Introduction

Current management of bone sarcomas is based on a multidisciplinary approach using a combination of surgery, radiotherapy, and chemotherapy specific for tumor type, histologic grade, and stage of disease. Because these tumors are relatively uncommon and are present in a variety of anatomic locations, most clinicians see these tumors infrequently. However, because they can often be successfully treated with good functional outcome by sarcoma centers with appropriate multidisciplinary expertise, referral to centers with experienced sarcoma teams is the most appropriate management strategy.
Surgery is the preferred treatment for the primary site in most patients with bone sarcomas and results in high rates of local control in patients with extremity tumors. In the case of primary extremity osteosarcomas, for example, the rate of local control with chemotherapy and surgical resection is over 90%.1 In contrast, in osteosarcoma lesions of the head and neck, spine, and pelvis, local control with surgery and chemotherapy is less favorable. The local recurrence rate for lesions in the pelvis was 70% in 67 patients reported by the Cooperative Osteosarcoma Study Group, with recurrence developing in 31 (62%) of 50 patients who underwent resection and in 16 (94%) of 17 who did not.2 Of 22 patients with spinal osteosarcomas reported by Ozaki et al,3 15 (68%) experienced local failure. For patients with head and neck osteosarcomas, local control is achieved in approximately 50% of patients, with the mandible the most favorable site, followed by the maxilla and then extranongenic sites (zygoma, orbit, nasoethmoid, and cranial bones).4,5

RT can be useful in helping to secure local control in these unfavorable sites.6,8 Radiation can be employed as neoadjuvant (preoperative), adjuvant (postoperative or intraoperative), or primary local therapy depending on the site and type of tumor, the availability and acceptability of the surgical option, and the efficacy of the chemotherapy. Neoadjuvant (preoperative) RT can be delivered prior to resection of sarcomas of the spine7 or pelvis.9 Adjuvant radiation is used for patients with bone sarcomas with positive or inadequate margins and in selected other situations that might include presentation with a pathologic fracture,9 poor histologic response to chemotherapy,10 inadvertent hematoma after biopsy, or intralesional excision of or intramedullary rod placement through a radiographically or cytologically benign-appearing lesion later found to be sarcoma on review of final pathologic material. RT as the primary local therapy without surgery is used for medically inoperable patients, for patients with axial Ewing’s sarcomas or extremity Ewing’s sarcomas where surgery would compromise function,11 and for patients with primary bone tumors involving the upper sacrum,12 portions of the pelvis, the base of skull, and the ethmoid/sphenoid sinus region where complete resection is either not technically possible or unacceptable to the patient.13,14

Ewing’s sarcomas are quite radiation sensitive, and the original description of this tumor by James Ewing made note of the fact that the radiation sensitivity of this tumor was one of the features distinguishing it from other bone sarcomas.15 Unresected tumor or gross residual disease is usually treated with 55.8 Gy in association with chemotherapy.11 Consideration of higher doses for high-risk bulky axial tumors might be appropriate. Due to spinal cord constraints, vertebral lesions have often been treated with doses to 45 to 50 Gy. Microscopic residual disease is usually treated to 50.4 Gy.

Chondrosarcomas and osteogenic sarcomas require doses of approximately 66 Gy for control of microscopic residual disease and doses of ≥70 Gy for control of gross residual disease. Because most osteosarcomas are treated in conjunction with chemotherapy, our policy for patients (particularly for younger patients) with unresectable or gross residual disease has been to start treatment with induction chemotherapy using doxorubicin platinum and methotrexate per established protocols and then, after approximately 12 weeks of chemotherapy, deliver radiation of 70.2 Gy in 39 fractions of 1.8 Gy daily via shrinking field technique concurrent with chemotherapy, generally ifosfamide/etoposide. Generally, chondrosarcomas in patients with gross disease have been managed with 70 to 77.4 Gy at 1.8 to 2 Gy daily, depending on the volume of disease and the RT tolerance of adjacent tissues. Chordomas require doses of approximately 70 Gy for microscopic residual disease and doses of >75 Gy for control of gross residual disease.16

Radiation is most commonly given by externally directed beams, but it can also be given by brachytherapy or intraoperative techniques. Brachytherapy has been most extensively employed in the adjuvant radiation of soft tissue sarcomas.17 More recently it has been applied on the dura and paraspinal tissues for spine and paraspinal tumors7,18,19 and for some Ewing’s sarcomas with inadequate surgical margins.20 Intraoperative RT with electron beam or orthovoltage is delivered to the tumor or tumor bed at the time of surgery and can be particularly useful to boost the dose to tumors around the pelvic girdle21 and spine. Brachytherapy and intraoperative RT, although technically challenging, have been adopted in many specialized centers because of their dosimetric advantages over conventional external-beam therapy and reduction in integral dose to normal tissue.

Intensity-modulated photon radiation therapy (IMRT) is increasingly being employed for treatment of challenging bone sarcomas of the axial skeleton because of the higher conformality of dose and sparing of selected normal tissues from the high-dose region.22 Because RT for sarcomas often requires high doses in close proximity to sensitive normal tissues, protons and other charged particles are an excellent treatment option for these patients when external-beam irradiation is part of the RT treatment plan. Sarcomas of the skull base and cervical spine were among the first tumors to be treated with protons on a concerted basis and one of the anatomic sites at which excellent clinical results have been achieved with this modality.14,23 With an increasing number of proton therapy facilities, experience with this modality continues to grow. Interesting results have also been reported with heavier charged particles, initially helium and neon from Berkeley Laboratory24 and more recently carbon ions from
the National Institute of Radiological Sciences in Chiba, Japan, and Gesellschaft für Schwerionenforschung (GSI) in Darmstadt, Germany.

Techniques of Radiotherapy

Intensity-Modulated Photon Radiation Therapy

IMRT uses modulated field intensity across the photon radiation field to improve coverage of the tumor volume while reducing the radiation dose to selected normal tissues (Fig 1A). Computer-controlled multileaf collimation provides high conformity, which makes it feasible to treat tumors of any shape, even those that are in close proximity to the spinal cord. Recent dosimetric studies comparing IMRT and 3-D conformal RT for sarcomas have been reported. When evaluating sarcomas arising in the extremities, pelvis, trunk, and paranasal sinuses, IMRT plans were more conformal. In the extremities, bone and subcutaneous doses were reduced by up to 20%. A conformal IMRT comparative planning study has been reported for a large extraskeletal chondrosarcoma of the extremity. Not surprisingly, IMRT produced excellent conformal treatment plans for this complex target volume, with a reduction of the maximum dose to the bone compared with the 3-D photon plan. In addition, IMRT can reduce hot spots in the surrounding soft tissues and skin. It should be noted, however, that IMRT treatment plans often include localized areas within the high-dose volumes where dose inhomogeneities can be in the range of 10% to 15% above the prescription dose. Because there can also be dose inhomogeneities in the range of 5% below the target dose, treatment plans are often normalized to the 95% isodose line, meaning that selected areas of the treatment volume are receiving daily fractions and total doses of 15% to 20% above the target dose. Depending on the location of these “hot spots,” there can be unanticipated acute normal tissue toxicity. Whether there are late effects attributable to these focal areas of high dose remains unclear.

