CHAPTER

19 Charged Particle Radiotherapy

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Interest in the use of charged particle radiotherapy derives from the superior dose distributions that can be achieved with these particles compared with those produced by standard photon therapy techniques, as well as the potential for higher biological effect in the tumor with heavier charged particles. Charged particles deposit energy in tissue through multiple interactions with electrons in the atoms of cells, although a small fraction of energy is also transferred to tissue through collisions with the nuclei of atoms. The energy loss per unit path length is initially relatively small and constant until near the end of the range where the residual energy is lost over a short distance, resulting in a steep rise in the absorbed dose (energy absorbed per unit mass). This portion of the particle track, where energy is rapidly lost over a short distance, is known as the *Bragg peak* (Figure 19-1).

The initial low-dose region in the depth-dose curve, before the Bragg peak, is referred to as the plateau of the dose distribution and delivers about 30% of the Bragg peak maximum dose. The Bragg peak is too narrow for practical clinical applications. For the irradiation of most tumors, the beam energy is modulated to achieve a uniform dose over a significant volume. This has traditionally been accomplished by superimposing several Bragg peaks of descending energies (ranges) and weights to create a region of uniform dose over the depth of the target; these extended regions of uniform dose are called *spread-out Bragg peaks* (SOBP; see Figure 19-1 and Techniques of Proton Delivery section). Although the SOBP beam modulation does increase the entrance dose, the proton dose distribution is still characterized by a lower-dose region in normal tissue proximal to the tumor, a uniform high-dose region in the tumor, and zero dose beyond the tumor. The protons are distributed laterally through the target volumes by a passive scattering foil, collimated with brass apertures, and contoured distally with customized range compensators to compensate for proton range differences from variable proton absorption by tissues of different radiologic density.

Increasingly, charged particle therapy is being delivered by raster scanning a pencil beam of charged particles through the deepest slab of the target volume, then reducing the energy of the particle beam and repeating the process iteratively through the target volume. The pencil beam scanning technique delivers lower proximal dose than the traditional SOBP modulation with passive scattering, can eliminate the need for machining customized apertures and range compensators, and provides greater flexibility in dose delivery including dose painting and intensity modulation.

Charged particles are generally characterized as having either high or low linear energy transfer (LET), which is the rate of energy loss by the particle in tissue. The LET influences the biologic impact of the energy deposited in tissue. X and gamma photons, protons, and helium ions are considered to be forms of low LET radiation. Heavier charged particles (e.g., neon ions, carbon ions) are considered to be forms of high LET radiation. There is an initial increase in the relative biologic effectiveness (RBE) with an increase in LET.[1] Carbon ions have an RBE of about 3, whereas the recommended RBE of protons is 1.1.[2] Higher-LET radiation is less influenced by tissue oxygenation and less sensitive to variations in the cell cycle and DNA repair. For particle radiation, the Gray equivalent dose is calculated by multiplying the physical dose administered by the RBE for that particle; the recommended nomenclature for expressing the dose is Gy(RBE) = physical dose in Gy × RBE.[3]

DEVELOPMENT OF PROTON BEAM RADIOTHERAPY

The vast majority of patients receiving charged particle therapy have been treated with protons. As of December 2012, more than 78,000 patients had received part or all of their radiotherapy by proton beams.[4] Table 19-1 lists currently operational proton beam treatment facilities worldwide. Multiple sites are scheduled to begin using proton beam therapy over the next several years.

In 1946, Robert Wilson proposed that proton beams would provide superior dose distributions over photons and should be considered for clinical radiotherapy.[5] Initially, patients were being treated at facilities designed and constructed for basic high-energy physics research, and this often meant that treatment delivery was cumbersome. The proton beams were limited to a fixed horizontal position, which meant that the patient had to be moved to align the tumor on the trajectory of the beam. This technique was in contrast to the isocentric capabilities of the modern linear accelerator, which rotates around a point in space and can effectively target any site in the body. In addition, for many of the proton machines, the energy of the beam (which defined the depth of the Bragg peak) was only sufficient to treat superficial lesions (such as those of the eye) or intermediate-depth lesions (such as those at the base of the skull). Because of these technical factors and the interests of the involved physicians, the tumors that initially received the most attention were uveal melanomas in the eye and sarcomas at the base of the skull. The major emphasis in proton therapy clinical research initially was on dose escalation for tumors for which local control with conventional (at that time, two-dimensional) radiotherapy was poor.

The development of hospital-based cyclotrons with higher-energy beams capable of reaching deep-seated tumors (up to ~30 cm with a 235-MeV beam), field sizes comparable to those of linear accelerators, and rotational gantries has greatly facilitated proton radiation therapy. Increasingly, researchers are interested in developing protocols that will reduce morbidity at sites where tumor control with photons has proven to be beneficial. At about the same time that hospital-based cyclotrons appeared in the 1990s, intensity modulated photon radiation therapy (IMRT) emerged as a technique that also facilitated dose escalation. IMRT may produce comparable or even higher conformality of the prescription dose compared to passively scattered protons, although the integral dose with protons may be ~50% to 60% lower. Intensity modulated proton radiation therapy (IMPT) can theoretically match the conformality of IMRT in the high-dose prescription volume while simultaneously reducing the integral dose, although making IMPT robust in the face of range and setup uncertainties requires careful treatment planning. For pediatric patients,

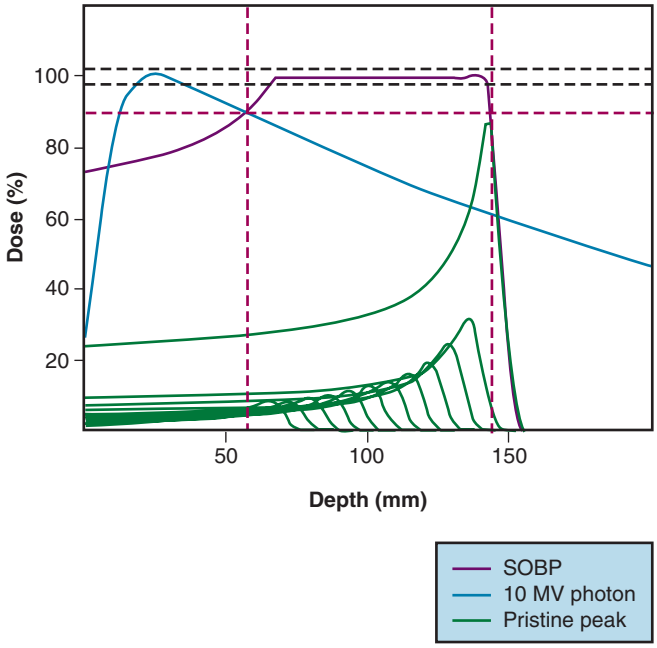

Figure 19-1 Depth-dose distributions for a spread-out Bragg peak (SOBP, *red*), its constituent pristine Bragg peaks *(green)*, and a 10-MV photon beam *(blue)*. The SOBP dose distribution is created by adding the contributions of individually modulated pristine Bragg peaks. The penetration depth, or range (measured as the depth of the distal 90% of the plateau dose), of the SOBP dose distribution is determined by the range of the most distal pristine peak. The *dashed lines (black)* indicate the clinically acceptable variation in the plateau dose of ±2%. The *dot-dashed lines (red)* indicate the 90% dose and the spatial, range, and modulation width intervals. The SOBP dose distribution of even a single field can provide complete target volume coverage in depth and lateral dimensions, in sharp contrast to a single photon dose distribution; only a composite set of photon fields can deliver an appropriate clinical target dose distribution. Note the absence of dose beyond the distal fall-off edge of the SOBP.
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the lower integral dose with protons has led many clinicians to conclude that protons are the preferred curative radiation treatment modality for children. In fact, if the cost of proton therapy were the same as photons, it has been argued that protons would also be the treatment of choice for adult patients. Because of the greater cost of accelerating and delivering protons to the tumor, however, cost and cost-effectiveness, particularly in an era of concern about rising healthcare costs, must be considered in the selection of treatment modality. Hence, the current primary focus of discussion about and research in proton radiation therapy is the magnitude of the reduction in clinical toxicity using protons (related to its lower integral dose), at which clinical sites protons provide the greatest clinical benefit and where they are cost effective, and the optimum strategy to assess the benefits in adult patients (i.e., are randomized clinical trials of photons versus protons ethical, can other comparative strategies such as registries provide valid comparisons?). A priori, large target volumes, large target volumes relative to the involved organ (i.e., eye tumors), or sensitive adjacent normal tissues (i.e., spinal cord, critical areas of the brain), particularly in young patients, would be clinical scenarios where the elimination of exit dose would seem to be most important for the use of protons but these will need to be further validated by clinical studies.

TREATMENT OF SPECIFIC CANCERS WITH PROTON BEAM RADIOTHERAPY

Ocular (Uveal) Melanoma

Uveal melanoma is the most common primary ocular tumor. Historically, the primary treatment has been enucleation. Conventional radiotherapy is an alternative to surgery but does not ensure preservation of sight because of the proximity of nearby structures such as the cornea, lens, retina, fovea, and optic nerve. Radioactive plaque therapy is also used for its dose distribution. Because preservation of vision is of utmost importance (secondary only to tumor control), particle beam therapy, with its favorable dose distribution characteristics, has increasingly been employed in the treatment of uveal melanomas.

At Massachusetts General Hospital (MGH), in cooperation with the Massachusetts Eye and Ear Infirmary, patients have undergone placement of tantalum clips to demarcate the location of the tumor for proton radiotherapy planning. When the patient is undergoing treatment, the clips can be identified by fluoroscopy to allow for accurate daily setup. Most institutions employ a fixed horizontal beam for treatment of uveal melanomas, so the patient is able to sit upright. Immobilization is achieved with a mask and a bite block. Patients are asked to stare at a small light to help set the eye position and are monitored with a video camera during treatment. Typically, a total of 70 Gy(RBE) is administered over five fractions.

