The Role of Radiation Treatment in the Contemporary Management of Bone Tumors

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Key Words
Radiation, bone tumors, Ewing’s sarcoma, osteosarcoma, side effects

Abstract
Radiotherapy is integral in the multidisciplinary approach to patients with musculoskeletal neoplasms. Multiple studies have established a role for radiotherapy as a definitive local treatment of unresectable lesions or when surgery might yield unacceptable functional outcomes, such as in Ewing’s tumor or base of skull chordoma. Radiotherapy is also used as an adjuvant treatment after surgery with close or positive margins. In the metastatic setting, external beam radiotherapy and bone-seeking intravenous radioisotopes are used on a case-by-case basis for palliation. As radiotherapy and its delivery techniques have evolved, so has its role in treating tumors such as Ewing’s sarcoma, chordoma and chondrosarcoma, osteosarcoma, primary lymphoma of bone, malignant fibrous histiocytoma of bone, and vascular tumors. Radiation can also be used successfully to treat unresectable or recurrent benign tumors, such as giant cell tumor and aneurysmal bone cyst. This article reviews the indications for radiotherapy for various bone tumors and summarizes some of the important data supporting its use. (JNCCN 2007;5:456–466)

Musculoskeletal malignancies, including bone tumors, are best managed in a multidisciplinary manner. Surgery is generally the preferred local treatment for a resectable primary bone sarcoma. The goal of surgery is optimal resection of the lesion, which usually means wide enough to minimize potential local recurrence but narrow enough to maximize patient function. Traditional amputation has been supplanted, when possible, by limb-sparing surgical techniques to allow for better functional and aesthetic outcomes. The role of surgery has increased over the years, primarily because innovative surgical techniques have been developed that allow for limb preservation and because more effective cytoreductive chemotherapies are being used that allow for resection of previously unresectable tumors. In addition, given the high rates of distant metastasis in osteosarcoma and Ewing’s sarcoma, chemotherapy administered before and after definitive surgical resection has resulted in improved survival and is considered standard in these tumor types.

In certain circumstances, radiotherapy remains an option in lieu of or in addition to surgery and may be preferred in cases where surgery cannot be easily attempted because of anatomic considerations. For example, chordomas often arise at the base of the skull and few of these tumors are considered for resection because of the complexity of the surgical approach and the associated risk of morbidity. Also, according to some estimates, up to 47% of Ewing’s sarcoma lesions arise in the pelvis or axial skeleton, making complete resection challenging and necessitating the use of radiotherapy.1 Radiation is also often used to treat recurrent benign or malignant disease after primary management has failed. Once a decision to use radiotherapy has been made, which type of therapy is best and any special planning requirements must be considered. The surgeon and radiation oncologist must consider the type of reconstruction planned and the timing of radiotherapy, because radiation may inhibit the healing of bone defects with bone graft, vascularized bone graft, bone morphogenic proteins, or ex-vivo bone morphogenic protein gene therapy.1,2 When a prosthesis has been inserted, the density of the alloy should be taken into account because it will affect the radiation dose distribution in the target volume and surrounding tissues. Attention to detail on the part of the physician and meticulous dosimetry and physics support are paramount in creating an
optimal plan for irradiating lesions around reconstructed limbs and joints.

Given the rarity of most primary bone tumors and the often-complex treatment schemes, an attempt should be made to treat patients with these tumors in clinical centers where participating physicians have experience and interact regularly with each other in a multidisciplinary setting.

