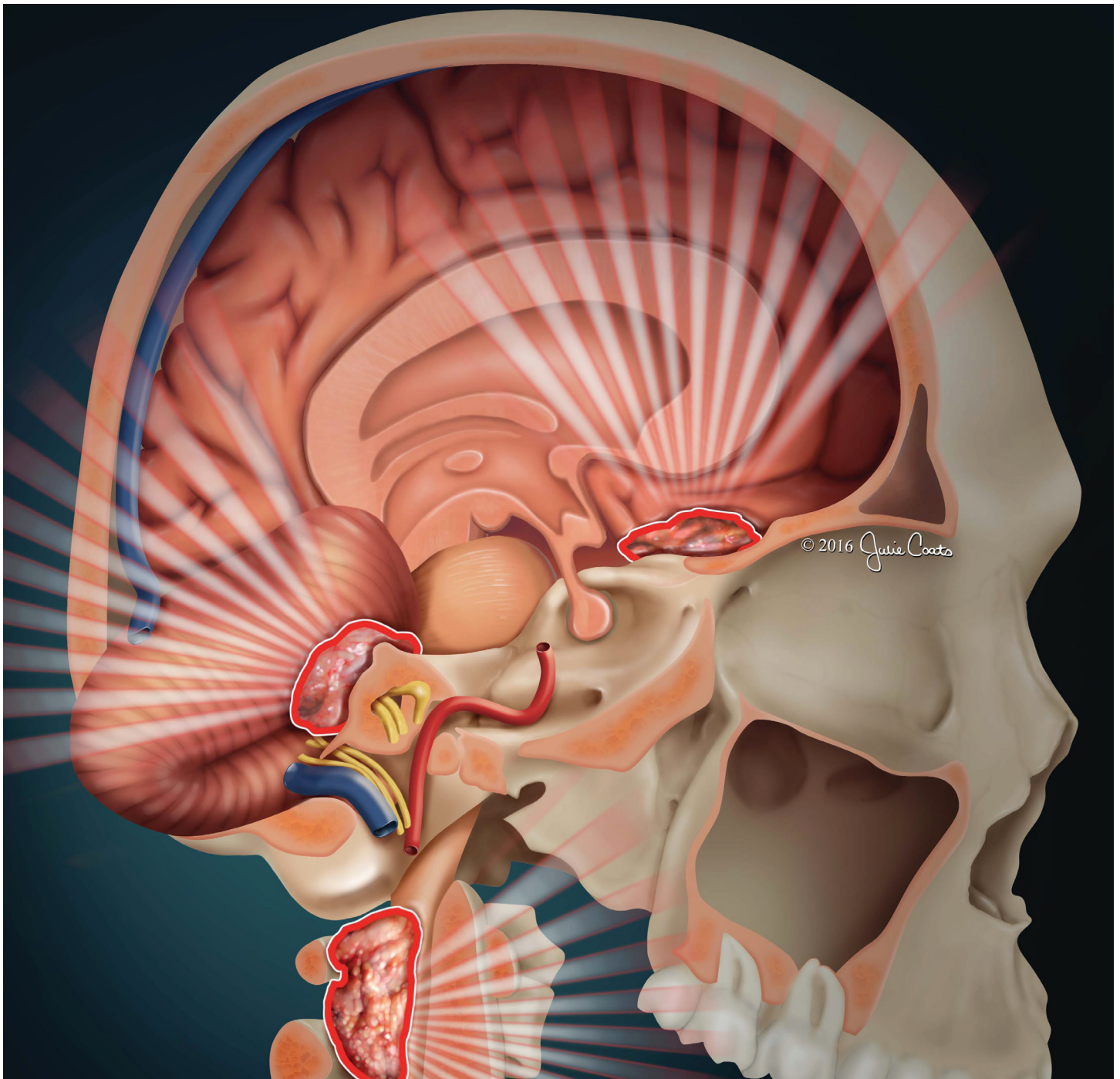


UH Neurological Institute Journal



UH Neurological Institute Journal

FROM THE EDITOR



Dear Colleague,

I am pleased to bring you the Fall 2016 issue of the UH Neurological Institute Journal.

Through continuing collaboration with scientists at Case Western Reserve University School of Medicine, physicians at the UH Neurological Institute test and refine the latest advances in treatment for patients with disabling neurological disorders. The Journal highlights these advances and demonstrates our interdisciplinary strengths. As an added benefit for our readers, CME credit is available for the busy practitioner interested in receiving *AMA PRA Category 1 Credits™*.

In this issue, Cliff Megerian, MD, and colleagues provide a pediatric case study and demonstrate that a successful staged multidisciplinary surgical management of multicompartmental en plaque meningiomas allows for optimal surgical resection as well as maximal patient well-being.

Andrew Sloan, MD, and colleagues attempt to expand current knowledge and detail their experience of utilizing stereotactic laser ablation (SLA) for deep-seated thalamic lesions in a follow-up to the recently completed Phase I clinical trial performed at University Hospitals Cleveland Medical Center for SLA for glioblastoma.

Simone Dekker, MD, and colleagues bring us a two-part series on treating tumors of the neuroaxis using proton beam therapy. In part 1, the authors introduce us to the principles of proton beam therapy and its particular application to chordomas and chondrosarcomas of the spine. Part 2 continues the discussion of this advantageous therapy, with a focus on chordomas and chondrosarcomas of the skull base. UH Cleveland Medical Center accepts patients for proton beam therapy in the newly built UH Proton Therapy Center. Proton beam therapy is currently offered at 24 centers in the United States, and UH Cleveland Medical Center is the first in Ohio and the region to offer this treatment as cancer therapy.

We at the NI Journal extend our thanks to each of the contributing authors as well as to our readers, and we wish everyone an enjoyable holiday season. As always, your comments and suggestions are welcome.

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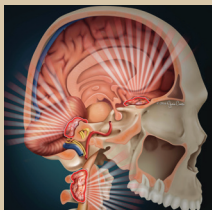
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Recognized by U.S. News & World Report as one of the nation's finest neuroscience programs, University Hospitals Neurological Institute delivers innovative, integrated and individualized care to patients with diseases affecting the nervous system.

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On the cover: Tumors of the neuroaxis being fired upon with the use of proton beam therapy. The new UH Proton Therapy Center at UH Seidman Cancer Center is one of the world's first "compact" proton therapy centers. It features a unique single-room system that is significantly smaller and more economical than first-generation proton therapy technology, while delivering the same powerful cancer-fighting radiation therapy. Read more about this topic in the article by Simone Dekker, MD, and colleagues on page 4. (Illustration by Julie Coats.)

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Introduction to Proton Beam Therapy and Its Implications for the Treatment of Spine Chordomas and Chondrosarcomas

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Introduction

Radiotherapy, together with surgery and chemotherapy, is a key component of cancer treatment. Shortly after the discovery of X-rays in 1895, photon therapy was developed for radiation treatment.¹ Its therapeutic mechanism is based on ionization of atoms in the DNA helix, which breaks atomic and molecular bonds and results in cell death.² Radiation therapy disproportionately affects tumor cells, as healthy cells generally possess better DNA repair mechanisms to survive radiation damage. Several modalities of photon radiotherapy are currently in clinical use. The most common approach is external beam radiotherapy (EBRT), which includes stereotactic radiotherapy, three-dimensional conformal radiotherapy and intensity-modulated radiotherapy (Table 1).³ In contrast, brachytherapy is a form of photon radiation therapy in which a radiation source is placed inside the target.

The suggestion to use energetic protons instead of photons came from Robert R. Wilson in 1946,⁴ and the first report on clinical outcomes following proton therapy was published in 1954.⁵ Since then, proton therapy has increasingly been used in the clinical setting and has been shown to be an effective treatment option for both children and adults with certain cancers, such as lung cancer, lymphomas, gastrointestinal cancer, and head and neck cancer. Proton therapy is similar to X-rays in that both are external beam radiation techniques. Yet, in contrast to photons, protons are positively charged particles, with a large rest mass, that continuously lose energy through interactions with surrounding atomic electrons and nuclei in the materials that they traverse.⁶

Proton therapy therefore has several important advantages over conventional photon radiotherapy. First, protons are able to deliver high-dose therapy due to the nature of their heavier and charged particles. This feature limits lateral side scatter of the beam into surrounding tissues. Second, the energy of the proton beam can be modulated to titrate the dose to the specific depth and shape of the tumor, which improves radiobiological effect.⁷ Third, protons display a finite range of penetration into the target lesion, thereby greatly limiting iatrogenic damage to surrounding healthy tissue. Researchers have previously found minimal exit dose associated with proton beam therapy (Figure 1).^{8,9} These points are all illustrated by the Bragg curve, which measures energy loss of ionizing radiation during its travel through matter (Figure 2). One of the main advantages of proton beam depicted by this curve is the sudden dose decline beyond the target, thereby allowing a greater dosage than conventional radiation therapy while minimizing harm to nearby healthy tissues.^{10,11} In contrast, photons in conventional radiotherapy attenuate in an exponential fashion and therefore deposit energy in healthy tissue distal to the lesion (Figure 2). Thus, proton beam therapy may be especially beneficial for tumors within critical organs, such as the brain and spinal cord.

There are other additional benefits from the utilization of proton beam therapy. First, proton beam therapy may reduce the risk of developing radiation-induced secondary neoplasms, secondary to the steep reduction in radiation dose to adjacent normal tissue. Patients who have already had conventional radiation treatment may also be candidates for proton beam therapy. Furthermore, proton beam therapy may induce fewer side effects that are typically associated with conventional radiotherapy, such as fatigue, diarrhea, headache and anorexia. However, it is noted that some side effects, such as hair loss and skin irritation, can be more pronounced with proton beam therapy compared to traditional radiation therapy due to the more focal region of application.

In this report, we give a brief overview of the different radiotherapy modalities and review the literature on the use of proton beam therapy for spinal chordomas and chondrosarcomas.

