Radiotherapy for Malignant Tumors of the Skull Base

Julian Johnson, MD, Igor J. Barani, MD*

KEYWORDS

• Linear accelerator • Gamma Knife • CyberKnife • Stereotactic • Skull base tumors

KEY POINTS

- Skull base tumors are a diverse group. They are often treated with adjuvant or definitive radiation for local control. This treatment concept arises from the difficulty of achieving aggressive gross total resections.
- Radiation therapy is a broad field, with many different treatment modalities, most of which are applicable to the skull base.
- Radiosurgery can be applied to smaller lesions if they are sufficiently far away from critical structures. Radiosurgery results in higher dose delivered to a tumor and structures very near to the prescription isodose line, with a rapid decline in radiation with distance.
- Conventional fractionation may be superior to radiosurgery in some cases. Generally, these are larger tumors interdigitated with a normal tissue, the radiotolerance of which exceeds that of the radiation dose needed to control a tumor.
- Conventional fractionation offers increasing conformality as a result of evolving treatment planning technology and beam arrangements, including three-dimensional conformal radiotherapy and intensity modulated radiation therapy.
- Proton beam radiotherapy offers unique advantages and is particularly useful in pediatric tumors and large tumors, which require more conformality than photon treatment plans may offer.

GENERATING THERAPEUTIC RADIATION

It is useful to be familiar with the scale of radiation under discussion. **Table 1** outlines radiation doses delivered in typical diagnostic and therapeutic procedures compared with common nonmedical radiation exposures.

When describing radiation doses, radiation oncologists use gray as the unit of choice. Proton doses are often expressed in Cobalt-Gray-Equivalents (CGE). Gray is a measurement of energy absorbed by tissue (joules per kilogram of tissue). Radiation safety typically uses units such as the sievert. The sievert expresses gray (absorbed dose) adjusted with a known constant, Q, which depends on the type of radiation in question. Protons, photons, and α particles each have different Q factors. The curie is a measurement that expresses radioactivity of a source before reaching a tissue. The curie is medically relevant when radioactive sources are used in brachytherapy. A detailed explanation of different means of measuring radiation is beyond the scope of this article.

Photons are the most commonly used therapeutic particle. High-energy electrons guided by a powerful magnet are directed toward a tungsten

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Department of Radiation Oncology, University of California, San Francisco, 505 Parnassus Avenue, Room L08, San Francisco, CA 94143-0226, USA
* Corresponding author.
E-mail address: BaraniI@radonc.ucsf.edu

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Table 1
Radiation doses delivered in typical diagnostic and therapeutic procedures compared with common nonmedical radiation exposures. The University of California San Francisco and many others now require an accurate documentation in the medical record of radiation dose delivered during diagnostic procedures

Flight from LA to NY: 0.015 mSv
Dental X-ray: 0.09 mSv
Chest X-ray: 0.1 mSv
Mammogram: 0.7 mSv
Chest CT scan (low-dose): 1.5 mSv
Background Radiation: 6.2 mSv/year
Chest CT scan: 7 mSv
Abdominal CT scan: 10 mSv
Therapeutic Radiation (whole-brain): 30,000 mSv (30 Gy)
Therapeutic Radiation (brain tumor only): 50,000-60,000 mSv (50-60 Gy)

Where 1 Gy = 1000 mSv. Sievert is a measure of radiation effects adjusted for the type of radiation.

target. When the electrons strike the target, photons are generated via either the photoelectric or Compton effect, depending on the energy of the incident electron. Linear accelerators achieve this effect on a massive scale. Photons and γ rays are biologically and physically equivalent. Photons (or X-rays) are man-made whereas Gamma rays are generated by natural decay of a radioisotope. Both protons and γ rays can be used in the treatment of skull base tumors.

Protons are typically generated via a cyclotron. Only a few centers in the United States have proton machines, but the number of centers is rapidly increasing. Protons differ from photons in their dose distribution. The proton beam deposits maximum dose at a certain tissue depth determined by its energy, and then dose decreases precipitously, so-called "Bragg Peak" phenomenon.[1] Its use has been favored for pediatric tumors because of the theoretic lower risk of radiation exposure to nontarget tissues.