Fig 1A-D. — Axial displays of an IMRT (A) and proton RT (B) plan for an 18-year-old patient with a large osteosarcoma of the left pelvis, which was managed by a combination of induction chemotherapy with methotrexate, cisplatin, and doxorubicin followed by concurrent ifosfamide/etoposide chemotherapy and RT. RT consisted of IMRT (25.2 Gy in 14 fractions, left) and protons (19.8 CGE in 11 fractions, right) to the clinical target volume (contoured with thin magenta line). This encompassed the gross tumor and areas at risk for microscopic extension followed by boost radiation of another 25.2 CGE in 14 fractions (C) with protons to the gross tumor volume (contoured with thin red line) visualized on the planning CT and MRI scans to bring the total radiation dose to 70.2 CGE (bold red isodose line on D). Note reduction in dose to bowel (contoured with thin green line) and other tissues anterior to the target, as well absence of dose to contralateral pelvis, with protons compared to IMRT. Figures courtesy of Judy Adams, CMD, Francis H. Burr Proton Therapy Center, Boston, Mass.
Proton Radiotherapy

The rationale for the use of protons rather than photons (ie, x-rays, which have traditionally been used for RT) is the superior dose distribution that can be achieved with protons.30 Protons and other charged particles deposit little energy in tissue until near the end of the proton range where the residual energy is lost over a short distance, resulting in a steep rise in the absorbed dose known as the Bragg peak.31,32 The Bragg peak is too narrow for practical clinical applications, so for the irradiation of most tumors, the beam energy is modulated by superimposing several Bragg peaks of descending energies (ranges) and weights to create a region of uniform dose corresponding to the depth of the target. These extended regions of uniform dose are called spread-out Bragg peaks (Fig 2). Although the beam modulation to spread out the Bragg peaks increases 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.31,32 Most proton facilities deliver the beam via passive scattering techniques that spread out and shape the beam with physical beam-modifying devices. On a beam-by-beam comparison, protons will always give less dose to normal tissue than photons. This will often result in a reduction in composite dose (integral dose) to normal tissue of 2- to 3-fold depending on the location of the tumor and the choice of fields.33 The primary physical interaction of protons with tissue is ionization of electrons and yields a biologic effect that is similar to that of x-rays, although the magnitude of the biologic effect is slightly greater.54 Thus, the physical dose of protons in the clinic is corrected for this difference in relative biological effectiveness (RBE) by an RBE factor (generally 1.1 in most clinical centers).34 Proton doses in the clinic have been expressed in cobalt Gray equivalents (CGEs), which represent the physical proton dose multiplied by the 1.1 RBE correction factor.

Before the advent of IMRT, protons were used to deliver higher radiation doses than could be given with photons. Hence, the major emphasis for proton therapy clinical research initially was dose escalation for tumors for which local control with conventional RT was poor,55 including base of skull and spine tumors,14 locally advanced prostate cancer,56 hepatocellular carcinoma,57 and non–small-cell lung cancer.58 The recent development of hospital-based cyclotrons with higher energy beams capable of reaching deep-seated tumors (up to approximately 30 cm with a 235 MeV beam), field sizes comparable to linear accelerators, and rotational gantries has greatly facilitated proton RT. Hence, proton-beam RT is being used for a wider range of clinical sites than in the past.

In tumor sites in which tumor control with photons is good, there is increasing interest in protocols aimed at morbidity reduction by exploiting the reduction in exit dose with protons to reduce normal tissue radiation doses and thus the toxicity of treatment. Many pediatric tumors fall into this category, and thus there is much interest in the use of protons to reduce the risk of late effects of RT on developing normal tissues in children (Fig 3A-C).59 It is to be emphasized that dose escalation and morbidity reduction are not mutually exclusive when using protons and that the opportunity for both might be present in any given patient (Fig 1A-D).

Photon IMRT can now deliver radiation doses to the target that are often competitive with those achievable with protons. The distribution of 3-D conformal proton doses is generally more homogeneous than IMRT, although focal hot spots can also arise where fields are junctioned or “patched.”40 Integral doses are higher with photon IMRT than with protons; thus, most experts would suggest greater toxicity with IMRT photons than with protons. The magnitude of the difference in acute and late toxicity between IMRT and protons is not currently known.

The definition of the treatment target volume (ie, the clinical target volume that encompasses the tumor and areas at risk for subclinical spread of tumor, which is by...
definition below the resolution of the imaging studies and is generally irradiated to doses of 45 to 50.4 Gy) and the gross tumor volume (ie, the tumor visualized on imaging studies) will be the same for 3-D conformal RT, IMRT, 3-D conformal protons, or intensity-modulated proton radiation therapy (IMPT). All of these techniques rely on the accuracy of tumor imaging for the definition of the gross tumor volume and the judgment of the treating physician about the margin to use around the gross tumor volume to allow for subclinical spread of tumor. This margin depends on multiple factors including tumor type, natural history, risk of nodal involvement, and historical patterns of failure. The dose gradient at the edge of the target volumes, however, will be sharper with IMRT, 3-D conformal protons, or IMPT than with 3-D conformal photons. Hence, there is increased importance on confirmation of positional accuracy of the patient and the beam. For this reason, image guidance can be of considerable importance for these tumors. In practice, daily pretreatment, diagnostic-quality positioning radiographs have been taken prior to each proton treatment to guarantee the accuracy of treatment. Diagnostic quality radiographs, cone-beam CT, megavoltage CT and other image guidance tools have been used to guarantee the accuracy of setup for IMRT.

Because of the defined range of the proton, a technique known as “smearing” has been used to compensate for insufficient proton range in the case of inaccuracy in daily patient setup (where, for example, bone interposed in the path of the proton when the treatment plan had only anticipated soft tissue would result in a shortfall in proton range and a geographic miss of the distal edge of the target). Smearing adds additional range to the proton in a given radius around the desired point, taking into account the different tissue heterogeneities that the proton is likely to encounter in traversing any point within that radius. Without this technique, the risk for geographic miss with the protons would be magnified. While this has been a safe technique to ensure target coverage, it underscores the importance of setup accuracy when using this modality; higher degrees of setup accuracy can reduce the radius required for smearing.

A subtle but important area that is the subject of ongoing clinical investigations is the greater sensitivity of proton treatment plans compared with photon plans to changes in tissue densities such as those in paranasal sinuses where air, bone, and soft tissues form a complex geometry. Changes in tumor configuration in this location from tumor shrinkage or normal tissue density...
from sinusitis, for example, are expected to have a more profound impact on a proton than on a photon treatment plan due to the exquisite range sensitivity of the proton. Thus, adapting the radiation treatment plan to the changes in tumor and normal tissue that occur over a course of treatment by repeated radiation planning CT scans with reevaluation and replanning as dictated by the clinical findings will be an even more important tool for protons than for photons for anatomic sites and tumor types where tumor regression and normal tissue changes occur over the course of treatment.