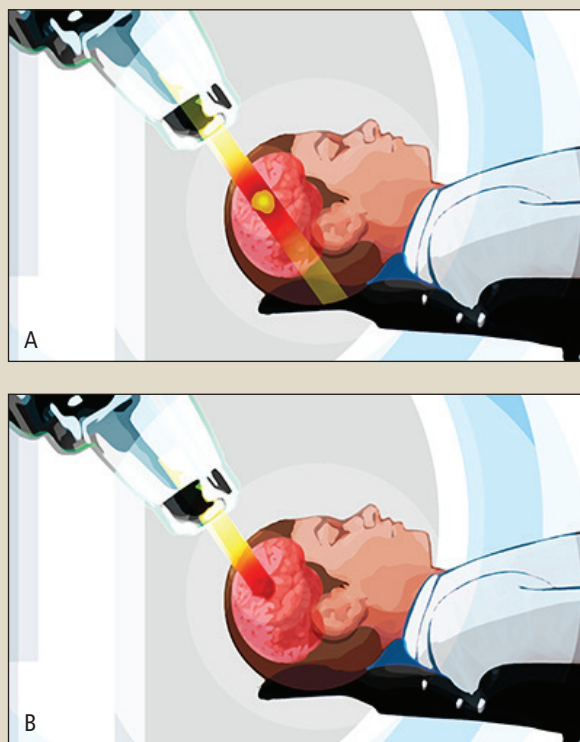


Figure 1: Photon therapy versus proton therapy. Representation of (A) conventional radiotherapy and (B) proton beam therapy. Note the difference in extraneous irradiation to the surrounding tissue. Proton therapy deposits most of its energy on the target and has a zero exit dose. Images courtesy of University Hospitals Cleveland Medical Center.

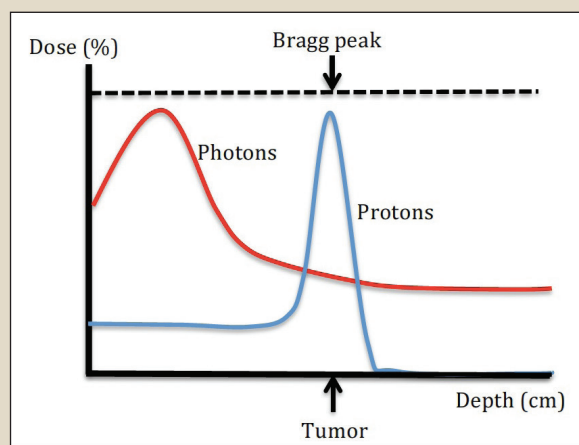


Figure 2: Dose deposition for photon and proton beams as a function of depth. Bragg curve outlining the penetration depth of protons, which eventually reach a maximum dosage at a specific depth (tumor) and then abruptly decrease to zero to spare healthy tissues. Note that even after traveling the distance to the tumor, conventional radiation still requires a relatively higher radiation dosage, potentially damaging surrounding healthy tissues.

Radiotherapy Modalities

Currently used modalities for radiotherapy are three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), stereotactic radiotherapy (STR), brachytherapy, proton therapy, proton-modulated arc therapy (PMAT), helical tomotherapy, intensity-modulated proton therapy (IMPT) and ion therapy. Table 1 illustrates the characteristics of different radiotherapy modalities currently in clinical use and summarizes the main advantages and disadvantages associated with the different radiotherapy techniques. In addition, we summarize the results of a literature review of spine chordomas and chondrosarcomas treated with radiation therapy (Table 2). The average overall survival of patients treated in this systematic review was 51.6 percent for photon therapy and 80.2 percent for combined photon/proton therapy.

Discussion

The present report shows promising results for proton beam therapy for the treatment of spinal chordoma and chondrosarcomas. Advancements in diagnostic imaging and surgical techniques, coupled with recent developments in more elegant radiation therapies, have contributed to improved local control and increased overall survival rates in patients with spinal chordomas and chondrosarcomas. The advantages of radiation therapy are partly due to the development of proton therapy, which has the ability to deliver a higher dose of radiation to the tumor compared to CRT or other photon-based techniques, while minimizing damage to the sensitive structures surrounding it.

The maximum radiation dose to the spinal cord is around 50 Gy.¹² However, it has been shown that chordomas and chondrosarcomas require doses in excess of this tolerance. For example, treatment of proton radiotherapy with doses of less than 60 Gy resulted in recurrence rates of 50 to 100 percent and five-year progression-free survival rates of less than 25 percent.¹³ Aggressive surgical management is important, as is the timing of postoperative radiotherapy. It is important to initiate postoperative radiation in a timely manner; a longer interval between surgery and radiation can result in poorer outcome. For example, a recent study compared patients who underwent early adjuvant proton therapy with patients who had “salvage” treatment. The two-year local control rate was 88 percent in the adjuvant group compared with 45 percent in the salvage group. The local control disparity was more pronounced at five-year follow-up, where 88 percent local control was maintained in the adjuvant group, but the salvage group local control fell to 9 percent.¹⁴ Other adverse prognostic factors were the presence of gross residual disease and sacral tumor location.

There are several limitations to the use of proton beam therapy. First, while certain side effects of traditional radiation therapy are ameliorated (e.g., fatigue, diarrhea, headache, anorexia), there is a tradeoff for other side effects being more pronounced (e.g., hair loss, skin irritation). In addition, proton treatment may generate neutrons as a byproduct, which can potentially scatter into adjacent normal tissues and increase the risk of secondary malignancies. However, this has not been confirmed in any studies to date.¹⁵ Finally, proton beam therapy is more expensive than photon therapy, as the cost of one proton session is around tenfold that of photon therapy.¹⁰

Conclusion

This report reveals more favorable outcomes of proton beam therapy compared to photon therapy in terms of local control and overall survival. The main advantages of proton beam therapy can be described by the “Bragg peak principle,” which allows delivery of high radiation doses to specific depths while sparing the surrounding tissues.

University Hospitals Cleveland Medical Center accepts patients for proton beam therapy in the newly built UH Proton Therapy Center. Proton beam therapy is currently offered at 24 centers in the United States, and UH Cleveland Medical Center is the first in Ohio and the region to offer this treatment as cancer therapy. For more information about proton therapy at University Hospitals, please contact the UH Proton Therapy Center at 216-286-PROT (7768) or visit UHhospitals.org/Seidman/Services/Radiation-Oncology/Our-Technology/Proton-Therapy.

The authors report no financial relationships with commercial interests relevant to the content of this article. Kevin Yoo's contribution includes discussion of unlabeled/ investigational uses of a commercial product.

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Table 1: Description of different radiotherapy techniques.

Modality	Subtype	Description	Advantages	Disadvantages
3-dimensional conformal radiotherapy (3D-CRT)		This term is typically used when the target volumes are defined on high-definition imaging studies (CT or MRI)	<ul style="list-style-type: none"> Because 3D-CRT uses targeting information for precise focus on the tumor, it increases efficiency in shrinking and killing tumors compared to traditional radiation therapy while sparing healthy tissue Standard in outpatient radiotherapy 	<ul style="list-style-type: none"> Can result in severe acute and late toxicities²⁴
Intensity-modulated radiotherapy (IMRT)		<ul style="list-style-type: none"> Advanced form of 3D-CRT Developed in the beginning of the 21st century Can change the intensity of radiation in different parts of a single radiation beam during treatment 	<ul style="list-style-type: none"> Can achieve more uniform dose distribution and is ideally suited for irregular-shaped tumors and tumors close to critical structures²⁵ 	<ul style="list-style-type: none"> Can result in severe acute and late toxicities²⁴
Stereotactic radiotherapy (STR)	Gamma Knife®	<ul style="list-style-type: none"> Multiple beams are focused on the target volume from different angles in an isocentric way Gamma Knife does not use inverse planning 	<ul style="list-style-type: none"> Can achieve a highest dose gradient and is ideally suited for targets of a simple shape Minimal toxicity 	<ul style="list-style-type: none"> Concave dose distributions cannot be achieved using Gamma knife [Torrens] Frame-based technology Useful only for the treatment of small tumors (less than 30 mm in diameter and at least 5 mm from tissue such as optic nerve and brainstem/spinal cord)
	Linear accelerators (CyberKnife®)	<ul style="list-style-type: none"> Multiple beams are focused on the target volume from different angles in an isocentric way Can be considered to be at the border between IMRT and SRT CyberKnife uses inverse planning 	<ul style="list-style-type: none"> Can deliver concave or even donut-shaped dose distributions Nonframe-based technology 	<ul style="list-style-type: none"> Similar limitations as other stereotactic radiotherapy modalities
Brachytherapy		<ul style="list-style-type: none"> Radiation source is near and/or in the tumor Ideal candidates are patients with superficial nasopharyngeal tumors Can be indicated as a boost after EBRT 	<ul style="list-style-type: none"> Higher localized dose around the target volume and a shorter overall treatment time Relative sparing of critical normal tissue Well tolerated with minimal morbidity 	<ul style="list-style-type: none"> Potential nontreatment of foci in areas outside the treated volume encompassed by the isodose surface corresponding to the minimal target dose
Proton therapy		<ul style="list-style-type: none"> Proton therapy with passive scattering 	<ul style="list-style-type: none"> Protons permit better sparing of critical organs²⁴ 	<ul style="list-style-type: none"> Treatment generates neutrons as a byproduct, which theoretically may scatter into adjacent normal tissues Limited in number of facilities in the country
Proton-modulated arc therapy (PMAT)		<ul style="list-style-type: none"> Proton arc therapy relies on multiple gantry angles, reducing the weight of each beam angle while maintaining conformal dose to the target by escalating the dose delivered at each gantry angle²⁶ 	<ul style="list-style-type: none"> Better conformity than single-field uniform dose proton therapy and intensity-modulated radiotherapy plans Superior to other proton therapies in most regions 	<ul style="list-style-type: none"> Potential for error in dose delivery from range uncertainties may be large (due to Bragg peak, as discussed above) Inferior to other proton therapy in pituitary region, temporal lobes and orbit
Helical tomotherapy		<ul style="list-style-type: none"> Utilizes computed tomography targeting; useful for malignancies of the spine 	<ul style="list-style-type: none"> Less target underdosing than conventional proton therapy and PMAT; over 90 percent of field obtains required dose Comparably better conformal dose than other therapies 	<ul style="list-style-type: none"> Limited clinical availability at this time
Intensity-modulated proton therapy (IMPT)		<ul style="list-style-type: none"> Proton therapy with active scattering Equivalent of intensity-modulated radiation therapy with photons 	<ul style="list-style-type: none"> Has the advantage over proton therapy as active scattering provides optimization of dose deposition in the target with less dose in the healthy tissues 	<ul style="list-style-type: none"> High cost, limited availability
Ion therapy		<ul style="list-style-type: none"> Currently uses carbon ions 	<ul style="list-style-type: none"> Effective treatments for less radiosensitive tumors due to a higher biological effectiveness 	<ul style="list-style-type: none"> Unfavorable side effect profile to adjacent tissue compared with other

Table 2: Results of the main series of spine metastasis treated with radiation therapy.