**Ewing’s Sarcoma**

**Treatment Considerations**

Ewing’s sarcoma is rare, constituting approximately 9% of all malignant primary bone tumors. Radiation therapy has had a prominent role in managing this tumor since James Ewing’s first described it in 1921. Approximately 53% of cases originate in the extremities, with the rest arising centrally in the pelvis, chest wall, or spine. Although most often arising from bone, Ewing’s sarcoma can also arise from soft tissues (extraosseous Ewing’s tumor). In addition, Askin’s tumor, a small cell tumor arising from the thoracopulmonary region, has also been linked to Ewing’s sarcoma based on similar histologic, immunohistochemical, and genetic characteristics. It is now widely recognized that these tumors represent a group of neoplastic diseases called the Ewing’s sarcoma family of tumors. Peripheral primitive neuroectodermal tumors also share histologic, immunohistochemical, and genetic characteristics with this family of tumors.

The general treatment approach to these entities is similar. Because overt metastatic disease is found in up to a quarter of patients and because most patients treated with local therapy alone tend to experience distant relapse, systemic chemotherapy has a central role in treating this entity. Based on data from the 3 Intergroup Ewing’s Sarcoma Studies (IESS-I, II, and III), 4 to 6 cycles of vincristine, doxorubicin, and cyclophosphamide (alternating with ifosfamide and etoposide) are usually administered before local therapy. More chemotherapy is typically given after local therapy, usually for 48 weeks.

Historically, radiotherapy has been the preferred local treatment with relatively good local control rates (Table 1). Some studies comparing surgery and radiation suggest that surgery is superior; however, selection bias favors surgery, because tumors managed with radiotherapy are, on average, larger or more extensive than those selected for surgical removal. Currently, surgery or radiotherapy may be used in the definitive local treatment of the primary lesion. The local treatment modality is chosen after careful consideration of the resection possibilities and the potential harm from radiation (e.g., growth retardation, risk for second malignancies). When the tumor arises in expendable bones, such as the fibula, small bones of hands and feet, or ribs, or when good reconstructive options exist, surgery is preferred. Alternatively, when safe or satisfactory surgical resection is deemed impossible, radiation alone is the preferred local therapy.

Careful consideration must be given to long-term side effects of radiotherapy when treating growing children. Growth plates and vertebral bodies should be avoided if possible or, alternatively, included in their entirety, as a way of preventing asymmetric growth and resultant functional deficits. Modern treatment techniques, such as 3-dimensional conformal radiotherapy and intensity-modulated radiotherapy (Figure 1), are preferred because they help limit the radiation dose to critical structures.

**Adjuvant Radiation**

Adjuvant postoperative radiation is usually reserved for lesions resected to a positive margin, with doses ranging from 45 to 50.4 Gy for microscopic disease and to 55.8 Gy for gross residual disease. The radiation dose necessary for local control after surgery was largely established through 2 cooperative studies: the Cooperative Ewing’s Sarcoma Study (CESS) 81 and

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<th>Table 1 Ewing’s Sarcoma Studies of Radiation with Chemotherapy</th>
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<td><strong>Study</strong></td>
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<td>EICESS92</td>
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<td>IESS-II (pelvis)</td>
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<td>IESS-II (no pelvis)</td>
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<td>IESS-I</td>
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<td>CESS-II</td>
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86. In CESS 81, a postoperative total dose of 36 Gy resulted in a local failure rate of 17% at 5 years.\(^\text{15}\) In contrast, roughly 5% of patients experienced local failure in CESS 86 after a dose of 45 Gy.\(^\text{16}\) Although these differences could potentially be attributed to improvements in radiation techniques between the studies, most radiation oncologists agree that a dose–response relationship favors the use of 45 Gy.

**Definitive Radiation**

Patients who undergo radiotherapy alone for local treatment tend to have larger tumors or tumors in less favorable locations. Therefore, these patients unsurprisingly fare worse overall. In a recent analysis of more than 1000 patients treated on EICESS trials, the recurrence rate after surgery with or without radiation was only 4% to 10%, whereas the recurrence rate of patients who underwent only radiotherapy was more than 20%.\(^\text{17}\) Grier et al.\(^\text{14}\) found that the addition of ifosfamide and etoposide was associated with an improvement in the rate of local failure from 15% to 5%. Although the local failure rates were not calculated specifically for patients undergoing radiotherapy alone, patients with pelvic primaries, who frequently have limited surgical options, seemed to show the greatest improvement in event-free survival.\(^\text{14}\) Patients treated definitively with chemotherapy and radiation alone generally receive 45 Gy to the initial prechemotherapy volume plus a 2-cm margin, followed by a 10.8-Gy boost to a smaller volume, including the site of the original lesion plus any residual soft tissue disease after chemotherapy.

