Proton Beam Therapy (For CNS Tumors)

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Learning Objectives

At the end of this chapter, readers should be able to:

- Understand the physical differences between proton beam therapy and photon beam therapy.
- Identify clinical indications for which proton beam therapy might be appropriate for patients with CNS tumors.
- Evaluate some of the existing data for which proton therapy has been used for patients with intracranial tumors, and understand that research in this field is still ongoing.
- Understand and apply simulation and treatment techniques that are specific to proton beam therapy delivery.
- Apply this knowledge to clinical situations in which patients may be appropriately referred for proton therapy.

Description and Evolution of Proton Beam Therapy

The use of proton therapy in a clinical setting was first suggested based on the inherent properties of the particle. The mass and the charge of protons confer several physical advantages when applied to radiation therapy. Compared to electrons, protons have approximately 1840 times the mass and therefore scatter at a significantly smaller angle. At certain depths, this results in a sharper lateral distribution than electron or photon beams and allows normal tissue on either side lateral to the target to be better spared [1, 2].

Furthermore, the rate of energy loss of a proton in matter is inversely proportional to its velocity, which results in a characteristic depth-dose distribution. There is a slow increase in dose with depth, followed by a sharp increase near the end of range, and this sharp increase at the end of the particle range is referred to as the Bragg peak. The proton beam can be modified with different techniques to encompass targets of greater thickness than a single Bragg peak. Several beams of various energies are combined and superimposed to result in a spread-out Bragg peak (Fig. 47.1) [3]. This form of passive-scattering delivery results in a beam that is wide enough to cover the target, with the advantage of very little dose distal to the target. Alternatively, the beam can be controlled with magnets and actively scanned across the width of targets with changes in energy to vary the depth.

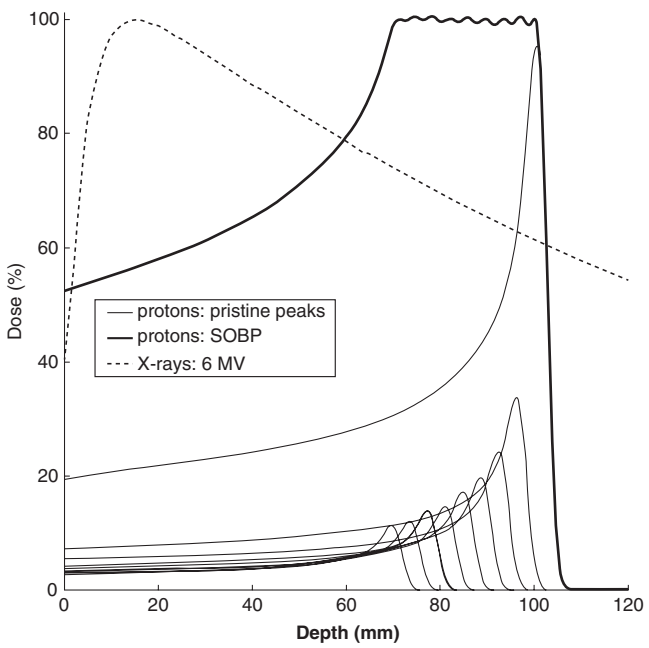

Fig. 47.1 Depth-dose curve of a proton spread-out Bragg peak (SOBP) with a 10.1 cm range and a 3.5 cm modulation formed by the summation of multiple pristine peaks varying ranges and weights. A 6 MV photon depth dose is plotted for reference

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This form of delivery is referred to as pencil-beam scanning and achieves higher conformality of radiation therapy than passive-scattering protons and importantly enables intensity-modulated proton therapy (IMPT).

Robert Wilson first anticipated the therapeutic benefits of protons in 1946 and suggested that proton therapy would result in a highly conformal dose distribution with far less collateral dose to adjacent normal tissues [4]. When applied to tumors in the central nervous system, there are several dosimetric advantages, particularly for tumors adjacent to more radiation-sensitive structures [5].

The trend in radiation techniques over time has been toward increasing conformality, to reduce exposure of radiation to normal tissue, whether 3D conformal planning is favored over 2D planning or IMRT is favored over 3D conformal planning [6, 7]. By this logic, the conformality of proton therapy could be considered one technological tool in improving targeted delivery of radiation therapy. In the 1960s, the Harvard Cyclotron Laboratory began preclinical and clinical studies to better characterize the therapeutic applications of proton therapy in partnership with the Massachusetts General Hospital Department of Neurosurgery [8]. In that era, the advantage of conformality from proton therapy was highly promising compared to available radiation techniques, but critics of proton therapy now argue conformality is less expensively achieved with IMRT. Thus, investigations on the potential clinical benefit of lowering nontarget dose radiation with the use of protons as compared to modern photon radiation techniques will be critical to defining the role of each in the future.

While proton therapy offers many physical and anatomic advantages, the energy and charge properties of protons have potential radiobiological advantages as well. Due to the charge of protons, these particles have greater linear energy transfer (LET) in matter, and therefore, they are estimated to have a greater radiobiological effectiveness for cell killing than photons [9]. Since the LET of charged particles increases as the particles slow down near end of range, the relative biological effectiveness (RBE) of the charged particle is greatest in the down slope of the Bragg peak.

There have been many radiobiological studies to determine the RBE of protons in various conditions using various endpoints [10]. Most proton treatment centers commonly apply an RBE of 1.1 for dose calculations and prescriptions, so that clinical workflows can be easily translated across modalities. However, these estimations do not take into account that proton dosimetry has a tendency to be more heterogeneous than the initial calculations estimated, and the true RBE is not fully quantified and remains an active area of study [11, 12]. Taking into account the estimated RBE of protons to photons, for equivalent doses prescribed to the tumor, protons and photons seem to have similar effects on tumor cell killing.

Clinical Indications

In general, the efficacy of radiation therapy is limited by the dose constraints of normal tissue, which is the primary determinant for unacceptable radiation-related toxicity. For patients with intracranial tumors, there are a variety of pathologies, ranging from incurable malignancies to benign tumors. Malignancies may require high doses for tumor control that far exceed certain normal tissue tolerance, and protons may allow dose escalation where it was previously unachievable with standard photon options. For patients with benign tumors, any additional dose of radiation may expose an otherwise healthy patient to an unnecessary risk of long-term toxicity with lifetime consequences.

For CNS tumors, treatment-related toxicity can have severe implications on a patient's quality of life when considering the treated tumor itself is often not life threatening. Common acute toxicities include alopecia, skin erythema and irritation, fatigue, headaches, nausea, and vomiting, which are managed during treatment with a combination of skin care, over-the-counter pain medications, antiemetics, and steroids. More concerning are the potential long-term consequences of radiation therapy, which include focal neurologic deficits, particularly sensory changes, such as vision, hearing, motor or sensory loss, or vestibular function [13]. In addition, risks of exposure to low doses of radiation, such as a secondary malignancy, are of significance to long-term survivors as seen with diagnoses of lower-grade gliomas, and pituitary adenomas, vestibular schwannomas, among others [14–16].