Treatment	Author	Tumor type	N of patients	Dose and fractioning (Gy)	Mean follow-up (months)	Local control (%)	Overall survival (%)
Photon	Boriani ⁹	Chordoma	21	NR; NR	65	NR	33
Photon	Catton ¹³	Chordoma	28	50; NR	48	NR (five years)	50
Photon	Schoenthaler ¹⁶	Chordoma	14	75.65; NR	60	NR	55
Photon	Prabhakaran ¹⁷	Chordoma	14	NR; NR	33	48 (five years)	56
Photon	Nowakowski ¹⁸	Chordoma, chondrosarcoma, other bone and soft tissue sarcoma, and metastatic or unusual histology tumors	52	70; NR	28	58.3 (for 36 previously untreated patients, three years); 43.75 (for 16 patients with recurrent disease, three years)	61 (for 36 previously untreated patients, three years); 51 (for 16 patients with recurrent disease, three years)
Average			25.8	65.2	46.8	-	51.6
Photon + proton	Noël ¹⁰	Chordoma (64), chondrosarcoma (26)	90	67; NR	34	69.2 (chordoma, three years); 91.6 (chondrosarcoma, three years)	NR
Photon + proton	Holliday ¹⁴	Chordoma, chondrosarcoma	19	70; 2.0	24	58 (two years)	93
Photon (45%), photon + proton (55%)	Indelicato ¹⁹	Chordoma	34	70.2; 1.8	48	67 (four years)	80
Photon (45%), photon + proton (55%)	Indelicato ¹⁹	Chordoma, chondrosarcoma	51	70.2; 1.8	48	58 (four years)	72
Photon + proton	Rotondo ²⁰	Chordoma	126	72.4; 1.8 – 2.0	60	62 (five years)	81
Proton only - 31/40, proton + photon - 9/40	Staab ²¹	Chordoma	40	72.5; 1.8 – 2.0	60	62 (five years)	80
Photon/proton	DeLaney ²²	Chordoma, chondrosarcoma and other sarcomas	50	76.6; 1.8	24	78 (chordoma, five years); 64 (chondrosarcoma, five years)	87
Photon/proton	Chowdhry ²³	Chordoma (50), chondrosarcoma (28), osteosarcoma (3), other sarcoma (11) and other (2)	124	70; NR	13	88.7 (five years)	NR
Average			73.6	71.3; 1.8	41	-	80.2

NR = no report

Proton Beam Therapy for Skull Base Chordomas and Chondrosarcomas:

Case Report and Review of the Literature

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Introduction

Tumors of the skull base can involve a variety of benign and malignant tumors, originating from meningeal sheets, nerves, nerve sheets, bone, cartilage, soft tissues, muscles, lymphatic tissue, mucosal epithelium and embryonic remnants.¹ As these tumors are proximate to critical structures, such as the brain parenchyma, brainstem and optic pathway, radical surgical resection is often impossible. For example, complete resection of skull base chordomas is seldom performed, as the 10-year recurrence-free survival is only 31 percent, even if macroscopic total resection was the primary aim.² Consequently, surgical resection of skull base tumors is often followed by radiotherapy. However, conventional photon radiation treatment can cause significant morbidity, as critical surrounding tissues may receive significant radiation exposure. For this reason, the photon dose must always be less than 60/70 Gy.

Proton beam radiotherapy, however, is a relatively new type of radiotherapy that greatly limits iatrogenic damage to surrounding healthy tissue, resulting in less toxicity. Therefore, it allows an increased dose to the tumor while sparing critical surrounding structures. Not surprisingly, the first studies on proton therapy focused on skull base tumors, as these are closely located to radiosensitive critical structures and require high-radiation doses.³ In this report, we describe a patient with a skull base chordoma treated with proton beam therapy. We furthermore review the literature on the use of this therapy for skull base chordomas and chondrosarcomas. Chordomas are uncommon locally aggressive malignancies of bone, with base of the skull presentations representing one-third of the cases.⁴ Chondrosarcomas are tumors composed of cells derived from transformed cells that produce cartilage. Both tumors often require aggressive radiation treatment (in the range of 70 Gy) but are located adjacent to critical central nervous system structures, such as brain parenchyma, the optic tract and the brainstem. These tumors are therefore ideal candidates for proton beam therapy.

University Hospitals Cleveland Medical Center is the first in Ohio and the region to offer proton beam therapy for cancer treatment. For more information on the principles of proton beam therapy, please refer to "Introduction to Proton Beam Therapy and Its Implications for the Treatment of Spine Chordomas and Chondrosarcomas" on pages 4 – 9 of this issue.

Illustrative Case

In this case report, we present a 25-year-old male who was diagnosed with a chordoma of the clivus and upper cervical spine and underwent surgical resection and radiation therapy (72 Gy) in 1999. The patient remained clinically and radiographically free of progressive disease for almost 10 years until the patient presented with headaches in June 2008. An MRI of the head showed the previously described skull base lesion involving the apex of the right petrous bone extending into the right clivus and right occipital bone (Figure 1A). In the following

months, the patient noted progressive head and neck pain, diplopia and episodes of dysphagia. A subsequent MRI in November 2008 showed an increase in size of the cystic component to the area of tumor recurrence. As the patient received a high dose of radiation therapy in the past, current therapeutic options included surgery, CyberKnife® radiosurgery and proton beam therapy. The patient underwent surgical resection of his chordoma on December 10, 2008. A postoperative MRI on December 11 measured the lesion at 4.1 x 2.1 cm in the axial dimension and 2.8 cm in the craniocaudal dimension (Figure 1B). His surgery was followed with proton beam therapy at the Indiana University Health Proton Therapy Center. An MRI of the brain in January 2010 revealed a marked decrease in size of the central skull base mass, indicating effective proton beam treatment (Figure 1C). However, a later follow-up MRI demonstrated lumbosacral drop metastases, and together with the patient the decision was made to suspend treatment.

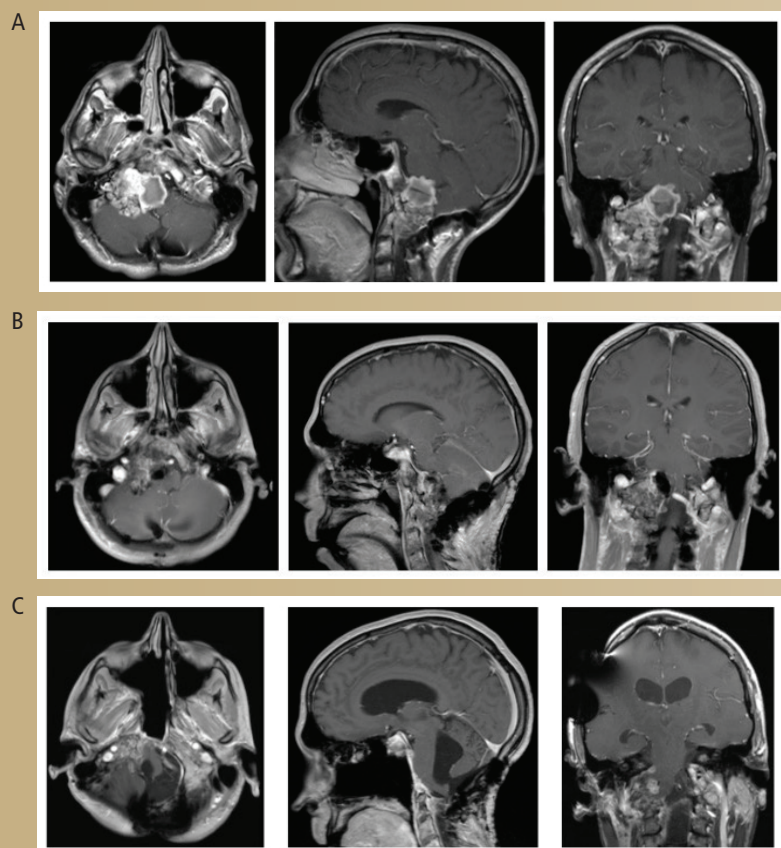


Figure 1: MRI images before and after the proton beam treatment: (A) preoperative, (B) postoperative and (C) post proton beam therapy.

Discussion

One of the first studies on proton beam therapy for chordomas and chondrosarcomas of the skull base was done in 1982.⁵ Since then, numerous studies have shown favorable results in terms of local control and limited toxicity.⁶⁻⁹ In 2008, Amichetti and colleagues systematically reviewed 47 studies that employed proton therapy in chordomas and chondrosarcomas of the base of the skull¹⁰ and compared this with other irradiation techniques. Most patients in this study underwent proton therapy (n = 416), followed by ion therapy (n = 206) and conventional therapy (n = 191). The main findings of this review are summarized in Table 1. In comparison to other treatment modalities, the best five-year local control rate was achieved by proton beam therapy (69.2 percent).^{10,11} The overall five-year survival was remarkably lower in patients treated with conventional therapy (53.5 percent) compared to proton therapy (79.8 percent). However, the overall five-year survival in proton therapy was not markedly different from stereotactic fractionated radiation therapy, radiosurgery or ion therapy (Table 1). Importantly, proton therapy has relatively few significant complications (5 to 17 percent) considering the high doses delivered with this therapeutic modality. This amount of complications is in contrast to other treatments, such as ion therapy, where complications are reported, mainly to optic pathways, in around 20 percent of the cases.^{12,13} It is also important to note that there are currently no randomized controlled trials comparing the different types of radiation treatment in chordoma or chondrosarcoma patients. The retrospective nature of most studies complicates the comparisons between treatment modalities. For example, Ammichetti and colleagues only included one study of 37 patients irradiated with fractionated stereotactic radiation therapy in the systematic review.¹⁴ Furthermore, included studies have different selection criteria and administered doses, and not all studies include both chordomas and chondrosarcomas. More recent studies found two-year local control rates for proton therapy of 86 percent and a two-year overall survival rate of 92 percent; 14 five-year local control values for photon radiotherapy of both chordomas and chondrosarcomas were 55.2 percent (CyberKnife).¹⁵ When studies separate chordomas and chondrosarcomas into different groups, chordomas are associated with poorer local control. For example, the five-year local control rate was found to range between 15 – 66 and 100 percent for chordomas and chondrosarcomas, respectively (Gamma Knife®),¹⁶⁻¹⁸ or 65 and 88 percent for chordomas and chondrosarcomas, respectively (IMRT).¹⁹ Fossati and colleagues conclude that photon therapy is an important treatment for benign tumors, but proton therapy may play a major role in the treatment of malignant tumors.¹

