Charged-Particle Proton Radiosurgery

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Introduction/History

The origins of intracranial SRS date back to 1951 when Dr. Lars Leksell first proposed the concept. The underlying basis of SRS is to utilize multiple, noncoplanar beam angles that isocentrically converge on the target volume; limiting the dose along each beam path ensures low-dose exposure of tissues in the path of the beam, whereas the central convergence ensures a high target dose. This methodology therefore allows for the delivery of hypofractionated regimens of high doses per fraction in one or a small number of treatments. Over the years, there has been a rapid increase in the adoption of intracranial SRS for a wide range of benign and malignant intracranial conditions, including, but not limited to, arteriovenous malformation (AVM), acoustic neuroma, pituitary adenoma, meningioma, trigeminal neuralgia, and metastatic tumors [1]. There has been rapid development of systems that allow for SRS delivery, primarily utilizing photon-based approaches. The utilization of proton beam therapy for SRS and/or fractionated stereotactic radiotherapy (FSRT) has to date been limited, in large measure due to the rapid proliferation of excellent photon SRS technologies and lack of rapid technology development in the proton sphere. However, given the superior dose distribution of proton radiation, and the burgeoning number of proton centers, as well as a spurt in technological development, there is a renaissance in evaluating the merits of proton-based SRS and/or FSRT.

Proton-based SRS was first pioneered by Dr. Raymond Kjellberg in 1960 at the Harvard Cyclotron Laboratory [2]. The initial phases of the program utilized a fixed beam with a couch that had to be manually maneuvered, thereby resulting in lengthy treatment sessions with limited availability of beam angles. However, under the guidance of Dr. Paul Chapman, the program progressed in developing the STAR device, in which the patient's head frame was attached to a couch apparatus that could be rotated relative to the fixed beam, thereby allowing increased degrees of freedom (Fig. 1a, b). With the ultimate advent of the mounted mobile beam nozzle on a gantry, analogous to modern-day proton units, full degrees of freedom were achievable (Fig. 2). Since the 1960s, multiple outcomes and toxicity data have been published evaluating the use of proton-based SRS/FSRT treatments for many indications. Herein, we provide a comprehensive review of the available dosimetric and clinical data.

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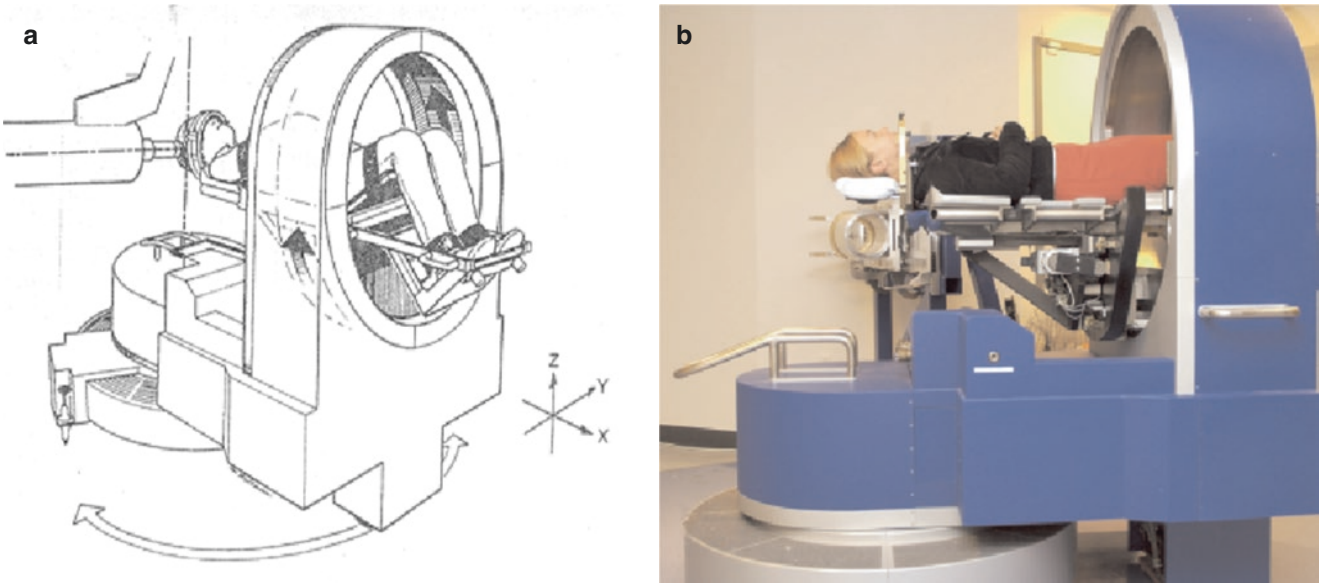

Fig. 1 (**a**, **b**) STAR Device as developed at the MGH-Northeast Proton Therapy Center. The patient's head frame is mounted to a rotating couch, with a directed fixed proton beam line thereby allowing five degrees of freedom (three linear motions and two rotational). (Used with permission from Chen et al. [2])