While these considerations seem to be compelling arguments for treating many brain tumor patients indicated for radiation therapy with proton radiation therapy, protons remain an expensive and limited resource for therapy and must be justly allocated across all patients with appropriate indications [17, 18]. At some institutions, a systematic regular review of patients who may potentially benefit from proton therapy is conducted with a team of physicists, dosimetrists, therapists, and physicians to ensure that candidates for proton therapy are appropriately selected. In general, there are a few consistently agreed upon indications that warrant consideration of proton therapy, including benign tumors or patients with malignant tumors with favorable prognoses, tumors requiring high doses of radiation adjacent to critical structures, patients considered for re-irradiation, and participation in clinical trials. In patients with poor prognoses, more advanced age, or with tumors in locations that are easily treated with little risk to normal tissue, it may be inappropriate to use this costly and limited modality.

Benign CNS Tumors

The management of patients with benign intracranial tumors is driven heavily by careful considerations of risks versus benefits [19, 20]. While these diseases are benign, intracranial tumors can still significantly impact quality of life, thus necessitating treatment. Because these patients generally have favorable prognoses without significant risk for mortality from their tumors, the guiding principle for treatment of benign conditions is to *Do No Harm*. Therefore, the acute and specifically the late toxicities of radiation therapy must be carefully considered before offering treatment. Proton therapy can offer some advantages, compared to photon-based therapies in this regard. Given the conformality to the target, the volume of normal tissue exposed to low doses of radiation therapy can be reduced (Fig. 47.2). These patients may live decades and have more years at risk for developing treatment-related late normal tissue injury and secondary malignancy.

For patients with arteriovenous malformations (AVMs), photon-based SRS has been used for obliteration, to ultimately reduce a small but real risk of a life-threatening intracranial hemorrhage. However, for patients with larger AVMs, a larger volume of collateral normal tissue is typically irradiated. Proton therapy can provide a way to minimize the integral dose to the surrounding brain and to achieve a superior risk-benefit balance in favor of treatment [21–23].

For patients with vestibular schwannomas (acoustic neuromas) with serviceable hearing, one goal of treatment is to maximize the amount of time with stable hearing. Therefore, patients are often candidates for observation or fractionated radiation treatment. For patients with small tumors and no serviceable hearing, proton radiosurgery can be considered with same dose practice as used with photons, of 12 Gy(RBE), and with both high tumor control and low rates of facial nerve dysfunction [24, 25].

Pituitary adenomas can also be managed with proton therapy with excellent disease control rates [26]. In most series, tumor local control rates are as high as 90–100% regardless of technique or technology, and biochemical control is comparative to photon experiences. In one study, patients with both functional and nonfunctional pituitary adenomas were treated

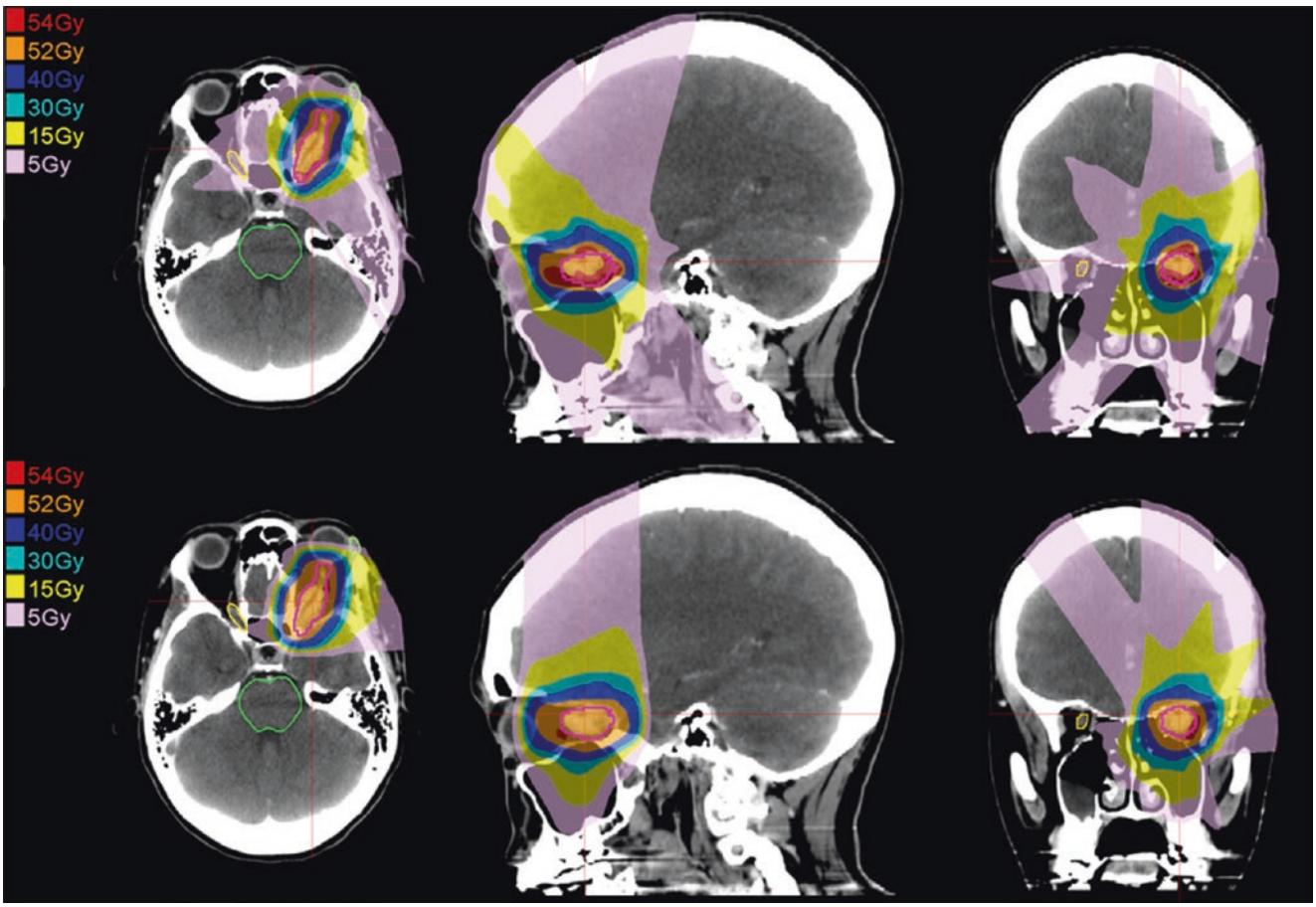

Fig. 47.2 Treatment plan of an optic nerve sheath meningioma treated with (**a**) photon IMRT versus (**b**) passively scattered proton therapy. Whereas target dose coverage is comparable between the two techniques, there is markedly less collateral irradiation of the normal tissues with proton therapy

with fractionated protons to a median dose of 54 Gy(RBE), with local or hormonal control in all patients assessed in follow-up [27]. Most patients in this series presented in the setting of residual or recurrent disease. In these patients, anticipated benefits of proton radiation are related to reducing exposure of normal brain tissue to low doses of ionizing radiation therapy.