THE EFFECTS OF RADIATION

A detailed discussion about the manner in which ionizing radiation interacts with living cells is beyond the scope of this article. For the practicing physician or surgeon, it suffices to know that ionizing radiation exerts antitumor properties via a variety of potential effects on DNA. Direct radiation damage to DNA is probably less important. The most accepted primary cause of cell death is the double strand break, which triggers the apoptotic pathway. DNA suffers double strand breaks after interacting with free radicals, which are in turn generated by radiation effects on oxygen and water.

Given the importance of the presence of oxygen, more oxygenated cells in theory suffer greater radiation-induced damage. Fractionation allows tumors to reoxygenate, thereby fueling the DNA damaging process.

Fractionated external beam radiation therapy (EBRT) exploits the decreased ability of malignant cells to repair sublethal DNA damage. With each fraction, a new portion of abnormal cells reach a damage threshold. Although normal tissue repairs the damage more effectively, a greater portion of abnormal cells undergo cell death. Therefore it is possible to include normal tissue within a treatment field without completely destroying it. Even if tissues do not reach a lethal threshold, significant radiation damage may impair cellular function. The ability of normal tissues to recover from radiation injury varies by tissue type. Also, tissue dose tolerances vary when single high doses are given compared with fractionated radiotherapy (RT). For example, the optic chiasm does not seem to sustain clinically relevant damage if total fractionated dose is less than 50–54 Gy versus 8 Gy for single dose (**Fig. 1**). This is a particularly critical concept in the skull base, to which we return later in this article.

Target cells that do not reach lethal threshold with initial fractions accumulate more damage as they seek to replicate their DNA during mitosis. Tumors with a low mitotic fraction, number of cells undergoing active mitosis from a total tumor cell population, may experience a lesser response to radiation,[2] Many skull base tumors are in this category with characteristically low mitotic activity, such as meningiomas and schwannomas. Tumor control for these tumors is often defined as lack of growth rather than diminished size.

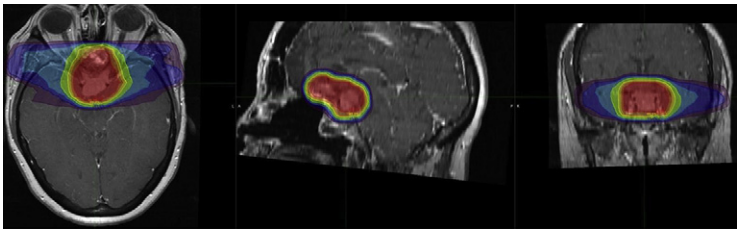

Fig. 1. Intensity modulated radiation therapy plan for a patient being treated for a WHO grade I meningioma that was resected 3 years before coming to our clinic. She presented with diplopia, headaches, and right lateral gaze palsy. Notice that the maximum radiation dose is focused around the tumor and a smaller, but not negligible, amount of radiation is delivered to surrounding structures. The red area represents the 95% isodose line. The other colors represent a gradient down to the 45% isodose line, which is in purple.

Radiosurgery uses very high doses of radiation, obliterating tumors and often inducing necrotic cell death. The entire target area receives 1 to 5 high, supralethal doses of radiation. These are often called ablative treatments because a greater portion of cells are directly destroyed by radiation rather than accumulating damage over time. The biological mechanisms underlying radiosurgical treatments are not well understood. A single fraction radiosurgery treatment may range from 10 to 80 Gy, whereas a typical fraction in conventionally fractionated RT is 1.8 to 2 Gy.

Often an increase in size may be observed after radiosurgery because of inflammatory reactions to necrotic tissue.[3] For example, Kollova and colleagues[4] observed perilesional edema in 15% of patients treated with stereotactic radiosurgery (SRS) for meningiomas. Once the necrotic tissue is cleared, tumors treated with SRS should decrease in size.

A BRIEF INTRODUCTION TO DELIVERY SYSTEM

With SRS of the skull base, it is critical to spare normal tissues in the immediate vicinity of the target in order not to cause normal tissue injury; therefore, tumors that encase functional structures are often not suitable for radiosurgical treatments. Radiosurgery is ideal for small targets (typically less than 2–3 cm), When targets are larger, the dose falloff with radiosurgery is less steep, the dose within the target less homogeneous, and the surrounding tissue exposed to significant levels of radiation increases. Radiosurgery can be accomplished with photons, γ rays, or protons. Linear accelerator based radiosurgery is performed with CyberKnife or a modified linear accelerator. Gamma Knife uses a Cobalt-60 source. There has been much debate about the merits of one SRS system over the other, but generally they are applied similar clinical situations Some institutions favor use of one radiosurgical modality over another despite absence of robust clinical data to justify such decisions. Most often, the use and type of radiosurgical modality is governed by its availability. SRS is also accomplished with protons as well (**Fig. 2**).