Historically, the entire bone involved was irradiated, followed by a boost to the primary tumor site. The seminal study addressing the proper field size for irradiation was POG-8346. Patients were randomized to undergo either whole bone irradiation to 39.6 Gy with a 16.2-Gy boost or involved-field radiation to 55.8 Gy. Overall, the 5-year event-free survival was 42%, with no difference between the arms.\(^\text{18}\) Based on this and other studies, the current approach is to use involved-field radiotherapy. Conventional once-daily fractionation with 1.8 Gy is adequate because no demonstrable benefit to hyperfractionation was seen in the CESS 86 and EICESS 92 trials.\(^\text{19}\)

**Radiation for Metastatic or Recurrent Disease**

Although IESS I showed that low-dose prophylactic irradiation of the lungs in addition to standard chemotherapy (VAC) could reduce the incidence of pulmonary metastases and improve survival compared with VAC alone, the addition of doxorubicin to VAC was superior to both other arms.\(^\text{10}\) Because of these results, use of prophylactic lung irradiation in patients without pulmonary involvement at diagnosis was abandoned in favor of adding doxorubicin. However, CESS studies documented a benefit from bilateral consolidative lung irradiation after chemotherapy in patients with pulmonary metastases at presentation.\(^\text{20}\) Doses from 15 to 18 Gy to the whole lung have generally been used in 1.5-Gy daily fractions. Patients with isolated pulmonary recurrence have also been shown to
benefit from pulmonary irradiation, with improved 5-year post-recurrence survival (30% vs. 16.7%).

Radiation also may be used as consolidative therapy for bone metastases after chemotherapy and for palliative treatment of painful bone metastases. Koontz et al.\(^2\) reported 55% complete symptom response and 29% partial symptom relief rates in patients treated for painful bone metastases. More focal or conformal boosts to 40 to 50 Gy for larger pulmonary foci or bone metastases may be appropriate in selected patients. With modern techniques, such as 4-dimensional CT imaging and active breathing control, higher doses of radiation can be safely administered even to mobile lung lesions.

**Osteosarcoma**

Neoadjuvant chemotherapy for 2 to 3 months followed by surgery and additional postoperative chemotherapy is generally the standard therapeutic approach to managing resectable osteosarcoma. When the response to chemotherapy is good and negative margins can be achieved, local control is generally good. Nonetheless, some cases pose a continued therapeutic challenge. For example, the Cooperative Osteosarcoma Study Group (COSS) found that the local recurrence rate for pelvic lesions after resection alone was high (62%).\(^3\) This illustrates both the difficulty of complete resection at such sites and the need for further local therapy. When gross total resection is not attainable, as is often the case with lesions of the axial skeleton, base of skull, and pelvis and lesions with poor response to chemotherapy, radiation after maximal safe debulking may confer further local control. Early studies showed that despite limited efficacy at doses between 30 and 60 Gy, most osteosarcoma lesions could in fact be well controlled with higher doses.\(^4\) More recently, DeLaney et al.\(^5\) reported encouraging results in patients with osteosarcomas that were either not resected or resected to close/positive margins and treated with external beam photons or protons. At 5 years, the local control rates were 78% for patients who underwent subtotal resection and 40% for those who underwent biopsy alone. Overall survival percentages were similar at 5 years, with survival significantly improved in patients treated with radiation up-front rather than at recurrence. Another study reported a 5-year local control rate of 56% in patients with osteosarcoma of the extremities who refused surgery and were treated with neoadjuvant chemotherapy followed by definitive radiotherapy (median dose of 60 Gy).\(^6\)