For patients with meningiomas, protons appear to be similarly beneficial with a higher margin of benefit for atypical or malignant meningiomas as compared to benign meningiomas, for which dose and margins are more modest. A study of 31 patients who underwent fractionated proton or photon radiation therapy for either atypical or malignant meningiomas demonstrated significantly improved local control for patients receiving proton radiation versus photon radiation, with target doses of greater than 60 Gy for both [28]. Presumptively, this was related to superior tumor target dose coverage as enabled by the use of protons.

For all of the above tumors, with small target sizes, tumor control outcomes from photon-based and proton-based treatments are likely similar, and doses for benign tumors rarely exceed normal tissue tolerance. However, these patients have excellent prognoses, and the possibility that they may experience late side effects of radiation must be considered. Particularly among long-term survivors of 10–20 years or greater, rare late adverse effects of radiation therapy are not negligible [29, 30].

Malignant CNS Tumors

The potential role of proton radiation therapy in patients with malignant intracranial tumors must be approached differently. In patients with low-grade gliomas, who have more favorable prognoses, and who are treated to a higher dose that exceed some intracranial normal tissue tolerance parameters, protons may offer real dosimetric advantages. A prospective study single-arm study of patients with grade 2 gliomas treated with 54 Gy(RBE) in 30 fractions demonstrated preservation of excellent quality of life. At a median follow-up of 5.1 years, there was no overall decline in cognitive function, visual ability, attention/working memory, or executive functioning. However, a subset developed predictable neuroendocrine deficiencies when disease involved or abutted the pituitary [31]. While it was a small single-arm study, the results are promising that sparing normal tissue may in fact translate to sustained quality of life outcomes.

For patients with high-grade gliomas, the role of proton radiation therapy is less well established. Late toxicities are less of a concern in this group, given that their competing risk for cancer-specific morbidity and mortality far outweighs the likelihood of developing discernible treatment-related toxicity. However, the potential application of proton therapy in this cohort may allow for safer radiation dose escalation. In a series of 23 patients treated with proton radiation to a dose of 90 Gy(RBE) at 1.8 Gy(RBE) BID, median survival was 18.6 months [32]. Despite the promising median survival outcome, 90 Gy(RBE) was associated with a high rate of tissue necrosis that led to progressive neurological symptoms and need for surgical intervention. The diagnostic skills, treatment planning, and treatment delivery techniques in this study are antiquated by today's standards and such the application of protons in this setting remains under current investigation.

Protons also have a dosimetric advantage with and expectant local control clinical benefit for patients with skull base tumors, such as chordomas or chondrosarcomas. Proton therapy may offer the same anatomic advantages that are anticipated in the treatment of patients with other benign processes of the skull base, such as pituitary adenomas, vestibular schwannomas, or meningiomas. However, the doses to control sarcomas often exceed normal tissue tolerance of adjacent critical intracranial structures, with doses often of 70 Gy(RBE) or higher. One study demonstrated that patients with skull base chordomas who received 3D conformal proton therapy to doses between 77.4 Gy(RBE) and 79.4 Gy(RBE) showed that local control at 2 years was 86% and overall survival was 92%, with grade 2 toxicity of unilateral hearing loss in 18% of the cohort, with no grade 2 or higher toxicities observed for optic structures or brainstem, suggesting that proton therapy allows effective doses of radiation therapy to be delivered without compromising local control or normal tissue function [33]. Pencil-beam scanning may enable even better control and sparing of toxicity. Long-term outcomes of patients with skull base chordoma or low-grade chondrosarcomas treated with pencil-beam scanning proton therapy showed 7-year local control rates of 70.9% for patients with chordoma and 93.6% of patients with chondrosarcoma with mean delivered dose of 72.5 Gy(RBE). However, the gross residual disease was abutting the brainstem or optic apparatus in 32% of patients, and this was ultimately found on multivariate analysis to be independent prognostic factors for poorer local control and overall survival, suggesting there are some patients for whom their target volumes are centered in or around a critical structure which precludes even the most conformal therapy from optimizing control. However, for many of these patients, local control was excellent, and at 7 years, 87.2% of patients survived without evidence of any grade 3 or higher toxicity, including unilateral or bilateral optic neuropathy, temporal lobe necrosis, cerebellum brain necrosis, spinal cord necrosis, and unilateral hearing loss [34].

Where melanomas of the eye have historically been managed with enucleation, proton radiation established the alternative of definitive radiation therapy to manage these small tumors, delivering high radiation doses with no collateral radiation delivered to the brain. Rationale for proton therapy is similar to many intracranial tumors, that of small target size, excellent tumor control to radiation, and the ability to minimize radiation-related toxicity to the structures in the eye. One study of 191 patients treated with either photon-based stereotactic

radiosurgery or proton beam therapy demonstrated excellent local control rates, with 98% eye preservation in the SRS group, and 95% in the proton beam therapy group. However, the patients in the SRS group showed poorer visual prognosis with 65% losing significant visual acuity, while only 45% in the proton therapy group had lost the same level of visual acuity. This suggests that while both modalities over excellent local control, proton therapy allows better preservation of function, and less late toxicity [35]. Further attempts to characterize visual acuity outcomes after proton beam therapy in a prospective way have shown that at 60-month follow-up, patients with favorable pretreatment visual acuity retained their visual acuity and will likely retain excellent long-term visual acuity. Multivariate analysis did reveal that the volume of the macula receiving 28 Gy(RBE) and optic nerve were independent dose-volume histogram predictors of post-proton therapy visual acuity loss in patients with good pretreatment vision [36].

Re-irradiation

For patients with recurrences or progression after initial definitive radiation therapy, proton therapy may facilitate a feasible way to re-irradiate patients and mitigate some risk of exceeding normal tissue tolerances in the setting of prior irradiation (Fig. 47.3) [37].

McDonald et al. reported a retrospective review of 16 patients with a diagnosis of progressive chordoma who under-

