



Dorothy Fox. *Card Game in Asolo*. Watercolor, 30" × 36".

*Modern radiotherapy options and techniques have improved outcomes for patients with sarcomas.*

# Advanced-Technology Radiation Therapy in the Management of Bone and Soft Tissue Sarcomas

Thomas F. DeLaney, MD, Alexei V. Trofimov, PhD, Martijn Engelsman, PhD,  
and Herman D. Suit, MD, DPhil

**Background:** For patients with sarcomas, radiotherapy can be used as neoadjuvant, adjuvant, or primary local therapy, depending on the site and type of sarcoma, the surgical approach, and the efficacy of chemotherapy.

**Methods:** The authors review the current status of advanced technology radiation therapy in the management of bone and soft tissue sarcoma.

**Results:** Advances in radiotherapy have resulted in improved treatment for bone and soft tissue sarcomas. Intensity-modulated radiation therapy (IMRT) uses modifications in the intensity of the photon-beam from a linear accelerator across the irradiated fields to enhance dose conformation in three dimensions. For proton-beam radiation therapy, the nuclei of hydrogen atoms are accelerated in cyclotrons or synchrotrons, extracted, and transported to treatment rooms where the proton beam undergoes a series of modifications that conform the dose in a particular patient to the tumor target. Brachytherapy and intraoperative radiation therapy have generally been used to treat microscopic residual disease in patients with sarcomas. These technologies deliver dose to tumor cells with irradiation of limited volumes of normal tissue. Patients who may benefit from technically advanced radiotherapy include those with skull base and spine/paraspinal sarcomas, Ewing's sarcoma, and retroperitoneal/extremity sarcomas.

**Conclusions:** Advances in radiation therapy technology, particularly IMRT, proton-beam or other charged-particle radiation therapy, brachytherapy, and intraoperative radiation therapy, have led to improved treatment for patients with bone and soft tissue sarcomas.

From the Department of Radiation Oncology, Northeast Proton Therapy Center, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

Submitted July 19, 2004; accepted November 3, 2004.

Address correspondence to Thomas F DeLaney, MD, Northeast Proton Therapy Center, Massachusetts General Hospital, 30 Fruit Street, Boston, MA 02114. E-mail: tdelaney@partners.org

No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.

This work is supported in part by grant CA21239 from the US National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

**Abbreviations used in this paper:** BT = brachytherapy, CGE = cobalt Gray equivalent, GyE = carbon Gray equivalent, IMPT = intensity-modulated proton radiation therapy, IMRT = intensity-modulated radiation therapy, IORT = intraoperative radiotherapy, LET = linear energy transfer, RBE = relative biologic effect, RT = radiation therapy.

## Introduction

Contemporary management of sarcomas often includes a multidisciplinary approach using a combination of surgery, radiotherapy, and chemotherapy specific for tumor type, histologic grade, and stage of disease. Radiotherapy can be employed as neoadjuvant (preoperative), adjuvant (postoperative), 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 radiotherapy is frequently used for large, deep soft tissue sarcomas<sup>1</sup> and can also be delivered prior to resection of spine<sup>2</sup> or pelvic sarcomas.<sup>3</sup> Adjuvant radiation is utilized in many centers following resection of soft tissue sarcomas if tumor, or surgically contaminated tissues in patients with incomplete excision, cannot be excised with a minimum of 1 cm of healthy tissue or an intact fascial plane.<sup>4</sup> It is also used for patients with bone sarcomas with positive or inadequate margins and in selected other situations that might include presentation with a pathologic fracture,<sup>5</sup> poor histologic response to chemotherapy,<sup>6</sup> 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. Radiotherapy as the primary local therapy without surgery or in conjunction with subtotal resection is used for soft tissue sarcomas that are medically inoperable,<sup>7</sup> for axial Ewing's sarcomas or extremity Ewing's sarcomas where surgery would compromise function,<sup>8</sup> and for primary bone tumors involving the upper sacrum,<sup>9</sup> the base of skull, and some arising in the ethmoid/sphenoid sinus region.<sup>10</sup>

Radiation therapy (RT) is most commonly given by externally directed beams but can also be given by brachytherapy (BT) or intraoperative techniques. BT utilizes temporary or permanent radiation sources that are placed either into or adjacent to tumor tissue. BT has been used in the adjuvant radiation of soft tissue sarcomas.<sup>11</sup> More recently, it has been applied on the dura and paraspinal tissues for spine and paraspinal tumors<sup>2,12,13</sup> and for some Ewing's sarcomas with inadequate surgical margins.<sup>14</sup> Intraoperative radiotherapy (IORT) with electron beam or orthovoltage is delivered to the tumor bed at surgery to boost the dose to retroperitoneal,<sup>15</sup> paraspinal and spinal, and pelvic sarcomas.<sup>16</sup> BT and IORT, although technically challenging, have been adopted in many specialized centers because of their dosimetric advantages over conventional external RT. BT and IORT allow higher radiation doses to the tumor while sparing normal tissue, which results in higher tumor control and fewer normal tissue complications. In the case of BT, this is achieved by placing radiation sources in close contact with the tumor bed and the rapid fall-off in dose away from the radiation sources. Traditionally, this has been done with low-dose-rate iridium-192 (and occasionally less energetic iodine-125), but more recently high-dose-rate sources have been

employed.<sup>17</sup> In the case of IORT, this is achieved by moving critical normal tissues such as bowel, kidney, or lung out of the IORT beam at the time of surgery.

## Historical Gains From Reductions in Treatment Volumes

The advantages of RT technology have been amply demonstrated over the years.<sup>18</sup> With the adoption of megavoltage cobalt units, RT doses were no longer limited by the acute skin reaction but could be increased to match the much greater radiation tolerance of the deeper structures. The use of linear accelerators in the 1970s further improved the achievable dose distribution, as did the use of RT simulators to plan treatment and the use of individually shaped portals. The adoption of BT and IORT improved dose distribution and the clinical results at a variety of clinical sites including sarcomas.<sup>15,19</sup> Most recently, the combination of computer-based treatment planning<sup>20</sup> and modern imaging technologies (computed tomography, magnetic resonance imaging, and positron emission tomography)<sup>21,22</sup> have enhanced the delivery of radiation to the tumor while minimizing normal tissue dose. Hence, the smaller treatment volumes, the reduction of normal tissue dose and volume irradiated, and the increase in achievable dose to the tumor target will likely result in clinical gains in cancer therapy.