Conventional radiation therapy delivered with linear accelerators is more widely available than SRS. Such treatments are ideal for larger targets not amenable to radiosurgery. EBRT is less conformal than radiosurgery and generally uses fewer beams. Each beam accounts for a higher portion of the total target dose, so exposure to surrounding tissues is inevitable (see **Fig. 1**).

All radiation treatments rely on strict, reproducible patient positioning and high-quality image guidance. The term "stereotactic" refers to the use of a three-dimensional coordinate space to which patient's anatomy and treatments are registered. Patient immobilization is therefore stricter for radiosurgery plans because high-doses of radiation are applied and the error is not distributed over many fractions. Patients being treated with Gamma Knife are immobilized with a metal frame affixed to the head. CyberKnife and EBRT treatments may be delivered with the patient's head immobilized using a custom-fitted thermoplastic mask that is used in conjuction with image-based corrections for deviations in patient position. New immobilization techniques are constantly evolving.

High-quality images are critical to radiation delivery. Obtaining images during treatment, the CyberKnife can automatically verify patient positioning in real time before delivering radiation. Conventional linear accelerators use cone beam computed tomography (CBCT) devices mounted on the linear accelerator to verify daily position with the images used to plan treatment. In the skull base, magnetic resonance imaging (MRI) scans fused with CT scans are increasingly used for planning purposes.

Brachytherapy is the use of a radioactive source isotope implanted into a patient (internal radiation) for dose delivery via catheters, seeds, or plaques. These sources are typically designed to have a rapid decline in dose delivered as a function of distance. They are particularly useful when it is necessary to deliver a high dose to an area that

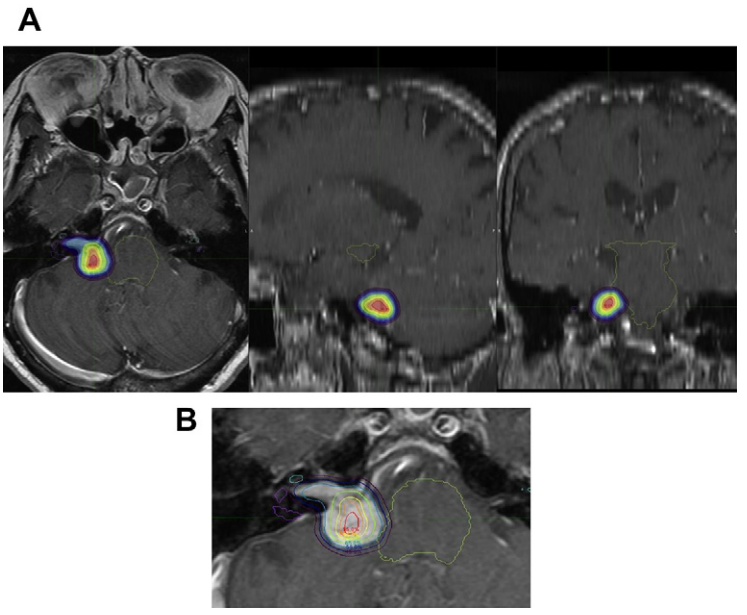

Fig. 2. (*A*) CyberKnife plan for a patient being treated for a vestibular schwannoma. She initially presented to our department with subjective hearing loss, poor word discrimination on audiometry, and some mild disequilibrium. Notice how the isodose lines compare with the plan shown in **Fig. 1**. This patient has a very high, yet inhomogeneous dose delivered to her tumor. The prescription is to 25 Gy, but, because 25 Gy is delivered to the 55% isodose line, 25 Gy is only 55% of the maximum dose within the tumor volume. Because of the physics of photons, dose falloff is sharpest near the 50% isodose line, so most SRS plans prescribe near this isodose curve. (*B*) Close-up on the target area to further define isodose curves. The brainstem, cochlea, and vestibular apparatus have been highlighted in this plan for the purposes of calculating dose to these structures. Contouring normal structures is one of the means of ensuring that dose tolerances of normal structures are not exceeded.

is readily accessible but not amenable to surgical excision. Cavities of various types fit this description.