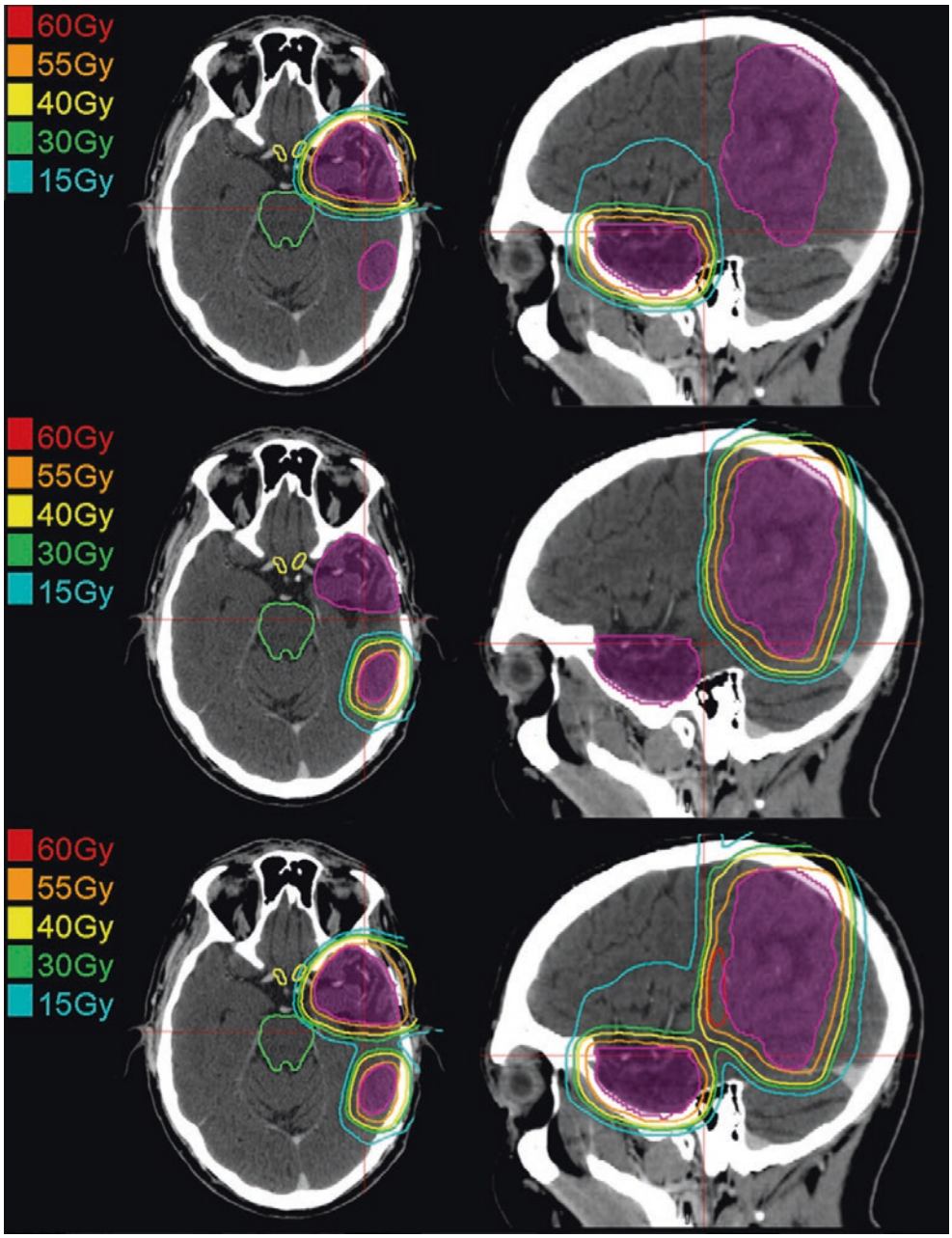

Fig. 47.3 Re-irradiation treatment plan

went re-irradiation with proton therapy and received a median dose of re-irradiation of 75.6 Gy(RBE) with local control of 85%, overall survival of 80%, and chordoma-specific survival of 88% at 2 years [38]. Late toxicity in this study included bitemporal lobe radionecrosis in one patient, cerebrospinal fluid leak in one patient, and brainstem stroke occurring outside of the radiation field in another. Whereas this study reports on the experience of applying proton therapy as a modality for re-irradiation, it still harbors significant risks and how much less than with photon-based treatments is as yet unclear.

Participation in Clinical Trials

There continues to be extreme controversy over the role of proton therapy, given the high capital costs of adopting the technology. In this vein, there have been strong calls for greater evidence and randomized clinical trials that study the efficacy and the potential benefits of proton therapy versus photon therapy. In order to answer this call, centers with proton therapy should be supported in their ability to conduct and participate in clinical trials. Furthermore, patients willing to participate in these studies should be allocated proton therapy, in order to justify its continued applications over time. There have been many ongoing clinical trials investigating the application of proton therapy for intracranial tumors. A recently published single-arm study examined overall survival, progression-free survival, and quality of life outcomes of proton therapy for patients with low-grade gliomas and found that patients tolerated proton therapy well with a subset of patients developing neuroendocrine dysfunction, as described above [31]. NRG BN001 is investigating hypofractionated dose-escalated photon IMRT or proton therapy in comparison to standard photon therapy for patients with glioblastoma with a primary endpoint of overall survival [39]. As previously described, there is also a great interest in proton therapy's ability to mitigate the negative quality of life impact of interest, and there is currently a trial of proton therapy for patients with meningiomas or hemangiopericytomas with primary endpoints of quality of life measures [40]. For this reason, participation in a clinical trial is taken into account in determining allocation for proton therapy [20, 41–43].

Immobilization Techniques and Image Guidance

Immobilization for proton therapy is of critical importance. Given the benefits of conformality with proton beam radiation therapy, immobilization is paramount to minimizing uncertainty and ensuring that ultimately the entire target is treated to the prescription dose. For intracranial tumors, many types of external frames have been developed for standard fractionated proton radiation treatment using doses ≤3 Gy(RBE) [44]. Because protons are more sensitive than photons to shape and density variations, immobilization equipment must be specifically designed to minimize these factors. Patient compliance and ability to tolerate the immobilization devices is also essential for successful proton treatment, and sedation or anesthesia can be used if patients have considerable difficulty tolerating treatment.

An example of an immobilization frame that has been developed for proton therapy of brain tumors is a modified Gill-Thomas-Cosman (mGTC) frame, comprising a rounded carbon fiber occipital support and low-density cushion in addition to the GTC frame (Fig. 47.4) [45]. This device is used to treat intracranial targets that do not extend to the base