Intensity-modulated radiation therapy (IMRT) allows higher radiation doses to selected volumes of tumor than could be achieved with earlier three-dimensional (3-D) conformal techniques and also allows shaping of the dose around selected adjacent normal tissues.<sup>23</sup> However, this usually comes at the cost of higher integral doses to larger volumes of normal tissue away from the tumor.<sup>24</sup> These doses may not have significant clinical consequences in older patients, but their potential late effects on developing normal tissues in pediatric patients, as well as their potential to induce second malignancies, present a concern.<sup>25</sup>

## Conformal Radiotherapy

Conformal RT refers to a variety of techniques that attempt to closely contour the radiation dose around the tumor and limit dose to surrounding normal tissue, simultaneously improving local tumor control and reducing normal tissue complications. These conformal techniques include proton or charged-particle RT,<sup>26</sup> 3-D conformal photon RT,<sup>20</sup> IMRT,<sup>27</sup> and stereotactic radiotherapy<sup>28</sup> or stereotactic radiosurgery.<sup>29</sup> From a technical perspective, it is worth noting that many specialized devices for radiosurgery have maximum collimator sizes of  $\leq 6$  cm, which limits their utility for treatment of many primary sarcomas.

The conformal radiation techniques all use computed tomography and/or magnetic resonance imaging of the

tumor and adjacent normal tissue. These are then transferred to a 3-D RT treatment-planning computer<sup>30</sup> to design beam trajectories in order to maximize dose to tumor and optimally spare adjacent normal tissues. Patient positioning is verified by diagnostic imaging prior to radiation delivery to assure that the tumor is aligned with the trajectory of the radiation beam.<sup>31,32</sup>

These increasingly conformal techniques allow higher doses to be delivered to the target volume, thus achieving a higher tumor control probability. Likewise, these more conformal treatment volumes, especially with proton therapy, should result in a reduced frequency and severity of comorbidity between radiation and chemotherapy, thus minimizing toxicity-induced interruptions in treatment that might compromise its efficacy.<sup>17,25,33,34</sup>

## Proton-Beam Radiotherapy

The rationale for the use of protons (or other charged particles) rather than photons (ie, x-rays, which have traditionally been used for RT) is the superior dose distribution that can be achieved with protons. 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 (Fig 1).<sup>35,36</sup> 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 over the depth of the target. These extended regions of uniform dose are called spread-out Bragg peaks. 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 (Fig 1).<sup>35,37</sup>

The major emphasis for proton therapy clinical research initially was dose escalation for tumors for which local control with conventional RT was poor,<sup>38</sup> including base of skull and spine tumors,<sup>10</sup> locally advanced prostate cancer,<sup>39</sup> hepatocellular carcinoma,<sup>40</sup> and non-small-cell lung cancer.<sup>41</sup> The 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 radiotherapy can be extended to a wider range of clinical sites than in the past. There is

increasing interest in protocols aimed at morbidity reduction in those tumor sites in which tumor control with photons is good. 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. It is to be emphasized that dose escalation and morbidity reduction are not mutually exclusive when using protons and that the opportunity for both may be present in any given patient.

## 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.<sup>42</sup> "X" and gamma 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 relative biologic effect (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.

The use of helium and heavier neon-charged particles for the treatment of sarcomas has also been reported. At the University of California Lawrence

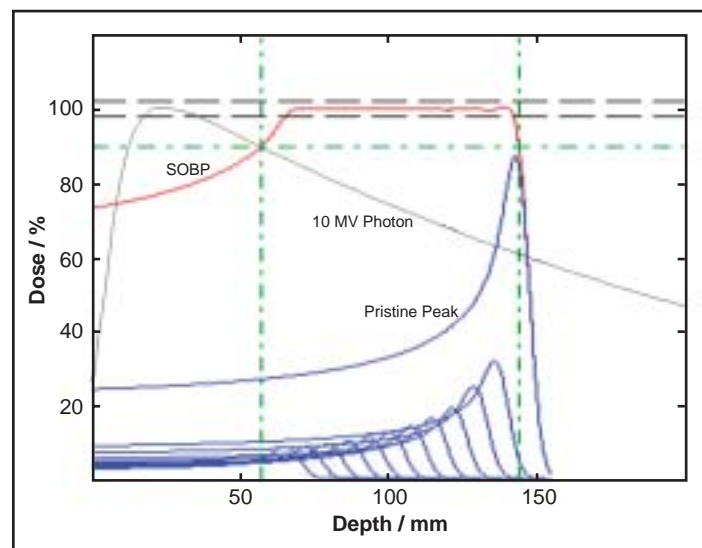


Fig 1. — Depth-dose distributions for a spread-out Bragg peak (SOBP), its constituent pristine Bragg peaks, and a 10-MV photon beam. The SOBP dose distribution is created by adding the contributions of individually modulated pristine Bragg peaks. The penetration depth, or range and measured as the depth of the distal 90% of plateau dose, of the SOBP dose distribution is determined by the range of the most distal pristine peak. The modulation width, as measured as the distance between the proximal and distal 90% of plateau dose values, of the SOBP dose distribution is controlled by varying the number and intensity of pristine Bragg peaks that are added, relative to the most distal pristine peak, to form the SOBP. The dashed lines indicate the clinically acceptable variation in the plateau dose of  $\pm 2\%$ . The dot-dashed lines indicate the 90% dose and spatial 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 depth-dose distribution. Note the absence of dose beyond the distal fall-off edge of the SOBP. Courtesy of Hanne M. Kooy, PhD, Northeast Proton Therapy Center, Massachusetts General Hospital, Boston, Mass.