As of December 2002, more than 3000 patients with uveal melanoma had been treated with protons at MGH in collaboration with the Massachusetts Eye and Ear Infirmary.[6] The 5-year actuarial local control rate was 96% for all sites within the globe, with an 80% survival rate. The probability of eye retention at 5 years was estimated to be 90% for the entire group and 97%, 93%, and 78% for patients with small, intermediate, and large tumors, respectively. Independent risk factors for enucleation were involvement of the ciliary body, tumor height greater than 8 mm, and distance between the posterior tumor edge and the fovea. These results compare favorably with the 5-year local control rates of 93% reported with protons in Nice, France,[7] and 98.9% from the Paul Scherrer Institute in Villigen, Switzerland.[8]

Because some patients have experienced deteriorating vision after doses of 70 Gy(RBE), a randomized trial of 50 Gy(RBE) versus 70 Gy(RBE) for small and intermediate-sized lesions located within 6 mm of the optic disc or macula was conducted. Interim analysis of 188 patients, with a median follow-up of 60 months, suggested no reduction in either local control or survival rates. No significant improvement in visual outcome or complications has been observed. However, visual field analysis does show a smaller mean defect in the patients randomized to 50 Gy(RBE).[9] Hence, smaller posterior tumors that are near the macula or optic disc can be treated with 50 Gy(RBE).

Egger et al[10] reported long-term results of eye retention after treatment of uveal melanoma with proton beam therapy. A total of 2645 patients (2648 eyes) were treated at the Paul Scherrer Institute between 1984 and 1999. The overall eye retention rate at 5, 10, and 15 years after treatment was 89%, 86%, and 83%, respectively. Enucleation was related to large tumor size (mainly, tumor height), male gender, high intraocular pressure, and large degree of retinal detachment at treatment time.

Sarcomas of the Skull Base and Spine

Treatment of patients with sarcoma of the skull base is challenging because of the proximity of critical structures, notably, the brain, brainstem, cervical cord, optic nerves, and chiasm.

TABLE 19-1 Particle Therapy Facilities Currently in Operation

Facility	Particle	First Patient	Patient Total	Date of Total
Tri-University Meson Facility (TRIUMF), Vancouver, Canada	Protons	1995	170	December 2012
WPTC, Wanjie, China	Protons	2004	1,078	December 2012
Lanzhou, China	Carbon	2006	194	December 2012
Clatterbridge, England	Protons	1989	2297	December 2012
CAL, Nice, France	Protons	1991	4,692	December 2012
Center for Proton Therapy, Orsay, France (CPO)	Protons	1991	5,949	December 2012
Hahn-Meitner Institute (HMI), Berlin, Germany	Protons	1998	2,084	December 2012
RPTC, Munich, Germany	Protons	2009	1,377	December 2012
HIT, Heidelberg, Germany	Carbon, protons	2010	1,232	December 2012
Instituto Nazionale di Fisica Nucleare–Laboratori Nazionali del Sud (INFN-LNS), Catania, Italy	Protons	2002	293	November 2012
(CNAO) Pavia, Italy	Protons	2011	53	November 2012
Heavy Ion Medical Accelerator (HIMAC), Chiba, Japan	Carbon ions	1994	7,331	January 2013
National Cancer Center (NCC), Kashiwa, Japan	Protons	1998	772	December 2010
Hyogo Ion Beam Medical Center (HIBMC), Hyogo, Japan	Protons	2001	3,198	December 2011
Hyogo Ion Beam Medical Center (HIBMC) Hyogo, Japan	Carbon ions	2002	1,271	December 2011
PMRC, 2, Tsukuba University, Japan	Protons	2001	2,516	December 2012
Shizuoka, Japan	Protons	2003	1,365	December 2012
Koriyama-City, Japan	Protons	2008	1,812	December 2012
Gunma, Japan	Carbon	2010	537	December 2012
MMRI, Ibusuki, Japan	Protons	2011	490	December 2012
Seoul, Korea	Protons	2007	1,041	December 2012
Krakow, Poland	Protons	2011	15	December 2012
ITEP, Moscow, Russia	Protons	1969	4,300	December 2012
St. Petersburg, Russia	Protons	1975	1,386	December 2012
JINR, 2, Dubna, Russia	Protons	1999	922	December 2012
iThemba LABS, South Africa	Protons	1993	521	December 2011
Uppsala, Sweden (2)	Protons	1989	1,267	December 2008
Paul Scherrer Institute, Villigen, Switzerland	Protons	1984	7,045	December 2012
Crocker Nuclear Laboratory, University of California, San Francisco	Protons	1994	1,515	December 2012
LLUMC, Loma Linda University, California	Protons	1990	16,884	December 2012
MPRI, 2, Bloomington, Indiana	Protons	2004	1688	December 2012
NPTC, Boston, Massachusetts	Protons	2001	1,688	December 2012
MDACC, Houston, Texas	Protons	2006	3,909	December 2012
University of Florida, Jacksonville, Florida	Protons	2006	4272	December 2012
ProCure, Oklahoma City, Oklahoma	Protons	2009	1,045	December 2012
University of Pennsylvania, Philadelphia, Pennsylvania	Protons	2010	1,100	December 2012
ProCure, New Jersey	Protons	2012	137	December 2012
CDH, Warrenville, Illinois	Protons	2010	840	December 2012
Hampton, Virginia	Protons	2010	489	December 2012

Courtesy of Martin Jemann, PTCOG Secretary.

Accordingly, surgery and conventional photon therapy have not been successful at controlling these tumors. Because of the necessity of delivering the dose in a precise manner, the use of proton therapy is becoming the treatment of choice for these tumors.

At the Harvard Cyclotron Laboratory, MGH, physicians used a combination of protons and photons to treat patients with tumors of the skull base and cervical spine.[11] A total of 169 patients with chordoma and 165 patients with chondrosarcoma were treated. The 10-year local control rate was highest for chondrosarcomas, intermediate for males with chordomas, and lowest for females with chordoma (94%, 65%, and 42%, respectively). For cervical spine tumors, 10-year local control rates were not significantly different for chordomas and chondrosarcomas (54% and 48%, respectively), nor was there any significant difference in local control rates between males and females. In a Cox multivariate analysis, predictors of local control included gender and equivalent uniform dose, or gender and target volume, or gender and minimum target dose.[12] Five-year actuarial rates of endocrinopathy were as follows: 72% for hyperprolactinemia, 30% for hypothyroidism, 29% for hypogonadism, and 19% for hypoadrenalism. The minimum target dose (Dmin) to the pituitary gland was found to be predictive of endocrinopathy: Patients receiving 50 Gy(RBE) or more at Dmin to the pituitary gland had a higher incidence of and greater severity of endocrine dysfunction. Posterior pituitary dysfunction, represented by vasopressin activity with diabetes insipidus, was not observed.[13]

Between 1998 and 2005, 64 patients with skull base chordomas (42 patients) and chondrosarcomas (22 patients) were treated at the Paul Scherrer Institute with protons using a spot-scanning technique.[14] Patients with chordoma received a mean dose of 73.5 Gy(RBE) (range, 67 Gy[RBE] to 74 Gy[RBE]), and patients with chondrosarcoma received a mean dose of 68.4 Gy(RBE) (range, 63 Gy[RBE] to 74 Gy[RBE]). With a mean follow-up of 38 months, actuarial 5-year local control rates were 81% and 94% for chordomas and chondrosarcomas, respectively. The actuarial 5-year rate for freedom from high-grade toxicity was 94%.

Torres et al[15] performed a planning study where they compared three-dimensional (3D) conformal proton (PR) therapy, IMRT with photons (PH), and combined proton and IMRT photon (PP) irradiation of skull-base chordomas to determine the optimal technique. For each of five patients, they generated four treatment plans: (1) an IMRT plan with a 1-mm planning target volume (PH1) for stereotactic treatment; (2) an IMRT plan with a 3-mm planning target volume (PH3) for routine treatment; (3) a PR plan with beam-specific expansion margins on the clinical target volume; and (4) a plan for PP treatment. The mean percentage of planning target volume (%PTV) receiving the prescription dose of 74 Gy(RBE) was highest in the PP plans and lowest in the PH3 plans. The PR plans were the least homogeneous and conformal. The PH3 plans had the highest mean percentage of volume (%V) of brain, brainstem, chiasm, and temporal lobes above the tolerance dose for those organs. The PH1 plans had the lowest brainstem mean %V receiving 67 Gy(RBE) and temporal lobe mean %V receiving 65 Gy(RBE). Global evaluation of the plans based on objective parameters revealed that the PP plans yielded the best target coverage and conformality. This study indicates that there may be dosimetric advantages to using a combination of IMRT and 3D protons, to optimize conformality and minimize integral dose, which may be an important option until intensity-modulated proton therapy is more widely available.

As with skull-base tumors, treatment of spinal and paraspinal tumors is complicated by the proximity of the spinal cord. Radiation tolerance of the spinal cord is generally quoted at 45 Gy to 50 Gy, well below the doses necessary to reliably control most sarcomas: doses of approximately 60 Gy are needed for subclinical microscopic disease, 66 Gy for tumors with microscopically positive margins, and more than 70 Gy for gross residual disease. Proton radiotherapy, with its ability to spare adjacent tissues, offers advantages for treatment of tumors in these locations.

Hug et al[16] presented results on combined photon/proton treatment of 47 patients with osteogenic and chondrogenic tumors of the axial skeleton. Radiation was delivered postoperatively in 23 patients, preoperatively and postoperatively in 17 patients, and as the sole treatment in 7 patients. Mean radiation doses of 73.9 Gy(RBE), 69.8 Gy(RBE), and 61.8 Gy(RBE), respectively, were delivered to group 1 (20 patients with recurrent/primary chordoma or chondrosarcoma), group 2 (15 patients with osteogenic sarcoma), and group 3 (12 patients with giant cell tumors, osteoblastomas, or chondroblastomas). Five-year actuarial local control and survival rates for patients with chondrosarcoma were 100% and 100% and with chordoma, 53% and 50%. The actuarial 5-year local control rate for patients with osteosarcoma was 59%. The 5-year actuarial local control and survival rates for the group 3 patients were 76% and 87%. Overall, improved local control was noted for patients with primary versus recurrent tumors, those who underwent gross total resection, and those who received target doses of more than 77 Gy(RBE).