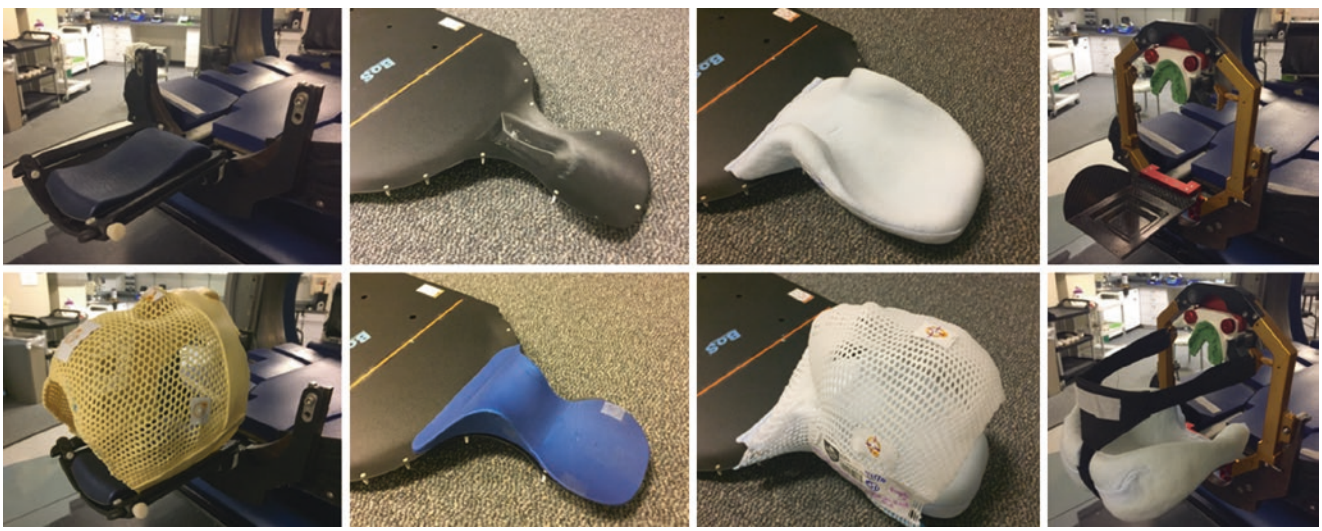

Fig. 47.4 Proton compatible immobilization devices used for cranial irradiation. Two leftmost images: intracranial mask system with a standard occipital cushion (top) and reinforced thermoplastic mask (top); middle four images: QFix base of skull immobilization system (QFix Products, Avondale, PA) with standard and custom head and neck cushions and mask and the modified Gill-Thomas-Cosman (MGTC) frame with and without a custom occipital cushion

of the skull but requires that the patient have good dentition, as the skull is immobilized using a fixed dental mold to create excellent and reproducible immobilization.

Alternative fixation devices, which do not use dental fixation, make use of thermoplastic masks and custom occipital cushions for a somewhat comfortable yet reproducible immobilization. An example of a proton compatible system is the intracranial (IC) frame assembly, which was originally designed for PET imaging and subsequently adapted for proton therapy (Carbon Head Holder 237HH, Tru-Scan Imaging Inc., Annapolis, MD). The IC frame can be used with a standard head cup or custom occipital cushion and a perforated thermoplastic mask reinforced with a solid sheet polyfoam [46]. The base of the IC device is made of carbon fiber to permit treatment beams to be employed through the frame, enabling lower fields and skull base tumors to be treated, unlike the MGTC frame. It can also be used in patients who have poor or no dentition. A readily available commercial alternative to the IC frame is the Base of Skull (BoS) frame (AccuFix BOS Frame RT-45, Q-Fix WFR-Aquaplast, Avondale, PA) specifically designed for proton therapy. The BoS is similar to the IC frame using a proton friendly designed carbon support in combination with a thermoplastic mask and custom or standard head and neck cushion.

The regular use of cone beam computed tomography (CBCT) and automated corrections is not commonly used with proton beam therapy, yet, and therefore, patients requiring intracranial proton stereotactic radiosurgery can undergo an additional step to improve localization, which may include placement of fiducial markers using minimal anesthetic into the outer table of the skull. This procedure can be performed as an outpatient procedure by a neurosurgeon in approximately 15 min with minimal blood loss. This allows triangulation of the skull for treatment with utmost accuracy [47].

Once these immobilization devices are created, patients undergo CT simulation in a supine position. The use of IV contrast is at the discretion of the treating physician, depending on the ability of the contrast to enhance regions of interest on the CT images and the patient's individual ability to tolerate contrast (with good baseline kidney function and no contrast-related allergies). The use of contrast must be used cautiously, as CT densities are used to estimate stopping power, from which proton ranges are ultimately derived [48]. The discrepancy between the artificial density of IV contrast and the true tissue density may be mitigated by using *pre-contrast* scans. Regardless, in most cases, a recent MRI is often registered to the planning CT scan to give additional anatomic information.

Treatment Planning

Target Delineation

Because the potential advantages of proton therapy are related to high-precision conformality, treatment planning demands accurate target and organs at risk (OAR) delineation. For intracranial tumors, MRI fusions are used to assist in delineation of the target volume as well as of critical structures. This fusion must be as accurate as possible to ensure precise tumor volume delineation. A dedicated anatomist can be helpful in delineating critical structures for consistency and highest accuracy for treatment planning.

Treatment Delivery Systems

Protons employed in therapeutic radiation therapy can be accelerated with either cyclotrons or synchrotrons. Accelerated protons are directed toward the gantry heads using a series of bending magnets, so the energy of each particle can be maintained until it is delivered to the target (Fig. 47.5) Because the beam is delivered as a single beam line, the particle beam must be spread to cover the target, and this can be achieved in a few ways. Protons can be spread from the source by either passive-scattering or by pencil-beam scanning [49]. A single-scattering system may be used for small tumors, while double-scattering allows larger tumors to be treated with a uniform lateral dose. Both forms require custom blocking for lateral conformality, as well as a range compensator, which allows for distal conformality to the target.

There has also been an increasing interest in the use of pencil-beam scanning, in which uniform fields can be produced without loss of range. In pencil-beam scanning, each beam is delivered in a certain array, with a specific spot size and defined energy [50, 51]. The energy for each spot is modulated to deliver dose to a particular depth, and then this is repeated for each position in the array, without the need for a range compensator for distal conformality (Fig. 47.6). Custom blocking with apertures can also be used to sharpen the penumbra but may not be necessary for some applications of pencil-beam scanning. Scanned beams may be delivered with single-field uniform doses (SFUD) where each field covers the target uniformly or using multi-field intensity-modulated proton therapy (IMPT) maps determined from inverse planning optimization. IMPT may be preferred for patients with irregularly shaped tumors, who would similarly benefit from IMRT treatments over forward-planning 3D conformal radiation therapy, with the added advantage of using protons to further spare dose to neighboring critical structures.

Proton therapy can also be used for radiosurgery. At the Massachusetts General Hospital, a fixed stereotactic single-scattering beamline used with a minimal penumbra can deliver highly accurate doses to intracranial tumors, such as brain metastases, arteriovenous malformations, pituitary adenomas, meningiomas, and vestibular schwannomas [52].

In the treatment planning process, there are several ways to account for uncertainty that are unique to proton therapy

