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Use of radiation therapy for patients with soft-tissue and bone sarcomas

ABSTRACT

Radiation therapy is recommended as an adjuvant to resection for intermediate- and high-grade soft-tissue sarcomas; its role in bone sarcomas is largely limited to select patients with Ewing sarcoma. Despite the integral role of radiation therapy in soft-tissue sarcoma management, its optimal timing—preoperative versus postoperative—is uncertain, with each timing scenario having advantages and disadvantages. Preparation for radiation therapy involves a detailed planning session to optimize and standardize patient positioning and determine the target volume. Side effects of radiation therapy may include skin changes, delayed wound healing and other wound complications, fatigue, reduced range of motion of the affected limb, pain, and bone fractures.

While radiation therapy (RT) has an integral role in the management of soft-tissue sarcoma, it has a limited role in that of bone sarcoma, with few exceptions (ie, Ewing sarcoma). In keeping with the rarity of these tumors, it has been demonstrated that patients treated at high-volume centers have significantly better survival and functional outcomes.[1–3] Accordingly, treatment should be delivered by a multidisciplinary team including orthopedic, medical, and radiation oncologists, as well as plastic and reconstructive surgeons, physical therapy specialists, and pathologists and radiologists with expertise in musculoskeletal sarcomas.[4] As the preceding articles in this supplement have addressed the major modalities in the treatment of sarcomas other than RT, this article will focus on how RT fits into the overall management mix, with a focus on soft-tissue sarcomas, where it figures most prominently.

BONE SARCOMAS: A LIMITED ROLE FOR RADIATION

The role of RT in the management of bone sarcomas is limited. Its primary application appears to be in Ewing sarcoma, for which curative treatment requires combined local and systemic therapy. For definitive therapy, limb-salvage surgery is preferable over amputation, but amputation may be an option for younger patients with lesions of the fibula, tibia, and foot. Based on the available data, postoperative RT is probably of benefit for all patients with Ewing sarcoma with close margins and/or those with a poor histologic response.[5] Further discussion of Ewing sarcoma management is beyond the scope of this article (see the second and fifth articles in this supplement).

For osteosarcoma, the current standard of care is surgical resection combined with neoadjuvant and adjuvant chemotherapy. RT had been used years ago, prior to the advent of effective chemotherapy regimens, but its use for osteosarcoma has now been relegated to a few select situations. These include lesions not amenable to surgical resection and reconstruction, cases in which the patient refuses surgery, cases where there are positive margins after resection, and cases where palliation is needed for symptomatic lesions.

SOFT-TISSUE SARCOMAS: RADIATION HAS A CLEAR ADJUVANT ROLE

The primary management of localized soft-tissue sarcomas is surgical resection to achieve a negative margin when feasible. Historically, local excision of soft-tissue sarcomas resulted in local failure rates of 50% to 70%, even when a margin of normal tissue around the tumor was excised. As a result, amputation became standard treatment.[6] In a landmark National Cancer Institute study 3 decades ago, patients were randomized to amputation or to limb-sparing surgery with the addition of RT.[7] Notably, disease-free and overall survival were not compromised by limb-sparing surgery plus RT, demonstrating that although lesser surgery in the absence of RT may be insufficient, limb-sparing surgery with RT was equal to amputation. Consequently, limb-sparing approaches have become the favored surgery for the majority of cases of soft-tissue sarcoma, as advocated in a consensus statement from the National Institutes of Health.[1]

Indications vary by lesion grade

In general, adjuvant RT is recommended for all intermediate- and high-grade soft-tissue sarcoma lesions. A potential exception is a superficial tumor smaller than 5 cm with widely negative margins after resection. For low-grade lesions, re-excision is favored over adjuvant RT for positive or close margins, and RT is avoided in the setting of negative margins.

Optimal timing of radiation remains unclear

The optimal timing of adjuvant RT—preoperative versus postoperative—remains unknown. The relative advantages of preoperative RT include smaller and well-defined treatment volume, ability to use a lower dose, lack of tissue hypoxia, increased tumor resectability (smaller surgery), and improved limb function with less late fibrosis and edema. The disadvantages include inability to precisely stage patients

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and higher risk of acute wound-healing complications.