At the Francis H. Burr Proton Therapy Center at MGH, a Phase II study was conducted of combined photon and proton beam radiation therapy, with or without surgical resection, for patients with spinal and paraspinal sarcomas.[17] Doses of 77.4 Gy(RBE) at 1.8 Gy(RBE) per day were used for patients with gross residual disease and 70.2 Gy(RBE) for patients with microscopic residual disease. A total of 50 patients (29 with chordoma, 14 with chondrosarcoma, and 7 with other cancers) underwent gross total (25 patients), subtotal (12 patients) resection, or biopsy (13 patients). With a 48-month median follow-up, the 5-year actuarial local control, recurrence-free survival, and overall survival rates were 78%, 63%, and 87%, respectively. Two of 36 patients (5.6%) treated for primary tumors versus 7 of 14 patients (50%) treated for recurrent tumors developed local recurrence ($p < 0.001$). The spinal cord center dose was limited to 54 Gy(RBE) and the cord surface dose to 63 Gy(RBE) over a length of 5 cm or less. The cauda equina was constrained to 70.2 Gy(RBE), except for areas in direct contact with tumor, where the dose limit was 77.4 Gy(RBE). Five patients developed late radiation-associated complications; no myelopathy developed, but three grade 3 sacral neuropathies appeared after doses of 77.1 Gy(RBE) to 77.4 Gy(RBE) had been delivered. A recent update with median follow-up of 7.3 years, continues to show excellent local control in patients with primary tumors, with estimated local control at 8 years of 85% with an acceptable rate of grades 3 to 4 complications of 13% at 8 years.[18]

Recently, the MGH group reported the results on 24 patients treated with high-dose proton based definitive radiotherapy for unresected spinal chordomas.[19] Tumor locations included cervical (2), thoracic (1), lumbar (2), S1 to S2 (17), and S3 or below (2). Median total dose was 77.4 Gy(RBE). Analysis at median follow-up of 56 months showed overall survival of 91.7% and 78.1%, chordoma specific survival of 95.7% and 81.5%, local progression free survival of 90.4% and 79.8%, and metastases-free survival of 86.5% and 76.3%, at 3 and 5 years, respectively. Long-term side effects included eight sacral insufficiency fractures (none required surgical stabilization), one secondary malignancy, one foot drop, one erectile dysfunction, one perineal numbness, two worsening urinary/fecal incontinence, and four grade-2 rectal bleeding. None required new colostomy. All surviving patients remained ambulatory.

Optic Pathway Glioma

At Loma Linda University, seven children with optic pathway gliomas were treated with proton radiation therapy.[20] At a median follow-up of 37 months, all tumors were locally controlled. A reduction in tumor volume was seen in three patients, and tumor volume was stable in the other four. Visual acuity was stable in those who presented with useful vision. Proton plans were compared with 3D conformal photon plans for individual patients. With proton therapy there was a 47% reduction in the dose to the contralateral optic nerve. There was an 11% reduction in the dose to the chiasm and a 13% reduction in the dose to the pituitary gland. There was also a reduction in the dose to the temporal lobes and frontal lobes.

Astrocytoma

Between 1993 and 1998, 48 patients were treated for nonresectable grades II and III intracranial tumors at the Center for Proton Therapy in Orsay, France.[21] Mean tumor doses ranged from 63 Gy(RBE) to 67 Gy(RBE) at 1.8 Gy(RBE)/fraction. With a median follow-up of 18 months, local control rates were 97% (33 of 34 patients) and 43% (6 of 14 patients) for nonparenchymal and parenchymal lesions, respectively.

At the Harvard Cyclotron Laboratory (HCL) and MGH a Phase II study was undertaken to assess whether dose escalation to 90 Gy(RBE) with conformal protons and photons in accelerated fractionation twice a day would improve local tumor control and survival rates.[22] A total of 23 patients were enrolled, with ages of 18 to 70 years. Actuarial survival rates at 2 and 3 years were 34% and 18%, respectively. The median survival time was 20 months, with 4 patients alive 22 to 60 months after diagnosis. All patients developed new areas of gadolinium enhancement during the follow-up period. Histologic examination of tissues obtained at biopsy, resection, or autopsy was conducted in 15 patients. Radiation necrosis only was demonstrated in 7 patients, and their survival was significantly longer than patients with recurrent tumor. Tumor regrowth occurred most commonly in areas that received doses of 60 Gy(RBE)to 70 Gy(RBE) or less; recurrent tumor was found in only 1 patient in the group that received a dose of 90 Gy(RBE). The authors concluded that attempts to extend local control by enlarging the volume would likely be complicated by a high incidence of radionecrosis.

Benign Meningioma

Surgical resection of meningiomas is often limited by their location, which may be the sphenoid ridge, parasellar area, or posterior fossa. Likewise, radiation therapy for these intracranial tumors is complicated by the proximity of critical structures, notably, the visual system. Proton beam radiation, with its high degree of conformality, therefore would seem to be an attractive treatment modality.

Between 1981 and 1996, 46 patients with partially resected, biopsied, or recurrent benign meningiomas were treated with combined proton/photon radiation at HCL/MGH.[23] The median dose to the tumor was 59 Gy(RBE). Overall survival rates at 5 and 10 years were 93% and 77%, respectively, and recurrence-free rates at 5 and 10 years were 100% and 88%, respectively. Three patients presented with local tumor recurrence at 61, 95, and 125 months. One patient died of focal brain necrosis at 22 months. Neurologic complications, including memory deficits and hearing loss, were also seen. Four patients developed ophthalmologic toxicity. In all of these cases, the maximum dose to the optic structures was more than 58 Gy(RBE). Endocrine abnormalities following treatment were also seen.

Investigators from the Paul Scherrer Institute reported on the treatment of 16 patients with recurrent, residual, or untreated intracranial meningiomas.[24] The median prescribed dose was 56 Gy(RBE) (range, 52 Gy[RBE] to 64 Gy[RBE]) at 1.8 Gy[RBE] to 2 Gy(RBE) per fraction. Cumulative 3-year local control, progression-free survival, and overall survival rates were 91%, 91%, and 92%, respectively. No patient died of recurrent meningioma. Radiographic follow-up (median, 34 months) revealed an objective response in 3 patients and stable disease in 12 patients. The cumulative 3-year toxicity-free survival rate was 76%. One patient with an optic nerve sheath meningioma presented with sudden visual field deterioration of the ipsilateral eye 30 months after irradiation with 56 Gy(RBE). Another patient with optic nerve encasement by disease developed visual deterioration at 9 months. A third patient developed symptomatic brain necrosis 7 months after treatment. No radiation-induced hypothalamic/pituitary dysfunction was observed.

Paranasal Sinus, Nasal, and Nasopharyngeal Tumors

Mock et al[25] performed a planning comparison study of various photon and proton techniques for the treatment of paranasal sinus carcinoma. In five patients, proton plans were compared with conventional, conformal, and IMRT photon plans. The evaluations analyzed dose-volume histogram findings of the target volumes and organs at risk (i.e., the pituitary gland, optic pathway structures, and brain).

The mean and maximal doses, dose inhomogeneities, and conformity indexes for the planning target volumes were comparable for all techniques. Photon plans resulted in greater volumes of irradiated nontarget tissues at the 10% to 70% dose level compared with the corresponding proton plans. Compared with conventional techniques, conformal and IMRT photon treatment planning options similarly reduced the mean dose to the organs at risk. The use of protons further reduced the mean dose to the organs at risk by up to 65% and 62% compared with conformal and IMRT techniques, respectively.

Truong et al[26] performed a retrospective review of 20 patients with locally advanced primary sphenoid sinus malignant tumors treated between 1991 and 2005 with proton radiotherapy to a median dose of 76 Gy(RBE) to determine treatment outcome and prognostic factors. With a median follow-up of 27 months, the 2-year local, regional, and freedom from distant metastasis rates were 86%, 86%, and 50%, respectively. The disease-free and overall survival rates at 2 years were 31% and 53%, respectively. In multivariate analysis, oropharyngeal involvement ($p = 0.005$) and anterior cranial fossa invasion ($p = 0.02$) were predictive for poor disease-free survival rates. Brain invasion was predictive for decreased overall survival ($p = 0.05$). No grade 3 or 4 late visual toxicity was reported.

Three patients developed chronic nasal symptoms after radiotherapy, consisting of common toxicity criteria (CTC) grades 2 to 3 nasal obstruction secondary to fibrous adhesions. One patient required surgical removal of adhesions to relieve chronic nasal congestion. One patient with symptomatic CTC grade-2 brain toxicity experienced seizures and short-term memory loss. The seizures were controlled with anticonvulsant medications and a short course of steroids. Two patients experienced cerebrospinal fluid leakage after surgery and irradiation. One patient developed a CTC grade-2 cerebrospinal fluid leak from the external auditory canal, secondary to tumor shrinkage and erosion of the petrous temporal bone 5 months after radiotherapy. One patient developed a CTC grade-5 cerebrospinal fluid leak without evidence of tumor recurrence at 2 months after completion of radiotherapy. The patient underwent four surgical repairs, including transethmoid packing of the ethmoid and sphenoid sinuses and placement of a lumboperitoneal shunt. The patient subsequently died from infectious meningitis. Two patients had endocrinopathies that were medically corrected. The authors concluded that proton radiation therapy results in excellent local control in patients with advanced primary sphenoid sinus malignant disease. Brain invasion and involvement of the oropharynx and anterior cranial fossa were important prognostic factors. Nasal symptoms, brain injury, endocrinopathies, and cerebrospinal fluid leaks, however, complicated treatment.

At Loma Linda University, 16 patients with recurrent nasopharyngeal carcinoma were treated with conformal proton irradiation.[27] Patients had initially been treated with photon therapy at doses of 50 Gy to 70 Gy. Conformal proton boost radiation was then delivered to bring the total dose to 59 Gy(RBE) to 70 Gy(RBE). With a mean follow-up of 23 months, the 24-month actuarial overall and locoregional progression-free survival rates were both 50%. No central nervous system complications were observed. An update now includes data on 39 patients. Twenty-four-month actuarial overall and locoregional progression-free survival rates were 49% and 70%, respectively. When critical central nervous system structures were reirradiated, doses were low (0 Gy[RBE] to 22 Gy[RBE]); one patient experienced grade-4 central

nervous system side effects. Grade-3 late head and neck toxicity occurred in seven patients and grade-4 toxicity in two patients.

Acoustic Neuroma

Between 1991 and 1999, 30 patients with acoustic neuroma were treated with proton therapy at Loma Linda University.[28] Patients with useful hearing before treatment received 54 Gy(RBE) in 30 fractions, and patients without useful hearing received 60 Gy(RBE). Follow-up ranged from 7 to 98 months (median, 34 months), during which no patients demonstrated disease progression on magnetic resonance imaging (MRI) scans. Eleven patients demonstrated radiographic regression. Of the 13 patients with useful hearing before treatment, 4 (31%) maintained their hearing. No transient or permanent treatment-related trigeminal or facial nerve dysfunction was observed. Investigators are now interested in evaluating a reduction in tumor dose in an attempt to increase hearing preservation rates.