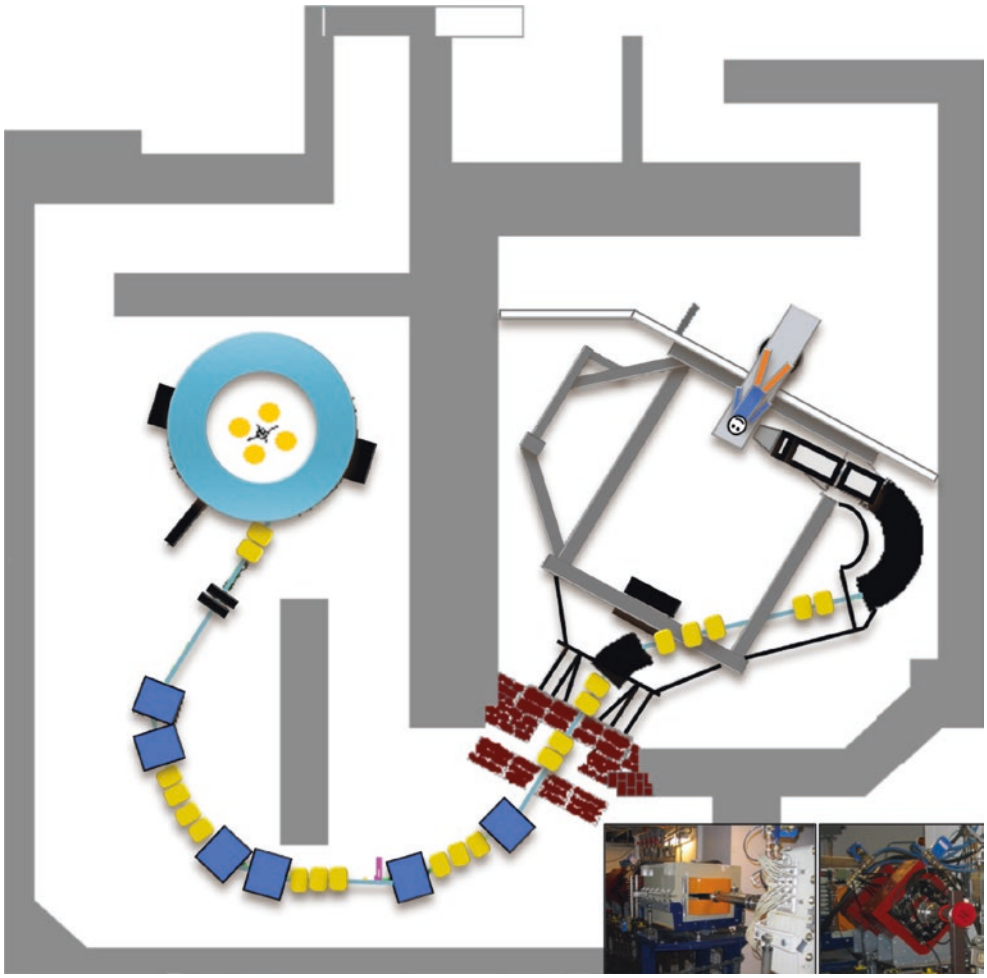

Fig. 47.5 Layout for a shielded single gantry system. Protons are extracted from the cyclotron and degraded to the desired energy before they are transported through a vacuum pipe to the treatment room. Dipole bending magnets (blue; left image insert) deflect the beam by degrees requiring refocusing with the aid of multiple quadrupole magnets (yellow; right image insert). The 35 ton gantry assembly includes two large bending magnets which direct the proton beam to the treatment head which can pivot 360° about isocenter

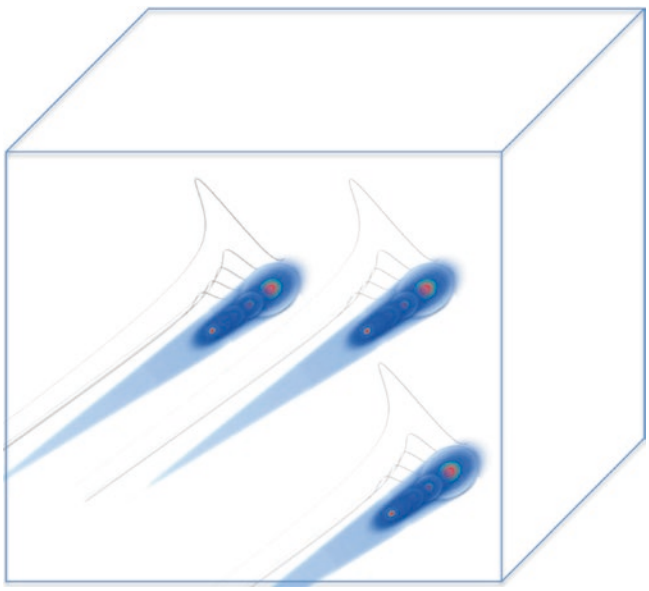

Fig. 47.6 The pencil-beam treatment head replaces the modulation wheel and scattering elements with fast-responding scanning magnets which are used to deflect un-scattered pristine peaks from the nominal beam-eye-view axis (x, y). A treatment plan provides the map defining the location (x, y, depth) of the individual peaks required to achieve a desired dose distribution. The irradiation sequence is performed one energy layer at a time. Changing the system's energy requires a brief pause in the irradiation

[53]. Variations in patient setup, organ and tumor motion, image guidance, tumor localizations, and uncertainties in dose calculations must be minimized. Adequate margins should be added to the tumor volume, but large margins lose the advantage of sparing normal tissue. In addition to range uncertainty originating from daily setup variations, there is also inherent uncertainty in the conversion of CT Hounsfield numbers to proton stopping power. Some institutions may assess target coverage using a uniform PTV expansion, but corrections should be applied on a per beam basis.

Each proton beam is known to have a degree of uncertainty regarding the range, and dosimetric calculations and distributions must take these uncertainties into account. These uncertainties can be mitigated using a "smearing technique" where the compensator dimensions are adjusted within the range of uncertainty to ensure target volume coverage.

Typical Dose Distribution

Dose distributions for proton therapy generally are characterized as more conformal as compared to photons with virtually no dose distal to the target per beam, as previously described. This may be varied, depending on the geometry of the tumor, the specifications of the plan, and

whether or not the patient is receiving passively scattered proton therapy or pencil-beam scanning. There have been studies that attempt to characterize and model the dose distribution of these various modalities [54–58]. However, special attention must be given to consider neutron dose distribution, which is unique to proton dosimetry and may be underestimated if dose from protons alone is accounted [59].

Dose Specification

For patients treated with fractionated passive-scattering proton therapy, like 3D photon therapy, prescription doses of radiation therapy are generally prescribed to the center of the spread-out Bragg peak [60]. For patients treated with pencil-beam scanning, the dose is prescribed to the volume because of the complexity of the dose distributions. The same is true for proton radiosurgery, where a GTV/CTV and PTV are delineated, and the dose is prescribed to the PTV, to maintain consistency with photon radiosurgery dose specifications.

Quality Assurance

Institutions should follow IAEA TRS-398 and ICRU Report 59 for absolute dosimetry characterization and undergo annual independent verification by an accredited laboratory [61, 62]. General quality assurance (QA) recommendations are provided by the ACR and AAPM [63]. However, there are currently no formal AAPM task group report for proton therapy. In absence of comprehensive quality assurance recommendations, references used for photon therapy should be used for guidance. Examples of such references include AAPM reports TG-142 (quality assurance of medical accelerators), TG-54 (stereotactic radiosurgery), TG-100 (application of risk analysis methods to radiation therapy quality management), TG-135 (quality assurance for robotic radiosurgery), TG-101 (stereotactic body radiation therapy), TG-179 (quality assurance for image-guided radiation therapy using CT-based technologies), TG-147 (quality assurance for non-radiographic radiotherapy localization and positioning systems), and TG-53 (quality assurance for clinical radiotherapy treatment planning). Similarly, IAEA 1583 (Commissioning of Radiotherapy Treatment Planning Systems: Testing for Typical External Beam Treatment Techniques) as well as the various AAPM/ACR and ASTRO/ACR practice guidelines should be reviewed [64–70].

