Proton beam therapy may be beneficial in reducing toxicity and improving outcomes in select tumors of the skull base.

Clinical Benefits of Proton Beam Therapy for Tumors of the Skull Base

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Background: The unique radiobiological properties of protons have been understood for many years. In addition, many of the clinical benefits of radiotherapy were first noted in tumors involving the skull base. More public attention has been given to proton beam therapy due to the increasing number of centers now in operation or in the planning stages for offering this treatment option.

Methods: We reviewed the physical properties of protons and the clinical studies performed to justify their use in the management of skull-base tumors and determine the benefits of proton beam therapy.

Results: Published reports suggest a benefit to proton beam therapy for use in tumors of the skull base, including craniopharyngiomas, chordomas, skull-base sarcomas, and unresectable meningiomas.

Conclusions: Use of proton beam therapy may be beneficial in select patients. Surgical and medical oncologists should have a general understanding of such cases to facilitate their appropriate referral.

Introduction

Proton beam therapy has risen in popularity in recent years as a treatment modality in the field of radiation oncology. More than 10 centers are in operation with many more proton centers under construction or in the planning stages.1 There are proven benefits to proton treatment in select patients, including those with chordomas, skull-base tumors, and in the setting of childhood malignancies where doses initiated in proximity to adjacent normal structures are of critical importance.2-5 The potential therapeutic benefit of proton beam therapy is being investigated in many other disease sites, including tumors of the lung, pancreas, esophagus, prostate, and cervix.6-10

In this review, we summarize the unique properties of protons that make them particularly beneficial for the treatment of skull-base lesions and review the results of clinical studies supporting their use.

Basic Proton Dosimetry

Although proton beam therapy has been receiving more attention in recent years, the unique physical properties of protons as charged particles have been understood for many years.1 Both photons and electrons deposit the majority of their energy at the surface close to their entrance at the body. After transferring this energy, the particle continues to deposit energy along its path but at a decreasing rate. Thus, the majority of the dose of radiation prescribed to a patient is often deposited outside of the target location. Therefore, the key goal of radiotherapy is to deliver high ablative doses to gross or microscopic disease while limiting the
dose of radiation to normal tissues and to avoid exceeding normal tissue tolerance, which can lead to toxicity.

Due to this concern, numerous strategies have been developed to decrease the dose of radiation delivered to normal tissues and include multiple fields, 3-dimensional (3D) conformal therapy, advanced intensity-modulated radiotherapy (IMRT)/computed tomography, stereotactic radiosurgery, and arc therapy. Treatment planning for IMRT and inverse radiotherapy has advanced the field of radiation oncology, reducing the doses received to normal structures and allowing the escalation of doses to target areas. Studies have shown significant improvement in tumor targeting and normal tissue sparing, thus improving local control and reducing toxicity rates.11-14 IMRT has now become the standard of care in select adult malignancies, including head and neck cancers,11 gastrointestinal malignancies (eg, esophageal,12 anal cancer13), and prostate cancer.14 Although these techniques can significantly reduce the dose delivered to normal tissues, both acute and late toxicities remain a concern.11-14

The pattern of dose deposition in proton particles differs from that of photons and electrons. As the proton beam travels through tissue and maintains velocity and energy, it begins to slow near the end of its path. At this point, it abruptly deposits the majority of its energy. No further energy deposition occurs at the end of this path. This phenomenon is known as the Bragg peak (Fig 1).15 This makes protons different from electrons and photons, which do not exhibit a similar Bragg peak phenomenon. All 3 particles — photons, electrons, and protons — have a place in modern radiotherapy, each with unique benefits and drawbacks. In tumors likely to benefit from proton beam therapy, the decision to use proton vs photon therapy either with IMRT or 3D conformal therapy should be made on a case-by-case basis, with the clinician evaluating the necessary target coverage and sparing of critical structures.

Range Modulation

Even though the fact that protons deposit the majority of their dose at a certain distance from their entrance seems appealing, few tumors are covered by the narrow range provided by a pristine Bragg peak. The solution to this has been to create a so-called spread-out Bragg peak (SOBP), which allows for radiation to be deposited throughout the extent of the tumor (Fig 2).15 The SOBP is created using a method known as range modulation. The rate of penetration is directly related to beam energy: A higher energy beam deposits its dose further than a lower energy beam.