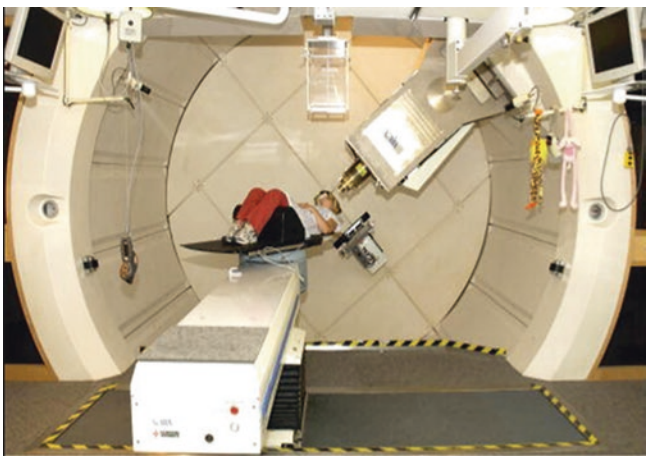

Fig. 2 Modern-day proton therapy unit utilizing a mounted proton beam line on a rotatable gantry with six degrees of freedom on a robotic patient positioning couch. (Used with permission from Chen et al. [2])

Dosimetric Data

Verhey and coauthors conducted one of the earliest dosimetric comparisons between photon and proton radiation therapy techniques for stereotactic radiosurgery of intracranial lesions [3]. In their analysis, they compared the dose-volume histograms for target and nontarget brain tissue for five patients with intracranial lesions treated with the following plans: Gamma Knife (GK), a five-field passively scattered proton plan, or a linear accelerator (linac) arc-based technique. The authors reported that the choice of optimal modality, as judged by the ability to reduce nontarget dose, was a function of size of the lesion, shape of the lesion, and location. For small regular target volumes, the proton plan was actually found to deliver more doses to the normal brain tissue, as a result of needing larger treatment planning margins to account for proton uncertainty, whereas for large regular targets, proton plans produced the greatest dosimetric benefit. For irregularly shaped lesions, both proton and GK plans were dosimetrically superior with respect to higher conformality than achievable with the arc-based treatments due to the restricted number of isocenters utilized for the linac plans. With regard to location, the more peripheral a tumor, the larger the dosimetric sparing achieved with protons, given the stopping ability relative to GK and linac photon beams.

In a companion paper, this group analyzed the tumor control probability (TCP) and normal tissue complication probability (NTCP) based on the DVH information from the abovementioned study. By comparing the various plans (linac vs. GK vs. protons) using biological assumptions, the authors concluded the superiority of proton beam therapy in reducing complication probabilities primarily for large target volumes and for those situated peripherally, whereas the advantage diminished with smaller centrally located tumors [4].

Baumert and colleagues conducted a dosimetric comparison of six intracranial lesions receiving stereotactic radiation therapy with IMRT, single-field optimized proton plans (SFO-PT), or multi-field optimized proton plans (MFO-PT/IMPT) to doses that ranged from ultra-hypofractionation to conventional fractionation [5, 6]. Their analysis revealed similar plan conformality with RTOG conformality indices of 1.03, 1.04, and 1.03 for IMRT, SFO-PT, and MFO-PT/

IMPT plans, respectively. However, similar levels of conformality were achieved with proton planning, albeit with fewer fields (~three fields) than with photon planning which generally needed a median of five fields. In comparing the amount of the normal tissue outside the PTV that received 20 to 90% of the prescription dose, IMPT had the greatest volume sparing effect for tissue receiving 20 to 50% of prescription dose. Minimal difference was seen among techniques when evaluating the volume of normal tissue receiving >50% of prescription dose.

Serago and colleagues compared target coverage of four hypothetical intracranial target volumes planned using the following techniques: (a) four, noncoplanar, multiple-arc, circular X-ray beams with single or multiple isocenters; (b) noncoplanar, irregular X-ray beam shaping with a single isocenter using either static IMRT or arc therapy; and (c) noncoplanar, irregular passively scattered proton plan with a single isocenter using 5 or 13 fields [7]. The target volumes selected were meant to represent a sampling of different shapes, sizes, and locations of lesions including nearly spherical and also irregularly shaped targets. The proton plans consistently yielded equal or superior results compared to X-ray techniques in reducing the integral dose to normal brain outside the target, with the greatest benefit present in the less than the 50% isodose region. Only minimal differences were observed between the 5 and 13 field proton plans. This normal tissue sparing effect reported by Serago and colleagues is analogous with the results of Baumert and colleagues.

Clinical Data

Meningioma

In contrast to the abundance of outcomes data for conventionally fractionated proton beam therapy in the management of meningiomas [8–12], studies utilizing radiosurgery or fractionated stereotactic proton therapy remain limited to a small set of institutions. Nevertheless, these data consistently reveal the ability to achieve excellent local control rates as will be highlighted in this section [13]. Vernimmen and colleagues reported one of the earliest experiences of 23 patients receiving proton beam therapy for the management of skull base meningiomas. Seventy-eight percent ($n = 18$) of the patients received a hypofractionated stereotactic regimen (HSRT) of 20.3 CGyE in 3 fractions, whereas 22% of the patients received fractionated stereotactic regimens (SRT) of 54.1–61.6 CGyE in 16–28 fractions [14]. With a mean follow-up of 40 months, the HSRT group achieved a 5-year local control rate of 88%, whereas the SRT group achieved a control rate of 100%. With respect to toxicity, in the HSRT group, 11% ($n = 2$) of the patients developed a transient new cranial neuropathy after treatment, whereas 11% ($n = 2$) developed a late side effect. In the SRT group, no acute toxicity was observed, whereas one patient suffered short-term memory disturbance. Overall, the control rates compared favorably to previously reported series utilizing photon-based SRS techniques. For instance, Morita and colleagues achieved a 5-year progression-free survival rate of 95% for skull base meningiomas after GK radiosurgery to a median tumor margin dose of 16 Gy [15]. Similarly, Chang and colleagues achieved 2-year control rate of 100% for cavernous sinus meningiomas treated with multiple noncoplanar linac arc SRS to a median dose of 17.7 Gy [16]. In summary, the results of this series demonstrated that proton irradiation was both safe and effective in the management of skull base meningiomas, especially for large irregularly shaped lesions.