Electrons are generally delivered only to body surfaces. They are generated with the linear accelerator by essentially removing the tungsten target from the path of the electrons. Electrons do not travel far through tissue and penetrate only deep enough to treat relatively superficial structures.

There are several reports in the literature of improved results after radiation therapy with the addition of image-guidance or MRI-based planning. For example, local control (LC) rates for meningiomas treated with radiation are excellent and seem to be improving with modern treatment techniques (MRI-based planning, strict treatment setup). Goldsmith and colleagues[5] reported that subtotally resected meningiomas treated with postoperative radiation after 1980 had better local control (LC) compared with meningiomas treated before 1980. Several more modern studies have shown excellent LC rates. For example, a series reported by Mendenhall and colleagues showed that EBRT may be equivalent to subtotal resection followed by EBRT; these investigators' 15-year LC rates exceeded 90% for both groups.[6,7]

Applications of the Delivery Methods

This article is an introduction to malignant skull base tumors. The most commonly encountered malignant skull base tumors in our practice are atypical and malignant meningiomas. Other malignant tumors of the skull base include sinonasal undifferentiated carcinoma and soft tissue sarcomas. Chondrosarcomas and chordomas are locally aggressive, malignant tumors,.

Atypical and Malignant Meningiomas

Meningiomas are the most common benign brain tumor. Atypical and malignant meningiomas represent only a small subset: 4% to 7% and less than 5%, respectively.[8–12] Since the World Health Organization (WHO) definitions changed in 2007, many believe that the proportion of all meningiomas that are reported as atypical may have increased to as much as 25%.[13] Much of the meningioma data combines or aggregates benign, atypical, and malignant meningiomas. Because of their relative rarity, specific data on atypical and malignant meningiomas are expectedly sparse, but evolving. The following discussion extrapolates the existing data on radiotherapeutic principles and outcomes to the skull base location. **Table 2** summarizes some relevant studies.

WHEN TO TREAT: RETROSPECTIVE DATA

Although completely resected WHO grade I meningiomas do not require postoperative radiation, subtotal resection followed by adjuvant radiation achieves equivalent progression-free survival (PFS) compared with gross total resection.[7,27,28]

Table 2
Summary of relevant studies regarding adjuvant RT in the treatment of WHO II and III meningiomas

Series (Number)	Treatments	Histology	Outcomes	Comment
Adeberg et al,[14] 2012 (85)	EBRT, S + EBRT, S→EBRT	WHO II-III	II: 5-y OS 81%, 5-y PFS 50% III: 5-y OS 53%, PFS 13%	Some patients treated with carbon ion[14]
Aghi et al,[15] 2009 (108)	S (GTR), S + EBRT, S→EBRT	WHO II	5-y recurrence rate: 41% 5-y recurrence rate 0% if EBRT	No recurrences if EBRT (n = 8) 2.7 craniotomies per patient if recurrence
Attia et al,[16] 2012 (24)	SRS (salvage or primary)	WHO II	>50% OS 5 y 5-y LC 44%	Improved LC with SRS >14 Gy
Dziuk et al,[17] 1998 (27)	Primarily surgery + RT	WHO III	All: 5-y OS 57% GTR + RT: 5 y DFS 40% RT No adjuvant: 5-y DFS 16%	Benefit >60 Gy adjuvant RT ↑ recurrence interval
Goldsmith et al,[5] 1994 (23) (grade III)	Surgery + RT	WHO III	58%	>53 Gy
Goyal et al,[18] 2000 (22)	Surgery, surgery + RT in only 8 patients	WHO II	GTR: 5-y OS 87% STR: 5-y OS 100%	No benefit with RT mean dose 54 Gy
Huffman et al,[19] 2005 (21)	GKRS 18 Gy	WHO II	40% recurrence at 18–36 mo	Ref.[19]
Hug et al,[20] 2000 (16)	EBRT + S Some protons	WHO II-III	II: 5-y OS 38% III: 5-y OS 52%	Benefit with higher doses and protons
Mattozo et al,[21] 2007 (12)	SRS, EBRT	WHO I-III	II: 3-y PFS 83% III: 3-y PFS 0%	Recurrence in resection cavity common[21]
Milosevic et al,[22] 1996 (42)	Primarily surgery + RT, some surgery only	WHO II-III	5-y OS 28% 5-y CSS = 42% if >50 Gy given	Better outcome if >50 Gy Reduced LR with RT
Pasquier et al,[11] 2008 (119)	S + EBRT, S only	WHO II-III	GTR: 5-y OS 46% GTR + RT: 5-y OS 78% STR: 5-y OS 0% STR + RT: 5-y OS 56%	RT improves OS in all patients
Rosenberg and Prayson et al,[23] 2009 (13)	S + RT S + SRS	WHO III	5-y OS: 47%	Trend toward longer survival if RT given
Sughrue et al,[24,25] 2010 (63)	S + RT	WHO II-III	61% 40% at 10 y (RFS 57%, 5 y) (RFS 40%, 10 y)	Survival benefit for less extensive resection
Yang et al,[29] 2008 (33 atypical, (41 anaplastic)	S, S + EBRT	WHO II-III	II: OS atypical 11.9 y RFS atypical 11.5 y III: OS anaplastic 3.3 y RFS anaplastic 2.7 y	Adjuvant RT improved outcomes in WHO III tumors and WHO II with brain invasion
Boskos et al,[26] 2009 (24)	EBRT Protons and photons	WHO II-III	5-y OS 65% 5-y LC 61%	OS significantly associated with higher doses[26]