Some concern has been raised recently about the potential late carcinogenicity of secondary neutrons associated with the beam-modifying hardware used to deliver passively scattered protons. The magnitude and relative contribution of these neutrons to late secondary malignancies are currently being debated. This is not a major concern for magnetically scanned protons (such as would be used for intensity-modulated proton therapy, IMPT). Because irradiation of normal tissue offers no possible advantage to the patient, there has been much discussion about the ethics and acceptability to patients of participation in randomized clinical trials of protons vs IMRT.

**Heavier Charged Particles**

One property of charged particles used to assess the biologic effect of a particular radiation is linear energy transfer (LET), the rate of energy loss by the particle in tissue. The LET influences the biologic impact of the energy deposited in tissue. X-ray and gamma ray photons, protons, and helium ions are considered low-LET radiation. Heavier charged particles (neon, carbon) and fast neutrons are considered high-LET radiation. There is an initial increase in the RBE with an increase in LET. Higher-LET radiation is less affected by tissue oxygenation and less sensitive to variations in the cell cycle and DNA repair. For these reasons, the use of heavier, higher LET charged particles is of interest. These higher LET particles have the superior physical dose distribution characteristics of charged particles and also have a higher RBE, thus potentially having both a physical and biologic advantage over protons. They present challenges for use in the clinic, however, because of uncertainties about potential differences in the RBE in different tissue types and changes in RBE over the path of the clinical beam. Higher rates of late normal tissue injury were seen in some studies with neutrons (which have a higher RBE than photons), although contributing to this was the fact that their physical dose distribution was much inferior to that which can be achieved with heavier charged particles. Hence, these heavier charged particles have been introduced in careful phase I and II studies to minimize the risk of potential normal tissue complications.

Heavier charged particles have been used in several centers for the treatment of sarcomas with promising results. To date, they have not been compared in any randomized clinical trials against protons to assess whether the higher RBE offers any clinical advantages over protons. This will depend on whether the higher LET results in an improved therapeutic ratio by achieving either a higher percentage of tumor control for a given level of normal tissue toxicity or a similar percentage of tumor control with less normal tissue toxicity. A practical consideration is that heavier charged particles such as carbon ions will be more expensive than protons to deliver because of their substantially higher mass (12-fold for the case of carbon) and the higher-energy cyclotrons and more powerful magnets needed to accelerate and steer them. Hence, comparative trials between protons and higher-LET heavier charged particles will be important.

**Intensity-Modulated Proton Radiation Therapy**

Intensity modulation can also be applied to proton beams, potentially optimizing the dose distribution even further. Dosimetric comparisons between photon IMRT and proton IMPT show a marked reduction in doses delivered to normal tissues that may prove to have a clinically significant impact on toxicity for the patient (Fig 4A-B). Although it is currently unresolved whether this optimized physical dose distribution will be accompanied by an important clinical advantage, randomized clinical comparisons might be difficult to conduct because patients and their treating clinicians might have concerns about randomizing patients to the photon IMRT arm with its associated higher normal tissue radiation doses.

IMPT with a spot-scanning beam has been used to treat a limited number of patients at the Paul Scherrer Institute in Switzerland. Raster-scanned carbon-ion RT is used to treat patients at the GSI in Darmstadt, Germany.

**Brachytherapy**

Even with IMRT or a particle beam, it is difficult to deliver tumoricidal doses of ≥70 Gy to the surface of the dura when, as is often the case, it is involved by spinal or paraspinal sarcomas. The physical properties of beam penumbra and the proximity of the surface of the spinal cord within 3 to 4 mm of the dura prevent delivery of adequate dose to the dural surface without exceeding spinal cord tolerance. A strategy developed at our institute is the use of a custom-designed yttrium-90 plaque to boost the dose to the dural surface intraoperatively. The percent depth dose characteristics of the applicator are favorable for this application, with 100%, 27%, and 8% doses measured at depths of 0 mm (dural surface), 2 mm, and 4 mm, respectively. Thus, 10 to 15 Gy can be delivered to the dural at the time of surgical resection, with minimal dose to the cord surface and essentially no dose to the cord center or the
contralateral side of the cord (Fig 5). Initial experience with this applicator has been favorable and has not shown any acute toxicity or any neurologic sequelae.7

Intraoperative Radiation Therapy

With the exception of tumors recurrent after prior external-beam radiation, when it may be used as the sole form of RT in the treatment course, intraoperative RT (IORT) has generally been administered as a boost dose given in conjunction with external beam radiation. During surgery, 10 to 15 Gy is delivered with electrons or high-dose rate intraoperative brachytherapy to sites of microscopically positive margins which require doses of radiation in excess of those tolerated by surrounding critical normal tissues such as bowel which can kept out of the IORT field. The risk of wound-healing complications does not seem to be enhanced with IORT. It is generally administered after preoperative, neoadjuvant external-beam RT, although it has also been given prior to external-beam RT. This technique is particularly advantageous for retroperitoneal and pelvic sarcomas for which the tolerances of surrounding critical normal tissues, including bowel, liver, spinal cord, and kidneys, constrain the dose that can be delivered to the tumor with external radiation.21

Preoperative RT at 45 to 50.4 Gy (1.8 Gy per fraction) has been preferred for retroperitoneal soft tissue sarcomas because the tumor acts as a tissue expander and moves normal structures out of the radiation beam.58 Because of the extent of surgery required for pelvic sarcomas that may include internal hemipelvectomy or partial sacral resection with a relatively high risk of surgical complications in the absence of any RT, we have explored the use of lower-dose preoperative RT for patients undergoing surgical resection when a positive margin is anticipated, as is frequently the case for sacral or pelvic bone sarcomas. We have delivered 19.8 to 20 Gy at 1.8 to 2.0 Gy per fraction, followed immediately by resection with intraoperative and additional postoperative radiation. The advantage of this technique is that the radiation fields for both preoperative and postoperative radiation are smaller compared with that of postoperative radiation alone. Surgical scars and drain sites do not need to be covered after this low-dose preoperative irradiation, which appears to be sufficient to prevent tumor seeding into the wound, surgical scars, and drain sites.59 This appears to

Fig 4A-B. — (A) Color wash dose distributions for IMRT, and (B) IMPT treatment plans for a patient with a paraspinal sarcoma. The isodose contours are represented by different colors (corresponding values, in Gy (or CGE) and are displayed on the lower border of each figure. From Weber DC, Trofimov AV, DeLaney TF, et al. A treatment planning comparison of intensity modulated photon and proton therapy for paraspinal sarcomas. Int J Radiat Oncol Biol Phys. 2004;58:1596-1606. Reprinted with permission by Elsevier.