The group from Uppsala, Sweden, compared their outcomes and toxicity data in a pilot study using hypofractionated passively scattered proton beam therapy for the treatment of skull base meningiomas [17]. Nineteen patients were analyzed, of which 79% ($n = 15$) had undergone prior surgical resection for a WHO Grade I meningioma, whereas the remaining 21% had either refused surgery or were deemed unresectable. All patients received a dose of 24 Gy in four 6-Gy fractions. With a minimum follow-up of 36 months, no patient was noted to have tumor progression. Two patients developed delayed edema 6 months after treatment, which responded to corticosteroids. None of the 19 patients developed any late cranial nerve dysfunction during follow-up.

In 2017, this group updated their series with a total of 170 patients receiving hypofractionated proton beam therapy as adjuvant or primary treatment for WHO Grade I benign meningiomas [18]. Of note, 91% of tumors were situated at the skull base. Passively scattered proton beam therapy was utilized for all patients with the majority of the patients (91%) receiving either a dose of 24 Gy in 4 fractions or 20 Gy in 4 fractions. The 5-year and 10-year PFS rates were 93% and 85%, respectively. With respect to toxicity, 2.9% of the patients suffered from radiation necrosis, whereas 4.4% of the patients displayed either visual deterioration or visual field deficits during follow-up. Additionally, 7.4% of the patients developed pituitary insufficiency during follow-up requiring medical supplementation.

In 2011, the group from Harvard reported their retrospective results using passively scattered proton SRS in 50 patients with 51 benign meningiomas [19]. In contrast to the prior studies which treated larger lesions, patients in this series were eligible for treatment with proton SRS only if the tumors were $\leq$4 cm in maximum diameter and were located $\geq$2 mm from the optic nerves and chiasm. Seventy-five percent ($n = 38$) of the lesions were at the skull base. Sixty-four percent of meningiomas were diagnosed radiographically, whereas 36% of tumors were diagnosed histologically. Median prescribed dose was 13 Gy with the goal

of having the 90% isodose encompass the PTV. With a median follow-up of 32 months, 3-year local control was 94%. Thirty-four patients with symptoms prior to treatment had adequate follow-up with 47% displaying improvement of symptoms, 44% showing unchanged symptoms, and 9% having symptom worsening. With regard to treatment-related toxicity, acute and late toxicity was only seen in 5.9% and 5.9% of the patients, respectively. No patients were noted to develop additional cranial nerve deficits following treatment. These control rates are analogous to those achieved by comparable published photon SRS series [20]. Additionally, the authors of this series provided a pictorial comparison of proton and photon SRS dose distribution for a left cavernous sinus meningioma showing the lower integral dose with proton therapy and potential for a lower risk of late sequelae (Fig. 3).