![Fig 1. Proton Bragg peak demonstrating peak energy deposition at the termination of the proton path. From McDonald MW, Fitzek MM. Proton therapy. Curr Probl Cancer. 2010;34(4):257-296. Reprinted with permission by Elsevier.](image1)

![Fig 2. Summation of individual Bragg peaks to create the spread-out Bragg peak. From McDonald MW, Fitzek MM. Proton therapy. Curr Probl Cancer. 2010;34(4):257-296. Reprinted with permission by Elsevier.](image2)
A range modulator places varying thicknesses of absorbing material in front of the beam to modify an otherwise monoenergetic beam. This yields a spectrum of proton beam energies, each with a different point of maximum dose deposition. When these individual beamlets are summed together, the SOBP is created. A consequence of employing such a strategy is that a once relatively low entrance dose of a single proton beam is repeated by each of the beam energies, such that the cumulative dose is increased when delivering the SOBP. However, the unique dose fall-off rate following dose deposition after the final Bragg peak is preserved.

**Through and Patch Fields**

Historically, the radiotherapy concepts of “dose” and “target” were, at best, 2 dimensional. The delivered dose was visualized as the intersection of few irregularly shaped cylinders within the patient to form an irregular polyhedron — and was almost always an oddly shaped box.16 Sometimes, with arc treatments, a partial plane of distributed dose was delivered, with increasing intensity to a high-dose apex at the target depth, then fanning out again at exit. Because software for noncoplanar calculation did not exist in the 1980s, noncoplanar beams were rare. Beam-eye view involved drawing block outlines on the skin, and clinicians were most comfortable with relatively few gantry angles.

In the 1990s, combined computed tomography/3D dose-calculation algorithms were introduced.17 Enhanced graphics added color and patient-specific organ anatomy to the 1980s framework, and clinicians could now visualize the patient’s body from any angle (Fig 3).16 Doing so allowed more frequent use of noncoplanar beams, off-axis calculations, multiple beam arrangements, and, ultimately, 3D conformal radiotherapy.17 Conceptually, however, the radiotherapy dose was generally delivered via a planar dose bath with more sites of beam entry/exit, although exceptions did exist (eg, use of oblique or tangential fields could minimize the axial volume treated for appropriate lesions).

In the 2000s, intensity modulation, dynamic multileaf collimation, and more sophisticated beam-eye view software and image-fusion capacity became available.18 In this 4-dimensional environment, the perception of “target” changed. The target volume was anatomically defined and, thus, usually irregular. It could contain different volumes receiving different delivery doses within the same duration of therapy. However, despite the sophistication of the display and the complexity of beams and fluences, the mental picture from the 1990s of a planar dose bath remained. The degree of “planarism” is based on the dose used; lower doses still outline a slice through the patient, with few arcs remaining dose free because they may provide no benefit.

The construct of the planar dose bath became obsolete with the introduction of proton beam therapy. No dose exists downstream of the Bragg peak for any individual beam; however, with compensation and range modulation, different depths of individual beams may be included in a plan. For instance, matching “through” and “patch” fields in a single plan allows for noncoplanar sparing of the brainstem, spinal cord, or optic chiasm (Fig 4).

The concepts of “through” and “patch” fields are not valid in photon radiotherapy and are infrequently used in proton radiotherapy. No conceivable benefit exists to their use in treating prostate cancer or in standard craniospinal proton beam therapy; however, these concepts are critical when treating extensive le-
sions of the brainstem and optic apparatus to high doses. A proton “through” field does not traverse the patient, but it does traverse the target. A proton “patch” field is added when the anatomical or spatial complexity of a lesion abuts a dose-limited normal structure, and the through field must sacrifice lesion coverage to avoid doses to normal tissue.

**Skull-Base Sarcomas**

The unique physical properties distinguishing proton beam therapy from other radiation modalities have been employed to treat select malignancies. Due to their proximity to critical structures in the brain, such as the brainstem, optic nerves, and optic chiasm, skull-base sarcomas can be challenging to manage. Complete resection of these malignancies is often not possible. Use of proton therapy for these malignancies offers clinicians the opportunity to deliver potentially ablative doses to areas of gross disease while avoiding toxicity in the brainstem and optic structures. Proton therapy also has the potential to preserve excellent local control while also limiting the dose to normal structures.