Fig 5. — Brachytherapy plaque on the posterior dural surface of a 55-year-old patient undergoing resection of a chondroblastic osteosarcoma involving the T6 vertebral body along with placement of spine stabilization hardware at the time of his posterior approach. A radiation dose of 10 Gy was delivered to the dural surface over 9 minutes 21 seconds. The patient had received 19.8 Gy of IMRT preoperatively and then a total of 50.4 CGE of combined IMRT and proton radiation postoperatively for a total dose of 70.2 CGE delivered via shrinking field technique. The dural brachytherapy was used to increase the dose to the dural surface, which received only 60 Gy with the external irradiation. Adjuvant chemotherapy was delivered after completion of surgery and RT.
be a promising technique for high-risk sarcomas involving the bone, particularly for patients managed in this manner at the time of initial treatment, with a 5-year local control rate of 91.8%.

**Sarcomas of the Spine**

Because of the proximity of the spinal cord, RT for treatment of sarcomas of the spine is constrained by the radiation tolerance of the spinal cord, which is well below that necessary to reliably control most sarcomas in the setting of close or positive margins or gross residual disease. The bone tumor histologies involving the spine include chondrosarcomas, chordomas, osteosarcomas, Ewing’s sarcoma, malignant fibrous histiocytomas of bone, fibrosarcomas, and giant cell tumors.

**Intensity-Modulated Photon Radiation Therapy**

Higher radiation doses to spine tumors and lower radiation doses to the spinal cord can now be delivered with the combination of intensity-modulated photon RT (IMRT), improved spine immobilization with body frames and/or spine tumor localization by in-treatment-room image guidance, and fusion of computed tomographic and magnetic resonance images. The group at Memorial Sloan-Kettering reported their experience involving 14 patients with primary spine or paraspinal sarcomas treated with multifractionated stereotactic and image-guided IMRT coupled with noninvasive body frames. In previously unirradiated patients, the median prescribed dose was 70 Gy (59.4 to 70 Gy) with a median planning target volume receiving the prescribed dose of 90%. The median dose maximum to the cord was 68% of the prescribed dose for previously unirradiated patients. Eighty-one percent of the primary lesions exhibited local control with 2 to 30 months of follow-up. No cases of radiation-induced myelopathy had been encountered to date. The investigators concluded that high-precision stereotactic and image-guided paraspinal IMRT allowed the delivery of high doses of radiation in multiple fractions to tumors within close proximity to the spinal cord while respecting cord tolerance. Although preliminary, the clinical results are encouraging.

**Proton Radiotherapy**

Proton radiotherapy, with its ability to spare the spinal cord and/or cauda equina and adjacent normal tissues such as the kidney, lung, heart, esophagus, and bowel, offers advantages for treatment of tumors in this location. Isacsson et al compared conformal RT treatment plans with photons and protons for a patient with a spinal Ewing’s sarcoma. Even when only the final 20% of the treatment (the boost to the gross disease) was given with protons, the authors noted a 5% improvement in local control for a comparable predicted risk of spinal cord injury.

Hug et al 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, pre- and postoperatively in 17, and as sole treatment in 7 patients. Mean radiation doses of 73.9 (CGE), 69.8 CGE, and 61.8 CGE were delivered to group 1 (20 patients with recurrent/chordomas or chondrosarcomas), group 2 (15 patients with osteosarcomas), and group 3 (12 patients with giant cell tumors, osteo- or chondroblasto- mas), respectively. The 5-year actuarial local control and survival rates for patients with chondrosarcomas were 100% and 100% and for those with chordomas were 53% and 50%, respectively. The actuarial 5-year local control rate for patients with osteosarcomas 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 primary vs recurrent tumors, gross total resection, and target doses >77 CGE.

The Massachusetts General Hospital (MGH) group recently reported on the results of treatment of 16 primary and 11 recurrent sacral chordoma patients managed with high-dose proton/photon treatment alone (6 patients) or combined with surgery (21 patients). There was a large difference in local failure rate between patients treated for primary and recurrent chordomas. Local control results by surgery and radiation were 12 of 14 patients for primary vs 1 of 7 patients for recurrent lesions. Local control results in margin-negative patients were 2 of 3 in the primary group and 1 of 2 in the recurrent chordoma group. For the margin-positive patients, local control results were 10 of 11 and 0 of 5 in the primary and recurrent groups, respectively. Mean follow-up on these local control patients was 8.8 years (including 4 patients followed for 10.3, 12.8, 17, and 21 years). Radiation alone was used in 6 patients, 4 of whom received 73.0 CGE or more; local control was observed in 3 of these 4 patients for 2.9, 4.9, and 7.6 years. These data indicate a high local control rate for surgical and radiation treatment of primary (12 of 14) as distinct from recurrent (1 of 7) sacral chordomas. Three of 4 chordomas treated by 73.0 CGE or more of radiation without surgery had local control; 1 was at 91 months. This indicates that high-dose photon/proton therapy offers an effective treatment option for these patients (Fig 6A-B).

Results of a prospective phase II study of high-dose proton/photon radiation treatment with or without surgical resection of sarcomas of the thoracic/lumbar spine/sacrum and paraspinal soft tissues have been recently reported that included 50 patients entered between December 1997 and March 2005. Forty-seven of the 50 patients had primary spine sarcomas and 3 patients had paraspinal tumors. Treatment consisted of maximal resection and photon (<50.4 Gy photon component)/proton radiotherapy; selected patients with
high-grade tumors received chemotherapy. Doxorubicin was not given concurrent with RT. Shrinking field technique was used to deliver 50.4 CGE to subclinical microscopic disease, 70.2 CGE to residual microscopic disease in tumor bed, and 77.4 CGE to gross disease at 1.8 CGE daily. Doses were reduced by 8% to 10% if chemotherapy was given or if diabetes or connective tissue disorders were present. For giant cell tumors or Ewing’s sarcomas, doses did not exceed 61.2 CGE. The spinal cord dose was limited to 63 CGE at the surface and 54 CGE at the center. No specific dose constraint was placed on the cauda equina, but dose was limited to nerve roots and the side of the cauda contralateral to the tumor if possible. If surgery was performed at MGH, preoperative RT of 19.8 Gy (sacrococcygeal) or 50.4 Gy (thoracolumbar) was given. When possible, intraoperative dural brachytherapy boost was given with a customized 90Y plaque. The most common histologies were chordomas (29) and chondrosarcomas (14); the sacrum (26) was the most common anatomical site. Thirty-six patients were treated at the time of primary presentation and 14 were treated for tumor locally recurrent after prior surgery. As part of their treatment on protocol, 25 patients underwent gross total resection of their tumor, with positive margins in 17 patients and negative margins in 8 patients. Tumor was subtotally excised in 12 patients and just biopsied in 13 patients. For patients undergoing biopsy only, the median size of the tumor was 7 cm (median 3 to 20 cm). One patient chose to not complete RT for social reasons. Otherwise, RT was given per the protocol within 3% of the specified dose, with the shortfall driven by the spinal cord dose constraint. The median radiation dose was 76.6 CGE (range 59.4 to 77.4 CGE). Three patients received a 10-Gy boost to the dural surface with a 90Y dural plaque.