The National Cancer Institute of Canada compared outcomes with preoperative versus postoperative RT among 190 patients with soft-tissue sarcoma in a prospective randomized trial.[8] Patients were stratified by tumor size (≤ 10 cm or > 10cm) and then randomized to preoperative RT (50 Gy in 25 fractions) or postoperative RT (66 Gy in 33 fractions).[8] There was no difference between the groups in local control, distant control, or survival rates, but a higher rate of late complications, including fibrosis and edema, was observed with postoperative RT.[8,9] On the other hand, the incidence of wound complications was higher in the preoperative group (35%) than in the postoperative group (17%).[8]

Likewise, the optimal sequencing and benefits of systemic therapy (chemotherapy) with relation to local therapy (surgery with pre- or postoperative RT) remain unclear. More than a dozen individual randomized trials of adjuvant chemotherapy, as well as a meta-analysis of 14 trials of doxorubicin-based adjuvant chemotherapy, have failed to demonstrate significant improvement in overall survival in patients with soft-tissue sarcomas.[10] With regard to neoadjuvant chemotherapy for soft-tissue sarcomas, there are studies suggesting improvement in local control but no consistent survival benefit.[11] Chemotherapy may yield a benefit in select cases, as detailed elsewhere in this supplement.

MECHANISMS OF ACTION: DIRECT AND INDIRECT

In simplified terms, radiation kills cancer cells through two basic mechanisms: indirect and direct.

The indirect effect (the most common mechanism) results from the generation of free radicals in the intracellular medium via ionization by photons. Free radicals, in turn, deposit large amounts of energy that damage DNA or some other vital component of the cell, resulting in cell death.

The direct effect is a consequence of photons themselves interacting directly with the cell in a lethal manner.

The goal of RT is to kill tumor cells selectively, without irreversibly injuring adjacent normal tissue. This is done by exploiting two abnormal aspects of tumor behavior: decreased ability for repair and increased susceptibility to ionizing radiation damage. Tumors are generally less able than normal tissue to repair DNA damage, owing to defective repair mechanisms. Tumor cells are also comparatively more radiosensitive than normal tissues, as they are more frequently in radiosensitive cell-cycle phases. Thus, dividing the radiation dose into a number of treatment fractions provides two advantages that further exploit the biologic differences between tumor and normal tissue: it allows DNA repair to take place within the normal tissues, and it allows proliferating tumor cells to redistribute through the cell cycle and move into the more radiosensitive phases.

TREATMENT PLANNING

Treatment simulation

Following initial consultation with a radiation oncologist, the eligible patient undergoes a simulation, or a treatment planning session in which he or she is positioned so as to allow treatment to be carefully designed and subsequently delivered with precision. This typically requires fabrication of a customized immobilization device to allow for consistent positioning over the treatment course. Sarcomas require that special care be taken to properly immobilize both the proximal and distal joints. Additionally, radiopaque wires are used to delineate the anatomic boundaries of the tumor or scar. Computed tomographic (CT) scans are then obtained to enable image-based three-dimensional treatment planning. The patient setup is photographed, and setup indicators are recorded and marked on the patient's skin, some with freckle-size tattoos and some with indelible marker.

The treatment fields are then designed on the CT-simulation data set with the aid of virtual reality–type techniques. In addition to delineation of tumor volumes, three-dimensional treatment planning is used to contour all nearby normal structures on each slice. The resulting structures can then be used to specify dose constraints and help determine the optimal beam geometries to ensure proper tumor coverage and minimize the potential for side effects by reducing the dose to organs at risk. In the case of sarcomas, several strategies for reducing the risk of side effects are especially relevant: (1) carefully sparing a portion of the circumference of uninvolved bone to minimize the risk of fractures; (2) carefully sparing a strip of normal tissue to minimize edema by permitting undisrupted lymphatic drainage from the extremity; and (3) keeping dosing to joint spaces and other adjacent organs below tissue tolerances as defined by Emami et al.[12]

Determining target volume

The target volume for RT is determined on the basis of physical examination, radiologic studies, anatomical considerations, and the natural history of the sarcoma.