Carcinoma of the Prostate

Investigators at MGH completed a Phase III trial comparing 67.2 Gy of photons with 75.6 Gy(RBE) of combined photons/protons using a conformal perineal proton boost.[29] From 1982 to 1992, 202 patients with stage T3 or T4 prostate cancer received 50.4 Gy by four-field photons. Patients then received either 25.2 Gy(RBE) with conformal protons or a 16.8-Gy photon boost. No differences between the two groups were found in overall survival, total recurrence-free survival, or local recurrence-free survival rates. The local recurrence-free survival rate at 7 years for patients with poorly differentiated tumors (Gleason score of 9 or 10) was 85% for the proton arm and 37% for the photon arm. Rates of grades 1 and 2 rectal bleeding were higher in the proton arm (32% versus 12%), as were those for urethral stricture (19% versus 8%). Dose escalation to 75.6 Gy(RBE) by conformal proton boost led to increased late radiation sequelae but not to increased total survival rates in any subgroup. However, there was an improved local recurrence-free survival rate in patients with poorly differentiated tumors.

The Loma Linda University experience of conformal proton therapy for prostate cancer was reported[30] for 1255 patients treated from 1991 to 1997. The overall biochemical disease-free survival rate was 73%, and it was 90% in patients with an initial prostate-specific antigen (PSA) level of ≤4 ng/mL; it was 87% in patients with posttreatment PSA nadirs of ≤0.50 ng/mL. Rates dropped with higher initial and nadir PSA values.

In general, conformal proton beam radiation therapy was well tolerated; the rate of Radiation Therapy Oncology Group (RTOG) grade 3 or higher acute gastrointestinal or genitourinary morbidity was less than 1%. RTOG grade-3 late morbidity was seen in 16 patients (1%) and grade-4 late morbidity in two patients (0.2%). Late gastrointestinal toxicity included grade-3 bleeding and pain in two patients and a bowel obstruction requiring diverting colostomy in one patient. All cases of severe gastrointestinal toxicity presented within the first 2.5 years after treatment. The actuarial 5-year and 10-year rates for freedom from grades 3 and 4 genitourinary toxicity were both 99%.

Late genitourinary morbidity was seen more frequently than gastrointestinal morbidity. Fourteen patients developed grade-3 late toxicity, with eight of them having urethral strictures, followed by hematuria (four patients) and dysuria (two patients). The actuarial 5-year and 10-year rates for freedom from grades 3 and 4 genitourinary toxicity were both 99%. One patient developed necrosis of the symphysis, which was partially included in the treatment field. Because of the low incidence of grades 3 and 4 side effects, no statistically significant prognostic variables for toxicity could be found. These results, when accounting for length of follow-up, compare favorably with those of conformal photon therapy and intensity-modulated photon therapy.

MGH and Loma Linda University conducted a Phase III randomized dose escalation trial in patients with early-stage prostate cancer.[31] Between 1996 and 1999, 393 men with stage T1b to T2b prostate cancer and PSA levels of 15 ng/mL or less were randomly assigned to a total dose of either 70.2 Gy Gy(RBE) or 79.2 Gy(RBE). No patient received androgen suppression therapy with irradiation. Conformal radiation therapy was given in two phases. In phase I, conformal proton beams were used to treat the prostate alone. Either 19.8 Gy(RBE) or 28.8 Gy(RBE) was given in 1.8-Gy(RBE) fractions. In phase II, all men—regardless of trial arm—received 50.4 Gy delivered with photons in 1.8-Gy fractions to the prostate and seminal vesicles. Rates of local failure, biochemical failure, and overall survival were measured as outcomes. With a median follow-up of 8.9 years, men receiving high-dose radiation therapy were significantly less likely to have local failure, with a hazard ratio of 0.57. The 10-year American Society for Therapeutic Radiology and Oncology defined biochemical failure rates were 32.4% for conventional-dose and 16.7% for high-dose radiation therapy ($p < 0.0001$). This difference held when only those with low-risk disease (227 patients; 58% of total) were examined: 28.2% for conventional-dose and 7.1% for high-dose radiation therapy ($p < 0.0001$). There was a strong trend in the same direction for the intermediate-risk patients (144 patients; 37% of total; 42.1% versus 30.4%, $p = 0.06$). Eleven percent of patients subsequently required androgen deprivation for recurrence after conventional-dose radiation therapy compared with 6% after high-dose radiation therapy ($p = 0.047$). There remains no difference in overall survival rates between the treatment arms (78.4% versus 83.4%; $p = 0.41$). Two percent of patients in both arms experienced late grade 3 or higher genitourinary toxicity, and 1% of patients in the high-dose arm experienced late grade 3 or higher gastrointestinal toxicity. This randomized controlled trial shows superior long-term cancer control for men with localized prostate cancer receiving high-dose versus conventional-dose radiation. This dose escalation was achieved with protons without an increase in grade 3 or higher late urinary or rectal morbidity.

Given the significant cost difference and lack of level-1 evidence showing a clear clinical benefit, great controversy exists about the use of proton radiation for prostate cancer instead of conventional photon radiotherapy. Treatment planning studies and retrospective analyzes addressing these issues exist, but prospective head-to-head comparisons between the two treatment modalities are lacking. With that in mind, investigators at MGH and the University of Pennsylvania developed a multiinstitutional randomized trial comparing proton therapy to IMRT in the treatment of patients with low or low-intermediate risk prostate cancer.[32] Patients are randomized to receive 79.2 Gy in 1.8 Gy fractions via IMRT or proton beam therapy. The primary endpoint is post-treatment bowel function. Secondary outcomes to be examined include, quality of life, clinical efficacy, biological, and physics endpoints, and cost.

Just as IMRT radically changed the delivery of photon-based radiation for the treatment of prostate cancer, IMPT offers the possibility of a similar change in the future. IMPT relies on the use of spots scanning to deliver a more conformal dose distribution of radiation, with the potential for an even greater reduction of treatment-related toxicity in comparison

to passive scatter techniques.[33] Another approach being investigated is the use of anterior-oriented beams, which may overcome the issues of tissue heterogeneity brought on by treating through the hip joints.[34]

Gastrointestinal Tumors

Investigators at Tsukuba University in Japan have reported impressive long-term control and survival in 122 patients with primary hepatocellular carcinoma treated with proton radiotherapy.[35] The dose per fraction was 4 Gy(RBE) and the mean total dose was 72 Gy(RBE) (the Tsukuba group did not correct for RBE, so these doses are in physical Gray; hence, the biologically effective dose may have been up to 10% higher). The 7-year local control and survival rates were 94% and 27%, respectively. Proton irradiation did not cause clinically symptomatic changes in liver function. The only notable change observed was a transient increase in liver transaminase levels. In 2012, the group from Tsukuba published a retrospective analysis of 259 patients who received pencil beam therapy for hepatocellular carcinoma between 2001 and 2007.[36] Univariate analysis revealed a significant association between the percentage volume abnormal liver receiving a particular radiation dose and the liver function, as quantitated by the Child-Pugh score.

Investigators at MGH carried out a feasibility study for neoadjuvant hypofractionated proton therapy for pancreatic adenocarcinoma.[36] Tumor and normal tissue dosimetry was evaluated for a treatment regimen of 5 Gy(RBE) × 5 fractions. These plans were compared with IMRT plans with conventional fractionation generated for the same nine patients. Both techniques yielded plans with acceptable target volume coverage and dose homogeneity. Dose-volume histograms for the kidneys, liver, and small bowel were significantly better for the proton plans, and stomach and duodenum doses were similar.

In 2012, the M. D. Anderson Cancer Center (MDACC) group reported results of a prospective study of patients treated with proton beam therapy and concurrent chemotherapy for esophageal cancer.[37] Normal tissue toxicity was the primary focus of this study. Passive scattering protons with a two- or three-field beam arrangement were used. The median dose was 50.4 Gy. The median follow-up for survivors was 20 months. The most common grades 2 to 3 adverse events were dysphagia (43.6%), esophagitis (46.8%), fatigue (43.6%), nausea (33.9%), anorexia (30.1%), and radiation dermatitis (16.1%). There were two cases of grades 2 and 3 radiation pneumonitis and two cases of grade 5 toxicities. The pathologic complete response rate for the surgical cohort (n = 29) was 28%.

Lung Cancer

At Loma Linda University, a prospective study was undertaken to assess the efficacy and toxicity of conformal proton beam radiotherapy for 37 patients with medically inoperable non–small cell lung cancer.[38] Eligible patients had clinical stage I to IIIa non–small cell lung cancer and were not candidates for surgical resection either for medical reasons or because of patient refusal. Patients with adequate cardiopulmonary function received 45 Gy to the mediastinum and gross tumor volume with photons with a concurrent proton boost to the gross tumor volume of an additional 28.8 Gy(RBE). Total tumor dose was 73.8 Gy(RBE) given over 5 weeks. Patients with poor cardiopulmonary function received proton beam radiotherapy to the gross tumor volume only, with 51 Gy(RBE) given in 10 fractions over a 2-week period. Follow-up ranged from 3 to 45 months, with a median of 14 months. Two patients in the proton and photon arm developed pneumonitis that resolved with oral steroids; otherwise, no significant toxicities were encountered. The 2-year actuarial disease-free survival rate for the entire group was 63%; for stage I patients, the 2-year disease-free survival rate was 86% and the local control rate was 87%.

The MDACC group carried out a treatment planning study on 10 patients with stage IIIB non–small cell lung cancer.[39] Dose-volume histograms were generated for plans using IMPT, IMRT, and passive scattering proton therapy (PSPT). The IMRT cases were planned to 60 Gy to 63 Gy, and the proton cases were planned to 74 Gy. The possibility of increasing the total tumor dose with IMPT for each patient without exceeding the dose volume constraints (maximum tolerated dose) was also investigated. Compared with IMRT, IMPT showed improved tissue sparing for virtually every parameter measured, even with dose escalation from 63 Gy to 83.5 Gy, with a mean maximum tolerated dose of 74 Gy. IMPT also showed dosimetric advantages for those cases with complicated tumor anatomies.