Berkeley Laboratory and Medical Center at San Francisco, helium ions were utilized mainly for their physical dose-distribution advantages, and heavier neon ions were employed mainly for their LET biologic advantages. Fourteen patients with sacral chordomas were treated with helium and neon ions between 1977 and 1989.<sup>43</sup> All patients were treated postoperatively, and 10 had gross residual disease. The median dose was 75.65 cobalt Gray equivalent (CGE). The actuarial survival rate at 5 years was 85%, and the overall 5-year local control rate was 55%. A trend to improved local control rate at 5 years was seen in patients treated with neon (62%) compared to patients treated with helium (34%), in patients following complete resection (75%) vs patients with gross residual tumor (40%), and in patients who had treatment courses less than 73 days (61%) vs longer than 73 days (21%). No patient developed neurologic sequelae or pain syndromes. One previously irradiated patient required colostomy, 1 had delayed wound healing following a negative postradiation biopsy, and 1 developed a second malignancy. On the basis of that experience, the investigators felt that additional evaluation of heavy charged particles was warranted.

Current interest in heavier charged particles is focused on carbon ions because of their excellent physical dose deposition and the higher RBE associated with their high LET. The Heavy Ion Medical Accelerator in Chiba, Japan, began clinical studies in 1994. Kamada et al<sup>44</sup> recently 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. Fifty-seven patients with 64 tumors not suited for resection received carbon ion RT. Tumors involved the spine or paraspinal 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 GyE/fraction). Seven of 17 patients treated with the highest total dose of 73.6 GyE 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 local control rate was 73% at 3 years, and the overall survival rate at 3 years was 46%.

Raster-scanned carbon ion RT at the Gesellschaft für Schwerionenforschung in Darmstadt, Germany, has been used to treat patients since 1997. Carbon ion RT alone (median dose of 60 GyE) was given to 87 patients with chordomas and low-grade chondrosarcomas of the skull base, and 17 patients with spinal (n = 9) and sacrococcygeal (n = 8) chordomas and chondrosarcomas were treated with combined photon and carbon ion RT. The actuarial 3-year local control rate was 81% for skull base chordomas and 100% for chondrosarcomas.<sup>45</sup> Local control was obtained in 15 of 17 patients with spinal (8 of 9 patients) and sacral (7 of 8 patients) chordomas or chondrosarcomas. Common

Toxicity Criteria grade 4 or 5 toxicity was not observed. The investigators believed that carbon ion therapy is safe with respect to toxicity and offers high local control rates for these lesions. Because of concern about potential late normal tissue effects with the higher LET/RBE carbon ions, further follow-up is warranted on these results.

## Intensity-Modulated Photon Radiation Therapy

Recent dosimetric studies<sup>20</sup> comparing IMRT and 3-D conformal RT for soft tissue sarcoma 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 extraskelatal chondrosarcoma of the extremity.<sup>46</sup> 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. Hong et al<sup>47</sup> performed treatment planning comparisons of IMRT and 3-D conformal RT for 10 patients with soft tissue sarcoma of the thigh. They reported a reduction in femur dose without compromise in tumor coverage. In addition, IMRT reduced hot spots in the surrounding soft tissues and skin. In the head and neck region, the normal tissue complication probabilities were correspondingly reduced.<sup>48</sup>

It should be noted 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.<sup>49</sup> Whether there are late effects attributable to these focal areas of high dose remains unclear. Distribution of 3-D conformal proton doses is generally more homogeneous, although focal hot spots can also arise where fields are junctioned or "patched."

## Intensity-Modulated Proton Radiation Therapy

Intensity modulation can also be applied to proton beams (IMPT), potentially optimizing the dose distribution even further. The unresolved question is whether this optimized physical dose distribution will be accompanied by an important clinical advantage. This question cannot be answered by physical analysis alone, and clinical trials are

needed to definitively address this issue. However, dosimetric comparison can display differences in doses to normal tissues that may prove to have a clinically significant impact on toxicity for the patient. At the Massachusetts General Hospital, we studied dosimetric optimization to compare IMRT to IMPT in the treatment of spinal and paraspinal sarcomas.<sup>50</sup> Gross tumor volume coverage was optimal and equally homogeneous with both photon and proton therapy plans. The use of IMPT consistently reduced doses to the heart, lung, kidney, and stomach by a factor of 1.8 to 40 compared to photon plans (Figs 2A-B). In addition, IMPT dose escalation (85.1 and 92.9 CGE) was possible in all patients, within the constraints of normal tissue tolerance.

IMPT with a spot-scanning beam has been used to treat a limited number of patients at the Paul Scherrer Institute in Switzerland.<sup>51</sup> Raster-scanned carbon ion RT is used to treat patients at the Gesellschaft für Schwerionenforschung in Darmstadt, Germany.<sup>45</sup>

## Brachytherapy

Managing soft tissue sarcomas with BT generally involves placement of after-loading catheters intraoperatively in the tumor bed. Most institutions use BT as a boost that is supplemented with external-beam RT, but it has also been used as the only form of adjuvant therapy. The catheters are fixed in position with absorbable sutures and are spaced at 1-cm intervals in a single plane. The dose of adjuvant BT, when it is used as the sole radiation modality, is generally 45 Gy, administered to a distance of 0.5 to 1 cm from the implant plane. The treatment volumes are typically defined by the tumor bed plus appropriate margins (2 cm superiorly/inferiorly and 1.5 cm laterally/medi-

ally). Because the target is defined under direct visualization, it is highly accurate. Importantly, the target area does not include the entire surgical bed or drain sites, in contrast with coverage of these areas with standard postoperative external-beam RT fields.

