactically localized target. Targets up to 3.0 cm in diameter are typically considered appropriate for management with SRS.[7] Stereotactic radiosurgery works by inducing radiation necrosis in the targeted tissue volume with the long-term goal being growth control of the tumor.[57] The patient's head is fixed with an MRI-compatible Leksell Stereotactic Frame (Elekta, Stockholm, Sweden) and 1.0-1.5 mm slice MRI is obtained. Tumor volume is measured based on the macroscopic tumor seen on MRI or CT, and dose fall-off to the cochlea and brainstem is calculated.[35] This procedure is typically well-tolerated, with few patients developing major acute effects.[58] Reduction in radiation dose from the previously used 16 Gy[59,60] has played the most critical role in reducing complications associated with AN radiosurgery. Current guidelines recommend 12-13 Gy to the 50% isodose line, as studies have shown a prescription dose of 12.5 Gy to the tumor margin yields the optimal combination of maximum tumor control and minimum complications like facial weakness and hearing loss.[55] Many institutions, including our own, have seen success with dose of 11.5 Gy to the 50% isodose line.[61,62]

The dose threshold above which hearing preservation rates decrease is 13 Gy, making this the upper limit of therapy, particularly for patients with intact hearing. Useful or intact hearing was defined as GR Class I (specifically speech discrimination scores of ≥ 80% and/or PTA < 20 dB) by Kano et al,[59] and as GR Class I or II by Iwai et al, with the latter specification more commonly cited.[60] Toxicities with SRS include trigeminal neuropathy or hyperesthesia and facial nerve neuropathy or palsy, all of which have been reported in < 5% of patients. Notably, despite the overall high rate of hearing preservation with SRS, hearing deficit is still a possible toxicity, with useful hearing preserved in only 40% to 60% of all patients.

Comparing and Contrasting Management Strategies

Efficacy and Safety of Stereotactic Radiosurgery and Fractionated Stereotactic Radiosurgery: Comparison to Observation as Management Strategy

Several studies have demonstrated the efficacy and safety of stereotactic radiotherapy in the management of AN. Modifications in dosing schedule and prescription, including lower marginal doses, and advancements in technique, including more sophisticated treatment planning software and use of MRI-based targeting, have allowed for reduction in cranial nerve complications following FSR with similar tumor control rates as external-beam fractionated radiotherapy and SRS.[63] A Harvard retrospective study[63] examined 70 patients with AN (47% newly diagnosed, 31% postoperative, 19% recurrent) treated with conventionally fractionated FSR with a median dose of 54 Gy in 30 fractions to 95% isodose line. Median tumor volume in this group was 2.4 cm^3 and median follow-up was 3.8 years. Results demonstrated 5-year local control at 98%, freedom from resection at 92%, freedom from any neurosurgical intervention at 97% if initial tumor volume is < 8.0 cm^3 and 47% if ≥ 8.0 cm^3. Preservation rates of facial nerve and trigeminal nerve at 3 years were 99% and 96%, respectively. Surgery before FSR was predictive of trigeminal nerve toxicity (86% vs. 98%). Conventionally

Table 2. Summary of Quality of Life Measures in Acoustic Neuroma Patients Receiving Microsurgical Resection Compared to Stereotactic Radiosurgery (SRS)

	Facial movement 3-month follow-up	Facial movement 1-year follow-up	Facial movement last follow-up	Serviceable hearing* at 3-month follow-up	Serviceable hearing at 1-year follow-up	Serviceable hearing at last follow-up
Surgery	61%	69%	75%	5%	5%	5%
SRS	100%	100%	96%	77%	63%	63%

*Defined as AAO-HNS Class A or B. Table based on data from Pollock et al.[44]

fractionated FSR resulted in favorable outcomes in this group, which included those with NF-2 as well as sporadic AN; intracanalicular and extracanalicular tumors; presenting after conservative management with observation, tumor progression, or history of 1-3 surgical resections; as well as a range of tumor volumes (0.05-21.1 cm^3). While the variety of patients included is encouraging for future generalizability of this study, the superior outcomes in patients with smaller (< 8.0 cm^3) tumors most strongly supports the benefit of FSR in treating smaller tumor volumes.

Only a few studies have evaluated the safety of SRS as an alternative to surgical resection for older patients or those with medical comorbidities precluding surgery, but who may prefer or benefit from intervention over observation.[32] This is particularly salient given evidence of slow growth and even good hearing outcomes in a significant number of untreated AN cases.[21,64] A meta-analysis of observation as a management strategy included 26 studies with 1340 patients total, in which tumor growth was observed in 46% of patients (mean growth rate: 1.2 mm/year). Subsequent active treatment was required by only 18% of patients receiving RT.[65] An observational study by Breivik and colleagues[66] sought to compare SRS with the natural course of AN progression. Over the course of almost 5 years, there was a significant reduction in tumor volume in the RT group, in which need for additional treatment was reduced, compared to the observation group.[66] This was done without compromising hearing. These results suggest that AN growth rate, and thereby incidence rate of future retreatment, can be controlled by RT in unilateral, small-to-moderately sized extracanalicular/extrameatal tumors, including those > 2.0 cm in this study.

A study by Boari et al[43] assessed the safety and efficacy of SRS as primary treatment in patients ages 23-85 years (mean 59 years) with sporadic AN, and found tumor control to be 97.1% in patients, as well as low morbidity associated with SRS. This group concluded that younger GR Class I patients (pure tone audiogram average 0-30 dB, speech discrimination 70% to 100%) had a significantly higher probability of retaining functional hearing, even at 10-year follow-up. Parameters considered as determinants of the clinical outcome were long-term tumor control, hearing preservation, and complications. They recommended that the time between symptom onset, diagnosis, and treatment be shortened given that observation carries the risk of irreversible hearing deterioration in patients with serviceable hearing prior to SRS, particularly in younger patients.

Radiation Therapy Compared to Surgical Resection

Newer studies explore the possibility of using SRS where surgery was previously used. There are presently no guidelines on the effectiveness and safety of SRS compared to observation or microsurgical resection.[13] According to the literature, the rates of tumor control appear to be comparable between microsurgery and SRS for tumors < 3.0 cm.[67] With SRS, the tumor control rate is 97%, normal facial function is > 99%, trigeminal function is 97%, and hearing is preserved in up to 77% of patients.[35] Potential for adverse radiation effects without the advantage of rapid volume reduction offered by neurosurgical resection have made this option less popular for larger AN (> 3.0 cm).[7] Despite these toxicities, radiation still carries a lower risk of facial or trigeminal nerve injury than surgery, prompting many to examine the possibility of using SRS in patients previously recommended for surgical resection.[51]

Several groups have prospectively compared surgery and SRS. Data from the Mayo Clinic found that among patients with tumors < 3.0 cm, SRS and surgery had similar tumor control rates (100% vs. 96%) but found worse quality of life after surgery (Table 2).[44,68] A meta-analysis by Maniakas et al included 16 studies yielding 1292 patients and dating from 1979-2011, with comparable length of follow-up, among which nearly all radiosurgery patients received SRS. Based on pooled results, overall tumor control rate in the SRS group was seen in 96.2% compared to the recurrence-free rate of 98.7% in the microsurgical resection subgroup.[51] Literature also reports that complications

Table 3. Summary of Significantly Different Functional Outcomes in Acoustic Neuroma Patients Receiving Microsurgical Resection Compared to Stereotactic Radiosurgery (SRS)

	Facial motor disturbance	CN V disturbance	Preserved hearing (GR Class I or II)*	Overall functional disturbance	Hospital stay (days)	Mean days missed from work
Surgery	37%	29%	37.5%	39%	23	130
SRS	0%	4%	70%	9%	3	7

*Among patients whose pre-intervention hearing was GR Class I. Table adapted from Regis et al.[70]

compared to microsurgical resection from any approach (70.2% SRS vs. 50.3% microsurgical resection).[51] Furthermore, patients in the radiosurgical group had significantly lower mean Dizziness Handicap Inventory (DHI) scores, suggesting fewer problems with imbalance. Patients who underwent surgical resection experienced significant decline in several of the subsets of the Health Status Questionnaire (HSQ) used to assess quality of life at 3 months, 1 year, and last follow-up, particularly in the "physical functioning" and "bodily pain" categories, while those who underwent radiosurgery had no decline on any component of the HSQ.[44] French data demonstrated the largest prospective study comparing surgery to SRS.[70] This nonrandomized prospective series used pre- and post-operative questionnaires to evaluate functional outcomes after SRS or microsurgical resection in patients who received only one of these approaches as their primary treatment for unilateral AN. The minimum follow-up was 3 years. These results found that functional side effects occurred during the first 2 years after SRS, and that after 4 years of follow-up, patients receiving SRS had better overall function compared to those receiving microsurgery (Table 3).[70] There was no significant difference found between the 2 modalities for post-intervention tinnitus, vertigo or imbalance.

A retrospective study by Karpinos et al[71] also explored outcomes in patients receiving either SRS or microsurgery, with similar results. Stereotactic radiosurgery was found to be significantly more effective than microsurgery in preserving any measurable hearing defined by GR Scale I-IV (57.5% vs. 14.4%). At long-term follow-up, patients in the SRS group experienced significantly more tinnitus than microsurgical patients (26.5% vs. 0%), while the microsurgery group had a significantly higher rate of facial neuropathy (35.3% vs. 6.1%), classified according to the House-Brackmann grading system, and trigeminal neuropathy (22% vs. 12.2%). The microsurgery group also had significantly higher peri-operative (immediate post-intervention) complications (47.8% vs. 4.6%) and hospital stay compared to the SRS group. However, there was no post-intervention difference in worsening imbalance, dysarthria, dysphagia, headache, or functional level[71] (as defined by the Karnofsky Performance Scale and Eastern Cooperative Oncology Group scale).