Now open to accrual, RTOG 1308 is a Phase 3 randomized trial comparing proton versus photon radiation with concurrent chemotherapy for inoperable stage II-IIIB non–small cell lung cancer.[40] The primary objective is to compare overall survival between arms. Secondary end points will measure toxicity, quality of life, and cost effectiveness of treatment.

Pediatric Cancers

Investigators in Switzerland looked at the potential influence of improved dose distribution with proton beams compared with conventional or intensity-modulated (IM) x-ray beams on the incidence of treatment-induced secondary cancers in children.[41] Two children, one with parameningeal rhabdomyosarcoma and a second with medulloblastoma, were used as models for this study. After defining the target and critical structures, treatment plans were calculated and optimized, four for the rhabdomyosarcoma case (conventional x-ray, IM x-rays, 3D conformal protons, and IM protons) and three for the irradiation of the spinal axis in medulloblastoma (conventional x-ray, IM x-rays, 3D conformal protons). The secondary cancer incidence was estimated using a model by the International Commission on Radiologic Protection. This model allowed estimation of absolute risks of secondary cancer for each treatment plan based on dose-volume distributions for nontarget organs. Proton beams reduced the expected incidence of radiation-induced secondary cancers for the patient with rhabdomyosarcoma by a factor equal to or greater than 2, and for the medulloblastoma cases a factor of 8 to 15 when compared with either IM or conventional x-ray plans. Risks were higher for the patients with medulloblastoma because the target and radiated volumes were larger. This study underscores the concern with using radiation therapy in the treatment of pediatric cancers. It is the goal of clinicians to not only eradicate the primary tumor but also to minimize the risk of radiation-induced malignant tumors over the lifetime of these patients.

In a second MGH study, treatment plans were compared from standard 3D conformal photon therapy to intensity-modulated x-rays (IMRT) and 3D conformal protons for craniospinal axis irradiation and posterior fossa boost in a patient with medulloblastoma.[42] Substantial normal tissue sparing was realized with IMRT and proton irradiation of the posterior fossa and spinal axis (Figures 19-2 and 19-3). The dose to 90% of the cochlea was reduced from 101% of the prescribed posterior fossa boost dose from conventional x-rays to 33% and 2% from IMRT and protons, respectively. The dose to 50% of the heart volume was reduced from 72% for photons to 30% for IMRT and 0.5% for protons.

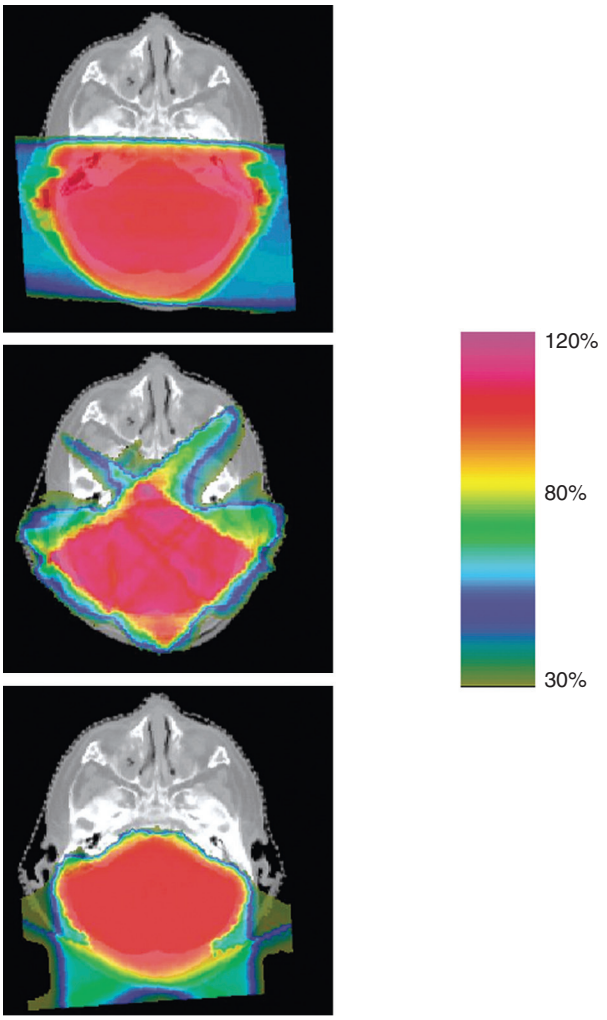

Figure 19-2 Three-dimensional conformal photon therapy *(upper panel)*, IMRT *(middle panel)*, and passively scattered proton therapy *(lower panel)* dose distributions for delivery of the posterior fossa boost in a patient with medulloblastoma. Note the absence of dose to the temporal lobes, pituitary, orbits, and cochlea that can be achieved with protons but that is not possible with three-dimensional conformal therapy or IMRT. This additional dose to nontarget normal tissues offers only potential morbidity to these young patients.
Reprinted, with permission, from St. Clair WH, Adams JA, Bues M, et al: Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. Int J Radiat Oncol Biol Phys 58(3):727–734, 2004.

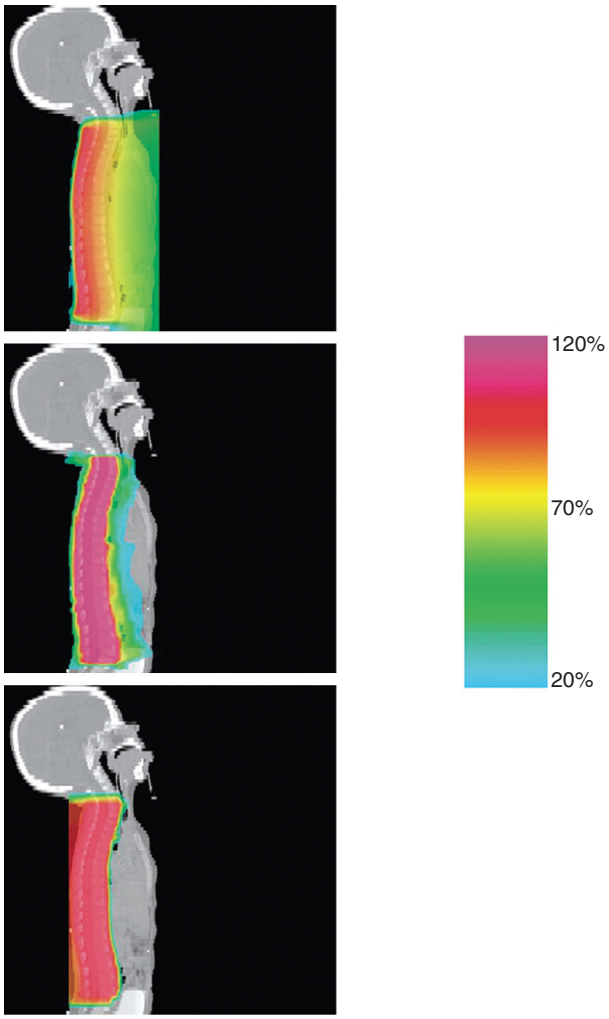

Figure 19-3 Sagittal dose displays for the spinal irradiation field in a child with medulloblastoma undergoing craniospinal irradiation with either three-dimensional conformal photons *(upper panel)*, IMRT *(middle panel)*, or passively scattered proton fields *(lower panel).* Note the absence of significant exit dose beyond the anterior border of the vertebral bodies with protons, so that the bowel, heart, and mediastinum are spared from potential side effects of radiotherapy.
Reprinted, with permission, from St. Clair WH, Adams JA, Bues M, et al: Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. Int J Radiat Oncol Biol Phys 58(3):727–734, 2004.

Merchant et al[43] modeled the dose characteristics to critical normal tissue volumes using data from patients with four types of childhood brain tumors. 3D imaging and treatment planning data, including targeted tumor and normal tissue contours, were acquired for 40 patients, 10 each with optic pathway glioma, craniopharyngioma, infratentorial ependymoma, and medulloblastoma. Dose-volume data were collected for the entire brain, temporal lobes, cochlea, and hypothalamus from each patient. The data were averaged and compared based on treatment modality (protons versus photons) using dose-cognitive effects models. Outcomes were estimated over 5 years. The results suggested that relatively small critical normal tissue volumes such as the cochlea and hypothalamus may be spared from radiation exposure when they are not adjacent to the primary tumor volume. It was found that larger normal tissue volumes such as the supratentorial brain or temporal lobes receive less of the low and intermediate doses with protons. When applied to longitudinal models of radiation dose-cognitive effects, these differences resulted in estimated clinically significant higher IQ scores for patients with medulloblastoma and craniopharyngioma and higher academic reading scores in patients with optic pathway glioma. Extreme differences between proton and photon dose distributions precluded meaningful comparison of protons and photons for patients with infratentorial ependymoma. The authors concluded that differences in the overall dose distributions, as indicated by modeling changes in cognitive function, showed that a reduction in the lower-dose volumes or mean dose with protons would have long-term, clinical advantages for children with medulloblastoma, craniopharyngioma, and optic pathway glioma.

Loma Linda University investigators evaluated the safety and efficacy of proton beam irradiation in the treatment of

pediatric patients with intracranial low-grade astrocytoma.[44] Between 1991 and 1997, 27 patients underwent fractionated proton radiation therapy for progression of recurrent low-grade astrocytoma. Patients were 2 to 18 years old. Twenty-five of the 27 patients (92%) were treated for progressive, unresectable, or residual disease following subtotal resection. The mean target dose was 55.2 Gy(RBE) (range, 50.4 Gy[RBE] to 63 Gy[RBE]) and the fraction size was 1.8 Gy(RBE). At a mean follow-up period of 3.3 years (range, 0 years to 6.8 years), 6 of 27 patients experienced local failure within the irradiated field and 4 of 27 had died. Local control and survival rates were 87% and 93%, respectively, for centrally located tumors, 71% and 86% for hemispheric tumors, and 60% and 60% for tumors of the brainstem. All children with local control maintained their performance status except one, who developed moyamoya disease. All 6 patients with optic pathway tumors and useful vision maintained or improved their visual status.

Atypical teratoid/rhabdoid tumors (AT/RT) are rare, aggressive tumors that often affect infants. Although they can occur anywhere in the body, they are frequently found in the central nervous system. Fear of significant long-term neurocognitive sequelae in this population has historically limited the use of radiation therapy. Recently, investigators at MGH published their early clinical experience for 10 consecutive patients (median age of 2.3 years) who underwent maximal resection followed by 3D-conformal proton therapy.[45] With a median follow-up of 27.3 months, 2 patients had a distant relapse; 1 patient was successfully treated with involved field irradiation and chemotherapy, whereas the second patient died of disease. At last follow-up, 9 patients were alive without evidence of disease without major radiation therapy-related toxicities.