Treatment is generally well tolerated, and wound complications requiring reoperation are not common (generally occurring in 10% of patients), especially when catheters are loaded 4 to 7 days after surgery.<sup>19</sup> Catheters can be safely placed adjacent to pedicle and free flaps. Patients who undergo periosteal stripping or bone resection may have a higher risk of developing bone fractures. Peripheral nerve damage occurs in approximately 5% of patients treated with postoperative BT.<sup>52</sup> Data from a randomized clinical trial of surgery and adjuvant BT vs surgery alone have demonstrated an improvement in local control with the addition of BT for patients with high-grade tumors.<sup>11</sup> The absence of an advantage for low-grade tumors is difficult to explain on radiobiological grounds, but it has prompted some clinicians to avoid BT for patients with low-grade tumors. There are no randomized comparisons of external-beam RT vs BT in the management of patients with soft tissue sarcomas. When treatment-related charges associated with external-beam RT and BT are compared for soft tissue sarcomas for the extremity, cost analysis suggests substantial savings per patient treated with BT.<sup>53</sup>

## Dural Plaque Brachytherapy

Even with IMRT or the proton beam, it is difficult to deliver tumoricidal doses of  $\geq 70$  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

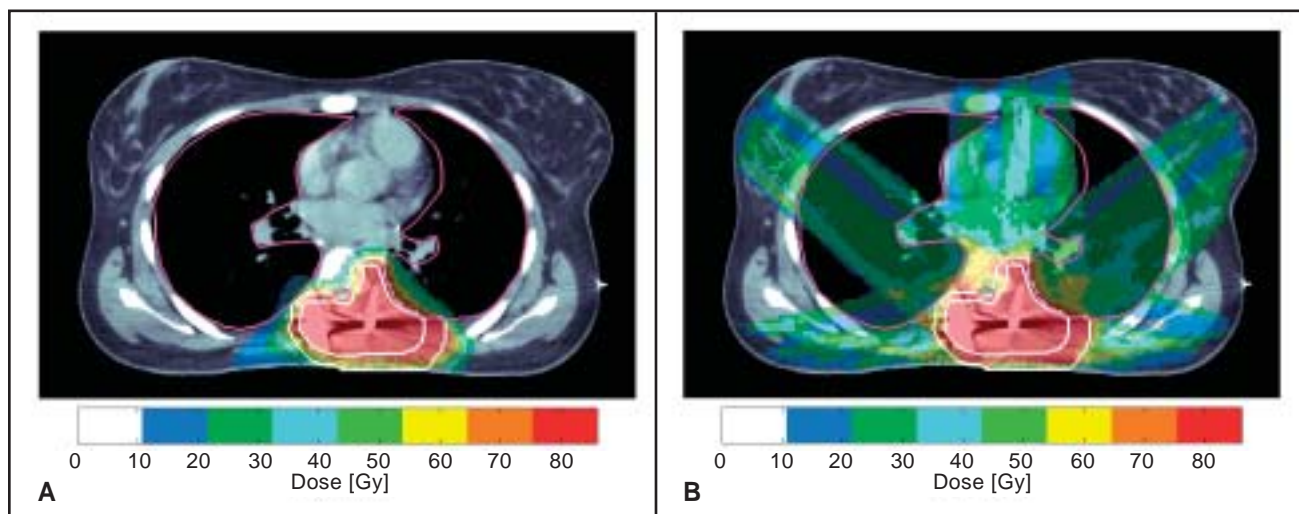


Fig 2. — Dose distribution for intensity-modulated protons (A) or intensity-modulated photons (B) in a transverse plane (computed tomography slice) through the center of the tumor in a patient with a thoracic paraspinal sarcoma. The isodose contours are represented by different colors (corresponding values in CGE are displayed below the figure). Note the significant reduction in lung and cardiac dose with intensity-modulated protons. 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 from Elsevier.

penumbra and the proximity of the surface of the spinal cord with 3 to 4 mm of the dura prevent delivery of adequate dose to the dural surface without exceeding spinal cord tolerance. One strategy that we have developed is to use 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% at the dural surface and with 27% and 8% at depths of 2 mm and 4 mm, respectively. Thus, 10 to 15 Gy can be delivered to the dura with minimal dose to the cord surface and essentially no dose to the cord center or the contralateral side of the cord. Initial experience with this applicator has been favorable and has produced no acute toxicity or any neurologic sequelae.<sup>2</sup>

## Intraoperative Radiation Therapy

With the exception of tumors recurrent after prior external-beam RT, when it may be used as the sole form of RT in the treatment course, IORT has generally been administered at a boost dose of 10 to 15 Gy delivered during surgery with electrons<sup>15</sup> or high-dose rate intraoperative BT.<sup>54</sup> This has generally been given after preoperative external-beam adjuvant RT,<sup>15</sup> although it has also been given prior to external RT.<sup>54</sup> IORT is particularly advantageous for retroperitoneal and pelvic sarcomas for which the tolerances of surrounding critical normal tissues constrain the dose that can be delivered to the tumor. For retroperitoneal sarcomas, 45 to 50.4 Gy of preoperative RT (1.8 Gy per fraction) is preferred because the tumor acts as a tissue expander and moves normal structures out of the radiation beam.<sup>15</sup> Promising results for retroperitoneal sarcomas have been reported from several institutions.<sup>15,55</sup>

There is less repair of radiation damage by normal tissues of the large single radiation fractions employed with IORT.<sup>56</sup> It remains an effective strategy, however, because many radiosensitive normal tissues can be excluded from the beam. When normal tissues such as nerves, gut, or ureter adherent to tumor cannot be moved out of the radiation field, IORT can be associated with normal tissue injury unless the radiation dose is reduced. Neuropathy has been the major complication reported with IORT, occurring in approximately 10% of patients. Fistulas and ureteral injury have also been reported in patients treated with aggressive surgery, external-beam irradiation, and IORT.<sup>15,55</sup> Whenever possible, nerves, gut, or ureter should be moved out of the radiation field or shielded to prevent injury.

## Technically Advanced Radiotherapy in Selected Patients

### *Sarcomas of the Skull Base*

Treatment of patients with these tumors is difficult and complex because of the proximity of the brain stem and

the base of the brain. These factors have limited both surgical approaches and treatment with conventional RT. The rapid fall-off of dose at the end of the range of the proton beam was judged to be particularly suitable for treatment of these tumors from the days of the initial use of protons in the clinic. In fact, the physical advantage of protons allowed for significant dose escalation for these patients. Rosenberg et al<sup>57</sup> reported the actuarial 5- and 10-year actuarial local control rates of 99% and 98%, respectively, for 200 patients treated for chondrosarcomas of the base of the skull who received a median dose of 72.1 CGE in 38 fractions. Although some reports in the oncology literature note that chondrosarcomas are not sensitive to RT, these results clearly contradict that assertion. Interestingly, patients with chordomas of the skull base treated to a similar median dose of 68.9 CGE experience worse treatment outcome, with actuarial local control rates of 59% and 44% at 5 and 10 years, respectively.<sup>58</sup> Similar results were reported by Hug et al,<sup>59</sup> who noted local control in 92% of patients with chondrosarcomas and in 76% of patients with chordomas. They reported symptomatic grade 3–4 toxicities in 5% of patients. These results are better than those observed in cases where patients with chondrosarcomas and chordomas of the skull base were treated with photons to a median dose of 55 Gy in which the estimated local control was only 36%.<sup>60</sup> A randomized proton dose evaluation study for patients with chordomas of the cervical spine and base of skull is currently underway at the Northeast Proton Therapy Center. Higher-risk patients, ie, all patients with cervical spine tumors and women with base of skull lesions, are randomized to receive either 75.4 or 82.9 CGE, while lower-risk men with base of skull lesions are randomized to receive 69.7 or 75.4 CGE.