There are several factors that influence the overall outcome of patients with chordomas and chondrosarcomas. Tumor location likely affects the outcome, as skull base tumors without any intracranial extension can undergo more aggressive radiation treatment compared to intracranially extended tumors with brainstem compression and optic chiasm displacement. Tumor location at the cranio-cervical junction,²⁰ brainstem compression and a tumor volume

of > 25 mm at the time of proton therapy negatively affected the likelihood of achieving tumor local control.⁹ Spine and sacral chordomas have a better overall survival than those reported for skull base chordomas, likely because spine chordomas can be treated with a higher radiation dose to a higher percentage of the target volume compared to the skull base.²¹ Moreover, wider resections are achievable in spine and sacral locations compared to skull base tumors.²¹ The contribution of age to the likelihood of local control and overall survival is still controversial.^{8,9}

Future Directions

Because of these recent developments, not only has radiotherapy become an effective complementary treatment to surgery, but it may also be an effective alternative to surgery in cases of unresectable disease or for achieving local control with minimal side effects.⁵ New developments within proton beam therapy have facilitated the transition from passive scattering to active scanning system allowing for intensity-modulated proton therapy (IMPT). IMPT allows optimization of dose deposition in the target neoplasm with lower irradiation of the healthy tissue.⁵ Furthermore, ion therapy may be a promising modality for less radiosensitive tumors as it uses higher biological effective carbon.^{5,10,22} Besides advantages in radiotherapy, other disciplines such as neurosurgery and otolaryngology have also developed advanced skull base surgical approaches, and medical oncology offers new chemotherapies and advanced molecular targeted drugs. Collaboration between these different disciplines plays an important role in the management of malignant tumors of the skull base and will be even more important in the future. It remains uncertain whether further dose escalation to doses > 75 Gy (RBE) will improve the likelihood of local control. Therefore, dose escalation studies for chordomas and chondrosarcomas as well as other skull base tumors are necessary to further optimize dose-complication relationships.

Conclusion

Skull base chordomas and chondrosarcomas are difficult to treat due to their complex shape and proximity to critical neurologic structures. Proton beam therapy is a promising new treatment modality that can play an important role in the treatment of skull base tumors. One of its primary advantages is the effective delivery of high-dose radiation to the neoplasm, while preserving the surrounding healthy tissue.

Proton beam therapy is currently offered at 24 centers in the United States, and University Hospitals Cleveland Medical Center is the first in Ohio and the region to offer proton therapy. For more information about proton therapy at University Hospitals, please contact the UH Proton Therapy Center at 216-286-PROT (7768), or visit UHhospitals.org/Seidman/Services/Radiation-Oncology/Our-Technology/Proton-Therapy.

The authors report no financial relationships with commercial interests relevant to the content of this article. Kevin Yoo's contribution includes discussion of unlabeled/investigational uses of a commercial product.

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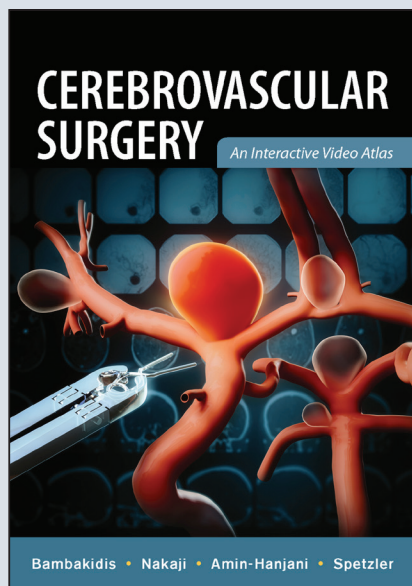
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Table 1: Comparison between different radiation modalities.

Treatment	# of patients	Radiation dosage	Mean follow-up time (months)	% Local control (follow-up)	% Overall survival (follow-up)	References
Proton therapy or combined proton + photon therapy	416	Range of 66 – 83 Gy	46	69.2 (5 years)	79.8 (5 years)	Munzenrider, ⁶ Hug, ⁷ Noel, ⁸ Hug, ²³ Igaki, ²⁴ Weber, ²⁵ Hoch ²⁶
Conventional photon radiotherapy	191	Mean of 52.7 Gy, Range of 22.93 – 69.36 Gy	65	36 (5 years), 23.8 (10 years)	53.5 (5 years), 50.3 (10 years)	Catton, ²⁷ Fuller, ²⁸ Foryth, ²⁹ Zorlu, ³⁰ Cummings, ³¹ Amenodola, ³² Chetyawardana, ³³ Raffel, ³⁴ Watins, ³⁵ Cho ³⁶
Stereotactic fractionated radiation therapy	37	Mean of 66.6 Gy	27	50 (5 years)	82 (5 years)	Debus ³⁷
Radiosurgery (GKS, CyberK)	109	Mean of 15.4 Gy, Range of 9 – 25 Gy	56.1	56 (5 years)	75 (5 years)	Krishnan, ³⁸ Martin, ³⁹ Chang, ⁴⁰ Crockard, ⁴¹ Hasegawa ⁴²
Ion therapy	206	Range of 48 – 80 CGE	38	64 (5 years)	79.9 (5 years)	Berson, ¹² Castro, ¹³ Schulz, ⁴³ Tsujii ⁴⁴

Table adapted from Amichetti et al.¹⁰

GKS: Gamma Knife; CyberK: CyberKnife; Gy: gray



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Management of en Plaque Skull Base Meningiomas with Intra- and Extradural Extension

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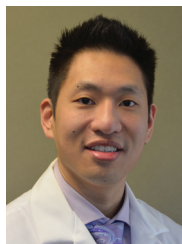
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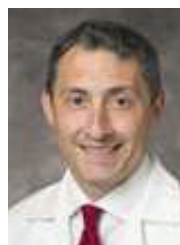
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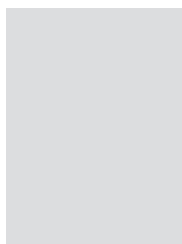
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Introduction

Meningiomas are common lesions of the central nervous system that comprise 30 percent of all primary central nervous system tumors.¹ En plaque meningiomas are a subset of these tumors that were first described by Cushing in 1939. Classically, they are defined as demonstrating sheetlike growth with dural and often osseous infiltration.² Hyperostosis of the involved bone can be seen secondary to osseous invasion.³ The most common site of en plaque meningiomas is the sphenoid ridge.⁴ While cerebellopontine angle (CPA) meningiomas are the second most common tumors found in the skull base, they account for less than 10 percent of CPA tumors; the most common tumors are vestibular schwannomas (80 percent).⁵ En plaque meningiomas presenting in the posterior fossa are rare occurrences, although there are multiple reports in the literature.^{6,7} For tumors that erode into the petrous bone and into the middle ear space, presenting symptoms often mimic those of chronic infectious middle ear disease.⁶

Extracranial locations for meningiomas are rare and defined as either primary or secondary. The primary type arises from displaced embryonic arachnoid cells or from pluripotent mesenchymal stem cells; secondary extracranial meningiomas are through direct extension of an intracranial mass. Therefore, the four etiologies of extracranial meningiomas are from (1) arachnoid cell caps associated with cranial nerve sheath, (2) extracranial arachnoid cell caps, (3) direct extracranial extension and (4) metastasis.⁸ The current report falls into the category of direct extracranial extension. The most common anatomic site of cervical extension of an intracranial meningioma is the infratemporal fossa,⁹ followed by the parapharyngeal space.¹⁰ It is important to note that the parapharyngeal space is often considered to be a part of the infratemporal fossa. The jugular foramen is often the pathway of tumor spread into the neck,¹¹ though cases of hypoglossal canal disease have been reported.¹² We believe that, in our patient, the tumor extended through the hypoglossal canal.

We present a rare pediatric patient who was admitted with incidental diagnosis of a multicompartmental meningioma with extension from the posterior petrous surface through the skull base along the carotid sheath. The staged resection and final reconstruction with an anterolateral thigh free flap are described.

Illustrative Case

A 15-year-old previously healthy female patient presented to the orthopedic clinic with concerns of right shoulder pain and progressive shoulder weakness over the past several months. On examination, the patient demonstrated right-sided hypoglossal as well as trapezius and sternocleidomastoid paralysis; she also had diminished palatal gag reflex and hearing loss in the right ear. Plain

radiographs of the shoulder revealed no bony erosion or lytic abnormalities. MRI of the brain and neck with and without contrast were obtained, which demonstrated a bulky soft tissue mass at the right CPA compressing the cerebellum and brain stem extending caudally to the right aspect of the foramen magnum. Additionally, there was lateral extension through the right hypoglossal canal into the anterior neck soft tissues, with further caudal extension into the right carotid space (Figure 1).

A computed tomography (CT) scan of the head, without contrast, with temporal bone windows showed partial calcification of the above-described mass and no direct involvement of the right internal auditory canal. A cerebral angiogram demonstrated only a faint tumor blush within the right cervical region and right skull base, without evidence of any major arterial internal carotid artery or external carotid artery feeders (Figure 2).

An incisional biopsy of the mass through a small anterior cervical approach was performed, and pathology was consistent with WHO grade I meningioma. A staged surgical resection of the tumor was planned.