Data comparing specific modalities (SRS, EBRT, protons) are sparse. Data exist suggesting doses greater than 50 to 60 Gy may be ideal. None of these studies is limited to the skull base. All are retrospective, some are multi-institutional. WHO grades may be reported using different criteria (eg, 2000, 2007). The most recent change in WHO grading primarily affected the proportion of tumors classified as WHO grade II.

Abbreviations: CSS, cause-specific survival; EBRT, EBRT given at progression; GKRS, gamma knife radiosurgery; LS, local recurrence rate; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; S, surgery.

It is generally accepted that completely resected grade II to III should be treated with radiation postoperatively.[13,15,22,23,29] This recommendation is based on several observational studies suggesting superior outcomes (overall survival [OS], progression-free survival (PFS), LC) with adjuvant RT (eg, Refs.[17,22]). The National Comprehensive Cancer Network (NCCN) guidelines recommend that physicians consider postoperative RT for WHO grade II tumors and refer all WHO grade III tumors for postoperative RT. There are no randomized data supporting this treatment strategy and some of the data conflict with this recommendation.[18,30]

Data regarding which RT modality to choose in each situation are not extensive enough to support generation of guidelines, but experienced radiation oncologists can make this determination. Some of the data and concepts behind this reasoning are discussed.

DOSING FOR EBRT AND SRS

EBRT doses prescribed for malignant meningiomas are generally 60 Gy in 2-Gy fractions (with a 1-2 cm margin) compared with 54 Gy for benign WHO grade I meningiomas. Adjuvant or definitive SRS doses vary from 10 Gy up to 25 Gy or more but the use of radiosurgery as the primary adjuvant treatment is generally discouraged. There are some retrospective data to suggest that doses greater than 14 Gy provide superior LC for atypical meningiomas.[16] There are no randomized data to support these dose constraints, but some series have suggested that doses more than 50 Gy improve outcomes in meningiomas of all histologies (see **Table 2**).[5,20]

RECURRENCE PATTERNS INFLUENCE TREATMENT FIELDS

Recurrence patterns have been instructive in our attempt to properly define adequate dose and appropriate margins. Treating only the enhancing tumor, as is practiced with benign meningiomas, may not be the ideal strategy to control WHO grade II to III meningiomas. Of the recurrences in their series of EBRT atypical and malignant meningioma, Adeberg and colleagues[14] reported 85% of recurrences in-field, 7% at border, and 7% distant failures. (Five of these patients were treated with carbon ions, a therapy with a more restricted availability than protons, but which follows a similar physical principles.) These patients were treated with an average dose of 57.6 Gy, with a margin of 1 to 2 cm. Attia and colleagues[16] reported a series of 24 patients treated with Gamma Knife. Of the 14 recurrences, 8 recurrences were in-field, 4 at the margin, and 1 distal. Huffman and colleagues[19] also reported 21 atypical meningiomas treated with Gamma Knife, with several recurrences noted at the treatment margin but none within the field. Their prescription dose was 18 Gy. Their recurrence pattern suggests that adjacent dura should be within the SRS target. This strategy limits the applicability of SRS; irregularly shaped targets and proximity to critical structures of the skull base make extension of the target volume difficult.