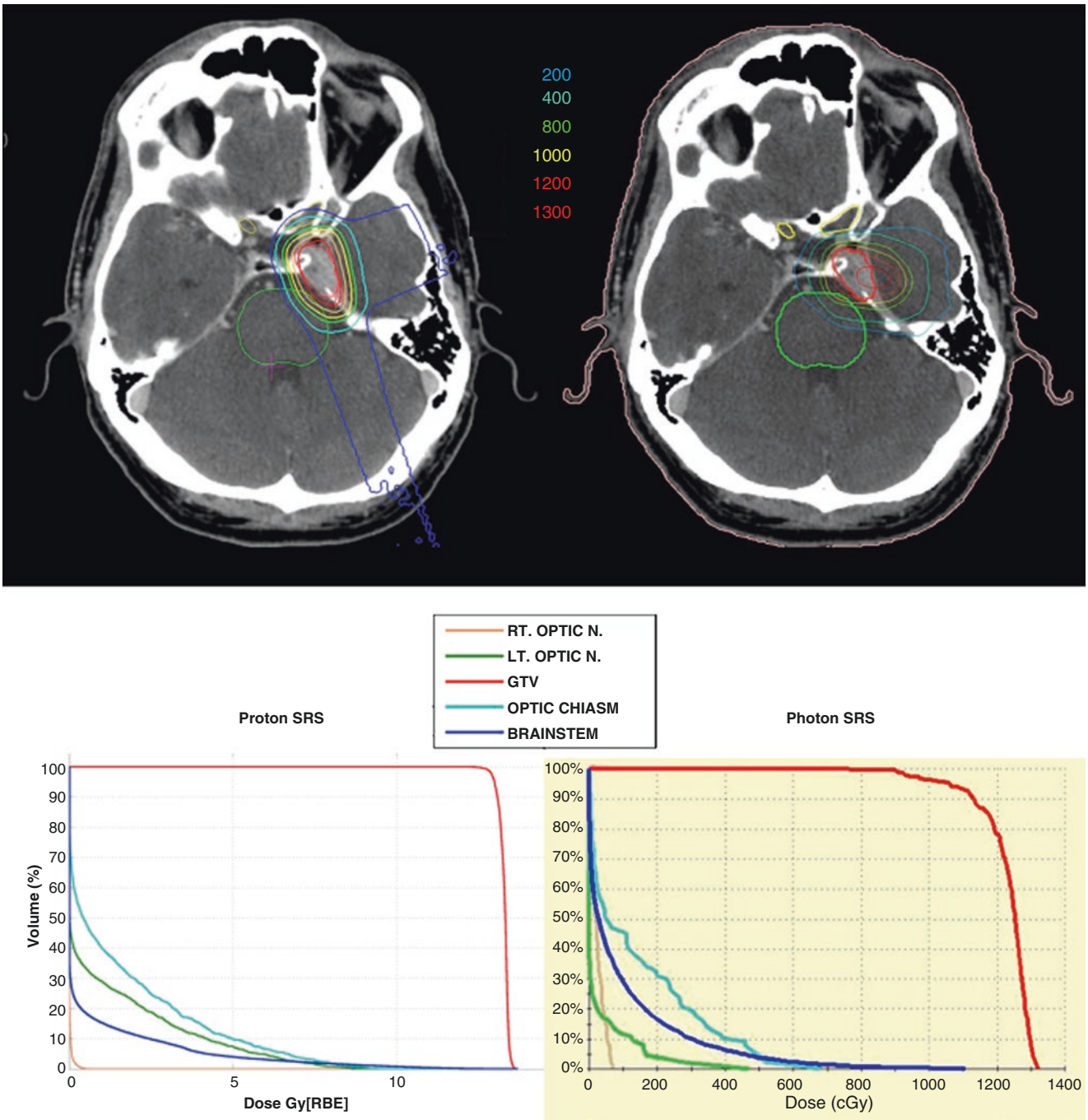

Fig. 3 Dose distribution comparison for a proton and photon SRS treatment for a left cavernous sinus meningioma. (Used with permission of Elsevier from Halasz et al. [19])

While the aforementioned series display that passively scattered proton beam therapy can serve an excellent modality, especially for skull base lesions, there is a paucity of data on the use of spot-scanning/intensity-modulated proton therapy fractionated stereotactic or radiosurgery techniques.

Practical Considerations When Utilizing PBT for Meningiomas

- Consider the volume of disease as well as its shape and location, especially its proximity to critical organs. Protons provide an enhanced dosimetric benefit over photon approaches for tumors that are larger and/or irregularly shaped; however, if the critical organ-at-risk (OAR) is immediately adjacent to the tumor, considerations of the end-of-range falling within the OAR could result in a degraded plan, and the possibility of an inferior lateral penumbra from protons, relative to photon radiosurgery techniques, could actually result in inferior OAR dosimetry from proton therapy.
- For small-sized lesions, consider single-session proton SRS as this approach excellent outcomes and enhanced dosimetric benefits over photon-based SRS approaches in certain select situations; however, photon SRS for small lesions, and especially geometrically symmetric lesions, can provide excellent dosimetric coverage which often will clinically not be surpassed by a proton plan; it must also be remembered that for very small targets, the lower spot size limit of pencil-beam scanning could provide another challenge [19].
- For large-sized lesions, including those arising from the cavernous sinus or skull base, consider that hypofractionated proton beam therapy achieves excellent outcomes with lower toxicity rates [14, 18].
- Consider referral to endocrinology for patients receiving proton beam therapy for centrally situated meningiomas, given the risk of late pituitary insufficiency.
- For lesions in and around the optic pathway, always involve a neuro-ophthalmologist in the care team.

Arteriovenous Malformations

An arteriovenous malformation (AVM) is an abnormal communication between arterioles and venules, without an intervening capillary bed, which creates a high-flow, turbulent flow situation through thin-walled vessels, highly susceptible to rupture and hemorrhage. The point of abnormal connection is termed the nidus and represents the radiation therapy target to achieve obliteration [2]. Given the occurrence of these lesions in younger patients, proton beam therapy presents a unique opportunity to limiting the overall integral dose while delivering the high doses necessary for obliteration [13].

In 1983, the group from the Massachusetts General Hospital (MGH), led by Kjellberg and colleagues, published the first series on the use of proton SRS for the management of AVMs [21]. They reviewed the results of the first 75 patients treated who had ≥2 years of follow-up, as well as the course of all 205 patients treated up to 1980, irrespective of follow-up time. The 90% isodose line was prescribed to the margin of the lesion, as determined by angiograms. The marginal dose was determined based on the size of the malformation, utilizing prior published data on isoeffective doses that correlate with the risk of brain necrosis. Median marginal doses were 16.5 Gy (range, 7.2–33 Gy) [22]. Follow-up arteriogram findings were available for 62 patients and revealed total obliteration greater than 50% reduction and no change in 20%, 56%, and 13% of cases, respectively. No lesion displayed any worsening on follow-up arteriograms. Four of the initial 27 patients incurred a complication. As a result, the group revised their planning and prescription technique and subsequently had no procedure-induced new persistent deficit in any patient. Additionally, no patient died of proton-related hemorrhage, thromboembolic events, or infection. Given these results, they subsequently continued utilizing proton beam therapy for AVMs not manageable by other means.

