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EDITORIAL – SARCOMA

IMRT Should Be Considered a Standard-of-Care Approach for Radiation Therapy for Soft Tissue Sarcoma of the Extremity

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The standard of care for management of nonmetastatic soft tissue sarcoma of the extremity is conservation surgery in combination with radiation therapy. The radiation therapy can be administered either pre- or postoperatively. Local control is achieved in over 90% of patients,[1,2] and the need for amputation of an affected limb is rare. However, potential acute and long-term complications of treatment are nontrivial.[2,3] Since establishment of the combined-modality limb-sparing approach as standard of care,[4] investigators have sought ways to mitigate the long-term effects of treatment that may impair functional outcomes or result in decrements in quality of life for patients as a result of their sarcoma treatment. The most common late-occurring effects of combined-modality local treatment that interfere with physical functioning include fibrosis of the soft tissues, extremity edema, and joint stiffness.[3] A rarer, but more serious, late complication is bone fracture—particularly long bone fracture such as femoral fracture. The significant morbidity of radiation-related femoral fractures can be compounded by high rates of delayed union or nonunion, likely a result of adverse effects from radiation dose exposure to the bone that results in impaired osteoblastic function and vascular fibrosis.

Studies have identified potential surgical maneuvers and radiation therapy planning considerations to reduce the risk of femoral fracture after combined radiation therapy and surgery to the lower extremity. Prophylactic stabilization of the femur can be achieved through intramedullary nailing at the time of surgical resection of a lower extremity sarcoma and can be considered in patients who are deemed at high risk of femoral fracture.[5,6] Such a prophylactic surgical approach offers the advantages of lower risks of subsequent fractures and nonunion of the bone. However, it does add time to what is often an already complicated surgical procedure and confers additional potential postoperative wound healing risks for patients who receive preoperative radiation therapy. An alternative approach to mitigate femur fracture risk is to modify the radiation therapy planning dose constraints on the femur toward that aim. Dickie and colleagues[7] at Princess Margaret Hospital have published dosimetric data that provide useful radiation dose parameters that can be incorporated into radiation therapy planning objectives. They demonstrated that radiation-related fracture rates were lower when the mean radiation dose to the femur was < 37 Gy or when the maximum radiation dose anywhere along the length of the femur was < 59 Gy. Their investigation also shows that limiting the volume of femur that receives 40 Gy to less than 64% of the bone reduces the risk of fracture. Bishop et al.[8] demonstrated that, to reduce femur fracture risk, a primary radiation therapy planning objective should be to keep the 50 Gy dose exposure to the femur to $< 100\%$ of the circumference of the bone. These radiation therapy planning maneuvers can be difficult to accomplish in patients with large, deep tumors that approximate the bone. Conventional radiation therapy planning techniques often require that large swaths of the bone are exposed to full dose in order to cover the tumor and accomplish the oncologic treatment objectives. Intensity-modulated radiation therapy (IMRT) provides a highly conformal alternative to conventional radiation therapy planning. IMRT is more complex and resource-intense to plan and deliver and consequently more costly than conventional radiation therapy. While it has been shown to be beneficial in improving toxicity outcomes for some cancers, such as head and neck cancer and anal cancers, there have been no published studies specifically addressing whether IMRT reduces treatment-related toxicity for patients treated for soft tissue sarcoma.

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In this issue, Folkert et al.[9] provide this evidence. The authors report their finding that treating lower extremity sarcomas with IMRT yields a lower than expected risk of femoral fracture when using a prediction nomogram tool developed by investigators at Princess Margaret Hospital[6] which was based on historical data of patients treated with conventional (non-IMRT) radiation therapy techniques. Specifically, the authors report a cumulative fracture risk of 6.7% at 5 years compared with the nomogram-predicted rate of 25.6% which was computed based upon patient, tumor, and clinical treatment factors known to be predictive of fracture risk after treatment for soft tissue sarcoma. The relatively low fracture rate observed in this study is of particular note given that the majority of patients in the study (86%) were treated with postoperative irradiation to a median dose of 63 Gy. The higher dose required to the surgical resection bed when postoperative irradiation is used can present challenges in meeting the dosimetric constraints to the femur described in the above paragraph, and the low fracture rate reported in this study speaks directly to the superiority of IMRT planning in delivering an adequate dose of irradiation around the femur while mitigating dose exposure that might confer a higher fracture risk. The authors provide dosimetric data confirming that those who experienced fractures in their study did have radiation therapy plans that exceeded the dose limitations recommended in the study by Dickie et al.[7] The authors do not comment on other radiation-associated complications such as soft tissue fibrosis, joint contracture, and edema that may also be differentially associated with use of IMRT versus conventional radiation therapy. This is of particular interest because the high degree of conformity of IMRT plans is attained by increasing the number of radiation fields using fixed-shape or dynamic conformal arcs or fields. The result is that larger volumes of tissues receive lower doses of radiation in IMRT plans than that affected by conventional radiation techniques. Future studies will be necessary to ascertain whether this higher integral dose associated with the use of IMRT confers higher risk of edema or fibrosis in the treated limb.

This is the first study to clearly show that advanced radiation therapy planning techniques, i.e., IMRT, do improve meaningful toxicity-related outcomes for patients with soft tissue sarcoma of the extremity. Specifically, the use of IMRT for patients with thigh sarcomas appears to reduce the risk of the complication of femur fracture, a relatively rare but disabling complication of radiation therapy for patients with this disease. IMRT is widely available in radiation oncology practices throughout the USA and certainly in centers that provide the specialized oncologic expertise preferable for management of patients with soft tissue sarcoma. What has been less easy to access is consistent payer allowance for the use of IMRT to treat patients with soft tissue sarcoma of the extremity. This study provides evidence that IMRT is differentially beneficial and the technique of choice for radiotherapeutic management of soft tissue sarcoma where dosimetric constraints to bone are difficult to achieve.

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