With a median follow-up after start of RT of 34 months, 6 patients have had local tumor recurrence (4 chondrosarcomas and 2 chordomas, \( P = .016 \)) to yield a 3-year actuarial local control rate of 87%. Two of the chondrosarcoma patients who recurred after proton RT had suffered 4 to 5 prior recurrences after previous surgeries performed without adjuvant RT; and 1 patient who had a dedifferentiated chondrosarcoma had experienced gross tumor cut-through at the time a prior surgical procedure at another institution. Patients who were treated with locally recurrent tumors after prior surgery were more likely to suffer another local recurrence — 4 of 14 vs 2 of 36 patients treated at the time of initial presentation, \( P = .013 \). Local control was the highest among the patients treated after gross total resection with negative margins — 8 of 8 vs 36 of 42 among patients with positive margins or gross residual tumor, \( P = .028 \). Actuarial overall survival at 5 years was 90%. Two of the locally recurrent patients with chondrosarcomas also developed distant metastases as did 4 other patients whose tumors were locally controlled. Four patients died of progressive tumor and 2 patients died of unrelated causes (cardiac death, oral tongue cancer). One patient was lost to follow-up. Acute grade 3 toxicity consisted of acute pain from a sacral stress fracture after preoperative RT and surgery without late sequelae. Late grade 3 toxicity occurred in 4 patients. This included 1 neuropathy at 5.5 years (left foot drop, right lower extremity weakness, poor rectal tone, stress urinary incontinence); 1 erectile dysfunction at 4 years.
unresponsive to sildenafil following 77.4 CGE to unresected sacral chordomas; a sacral stress fracture following a fall 3 months after delivery of 77.4 CGE that was managed with sacral nail fixation; and 1 rectal bleeding requiring transfusion following surgery and 70.4 CGE of RT for a sacral chordoma.

This experience demonstrates that high-dose photon/proton RT can be given to tumors involving the spine and paraspinal tissues. To date, morbidity appears to be acceptable. Although follow-up to date is still relatively short, encouraging results have been achieved with this treatment approach in a patient population with tumors that historically have been difficult to control. The high-dose photon/proton RT treatment plan of an 18-year-old woman with an unresected osteosarcoma of the sacrum treated by chemoradiation is shown in Fig 7. This patient remains free of tumor or radiation-associated complications over 4 years after the end of RT.

Intensity-Modulated Proton Therapy

Intensity modulation can also be applied to proton beams (IMPT), potentially further optimizing the dose distribution. The unresolved question is whether this optimized physical dose distribution will be accompanied by an important clinical advantage. This cannot be answered by physical analysis alone, and clinical trials are needed to definitively answer this question. Dosimetric comparisons, however, demonstrate reductions in doses to normal tissues with IMPT that may prove to have a clinically significant impact on toxicity for the patient.

Lomax et al\textsuperscript{33} compared the merits and limitations of IMRT and IMPT. The comparison suggested that the use of IMRT, when compared to IMPT, resulted in similar levels of conformity of dose around the tumor. However, compared to IMRT, IMPT substantially reduces the integral (normal tissue) dose to organs at risk.\textsuperscript{45} At our institute, we undertook a dosimetric optimization effort to compare IMRT to IMPT in the treatment of spinal and paraspinal sarcomas.\textsuperscript{35} Gross tumor volume coverage was excellent with both IMRT and IMPT plans. The use of IMPT led to a substantial reduction of the integral dose in the low- to mid-dose level to organs at risk (Fig 4). Median heart, lung, kidney, stomach, and liver mean dose and dose at the 50% volume level were consistently reduced by a factor of 1.3 to 25 compared with IMRT. In addition, IMPT dose escalation (85.1 and 92.9 CGE) was possible in all patients, within the specified normal tissue dose constraints.

IMPT with a spot scanning beam has been delivered for the boost component of treatment at the Paul Scherrer Institute in Switzerland.\textsuperscript{56} Raster-scanned carbon-ion RT is used to treat patients at GSI in Germany.\textsuperscript{26}

Heavier Charged Particles

Encouraging results have been achieved in 52 patients with tumors adjacent to and/or involving the cervical, thoracic, or lumbar spine who were treated between 1976 and 1987 with heavier-charged particle therapy at the University of California Lawrence Berkeley Laboratory.\textsuperscript{64} Patients were treated with helium ions, which have physical dose-distribution advantages and biologic characteristics similar to protons; they were also treated with heavier neon ions, which are high LET particles that have excellent physical dose localization and also a higher RBE that might have additional biologic advantage against hypoxic or slowly proliferating tumors. The histologies included chordoma and chondrosarcomas in 24 patients, other bone and soft tissue sarcomas in 14, and metastatic or unusual histology tumors in 14. Radiation doses ranged from 29 to 80 CGE (median 70 CGE). Twenty-one patients received a portion of their treatment with photons. Median follow-up was 28 months. Local control was achieved in 21 (58%) of 36 previously untreated patients, and the 3-year actuarial survival rate was 61%. Seven of 16 patients treated for recurrent disease were locally controlled, and the 3-year actuarial survival was 51%. For patients treated for chordomas and chondrosarcomas, the probability of local control was influenced by tumor volume (less than 100 cc or greater than 150 cc) and whether disease was recurrent or previously untreated. Six of the 52 patients experi-
enced complications including one spinal cord injury, 1 cauda equina, 1 brachial plexus injury, and 3 instances of skin or subcutaneous fibrosis.

Schoenthaler et al from the same institute reported on 14 patients with sacral chordomas who were treated postoperatively; 10 had gross residual disease. The median dose was 75.65 CGE and the Kaplan-Meier survival rate at 5 years was 85%. The overall 5-year local control rate was 55%. A trend towards improved local control at 5 years was seen in patients treated with neutron compared with patients treated with helium (62% vs 34%), in patients following complete resection compared with patients with gross residual tumor (75% vs 40%), and in patients who had treatment courses under 73 days (61% vs 21%). No patient developed neurologic sequelae or pain syndromes. One previously irradiated patient required a colostomy, 1 had delayed wound healing following a negative postradiation biopsy, and 1 developed a second malignancy. There were no genitourinary complications. On the basis of that experience, the investigators concluded that additional evaluation of heavy charged particles was warranted.

Current interest in heavy charged particles is focused on carbon ions because of their excellent physical dose deposition and the higher RBE associated with their high LET. Kamada et al reported the results of a phase I/II study evaluating the tolerance for and effectiveness of carbon-ion RT in patients with unresectable bone and soft tissue sarcomas treated on the Heavy Ion Medical Accelerator (HIMAC) at the National Institute of Radiological Sciences in Chiba, Japan. Fifty-seven patients with 64 sites of bone and soft tissue sarcomas not suited for resection were treated. 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 gray equivalent (GyE) and was administered in 16 fixed fractions over 4 weeks (3.3 to 4.6 CGE/fraction). Seven of 17 patients treated with the highest total dose of 73.6 CGE experienced Radiation Therapy Oncology Group grade 3 acute skin reactions. Dose escalation was then halted at this level. No other severe acute reactions (grade ≥3) were observed in this series. The overall local control rates were 88% at 1 year and 75% at 3 years of follow-up. The 1- and 3-year overall survival rates were 82% and 46%, respectively. A more recent report describes the successful treatment of a patient with a cervical osteosarcoma using carbon ions.