Although the optimal radiation dose remains unclear, these and other retrospective studies suggest that radiotherapy has some usefulness when resection is not possible and when the tumor is subtotally resected or resected to positive margins. With recent advances in imaging and radiation delivery techniques (e.g., intensity-modulated radiation therapy, proton-based therapy), doses exceeding 50 Gy can be delivered safely to most sites. These developments, along with recent data showing a local control benefit with radiotherapy in certain situations, may make external beam radiation a more viable option for managing osteosarcoma.

Finally, emerging evidence shows that high-dose systemic radioisotope administration (Samarium-153) may be beneficial in patients with bone metastases.\(^7\) Because samarium is preferentially taken up in areas of increased osteoblastic activity, radiation can be delivered to lesions that are active on bone scan. External beam radiotherapy can also be used in the palliative setting for metastatic lesions or unresectable recurrent lesions. In these cases, doses higher than the traditional 30 Gy should be attempted if possible. The roles of prophylactic whole lung irradiation, intraoperative radiation, and extracorporeal irradiation require further study.

**Chondrosarcoma and Chordoma**

Chondrosarcoma arises from cartilaginous tissues and is most frequently found in the long bones, pelvis, spine, ribs, and occasionally head and neck. The treatment of chondrosarcoma is wide surgical excision. Radiotherapy is used for lesions in inaccessible locations, such as the base of skull, after maximal surgical debulking, or as definitive therapy. Reports of radiation using proton beam therapy (with or without photons) for skull base chondrosarcoma show local control rates in excess of 90% (Table 2).

Chordoma is a somewhat less common malignancy and arises from remnants of the notochord, occurring most frequently in the sacrum (50%), base of skull and clivus (35%), and vertebrae (15%).\(^8\) Because these tumors are often slow growing and rarely metastasize, complete surgical excision can be curative; however, local failure after surgery alone is common. Radiotherapy is used after surgery when positive margins or gross residual disease remain, and may be
Table 2 Radiotherapy Results for Chordoma and Chondrosarcoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Radiotherapy Type</th>
<th>Local Control (5-y)</th>
<th>Dose (Gy/CGE)</th>
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<tr>
<td>Munzenrider and Liebsch</td>
<td>1999</td>
<td>621</td>
<td>Protons + photons</td>
<td>73% (C)</td>
<td>66–83</td>
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<tr>
<td>Hug et al.</td>
<td>1999</td>
<td>58</td>
<td>Protons</td>
<td>79% (C)</td>
<td>70</td>
</tr>
<tr>
<td>Austin-Seymour et al.</td>
<td>1989</td>
<td>68</td>
<td>Protons +/- photons</td>
<td>82%</td>
<td>69</td>
</tr>
<tr>
<td>Schulz-Ertner et al.</td>
<td>2003</td>
<td>67</td>
<td>Carbon ions</td>
<td>87%/3 y (C)</td>
<td>60</td>
</tr>
<tr>
<td>Castro et al.</td>
<td>1994</td>
<td>223</td>
<td>Helium ions</td>
<td>63% (C)</td>
<td>65</td>
</tr>
</tbody>
</table>

Abbreviations: C, chordoma; CGE, cobalt grey equivalents; CS, chondrosarcoma.

considered as adjuvant therapy after margin-negative surgery. When these lesions arise in surgically inaccessible locations, primary radiotherapy becomes the preferred treatment. In addition, irradiation can be considered for recurrent disease.