One group of researchers reported dosimetric differences between proton beam plans with photon IMRT for the treatment of parameningeal rhabdomyosarcomas in pediatric patients. Acceptable target volume coverage was achieved using both modalities, and the proton plans resulted in significant sparing of all examined normal tissues, except for the ipsilateral cochlea and mastoid. In a series involving 16 children with rhabdomyosarcoma, similar results were found, including rates of good local control and acceptable toxicity profiles. Furthermore, when comparing 3D proton planning to 3D photon planning, another study showed that protons were able to spare radiation to normal tissues in the brain and contralateral orbital structures while also maintaining tumor coverage in 7 children with orbital rhabdomyosarcoma who received treatment.

**Craniopharyngiomas**

Craniopharyngiomas are histologically benign but aggressive tumors originating from the remnants of the Rathke pouch, and they typically affect children and adolescents. Because of the location of these tumors in the suprasellar region, the temporal lobes, hippocampus, hypothalamus, optic nerves, and chiasm may be at risk for acute and late effects of radiotherapy.

Several institutions have reported their results in the treatment of these rare tumors. A study from a proton facility reported 5- and 10-year local control rates of 93% and 85%, respectively, in a group of 5 children and 10 adults. Similar outcomes were reported by Luu et al in a group of 16 patients with acceptable toxicity profiles. Bishop et al compared the results of 52 children treated with proton beam therapy (n = 21) vs photon IMRT (n = 31). No difference was detected between the treatment modalities in rates of survival, solid and cystic disease control, and late toxicities when measured for a median of 33 months for those receiving proton beam therapy and 106 months for those receiving IMRT. However, another study reported on significant reductions in doses to normal structures such as the hippocampus, dentate gyrus, subventricular zone, and vascular structure while preserving target coverage in a comparison of 3D proton and intensity-modulated proton beam therapy with photon IMRT. However, prospective, quality-of-life and formal neurocognitive testing are needed for more sensitive measures of benefit to determine how long-term toxicity profiles differ between the management of these rare malignancies and when comparing proton beam therapy with photon treatment.

**Chordomas**

Chordomas are rare primary bone tumors thought to arise from remnants of the embryonal notochord, although they can arise anywhere along the spine as well as the base of the skull. When affecting the base of skull, chordomas can invade the clivus, petrous bone, and extend to the cavernous sinus with direct involvement of cranial nerves, potentially leading to cranial nerve palsies. These tumors are challenging to treat when located in the skull base because surgical resection may lead to poor outcomes, with gross residual disease requiring postoperative radiotherapy. However, dose escalation with radiation doses greater than 60 Gy has been proven to lead to improved outcomes. Due to the proximity to critical structures, the delivery of acceptable doses of radiation to achieve local control can represent a challenge for many clinicians. Many studies have been conducted on the benefit of proton beam therapy for the management of chordomas, making it the current standard of care for managing these rare tumors.

Protons have also been instrumental in the dose escalation of chordomas (> 70 Gy); a steep dose-gradient limits toxicity to critical normal tissues. Long-term follow-up of patients with chordomas whose conditions were managed with proton beam therapy has also been reported. With a median dose of 72.1 Gy for combined proton/photon beam therapy, a 5-year local control rate of 73% has been reported. Similar findings have been demonstrated in a report of 33 patients with chordomas and 25 with chordosarcomas who received radiotherapy. The mean target dose was 70.7 Gy equivalent (range, 64.8–79.2), and local control rates of 76% were achieved for those with chordomas and 92% for those with chordosarcomas. Similar local control results were reported by Ares et al in a cohort of 64 patients who had skull-base chor-
domas (n = 42) or chondrosarcomas (n = 22). They were treated with protons using a spot-scanning technique, and the median total dose was 73.5 Gy for those with chordomas. The 5-year disease-specific survival rate was 81% with a 5-year rate of freedom from high-grade toxicity of 94%.26

In the setting of reirradiation for 16 study participants with progressive or recurrent chordomas, McDonald et al30 demonstrated that definitive proton beam therapy, with or without salvage surgery, was encouraging for initial disease control and overall survival. The median prior dose of radiation was 75.2 Gy, and the median dose of reirradiation was 75.6 Gy (relative biological equivalent).30 The 2-year local control rate was 85%, the overall survival rate was 80%, and the rate of developing distant metastasis was 20%.30 Despite high cumulative, lifetime doses of radiation, acceptable toxicities were reported in 3 patients who experienced grade 3/4 events but no grade 5 events; however, the researchers noted that additional toxicities could potentially develop with a longer follow-up period.30

Thus, these reports show that proton beam therapy has some benefit for the management of chordomas.