This supported the continued use of single-fraction proton beam stereotactic radiosurgery for AVMs at MGH, and in 2014, they reported additional results reviewing their modern experience of 254 lesions treated from 1991 to 2010 [23]. Of note, lesions with an AVM nidus generally >10–14 cc, nidus in a central/eloquent location (brainstem, basal ganglia, motor strip), or both were generally treated with a 2-fraction proton SRS approach, which will be discussed separately below. In this series, 9% of lesions had previously received radiation before 1991 with single-fraction SRS to a median dose of 12 Gy, with a median of 10 years to the second treatment. Median AVM nidus size in this report was 3.5 cc. All patients received SRS single treatment using 2–4 beams using passively scattered proton therapy to a median prescription dose of 15 Gy (range, 10–20 Gy (RBE)) targeting the entire nidus. Patients underwent yearly MRI, angiography, or both, with primary outcome being AVM obliteration with results defined as total (entire obliteration), partial (<100% obliteration), or stable disease (no change in nidus size). With a median follow-up of 35 months, total and partial obliterations rates were 64.6% and 35.4%, respectively, with a median time to obliteration of 31 months. The 5- and 10-year cumulative incidences of obliteration were 70 and 91%, respectively. On multivariate analysis, critical/deep location and target volume/nidus size were associated with lower rates of obliteration. Of note, after receiving proton SRS, 5.1% of lesions hemorrhaged with a 5-year cumulative incidence of 7%. With regard to acute and long-term complications, the majority of the patients (88%) experienced no

acute side effects. About 7.9% of the patients experienced mild seizures acutely, which were self-limiting. Additionally, the most common long-term side effect was also seizures, in 9.1% of the patients, controlled with antiepileptics. Apart from this, one patient developed memory disturbances at 1-year post-treatment, whereas another patient developed partial right hemiplegia 1-year post-treatment despite total obliteration of a left frontal AVM. These rates of obliteration with proton SRS compare favorably to those reported using Gamma Knife or linac-based approaches for similarly sized AVMs [24, 25].

For larger lesions, and those situated in critical areas such as the thalamus or brainstem, the group from MGH completed a retrospective review of 1250 patients treated with single-fraction proton SRS [26]. In this analysis published in 2003, they evaluated 1250 patients with median treatment volume of 33.7 cc with 77% of lesions being larger than 10 cc. The median treatment dose was 10.5 Gy, dose selection being based on the Kjellberg isoeffective doses for brain necrosis. With a median follow-up of 6.5 years, 4.1% of the patients suffered permanent neurological complications with a median time to complication of 1.1 years. Of note, the rate of complications correlated with treatment dose, with only 0.5% of the patients suffering a complication below 12 Gy. On the contrary, the median dose for a patient with a complication was 17 Gy. Additionally, a thalamic or brainstem location predicted a higher rate of complications.

As a result of these increased toxicities, the group at MGH transitioned to a 2-fraction proton SRS approach for high-risk lesions. In 2011, they reported the outcomes and toxicity data of 59 patients with lesions that were large (nidus size >10 cc) or if the AVM was in an eloquent location (brainstem, basal ganglia, motor strip). Of note, 12% of the patients had prior proton SRS to a median dose of 10.5 Gy. Median nidus volume was 22.9 cc. The 90% isodose line encompassed the volume with a median prescription dose (includes both fractions) of 16 Gy (RBE) (range, 12–28 Gy). The median number of days between fractions was 7 (range, 1–56 days). At a median of 56.1 months, complete and partial obliteration rates were 15.3%, and 33.9%, respectively. The 5-year rates of total or partial obliteration rates were 8%, and the 5-year actuarial rate of hemorrhage was 21.9%. With regard to acute complications, 67.8% had no acute complications, with the most common side effect within the first 3 months post-treatment being Grade 1 headaches. Additionally, 12% of the patients experienced partial seizures within 48 hours of proton SRS. Eighty percent of the patients did not experience a late complication. Grade 1 headaches were the most common late side effect. Despite the low rates of toxicity, given the high-risk AVM lesions included in this series, the authors concluded that their 2-fraction approach did not achieve the intended rates of obliteration. Irrespective of radiation modality used (photon or proton), larger lesions and those in critical locations remain a challenge to treat and require alternative strategies.

The group from Uppsala, Sweden, has similarly reported on this challenge [27, 28]. In 2016, they published their updated results of outcomes and toxicity in 67 AVM lesions receiving proton-fractionated stereotactic radiotherapy. Median nidus volume in this series was 3 cc. Prescription doses were 18–25 Gy delivered in 2 equal fractions (separated by 24 hours) to 64 lesions, whereas the remaining 3 lesions received 35 Gy in 5 equal fractions. Their results revealed complete obliteration, partial obliteration, and lesion stability rates of 68%, 18%, and 14%, respectively. Of note, there was a statistically significant difference in the median target volume between the lesions that totally regressed and those with partial regression/stability (3 cc vs. 10.5 cc, $p < 0.03$). When dividing lesion volumes into cohorts, occlusion rates for target volume 0–2 cc, 3–10 cc, 11–15 cc, and 16–51 cc were 77%, 80%, 50%, and 20%, respectively. Twenty-two patients had seizures at diagnosis, of whom 68% reported an improvement in seizure symptoms after proton radiation therapy. Sixty-two percent of the patients developed edema after proton treatment, with most cases being mild and transient. Two patients developed late permanent neurological deficits with otherwise low rates of toxicity. These results confirmed the efficacy of proton beam SRS/fractionated stereotactic approach in smaller AVM lesions, with comparably low obliteration rates (15–20%) for larger sizes.