The main therapeutic challenges are that these tumors require high doses of radiation (> 60–70 Gy) for adequate local control and that they are often located near critical structures that make safe delivery of these high doses of radiation impossible, at least with conventional external beam techniques. Multiple retrospective studies have shown that although external photon beam radiation can provide adequate palliation, the need for higher doses remains a problem. The physical characteristics of proton beams permit superior dose distribution and allow higher doses to be concentrated in the target while minimizing normal tissue toxicity, making them ideal for targeting these tumors. Protons deposit little energy in tissue until the end of their range, where most of the residual dose is deposited over a very short distance, resulting in a steep and relatively narrow rise in absorbed dose known as the Bragg peak. This allows structures beyond the target tissue to receive a negligible dose and has enabled radiation oncologists to deliver doses as high as 83 cobalt grey equivalents (CGE) to inaccessible lesions at the base of skull and the spine without long-term injury to the brainstem or spinal cord.

In series from the Massachusetts General Hospital and Loma Linda University, patients with skull base chordoma treated with proton therapy after biopsy or subtotal resection had 5-year local control rates of 70% (Table 2). The current recommendations for treatment after resection of sacral chordomas at the Massachusetts General Hospital include proton/photon irradiation to 70.2 CGE for negative margins, 73.8 CGE for microscopically positive margins, and 77.4 CGE for gross residual or unresectable disease. The number of proton treatment facilities in the United States is increasing, but this treatment continues to have limited availability.

Technical advances in delivering photons (x-rays), such as IMRT, stereotactic radiotherapy, and tomotherapy, may provide additional treatment options for selected patients. Encouraging results from the Mayo Clinic and University of Pittsburgh using gamma-knife radiosurgery have been reported for patients with skull base tumors; doses from 10 to 20 Gy (to 50% isodose line) have been successfully administered with good local control rates. Fractionated stereotactic radiotherapy confers similar rates of local control with perhaps less long-term toxicity. Finally, charged-particle irradiation (e.g., with helium ions) also offers superior physical characteristics and dose distribution and has been reported in the treatment of chordomas. At the University of California Lawrence Berkley Laboratory and Medical Center, 14 patients with sacral chordomas were treated postoperatively (10 had gross residual disease). The actuarial survival rate was 85%, and the local control rate at 5 years was 55%. Although these results compare favorably with other radiation methods (Table 2), the general lack of availability of this treatment modality precludes its widespread use.

Aneurysmal Bone Cyst

Aneurysmal bone cysts (ABCs) are benign but often rapidly expanding and destructive tumors that have a propensity for local recurrence. They represent 1% of all primary bone lesions, occurring most commonly
between ages 10 and 20 years with a slight female predominance. The preferred treatment is usually surgery, which results in excellent control rates. Curettage with or without adjuvants followed by bone grafting is generally the preferred treatment, with control rates ranging from 70% to 85%. For expendable bones or when the amount of bone destruction precludes curettage, en bloc resection yields local control rates approaching 100%.

Radiotherapy may be considered for patients with unresectable primary or recurrent disease (Figure 2). Historically, radiation alone has compared favorably with results from surgical series with local control rates of 75% to 100%. For example, Nobler et al. treated 6 patients with radiation alone and 1 with radiation after curettage, reporting excellent local control in 6 of 7 patients at a follow-up of 12 to 32 years. The one patient who experienced local failure underwent successful salvage therapy using radiation. Unfortunately, these and other investigators reported unacceptably high rates of radiation-induced malignancies, causing radiation to fall out of favor. Some investigators have linked this result with low-energy photon (orthovoltage) irradiation and outdated delivery techniques. More recent studies have reaffirmed the role of radiotherapy in this condition by showing that high-energy photon (megavoltage) radiation may be used successfully in the small subset of patients with unresectable or incompletely resected and recurrent ABCs without unacceptable long-term toxicity. For example in 2001 Feigenberg et al. reported on 9 patients treated for de novo or recurrent ABCs. They treated 6 patients definitively after biopsy and irradiated 3 adjuvantly after subtotal curettage to doses of 20 to 60 Gy. At a median follow-up of 17 years, no patients experienced a local recurrence or developed secondary malignancies. A dose of 26 to 30 Gy in 1.8- or 2-Gy daily fractions is currently used.