### *Sarcomas of the Spine and Paraspinal Tissues*

Because of the proximity of the spinal cord, RT for treatment of tumors of the spine and paraspinal soft tissues is constrained by the radiation tolerance of the spinal cord, which is generally quoted at 45 Gy. This dose is below that necessary to reliably control most sarcomas, which require doses of approximately 60 Gy for subclinical microscopic disease, 66 Gy for microscopically positive margins, and more than 70 Gy for gross residual disease. With its ability to spare adjacent tissues, proton RT offers advantages for treatment of tumors in this location. Isacson et al<sup>61</sup> compared conformal RT treatment plans with photons and protons for a patient with a cervical Ewing's sarcoma. Even when only the final 20% of the treatment — the boost to the gross disease — was given with protons, they noted a 5% improvement in local control for a comparable predicted risk of spinal cord injury. In a comparison of IMRT with IMPT treatment plans for spine and paraspinal sarcomas, Weber et al<sup>50</sup> noted that although the results were similar in levels of tumor conformation, IMPT reduced the integral (normal tissue) dose to organs at risk.

Hug and colleagues<sup>9</sup> presented results on combined photon/proton treatment of 47 patients with osteogenic and chondrogenic tumors of the axial skeleton. RT was delivered postoperatively in 23 patients, preoperatively and postoperatively in 17, and as sole treatment in 7 patients. Mean RT doses of 73.9 CGE, 69.8 CGE, and 61.8 CGE were delivered to group 1 (20 patients with recurrent/primary chordoma or chondrosarcoma), group 2 (15 patients with osteogenic sarcomas), and group 3 (12 patients with giant cell tumors, osteblastomas, or chondroblastomas), respectively. For patients in group 1, the 5-year actuarial local control and survival rates for patients with chondrosarcomas were both 100%, and for those with chordoma, these rates were 53% and 50%, respectively. For patients in group 2, the 5-year actuarial local control rate was 59%. For patients in group 3, the 5-year actuarial local control and survival rates were 76% and 87%, respectively. Overall, improved local control was noted for primary vs recurrent tumors, gross total resection, and target doses >77 CGE. Similar results have been reported with charged-particle therapy.<sup>62</sup> We currently are conducting an ongoing phase II study of combined photon and proton-beam RT in conjunction with maximal surgical resection (and dural plaque BT when possible) at the Northeast Proton Therapy Center for patients with spinal and paraspinal sarcomas.

### Ewing's Sarcoma

Management of truncal, craniofacial, spinal, and pelvic Ewing's sarcomas is complex due to the critical importance of the normal structures in the vicinity of the tumor and also due to the frequent surgical resection with positive or close margins. For these sites, surgical resection and RT can be limited by the proximity of the tumor to critical organs. Local failure rates are often more than 50%.<sup>63</sup> Highly localized dose distributions offer the possibility of increasing local control as well as decreasing late effects. Smith et al<sup>64</sup> performed comparative treatment planning comparing IMRT with IMPT for a pelvic Ewing's sarcoma patient and noted sparing of the intestine, rectum, bladder, and femoral head with IMPT (Fig 3). These results demonstrate a significant potential for reduction of treatment morbidity with protons. In addition to less acute morbidity to bowel and marrow during concurrent chemoradiation, one would anticipate a reduction in late radiation-induced tumors, a problem with conventional photon radiotherapy for these patients.<sup>65</sup> Proton-beam RT has been approved for use in Children's Cooperative Oncology group protocols.

### Retroperitoneal Sarcomas

Normal tissue, including bowel, liver, kidneys, and spinal cord, can limit the radiation doses that can be delivered for patients with retroperitoneal sarcomas. Treatment comparisons have shown a reduction in dose to normal tissue organs at risk with IMRT compared to 3-D conformal pho-

tons for patients with retroperitoneal sarcomas.<sup>66</sup> Additional dose reductions are anticipated with proton-beam RT. When combined with IORT, these techniques should result in improved outcomes.<sup>15,55</sup>

### Extremity Sarcomas

Compared with postoperative RT, preoperative RT for extremity soft tissue sarcomas is associated with a higher rate of acute wound-healing complications but fewer late complications.<sup>67</sup> IMRT may reduce the dose delivered to the skin and subcutaneous tissues in some patients,<sup>47</sup> thereby reducing wound-healing complications associated with preoperative RT. Similar or greater advantages are to be expected with the proton beam. Potential late effects on bone, such as pathologic fractures following periosteal stripping, might also be reduced because of reductions in dose to the femur. These potential advantages need to be validated in clinical trials.<sup>67</sup>

## Discussion

Improvements in dose localization can increase local control and disease-free survival, reduce early and late effects of RT,<sup>68</sup> lessen acute comorbidity from radiation and chemotherapy treatments, improve treatment compliance, and decrease the number of treatment breaks, which should further improve tumor control. This is especially important in the era of multimodality treatments where chemotherapy plus RT has become the standard of treatment in many disease sites. Highly localized dose distributions may make it possible to re-treat patients who have failed locally and have been treated to the limit of tolerance