Investigators at Loma Linda and MGH developed a proton radiation technique for the treatment of orbital rhabdomyosarcoma. The technique, along with a dosimetric analysis for two patients was recently published.[46] Dose-volume histograms were obtained for target and nontarget regions, including the lens, bony orbit, pituitary gland, optic chiasm, optic nerves, lacrimal gland, and ipsilateral frontal and temporal lobes. Doses to 90%, 50%, and 5% of lens volume were kept at less than 1%, less than 2%, and less than 8%, respectively. At a mean follow-up of 3 years, visual acuity for both patients was excellent and there was no evidence of cataract formation. Furthermore, pituitary function was normal; cosmetically, only mild enophthalmos was noticeable. The steep dose gradient beyond the orbit minimized irradiation of normal brain parenchyma, with sparing of the pituitary gland (Figure 19-4).

The MGH group recently updated their experience for pediatric patients treated with proton irradiation for intracranial ependymoma.[47] Seventy patients with localized ependymoma were treated with conformal proton radiation using at least three fields. The median age at diagnosis was 38 months (range, 3 months to 20 years). At a median follow-up of 46 months, 3-year local control, progression-free survival, and overall survival were 83%, 76%, and 95%, respectively. In a subset of patients (n = 14), mean intelligence was 108.5 at baseline and 111.3 after a mean 2.05 years of follow-up. In a larger group of patients (n = 28), overall adaptive skills were 100.1 at baseline and 100.8 after 2.21 years of follow-up. Few patients developed evidence of growth hormone deficiency, hypothyroidism, or hearing loss (Figure 19-5).

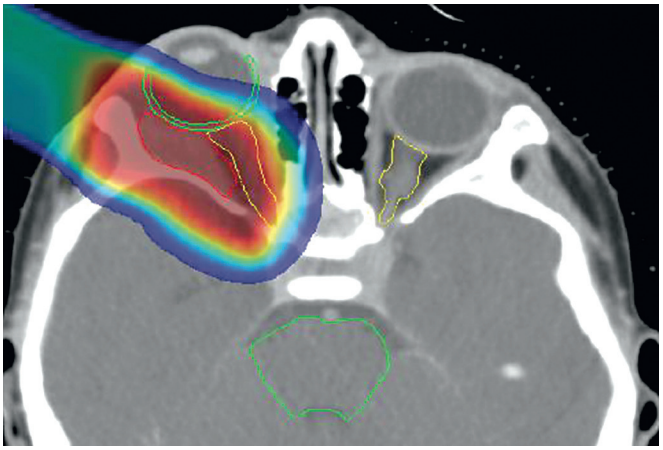

Figure 19-4 Right anterior oblique proton beam radiation therapy field for treatment of a child with a right orbital rhabdomyosarcoma. Note the absence of exit dose to the pituitary, contralateral orbit, and contralateral temporal lobe.
Courtesy Nancy Tarbell, MD, Torunn Yock, MD, and Judy Adams, CMD.

Breast Cancer

Some patients with breast cancer have anatomic configurations that make it difficult to adequately treat the breast while sparing the underlying lung and heart. A treatment planning exercise was undertaken comparing standard photon therapy with IMRT and proton therapy in the treatment of breast cancer.[48] Using computed tomography (CT) data from a patient with breast cancer, treatment plans were computed for the different treatment techniques. A dose of 50 Gy was prescribed to the target volume consisting of the involved breast and the internal mammary, supraclavicular, and axillary nodes. Comparison of plans revealed worse dose heterogeneity for the photon plan versus the other two plans. Lung dose-volume histograms for the photon and IMRT plans were comparable, whereas the proton plan showed the best sparing over all dose levels. Mean doses to the ipsilateral lung for the three plans were 17 Gy, 15 Gy, and 13 Gy, for the photon, IMRT, and proton plans, respectively. For the heart, the IMRT plan delivered the highest mean dose (16 Gy), reflecting the extra dose delivered through this organ to spare the lungs. This was reduced somewhat by the standard plan (15 Gy), with the best sparing being provided by the proton plan (6 Gy). When the IMRT plan was reoptimized with an increased precedence to the normal tissues, the mean doses to all neighboring organs at risk could be reduced but only at the cost of substantial target dose heterogeneity. Only the two-field, energy-modulated proton plan had the potential to preserve target dose homogeneity while simultaneously minimizing the dose delivered to the lungs, heart, and contralateral breast.

The MGH group recently published results of a prospective study investigating the use of proton therapy for the delivery of postmastectomy radiation.[49] The 12 patients enrolled received proton radiation to a dose of 50.4 Gy(RBE) to the chest wall and 45 Gy(RBE) to 50.4 Gy(RBE) to the regional lymphatics. The maximum skin toxicity observed was grade 2. No cases of radiation pneumonitis have been reported.

Proton therapy is also being investigated for partial breast irradiation. The Loma Linda group recently reported results of their Phase II trial.[50] Fifty patients who underwent lumpectomy for early stage breast cancer were enrolled. The median follow up was 48 months. Acute toxicities were limited to mild radiation dermatitis. Late skin toxicities included three grade 1 telangiectasias. There were no posttreatment infections or ulcerations and no cases of fat necrosis, rib fractures, radiation pneumonitis, or cardiac events. Actuarial 5-year overall survival and disease-free survival rates were 96% and 92%, respectively.

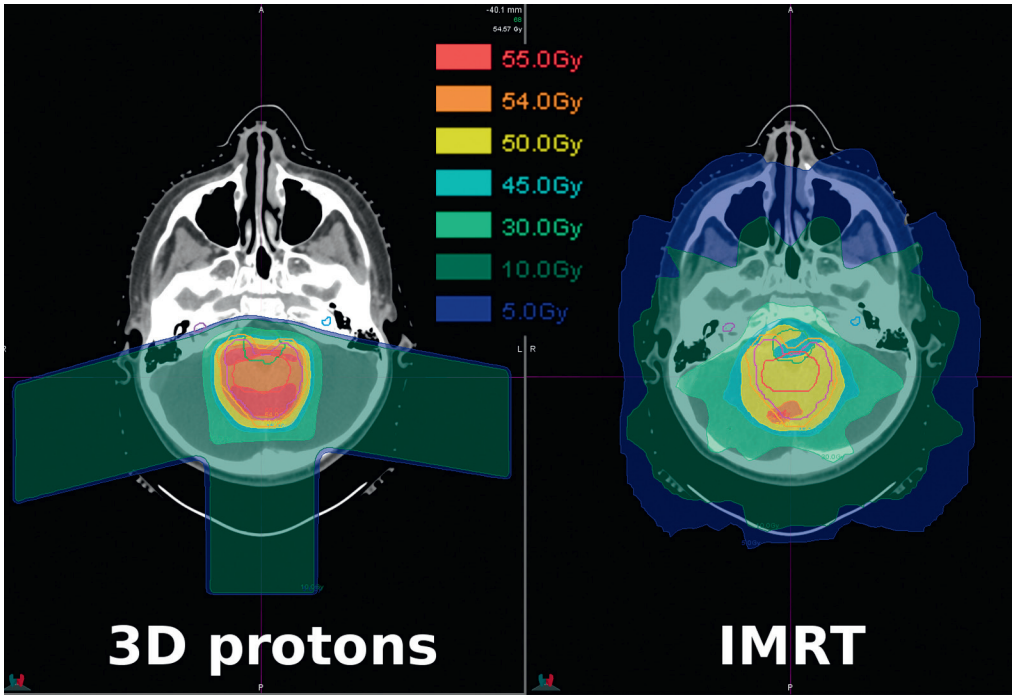

Figure 19-5 Intensity-modulated radiation therapy (IMRT) and three-dimensional proton radiation dose distributions for treatment of the posterior fossa.
Courtesy Shannon MacDonald, MD.

TECHNIQUES OF PROTON BEAM DELIVERY

Currently, most proton facilities use passive scattering for beam delivery. With this technique, a spatially uniform dose distribution is achieved by scattering and degrading the primary proton beam in a set of distributed absorbers. Passive systems use either single- or double-scattering foils. The foil is made of high-Z material such as lead, and effectively scatters the beam while keeping energy loss to a minimum. Generally speaking, double-scatter systems are preferred because larger, more uniform beams can be generated (Figure 19-6).

Beam shaping is accomplished with the use of some devices that are patient- and field-specific and some that are not. *Range modulation* refers to the concept that pristine Bragg peaks must be spread out to be clinically useful. In the passive scatter system this is done with either a propeller-shaped modulator (Figure 19-7) or a ridge filter, which is not patient-specific but may be range-specific, with a small library of range modulators available to address the different range modulator options that might be clinically desired. The Bragg peaks are spread out by placing these devices, which have variable thicknesses in the path of a given beam. The thicker the modulator, the more the beam is shifted in range.

Additional beam conformality is achieved with the use of patient-specific devices (Figure 19-8). Brass apertures are formulated to be used for a specific field for a given patient. Apertures are equivalent to the blocks used in conventional radiation therapy. In January 2010, the University of Pennsylvania Health System received approval from the Food and Drug Administration (FDA) to use multileaf collimators in their new proton facility.

A range compensator is another patient-specific beam modulator. This device is a block of plastic that is milled by a computer lathe for a specific field and is responsible for conforming the distal edge of the beam, necessary because of the variability in individual proton range secondary to differences in radiologic density in the tissue along their particular trajectory. Unfortunately, for historical reasons, a range compensator is sometimes referred to as a "bolus." But this should not be confused with the bolus that is directly applied to the patient's skin in conventional radiation therapy. This device is actually located adjacent to the brass aperture in the snout of the accelerator, above the patient.