**Giant Cell Tumor of Bone**

Giant cell tumors represent 4% to 8% of all primary bone tumors, with 8% to 15% behaving malignantly and 5% with evidence of distant metastases at presentation (most in lungs). They occur most commonly between ages 20 and 40 years and are, like ABCs, more common in women. Giant cell tumors are generally treated with curettage with or without surgical adjuvants (e.g., cementation, phenol, ethanol, liquid nitrogen), resulting in local control rates approaching 85% to 90%. However, patients with gross residual disease, positive margins, or recurrent disease may have a significantly greater risk for recurrence and may benefit from radiotherapy. Chen et al. reported a series of 35 patients, most of whom had skull or spine lesions with gross residual disease, treated with variable doses of radiation. Most patients who received doses less than 30 Gy experienced local failure (5 of 8), whereas only 3 of 17 patients experienced local failure with doses of 35 Gy or greater. Based on these findings, the authors recommend a dose of 50 to 60 Gy to the tumor volume with a 1- to 2-cm margin when radiation is used definitively and a dose of 30 to 40 Gy when it is used adjuvantly.

Similarly, investigators from Poland reported their results of 14 patients treated with radiation alone and 23 patients treated with radiation after surgery or for recurrence after surgery. The mean dose was 52 Gy and the overall actuarial 5- and 10-year local control rate was 77%. Tumor size was the only statistically significant variable that affected local control in multivariate analysis. More recently, investigators from M. D. Anderson Cancer Center and The University of Florida reported similar local control rates for patients irradiated definitively or after recurrence, with the latter group reporting better local control rates with doses higher than 40 Gy (86% vs. 67%).
addition, the Florida investigators reported encouraging results for whole lung radiation (16 Gy in 10 fractions) followed by a boost to a total of 35 to 45 Gy to gross disease in patients with lung metastases, with 2 of the 3 treated patients still alive and disease-free more than 7 years later.\textsuperscript{51}

A major concern about using radiotherapy to treat giant cell tumors has been the induction of malignant transformation or secondary sarcomas. Experts now recognize that a small proportion of giant cell tumors may undergo transformation even without exposure to radiotherapy. This risk may be higher in patients with multiple recurrent lesions, who often require radiotherapy. Recent studies with small numbers of patients have shown transformation or secondary sarcoma development in approximately 5\% to 10\% of patients treated with radiotherapy.\textsuperscript{51,52} Patients must be counseled carefully regarding this potential complication.

In conclusion, surgery remains the definitive therapeutic option for most patients with this rare and usually benign bone tumor. However, multiple studies have established a role for radiation, usually ranging from 40 to 50 Gy, in patients with unresectable, incompletely resected, or recurrent lesions (Figure 3). Radiation using modern equipment and techniques is generally safe, without many of the long-term side effects observed in older series.

**Malignant Fibrous Histiocytoma of Bone**

Malignant fibrous histiocytoma of bone (MFHB) accounts for less than 1\% of all primary bone tumors, is more common in men, and occurs most frequently between the third and sixth decades of life. Histologically, it is generally intermediate to high-grade and behaves aggressively with frequent metastases to distant sites, especially the lungs. The preferred local therapy is wide surgical resection with reconstruction or amputation, if necessary, to achieve clear margins. A study from Australia found that patients undergoing initial amputation or wide excision experienced a higher 5-year survival rate (86\%) compared with patients who underwent an initial marginal or intralesional excision (30\%).\textsuperscript{44} Because local control is generally worse for patients with incomplete excisions, positive, or very close margins, a few investigators have used radiotherapy in the adjuvant setting to try to reduce the local failure risk. Reagan et al.\textsuperscript{55} administered a median dose of 60 Gy alone or postoperatively to approximately 20 patients with an overall local control rate at 5 years of 65\%. Most patients in