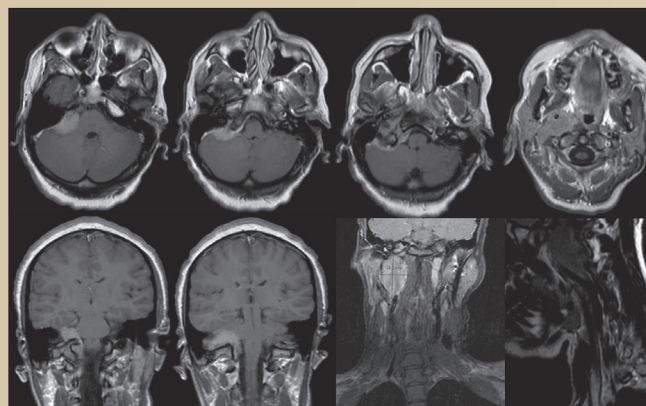


Figure 1: (Top) Axial T1 postcontrast images demonstrate a bulky soft tissue mass at the right cerebellopontine angle with extension into the right hypoglossal canal and encasement of the right carotid artery. (Bottom) Coronal T1 postcontrast images and sagittal T2 further delineate the extension of the mass and right carotid encasement.

Operative Course

Stage One: Posterior Fossa Far Lateral Craniotomy with Partial Mastoidectomy

After induction of general anesthesia, a lumbar drain was placed and facial nerve monitoring was applied. The patient was then placed in the left lateral decubitus position for a right-sided far lateral transcondylar approach to the posterior cranial skull base. The posterior fossa bone was exposed, a C1 hemilaminectomy was completed, and a posterior fossa far lateral craniotomy was performed. The occipital condyle was drilled in the posterior half, along with bone around the sigmoid sinus. A partial mastoidectomy was performed by the otolaryngology team along with skeletonization of the facial nerve, middle fossa dura, sigmoid sinus and jugular bulb. Dura was opened and the sigmoid sinus was ligated. Frameless stereotactic computer-assisted navigation was utilized to expose the posterior fossa extra-axial component of the tumor extending intracranially. Cranial nerves of the inferior CPA were carefully freed from the tumor, cautiously peeling off the arachnoid plane. Gross total resection of the intradural component of the tumor was then completed. The tumor was then followed into the hypoglossal canal with removal of extradural component in that area. Tumor

adherent to dura mater was removed along with the attached local dura mater (Figure 3).

Stage Two: Transtemporal-Infratemporal Approach

The second operation was performed five and a half weeks later by the neuro-otology and head and neck surgery teams. A right postauricular transtemporal approach to the skull base was taken. Once an incision was made, care was taken to avoid contamination of the previous craniotomy defect and the prior transcervical biopsy site was excised. To gain surgical access to the infratemporal fossa, the neuro-otology team performed a canal-wall down mastoidectomy. Once completed, the high cervical carotid artery, the vertical segment of the facial nerve and the temporomandibular joint were exposed. No tumor was found to be encasing the petrous segment of the internal carotid artery.

To gain access to the superior aspect of the parapharyngeal space and infratemporal fossa, a transparotid/transcervical approach was employed, allowing for better tumor exposure and preservation of the facial nerve. The lateral aspect of the gland was mobilized but left attached anteriorly, and the deep lobe was removed to allow for access deep to the facial nerve. Next, the muscular and ligamentous

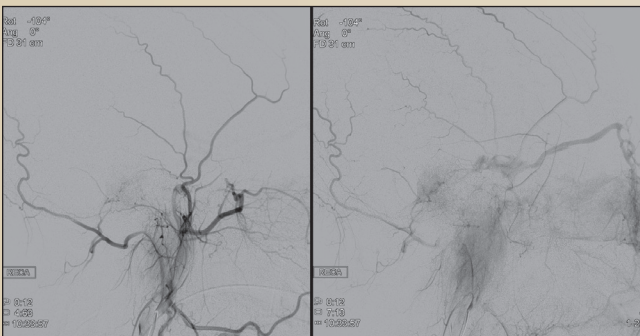


Figure 2: (Left) Right external carotid artery anteroposterior angiographic run is without evidence of early enhancement. (Right) Two right external carotid artery lateral angiographic runs demonstrate a faint tumor blush within the right cervical region and right skull base, without evidence of any major internal carotid artery or external carotid artery feeders.

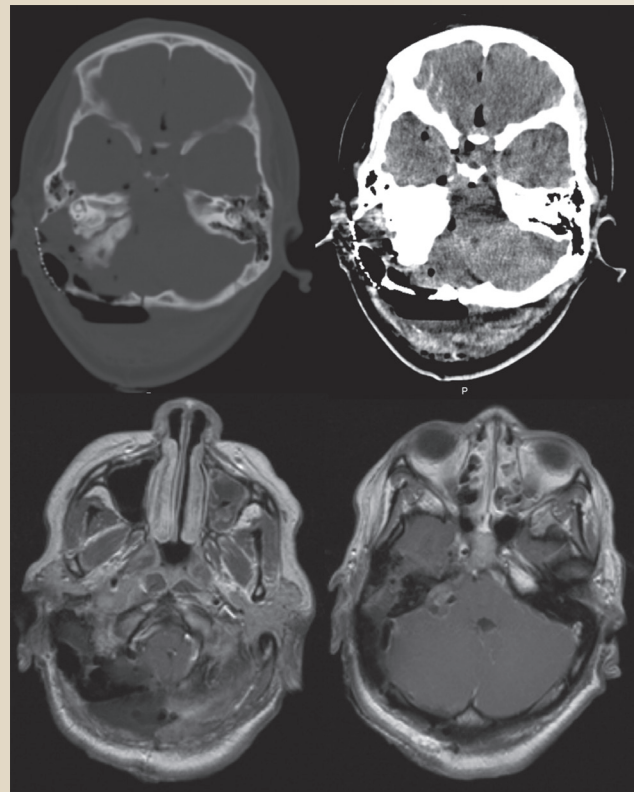


Figure 3: Stage one: Posterior fossa far lateral craniotomy with partial mastoidectomy. (Top) Axial CT images in bone and soft tissue algorithms. (Bottom) Axial T1 postcontrast images. Tumor is still seen extending into the hypoglossal canal.

attachments to the styloid process and mandible were released to allow for mandibular retraction and better access to the parapharyngeal space from below. Further dissection demonstrated that CN X, XI and XII were deeply embedded in the tumor, and these nerves were isolated and sacrificed. The tumor was then traced rostrally and mobilized off the mastoid tip. Attention was then turned to the carotid space. The jugular vein was transected at the level of the jugular foramen (oversewing of the sigmoid sinus and compression/obliteration of the jugular bulb had already been performed previously), and the tumor was mobilized off the deep prevertebral and paravertebral soft tissue extending inferiorly to the C3 level and then traced superiorly along the carotid artery to the entrance of the carotid canal, which allowed for total and en bloc removal of the tumor from the skull base and neck (Figure 4). An obliteration of surgical defect was performed with an anterolateral thigh myocutaneous free flap. It was harvested for dead space obliteration and to prevent the development of a large soft tissue defect and cosmetic deformity. The free flap also allowed for coverage of the carotid artery and separation of the site of dural repair from the obliterated middle ear space. Microanastomosis and de-epithelialization of the free flap was performed, and skin incisions were closed primarily (Figure 5).

Postoperative Course

The patient's cranial nerve function was abnormal on the right side: preoperatively, she demonstrated stable lack of palatal movement, inability of shoulder elevation and tongue paralysis. Intraoperatively, right-sided cranial nerves IX, X, XI and XII were resected due to tumor encasement.

The facial nerve was spared with preservation of corresponding function and sensation. Mild vocal hoarseness was noted postoperatively. The expected postoperative cranial nerve deficits were managed with right vocal medicalization and right vocal fold open arytenoidopexy as well as speech and physical therapy. Otherwise her neurologic exam remained stable. The early postoperative course was complicated by surgical site cerebrospinal fluid (CSF) leak, which resolved after lumbar drain placement, with no signs of CSF infection. In addition, the patient experienced persistent dysphagia and the associated weight loss, which was managed with speech therapy and careful nutritional supplementation. She did not require placement of a percutaneous endoscopic gastrostomy tube. Long-term follow-up showed appropriate weight gain, but she did require an additional vocal cord medicalization procedure to assist in phonation and swallow.

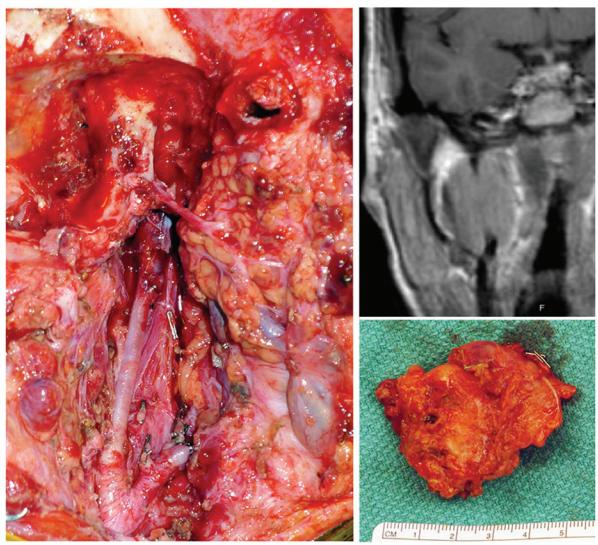


Figure 4: (Left) Intraoperative image showing successful resection of the parapharyngeal portion of the meningioma that was encasing the right carotid artery. Note the temporal bone defect and preserved neurovascular structures in the resection bed. (Top right) Preoperative coronal T1 postcontrast image demonstrating encasement of the right carotid artery. (Bottom right) Gross specimen of cervical portion of the en plaque meningioma.