As with Linac-based equipment, a comprehensive quality assurance program involves daily, monthly, and annual checks. Daily quality assurance is completed prior to the first patient treatment and may differ depending on the treatment delivery system. For passive scattering, the machines can be tested both in service mode with a range verifier installed in the nozzle that can be used to verify first and second scatterers, timing of modulator wheels, and beam range. Treatment mode can be verified using an ion chamber and Lucite phantom to measure dose outputs for standard fields spanning various equipment settings. More comprehensive dose measurements can be performed using planar ion chamber arrays. Daily QA also incorporates other checks including but not limited to safety interlocks, imaging alignment, and audio/visual monitoring systems. Monthly quality assurance expands on the daily checks, verifying beam range, modulation, field flatness, and symmetry for a fixed set of fields that spans the full set of equipment settings. Proton versus X-ray field coincidence is also measured at regular intervals. Annual QA significantly expands on daily and monthly QA. As with 3D conformal photon plans, individual measurements may not be necessary if an independent verification system is used. However, beam-modifying hardware such as apertures and compensators must be subjected to a QC process.

For individual pencil-beam scanning, patient fields, dose profiles at two to three depths are verified in phantom. A quality assurance program similar to passive scattering, encompassing daily, monthly, and annual checks ensures delivery constancy. In addition to those items described for passive scattering, beam spot position, size, and dose is monitored.

Case Study

A patient is a 55-year-old woman with no significant past medical history, who initially presents with diplopia and right facial nerve numbness in the V2 and V3 distribution. She undergoes MRI of the brain which demonstrated a complex skull base well-circumscribed and enhancing lesion of the suprasellar, cavernous sinus, sella, Meckel's cave, and petroclival region with spillage into the posterior fossa. The image is consistent with a meningioma. She then undergoes transsphenoidal surgery as well as a right suboccipital craniotomy, with final pathology demonstrating a WHO grade 2 meningioma with prominent nucleoli, architectural sheeting, foci of necrosis, and Ki-67 of 12.4%. Postoperatively, an MRI shows 40% debulking of the tumor beneath the sella in the prepontine cistern and stable component inferior to the right of the chiasm, right of Meckel's cave, and residual tumor in the dorsum of the sella turcica (Fig. 47.7).

She is referred for consultation with radiation oncology, and full history and physical are reviewed. At the treating physician's discretion, several factors are considered, including aggressive pathology, no clinical comorbidities that suggest competing risk, relatively young age, and

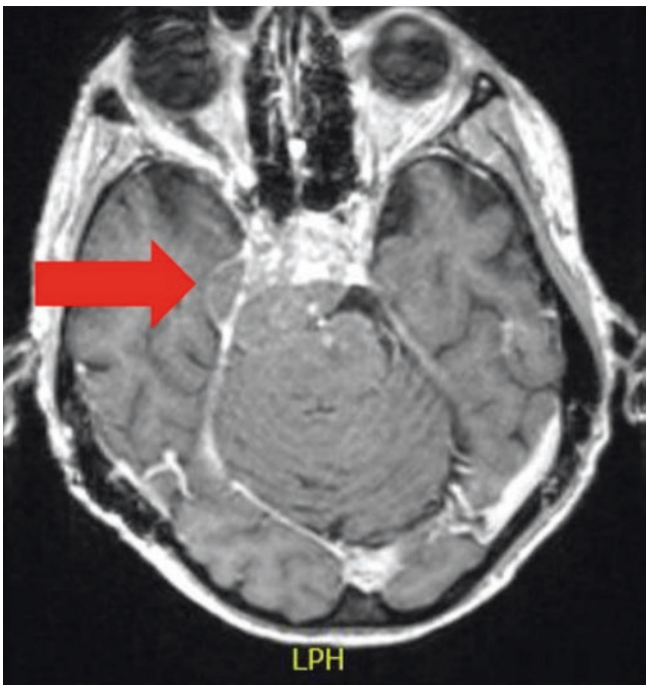

Fig. 47.7 Preoperative and postoperative MRI of a patient

proximity of the tumor to critical structures that are important for the patient's quality of life. Given these considerations, the treating physician discusses external beam therapy options with the patient, including photon versus proton irradiation, and delineates potential geometric advantages and also discloses that there is no level I evidence that protons are superior to photons but the dosimetric difference is compelling in favor of protons as a safer treatment modality (Fig. 47.8). Furthermore, the patient is eligible for a clinical trial, and she expresses interest in participating.

The patient is then presented to a multidisciplinary team, including other physicians, physicists, and administrative staff, and the case is reviewed for potential benefit of proton therapy. At this meeting, scans are evaluated by physicists to best choose a treatment delivery modality based on size and projected geometry. Physicians examine the clinical history to determine appropriateness of allocation of proton therapy. Schedulers examine wait times for the machines and prioritization of other cases. Enrollment on a clinical trial and contribution to general medical knowledge are also given importance in consideration of allocation of proton therapy. For all of these reasons, the patient is ultimately deemed to

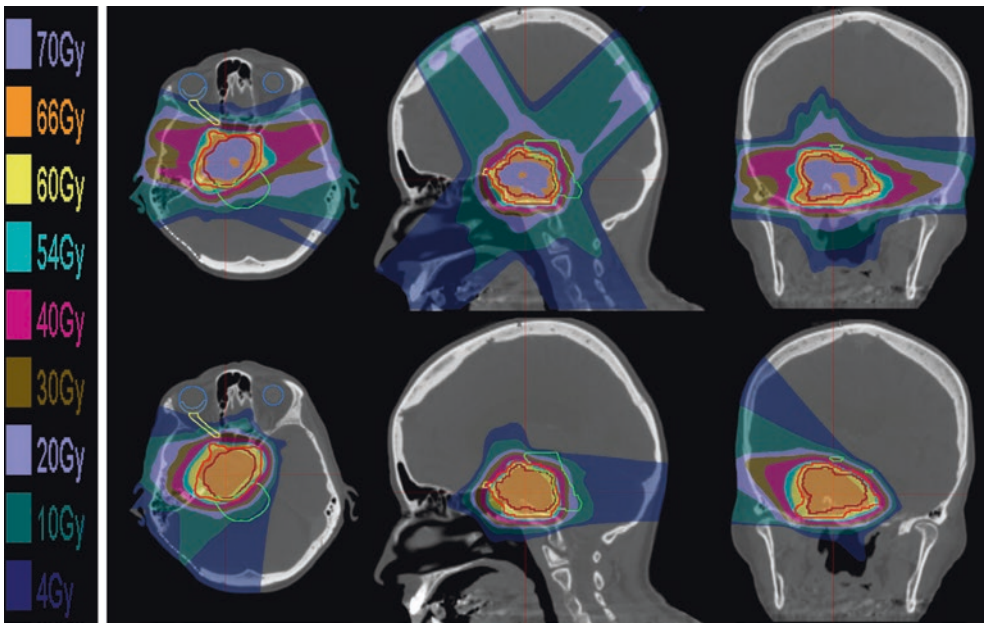

Fig. 47.8 Comparison of an IMRT (top) and passively scattered proton plan (bottom) for a complex atypical skull base meningioma. The clinical goals included coverage of the target with 59.4 Gy(RBE) with an integrated simultaneous boost to 66 Gy(RBE) to the GTV while limiting the brainstem surface to 66 Gy(RBE), brainstem center to 54 Gy(RBE), optic nerves and chiasm to 60 Gy(RBE), cochlea to 45 Gy(RBE), retina to 45 Gy(RBE), and mean lacrimal glands to 26 Gy(RBE)

be appropriate for proton therapy and is appropriately scheduled as a medically nonurgent case.