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\caption{(A and B). Pre- and post-radiotherapy magnetic resonance images of a large soft tissue metastasis in the forearm of a 34-year-old man with a primary giant cell tumor arising in the third metacarpal bone of the hand. The soft tissue mass decreased significantly in size 3 months after completion of radiotherapy (arrows).}
\end{figure}
this study were irradiated after surgical debulking and had a local control rate of 75%. Patients with extensive soft tissue disease or close/positive margins are considered candidates for adjuvant radiotherapy in the authors’ institution. Neoadjuvant or adjuvant chemotherapy should also be considered for patients with MFHB.48

Primary Lymphoma of Bone

Primary non-Hodgkin lymphoma of bone is an extremely rare entity constituting roughly 5% of all extranodal non-Hodgkin lymphomas. It is slightly more prevalent in men and is most commonly diagnosed in middle age.51 The most common histology is diffuse large B-cell lymphoma (DLCL) and most patients present with disease localized to the involved bone (stage I) or the bone and adjacent lymphatics (stage II). Historically, treatment of localized DLCL (stage I or II) consisted primarily of radiation to the bone and its nodal basin. For example, in the early 1980s, Dosoretz et al.49 reported an overall 5-year survival of 63% with doses of 45 to 50 Gy to the entire bone, followed by a boost to the tumor and margin. With the advent of effective chemotherapy and the findings that a substantial proportion of patients experienced recurrence in distant sites after undergoing radiotherapy alone, the treatment paradigm for non-Hodgkin lymphoma changed to multimodality therapy with initial chemotherapy followed by involved-field radiotherapy.

A combined approach using chemotherapy (3–6 cycles) followed by involved-field radiotherapy with 30 to 40 Gy is currently recommended for patients with early-stage disease.53 Patients presenting with localized indolent or low-grade lymphoma of bone would generally be managed with definitive radiotherapy alone with doses ranging from 36 to 40 Gy. Surgery is not generally required for definitive therapy but may be necessary for patients presenting with a pathologic fracture or an impending fracture.

Vascular Tumors of Bone

Hemangioendothelioma, epithelioid hemangioendothelioma, and angiosarcoma are vascular tumors that occasionally arise in bone. Experts now believe that these tumors are separate entities, both clinically and histologically.60 Hemangioendotheliomas tend to be multifocal and are generally considered to be borderline to low-grade sarcomas of bone. Epithelioid hemangioendotheliomas also tend to be multifocal, frequently appear in a regional pattern, and can involve viscera. They are generally considered a form of low-grade sarcoma but may sometimes behave in an aggressive fashion. In contrast, angiosarcomas are high-grade tumors with a strong metastatic potential. Although complete surgical removal is the preferred therapeutic modality, this is often difficult to achieve because of the propensity of these tumors to bleed.

The role of adjuvant treatment for these tumors is not well defined. Nonetheless, various investigators have suggested that adjuvant radiotherapy with or without chemotherapy may be beneficial in cases of unresectable or residual disease or those with a high likelihood for local recurrence (as with angiosarcoma).61 Even fewer data exist on the optimal radiation dose for these entities. Although 50 Gy to an involved field may be sufficient to achieve local control for hemangioendothelioma, higher doses to a larger field may be necessary for the more aggressive angiosarcoma. Patients with multifocal epithelioid hemangioendothelioma may be candidates for definitive radiotherapy if the disease is not amenable to limb-sparing surgical resection. Doses of 45 to 50 Gy have been reported to be beneficial in small numbers of patients62 and have resulted in local control at the authors’ institution. As with other primary osseous malignancies, a multidisciplinary approach is essential for treating these tumors, and additional studies of these poorly understood malignancies are desperately needed.