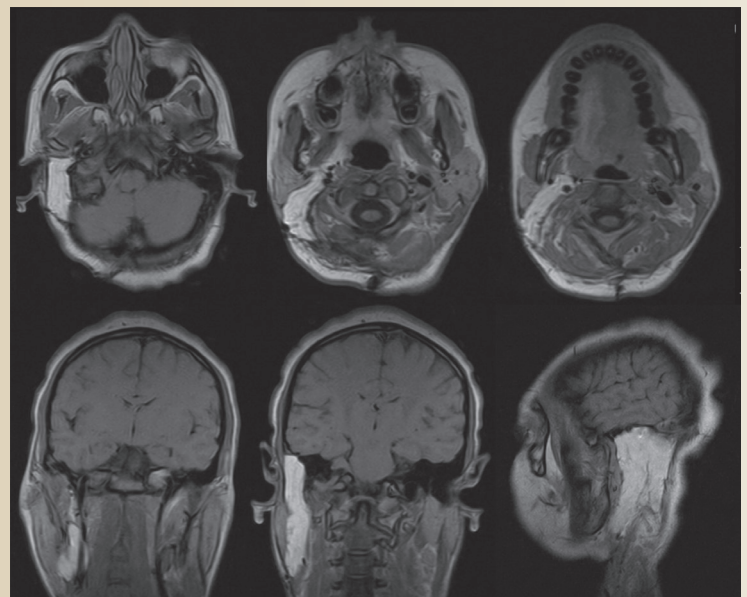


Figure 5: Stage two: Transtemporal-infratemporal approach with myocutaneous free flap reconstruction. (Top) Axial T1 postcontrast images demonstrate near complete resection of meningioma en plaque with a minimal residual tissue noted within the right hypoglossal canal and posterior carotid space. (Bottom) Coronal T1 postcontrast images display near complete removal of meningioma previously encasing the right carotid artery and placement of overlying myocutaneous free flap. Sagittal T1 postcontrast image again shows minimal residual tumor within the posterior right carotid space and hypoglossal canal.

Discussion

Large posterior fossa CPA en plaque meningiomas with cervical extension provide multiple surgical challenges in regards to optimal resection and reconstruction. We utilized a multidisciplinary surgical team consisting of neurosurgeons, neuro-otologists and neck oncologic surgeons. In addition, a two-staged approach of central nervous system tumor resection and cervical tumor ablation and reconstruction was employed. Previous cases of successful multistage resections of meningiomas with extracranial extension have been reported in the literature. In their series of jugular foramen meningiomas, Sanna and colleagues describe one case with extensive cervical component.¹¹ The surgical technique used was an inferior modified transcochlear approach for the first-stage intradural tumor removal followed by a second-stage transcervical procedure for removal of the extracranial component. Complete tumor resection was achieved without evidence of postoperative CSF leak. Kawahara and colleagues present two cases with huge dumbbell-type jugular foramen meningiomas with parapharyngeal space extension.¹³ In the first stage, tumors were removed via a transjugular approach. During the second stage, cervical tumors were resected with the carotid artery sacrifice, followed by vascular reconstruction from ipsilateral carotid artery to the middle cerebral artery.

Preoperative evaluation with the utilization of extensive imaging – including CT, MRI and catheter-based angiography – is key. These studies allowed for optimal assessment of local tumor invasion into critical neurovascular structures, specifically in search of internal carotid artery compromise and collateralization. Preoperative cerebral angiogram also allows for the evaluation of tumor vascularity. Specifically, angiography allows for the evaluation of feeding arteries and the possibility for embolization, the need for vessel sacrifice during tumor resection and the need for arterial bypass grafting. The extension of tumor into various compartments of the suprahyoid neck such as the buccal, masticator, parotid, pharyngeal, parapharyngeal, retropharyngeal and perivertebral, among other more ill-defined and the most well-described carotid sheath. These spaces have characteristic anatomical contents and pathologies corresponding to the anatomy within.

It is important to note that clear boundaries do not exist between all of these compartments, but the cervical fascia and musculature often delineate the boundaries for each. Unlike the superficial fascia of the neck that encases the voluntary musculature of the face as well as the platysma, the deep cervical fascia is more complex and further divided into the superficial or investing layer,

the less well-defined middle layer and the deep layer. The investing layer, which is the most superficial layer of the deep fascia, extends from the hyoid bone, inferior border of the mandible, zygomatic arch, mastoid portion of the temporal bones, external occipital protuberance and superior nuchal line inferiorly to the manubrium, clavicles, acromion and spine of the scapula. It surrounds the structures of the neck deep to the platysma as well as envelops the parotid gland superiorly and the sternocleidomastoid and trapezius musculature inferiorly. The deep layer of the deep cervical fascia is also well delineated and can be broken down into the prevertebral and alar layers. The prevertebral plane runs from the base of the skull inferiorly to the endothoracic fascia and anterior longitudinal ligament at approximately T3. Although termed “prevertebral” layer, it encloses the perivertebral space, which encases the vertebral bodies as well as the longus colli, perispinal and muscles of the posterior triangle of the neck. The alar plane of the deep cervical fascia runs immediately anterior to the prevertebral layer and is interposed between the retropharyngeal and the perivertebral spaces. Although the deep cervical fascia’s alar and perivertebral layers are in close proximity, there is the potential for pathologies arising from the retropharyngeal space, which is limited inferiorly at approximately the T3 level, to break through the alar layer into this “danger” space and inferiorly into the deep thorax and retrocardiac location.¹⁴ The middle layers of the deep cervical fascia weaves between the superficial and deep layers of the deep cervical fascia but is not as well delineated and therefore will not be expanded upon. Cross sectional imaging of the suprahyoid neck is thus vital in planning planes of resection.

The carotid space begins at the skull base and, in addition to the carotid artery, contains the internal jugular vein, cranial nerves IX through XII, sympathetic nervous plexus and branches of the ansa cervicalis/hypoglossi (C1 – C3 roots). Many of the aforementioned fascia together form the carotid sheath. Specifically, the upper portion of the carotid sheath is bound by the superficial layer of the deep cervical fascia laterally, the deep layer of the deep cervical fascia posteriorly, the cloison sagittale medially, and the stylopharyngeal aponeurosis or the middle layer of the deep cervical fascia anteriorly. Therefore, in addition to being termed the carotid space, this space is also sometimes referred to as the poststyloid parapharyngeal space. The prestyloid parapharyngeal space only contains fat and connective tissue. Per Som and colleagues, the boundaries of the parapharyngeal space are recently described as follows. The medial fascia of the masticator space and deep surface of the parotid gland form the lateral boundary. The medial wall

is formed by the buccopharyngeal fascia or visceral fascia and posteriorly by the aforementioned carotid sheath and stylopharyngeal aponeurosis or the middle layer of the deep cervical fascia.¹⁵ In our current case, CT and MRI of the head and neck suggested the meningioma en bloc to extend from the extra-axial space at the level of the skull base and CPA into the hypoglossal canal and into the carotid sheath with parapharyngeal extension. It is important to note that, although the carotid sheath inferior to the carotid bifurcation is complete, there are multiple regions of dehiscence superiorly, thereby explaining how the lesion in this case transitioned from the carotid space into the parapharyngeal space.

Our rationale for staged operations was primarily based on minimizing surgical and anesthetic complications. In regards to reducing complications, staging of the tumor resection allowed us to decrease the risk of prolonged single-stage anesthesia, preventing large volume CSF leak secondary to extensive cervical surgical exposure, as well as reduce the risk of CSF infection secondary to contamination from middle ear flora. In addition, this surgical management allowed for optimal surgical control of critical neurovascular structures (facial nerve/ICA) as well as the ability to define and utilize microvascular free tissue transfer. The functional considerations for this case, with respect to intact preoperative facial nerve function in a young female patient who was otherwise healthy, were managed by working through a transparotid/transmastoid aspect of the secondary approach. In addition, the supplementation of the free tissue flap into the defect site was not only cosmetic, as it reshaped the contours of the mastoidectomy void, but also functional, as it divided the previously ablated middle ear cavity from the sterile site of dural entry.

A far lateral approach provides surgical access to lesions of the craniovertebral junction that are located on the anterolateral margin of the foramen magnum. The approach is hallmarked by removal of a portion of the occipital condyle, which in turn is located on the lateral margin of the anterior half of foramen magnum. The classic “transcondylar” approach traditionally involves a suboccipital or retrosigmoid craniotomy, laminectomy of the posterior arch of C1, and removal of the posterior portion of the occipital condyle. The posterior half of the condyle can be removed without introducing instability. We performed a C1 hemilaminectomy with posterior fossa far lateral craniotomy along with occipital condyle partial drilling. The far lateral transcondylar approach allows for early identification of the vertebral artery either above the posterior arch of the atlas or in its ascending course between the transverse processes of the atlas and axis. This approach provides access to the lower clivus and the area anterior to the medulla. Importantly, it can allow for adequate exposure of the hypoglossal canal.

Variations of the far lateral approach can be tailored depending on the anatomy needing to be surgically exposed in each case.¹⁶ These include a transcondylar approach directed through the occipital condyle or the atlanto-occipital joint and adjoining parts of the condyle (a more lateral approach that provides access to the lower clivus and pre-medullary area). The supracondylar approach directed through the area immediately above the occipital condyle provides access to the region of and medial to the hypoglossal canal and jugular tubercle. The para-condylar exposure directed through the area lateral to the occipital condyle by drilling the jugular process of the occipital bone in the area lateral to the occipital condyle provides access to the posterior part of the jugular foramen, the posterior aspect of the facial nerve and mastoid on the lateral side of the jugular foramen. Understanding the bony anatomy as seen on preoperative CT scan is pivotal in determining the extent of bone removal because distances between and relationships of the occipital condyle to the foramen magnum, hypoglossal canal, jugular tubercle, jugular process of the occipital bone, the mastoid and the facial canal are extremely important. For example, the hypoglossal canal is located above the middle third of the occipital condyle and is directed from posterior to anterior and from medial to lateral. The intracranial end of the hypoglossal canal is approximately 5 mm above the junction of the posterior and middle third of the occipital condyle and approximately 8 mm from the posterior edge of the condyle. The extracranial end of the canal is located approximately 5 mm above the junction of the anterior and middle third of the condyle. The average length of the longest axis of the condyle is 21 mm, and the condylar canal passes above and usually does not communicate with the hypoglossal canal. Of note, condylar canal transmits the posterior condylar emissary vein that connects the vertebral venous plexus with the sigmoid sinus just proximal to the jugular bulb. The jugular process of the occipital bone extends laterally from the posterior half of the occipital condyle to form the posterior margin of the jugular foramen. The condylar veins and jugular fossa could potentially be major sources of intraoperative hemorrhages, and drilling of condyle has to be meticulous to avoid inadvertent iatrogenic hypoglossal nerve damage. Similarly, rectus capitis lateralis muscle attached to the jugular process at the posterior edge of the jugular foramen offers a reliable anatomical landmark for protecting the facial nerve, which exits the stylomastoid foramen just lateral to the jugular foramen. In our case, the hypoglossal nerve was affected by the tumor, while the facial nerve was intact preoperatively and preserved successfully during surgery. Of note, there was a small amount of residual tumor at the skull base, which has remained stable during subsequent follow-up MRI, and the patient remained stable clinically. The current plan is to observe with serial imaging and treat

with radiosurgery if the tumor shows interval increase in size with symptoms. A lateral expanded endonasal approach may be potentially used as a surgical method of treating this residual tumor. The cosmetic result from the described surgical procedure has been excellent (Figure 6).