In the preoperative setting, longitudinal margins of 5 cm beyond the tumor and tumor-associated edema and radial margins of 2 cm are treated to 50 Gy in 25 fractions. Surgery is undertaken approximately 4 weeks after completion of RT to allow for repair in normal tissues and minimize operative and postoperative complications. Following surgery, an RT boost may be added for positive margins (16 Gy) or gross residual disease (25 Gy).

In the postoperative setting, details on the extent of dissection or observations from the surgeons themselves must be considered. Information regarding the surgical approach must be noted and can influence the effectiveness of postoperative RT as well as the incidence of late side effects. When experienced surgeons are involved, scars and drain sites, which are at risk for subclinical disease, can be planned so that their inclusion in the RT portal allows for sparing a strip of skin to minimize complications. Surgical clip placement at the boundaries of the tumor bed also facilitates RT planning.[13] Finally, prophylactic bone stabilization may reduce the risk of subsequent fracture in cases where circumferential bone radiation in high-risk sites is anticipated.

Recommendations on the volume that must be treated vary among different authorities. Some advocate treating the entire compartment because of the risk for microscopic

seeding.[14] Others recommend margins around the tumor or tumor bed ranging from less than 5 cm up to 15 cm.[15] Most often the postoperative approach is to include the resection bed with a 2-cm radial margin, the incision, and any drain sites in the initial treatment volume and to base the longitudinal margin on the grade and size of the primary tumor (5–15 cm). This volume is treated to 50 Gy in 25 fractions followed by two sequential reductions in field size, with the total dose determined by the extent of resection: 60 Gy for negative margins, 66 Gy for microscopically positive margins, and 75 Gy for gross residual disease.

TREATMENT DELIVERY

Once treatment planning is completed, treatments begin and are given daily Monday through Friday. Each day, the patient is positioned in the immobilization device, the field measurements are set, and positioning is checked with measurement tools and external marking of the field borders on the skin. Daily image guidance techniques may be used to increase setup reproducibility. Typical treatment times, including setup and actual delivery, are roughly 20 to 30 minutes daily.

While external beam RT is most commonly delivered as described above, brachytherapy, or intraoperative electron beam techniques, as well as proton or other charged-particle therapies, are also applied in selected cases.[16–18]

SIDE EFFECTS

Side effects of RT in the setting of sarcomas can be divided according to their onset—ie, acute versus delayed.

Acute effects. Skin changes ranging from erythema to moist desquamation in the skin overlying the high-dose volume are common. Major wound complications (delayed wound healing or need for surgical intervention) occur in approximately 17% of patients after surgical resection with postoperative RT, and perhaps more commonly (35%) with preoperative RT,[8] though these rates vary widely in the literature. Another frequently reported acute side effect is fatigue.

Delayed sequelae after conservative resection and RT of extremity lesions include a reduction in range of motion secondary to joint contracture, edema, and fibrosis, as well as pain and bone fractures, all of which can significantly limit function of the preserved limb. In centers treating high volumes of patients with soft-tissue sarcoma, the incidence of moderate to severe late effects is less than 10%.[19] In contrast to acute wound complications, a higher rate of late complications, including fibrosis and edema, have been observed with postoperative RT relative to preoperative RT.[9] When necessary, high-dose RT does not appear to compromise the viability of skin grafts used to repair defects after sarcoma surgery if adequate time is allowed for healing.[20]

Regardless of the management approach, intensive rehabilitation led by physical therapy specialists is imperative in minimizing disabilities after treatment of soft-tissue sarcomas.

CONCLUSION

Outcomes of patients with musculoskeletal sarcomas are optimized at specialized sarcoma centers. For patients with soft-tissue sarcomas, effectively implementing an approach that combines conservative surgery and RT—and, in select cases, chemotherapy—achieves excellent local control rates while minimizing morbidity and maximizing long-term extremity function relative to aggressive surgery alone.

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