Of particular interest in potentially expanding the population of patients recommended for SRS, a study by Yang et al[56] examined SRS in vestibular schwannomas 3.0-4.0 cm in diameter. This range falls above the 3.0 cm threshold above which surgery is recommended over radiation therapy. In this study population, 26% had prior surgical resection. After 36 months of follow-up, 18 (82%) of 22 patients with serviceable hearing before SRS still had serviceable hearing after SRS more than 2 years later. Three patients (5%) developed symptomatic hydrocephalus and underwent placement of a ventriculoperitoneal shunt. In 4 patients (6%) trigeminal sensory dysfunction developed, and in 1 patient (2%) mild facial weakness (House-Brackmann Grade II) developed after SRS. Overall tumor control rate for SRS was 87% over > 2 years. Microsurgical resection was recommended as primary management for patients with low comorbidities allowing toleration of surgery. However, this study concluded that SRS could satisfactorily manage AN of maximum diameter < 4.0 cm without significant mass effect based on patient preference. If implemented, this guideline would expand the number of patients that could choose radiation over surgical resection for tumors by including those with AN 3.0-4.0 cm in diameter.[56]

Synthesizing the existing data, the majority of studies conclude that patients with larger tumors or tumors causing mass effect are recommended to receive surgery, since this intervention seeks to remove all or part of the tumor, and the possibility of total resection exists only with surgery.[13] However, small or medium-sized tumors with minimal symptoms, or symptomatic tumors not requiring urgent decompression with surgery, can be treated with a variety of modalities. In these cases, the goal could either be tumor removal or tumor growth arrest, which should be carefully weighed given the possible morbidity associated with surgery.[13] Complicating the decision is that ideal candidates for SRS are typically

also ideal candidates for microsurgical resection. These patients have easily resectable, small-to-moderately-sized tumors.[7] Other considerations in choosing microsurgical resection or SRS include time-course of side effects, which tend to be immediate postoperatively, but can take months to years after completion of radiation therapy. Ultimately, all of these studies stressed the need for more follow-up data on patients receiving SRS for AN, particularly those who could have easily been recommended for microsurgical resection. It is especially important to track post-SRS symptoms and hearing preservation in this population. Many papers and review articles report satisfactory tumor growth control and few side effects with SRS, but there is no compelling evidence of the superiority of SRS to microsurgical resection or even conservative management.[13,72] Some studies support that SRS can be considered as the primary modality of choice for treatment of most AN that are < 3.0 cm.[67] Others conclude by recommending SRS to treat postoperative residual tumors as well as tumors in patients with medical conditions precluding surgery, while reserving microsurgical resection whenever a surgeon can confidently remove the tumor with the risk-benefit ratio exceeding that of SRS.[73]

Role of FSR Compared to SRS

Once the decision has been made to treat AN with radiation, the challenge becomes choosing to apply stereotactic irradiation in fractionated or unfractionated schedules.[74] Fractionated stereotactic radiosurgery has been used as an alternative to SRS with comparable local control and complication rates, with some studies reporting less morbidity with FSR than either SRS or surgical resection.[30,75] Several sources supporting FSR argue that dose fractionation, compared to SRS, permits the differential sparing of normal tissues (eg, vestibulocochlear nerve) as well as potential total dose escalation.[44,53,76] This is critical for AN, for which, as noncancerous entities that grow near critical structures, consideration of toxicity plays a key role in discussions on management. With FSR, the patient's head is immobilized in a mask and a linear accelerator is used to apply the radiation. A dose of 50-55 Gy total (in 25-30 fractions at 1.8 Gy/fraction to the 80% isodose line) have been used for lesions > 2.0-3.0 cm, while 25 Gy (5 Gy in 5 fractions) have been used for smaller lesions.[77]

Hearing preservation rates with FSR compared to SRS have been controversial, with different centers showing wide variation in the proportion of their patients reporting useful hearing.[44] These rates are thought to be slightly better with FSR than SRS or surgery according to Combs et al [31](94% with FSR) and Andrews et al[12] (81% with FSR vs. 33% with SRS). Meanwhile, other studies suggest equivalent rates of useful hearing between FSR and SRS if the SRS dose is ≥ 13 Gy.[78] Modern series have reported facial nerve preservation rates ranging from 95% to 100% and trigeminal nerve preservation rates from 84% to 100% in both FSR and SRS.[74]

A single-institution prospective study by Meijer et al[74] selected 129 patients with AN from 1992-1999 for either SRS (10 Gy and 12.5 Gy) or FSR (20 Gy/5 fractions and 25 Gy/5 fractions) and followed them for a mean interval of 33 months. These patients had documented tumor progression on MRI, progression of symptoms (particularly unilateral sensory hearing loss), and largest measured tumor diameter to be < 4.0 cm. Comparable rates of tumor control, preservation of hearing, trigeminal and facial nerve function were found between the 2 methods (Table 4). However, this series suggested that, in contrast to the facial nerve, the trigeminal nerve was more susceptible to injury by not fractionating the radiation treatment in a small proportion of patients.[74] Further studies are necessary to determine optimal regimens to minimize toxicity. There was no statistically significant treatment-related difference in trigeminal or facial nerve toxicity, hearing loss, or tumor control probability in patients with tumors < 2.5 cm compared to those with tumors ≥ 2.5 cm.[74] This is consistent with existing literature.[30,55,73] Given the ambiguity in optimal treatment of patients with tumors < 4.0 cm, it is important to note that tumor diameter did not predict for tumor control. This could suggest that a lower radiation dose may be sufficient for smaller tumors.[74]

A retrospective study by Andrews et al also compared SRS (dose 12 Gy) to FSR (mean dose 50 Gy in 25 fractions) in AN in 125 patients in a single-institution study for a mean follow-up of 2.3 years. Tumor control was found to be 98% for SRS compared to 97% for FSR. Toxicity was comparable for CN V (95% for SRS vs. 93% for FSR) and CN VII (98% for both SRS and FSR) preservation. However, in patients with sporadic AN and pre-intervention serviceable hearing, functional hearing was statistically significantly different, 33% in SRS group vs. 81% in the conventionally fractionated FSR group.[12] This rate was described as superior not only to SRS, but also microsurgery and the natural history of AN progression. Patients with GR Grade I hearing had a significantly higher probability of preserving functional hearing than did GR Grade II patients (especially among patients receiving FSR). This suggests the importance of early intervention in preserving hearing, specifically immediate treatment of GR Grade I patients with FSR to maximize probability of hearing preservation.[79] The results of this series were compared to other studies measuring post-treatment serviceable hearing in patients receiving either SRS or FSR,

Table 4. Actuarial 5-Year Outcomes with Stereotactic Radiosurgery (SRS) Compared to Fractionated Stereotactic Radiation Therapy (FSR)

	Local tumor control[7,1,74]	CN V preservation[71]*	CN V toxicity[74]	CN VII preservation[71]	CN VII toxicity[74]	Hearing preservation[71]^	Post-treatment serviceable hearing[12]^°
SRS	88-100%	92%	4.4-27%	93%	0-23%	75%	33-56%
FSR	94-100%	98%	0-13%	97%	0-3%	61%	78-81%

*Statistically significant difference in favor of FSR group. ^In patients with useful hearing prior to treatment. °Comparison of patients receiving stereotactic radiosurgery to those receiving stereotactic radiotherapy (linac) or hypofractionated stereotactic radiosurgery (linac). Table adapted from Combs et al,[77] Meijer et al,[74] and Andrews et al.[12]

which demonstrated comparable rates (Table 4).

The higher dose conformality achieved with SRS might suggest a higher rate of tumor control, and the higher dose homogeneity achieved with FSR linear accelerator might suggest less treatment-related morbidity.[12] As such, the 2.5-fold difference in hearing preservation in the Andrews et al study may not have been due to the fractionation schedule, but rather due to the higher dose inhomogeneity (number of isocenters) within the target volume in the SRS treatment group.[12] This is supported by data from earlier studies noting that, in addition to tumor diameter, a higher number of isocenters was significantly associated with higher rate of cranial and noncranial neuropathies, including trigeminal, facial, and vestibulocochlear nerve dysfunction.[80,81] Additionally, it is possible that the SRS group received a higher maximum dose to the acoustic nerve, as the acoustic nerve passes through the target volume.[74] This discussion of dose conformality and homogeneity remains controversial, particularly as other reports of SRS outcomes demonstrated lower incidence of cranial neuropathy with smaller collimators, more isocenters, and the use of MRI to enhance target identification (and, in the process, dose conformality).[82,83] Despite these controversies, more recent radiosurgery series demonstrate comparable outcomes between FSR and SRS.[30,84]

Combs et al performed one study evaluating the effectiveness and long-term outcome of SRS for AN,[31] and another assessing the long-term outcome and toxicity of FSR for AN.[77] Actuarial local tumor control rates at 3 and 5 years after FSR and SRS were comparable (Table 4). Two patients receiving SRS developed tumor progression at 36 and 48 months. Actuarial useful hearing preservation was 94% at 5 years for patients with pre-intervention useful hearing (Table 4). The hearing preservation rate in patients with useful hearing before SRS was 55% at 9 years. However, they discuss the importance of studying variation in hearing preservation, as it is the most common presenting symptom of symptomatic patients and one of the most valuable post-intervention outcomes. In addition, Combs et al cite existing studies at time of publication comparing FSR to SRS, demonstrating comparable local control and CN V and VII toxicity rates (Table 4). Cranial nerve toxicity other than hearing impairment was rare in this study. Among those at risk of treatment-related facial nerve toxicity, one patient developed a complete facial nerve palsy after SRS (5%). A total of 93% of the lesions treated were at risk of radiation-induced trigeminal neuralgia, and two of these patients (8%) developed mild dysesthesia of the trigeminal nerve after SRS.

The combined results of their studies concluded that FSR was safe and efficacious for the treatment of AN, with mild toxicity with regard to hearing loss and cranial nerve function. They described FSR as an alternative therapy for patients with AN, as it has been an equivalently effective treatment modality compared to neurosurgery. Meanwhile, SRS results in good local control rates of AN with acceptable risk of cranial nerve toxicities. As toxicity is lower with FSR, they recommend SRS be reserved for smaller lesions. Current recommendations include the use of SRS for tumor control in patients desiring one treatment session. The role of SRS in the management of small to moderate (< 3.0 cm) AN, for which surgical resection has traditionally been the recommended intervention, remains controversial.[56] Several advances have aided in improving outcomes while reducing adverse radiation effects, such as improvements in radiosurgical technique, development of more sophisticated dose-planning software, and the use of high-resolution stereotactic MR imaging and dose optimization.[56]

Due to differences in study population, tumor assessment, definitions used for hearing preservation, follow-up times, and treatment techniques, comparison of these series cannot reliably detect small differences between FSR and SRS outcomes and toxicities.[74] There has also been some evidence that at longer follow-up intervals, there appears to be lower rates of hearing preservation compared to preliminary studies that suggested superiority of FSR for this outcome.[44] Finally, toxicity associated with SRS has decreased since the introduction

of lower doses of radiation. Overall, evidence shows comparable rates of hearing preservation, local tumor control, and radiation-associated side effects between FSR and SRS, allowing for institutional experience and patient preference to guide the chosen modality. It is also worth noting the lack of randomized studies comparing FSR to SRS techniques, as a possible area of future study.