Conclusion

The complexity of meningiomas in the skull base region lies in the high variability of dural invasion of their local transforaminal extension causing neurovascular defects. The surgical strategy must take into consideration the size, extension and vascular involvement, apart from the

patient's age and clinical presentation. The unique nature of our case is twofold; not only do we present the first reported case of pediatric multicompartmental en plaque meningioma of the CPA requiring multistage resection, but also this case is the first pediatric one of free tissue transfer utilized for en plaque meningioma reconstruction. We demonstrate that a successful staged multidisciplinary surgical management of multicompartmental en plaque meningiomas allows for optimal surgical resection as well as maximal patient well-being.

The authors report no financial relationships with commercial interests relevant to the content of this article.



Figure 6: (Top) Intraoperative and two-year follow-up images show appropriate healing with only minimal scar formation. (Bottom) Coronal T1 postcontrast and sagittal T1 postcontrast images highlight the corresponding myocutaneous flap reconstruction.

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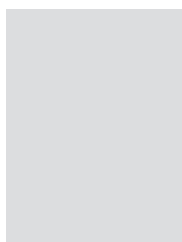
Minimally Invasive Treatment of Recurrent/Progressive Thalamic Tumors with Stereotactic Laser Ablation

Author



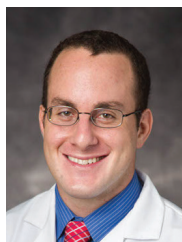
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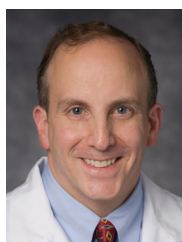
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Introduction

Glioblastoma multiforme is the most common type of primary malignant brain tumor in adults. The current standard treatment for patients with glioblastoma multiforme (GBM) includes surgical intervention followed by adjuvant radiotherapy and chemotherapy with temozolomide.¹ Survival benefit with resection has been shown in several series.²⁻⁸ In a retrospective analysis of more than 400 patients, Lacroix and colleagues showed that resection of 90 – 98 percent of the tumor improved survival.³ Further studies have shown a statistically significant survival benefit for those with resections of as little as 78 percent of the total tumor mass, though those with 95 – 100 percent resection showed an incremental improvement.⁸

Unfortunately, thalamic gliomas are usually not amenable to surgical resection due to associated surgical morbidity and mortality.^{4,9,10} Early series have demonstrated mortality as high as 30 percent.¹¹ Though the advent of stereotactic microsurgical approaches decreased morbidity and mortality for resection of diffuse adult gliomas to 14 and 6 percent, respectively,¹² the extent of resection did not correlate with survival advantage for patients with diffuse high-grade gliomas (HGGs).^{10,13} The combination of marginal benefit along with increased risk has led most surgeons to limit surgery on thalamic HGG to stereotactic biopsy rather than resection.

Stereotactic radiosurgery (SRS) has been proposed as an alternative method of cytoreduction for nonoperable tumors; however, although a few small retrospective studies have supported the use of radiosurgery as an alternative treatment option, a large 2004 randomized trial by Souhami and

colleagues demonstrated no survival benefit for GBM treated with radiosurgery in addition to conventional radiation. Both subgroups – radiosurgery and standard therapy – had similar outcomes in terms of overall survival, and in quality of life or rate of neurological decline.^{6,14}

Stereotactic laser ablation (SLA) is a relatively new and minimally invasive therapy that may be employed for treatment of difficult-to-access tumors such as those in the thalamus.¹⁵ Preoperative MRI is used to define the target lesion area. Lesions are then thermally ablated following the placement of a probe with a highly specific and focused laser that heats the tumor and induces thermal ablation. Real-time MRI thermography is used to track the progress of lesion destruction during the procedure, and serial postoperative MRI is used to track the status of the lesion after surgery.^{9,12,16} There is a relative paucity of data on the efficacy and complications of SLA as a treatment for deep-seated glioblastoma.^{9,15,16} In a follow-up to the recently completed Phase I clinical trial performed at University Hospitals Cleveland Medical Center for SLA for glioblastoma, we attempt to expand current knowledge and detail our experience of utilizing SLA for deep-seated thalamic lesions.¹⁵

Methods

This is a retrospective single-center review of patients with biopsy proven HGG or metastatic adenocarcinoma of the thalamus treated with the SLA using the NeuroBlate System (Monteris Medical, Inc.) at UH Cleveland Medical Center.

Surgical Procedure

Preoperative imaging includes volumetric MRI with post-contrast enhanced T1 sequences. Tumor volumes were estimated by using iPlan software (Brainlab). Trajectory planning and insertion of the probe were performed using the NeuroBlate software. After the induction of general anesthesia, patients were placed in the Atoma head holder system (Monteris Medical), which was affixed to the Brainlab navigation system. A single burr hole was made in line with the planned probe trajectory. Patients were then transported, under sterile conditions, to the MRI suite immediately adjacent to our operating suite.

The NeuroBlate System utilized a 3.3 mm probe encasing a solid-state diode laser, which was internally cooled via carbon dioxide (CO₂) gas. The laser allows for thermal ablation of target lesion, while the CO₂ cooling mechanism prevents damage to surrounding tissue. The NeuroBlate SideFire probe was used, which permitted for ablation of nonsymmetrical lesions through rotation and adjustment of probe depth. Real-time magnetic resonance thermography guided the treatment course in the MRI suite. Thermal ablation was based on thermal damage threshold lines representing the relationship between treatment duration and temperature achieved. Zones of thermal damage were defined as blue and yellow based on exposure to 43°C for 10 and 2 minutes, respectively.

At the conclusion of the ablative procedure, patients were transported back to the operating room. The wound was closed in a routine fashion, and the patients were moved to the post-anesthesia care unit following extubation. All patients were then monitored in the neurological intensive care unit. Contrasted MRI was obtained within 72 hours of the procedure in all patients.

Results

The median age at time of treatment was 57 years, with a range of 54 to 63. There was only one female patient in this series. Three patients carried diagnoses of recurrent GBM, and two patients had non-small cell carcinoma (NSCCA) metastases to the thalamus. All three patients with HGG had previously been treated with combination radiation and chemotherapy. Similarly, the patients with metastases had been previously treated with systemic chemotherapy, and one patient had previously undergone stereotactic radiosurgery. The second patient's metastasis was too large for stereotactic radiosurgery, and the patient refused to undergo whole brain radiation therapy.

Six total SLA procedures were performed, with one patient (GBM) receiving bilateral treatments performed in separate sessions. In this case the second treatment was performed three days after the initial procedure. Preoperative median tumor size was $22.6 \pm 9.4 \text{ cm}^3$ (range was 8.8 to 34.5 cm^3). Post-treatment median tumor size was $22.6 \pm 7.8 \text{ cm}^3$ (range was 16.3 to 36.3 cm^3). Total blood loss for all procedures was less than 10 cc (range 5 – 10 cc). The mean time of length of treatment (time in MRI) was 2 hours and 42 minutes. The mean laser "on" time was 40 minutes. The mean length of hospitalization following SLA was 5.5 days, with a range of 3 – 8 days. The pre- and immediate post-procedure post-contrast MRI is illustrated in Figures 1 through 5.

There was one death in this series due to development of acute hydrocephalus requiring placement of an external ventriculostomy drain. The patient's family ultimately chose to pursue hospice care, and the patient expired on postoperative day 12. This patient was the sole patient to undergo bilateral treatment in this series. A second patient experienced transient weakness of the upper extremity and an associated expressive aphasia. These symptoms improved, and the patient returned to neurologic baseline by postoperative day 14. The second patient required placement of an external ventricular operatively. The remaining three patients did not experience adverse events. Post-procedure MRI demonstrated increased edema in all patients at 72 hours.

Of the three patients with GBM, one received temozolomide and bevacizumab in addition to radiation therapy as adjunct therapy following SLA. One patient was lost to follow-up after discharge. Of the two patients with NSCCA, one received preoperative radiation and chemotherapy and the other received adjunct radiation therapy after SLA had been performed. All patients showed evidence of progression of disease on follow-up imaging except for one patient with NSCCA whose imaging remained stable for more than 12 months.

The overall survival of the group ranged from 12 to 729 days; overall survival of those patients with HGG was 98 to

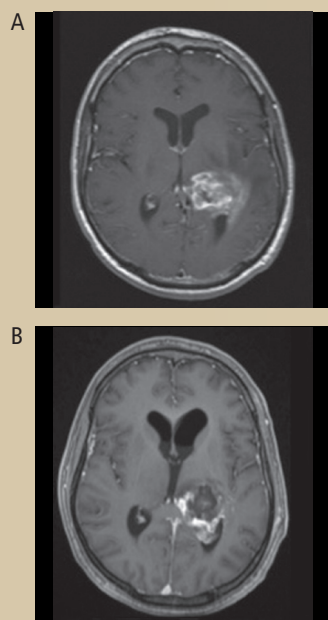


Figure 1: (A) Preoperative image of Patient 1 reveals heterogeneous left thalamic glioblastoma multiforme with extension into the lateral ventricle. (B) Postoperative day 2, image reveals a central cavity consistent with ablation of the tumor. Interval increase of edema and mass effect with pneumocephalus.

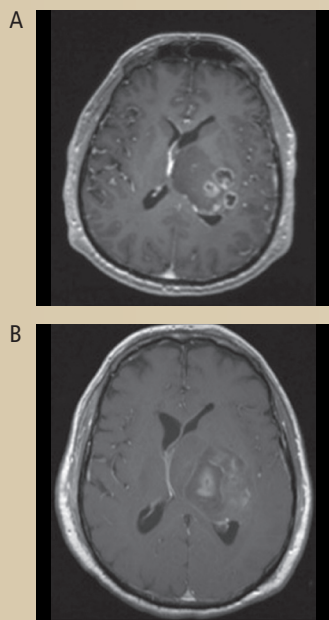


Figure 2: (A) Preoperative image of Patient 2 reveals heterogeneous left thalamic glioblastoma multiforme with associated ring enhancing nodules. (B) Postoperative day 2, image reveals post-treatment central hemorrhagic changes without increase in size.