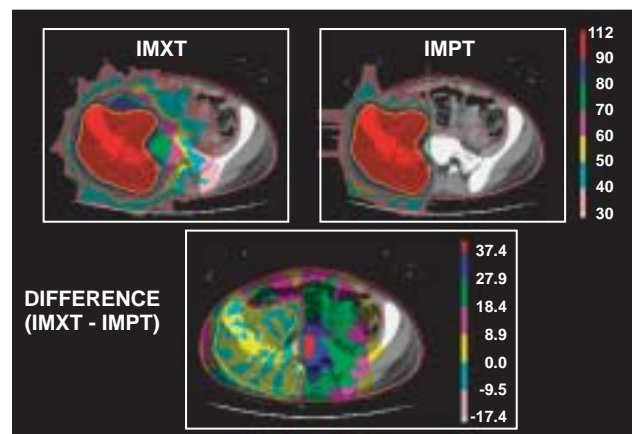


Fig 3. — Comparative dose distributions for 9-field photon intensity-modulated photon (IMXT) and 3-field intensity-modulated proton radiation (IMPT) treatment plans for a patient with a pelvic Ewing's sarcoma. Courtesy of A.R. Smith of the M.D. Anderson Cancer Center and A.J. Lomax of the Paul Scherrer Institute, Villigen, Switzerland. Dosage in Gy or CGE is shown on the scale on the right. The lower panel shows the dose difference (IMXT-IMPT) distribution. From DeLaney TF, Smith AR, Lomax A, et al. Proton beam radiation therapy. *Principles & Practice of Oncology Updates*. Philadelphia, Pa: JB Lippincott; 2003;17:1-10. Reprinted with permission of Lippincott Williams & Wilkins.

with previous therapy. IMRT represents an advance over 3-D conformal RT. Based on physical principles, beam for beam and technique for technique, proton beams will deliver more localized dose distributions than photons. These improved dose distributions have the potential to provide substantial improvements in treatment outcomes.

Based on the physical nature of protons and the excellent clinical results obtained thus far, proton therapy has the potential to improve clinical outcomes at a number of anatomic sites. The studies noted above have shown that for both conventional techniques and intensity-modulation techniques, proton treatment plans have improved, to varying degrees, dose localization compared to photons, especially when critical normal tissues are near the tumor. A recent survey by Glimelius et al<sup>69</sup> summarizes many of the above studies and provides additional information on the physical and biological properties of protons and proton treatment planning. IORT and BT can be integrated with proton-beam treatment for selected patients with retroperitoneal tumors, pelvic tumors, and spinal/paraspinal sarcomas to maximize clinical advantage for the patient.

A review of the clinical results of proton therapy<sup>70</sup> describes impressive results from several proton therapy centers. However, with the exception of two clinical trials for prostate cancer conducted jointly by Massachusetts General Hospital and Loma Linda University Medical Center, few prospective, randomized trials have been conducted. The primary reasons for this are the limited number of proton therapy facilities, limitations in capacity and energy at existing facilities, and lack of modern delivery systems including isocentric gantries and beam-scanning capabilities. Therefore, even though more than 40,000 patients have been treated with protons worldwide,<sup>71</sup> only a few hundred have been treated in prospective, randomized clinical trials. However, this situation is rapidly changing; there are now 25 facilities around the world that treat patients with proton beams, with approximately 10 more being built or under serious planning.<sup>71</sup> A third facility in the United States was opened in Bloomington, Indiana, in 2004, while facilities due to open in 2006 are currently under construction at University of Florida and at the M.D. Anderson Cancer Center. Additional facilities are being planned at the University of Pennsylvania and elsewhere in the United States. Many of the new facilities will be hospital-based, with the capacity of treating large numbers of patients. It will be necessary to conduct prospective, randomized clinical trials for sarcomas and other clinical sites in order to quantify the improvements in clinical outcomes with protons.

IMPT is currently under clinical development. To date, only a small number of patients have been treated to date, but this is an area of ongoing technical development. Scanning beam nozzles are currently being designed and tested, and treatment-planning software is being refined. It is anticipated that there will be a substantial increase in patients so treated in the near future.

IMPT offers the potential to reduce both entrance and exit doses from any given beam trajectory. Thus, in addition to extreme conformality of the dose to the target, further dose reduction to normal tissue over nonmodulated proton beams are anticipated.