Integrating Literature and Future Directions

Limitations in AN Treatment

Major limitations of SRS include delayed-onset side effects and inability to remove the AN compared to surgical resection, and the potential for worse side effects related to higher dose at single fraction compared to FSR. Of note, most studies reporting on the control of tumor growth after treatment by SRS include patients without documented tumor growth rate before the initiation of treatment.[7] Much of the literature includes studies that have compared interventions separately, in a nonrandomized (and often nonprospective) fashion. There are limitations with comparing the efficacy and morbidity rates across interventions, due to selection bias and other confounding factors.[13] Additionally, many studies have cited inter-practitioner variation as a potential source of bias due to variations in surgical or radiation planning. Different institutions and practitioners also have varying degrees of availability and experience with stereotactic radiotherapy, or may otherwise have preferences toward one of the 3 mentioned treatment modalities.[7]

Future Directions

The recommendation based on many studies, including prior reviews, is the need for standard outcome measures,[44] specifically, consistently defined outcomes. These include hearing preservation, which would require clearer guidelines for when to perform audiology examinations over the course of follow-up and in relation to the chosen intervention. Many studies emphasize the need to use standardized reporting guidelines for AN resection results.[85] Another important opportunity for clarification lies with measurements and techniques employed for measuring tumor volume and response to treatment.[7] For example, in many studies, the definition of a treatment failure or success differs based on modality used. Often, a "failed" tumor outcome in microsurgical resection is defined as recurrence of tumor, whereas for radiosurgery, it is defined as growth of the tumor. Consistent definitions with subsequent consistent application of these terms to future studies can aid in interpreting these results and forming clearer guidelines for AN management. Despite the efficacy of radiosurgery for treatment of AN, many studies urge the importance of adequate follow-up duration, as treatment failures typically occur within 3 years after SRS,[74] and rare but potential adverse radiation effects such as cyst formation and secondary malignant transformation (estimated as a complication in 0.01% to 0.1%) have a latency period of 5 years or more after SRS.[32,44]

Tumor volume has been shown in some studies to be a better indicator of response to SRS than maximum tumor diameter, which is the measurement currently cited in studies making treatment recommendations. Yang et al examined AN control with SRS, and after 36 months found that 16 tumors (25%) had a volume reduction of more than 50%, 22 (35%) tumors had a volume reduction of 10% to 50%, 18 (29%) were stable in volume (volume change < 10%), and 7 (11%) had larger volumes (5/7 patients underwent resection and 1/7 underwent repeat SRS). In univariate analysis at 2 years, patients who had a previous resection, those with a tumor volume exceeding 10 ml, those with Koos Grade Classification[86] 4 tumors, and pre-SRS facial weakness, had significantly lower likelihood of tumor control after SRS.[56] In multivariate analysis, patients with no history of a resection and with Koos Classification Grade 3 tumor extension had better tumor control.[56] RECIST (Response Evaluation Criteria in Solid Tumors) guidelines[87] are tumor-centric criteria published to define when tumors improve ("respond"), stay essentially unchanged by ("stabilize"), or worsen ("progress") during the course of treatment. These outcome assessments are determined based on evaluation of target lesions for degree of response: complete response (disappearance of all target lesions), partial response (≥ 30% decrease in the sum of the longest diameter (LD) of target lesions), stable disease (neither sufficient shrinkage nor increase compared to smallest sum of LD of lesions), and progressive disease (≥ 20% increase in the sum of LD of target lesions).

Summary of Key Findings

There is no international consensus on the optimal treatment for AN.[7] Likewise, there are presently no guidelines on the effectiveness and safety of SRS compared to observation or microsurgical resection. Many papers and review articles describe satisfactory tumor growth control and few side effects with stereotactic radiotherapy.[13,72] But despite these promising results, there is no clear evidence that this treatment modality is superior to microsurgical resection. To date, there are no prospective randomized controlled trials comparing conservative management with observation, microsurgical resection, and stereotactic radiotherapy.[7] Prospective evaluation of these modalities in a comparable population of patients who could opt for any of these modalities is needed. Ideally,

these studies would be performed in a single institution setting with the same physician performing resection as being involved with RT to minimize inter-practitioner bias.[44] By examining outcomes in patients presenting with symptoms as well as those with incidentally discovered AN in the small-to-medium range, more consistent recommendations can be made on how to optimally treat these populations in an interdisciplinary fashion.

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Glioblastoma: Multidisciplinary treatment approaches

Luis Moreno Sánchez, MD

Glioblastoma, also known as glioblastoma multiforme (GBM), is the most common and most malignant primary tumor of the central nervous system (CNS) (Figure 1). According to the Central Brain Tumor Registry of the United States (CBTRUS) 2007-2011, 52.751 of 343.171 brain tumors (15.37%) were GBM, representing 45.6% of all malignant primary brain tumors.[1]

During the early 19th century, glioblastoma was considered GBM of mesenchymal origin and was defined as a sarcoma. In 1863, Rudolf Virchow demonstrated its glial origin,[2] and in 1914 Mallory proposed the term glioblastoma multiforme. However, it was not until 1925 that Globus and Strass presented a complete description of the neoplasm, at which point the most common term became spongioblastoma multiforme. Finally, in 1926, Bailey and Cushing successfully reintroduced the term originally proposed by Mallory: glioblastoma multiforme.

There are two types of GBM, each distinguished by origin and molecular phenotype: primary, which represents the majority of GBM patients and develops rapidly over the course of several weeks; and secondary, which presents as lower-grade gliomas and eventually progresses to grade IV. Once a patient is diagnosed with GBM, the overall median survival time for those treated with the Stupp scheme is approximately 15 months.[3]

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Technology

Treatment protocols for GBM combine surgery followed by concurrent radiation therapy with temozolamide and adjuvant temozolamide (TMZ). These approaches provide palliation and moderate survival benefit.[3-5]

Clinical Applications

Surgery

In multidisciplinary regimens, glioma resection remains the mainstay given its central role in establishing a histologic diagnosis and in relieving symptoms of mass effect by mechanical cytoreduction. The objective is to provide maximal tumor resection with preservation or restoration of neurologic function.[6,7] Unfortunately, patients nearly always experience tumor recurrence, as these tumors invade and infiltrate surrounding normal tissue, making curative resection unlikely.

Advanced Surgical Techniques

The best established technique for assessing the eloquent cortex to guide resection is direct cortical stimulation (DCS).[8,9] With this approach, low-current stimulation of the brain creates a transient localized lesion, and testing of language function during DCS can help assess the site of importance in language function. The mapping of motor and language areas of the brain has allowed for more aggressive resections of high-grade gliomas by minimizing the risk of potential deficits.

In fluorescence-guided resections, 5 aminolevulinic acid (5-ALA) is used as an orally administered prodrug, which is metabolized intracellularly to protoporphyrin IX and emits a red-violet fluorescent signal evidenced by blue light. This agent accumulates in certain tumor types and, thus, can help differentiate tumor from normal surrounding brain tissue.[10]

Image-guided surgical techniques have helped safely assist the extent of surgery in eloquent cortical areas where resection is frequently abandoned before gross total resection to avoid neurologic deficits. This is the reason for neuro-navigation based on preoperative functional MRI (fMRI), the most common noninvasive tool that can provide additional information on the anatomical relationship between borders of the tumor, specifically infiltrating tumors and eloquent areas.[11-14] Motor mapping can be performed either with the patient awake or under general anesthesia, while speech mapping requires the use of an awake anesthesia technique,

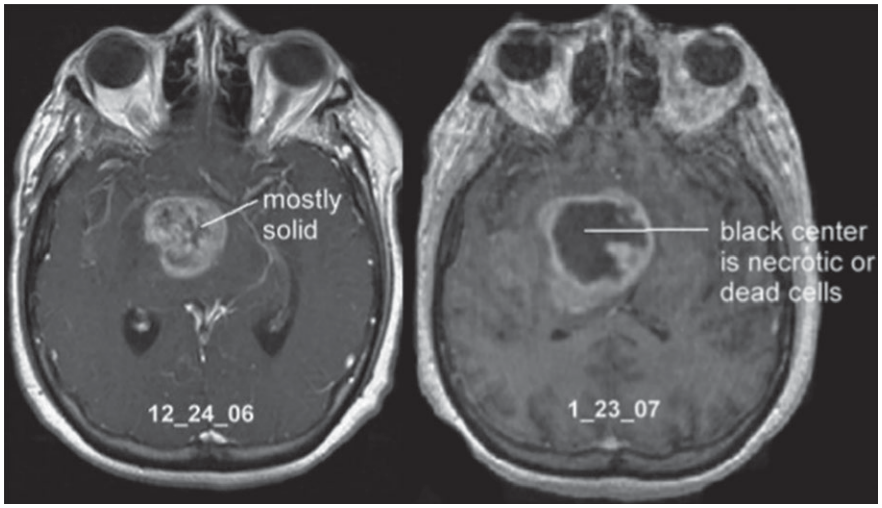

FIGURE 1. *Progression in 1 month of untreated GBM.*

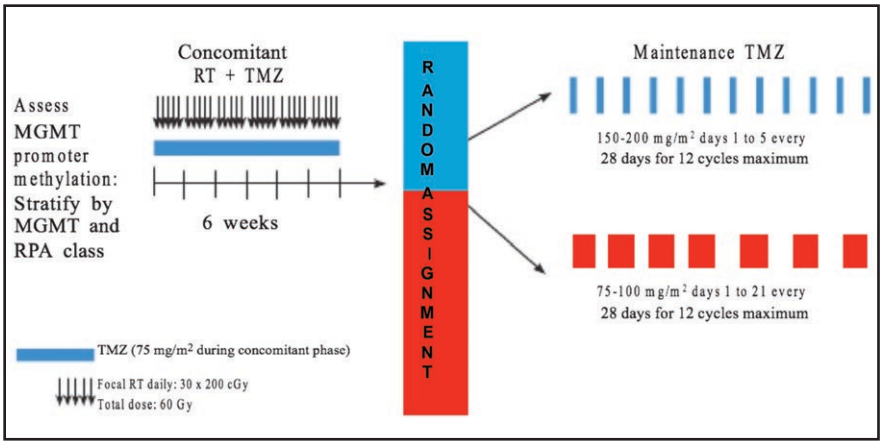

FIGURE 2. *Stupp regimen (blue) and dose-dense temozolomide regimen (red) for newly diagnosed GBM.*

at least during the mapping portion. Concomitant with neuronal activity is an increase of blood flow through local cerebral vessels. These changes in cerebral blood flow can be visualized by a method of fMRI that measures variations in the area of interest that are dependent on blood oxygen level.