The group from South Africa led by Vernimmen and coauthors similarly reported their results of hypofractionated stereotactic proton approaches for large AVMs, primarily >14 cc [29]. Overall 64 patients were included in their analysis with 41% ($n = 26$) having lesions <14 cc, whereas the remaining 59% ($n = 38$) had lesions >14 cc. Radiation dose was administered as per AVM volume cohorts of <10 cc, 10–13.9 cc, and >14 cc. Median total dose and median number of fractions was 27.24 Gy in 2 fractions, 23.2 Gy in 2 fractions, and 27 Gy in 3 fractions for lesions <10 cc, 10–13.9 cc, and >14 cc, respectively. With a median follow-up of 62 months, complete and partial obliteration rates for lesions <14 cc were 67% and 17%, respectively. In the group with lesions >14 cc, complete and partial obliteration rates were 43% and 21%, respectively. About 15.6% of the patients developed acute complications, ranging from transient cranial nerve palsy, nausea, vomiting, and status epilepticus. While 23% of the patients experienced transient late side effects, 80% had complete recovery with no late permanent side effects. In all, only 4% of the patients developed a permanent late Grade III or IV side effect. These results utilizing a longer hypofractionated approach with a median of 3 fractions for larger AVMs (>14 cc) seem to provide superior control probabilities in comparison to the low obliteration rates achieved in the aforementioned Uppsala and MGH series.

In 1994, the group from Keil, Germany, also reported their outcomes data on 63 lesions treated over a 10-year period [30]. AVM diameters were <3 cm, 3–6 cm, and >6 cm in 26.9%, 58.7%, and 14.2% of lesions, respectively. In 88.3% of the patients ($n = 60$), stereotactic proton beam therapy was used alone, whereas in the remaining patients, embolization or ligation preceded proton beam therapy. One of the major limitations of this series was the lack of reporting regarding the dosimetry or target volumes. Results revealed a strong correlation between obliteration rates and initial diameter of the AVM. Of the AVMs <3 cm in size, 58.8% were completely obliterated, 0% were partially obliterated, and 41.2% were unchanged on angiography. Whereas for AVMs between 3–6 cm and >6 cm, none were partially or completely obliterated. Of all the 63 lesions treated, only 15.3% were completely obliterated, whereas 84.1% showed no change. Unfortunately, while these results display a lack of benefit for proton beam therapy in medium- to large-sized lesions, this is in stark contrast to the higher rates of obliteration observed by Vernimmen and coauthors [29]. As such, it appears that there may be an inherent limitation in methodology or in patient selection that resulted in poorer outcomes seen in this series than would be expected.

Approximately around this time, in the late 1990s, Russia and the Soviet Union experienced a renaissance in proton therapy [31]. This increased the utilization of proton radiosurgery for the treatment of benign lesions such as AVMs. In 1991, the group from Russia reported on the use of proton radiosurgery in 46 lesions with a mean volume of 14.22 ± 2.14 cc. Of note, all AVM lesions were prospectively assigned to size-based cohorts for stratification: <4.9 cc, 5–9.9 cc, 10–24.9 cc, and >25–82 cc. Dose prescription was defined at the isocenter and corresponded to the 100% isodose point. For small (up to 5 cc)- and medium-sized (up to 25 cc) lesions away from critical areas, the dose was 25 GyE. For small and medium lesions near critical structures, the dose prescription was 24 GyE, whereas for larger AVMs (>25 cc), the dose was 20–23 GyE. With a minimum of 2 years of follow-up, complete obliteration, partial obliteration, and no change occurred in 50%, 47%, and 3%, respectively. Complete obliteration rates for AVM lesions <4.9 cc, 5–9.9 cc, 10–24.9 cc, and >25 cc were 89%, 43.8%, 46.6%, and 16.6%, respectively. Acute radiation reactions were mild to moderate. Eleven percent of the patients developed a late reaction, most commonly 12 months after radiosurgery. This group reports some of the best obliteration rates achieved with proton beam therapy for large (>10 cc) AVMs, possibly as a result of their higher doses, in comparison to the obliteration achieved by the MGH and Uppsala groups (15–20%).

Practical Considerations When Utilizing PBT for AVMs

- Consider the size and location of the AVM and associated nidus in deciding between hypofractionated regimens.
- For small (about 3–3.5 cc) peripherally situated AVMs, either single- or 2-fraction proton regimens yield high obliteration with low rates of toxicity [23, 27, 28].
- Large (usually >10 cc) peripherally situated lesions treated with single proton SRS fractions should be considered for dose-escalated approaches or treated with hypofractionated [2, 3] proton beam therapy [29, 31].
- Appreciate that centrally/eloquently situated AVMs present significant risks of late toxicities with single-fraction proton beam regimens [22].
- Appreciate that achieving obliteration for centrally/eloquently situated AVMs with proton beam therapy suffers the same challenges as with photon-based therapies. As such, consider multidisciplinary or staged approaches.