## References

1. Barkley HT Jr, Martin RG, Romsdahl MM, et al. Treatment of soft tissue sarcomas by preoperative irradiation and conservative surgical resection. *Int J Radiat Oncol Biol Phys.* 1988;14:693-699.
2. DeLaney TF, Chen GT, Mauceri TC, et al. Intraoperative dural irradiation by customized 192iridium and 90yttrium brachytherapy plaques. *Int J Radiat Oncol Biol Phys.* 2003;57:239-245.
3. Dunst J, Schuck A. Role of radiotherapy in Ewing tumors. *Pediatr Blood Cancer.* 2004;42:465-470.
4. O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet.* 2002;359:2235-2241.
5. Scully SP, Ghert MA, Zurakowski D, et al. Pathologic fracture in osteosarcoma: prognostic importance and treatment implications. *J Bone Joint Surg Am.* 2002;84-A:49-57. Erratum in: *J Bone Joint Surg Am.* 2002;84-A:622.
6. Picci P, Sangiorgi L, Bahamonde L, et al. Risk factors for local recurrences after limb-salvage surgery for high-grade osteosarcomas of the extremities. *Ann Oncol.* 1997;8:899-903.
7. Tepper JE, Suit HD. Radiation therapy alone for sarcoma of soft tissue. *Cancer.* 1985;56:475-479.
8. Sailer SL. The role of radiation therapy in localized Ewing's sarcoma. *Semin Radiat Oncol.* 1997;7:225-235.
9. Hug EB, Fitzek MM, Liebsch NJ, et al. Locally challenging osteo- and chondrogenic tumors of the axial skeleton: results of combined proton and photon radiation therapy using three-dimensional treatment planning. *Int J Radiat Oncol Biol Phys.* 1995;31:467-476.
10. Munzenrider JE, Liebsch NJ. Proton therapy for tumors of the skull base. *Strahlenther Onkol.* 1999;175(suppl 2):57-63.
11. Harrison LB, Franzese F, Gaynor JJ, et al. Long-term results of a prospective randomized trial of adjuvant brachytherapy in the management of completely resected soft tissue sarcomas of the extremity and superficial trunk. *Int J Radiat Oncol Biol Phys.* 1993;27:259-265.
12. Rogers CL, Theodore N, Dickman CA, et al. Surgery and permanent 125I seed paraspinal brachytherapy for malignant tumors with spinal cord compression. *Int J Radiat Oncol Biol Phys.* 2002;54:505-513.
13. Armstrong JG, Fass DE, Bains M, et al. Paraspinal tumors: techniques and results of brachytherapy. *Int J Radiat Oncol Biol Phys.* 1991;20:787-790.
14. Ozaki T, Hillmann A, Rube C, et al. The impact of intraoperative brachytherapy on surgery of Ewing's sarcoma. *J Cancer Res Clin Oncol.* 1997;123:53-56.
15. Gieschen HL, Spiro IJ, Suit HD, et al. Long-term results of intraoperative electron beam radiotherapy for primary and recurrent retroperitoneal soft tissue sarcoma. *Int J Radiat Oncol Biol Phys.* 2001;50:127-131.
16. Hoekstra HJ, Sindelar WF, Szabo BG, et al. Hemipelvectomy and intraoperative radiotherapy for bone and soft tissue sarcomas of the pelvic girdle. *Radiother Oncol.* 1995;37:160-163.
17. Nag S, Shasha D, Janjan N, et al. The American Brachytherapy Society recommendations for brachytherapy of soft tissue sarcomas. *Int J Radiat Oncol Biol Phys.* 2001;49:1033-1043.
18. Suit HD, Urie M, Efid JT. Proton beams in clinical radiation therapy. In: DeVita V, Hellman S, Rosenberg, eds. *Principles & Practice of Oncology Updates.* Philadelphia, Pa: JB Lippincott; 1992:1-15.
19. Harrison LB, Zelefsky MJ, Armstrong JG, et al. Brachytherapy and function preservation in the localized management of soft tissue sarcomas of the extremity. *Semin Radiat Oncol.* 1993;3:260-269.
20. Verhey LJ. Comparison of three-dimensional conformal radiation therapy and intensity-modulated radiation therapy systems. *Semin Radiat Oncol.* 1999;9:78-98.
21. Bland KI, McCoy DM, Kinard RE, et al. Application of magnetic resonance imaging and computerized tomography as an adjunct to the surgical management of soft tissue sarcomas. *Ann Surg.* 1987;205:473-481.
22. Nieweg OE, Pruim J, van Ginkel RJ, et al. Fluorine-18-fluorodeoxyglucose PET imaging of soft-tissue sarcoma. *J Nucl Med.* 1996;37:257-261.
23. Bortfeld T, Burkelbach J, Boesecke R, et al. Methods of image reconstruction from projections applied to conformation radiotherapy. *Phys Med Biol.* 1990;35:1423-1434.