Side Effects from Radiation

Radiation, surgery, and chemotherapy can all result in adverse short- and long-term outcomes in patients with primary bone tumors. Determinants of radiation toxicity include total dose, dose per fraction, length of therapy, treatment volume and site, and dose distribution. Over the past few decades, great strides have been made to reduce unnecessary normal tissue exposure to radiation. Predicting the extent of side effects from radiation remains difficult, however, because patients with primary bone tumors often undergo other therapies (e.g., surgery, chemotherapy) in addition to radiation; radiation modalities and techniques have
changed substantially over the past 10 to 20 years; and patients undergoing radiation may not live long enough for certain side effects to manifest. Because the side effects of radiation are mostly site-dependent and most bone tumors arise in the extremities, this article emphasizes the risk for growth retardation and secondary malignancies among the long-term side effects from radiation. Short-term side effects from radiation of the extremities include erythema and occasionally moist desquamation. Both are generally easily managed with topical wound care and resolve within a few weeks from completion of radiotherapy. Significant skin reactions are less common with multifield conformal therapy because the dose to any particular area of skin can be reduced. Fatigue is commonly noted, but is generally mild to moderate and resolves after therapy is completed.

Long-term side-effects, such as edema, fibrosis, risk for fracture and, in children, growth retardation, are typically irreversible. Bone and muscle growth can be adversely impaired by radiation, and radiation exposure in growing children can cause soft tissue hypoplasia, limb asymmetry, and growth disparities. Multiple studies attribute the severity of these problems to dose and field design, in particular inclusion of the epiphyses in the radiation field. Limiting the number of vertebral bodies exposed and including entire vertebral bodies in the radiation field help minimize the likelihood of shorter stature and deformities of the spine, such as scoliosis or kyphosis. Furthermore, 20 Gy seems to be the dose above which both muscle hypoplasia and limb-length discrepancy become more common, and doses of 40 Gy or more are associated with bone weakening and a higher risk for pathologic fractures. Although most published data on this topic are from the 1970s and 1980s and reflect treatment with orthovoltage techniques, larger fields, and higher doses, pediatric radiation oncologists must counsel parents about the possibility of limb-length discrepancy, muscle hypoplasia, and growth retardation.

Perhaps the most feared adverse event from radiation to the extremities is a second malignancy. Osteosarcoma is the most common second malignant neoplasm during the first 20 years after a child is diagnosed with cancer. An association between the development of secondary malignancies and the administration of radiotherapy has been well established. In one study, the risk for developing a bone tumor was 2.7 times higher in patients who underwent radiation therapy and was up to 40 times higher for doses to the bone of more than 60 Gy. Interestingly, treatment with alkylating agents was also linked to bone cancer in this study. This again illustrates the difficulty in separating the risk incurred from radiation from other factors such as the administration of chemotherapy or the patient’s inherent predisposition to developing another malignancy.

A larger study from the United Kingdom corroborates these findings, showing that the risk for bone cancer increased linearly with the cumulative dose of radiation to the bone and the cumulative dosage of alkylating agents. Although most studies have found a lower risk for secondary sarcomas at low doses, a recent analysis by Koshy et al. of 109 radiation-induced osteosarcomas shows that well over a third (35.9%) were associated with doses less than 45 Gy. This study shows the importance of informing parents, regardless of dose or latency considerations, of the risk for a radiation-induced malignancy, especially when it is as devastating and potentially lethal as osteosarcoma.

**Conclusions**

Primary bone tumors are uncommon entities in both adults and children. Radiation therapy generally has a role as an adjunct to surgery or for unresectable or recurrent disease. Treatment must always be balanced with the potential for long-term side effects. Improved imaging, target definition, and delivery of radiation will undoubtedly help reduce side-effects and increase local disease control. As the systemic spread of disease is controlled better, the need for long-term local control while maintaining function will become more important. Therefore, radiation therapy is likely to remain important, and close coordination among orthopedic, adult and pediatric medical, and radiation oncologists will continue to be critical.

**References**