Pituitary Adenomas

In the early era of proton therapy, proton SRS was limited by the relatively inadequate neuroradiological techniques, limited imaging options, rudimentary treatment planning systems, and lack of onboard volumetric imaging [32]. Nevertheless, treatment of pituitary tumors remained feasible even at this time given the visibility of the sella turcica on radiographs. As such, the utilization of proton SRS for the management of pituitary tumors has one of the longest histories. The group from the Lawrence Radiation Laboratory at the University of California-Berkeley described one of the earliest reports of managing Cushing's disease with charged particle therapy in 1963. This group highlighted that the increased depth-dose penetration and biological effectiveness of particles such as protons provided a significant advancement at the time when orthovoltage X-rays and gamma rays limited the ability of delivering ablative doses to the depth of pituitary gland [33]. The early experience of the group from the Lawrence Laboratory successfully utilized proton irradiation with conventional fractionation of 20,000–30,000 rads in patients with either metastatic breast cancer to the pituitary, diabetes mellitus with retinopathy, or acromegaly with resultant hormonal dysfunction [34].

Additionally, in 1991, this group reported their results treating 840 patients with the aforementioned pathologies using either proton radiosurgery or helium ion beams. Dose prescriptions included 30–50 Gy in 4 fractions, 30–150 Gy in 3–4 fractions, and 50–150 Gy in 4 fractions for acromegaly, Cushing's disease, and prolactinomas, respectively. Overall, the majority of patients achieved control of neoplastic growth and/or reduction of hormonal hypersecretion states. While hypopituitarism occurred in a subset of patients, this was corrected with supplemental therapy [35].

Around the 1960s, while the proton SRS program at the Lawrence Laboratory was burgeoning, the group at MGH was also utilizing proton radiosurgery for the management of pituitary hypersecretion. In 2014, the group from MGH published their updated results of proton therapy for func-

tional pituitary adenomas treated between 1992 and 2012 [36]. Ninety-two percent of the patients were treated with three-dimensional conformal passively scattered proton therapy using 2 to 5 beams to a median dose of 20 Gy(RBE) (range, 15–25 Gy) encompassing the visible tumor and entire sella with a superior margin defined to limit the undersurface of the chiasm to 8 Gy (RBE) maximum dose. Eight percent of the patients received fractionated stereotactic treatments to a median dose of 50.4 Gy due to proximity of critical structures. With a median follow-up of 52 months, the 5-year rate of biochemical complete response, defined as at least 3 months of sustained normalized hormonal levels, was 59%. With a median of 43 months, 98% of the patients had local radiographic control, defined as absence of disease or stable residual disease. Overall late toxicity was limited, with the most common adverse event being hypopituitarism. The 5-year rate of developing a new hormonal deficiency was 62%. Four patients developed temporal lobe seizures. Otherwise, no documented cerebrovascular events or radiation induced tumors occurred in this cohort. In summary, the hormonal control rate achieved in this series is superior to rates (44.7–54%) reported by various photon SRS publications [37, 38] with overall an excellent tumor control rate.

Practical Considerations When Utilizing PBT for Pituitary Adenomas

Proton radiosurgery approaches provide effect local control and biochemical response rate, comparable to rates achieved with photon SRS treatments [36].

- In utilizing proton radiosurgery, consider the proximity of normal organs at risk such as the optic nerves and chiasm to reduce long-term risks.
- Appreciate the lower integral dose with proton-based SRS and the resultant potential to reduce long-term side effects such as cerebrovascular events or radiation-induced tumors.
- Consider referral to endocrinology for patients receiving proton beam therapy of the pituitary given the high rate of developing additional hormonal deficiency [36].

Vestibular Schwannoma/Acoustic Neuroma

Proton therapy, with varying fractionation schema ranging from conventional to hypofractionation to single-session SRS, has been utilized for the treatment of vestibular schwannomas with overall progression-free survival rates of 85–100% [39].

One of the earliest series evaluating single-session proton SRS for vestibular schwannomas was published in 2002 [40]. Sixty-eight patients received passively scattered proton beam therapy using 3–5 fields, to a prescription dose of 12 Gy to the 70% isodose line at the tumor margin while constraining the maximum brainstem dose to 12 Gy. The 5-year tumor control rate was 84%, with an overwhelming majority (95.3%) of the patients reporting satisfaction with the procedure and outcomes. Acute toxicities were minimal, with new cranial nerve (CN) neuropathies being infrequent. Severe permanent V and VII nerve injury occurred in each of the 4.7% patients. Mild transient V and VII nerve injury occurred in 9.4% and 18.8% of the patients, respectively.

In 2003, the same group updated their results, now reporting on 87 patients. The median tumor diameter was 1.6 cm; the median prescribed dose was 12 Gy CGE (range, 10–18) to a median isodose line of 70% (range, 70–108%) [41]. With a median follow-up of 38.7 months, the 5-year local control rate was 93.6%. The 5-year rate of hearing preservation rate in the 21 patients (24%) who had pre-SRS functional hearing was 22%. After proton SRS, the 5-year V and VII normalcy rates were 89.4% and 91.1%. No radiation therapy-induced secondary malignancies were noted.