24. Lomax AJ, Bortfeld T, Goitein G, et al. A treatment planning inter-comparison of proton and intensity modulated photon radiotherapy. *Radiother Oncol.* 1999;51:257-271.
25. Miralbell R, Lomax A, Cella L, et al. Potential reduction of the incidence of radiation-induced second cancers by using proton beams in the treatment of pediatric tumors. *Int J Radiat Oncol Biol Phys.* 2002;54:284-289.
26. Miller DW. A review of proton beam radiation therapy. *Med Phys.* 1995;22:1943-1954.
27. Convery DJ, Rosenbloom ME. The generation of intensity-modulated fields for conformal radiotherapy by dynamic collimation. *Phys Med Biol.* 1992;37:1359-1374.
28. Bilsky MH, Yamada Y, Yenice KM, et al. Intensity-modulated stereotactic radiotherapy of paraspinal tumors: a preliminary report. *Neurosurgery.* 2004;54:823-830; discussion 830-821.
29. Loeffler JS, Siddon RL, Wen PY, et al. Stereotactic radiosurgery of the brain using a standard linear accelerator: a study of early and late effects. *Radiother Oncol.* 1990;17:311-321.
30. Goitein M, Abrams M, Rowell D. Multi-dimensional treatment planning II: beam's eye view, back projection, and projection through CT sections. *Int J Radiat Oncol Biol Phys.* 1983;9:789-797.
31. Kai J, Shiomi H, Sasama T, et al. Optical high-precision three-dimensional position measurement system suitable for head motion tracking in frameless stereotactic radiosurgery. *Comput Aided Surg.* 1998;3:257-263.
32. Ryu SI, Chang SD, Kim DH, et al. Image-guided hypo-fractionated stereotactic radiosurgery to spinal lesions. *Neurosurgery.* 2001;49:838-846.
33. Nag S, ed. *High Dose Rate Brachytherapy: A Textbook.* Armonk, NY: Futura Publishing Co; 1994.
34. Nag S, Orton C. Development of intraoperative high dose rate brachytherapy for treatment of resected tumor beds in anesthetized patients. *Endocuriether Hypertherm Oncol.* 1993;9:187-193.
35. Wilson RR. Radiological uses of fast protons. *Radiology.* 1946;47:487-491.
36. Austin-Seymour M, Munzenrider J, Goitein M, et al. Fractionated proton radiation therapy of chordoma and low-grade chondrosarcoma of the base of skull. *J Neurosurg.* 1989;70:13-17.
37. Munzenrider JE. Proton therapy for uveal melanomas and other eye lesions. *Strahlenther Onkol.* 1999;175(suppl 2):68-73.
38. Loeffler JS, Smith AR, Suit HD. The potential role of proton beams in radiation oncology. *Semin Oncol.* 1997;24:686-695.
39. Shipley WU, Verhey LJ, Munzenrider JE, et al. Advanced prostate cancer: the results of a randomized comparative trial of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone. *Int J Radiat Oncol Biol Phys.* 1995;32:3-12.
40. Matsuzaki Y, Osuga T, Chiba T, et al. New, effective treatment using proton irradiation for unresectable hepatocellular carcinoma. *Intern Med.* 1995;34:302-304.
41. Bush DA, Slater JD, Bonnet R, et al. Proton-beam radiotherapy for early-stage lung cancer. *Chest.* 1999;116:1313-1319.
42. Hall EJ. *Radiobiology for the Radiologist.* 3rd ed. Philadelphia, Pa: Lippincott; 1988.
43. Schoenthaler R, Castro JR, Petti PL, et al. Charged particle irradiation of sacral chordomas. *Int J Radiat Oncol Biol Phys.* 1993;26:291-298.
44. Kamada T, Tsujii H, Tsuji H, et al. Efficacy and safety of carbon ion radiotherapy in bone and soft tissue sarcomas. *J Clin Oncol.* 2002;20:4466-4471.
45. Schulz-Ertner D, Nikoghosyan A, Thilmann C, et al. Results of carbon ion radiotherapy in 152 patients. *Int J Radiat Oncol Biol Phys.* 2004;58:631-640.
46. Chan MF, Chui CS, Schupak K, et al. The treatment of large extraskelatal chondrosarcoma of the leg: comparison of IMRT and conformal radiotherapy techniques. *J Appl Clin Med Phys.* 2001;2:3-8.
47. Hong L, Alektiar KM, Hunt M, et al. Intensity-modulated radiotherapy for soft tissue sarcoma of the thigh. *Int J Radiat Oncol Biol Phys.* 2004;59:752-759.
48. Millar BM, Bragg CM, Conway J, et al. Investigation of the use of intensity modulated radiotherapy (IMRT) in comparison with conformal radiotherapy in the management of soft tissue sarcoma. *Int J Radiat Oncol Biol Phys.* 2001;51S1:412.
49. Lee N, Chuang C, Quivey JM, et al. Skin toxicity due to intensity-modulated radiotherapy for head-and-neck carcinoma. *Int J Radiat Oncol Biol Phys.* 2002;53:630-637.
50. 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.
51. Lomax AJ, Boehringer T, Coray A, et al. Intensity modulated proton therapy: a clinical example. *Med Phys.* 2001;28:317-324.
52. Alektiar KM, Leung D, Zelefsky MJ, et al. Adjuvant brachytherapy for primary high-grade soft tissue sarcoma of the extremity. *Ann Surg Oncol.* 2002;9:48-56.
53. Janjan NA, Yasko AW, Reece GP, et al. Comparison of charges related to radiotherapy for soft-tissue sarcomas treated by preoperative external-beam irradiation versus interstitial implantation. *Ann Surg Oncol.* 1994;1:415-422.
54. Alektiar KM, Hu K, Anderson L, et al. High-dose-rate intraoperative radiation therapy (HDR-IORT) for retroperitoneal sarcomas. *Int J Radiat Oncol Biol Phys.* 2000;47:157-163.
55. Petersen IA, Haddock MG, Donohue JH, et al. Use of intraoperative electron beam radiotherapy in the management of retroperitoneal soft tissue sarcomas. *Int J Radiat Oncol Biol Phys.* 2002;52:469-475.
56. Thames HD Jr, Withers HR, Peters LJ, et al. Changes in early and late radiation responses with altered dose fractionation: implications for dose-survival relationships. *Int J Radiat Oncol Biol Phys.* 1982;8:219-226.
57. Rosenberg AE, Nielsen GP, Keel SB, et al. Chondrosarcoma of the base of the skull: a clinicopathologic study of 200 cases with emphasis on its distinction from chordoma. *Am J Surg Pathol.* 1999;23:1370-1378.
58. Terahara A, Niemierko A, Goitein M, et al. Analysis of the relationship between tumor dose inhomogeneity and local control in patients with skull base chordoma. *Int J Radiat Oncol Biol Phys.* 1999;45:351-358.
59. Hug EB, Loreda LN, Slater JD, et al. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. *J Neurosurg.* 1999;91:432-439.
60. Austin-Seymour M, Munzenrider JE, Goitein M, et al. Progress in low-LET heavy particle therapy: intracranial and paracranial tumors and uveal melanomas. *Radiat Res Suppl.* 1985;8:S219-226.
61. Isacsson U, Hagberg H, Johansson KA, et al. Potential advantages of protons over conventional radiation beams for paraspinal tumours. *Radiother Oncol.* 1997;45:63-70.
62. Nowakowski VA, Castro JR, Petti PL, et al. Charged particle radiotherapy of paraspinal tumors. *Int J Radiat Oncol Biol Phys.* 1992;22:295-303.
63. Marcus KC, Grier HE, Shamberger RC, et al. Childhood soft tissue sarcoma: a 20-year experience. *J Pediatr.* 1997;131:603-607.
64. Smith AR, Loeffler JS, Adams JA, et al. The potential for proton therapy to improve clinical outcomes: comparisons of proton and x-ray treatment plans for the purpose of tumor dose escalation and/or reduction of treatment-related morbidity. *Int J Radiat Oncol Biol Phys.* 2000;48(S):338.
65. Kuttusch JF Jr, Wexler LH, Marcus RB, et al. Second malignancies after Ewing's sarcoma: radiation dose-dependency of secondary sarcomas. *J Clin Oncol.* 1996;14:2818-2825.
66. Koshy M, Landry JC, Lawson JD, et al. Potential for toxicity reduction using intensity modulated radiation therapy (IMRT) for retroperitoneal sarcoma. *Int J Radiat Oncol Biol Phys.* 2003;57(2 suppl):S448-S449.
67. O'Sullivan B, Davis A, Turcotte R, et al. Five-year results of a randomized phase III trial of pre-operative vs post-operative radiotherapy in extremity soft tissue sarcoma. *Proc Annu Meet Am Soc Clin Oncol.* 2004;22:145. Abstract 9007.
68. Suit HD, Goitein M. Dose-limiting tissues in relation to types and location of tumours: implications for efforts to improve radiation dose distributions. *Eur J Cancer.* 1974;10:217-224.
69. Glimelius B, Isacsson U, Blomquist E, et al. Potential gains using high-energy protons for therapy of malignant tumours. *Acta Oncol.* 1999;38:137-145.
70. DeLaney TF, Smith AR, Lomax A, et al. Proton beam radiation therapy. *Principles & Practice of Oncology Updates.* Philadelphia, Pa: JB Lippincott; 2003;17:1-10.
71. Sisterson J. *Particles Newsletter.* July 2004(34):1-12.