Chemoradiotherapy

After surgery, chemoradiotherapy is considered the standard treatment. During the delineation and planning of radiotherapy treatment, the radiation oncology team uses acronyms like GTV (gross tumor volume), CTV (clinical target volume) and PTV (planning target volume). The doses and treatment phases are based on protocols determined by the European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG). Based on the RTOG guidelines, the initial volumes (T2/FLAIR + gross/residual tumor plus resection cavity) receive 4600 cGy/23 fractions followed by a boost to 1400 cGy/7 fractions to gross/residual tumor plus resection cavity. In a study by Kelly et al,[15] the isolated tumor cells were noted to extend to cover T2 changes and beyond on MRI, which was confirmed with serial stereotactic biopsies; this is the reason for the definition of the initial GTV treated to lower doses (eg, 46 Gy). These PTV are based on the 1980 study by Hochberg

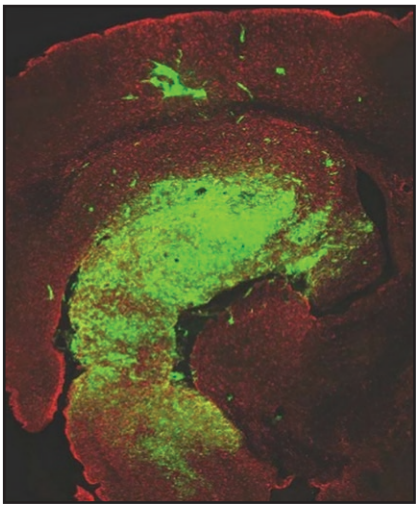

FIGURE 3. *GBM cells (in green) spread diffusely.*

and Pruitt[16] that showed, using computed tomography (CT), 78% of recurrences were within 2 cm of the margin of the initial tumor bed, and 58% were within 1 cm. This pattern was validated by Wallner et al.[17] These data are the basis for the definition of the boost to GTV treated to higher doses (eg, 60 Gy). According to the EORTC, only a treatment volume receives 60 Gy in 30 fractions. The GTV corresponds to the surgical resection cavity plus any residual enhancing tumor (postcontrast T1-weighted MRI scans); the CTV comprises the GTV plus a margin of 20 mm; and finally, PTV is equal to CTV plus a margin of 3-5 mm.

Better results have been obtained with a combination of RT and temozolamide (TMZ), with standard dosing for concomitant TMZ therapy being 75 mg/m2/d given daily during radiation therapy (RT) followed by 150-200 mg/m2/d for 5 days every 28 days for a total of 6 cycles.[3] The RTOG-0525, which consisted of 833 patients, did not show a statistically significant difference between a conventional TMZ regimen and a dose-dense TMZ protocol. The overall survival (OS) was 16.6 vs. 14.9 months, and progression-free survival (PFS) was 5.5 vs. 6.7 months, respectively. The dose-dense protocol increased grade 3 toxicities from 34% to 53% (Figure 2).

Table 1. Alternative Temozolamide Regimens for Recurrent GBM

Author	Regimen	Dosage	# Patients	Results
Wick et al[48]	1 week on / 1 week off	150 mg/m2 on days 1-7 and 15-21 of 28-day cycles	64	PFS: 6 month 43.8%; 12 month 12.5%; median: 24 weeks
Brandes et al[49]	3 weeks on / 1 week off	75 mg/m2 on days 1-21 of 28-day cycles	33	PFS: 6 month 30.6%; median: 16.1 week OS 6 and 12 month 73% and 38%
Balmaceda et al[50]	Twice daily for days 1-5	200 mg/m2 initial dose then 90 mg/m2 every 12 hours for 9 doses	68	PFS: 6 month 35%; median: 4 month. OS 6 and 12 month 71% and 35%
Khan et al[51]	42 days on / 28 days off	75 mg/m2 on days 1-42 of 70-day cycles	28	PFS: 6 month 19%; OS 6 month 60%; median survival 7.7 months
Perry et al[52]	Continuous	50 mg/m2/day	35	Group 1. PFS 2nd relapse: 6 month 17%. Group 2. PFS 1st relapse 57%
Perry et al[53]	Continuous	50 mg/m2/day	88	PFS: Group 1, 2, 3 at 6 month 73%, 7.4% and 35.7%

In an attempt to shorten treatment duration in older patients, hypofractionated radiation therapy (HFRT), which gives a higher radiation dose per fraction in fewer total fractions over a shorter period (eg, 40 Gy in 15 fractions over 3 weeks), has been shown to be equivalent in older patients to the standard of 60 Gy in 30 fractions over 6 weeks.[18]

Stereotactic radiosurgery (SRS) has been used as a boost after conventional treatment or in cases of recurrence.[19,20] Some authors theorize that SRS could be useful as a local radiation boost to the "worst" part of the tumor, which could be identified with MR perfusion imaging, or in areas with the highest creatine to coline ratio on MR spectrocospy; however, some publications have shown no benefits[21,22] (Figure 3). There is no level I evidence that supports the addition of SRS as an initial treatment. Level II evidence suggests a modest survival benefit after SRS in selected patients; on the other hand, attempts to deliver a higher cumulative dose of 70.4 Gy using hyperfractionation schemes also failed to show a survival advantage.[23] With the implementation of TMZ into standard GBM therapy, the role of SRS in both newly diagnosed and recurrent GBM continues to be investigated. Clinical oncologists should consider different schemes (Table 1) in treatment regimens with TMZ (recurrence), which can be monitored closely, considering the advances in imaging techniques, localization, chemotherapy (CHT), biological agents and radiosensitizers.

Chemotherapy

CHT includes alkylating agents, nitrosoureas, procarbazine, topoisomerase inhibitors, platinoids, vincristine, and estrogen receptor antagonists.[24-32] Before TMZ therapy, the role of CHT in GBM was controversial. A meta-analysis of 12 randomized trials (> 3000 patients) showed an increase in 1-year survival from 40% to 46% with CHT.[33] TMZ is an alkylating agent stable only at acidic pH.[34] This prodrug undergoes rapid chemical conversion in the systemic circulation at physiological pH to the active compound, which will react with water. This results in an unstable cation, which transfers a methyl group to the DNA, causing the cytotoxic effect of temozolomide because it depletes the DNA-repair enzyme O6-methylguanine-DNA methyltransferase (MGMT). In 2009, bevacizumab, an anti-VEGF inhibitor, was approved for the treatment of recurrent glioblastoma. It has been administrated as a single agent or in combination with cytotoxic therapy; however, neither regimen has been shown to prolong OS.

Molecular Diagnostics

Molecular diagnostics are important because low levels of MGMT in tumor tissue are associated with longer survival among patients with GBM.[35-36] Approximately 45% of patients with newly diagnosed GBM have methylation of the MGMT promoter that responds better to TMZ.[37]

Recently, a paper by Parsons and colleagues[38] demonstrated the existence of a glioma-associated mutation in isocitrate dehydrogenase-1 (IDH1) in 12% of patients with GBM. IDH is an enzyme involved in oxidative metabolism.[39] Mutations in IDH1 were associated with younger age, secondary GBMs (grade IV tumors that arise from biopsy-proven, lower-grade predecessors), and increased OS. IDH1 mutations have been found more frequently in secondary GBM (sGBM) compared with primary GBM (pGBM); patients with GBM with IDH1 mutations have improved survival (45.6 vs 13.2 months).[40,41] Additionally, Sanson and

FIGURE 4. *Example of tumor-treating fields (TTF). These low-intensity, medium-frequency, alternating electric fields are administered using insulated electrodes on the skin surrounding the region of a malignant tumor.*

colleagues[42] found improved progression-free survival (PFS) of 55 months in patients with IDH1 mutation vs 8.8 months in those without mutation. Secondary GBM is characterized by IDH1, TP53, and ATRX mutations, while primary GBM frequently show molecular alterations in EGFR, PDGFRA, PTEN, TP53, NF1, and CDKN2A/B, as well as TERT promoter mutations, but not IDH mutations.

Another molecular prognosticator is alpha thalassemia/mental retardation syndrome X-linked (ATRX), a gene that produces a protein involved in chromatin remodeling. Jiao et al[43] showed that ATRX mutations appear in 57% of patients with secondary GBM, and are rare in primary GBM (4%), noting that nearly half of adult-infiltrating gliomas that harbored an ATRX mutation also contained an IDH1 mutation.[44]

Electrical Fields

Tumor-treating fields (TTF) are low-intensity, medium-frequency, alternating electric fields administered using insulated electrodes on the skin surrounding the region of a malignant tumor (Figure 4). This disrupts cancer cell mitosis. TTF selectively affects dividing cells while quiescent cells are left intact, acting in 2 modes: arrest of cell proliferation and destruction of cells while undergoing division.[45]

In 2011, the NovoTTF-100A system (Novocure Ltd., Haifa, Israel) was approved by the U.S. Food and Drug Administration for treating recurrent glioblastoma. While a phase 3 clinical trial comparing stand-alone TTF with TMZ for recurrent glioblastoma failed to demonstrate a significant difference in OS between both groups,[46] it is important to mention that a comparative subgroup analysis of the original trial demonstrated that TTF accounted for a proportion of the responders to treatment than the conventional CHT group, with a median response duration of 7.3 vs 5.6 months.[47] At interim analysis, the EF-14 Trial,[117] which enrolled 700 patients from the United States, Europe, South Korea, and Israel, showed that 315 patients who received TMZ and treatment with the NovoTTF-100A system (now called Optune) survived an average of 19.6 months vs. 16.6 months for those receiving only TMZ. Additionally, patients treated with Optune had an increased PFS of 3 months compared to those who did not (7.1 vs 4.0 months). The OS at 2 years was 43% with Optune and TMZ, and 29% with TMZ alone.This phase 3 clinical trial was terminated at interim analysis due to early success, and was presented at the Society of Neuro-Oncology (SNO) 2014 Annual Meeting in Miami, Florida, by Dr. Roger Stupp.

Toxicity

The presence of neurological deficits following neurosurgery is declining, thanks to advances in tumor localization and delineation, functional imaging, and operative techniques. Despite these advances, some tumor localizations remain a common cause of cranial nerve injury.

Common radiation-induced adverse effects include: fatigue, anorexia, alopecia, erythema of the scalp, serous otitis, nausea, vomiting, exacerbation of neurologic deficits, headaches and seizures. Considering the poor prognosis of these patients, reports of long-term complications in high-grade gliomas (other than radiation necrosis) are rare.

CHT is generally neurotoxic,[54] but the CNS is protected when the blood-brain barrier is intact. Therefore, signs of encephalopathy such as headaches, altered cognition, or arousal with or without seizures are rare after systemic administration of conventional CHT doses. The use of glucocorticosteroids,[55] opioids and antiepileptics may result in behavioral and mental changes, anxiety, nervousness, insomnia, or euphoria. The toxicity caused by TTF is low and consists mainly of skin reactions at the site of the electrodes.