Considering these data, we recommend that atypical and malignant meningiomas should receive higher doses (likely greater than or equal to 60 Gy for EBRT and greater than or equal to 14 Gy for SRS), but the dose constraints imposed by normal structures must be respected. EBRT is the preferred primary adjuvant treatment for these tumors, but SRS has and is still being used by some practictioners. A margin of 1–2 cm should be applied to malignant meningiomas. The radiation oncologist restricts and expands the margins according to anatomic barriers.

TREATMENT WITH LIMITED OR NO SURGERY

The skull base is replete with sensitive neurologic structures so gross total resections are not often feasible. It may be difficult to even perform a biopsy. Physicians are becoming increasingly comfortable treating meningiomas with RT based on imaging criteria alone. A recent series from investigators at Emory University showed that meningiomas may be treated with primary RT alone based on imaging findings. In that series, 8-year LC exceeded 90%.[31] In the absence of biopsy data, it is possible that this group contained some atypical meningiomas.

Fractionated radiation regimens typically require daily treatments for several weeks.[32] Fractionated radiation is still commonly used in the treatment of WHO grade I meningiomas in close proximity to the optic chiasm or optic nerves. This strategy is based on the observation that the EBRT can achieve effective doses for tumor control and spare function of the visual apparatus.[5,7,33] Meningiomas affecting the optic nerve sheath are exclusively treated with EBRT, with many patients reporting improved vision during treatment. No other treatment modality or combination modality has been shown to improve vision as well as RT alone for this select cohort of patients, so surgical decompression is reserved for patients with intracranial extension and rapidly evolving deficits.[34–36] Clinical symptoms and cranial nerve deficits commonly improve after radiation therapy, despite the low portion of meningiomas that recede in

response to therapy.[37–40] Using these data, an atypical or malignant meningioma in this location may be treated in the same way, albeit a higher dose should be applied when possible.

Although the optic nerve may be spared with doses ranging from 50 to 54 delivered in 1.8-Gy to 2-Gy fractions, the retina and lacrimal glands may receive enough radiation to cause retinopathy or dry eyes. Also, the lens is one of the most radiosensitive structures in the body, with doses greater than 10 Gy delivered by EBRT leading to delayed cataract formation. Thus, for optic nerve sheath meningiomas treated with fractionated RT, vision is preserved but the radiation oncologist must be attentive to potential late effects of therapy. A small British series of 34 patients showed dry eyes in 14% patients, cataracts in ~9%, and retinopathy in ~12% patients treated with optic nerve sheath meningiomas with radiation.[41]

Cavernous sinus and petroclival meningiomas represent an area of high surgical morbidity with extensive resection, so the use of RT is often preferred either as a primary or adjunct treatment to subtotal resection. Based on a recent literature review of cavernous sinus meningiomas treated with SRS alone, SRS results in a 3% recurrence risk, whereas subtotal resection (STR) and gross total resection (GTR) resulted in recurrence risks of 11%. Also, cranial nerve deficits were more common in the group undergoing resection.[24] One recent study involving 64 patients with cranial neuropathies showed that 53% of patients with cranial neuropathies treated within 1 year of symptom onset experienced relief compared with 26% treated more than 1 year after symptom onset, which argues for earlier therapy.[42] A second recent series published by a group in Norway showed that Gamma Knife achieved LC in 84% of patients with cavernous sinus meningioma at a median follow-up of 82 months,[43] which agrees with other data.[44,45]

PROTON THERAPY

There is a growing body of evidence supporting the use of proton radiotherapy to treat meningiomas. For example, Wenkel and colleagues[46] achieved 10-year recurrence-free rates of 88% for meningiomas treated with a combination of photons and protons, but this study was not restricted to the skull base and there were no malignant meningiomas. Also, the toxicities from treatment were slightly higher than expected for EBRT for meningiomas (1 patient death, 4 severe ophthalmologic, 4 severe neurologic, and 2 severe otologic toxicities). One report of 51 patients treated with proton SRS showed 3-year tumor control rates of 94%, with 5.9% risk of adverse effects.[47,48] Hug and colleagues had a case series of 31 patients treated with EBRT using protons. There have been other successful studies, but preferential use of protons over conventional RT or SRS is not yet supported.