Imai et al reported a retrospective analysis of 30 patients with unresectable sacral chordomas treated with carbon-ion RT at HIMAC in Chiba, Japan. Twenty-three patients presented with no prior treatment, and the remaining 7 patients had locally recurrent disease following previous surgical resection. The median clinical target volume was 546 cm³. The applied carbon-ion dose ranged from 52.8 to 73.6 CGE (median 70.4) in 16 fractions over 4 weeks. At a median follow-up of 30 months (range 9 to 87 months), 20 patients were still alive and 24 patients remained continuously disease-free. Overall and cause-specific survival rates at 5 years were 52% and 94%, respectively. The overall local control rate at 5 years was 96%. Two patients experienced severe skin/soft tissue complications requiring skin grafts. No other treatment-related surgical interventions, including colostomy or urinary diversion, were carried out. All patients have remained ambulatory and able to stay at home after carbon-ion RT. These results suggest that carbon-ion RT is effective and safe in the management of patients with unresectable sacral chordomas and offers a promising alternative to surgery.

At GSI, 87 patients with chordomas and low-grade chondrosarcomas of the skull base received raster-scanned carbon-ion RT alone (median dose 60 CGE). Seventeen patients with spinal (n = 9) and sacrococcygeal (n = 8) chordomas and chondrosarcomas were treated with combined photon and carbon-ion RT. Actuarial 3-year local control rates were 81% for chordomas and 100% for chondrosarcomas. Of these 17 patients, local control was obtained in 15 patients (8 with spinal and 7 with sacral chordomas or chondrosarcomas). Common Toxicity Criteria grade 4 or grade 5 toxicity was not observed. The investigators concluded that carbon-ion therapy was safe with respect to toxicity and offers high local control rates for skull base tumors such as chordomas and low-grade chondrosarcomas. Because of concern about potential late normal tissue effects with the higher LET/RBE carbon ions, further follow-up is warranted on these interesting results.

### Bone-Seeking Radioisotopes

Osteoblastic metastases and osteosarcomas can avidly concentrate bone-seeking radiopharmaceuticals. High-dose 153Sm-samarium-ethylenediaminetetramethylene phosphonate (153Sm-EDTMP, Quadramet) has been evaluated for its efficacy against osteosarcomas, both alone and in conjunction with using a radiosensitizer, gemcitabine. Anderson et al initially treated 30 patients with locally recurrent or metastatic osteosarcomas or skeletal metastases avid on bone scan with escalating doses (1, 3, 4.5, 6, 12, 19, or 30 mCi/kg) of 153Sm-EDTMP. Transient symptoms of hypocalcemia were seen at 30 mCi/kg. Cytopenias also occurred in all subjects and were dose-related. After peripheral blood progenitor cells (PBPCs) or marrow infusion on day +14 after 153Sm-EDTMP, recovery of hematopoiesis was problematic in 2 patients at the 30 mCi/kg dose infused with less than 2 × 10⁶ CD34+ cells/kg on day +14 but not in other patients. Reduction or elimination of opiates for pain was seen in all patients. Patients had no adverse changes in appetite or performance status. The authors believed that 153Sm-EDTMP with PBPC support could provide bone-specific therapeutic irradiation.
tion (estimates of 39 to 241 Gy). Hematologic toxicity at 30 mCi $^{153}$Sm-EDTMP/kg required PBPC grafts with more than $2 \times 10^9$ CD34+/kg to overcome the myeloablative effects of skeletal irradiation. Nonhematologic side effects were minimal.

These investigators later evaluated the addition of gemcitabine to this approach. They used 30 mCi/kg $^{153}$Sm-EDTMP to treat 14 patients with osteoblastic lesions. Gemcitabine was administered 1 day after samarium ($^{153}$Sm) infusion. All patients received autologous stem cell reinfusion 2 weeks after $^{153}$Sm to correct expected grade 4 hematopoietic toxicity. PBPCs were infused in 11 patients, and 3 patients had marrow infused. Blood count recovery was uneventful after PBPCs in 11 of 11 patients. Toxicity from a single infusion of gemcitabine (1,500 mg/m$^2$) in combination with $^{153}$Sm-EDTMP was minimal (pancytopenia). However, toxicity from a daily gemcitabine regimen (250 mg/m$^2$ per day $\times$ 4 to 5 days) was excessive (grade 3 mucositis) in 1 of 2 patients. There were no reported episodes of hemorrhagic cystitis (hematuria) or nephrotoxicity. At the 6- to 8-week follow-up, there were 6 partial remissions, 2 mixed responses, and 6 patients with progressive disease. The investigators believed that this strategy of radioactive drug binding to a target followed by a radiosensitizer may provide synergy and improved response rate. Nevertheless, in the 12 patients followed for more than 1 year, there were no durable responses. Thus, although high-dose $^{153}$Sm-EDTMP plus gemcitabine had moderate palliative activity (improved pain, radiologic responses) in this poor-risk population, additional measures of local and systemic control were thought to be necessary for durable control of relapsed osteosarcomas with osteoblastic lesions.

**Sarcomas of the Skull Base**

Proton RT for skull base and cervical spine chordomas and chondrosarcomas has resulted in the best long-term outcome data ever reported for these entities. Proton irradiation is considered by many neurosurgeons and radiation oncologists around the world to be the treatment of choice following surgical resection. Fractionated proton radiotherapy allows the delivery of high radiation doses to tumors of the skull base while respecting normal tissue constraints. Relatively few significant complications have been observed, when considering the high doses delivered and when weighed against the certainty of major morbidity associated with otherwise uncontrollable tumor growth in such patients.

Outcome is substantially more favorable with chondrosarcomas than with chordomas, with local control at 10 years of 94% and 54%, respectively. In the MGH Harvard Cyclotron Laboratory (MGH/HCL) series of patients with chordomas, male patients had more favorable outcome that female patients, with local recurrence-free survival rates at 5 years of 81% vs 65% ($P=0.035$) and at 10 years of 65% vs 42% ($P=0.007$), respectively. Hug et al. reported a more favorable outcome in skull base chordomas if the tumor volume at the time of proton radiotherapy was $\leq 25$ cc. Patients with extensive abutment or compression of critical organs at risk (ie, brainstem, optic structures) by chordomas fare worse because normal tissue radiation constraints compromise the dose that can be delivered to the tumor target. Patients with chordomas also appear to have a favorable prognosis if they undergo proton radiotherapy at the time of primary disease, if they are of younger adult age, and if they have the non-chondroid variant.