Diagnosis of Recurrence

Tumor recurrence occurs in almost all patients, and standards of care are incompletely defined in recurrent or progressive glioblastoma. All therapeutic modalities mentioned above can be used again, modified as needed with each case. However, one should note that the appearance of enhancing lesions on MR imaging within the first 6 months after completing chemoradiation therapy poses a challenge as it can reflect true progression (TP) or treatment-related changes known as pseudoprogression (PSP). Criteria for response and progression in GBM should be discussed 3 to 6 months after completing chemoradiation, as many patients show increased contrast enhancement and T2/FLAIR hyperintensity in the radiation treatment field. As a result, MR imaging every 3 months remains the gold standard for diagnosing response or progression in GBM. Given the uncertainty of PSP and TP, it is important to consider criteria such as the MacDonald criteria and RANO criteria (Table 2). MacDonald criteria does not take PSP into account when defining disease progression,

Table 2. MacDonald Assessment and Response Assessment in Neuro-Oncology (RANO)

	Criteria	
Response	**MacDonald**	**RANO**
Complete	All: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks, no new lesions, no corticosteroids, and being stable or improved clinically.	All: T1 gadolinium enhancing disease, none; T2/FLAIR, stable or decreasing; new lesion, none; corticosteroids, none; clinical status: stable or improving.
Partial	All: ≥ 50% decrease in sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks, no new lesions, stable or reduced corticosteroid dose, and being stable or improved clinically.	All: T1 gadolinium enhancing disease, ≥ 50% decrease; T2/FLAIR, stable or decreasing; new lesion, none; corticosteroids, stable or decreasing; clinical status: stable or improving.
Stable	All: not being qualified for complete response, partial response, or progression; being stable clinically.	All: T1 gadolinium enhancing disease: < 50% decrease but < 25% increase; T2/FLAIR: stable or decreasing; new lesion: none; corticosteroids: stable or decreasing; clinical status: stable or improving.
Progression	Any: ≥ 25% increase in sum of the products or perpendicular diameters of enhancing lesions, any new lesion, or clinical deterioration.	Any: T1 gadolinium enhancing disease: ≥ 25% increase; T2/FLAIR: increasing; new lesion: none; corticosteroids: not applicable; clinical status: deteriorating.

whereas the more contemporary RANO criteria defines progression as the development of a new area of enhancement outside of the prior radiation field at < 12 weeks after completion of chemoradiotherapy, confirmed by biopsy or clinical decline. Currently, the best standardized tool for evaluating response or progression is the RANO criteria.

Conventional MRI, such T1-weighted, gadolinium-enhanced (T1-Gad); T2-weighted; or fluid-attenuated inversion recovery (FLAIR) sequences, do not differentiate recurrent tumors from radiation injury. Advanced MRI techniques such as MR spectroscopy (MRS), perfusion-weighted imaging (PWI), and diffusion-weighted imaging (DWI); and biological imaging such as positron emission tomography (PET), have shown promise in differentiating glioma recurrence or progression from treatment changes.[56] Several studies evaluating the use of either MR spectroscopy or MR perfusion found that relative cerebral blood volume (rCBV),[57-61] as well as Cho/Cr and Cho/NAA ratios,[62-68] are good predictors of recurrent tumor. The Cho/NAA and NAA/Cr ratios[44] are good for differentiating tumor recurrence from radiation necrosis, and higher Cho/NAA ratios were associated with a greater probability of tumor infiltration and recurrence.[41,45] With PET techniques, imaging with radiolabeled amino acids offers a powerful approach for noninvasive evaluation of brain tumors. Recent studies demonstrated that [11 C]-methionine (MET), O-2-[18 F]-fluoroethyl-L -thyrosine (FET), as well as 3,4-dihydroxy-6-[18 F]-fluoro-L-phenyl-alanine (FDOPA) could be good techniques for detecting glioma recurrence and complementing MRI.[69-77] Amino acid PET can detect a metabolically active tumor, and this amino acid uptake in patients with suspected glioma recurrence may be useful in guiding new treatment options to optimize effects in patients with recurrent malignant GBM.

Treatment Options for Tumor Recurrence

The option of repeating surgery in patients with progressive or recurrent glioblastoma remains controversial. Some retrospective studies proposed a survival benefit after reoperation[78-81] taking into account age, Karnofsky (KPS) and Eastern Cooperative Oncology Group (ECOG) scales, MGMT promotor methylation, tumor volume, localization, extent of resection, ependymal involvement and tumor in noneloquent areas, while others did not.[82-84] Ringel et al[85] assessed 503 patients undergoing 1 to 4 re-resections for recurrent GBM with a median OS of 25.0 months after initial surgical treatment, and 11.9 months after first re-resection.

Re-irradiation is a similarly controversial option for patients with recurrent glioblastoma; total doses between 30-36 Gy in 2-3.5 Gy fractions with or without intensity modulation have been used.[86,87] In an attempt to retreat larger volumes of recurrent disease with higher doses, the departments of human oncology, medical physics, and biostatistics at the University of Wisconsin, explored pulsed reduced-dose-rate radiation therapy (PRDR), in which the dose-rate effect is most dramatic between 0.01 and 1 Gy/min compared to conventional

radiation therapy, in which a dose of 2 Gy is delivered at a dose rate of 4-6 Gy/min. The Wisconsin reirradiation experience consisted of PRDR in a series of 0.2-Gy pulses separated by 3-min intervals, creating a dose rate of 0.0667 Gy/min, reducing the linac dose rate to 1 Gy/min during each 0.2-Gy pulse, which would enhance the therapeutic ratio, taking advantage of the sublethal damage repair of normal tissue and the phenomenon known as low-dose hyper-radiosensitivity (LDHRS) of the tumor.[118] On the other hand, SRS can be considered in patients with small volume and well-defined disease.[88] Given that GBM recurrences are predominantly local, proponents of using SRS note that it allows for dose escalation with a rapid fall-off of gradient doses limiting exposure to organs at risk (OARs). Skeptics report that GBM is a highly infiltrative disease that extends beyond the apparent margins, making the use of a highly conformal technique inadvisable. In 2014, Larson et al reviewed the literature and found 9 studies describing the use of Gamma Knife (Leksell Gamma Knife; Elekta, Stockholm, Sweden) radiosurgery for recurrent GBM,[89] with a median OS range of 9-17.9 months from salvage SRS, and a median progression-free survival (PFS) range of 4.6-14.9 months.[90-98]

Beyond chemotherapy with alkylating agents (TMZ or nitrosoureas), other classical non-alkylating chemotherapeutics have been studied, including carboplatin (CABARET trial) and irinotecan (BRAIN trial). Evaluated in randomized phase 2 trials as add-ons to bevacizumab,[99,100] these agents showed no difference in outcome, and caused additional toxicity.

Another therapeutic option to consider is an intravenous humanized anti-VEGF monoclonal antibody that impairs angiogenesis by targeteing the VEGF ligand (bevacizumab). The induction of VEGF by ionizing radiation enhances blood vessel protection and, subsequently, tumor resistance. Anti-VEGF therapies block this protection, and enhance the effect of therapeutic radiation,[101,102] but the future role of bevacizumab is uncertain since the EORTC 26101 trial failed to demonstrate superiority for OS of lomustine plus bevacizumab over lomustine alone.[103]

Extracranial Metastatic Disease

The first case of extracranial metastasis was reported by Davis in 1928,[104] with a GBM disseminated to the lung, chest wall and soft tissue of an arm. Extracranial metastasis is a unique but rare manifestation of GBM reported in < 2% of cases,[105-112] with only 83 cases published between 1928 and 2009. This rarity is related to patients' short period of life, with a median OS of 10.5 months, a median time from symptom onset to diagnosis of primary GBM of 2.5 months, a diagnosis to extracranial metastasis detection time of 8.5 months, and metastasis to death time of 1.5 months.[113,114] The infrequency of this extracranial demonstration is perhaps due to intrinsic biological obstacles that prevent tumor GBM cells from infiltrating and surviving beyond the neural environment, such as the blood–brain barrier, absence of a lymphatic system within the brain and spinal cord to allow systemic dissemination, thickened basement membrane of blood vessels, and thickened dura mater around intracranial veins that prevents tumor cell penetration.

Conclusion

In general, overall survival of GBM patients has improved little over time, despite advances in molecular diagnostics, neurosurgery, radiation therapy, chemotherapies, imaging techniques, and immunotherapy, and continues to pose a difficult challenge for patients, family and clinicians. Life expectancy in patients with unmethylated MGMT is 14.8% and 8.3% at 2 and 5 years, respectively, vs. 48.9% and 13.8% in those with MGMT promoter methylation.[115] In 2009, the randomized phase 3 study of a 5-year analysis of the EORTC-NCIC trial[119] showed that OS in 573 patients was 27.2%, 16.0%, 12.1% and 9.8% at 2, 3, 4 and 5 years, respectively, with radiotherapy and TMZ, vs. 10.9%, 4.4%, 3.0% and 1.9% with radiotherapy alone. The methylation of the MGMT promoter was the strongest predictor of results with TMZ. Research must continue to guide treatment based on current developments, taking into account prognostic factors to offer patients a greater quantity and/or quality of life.

While standard treatment for intracranial GBM is surgical resection followed by concurrent radiotherapy and chemotherapy,[116] treatment strategies for metastatic disease are sparse, and optimal treatment has not been determined. Clinical trials[120] are attempting to establish the most appropriate therapy for recurrent GBM. In the case of metastatic lesions, it would be an interesting option to recruit patients for clinical trials to establish the most promising treatment; however, the rarity of this condition and its prognosis would hamper success.

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RADIATION ONCOLOGY CASE

Congratulations to our Clinical Case Contest winner for March 2016!

Metastases from glioblastoma disguised as a new primary malignancy

Joshua L. Rodriguez-Lopez, BS; Zachary D Horne, MD; John C Flickinger, MD

CASE SUMMARY

A 65-year-old man with a history of glioblastoma (GBM) of the right frontotemporal lobes who was treated with radiation therapy and concurrent/adjuvant temozolomide (TMZ) had a recurrence 3 months after standard chemoradiotherapy. He was subsequently treated with bevacizumab, lomustine, and Gamma Knife (Elekta, Stockholm, Sweden) stereotactic radiosurgery (GKSRS). Following GKSRS, he was treated with NovoCure tumor treating fields (NovoTTF; NovoCure, Portsmouth, New Hampshire). Approximately 9 months later, he developed back pain, right-sided ptosis, and sinus congestion-like symptoms. Spinal computed tomography (CT) imaging showed multilevel spinal disease, and MR imaging showed lesions in the T8-10 vertebral region. Imaging of the head suggested a new paranasal sinus primary tumor, suspicious for the origin of his metastatic disease. The patient underwent a T7-8 kyphoplasty, the pathology from which showed glial fibrillary acidic protein (GFAP), epithelial membrane antigen (EMA), and CD138 positivity, which was suggestive but not definitive for metastatic GBM. He presented 1 week later with worsening sinus congestion/ptosis, and had repeat imaging of the head (see below). Body imaging showed pulmonary and hepatic lesions. The patient underwent a biopsy of his paranasal sinus disease and the result was consistent with metastatic GBM.