WHEN DO MENINGIOMAS RECUR?

Most meningioma recurrences after RT are noted within 2.5 years after therapy.[43,49] This situation forms the basis for close follow-up. Many centers maintain their closest follow-up within this time period (eg, MRI every 6 months for 1 year after treatment, then yearly MRI scans). A recent series of 24 patients reported by Aghi and colleagues[15] showed that atypical meningiomas fail within a similar time frame, with 7%, 41%, and 48% recurrence rates at 1, 5, and 10 years, respectively. Of the tumors treated with re-excision, only 1 of 22 transformed from atypical to malignant. Twelve of the 14 recurrences seen in a 24-patient series reported by Attia and colleagues[16] recurred within 2.5 years. Huffman and colleagues[19] reached a similar recurrence rate of 40% at 21 to 67 months' follow-up in their Gamma Knife series of 15 patients with atypical meningiomas.

TREATING A RECURRENCE

Atypical and malignant meningioma series show frequent recurrences after treatment with EBRT, SRS, and surgical resection. Overall, the retrospective data seem to support decreased recurrence risk for WHO III meningiomas treated with RT after surgery (see **Table 2**). The ideal sequence of treatment has not been established. Aghi and colleagues'[15] retrospective series showed that 53% of patients with recurrent tumors were symptomatic at diagnosis and reported an 86% OS rate 5 years after recurrence for atypical meningiomas. Symptoms notwithstanding, most patients are undergoing regular MRI surveillance when a recurrence is noted.

Encouraging data exist for treatment outcomes after recurrence. Aghi and colleagues[15] reported a disease-specific survival (DSS) after recurrence of 86% at 5 years for their atypical meningioma series. Sughrue[25] reported a malignant meningioma series with 63 patients treated with surgery followed by adjuvant RT. There was a survival benefit observed for patients who had undergone repeat operation. Also, there was a survival benefit for STR with EBRT compared with GTR with EBRT (107 months compared with 50 months). These investigators did not observe any benefit to repeat SRS or salvage brachytherapy after a recurrence.[25]

It seems that only a few recurrences transform into WHO grade III. Retreatments after primary therapy are common in patients with both atypical and malignant meningiomas; patients often receive multiple courses of radiation therapy (either EBRT or SRS), and may even be treated with brain brachytherapy. No guidelines exist for retreatment (or salvage therapy) based on available evidence.

SUMMARY

The heterogeneity and retrospective nature of data highlight the need for prospective clinical trials. RTOG 0539 from the Radiation Therapy Oncology Group aims to address basic management questions in meningioma patients. This trial assigns patients with low-risk meningiomas to observation. Higher-risk patients receive fractionated EBRT to 54 Gy after GTR. Patients with STR, recurrences, and WHO grade II meningiomas receive 60 Gy. EORTC 22042 trial from the European Organisation for Research and Treatment of Cancer is a phase II study in which 54 Gy is given after GTR for atypical meningiomas and 60 Gy is given malignant meningiomas or any resection extent, or atypical meningomas after STR or after recurrence. It is expected that clinical data gained from these trials will guide future treatment approaches for these common skull base tumors. At the time this article was written, data from these trials were not available.

Based on the available data, most patients with atypical meningioma can expect a prolonged disease-free interval with recurrence to be treated with a variety of modalities (see **Table 2**). Yang and colleagues[29] reported a median OS of 11.9 years in patients with atypical meningiomas and 3.3 years for anaplastic meningiomas. However, these figures were reported using WHO 2000 pathologic classification.

Chordomas and Chondrosarcomas

Chordomas are rare tumors that arise from the primitive notochord.[50] Thirty-five percent of these tumors occur at the skull base, particularly the clivus, where they invade locally. Chondrosarcomas are malignant primary bone tumors.

Chordomas invade locally and recurrence rates are high after surgery. Most recurrences are local, but many patients survive for years after recurrence. Surgery is not considered curative. There has been considerable interest in subtotal resection and adjuvant RT.