Use of patient-specific devices that must be formulated for each beam angle is not a trivial matter in terms of labor and

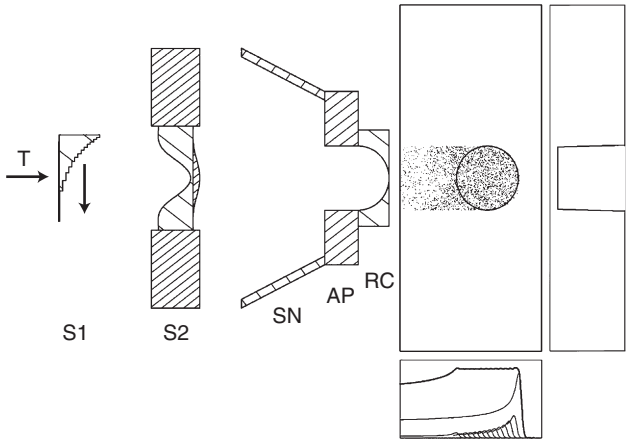

Figure 19-6 Double scattering system uses a first *(S1)* and second *(S2)* scatterer with a beamline snout *(SN)*, which shields scattered protons and permits the mounting of patient-specific apertures *(AP)* and range compensators *(RC)*. The example illustrates the effect of the range compensator in water and indicates the sharp lateral fall-off achieved by the aperture.
Reprinted with permission from Gottshalk B: Passive beam scattering. In DeLaney TF, Kooy H, editors: Proton and charged particle radiotherapy. Philadelphia, 2007, Lippincott Williams and Wilkins, Figure 5A.6, p 37.

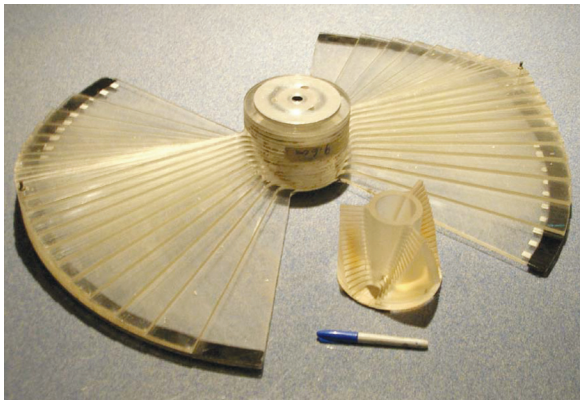

Figure 19-7 Two examples of range modulators, upstream *(small)* and downstream. Both are characterized by a "staircase" structure to achieve the differential pullback of the pristine proton beam and variable widths of the "stair steps" to achieve differential weighting of the shifted pristine peak contribution to the spread-out Bragg peaks. The downstream range modulator is large to cover the clinical area of the scattered proton beam at the downstream position.
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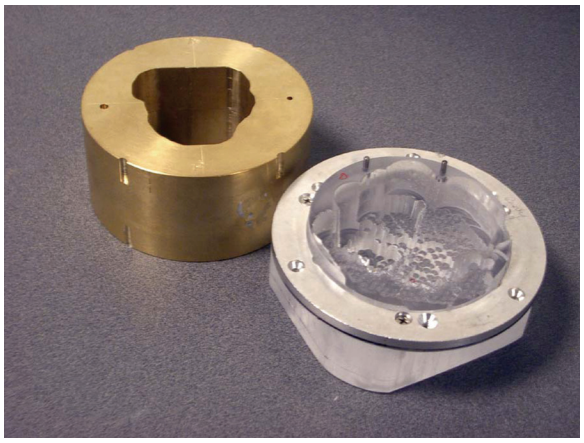

Figure 19-8 Patient-specific brass aperture to achieve lateral field confirmation to the target volume and a polymethyl methacrylate (PMMA) range compensator to achieve distal confirmation.
Reprinted with permission from Gottshalk B: Passive beam scattering. In DeLaney TF, Kooy H, editors: Proton and charged particle radiotherapy. Philadelphia, 2007, Lippincott Williams and Wilkins, Figure 5A.6, p 37.

cost. Furthermore, insertion and removal of the heavy apertures for each field is time-consuming and potentially dangerous for therapists and technicians. This process adds a significant amount of time to each patient's treatment and limits the total number of patients treated by an accelerator.

Although proton therapy has the potential to spare more healthy tissue than x-ray therapy, by virtue of physical qualities of the Bragg peak, there is a concern for increased neutron production. Neutrons can be generated whenever high-energy protons are slowed down by nuclear interactions. Such events can take place inside or outside of the patient. There is a certain amount of neutron production that takes place from proton interactions within the patient, and this is unavoidable and relatively modest. But with the passive scatter system, neutrons are primarily produced from proton interactions with scattering material and collimators in the accelerator. Hall[51] determined that this external neutron dose was more than 100 times the internal dose. Others argue that Hall's technical assumptions and calculations reflect the worst case scenario of treatment of a small target with a large amount of brass in the aperture, and still other investigators have measured substantially lower levels of neutrons, because the number of neutrons generated will be a function of the specific beam line as well as the beam-modifying hardware upstream from the patient.[52]

Chung et al[53] quantified the risk of a second malignant tumor associated with the use of proton therapy compared with photon radiation therapy. In this retrospective cohort analysis, 558 patients treated with protons at the HCL from 1973 to 2001 were matched with 558 patients from the Surveillance Epidemiology and End Results (SEER) Program database. With a median follow-up of more than 6 years, a second cancer developed in 5.2% of proton patients and 7.5% of photon patients (adjusted hazard ratio of 0.52 [0.32 to 0.85]; $p = 0.009$). Although the magnitude of neutron production and its clinical significance in contributing to radiation-induced malignant disease have been hotly debated, these data indicate that the use of proton radiotherapy was not associated with a significantly increased risk of secondary malignancies compared with photon therapy. Furthermore, active beam scanning will markedly reduce external neutron contamination, and for this reason, will be preferred over the passively scattered beam technique.

Active Scanning

The next step in the evolution of proton beam delivery is active (spot or pencil beam) scanning. With passive scanning, it is difficult to obtain large, uniform fields without significant energy loss, even with double scattering systems. In 1980, investigators in Japan first described a spot scanning system.[54] The technique was further refined by the group at the Paul Scherrer Institute in Switzerland.[55] With this technique, the beam is not spread out or scattered; rather, a narrow pencil beam is precisely steered through the treatment volume by magnets in the beam line nozzle. One of the benefits of this system is that there may not be any field-specific or patient-specific hardware; therefore, the time and cost of fabrication are avoided. Furthermore, the speed of the treatment is increased because these heavy devices do not need to be changed for each treatment field. Most importantly, neutron production is greatly diminished with the absence of this hardware.

These pencil beams deposit the dose layer by layer, with the distal edge treated first and the more superficial layers treated thereafter (Figure 19-9). Active scanning also allows for good conformation of the proximal edge of the treatment volume, which is typically not the case with passive scanning. This ability to conform the dose to the proximal tumor volume may further be enhanced with the use of IMPT. This excellent dose-shaping ability of IMPT makes it the best technique for the treatment of irregularly shaped tumors.

Perhaps the greatest concern about active scanning is the issue of organ motion. Because of this, active scanning should be reserved for tumor sites that have minimal motion and can be well immobilized, such as the head and neck, spinal cord, and low pelvis unless specific organ motion strategies are implemented. Several strategies have been developed to address the problem of organ motion. One technique is to repaint the same volume several times with the scanning beam, allowing for an averaging effect of the dose. Gating, as is used in the treatment of lung cancer, with photons is also an option. The spot size of the beam, as well as the scanning speed, can be manipulated as well.

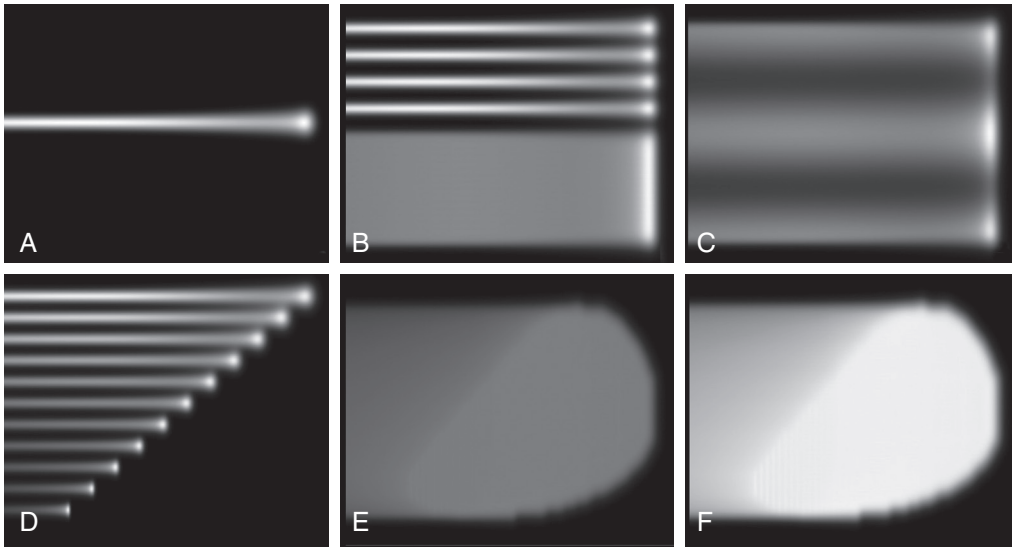

Figure 19-9 **A,** The proton pencil, with a (gaussian) spread of about 3 mm, enters into the patient. The lateral broadening of the pencil beam resulting from multiple coulomb scattering (MCS) in the patient body is small but not negligible. The dose distribution of such a pencil beam shows a sharp maximum near the end of the range and is well localized in the Bragg peak in all three dimensions within a "spot" volume of about 1 cm^3. The superposition of these spots, scanned on a three-dimensional grid in steps of ~5 mm, can be delivered to produce a three-dimensional dose distribution that conforms to the target volume in all three dimensions **(F),** albeit with an unavoidable entrance dose. **A,** Single pencil beam. **B,** Lateral scanning. **C,** The dose is shaped by changing the dosage of each spot, the speed of the scan, or the intensity of the beam. **D,** A homogeneous dose is produced by changing the energy of the beam. **E,** Repainting delivers a lower dose to the target volume per painting and is repeated to deliver the total target dose. **F,** The summation of many pencil beams in the lateral direction and in depth results in a conformal homogeneous dose distribution. *Reprinted with permission from Pedroni E: Pencil beam scanning. In DeLaney TF, Kooy H, editors: Proton and charged particle radiotherapy. Philadelphia, 2007, Lippincott Williams and Wilkins, Figure 5B-1, p 42.*