Late, severe adverse events were reported by the MGH/HCL group in 8% of their patient population (20 patients), including 12 instances of symptomatic or asymptomatic brain changes, 3 patients with unilateral and 2 patients with bilateral blindness, and 4 instances of unilateral deafness. Several risk factors have been identified predicting severe adverse events. Debus et al. found that a dose of $\geq 60$ Gy (RBE) to a volume of brainstem $\geq 0.9$ cc was more important in predicting brainstem damage than was the maximum dose. Diabetes, a history of smoking, hypertension, and repeat surgical resections led to reduced tolerance of the normal brainstem.

Prior to the advent of 3-dimensional treatment planning and highly conformal radiation techniques such as protons and IMRT, attempts to deliver tumoricidal radiation doses to tumors in the skull base were limited by critical normal tissue tolerance. In that era, photon radiation doses ranged between 50 and 60 Gy and, not surprisingly, tumors recur locally in 70% to 100% of the patients treated. However, the recently published series of Hacettepe University in Ankara, Turkey, used modern imaging and radiation treatment techniques but at conventional doses. A 5-year progression-free survival rate of 23% and an overall survival rate of 35% in 18 patients with clival chordomas following 50 to 64 Gy confirm the poor outcome with these doses and emphasize the importance of high target doses.

In stark contrast, proton radiotherapy with mean doses of 71 CGE in the Loma Linda series and of doses up to 85 CGE at MGH/HCL resulted in improved tumor control. At present, almost all patients undergoing proton radiotherapy worldwide receive fractionated doses greater than 66 CGE. Stereotactic and IMRT photon techniques now permit the delivery of higher radiation doses to skull base tumors with photons than had been possible in the past. No phase III trial has been conducted that prospectively compares various photon-based radiation modalities with protons. The scientific value of comparing single institution data is limited, given for example the differences in patient selection criteria. Using 3-dimensional conformal, fractionated techniques under stereotactic guidance, Debus et al.
reported results of stereotactic photon radiotherapy in 45 patients with skull base chordomas or chondrosarcomas. Median dose levels were 66.6 Gy for chordomas and 64.9 Gy for chondrosarcomas, thus lower compared to photons but higher than historic, conventional photon techniques. All patients with chondrosarcomas remained locally controlled at 5 years. The local control rate for chordomas was 50% at 5 years and appeared to be improved compared to conventional photons but still inferior compared to photons.

The most mature data on Gamma knife radiosurgery have been reported by the Mayo Clinic. Krishnan et al analyzed 29 patients, 4 with chondrosarcomas and 25 with chordomas, treated radiosurgically and followed for a median 4.5 years. All 4 patients with chondrosarcomas remained locally controlled. However, the 5-year actuarial local control rate had dropped to 32% for patients with chordomas, despite the rather modest median pretreatment tumor volume of 14.4 cm³. Ten patients (34%) experienced radiation-related complications.

Chang et al noted only 2 failures in 12 patients treated with either radiosurgery or hypofractionated stereotactic radiotherapy for chordomas of the skull base or cervical spine. Tumor volumes ranged from 1.1 to 21.5 mL and follow-up averaged 4 years. A similar report from Seoul, Korea, on the use of hypofractionated, stereotactic radiotherapy noted one failure in 9 patients at a median follow-up period of 24 months but also 2 occurrences of myelopathy. Several groups are currently exploring IMRT for use in skull base sarcomas, and it is anticipated that results with this technique will be reported in the near future.

Carbon-ion RT has been used by the German group at GSI. Four-year local control rates for chordomas and low-grade chondrosarcomas of the skull base in 67 patients were 74% and 87% at 4 years, respectively. This translated into overall survival rates at 4 years of 86% for chordomas and 100% for chondrosarcomas. Toxicity was reported to be mild.

Pelvic Sarcomas

Surgical resection has been used for the treatment of the primary tumor in the majority of patients with pelvic sarcomas, although for patients with radiation-sensitive tumors such as Ewing’s sarcoma, primary RT has also been employed. Aggressive surgery improves local control in pelvic tumors. Limb salvage is possible in patients with a pelvic sarcoma but such surgery is extensive and can be associated with a substantial rate of local complications along with functional and cosmetic disadvantages. Because radical surgery can cause severe morbidity, quality of life and function must be considered along with survival when outcomes are analyzed for these tumors. Conventional RT for pelvic sarcomas can also be associated with significant morbidity. In young patients (median age 14.5 years) undergoing radiation in conjunction with chemotherapy for pelvic Ewing’s sarcoma, significant late effects include muscular atrophy and limb length growth delay. Recent planning studies have shown that protons deliver superior target dose coverage and better sparing of normal tissue than 3-D conformal radiotherapy or IMRT for pelvic sarcomas. As dose-volume parameters are expected to correlate with acute and late toxicity, proton therapy should receive serious consideration as the preferred radiation technique for the treatment of these tumors. We have had some initial experience with management of these pelvic sarcomas. On the basis of our favorable experience with proton treatment for chondrosarcomas of the base of the skull with local control of 95% at 10 years and our experience with protons for spine osteosarcomas and chondrosarcomas, we have treated 3 patients who declined radical surgery for treatment of periacetabular chondrosarcomas. They were irradiated with protons following biopsy only or curettage and methylmethacrylate (MMA) cement or bone packing to doses of 74 CGE (Fig 8). With follow-up of 18 to 36 months, the tumor has been locally controlled in 2 of the patients; the third has experienced a marginal recurrence of tumor at the edge of the treated volume, requiring radical surgery for salvage. There has been no significant morbidity related to treatment to date and patients were able to ambulate free of assistive devices after radiotherapy. We have proposed a protocol of conservative surgery and proton RT as an alternative treatment for those patients with pelvic sarcomas who decline radical surgery. We think it is reasonable to also include patients with periacetabular and sacral osteosarcomas who decline radical surgery in the protocol based on recent data supporting a role for RT in patients with osteosarcomas who respond to chemotherapy.
Ewing’s Sarcoma

Management of truncal, craniofacial, spinal, and pelvic Ewing’s sarcoma is complex due to (1) the critical importance of the normal structures in the vicinity of the tumor and (2) the frequent need for surgical resection with positive or close margins. For these sites, surgical resection and radiation can be limited by the proximity of the tumor to critical organs such as liver, kidney, bowel, and great vessels. Local failure rates are often more than 50%. Highly localized dose distributions offer the possibility of increasing local control as well as decreasing late effects. Smith et al. performed a treatment planning comparison between intensity-modulated photons with intensity-modulated protons for a patient with a pelvic Ewing’s sarcoma and noted sparing of the intestine, rectum, bladder, and femoral head in the proton plan compared to the photon plan. These results demonstrate a significant potential for reduction of treatment morbidity for the proton plan compared to the photon plan. In addition to less acute morbidity to bowel and marrow during concurrent chemoradiation, one would anticipate a reduction in late radiation-induced tumors, which are a problem with conventional photon RT for these patients. Proton beam RT has been approved for use in Children’s Cooperative Oncology Group protocols.