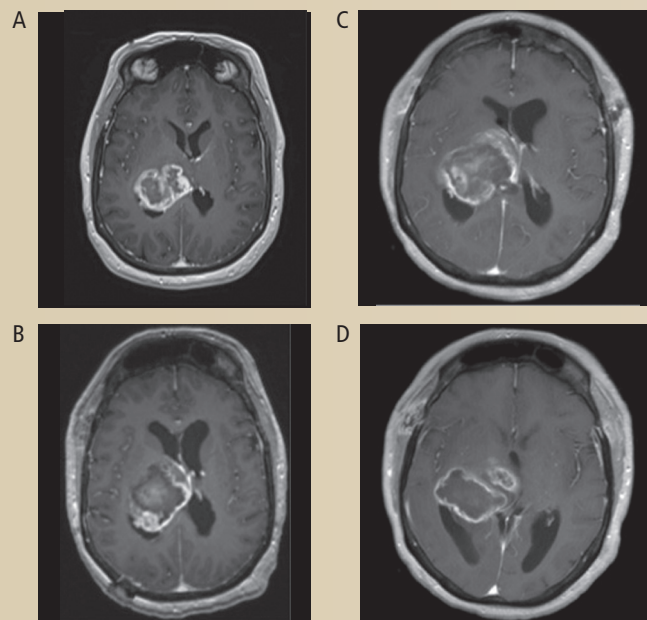


Figure 3: (A) Preoperative image of Patient 3 reveals heterogeneous right thalamic glioblastoma multiforme with enlargement of the ventricular atrium. (B) Postoperative day 1, first treatment, image reveals a central cavity consistent with ablation of the tumor. Interval increase of edema and mass effect. Note the ventricular enlargement. (C) Postoperative day 3, second treatment, images reveal interval increase in mass effect. Note the right frontal external ventricular drain and increase in the size of bilateral occipital horns. (D) Postoperative day 5, second treatment, postoperative images reveal interval decrease in mass effect. Note the right frontal external ventricular drain and increase in the size of bilateral occipital horns.

130 days (excluding the patient discharged to hospice), and survival was 52 to 729 days in the subset of patients with brain metastases. The median survival for both groups following SLA, excluding the patient who was discharged to hospice, was 109 ± 278 days.

Discussion

While SLA has been shown to be similarly effective as surgical intervention as a cytoreductive therapy in a small number of patients, the literature supporting its use for thalamic tumors is limited. In a Phase I trial of SLA for central nervous system tumors, Sloan and colleagues demonstrated the feasibility, safety and survival characteristics in a small subset of patients with recurrent GBM.¹⁵ Only a few contemporary publications are specific to this treatment modality, and only four reported data in a way that allows tracking of patients with thalamic tumors (Table 2).^{9,16} In a recent report by Hawasli and colleagues, which examined outcomes in 17 patients who underwent SLA for HGG or recurrent metastases, only four patients were included with thalamic lesions. Progression-free survival was reported as 4.2 months after SLA for the subgroup with thalamic tumors.¹⁶ In a similar report by Mohammadi and colleagues, SLA was employed in 34 patients with difficult-to-access HGG. Of these patients, only seven had lesions of the thalamus.

The authors reported an estimated overall one-year survival of 68 percent, with a median survival of 3.2 months.⁹

The median overall survival of patients in our series was 3.9 months, and the complication rate was comparable to those previously reported. The most common complication of other reported series was transient neurologic deficit, which was noted in our series to occur at a rate of 20 percent. Instances of other complications, such as hyponatremia and deep vein thrombosis, which were relatively common in other series, were not observed in our subset of patients.^{9,12,16} As described in the patient who underwent bilateral treatments, the surgeon must take into account, in the pre-procedural planning period, the likelihood of significant post-procedural edema, which may lead to transient neurological deficits or hydrocephalus, as in this case. The location of the thalamus to the ventricular system may lead to swelling and subsequent hydrocephalus as a result of compression of the third ventricle, trapping of a ventricular horn or tectal compression. Since this case, it has become our practice to inform patients of the possible need for placement of ventriculostomy catheters in the operating suite or in the immediate postoperative period with possible need for postoperative shunt for those with large thalamic tumors.

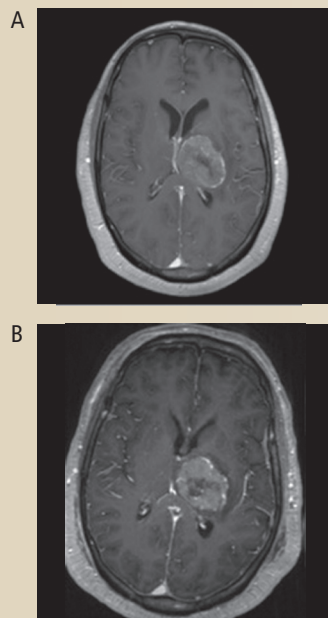


Figure 4: (A) Preoperative image of Patient 4 reveals heterogeneous left thalamic metastasis causing partial compression of the third ventricle. (B) Postoperative day 2, image reveals a central cavity consistent with ablation of the tumor. Minimal increase of edema and mass effect.

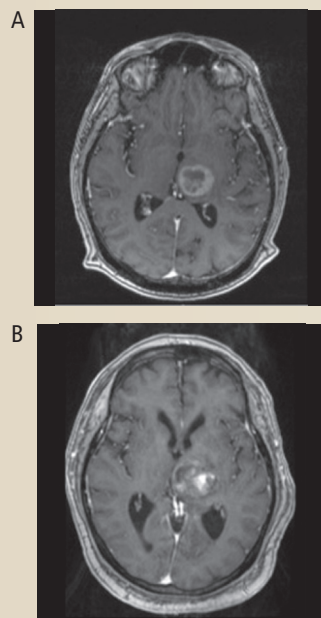


Figure 5: (A) Preoperative image of Patient 5 reveals heterogeneous left thalamic metastasis with hemorrhagic characteristics. (B) Postoperative day 2, image reveals a central cavity consistent with ablation of the tumor. Interval short-term increase of edema and mass effect.

All patients in this series were placed on high-dose dexamethasone with planned slow wean over a period of seven to 14 days. Further studies are needed to better predict and anticipate the extent of postoperative swelling as well as peak swelling/edema time; however, in our experience, peak edema typically occurs within 24 – 72 hours. There have been no instances of significantly delayed edema leading to need for placement of ventriculostomy drain or medical interventions outside of this period.

One other major consideration that arises from this series is long duration of operative time and time under general anesthesia. However, as our experience with this technology has expanded, operative times have decreased significantly, and, with new diffusion-tip probes, these times will continue to decrease.

The limited number of patients in this series is the major limiting factor to determination of outcomes and comparability of overall survival with traditional surgical/medical therapies. While it is difficult to draw firm conclusions regarding the efficacy and safety of SLA for thalamic lesions, this series serves to contribute to the experience in the literature with this new treatment modality. It is anticipated that our preliminary experience, combined with review of other published series of SLA for thalamic neoplasms, will improve patient safety and perhaps enable more aggressive treatment of these difficult to treat tumors.^{3,6,17}

Conclusions

SLA offers several promising attributes that make it a therapeutic option for the subset of patients with limited surgical and medical treatments and may provide an avenue for therapy for those patients with tumors previously deemed inoperable. Even if this therapy is eventually determined to offer only limited increase in survival, this increase may be preferable to biopsy alone. Further technical advances and additional study of the relationship between tumor size/location and patient outcome will further advance the field. In addition to other risks, the possibility of inducing hydrocephalus remains high for patients with thalamic or centrally located neoplasms and should be discussed prior to the procedure.

Dr. Sloan and Dr. Wright are consultants for Monteris Medical. The other authors report no financial relationships with commercial interests relevant to the content of this article.

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Table 1: Demographics.

Patient	Sex	Age	Pathology	Preop vol cc	Post vol cc @ 72 hours	Laterality	Trajectories	Length of treatment	Laser on time (hr/min/sec)	Perioperative exam change	ICU LOS	Hospital LOS	OS (days)
1	M	57	glioblastoma multiforme	13.5	34	Left	1	2:24 hours	0:20:56	—	1	4	98
2	M	60	glioblastoma multiforme	28	21	Left	1	2:35 hours	0:48:47	transient right hemiparesis, aphasia	1	8	130
3	F	63	glioblastoma multiforme	34.5	43.5/46	Right	2	3:03/4:36 hours	0:51:57/1:32:24	hydrocephalus with worsened left hemiparesis/somnolence	7	9	12
4	M	55	mets adenocarcinoma	22.6	22.6	Left	1	2:03 hours	0:24:49	—	0	7	729
5	M	54	mets squamous lung	8.8	16.5	Left	1	1:16 hours	0:04:39	—	1	11	52

ICU: intensive care unit

LOS: length of stay

mets: metastasized

OS: overall survival

Post vol cc: postoperative volume cubic centimeters

Preop vol cc: preoperative volume cubic centimeters

Table 2: Thalamic lesions.

Series	Number of patients with thalamic lesions	Number of treatments	Morbidity	Mortality	Survival	Range
Shroeder J et al., 2013 ¹³	6	8	50%	20%		
Jethwa PR et al., 2012 ⁵	1	1	0%	0%		
Mohammedi A et al., 2014 ⁸	7		37%*		3.2 months*	
Hawasi A et al., 2013 ³	4		50%	25%	4.2 months	4 days to 10.7 months
Wright J et al., 2015, current study	5	6	40%	20%	3.9 months	12 days to 26 months

*pooled data; not exclusive to thalamic tumors

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Target Audience

This continuing medical education (CME) program is provided by Case Western Reserve University School of Medicine and is intended for all physicians, particularly neurologists and neurological surgeons, family practice and internal medicine physicians, interested in the latest advances in the management of neurological disorders.

Educational Objectives

Upon completion of this educational activity, the participant should be able to:

- Identify the advantages of proton beam therapy for the treatment of chordomas and chondrosarcomas of the spine
- Evaluate the use of proton beam therapy for chordomas and chondrosarcomas of the skull base
- Describe the presentation and the staged resection of a multicompartmental meningioma
- Explain how stereotactic laser ablation may be employed for treatment of difficult-to-access tumors such as those in the thalamus

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