COST COMPARISONS FOR PROTON BEAM RADIOTHERAPY

All of the clinical and treatment planning results that have been reported indicate that proton beams offer a significant potential for improvements in clinical outcomes for cancer patients over a broad range of disease sites. There is hope that prospective clinical trials that have begun in the new hospital-based proton therapy facilities will establish the magnitude of these improvements. It will be important for physicians and patients and even society in general to have some sense of the cost of these benefits, to be able to place them in an appropriate context and allow comparison with other medical interventions. Goitein and Jermann[56] performed cost comparisons between proton radiation therapy and technically sophisticated photon radiation therapy in an effort to define the relative costs of the technologies. The expense of proton therapy per patient is expected to decrease as more facilities are built and greater numbers of patients are treated. The adoption of hypofractionation and beam scanning, as well as technical advances including smaller proton facilities, is expected to further reduce the cost. At the present time, when neither costs nor benefits have been adequately determined, it is not possible to carry out a reliable cost-benefit analysis. Goitein and Jermann[56] were able to estimate that the relative cost of proton beam radiation therapy compared with intensity-modulated photon beam radiation therapy was in the range of 2.4 in 2003 but might come down to 1.7 to 2.1 over time. Studies that have assessed cost-effectiveness suggest that protons will be cost-effective for pediatric malignant disease because of the reduction in late effects associated with the 50% to 60% reduction in integral dose associated with protons.[57]

CARBON ION RADIOTHERAPY

Carbon ions have a slight physical advantage over protons in that they will have a narrower penumbra than protons, particularly for deep-seated tumors.[58] On the other hand, carbon ions will also produce some spallation products deep to the Bragg peak. Whether the higher RBE and differential effect on hypoxic cells of carbon ions will translate into a clinical advantage remains to be determined, particularly because the clinical use of carbon has generally been with larger fraction sizes where there will be less RBE difference between carbon ions and protons. Because of the higher ionization and double-strand break density with carbon ions, they would logically of the greatest potential value in areas of gross tumor to minimize late normal tissue injury.

The Heavy Ion Medical Accelerator (HIMAC) in Chiba, Japan, began clinical studies in 1994. Kamada et al[59] reported the results of a Phase I/II study evaluating the tolerance and effectiveness of carbon ion radiotherapy in patients with unresectable bone and soft-tissue sarcomas. Fifty-seven patients with 64 sites of sarcomas not suited for resection received carbon ion therapy. Tumors involved the spine or paraspinous soft tissues in 19 patients, pelvis in 32 patients, and extremities in 6 patients. The total dose ranged from 52.8 to 73.6 carbon GyE and was administered in 16 fractions over 4 weeks (3.3 GyE/fraction to 4.6 GyE/fraction). Seventeen of the patients treated with the highest total dose of 73.6 GyE experienced RTOG grade-3 acute skin reactions. No other severe acute reactions (grade >3) were observed. The overall local control rates were 88% and 73% at 1 and 3 years of follow-up, respectively. The 1- and 3-year overall survival rates were 82% and 46%, respectively. It will be important to continue close follow-up to ensure that the large dose fractions are not associated with late injury of normal tissue.

Raster scanned carbon ion radiation therapy was used to treat patients at the Gesellschaft für Schwerionenforschung in Darmstadt, Germany, from 1997 to 2009, following which the program was transferred to the Heidelberg Ion Therapy Center. Between November 1998 and July 2005, a total of 96 patients with chordomas of the skull base were treated with carbon ion radiation therapy.[60] All patients had gross residual tumors. The median total dose was 60 Gy(RBE) (range, 60 Gy[RBE] to 70 Gy[RBE]), delivered in 20 fractions within 3 weeks. The mean follow-up was 31 months (range, 3 months to 91 months). Fifteen patients developed local recurrences after carbon ion radiation therapy. The actuarial local control rates were 80.6% and 70% at 3 and 5 years, respectively. Target doses in excess of 60 Gy(RBE) and primary tumor status were associated with higher local control rates. Overall survival rates were 91.8% and 88.5% at 3 and 5 years, respectively. Grade 3 toxicity was seen in 4% of patients and consisted of fat necrosis and optic neuropathy.

Kato et al[61] from Chiba, Japan, recently reported the results of a carbon ion dose escalation study for 24 patients with hepatocellular carcinoma. Fifteen fractions were delivered over 5 weeks, and total doses ranged from 49.5 Gy to 79.5 GyE. During a median follow-up of 71 months (range, 63 months to 83 months), no severe adverse effects or treatment-related deaths occurred. The overall tumor response rate was 71%. The local control and overall survival rates were 92% and 92%, 81% and 50%, and 81% and 25% at 1, 3, and 5 years, respectively.

Additional encouraging results with carbon ions have been reported for uveal melanoma, head and neck malignancies of multiple histologies, prostate cancer, and early stage non–small cell lung cancers. No clinical trials directly comparing lower LET protons with higher LET carbon ions have been completed to date but these are now under way. Randomized clinical trials of carbon ions versus protons are now being conducted at the Heidelberg Ion Therapy Center for patients with glioblastoma and skull-base chordomas and chondrosarcomas.

NEON ION RADIOTHERAPY

High-LET charged particle therapy with neon ions was studied in the treatment of glioblastoma of the brain because of the neon ion's increased biologic potential for destruction of radioresistant tumors. At the University of California, San Francisco (UCSF), and Lawrence Berkeley Laboratories (LBL), 15 patients were entered into a randomized protocol comparing two dose levels of neon ion irradiation,[62] either 20 Gy or 25 Gy in 4 weeks. However, there was no significant difference in overall survival time (13 to 14 months). Furthermore, an optimal dose level was not identified. Neon ions are not in current clinical use.

π-MESON RADIOTHERAPY

Subatomic particles called *π-mesons* provide the nuclear binding force between nuclei. These particles are produced when protons (600+ MeV) affect a target. Three types of mesons are produced: a neutral form, a positive form, and a negative form. It is the negative form, π^-, that is used for radiotherapy. When the π^- slows down, it is "captured" by a nucleus, causing it to "explode" in a "star" event, producing neutrons and charged nuclear fragments having high-LET properties[63] (Figure 19-10).

Negative π-mesons (pions) were used to treat 228 patients at the Los Alamos Meson Physics Facility between 1974 and 1981. One hundred twenty-nine patients received pion therapy only. All patients had locally advanced disease, and a number of different sites were treated. Local control was achieved in

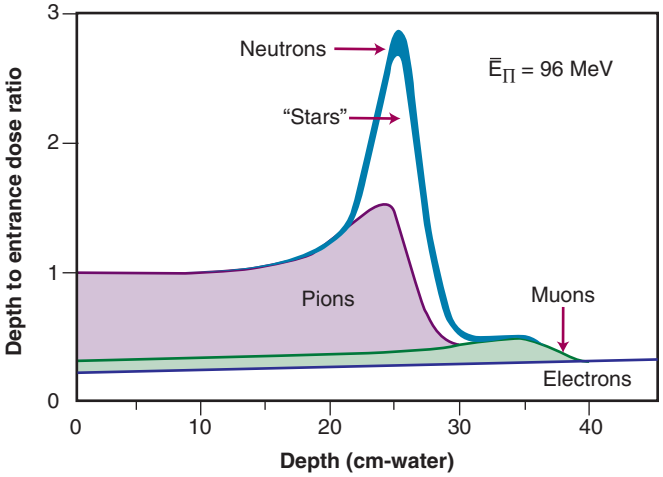

Figure 19-10 Illustration of negative π^- meson capture. When the π^- slows down, it is "captured" by a nucleus, causing it to "explode" in a "star" event, producing neutrons and charged nuclear fragments with high-LET properties.

86% of patients with prostate cancer, in 26% with head and neck cancers, and in none with pancreatic cancer. A steep rise in the complication rate was seen beyond a dose level of 3750 cGy.[64] π-Mesons are also no longer in clinical use.

HELIUM RADIOTHERAPY

A retrospective study was done at UCSF and LBL to evaluate the use of helium ions in the treatment of uveal melanomas.[65] Ten years after helium ion radiation, 208 of the 218 eyes irradiated had local tumor control (95.4%). At 10 years, 46 eyes (22%) had been enucleated; the majority resulting from anterior ocular segment complications. At 10 years, 51 patients (23%) had died of metastatic melanoma. The best corrected visual acuity after irradiation was greater than 20/40 in 21 of 93 eyes (23%) of patients who were alive and who had retained their eyes 10 or more years after treatment. Visual acuity was related to height of tumor and location near the nerve or fovea.

Schoenthaler et al[66] reported on the use of charged particle irradiation for sacral chordomas. At LBL, 14 patients with sacral chordomas were treated with charged particles, either lower LET helium or higher LET neon. All patients were treated postoperatively; 10 had gross disease. The median dose was 7565 cGy and the median follow-up was 5 years. The Kaplan-Meier survival rate at 5 years was 85%, and the overall 5-year local control rate was 55%. A trend in improved local control at 5 years was seen in patients treated with neon ions compared with patients treated with helium ions (62% versus 34%), in patients following complete resection versus patients with gross residual tumor (75% versus 40%), and in patients who had treatment courses less than 73 days (61% versus 21%). No patient developed neurologic sequelae or pain syndromes. One patient who had been previously irradiated required colostomy; 1 patient had delayed wound healing following a negative postradiation biopsy; and 1 patient developed a second malignant tumor. There were no genitourinary complications.

CONCLUSIONS

As discussed, the main benefit of protons over conventional photon beam radiotherapy is a reduction in integral dose. With intensity modulation, dose conformality with protons

and photons are comparable (assuming a small enough proton pencil beam diameter). It remains to be determined how much clinical benefit this reduction in integral dose achieves for patients. From planning studies, the greatest benefit is projected for larger targets (or larger targets relative to the size of the involved or closely approximated critical organ such as would be the case for eye tumors or skull-base tumors) and in younger patients, where studies project a reduction in second cancers[68] and other late effects to render protons cost-effective.[57] With minimization of the normal tissue dose, protons may allow for better tolerance of combined chemotherapy and radiation therapy regimens; indeed, many of the trials of pediatric proton radiation therapy employ chemotherapy in the same way that it has been commonly employed in pediatric protocol-directed therapy for solid tumors.[67]

Heavier charged particles have a sharper penumbra than protons when treating deep targets and may also confer a biologic advantage against tumor because of the higher RBE and differential effect on hypoxic cells, although comparison studies with protons are recommended to see if there indeed is a clinical advantage in using carbon ions over protons, because of the greater complexity and cost of carbon or other heavier charged particles.

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