Because of his significant back pain, we simulated him for palliative radiation therapy to his cervical and thoracic spinal disease, as it was having the greatest impact on his quality of life. We treated his cervical disease (8 Gy × 1) and then he requested we defer the thoracic radiation therapy to another day because of discomfort from lying on the table. The next day, the treatment conditions became unsafe secondary to the patient's inability to lie on the table and his thoracic radiation therapy was terminated. He was discharged to home with hospice and died approximately 3 weeks later.

Mr. Rodriguez-Lopez *is a medical student at Ponce Health Sciences University School of Medicine, Ponce, Puerto Rico.* ***Dr. Horne*** *is a PGY-3 resident, and* ***Dr. Flickinger*** *is professor of radiation oncology and neurosurgery at the University of Pittsburgh Cancer Institute, Department of Radiation Oncology, Pittsburgh, PA.*

IMAGING FINDINGS

An MRI of the head showed destructive changes in the paranasal sinuses with destruction of the left maxillary sinus and extension into the left retroantral fat, pterygopalatine fossa, and hard palate. The left lamina papyracea and left orbital roof were being invaded by a soft tissue mass in the left orbit measuring 2.6 × 0.9 cm, which engulfed the superior rectus, oblique, and medial rectus muscles (Figures 1 and 2).

DIAGNOSIS

The patient was diagnosed with widely metastatic glioblastoma. The initial suspicion was that he had developed a metastatic paranasal sinus primary tumor, which was disproved by his biopsy.

DISCUSSION

GBM is the most common histology of malignant primary brain tumors in adults.[1] Despite advances in surgical,

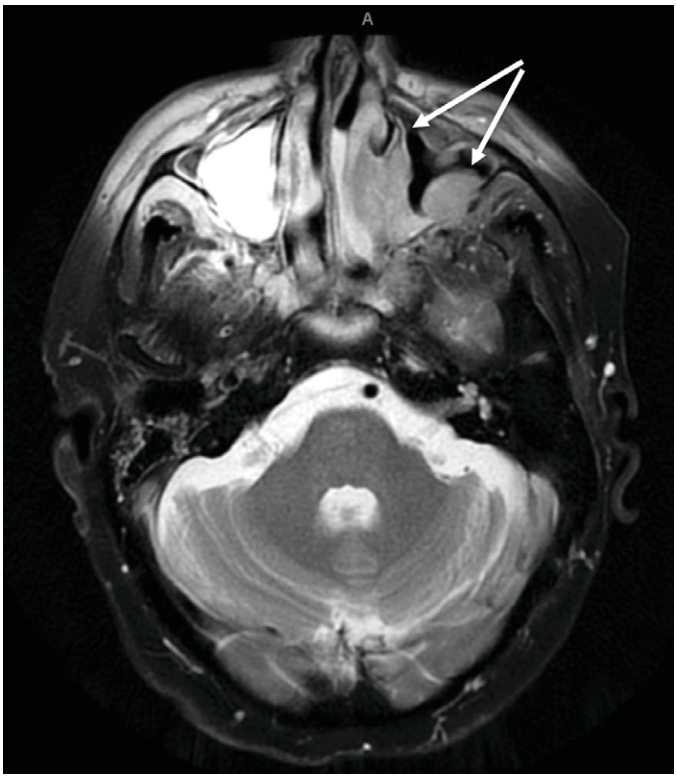

FIGURE 1. *An MRI of the brain and sinuses in T2/FLAIR sequence showing abnormal soft tissue within the superior/medial aspect of the left orbit, which appears to be contiguous with abnormal soft tissue filling the left frontal, ethmoid, and maxillary sinuses (white arrows). A small amount of mass effect is on the left medial rectus muscle.*

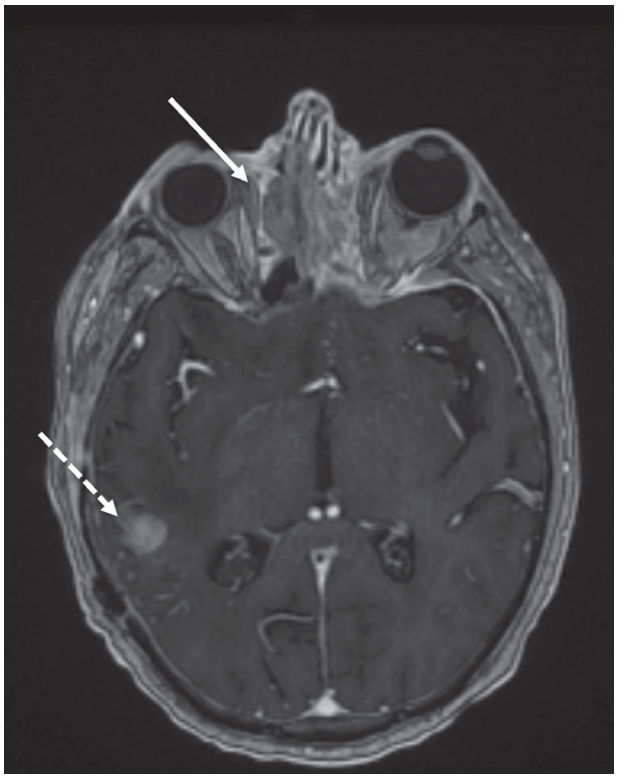

FIGURE 2. *An MRI of the brain and sinuses in spoiled gradient (SPGR) post-contrast sequence again showing the left-sided abnormal soft tissue within the left ethmoid sinus with some mass effect on the left medial rectus muscle. Also imaged is abnormal soft tissue extending into the inferior aspect of the right orbit (solid white arrow) as well as a focus of intra-cerebral disease (dashed arrow).*

medical, and radiation therapies, the mortalities of GBM remain high, with a median survival ranging between 40 and 70 weeks,[2] although recent clinical trial data has shown promise for improving outcomes with the addition of NovoTTF.[3] The majority of GBM recur locally, and distant metastasis is rare, estimated to occur in < 2% of patients.[4] In spite of infrequent clinical presentation of distant metastases, circulating GBM cells have been detected in up to 20.6% of patients,[5] which may lead to metastases to the lymphatics, lungs, bone, liver, and other organs.[6]

CONCLUSION

A diagnosis of GBM is a grim diagnosis from the start. When patients survive long enough to develop metastatic disease, however, the median time from detection of metastatic disease to death has been reported to be as short as 1.5 months.[6] Although data is limited, it has been suggested that metastases to the liver have a lesser impact on survival than metastases to the lung.[7] The treatment of choice for asymptomatic patients is systemic therapy, although when quality of life is affected by disease burden, surgical intervention or focal radiation therapy can be considered, as was the case with our patient.

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RADIATION ONCOLOGY CASE

Pain flare and vertebral fracture following spine stereotactic radiosurgery for metastatic renal cell carcinoma

Jacob A. Miller, BS; Ehsan H. Balagamwala, MD; Alireza Mohammadi, MD; Nagy Mekhail, MD, PhD; John H. Suh, MD; Samuel T. Chao, MD

CASE SUMMARY

A 56-year-old man presented in December 2013 with lower extremity radicular pain, numbness, and weakness. His medical history was significant for a pT3b renal cell carcinoma (RCC) diagnosed in January 2013 following nephrectomy. At the time of consultation, physical exam demonstrated decreased sensation over the lateral aspect of his right leg. Two months earlier, chest computed tomography (CT) had revealed several subcentimeter nodules suspicious for metastatic disease, and the patient was started on sunitinib. Due to concern for epidural disease, MRI of the lumbar spine was performed, which revealed a destructive lesion within the L4 vertebra (Figure 1).

The patient met inclusion criteria for and was offered RTOG 0631, a phase II/III study of single-fraction stereotactic radiosurgery (SRS) vs. conventional external-beam radiation therapy (EBRT). The primary endpoint of this study is pain control. The patient was randomized to SRS, and 16 Gy was prescribed to the L4 vertebral body and posterior elements (Figure 2). The cauda equina was constrained to V12 Gy ≤ 10% and maximum point dose < 16 Gy.

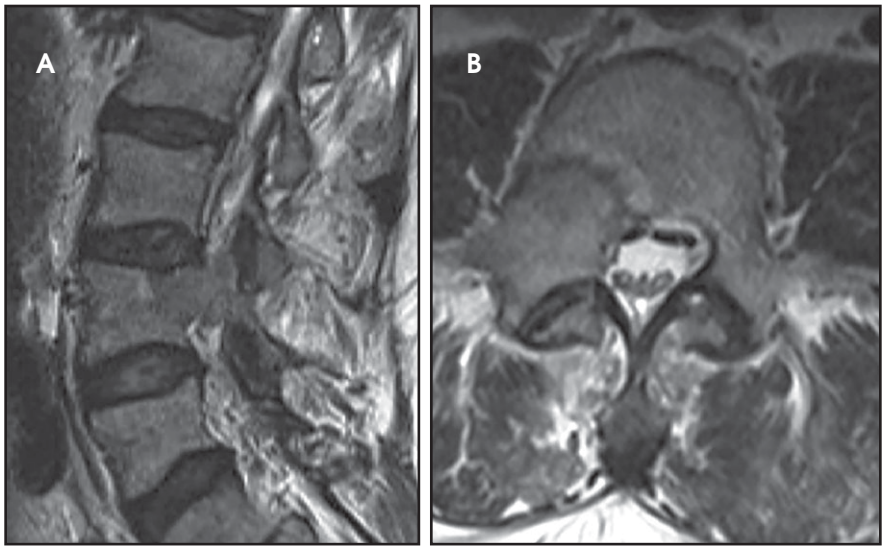

FIGURE 1. *(A) Sagittal and (B) axial T2-weighted MR images of the lumbar spine upon presentation (12/2013) with lower extremity radicular symptoms. A lesion is present within the right posterolateral aspect of the L4 vertebral body, extending through the right pedicle and into the epidural space without effacement of the cauda equina.*

Shortly after completing SRS, the patient suffered from a pain flare at the treated site. A steroid taper was prescribed, and the pain rapidly resolved. Two weeks after SRS, the patient was seen in clinic and reported significantly decreased pain, resolved numbness, and increased strength.

Six months after SRS, follow-up imaging demonstrated slight posterior wedging of the L4 vertebral body (Figure 3), and the decision was made to proceed with kyphoplasty. His systemic disease remained stable through May 2015, at which time an L2 metastasis was observed. The L4 metastases remains controlled through 25 months of follow-up (Figure 4).