Chest Wall Sarcomas

Ewing’s sarcoma/primitive neuroectodermal tumor (ES/PNET) is the most frequent malignant tumor of the chest wall in children and young adults. A review of patients with chest wall PNET treated on two consecutive cooperative group studies (Intergroup 0091 and Pediatric Oncology Group 9354) demonstrated a higher rate of negative surgical margins with delayed resections at week 12 following induction chemotherapy (77%) vs initial resections at presentation (50%; P=.043). Because the indications for RT in patients with Ewing’s sarcoma are generally positive surgical margins or unresected tumors, the use of initial chemotherapy decreased the percentage of patients needing RT. Seventeen (70.8%) of 24 patients with initial surgery received RT compared with 34 (47.9%) of 71 patients who started with chemotherapy (P=.061). For patients needing RT, protons can markedly reduce the radiation dose to underlying lung and heart. For patients in whom positive surgical margins are anticipated, preoperative irradiation has conceptual appeal as it can avoid seeding of tumor and unnecessary irradiation of scars and drain sites. For patients presenting with malignant pleural effusions, pleural seeding, or operative contamination of the pleural surfaces at presentation, hemithorax irradiation (generally 15 Gy in 10 fractions for children ≥6 years of age and 12 Gy in 8 fractions for children <6 years of age) has been employed in addition to irradiation of the primary site.

Cost of Proton Radiation Therapy

Although proton therapy clearly is capable of providing superior dose distributions compared to photon therapy, the treatment comes at a greater financial cost. Many of the current-generation, hospital-based facilities are expected to cost approximately $100 million US. The issue of cost effectiveness for proton treatment is starting to be explored and is likely to receive more attention in the near future as the clinical outcomes of proton therapy trials become available. Before attempting to determine if clinical gains justify increased cost, it is important to be aware of the relative cost of proton therapy compared to the cost of photons. This is not determined easily and is likely is to change with time but has been estimated.

Goitein et al performed a detailed study comparing the cost for a single treatment with the most technologically advanced forms of proton and photon treatment available, IMPT and IMRT. The authors’ 2003 estimate was that the cost of proton treatment was a factor of 2.4 times higher than photon treatment, but a decrease in this disparity was projected to occur with time. Capital expenditure (construction costs) and operating expenditure were considered separately. Construction costs were the dominant factor responsible for the cost difference. It was anticipated that, as more proton facilities are built, construction costs would decrease due to competition, re-engineering, and recovery of costs. A 25% decrease was expected for protons but not for photon therapy due to the fact that this technology is more mature. In terms of operating costs, a decrease was also projected for the cost for protons as more experience is gained in machine maintenance and treatment delivery becomes more efficient. Together, these improvements would bring the ratio of proton to photon cost down to 2.1. With additional improvements, the authors estimated that the cost ratio could drop to as low as 1.7. If capital expenditure were to be provided by the state or philanthropic means, this ratio could decrease even further to a ratio of 1.3 or less. There has also been interest recently in smaller, “single-room” proton treatment facilities; these may be less expensive but as these have not been built yet, the actual cost associated with these facilities remains to be determined.

Lundkvist et al have studied the potential cost effectiveness of proton therapy in two groups of patients: pediatric patients with medulloblastoma and breast cancer patients with left-sided tumors. Though limited data are available on the long-term consequences of radiation and the cost to the healthcare system and to society, the authors concluded that proton therapy can be cost effective for select groups of patients. RT, an important component in the treatment of medulloblastoma, is associated with late adverse events in some patients. Because of the absence of exit dose, proton RT has potential to reduce the risk of
adverse events compared with conventional radiation, but it is associated with a higher, initial treatment cost. The authors assessed the cost effectiveness of proton therapy compared with conventional RT in the treatment of a 5-year-old child with medulloblastoma. The patients were considered to be at risk of several types of adverse events, including hearing loss, intelligence quotient (IQ) loss, hypothyroidism, growth hormone deficiency (GHD), osteoporosis, cardiac disease, and secondary malignancies. The patients also were at risk of death and were divided into risk groups for normal death, death due to tumor recurrence, treatment-related cardiac death, treatment-related subsequent tumor death, or treatment-related other death. A review of the literature was conducted to estimate the parameters in the model. The base-case results showed that proton therapy was associated with €23,600 Euro (approximately $34,500 US at this writing) in cost savings and 0.68 additional quality-adjusted life-years per patient. The analyses showed that reductions in IQ loss and GHD contributed to the greatest part of the cost savings and were the most important parameters for cost effectiveness. The results indicated that proton RT could be cost effective and cost saving compared with conventional RT in the treatment of children with medulloblastoma if the appropriate patients are selected for the therapy. However, they also stressed that there have been few long-term follow-up studies, and more information on the long-term consequences of RT is needed.

This group of investigators also studied patients with left-sided breast cancer and documented that a decrease in cardiac death would be anticipated with proton treatment compared with conventional RT. The authors were interested in evaluating whether the medical benefits of proton therapy were large enough to justify the higher treatment costs. They assessed the cost effectiveness of proton therapy in the treatment of 55-year-old women with left-sided breast cancer. Cost and quality-adjusted life years (QALYs) were the primary outcome measures. The study found a cost per QALY gained of €67,000 Euro (approximately $91,000 at this writing) for the base case analysis of an average breast cancer patient. However, the cost per QALY gained would be considerably lower if a population with high risk of developing cardiac disease was treated. The results indicate that proton therapy for breast cancer could be cost effective if appropriate risk groups were chosen as targets for the therapy.

Carbon-ion facilities are anticipated to be more costly than proton facilities. Relatively little comparative cost information is available. The proton/carbon-ion facility in Hyogo, Japan, which opened in April 2001, was built at a cost of 28 billion yen (approximately US $253 million), which suggests that these facilities will present significant cost issues. Commercial vendors, however, are currently offering fixed carbon-ion beam facilities that are expected to be less costly.

Conclusions

High-technology intensity-modulated photon and charged-particle radiation techniques are allowing the delivery of substantially higher radiation doses than could be delivered in the past to patients with bone sarcomas while simultaneously reducing the doses to critical normal tissues. Local control has been improved with these high doses. These techniques are particularly promising for lesions in challenging axial sites where resections are often incomplete or associated with significant morbidity. The use of protons reduces the integral dose to normal tissue, often by 2- to 3-fold; this can only reduce the risk of late radiation-associated complications. Protons have been successfully combined with chemotherapy for the treatment of adult and pediatric sarcomas. Heavier charged particles have greater RBE because of their higher LET properties, and some interesting results are available with neon and carbon ions for bone sarcomas. Randomized comparative trials are warranted to determine if they are more effective than protons.

Appreciation is expressed to Judy Adams, CMD, and her colleagues at the Francis Burr Proton Therapy Center for their assistance in providing the treatment planning images.

Disclosures

This work was supported in part by NIH grant 5 P01 CA021239-28. No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.

The editor of Cancer Control, John Horton, MB, ChB, FACP, has nothing to disclose.

References

36 Cancer Control

January 2008, Vol. 15, No. 1