In 2009 the group from South Africa initiated a proton hypofractionated stereotactic radiation therapy program using passively scattered proton beam radiosurgery for acoustic neuromas treating 21.4 CGyE in 3 fractions to a median isodose line of 85%. [42] With a median follow-up time of 72 months, they achieved a 5-year local control of 98%. Of patients with pre-RT serviceable hearing, the 5-year rate of hearing preservation was 43%. New VII nerve dysfunction was seen in 8.3% of the patients, of which two cases were mild and two were complete paralysis, with an overall 5-year rate of normal CN VII function of 90.5%. New cranial nerve V nerve dysfunction was also seen in 8.3% of the patients, all of which were mild, with an overall 5-year rate of normal CN VII function of 93%.

Considerations for VS/AN

- Appreciate the size of the lesion and its proximity to the brainstem, especially compression and effect on CSF flow, when considering a proton SRS/hypofractionated treatment approach.
- Consider limiting the maximum brainstem surface dose to 12 Gy, in an effort to minimize the risk of long-term side effect [41].
- Both proton SRS and hypofractionated (3-fraction) approaches provide excellent local control rates, comparable to rates achieved with photon-based therapy [41, 42]. Both fractionation schedules provide comparable rates of CN V and VII toxicity.
- Consider a protracted hypofractionated (3-fraction) proton therapy course for patients with functional hearing as it may better preserve hearing, although the data supporting this are sparse and weak [42].

Limitations

The published clinical data for proton SRS and hypofractionated stereotactic regimens reveal excellent local control rates of benign conditions such as meningiomas, schwannomas, pituitary adenomas, and AVMs. However, several limitations in these series exist. For example, in the modern era, proton therapy delivery techniques have undergone an evolution from a passively scattered approach to a spot scanning intensity-modulated ability. The generalization and applicability of results achieved with passive scattering to spot-scanning remain a question, strongly necessitating publication of modern clinical results.

Additionally, while the studies presented herein display excellent overall results comparable to those achieved with photon SRS approaches, the retrospective nature of these studies presents an inherent limitation. As highlighted by Wattson and coauthors, the predominant benefit of proton SRS is in optimally reducing integral dose to normal tissue [36]. Given the reported occurrence of radiation necrosis [43], secondary malignancies [44], and cerebrovascular accidents [45] after photon radiation for benign pathologies, proton SRS has significant potential to reduce these risks, especially in long-term survivors. Since the event rate for these sequelae is low, it would require rather large-sized sample studies with extremely long follow-up periods to statistically prove this.

A common limitation to the use of proton therapy for any disease site is the lack of an absolutely precise estimate of the relative biological effectiveness (RBE) of protons to photon therapy. While a general RBE of 1.1 is currently utilized, many studies reveal significant RBE variability [46]. Greater understanding of this will be critical in ensuring that appropriate tumor control doses are being utilized with proton approaches, as well as to ensure that proton-specific normal tissue dose constraints are adhered to.

Decision Criteria When Deciding Between Proton and Photon Treatments

As mentioned above, there are no significant publications prospectively comparing photon and proton outcomes using SRS/hypofractionated regimens for the pathologies discussed in this chapter. Given the understanding that proton regimens will likely achieve their greatest benefit in reducing the risk of long-term side effects, a patient's age, performance status, as well as associated co-morbidities must be taken into account when considering the treatment modality of choice. For patients who are judged to have a relatively poor prognosis or estimated to have a shortened life span, the utilization of protons may not provide the greatest magnitude of benefit relative to cost. An exception for stronger consideration of proton beam therapy would be for patients with intracranial comorbidities such as multiple sclerosis, severe end-arteriolar disease processes, or neurofibromatosis for which a reduction in the integral dose would reduce the risk of potential acute as well as late toxicities. Additionally, for patients who are otherwise young, and/or those patients with excellent performance status, proton therapy should be strongly considered given the benign nature of the disease processes resulting in decades of longevity and hence a higher likelihood of delayed radiation toxicities.

Pencil-beam scanning intensity modulated proton therapy (IMPT) is rapidly replacing older techniques, especially because of its ability to better sculpt dose around OARs that lie proximal to target volumes, and data for this modality are rapidly emerging but not yet adequately published [47].

When comparing photon to proton-based plans, one must consider not only set up uncertainties but also range uncertainties. This is generally completed with the creation of a beam-specific PTV with margins created to prevent geometric and range miss and in addition to analyze these plans robustly. When deciding on field directionality for proton-based plans, it is important to appreciate the potential for enhanced RBE at the distal end of the beam, which therefore should provide caution about ranging into a critical OAR, especially when only one or one very heavily weighted beam is used. Multiple fields [2, 3] should be utilized when treating and angles chosen so as to limit the number of beams ranging on critical OARs. Additional risk reduction can be achieved by ensuring that heavily weighted spots are not in close proximity to OARs.

Conclusion

Proton SRS has a longstanding history and has proven itself to be an effective treatment strategy to achieve excellent control for benign intracranial conditions. The dosimetric benefit of proton therapy in reducing dose to normal tissues has been associated with low acute and late toxicities, at least in retrospective series. Modern-day proton series, including prospective evaluations against photon approaches, remain warranted.

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