IMAGING FINDINGS

Imaging of the lumbar spine at presentation demonstrated a 3.4-×-2.8-cm

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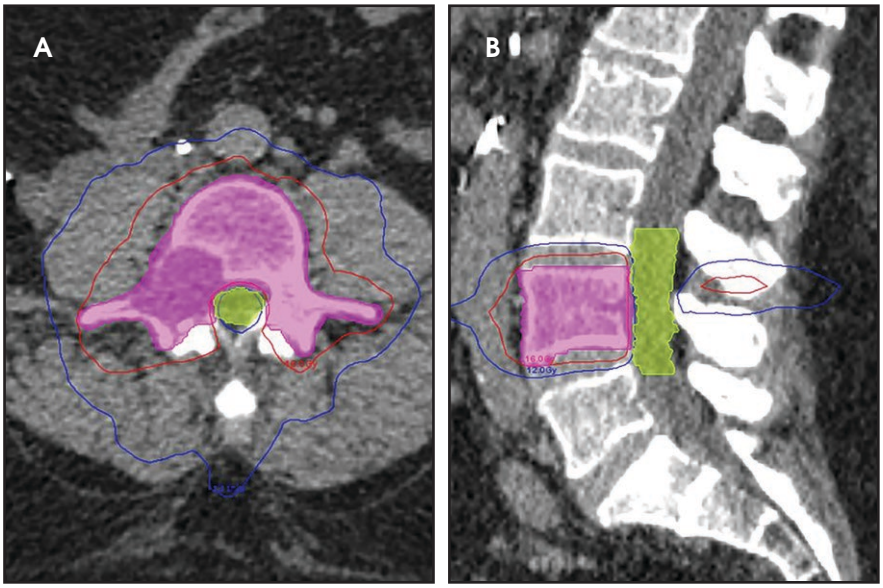

FIGURE 2. *(A) Sagittal and (B) axial images of stereotactic radiosurgery plan for L4 vertebra, with 10 Gy (blue) and 16 Gy (red) isodose lines.*

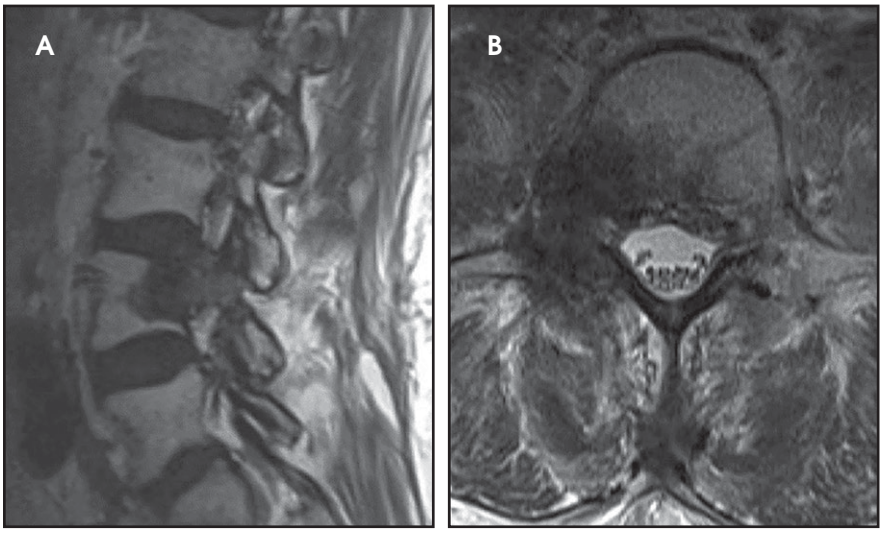

FIGURE 3. *(A) Sagittal and (B) axial T2-weighted MR images of the lumbar spine 6 months following SRS (6/2014). The volume of epidural disease has decreased, and there is no evidence of local progression. However, there is slight posterior wedging of the L4 vertebral body.*

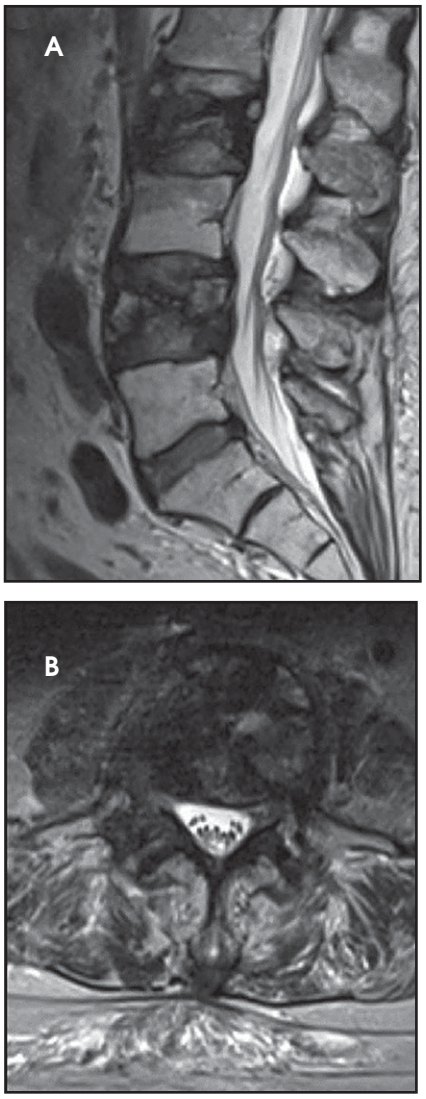

FIGURE 4. *(A) Sagittal and (B) axial T2-weighted MR images of the lumbar spine 25 months following SRS (2/2016). There has been significant interval collapse of the L4 vertebral body without local progression, and an L2 metastasis is evident.*

lesion within the right posterolateral aspect of the L4 vertebral body. This extended into the right pedicle, epidural space, and encroached upon the superior and inferior neural foramina (Figure 1).

After SRS, follow-up imaging in June 2014 demonstrated slight posterior wedging of the L4 vertebral body (Figure 3). Despite kyphoplasty, progressive asymptomatic height loss was observed. (Figure 4).

DISCUSSION

This report demonstrates several areas of interest in the field of stereotactic radiosurgery of the spine. The incidence, time course, and risk factors for pain flare and vertebral compression fracture have been well-studied in multi-institutional and prospective investigations.[1,2] In contrast, the use of targeted therapies with SRS has not been investigated in controlled settings, with conflicting evidence on safety and efficacy.[3-5] While many retrospective and single-arm prospective investigations have suggested increased durability of symptomatic and radiographic control, results from RTOG 0631 are awaited to determine the relative benefit of SRS over EBRT.

Pain flare is a common and transient complication after radiation therapy to the spine. This complication arises within

2 weeks of treatment and is thought to occur secondary to ablation of neoplastic tissue and its associated bony instability. In general, however, these flares subside quickly and are generally amenable to a steroid taper.[6] A 2013 prospective observational study of 41 patients undergoing hypofractionated SRS (24-35 Gy / 2-5 fractions) reported a 68% incidence of pain flare.[2] Accordingly, select institutions have chosen to administer prophylactic steroids to all patients undergoing SRS.[7] Once-daily dexamethasone (8mg) prior to SRS and for 4 days thereafter suffices. This practice is supported by a recent double-blind randomized trial that reported a decreased incidence of pain flare among patients administered prophylactic steroids undergoing palliative radiotherapy.[8] In contrast, other investigations have reported modest rates of pain flare (15%) in the absence of prophylactic steroids, likely secondary to differences in prescription dose.[6,9] Given the relatively low incidence of pain flare noted in our institutional series, we do not routinely treat patients undergoing spine SRS with prophylactic steroids.

Vertebral compression fracture is the most common late toxicity following SRS. While SRS and EBRT offer palliation of tumor-related discomfort, pain secondary to bony instability cannot be treated with radiation therapy, but may be alleviated with vertebral augmentation.[10] In a multi-institutional study of 410 spinal segments treated with SRS, the 12-month cumulative incidence of fracture was 12%.[1] A dose-response relationship was identified, with doses > 20 Gy per fraction associated with an increased risk for fracture. Because these fractures may lead to chronic mechanical pain, spinal segments may be reliably risk-stratified using the Spinal Instability Neoplastic Score.[11] In high-risk cases, dose reduction may be appropriate in an effort to maximize patient quality of life.

Finally, an area of particular interest is the use of high-dose, hypofractionated radiation therapy with concurrent targeted therapies. Preclinical models have supported a synergistic relationship between angiogenesis inhibition and radiation, and uncontrolled retrospective series have reported excellent local control with combined therapy.[5] Furthermore, the immunogenic characteristics of hypofractionated radiation therapy have been hypothesized to augment targeted immunotherapies.[12] In the present report, a patient with oligometastatic renal cell carcinoma undergoing concurrent systemic therapy with an anti-angiogenic tyrosine kinase inhibitor (TKI) was treated with SRS. For patients undergoing upper thoracic or cervical SRS with concurrent TKIs, esophageal toxicity may be a significant concern.[3] In addition, it is unknown whether rates of pain flare or fracture are increased with the use of combined therapy. Despite these concerns for safety, retrospective evidence has suggested a significant local control benefit with the addition of TKIs to SRS. In support of this hypothesis, local control has been durable through 25 months of radiographic follow-up in this patient. This efficacy may support a role for upfront aggressive treatment of oligometastatic disease with definitive intent. To explore this role, an ongoing cooperative trial (NRG-BR001) is investigating the safety of stereotactic body radiation therapy for oligometastatic disease.

CONCLUSION

This report demonstrates several key considerations associated with the use of spine stereotactic radiosurgery. Pain flare and vertebral compression fracture are common complications, which may be managed with steroids and vertebral augmentation. However, sequelae of tumor ablation may be irreversible, and fracture progression may lead to chronic mechanical pain. Despite this, SRS appears to achieve high rates of symptomatic and radiographic control, with limited data available describing the efficacy of SRS combined with targeted therapies.

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Updates in volumetric-modulated arc therapy for prostate cancer

Mary Beth Massat

Clinical use of volumetric-modulated arc therapy (VMAT) has grown significantly since its debut in 2007. An earlier form of VMAT known as intensity-modulated arc therapy (IMAT) was introduced in 1995 by Cedric X. Yu, DSc, FAAPM, professor of radiation oncology at the University of Maryland School of Medicine, Baltimore. The difference was that IMAT required the use of multiple superimposed arcs for dose distribution, while VMAT allows the entire target volume to be treated using 1 or 2 arcs.[1] Essentially, VMAT is an arc-based approach to intensity-modulated radiation therapy (IMRT).

Since the prostate is one of the most common sites treated with IMRT, it's no surprise that VMAT may soon supplant IMRT as a preferred method for delivering external-beam radiation therapy. A 2011 review of literature and clinical use found that several studies reported significant improvement in OAR (organs at risk) sparing with VMAT. Most studies also determined that the key difference between VMAT and fixed-field IMRT is VMAT's ability to reduce treatment delivery time and monitor units (MU).[1]

"The application of VMAT for prostate cancer has been well-demonstrated for both plan quality and efficiency," says Dr. Yu, who has studied VMAT techniques and published numerous papers and book chapters on the topic.