Meningiomas

In general, meningiomas are benign tumors that arise from the meninges. Surgical resection is the standard of care, and radiotherapy is typically reserved for incomplete resections, adverse pathology, or for those tumors that are not resectable.31,32 For tumors that involve the base of the skull, cavernous sinus, or optic chiasm, radiotherapy alone may represent a management option. Although intensity modulation and daily image guidance allows these lesions to be treated with photons and a relatively low relative dose to the normal brain, the volume of normal brain in the treatment field is often extensive. Although using vertex or angled, superior photon fields may be a viable option to decrease brain hemispheric coverage, doing so often leads to a high exit dose to the brainstem. Due to the benign nature of these tumors, acute and late sequelae of treatment represent a primary concern.

Proton therapy offers benefits to select meningiomas located proximal to critical structures or in the setting of recurrence.33-35 One such experience was reported in 46 study patients receiving treatment, 9 of whom received treatment following incomplete tumor resection, 8 following tumor biopsy, and 29 following tumor recurrence after gross total resection and combined photon/proton beam treatment plans.33 A 10-year recurrence-free survival rate of 88% was achieved, as was a 10-year toxicity-free survival rate of 80%.33 Noël et al34 reported on 51 study patients treated with combined proton beam/photon radiotherapy, noting excellent rates of local control and 2 cases of grade 3 toxicity. Improvements were seen in eye-related symptoms for the majority of the study patients.34

Another study reported on the management of atypical and malignant meningiomas.35 In this series, 24 study patients were treated with a mean proton total dose of 34.05 Co Gy equivalent and a mean photon total dose of 30.96 Co Gy equivalent.35 The authors of that study suggested that a proton boost may improve outcomes and rates of survival with dose escalation.35 No acute cases of morbidity related to radiotherapy were reported.

Midsagittal Lesions

Midline central nervous system lesions are optimally treated with proton beam therapy using modified midsagittal proton schemas that allow normal tissue to be spared in most of the uninvolved brain while also limiting doses to at-risk organs. Estabrook et al36 demonstrated the dosimetric advantage of using protons in 9 study patients (n = 5 craniopharyngiomas; n = 4 meningiomas). The Bragg peak characteristic of protons allowed for the use of vertex and anterior and/or posterior superior oblique beams along the midsagittal plane to achieve a mean dose of 52.2 Gy (relative biological equivalent) to the target.36 The decreased number of treatment beams and unique angles achieved with protons resulted in an improved plan distinct from what is currently possible with IMRT photons.36 The reported midline central nervous system proton plans resulted in minimal doses to the normal tissue of the brain, as demonstrated by average mean doses of 18 Gy (relative biological equivalent) to the brainstem (range, 0.0–40.1) and 17.1 Gy (relative biological equivalent) to the hippocampi (range, 0.0–45.9).36

Fig 5 depicts a proton beam arrangement for parafalcine meningioma.37

Conclusions

The radiobiological benefits of proton beam therapy have been understood for many years. As proton beam therapy becomes available for more and more patients, it will become increasingly important that the benefits of this treatment be based on solid clinical evidence. The majority of the studies reviewed were retrospective in nature. As more institutions become equipped to deliver this therapeutic option, more opportunities will exist for the development of prospective trials to study proton beam therapy.

Due to the rare nature of these tumors, multi-institutional and collaborative efforts will be important to increase our knowledge. At this time, many tumors encompassing regions of the skull base have demonstrated a proven benefit from proton treatment based on retrospective results. Studies into dose escalation and conformal treatment plans with proton beam
therapy may further improve outcomes in these disease sites without compromising the risk of toxicity to normal structures. In addition, future research might also reveal that the benefits of proton beam therapy to skull-base lesions can translate to treatment options for other malignancies.

References