She undergoes placement of three stainless steel fiducials using local topical anesthetic for target localization. She undergoes CT simulation in the supine position. A modified GTC head frame is used for immobilization. Using treatment planning software, recent MRI is fused with the planning CT to aid in target delineation. The treating physician delineates target volumes, and a dedicated anatomist contours neighboring normal tissue critical structures.

Based on these contours, proton-specific planning software is used to generate a proton stereotactic fractionated radiation therapy plan using a single-scattering, passive-scattering, or scanning system. Custom apertures and compensators are fabricated. Treatment planning is executed with prioritization of gross tumor volume coverage, and limiting dose to critical structures under their respective tolerances. A physics peer review is performed before presenting the plan to the physician. Once approved, these plans are then reviewed in chart rounds for broader peer review quality assurance, and the treatment is delivered. Patients are monitored throughout the course of the treatment by nursing staff and undergo weekly treatment management visits with the physician. After the completion of the treatment course, the patient is then closely followed for long-term treatment toxicity and tumor stability.

This case highlights several of the complexities of treating a patient with proton therapy. Clinicians must use stringent clinical criteria to evaluate the appropriateness of resource allocation but allow for some flexibility, given the unique nature of certain cases, and this requires a priori knowledge of the potential benefits of proton therapy. Her enrollment on a clinical trial will also allow the medical community to learn more about the capabilities of proton therapy.

Special Considerations

There is a great deal of controversy surrounding the use of proton therapy, primarily arising from the high capital cost. Cost ratios per fraction of proton therapy compared to IMRT are the same in 2016 as in 2003: 2.34 times that of IMRT [71]. With the increased number of proton centers being deployed, there have been multiple discussions regarding the utility, the cost-effectiveness, and the appropriate indications for proton therapy. Even in institutions where proton therapy is readily available and used regularly, there is a sense of guardianship over proton therapy as a limited resource, given the high costs. There have been some attempts to study the absolute costs of proton radiation therapy. The subjective arguments range from never using it at all on the basis of cost, using it judiciously and cautiously, and using it more generously with the intent to clarify clinical indications for which the costs are worth it[72–74]. One cost-effectiveness study attempted to model the costs associated with the quality-adjusted life years across four groups of patients: left breast cancer, prostate cancer, head and neck cancer, and childhood medulloblastoma [75]. In this model, they argue that the capital costs may be worth the investment to treat certain patients on the basis of cost alone. As more prospective research comparing proton therapy and standard photon therapy emerge, and toxicity data is quantified, stronger evidenced-based data may emerge that ultimately favor the use of proton therapy for certain indications on the basis of quality of life and cost, while limiting its use when clinically equivalent and wasteful. While rigorous study remains an academic priority, further innovation may make proton therapy less expensive to deliver in the future, obviating much of this controversy.

Summary

- Proton therapy has been in clinical use for over 50 years, with several clear physical advantages that improve conformality of radiation dose delivery.
- Proton therapy applied for adult CNS indications is most commonly rationed for patients with benign disease or malignant disease adjacent to critical radiation-sensitive structures that can be spared by the use of protons.
- Proton therapy may allow patients to more safely and feasibly undergo re-irradiation.
- There is a need for further level I evidence to characterize the potential clinical benefits of proton therapy compared to photon therapy.

- Patients require special consideration for immobilization for proton intracranial irradiation.
- Proton treatment planning and delivery are complex and can either employ the use of passive-scattering or pencil-beam scattering technology.
- Typical dose distributions of proton therapy depend on the tumor, anatomical site, and plan but generally result in more conformal plans, although the role of neutron scatter must not be ignored.
- There are specific quality assurance guidelines that can be used to ensure maximally safe proton treatment delivery.
- Proton therapy has high capital costs, and cost-effectiveness research is ongoing to identify indications for which it would be financially sustainable.
- Well-selected patients may undergo a complex selection and treatment planning process, resulting in potentially beneficial treatment option with proton therapy and which merits future studies.

Self-Assessment Questions

1. Proton therapy differs from photon therapy in that:
   A. Protons have a lower RBE.
   B. Protons have increased distal conformality.
   C. Protons are less laterally conformal.
   D. Protons are universally accepted as better treatment for pediatric patients.

2. Which patient might be a suitable candidate for proton therapy?
   A. A 92-year-old gentleman with widely metastatic melanoma with numerous intracranial lesions.
   B. A 51-year-old woman with metastatic breast cancer with diffuse leptomeningeal disease.
   C. A 33-year-old gentleman with NF1 who presents with a low-grade glioma of the cerebellum.
   D. A 63-year-old woman with metastatic lung cancer with a single hemorrhagic brain metastasis in her frontal lobe.

3. Which patient would NOT be a suitable candidate for proton therapy?
   A. A 34-year-old woman with residual functional pituitary adenoma after surgery
   B. A 52-year-old gentleman with an acoustic neuroma with gradual hearing loss
   C. A 21-year-old woman with medulloblastoma
   D. A 75-year-old woman with a completely resected frontal WHO grade I meningioma

4. The following quality assurance guidelines can be used for absolute dosimetry of standard fractionated proton delivery:
   A. No guidelines are available yet, as proton therapy is still a novel technology.
   B. AAPM TG-54.
   C. IAEA TRS-398.
   D. AAPM TG-170.

5. True or false: Full-dose proton therapy can always be used for patients with recurrent disease after prior definitive radiation therapy.

Answers

1. B
   Protons have higher RBE, increased distal and lateral conformality, and are considered to be potentially beneficial for pediatric patients, although this is not universally accepted.
2. C
   Patients who are younger and may live to see radiation toxicity, including secondary malignancy, should be considered for proton therapy. Older patients with poor prognoses or patients with diffuse disease who have less to benefit from proton radiation dosimetrically are less compelling to be treated with costly and limited technology with unlikely benefit.
3. D
   The patient may be closely observed and can likely be treated with photons without concern for radiation-related toxicity or development of secondary malignancy
4. C
   IAEA TRS-398 can be used. TG-54 is for radiosurgery quality assurance.
5. False
   For patients with in-field recurrences, proton therapy may not necessarily be safely feasible

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