Although these tumors grow slowly, a retrospective French series showed the merits of aggressive up-front management: patients who received RT immediately after surgery versus at recurrence had a 10-year survival of 65% versus 0% for those patients treated with RT at the time of recurrence.[51] The largest series of chordomas treated with RT was conducted at Harvard University. Patients received 60 to 79.2 Cobalt-Gray-Equivalent (CGE), with LC rates at 10 years of 44%.[52,53] A recent review that pooled more than 400 patients showed that 5-year LC is nearly 70% and OS is more than 80%.[54]

RT is still associated with some morbidity: in a series reported by Noel and colleagues[55] of skull base chordomas treated with RT, hypopituitarism was seen in 25%, memory impairment in 2%, oculomotor impairment in 3%, hearing loss in 2%, and bilateral visual loss in 2%.

Chondrosarcomas are a group of different sarcomas that commonly occur at the skull base. Because of their rarity and presentation, which are similar to chordomas, chordomas are often grouped along with chondrosarcomas for retrospective and prospective series. For example, Hug and colleagues[56] studied adjuvant proton beam EBRT after resection for chordomas and chondrosarcomas. Five-year LC and OS exceeded 90%, better than LC and OS seen in chordomas. Studies from MGH concurred with this finding.[57,58]

Adjuvant therapy with chondrosarcomas and chordomas is largely accomplished with proton EBRT. Protons are particularly useful in these tumors: they may encompass an area too large for SRS, and achieve a high enough dose with generally acceptable toxicity that is not otherwise achievable with EBRT. However, advanced treatment planning technologies are able to compensate for the less favorable dose distribution traditionally achieved with conventional EBRT techniques. Some practitioners are increasingly using sophisticated planning strategies to treat these tumors and improve access for patients who otherwise may not be able to afford logistics costs of a proton treatment at a distant center.

Other Sarcomas of the Head and Neck

Soft tissue sarcomas of the skull base are usually treated maximal surgical excision, followed by post-operative radiation therapy. Recurrence risk is higher than soft tissue sarcomas of the extremities, because clean surgical margins cannot often be achieved. The techniques applied to other soft tissue sarcomas of the head and neck include: EBRT, SRS, intraoperative RT, and brachytherapy. Specific data on skull base sarcomas are even more limited than the other entities discussed in this article, and no clear treatment standard is defined.

Sinonasal Carcinoma

The sinonasal cavities present the surgeon with a difficult anatomic location, which often precludes safe debulking and clear margins. RT is critical in these tumors. The high doses of radiation necessary for controlling these tumors are often limited by the adjacent critical structures (optic nerves, oropharynx, brain parenchyma, eye, and retina). Orbital invasion and invasion through the cribriform plate necessitate a multidisciplinary approach involving neurosurgeons and head and neck surgeons. This is an extraordinarily rare tumor, so data are sparse.

INDICATIONS FOR RT

RT may be given to the tumor bed after resection or it may be used for primary treatment along with chemotherapy in unresectable tumors.[58]

RT TECHNIQUES

The sinonasal carcinomas are an ideal example to discuss advances in treatment planning. In the early days of radiation therapy, anteroposterior/posteroanterior fields were common for all body sites. Modern EBRT delivered to sensitive sites uses three-dimensional conformal RT (3D-CRT) and intensity modulated radiation therapy (IMRT). 3D-CRT delivers radiation usually in a coplanar fashion, but from multiple beam angles like spokes on a wheel. IMRT is the technique that allows beam energies to vary at different beam positions. This technique has significantly advanced our ability to treat tumors in sensitive locations.

Hoppe and colleagues found a lower than expected incidence of grade 3 toxicities in their series with a 5 yr OS of 67%, survival comparable to other published series but with lesser observed toxicity.[59–62]

In a study by Monroe and colleagues[63] focusing on radiation retinopathy, hyperfractionation (2 smaller doses delivered per day) resulted in lower rates of radiation-induced retinopathy, even when total doses were comparable. The series included 168 patients, 64 of whom had paranasal sinus tumors. Recall that normal tissue recovers from radiation with time, so dividing the dose into smaller fractions should logically spare normally functioning tissues to a greater degree and this study seems to support this.

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