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At Terk Oncology Center for Prostate Cancer and Breast Conservation, Jacksonville, Florida, radiation oncologists Mitchell D. Terk, MD, and Jamie Cesaretti, MD, have treated more than 8,000 men for prostate cancer, exclusively using VMAT for external radiation therapy of the prostate. "Modulated arc therapy is ideal for small, centrally located cancers, such as prostate," Dr. Terk says. "With a 360-degree modulated arc, we can spread the dose away from critical structures such as the rectum and bladder."

When Drs. Terk and Cesaretti opened a new clinic 2 years ago, they implemented a linac and treatment planning system capable of performing VMAT. Today, their prostate treatment plans with VMAT can routinely deliver over 81 Gy up to 86.4 Gy for patients with bulky tumors, while keeping the bladder and rectum doses at less than half of the tolerance doses recommended by the Radiation Therapy Oncology Group (RTOG) and the Proton Therapy Consortium guidelines, significantly lowering complication rates.

Dr. Terk uses VMAT for treating prostate cancer patients unless patients opt for brachytherapy. His team has performed 5,000 seed implants since 1997. Typically, they offer brachytherapy as an option for monotherapy in men with early stage prostate cancers, or if the patient has recurrent, localized disease after prior external radiation such as proton therapy. For more locally advanced disease, patients may receive combined brachytherapy and a lower dose of VMAT.

VMAT can be delivered as either constant-dose-rate or variable-dose-rate plans. In the literature, VMAT is most often described as a single arc technique that employs dose rate variation.[1]

"In theory, variable dose rate is not absolutely needed to achieve the best plan quality," Dr. Yu explains. "However, most planning system vendors did not restrict the dose rate to be constant, and therefore require the variable dose rate capability." He cautions that not all linacs can be upgraded to support variable dose rate.

Similarly, the use of single arc or dual arc has also been studied. "Generally speaking, when 2 arcs are used, the planning system has an easier task in keeping the lengths of MLC movements within the MLC's abilities, and results in a better plan and smoother delivery," says Dr. Yu. "For the same reason, the plan quality also improves with dual arcs."

James Chow, PhD, FCCPM, assistant professor and medical physicist at Princess Margaret Cancer Centre in Toronto, Ontario, Canada and the University of Toronto, agrees that the more arcs used, the better the plan. However, it is important to minimize the number of arcs to decrease the time the beam is on, he says. "The double-arc technique resulted in a prostate VMAT plan with better prostate coverage and rectal dose-volume criteria compared to the single-arc," with a tumor control probability of 0.16% higher than the single-arc,[2] wrote Dr. Chow and co-author Runqing Jiang, PhD, MCCPM, in a 2013 paper.

Dr. Chow explains that the prostate typically has one target compared to the

At Terk Oncology Center for Prostate Cancer and Breast Conservation, Jacksonville, Florida, prostate treatment plans with VMAT can routinely deliver over 81 Gy up to 86.4 Gy for patients with bulky tumors. Pictured here is the center's linac used in VMAT. Photo courtesy Terk Oncology.

head and neck, which has more critical structures and often multiple targets. Determining the number of arcs when using VMAT depends on the complexity of the target and surrounding anatomy, he says.

While VMAT plans using 2 arcs may surpass one-arc plans, the decision is patient-specific, Dr. Terk says. The important considerations are dose distribution, patient-specific anatomy, and prostate size. A large or unusually shaped prostate, small bladder, or hip replacement are the most common factors increasing treatment plan complexity. "The more complicated the patient, however, the greater the benefit of these advanced technologies," he says.

Gains in Efficiency

A well-known advantage of VMAT is its ability to deliver faster treatments. According to Dr. Chow, one technology that enhances the efficiency of treatment technology is flattening filter-free beams (FFF). FFF beams operate at higher dose rates—over 1,000 MU/min and greater—which also shortens beam-on time and reduces overall treatment time.

A recent study examining the effect of FFF and VMAT delivery found that a 10 MV (maximum dose rate of 2400 MU/min) FFF VMAT plan configuration provided the greatest improvement in treatment efficiency, with high dose per fraction cases (stereotactic radiation therapy and stereotactic body radiation therapy) realizing the highest gain.[3]

"VMAT is beneficial for the hospital and the patient," Dr. Chow explains. "Because treatment is completed quicker, it helps reduce the possibility that intra-fraction motion will occur, which can lead to the beam hitting something that is not targeted. By finishing patient treatments sooner, the hospital can also increase patient throughput."

While patient motion is a concern, respiration typically is not a significant issue when treating the prostate with VMAT, although some sites may use gating. However, whether the bladder and rectum are filled or empty makes a difference, Dr. Chow says. At Princess Margaret Cancer Centre, patients are treated with a full bladder and empty rectum to help ensure the location of the anatomy is consistent for each treatment.

At Terk Oncology, a patient's immobilization device and rectal balloon are routinely used to minimize patient motion, intra-fraction prostate motion, and rectal doses. The balloon helps distend the rectum away from the prostate, further reducing dose to the critical area, Dr. Terk explains. Fiducial markers and daily kilovoltage cone-beam CT (CBCT) imaging is also performed to verify alignment of the prostate and critical structures before each treatment.

Improving Accuracy

In terms of treatment delivery, little more can or should be done to improve the process; however, there is room for improvement in geometric accuracy, Dr. Yu adds. One way to accomplish this is with real-time guidance of the linac based on imaging performed immediately before treatment delivery, such as with CBCT affixed to the linac.[2] Dr. Yu predicts that over the next decade, the industry will see more advanced image-guided radiation therapy (IGRT) systems and wider adoption of the technique.

MRI also can play a role, evidenced by Dr. Terk who has routinely used MRI treatment planning since 2009 to assist with IGRT. "We can far better visualize the prostate and surrounding anatomy with MR compared to CT," Dr. Terk says. "We fuse the MR image with CT in our treatment planning system to outline the anatomy and ensure we don't miss the lesion or hit any critical structures."

In fact, Dr. Terk believes that MR-guided radiation therapy will provide notable incremental improvements in treatment quality. "Image guidance is the big advantage of VMAT over proton therapy," he says. Because of the imaging capability, Dr. Terk believes VMAT is superior to proton therapy for treating prostate cancer.

While advances in treatment delivery technology have been limited since the inception of IMRT nearly 20 years ago—and by extension VMAT— the future holds promise. "A method that can deliver proton-like dose distribution with photons," would be ideal, says Dr. Yu.

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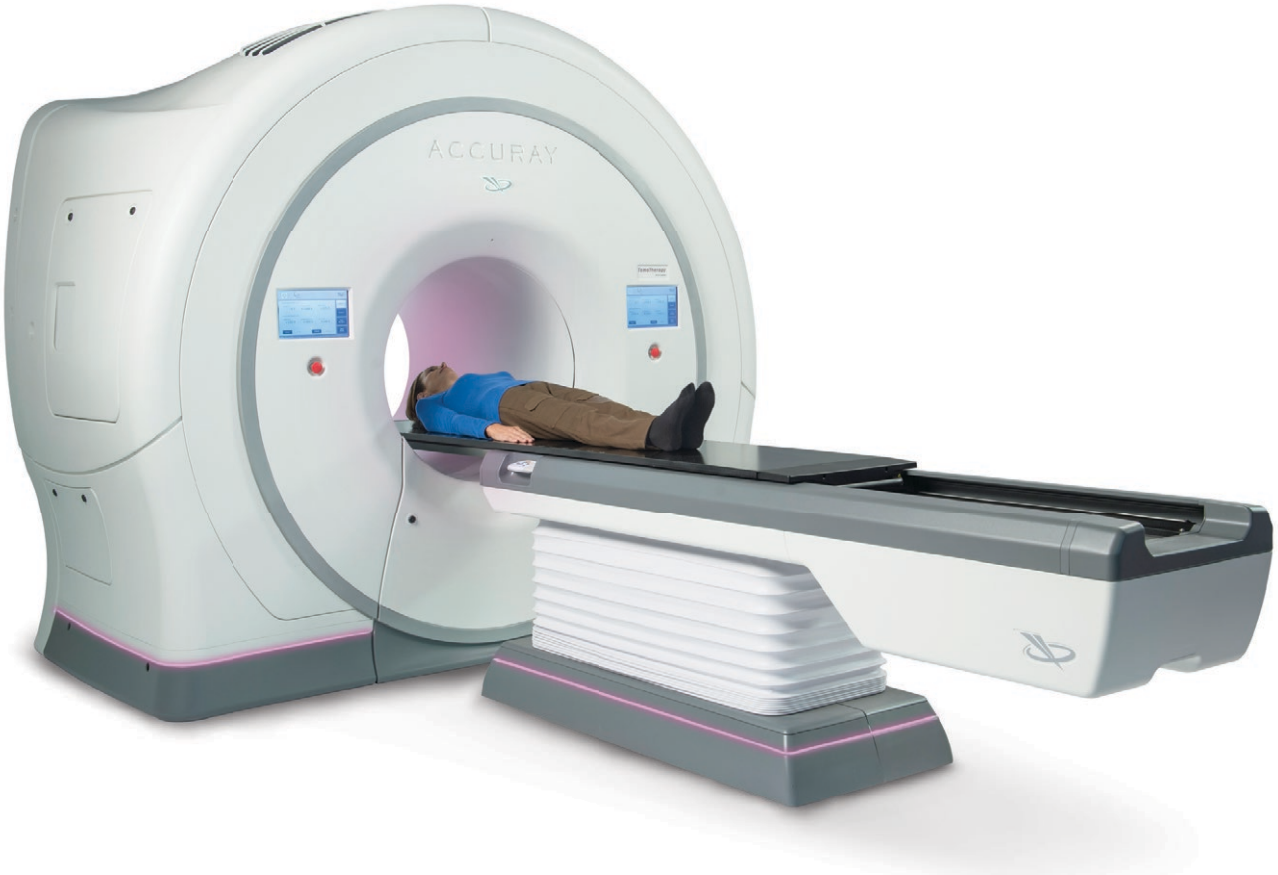

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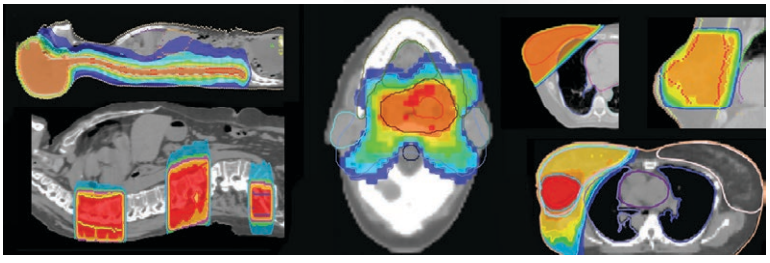

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