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Clinical Investigation: Sarcoma

Dose–Effect Relationships for Femoral Fractures After Multimodality Limb-Sparing Therapy of Soft-Tissue Sarcomas of the Proximal Lower Extremity

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Summary

We investigated clinical and dosimetric predictors for radiation-associated femoral fractures in patients who received limb-sparing surgery and radiation therapy for proximal lower extremity soft-tissue sarcomas. We show that the femoral neck is particularly susceptible to fractures compared with other femur subregions and that mean femoral neck doses >40 Gy greatly increase this risk. Prophylactic femoral nailing also reduces the fracture risks associated with periosteal excision.

Purpose: We investigated the clinical and dosimetric predictors for radiation-associated femoral fractures in patients with proximal lower extremity soft tissue sarcomas (STS).

Methods and Materials: We examined 131 patients with proximal lower extremity STS who received limb-sparing surgery and external-beam radiation therapy between 1985 and 2006. Five (4%) patients sustained pathologic femoral fractures. Dosimetric analysis was limited to 4 fracture patients with full three-dimensional dose information, who were compared with 59 nonfracture patients. The mean doses and volumes of bone (V_d) receiving specified doses ($\geq$30 Gy, 45 Gy, 60 Gy) at the femoral body, femoral neck, intertrochanteric region, and subtrochanteric region were compared. Clinical predictive factors were also evaluated.

Results: Of 4 fracture patients in our dosimetric series, there were three femoral neck fractures with a mean dose of 57.6 $\pm$ 8.9 Gy, V30 of 14.5 $\pm$ 2.3 cc, V45 of 11.8 $\pm$ 1.1 cc, and V60 of 7.2 $\pm$ 2.2 cc at the femoral neck compared with 22.9 $\pm$ 20.8 Gy, 4.8 $\pm$ 5.6 cc, 2.5 $\pm$ 3.9 cc, and 0.8 $\pm$ 2.7 cc, respectively, for nonfracture patients ($p < 0.03$ for all). The femoral neck fracture rate was higher than at the subtrochanteric region despite lower mean doses at these subregions. All fracture sites received mean doses greater than 40 Gy. Also, with our policy of prophylactic femoral intramedullary nailing for high-risk patients, there was no significant difference in fracture rates between patients with and without periosteal excision. There were no significant differences in age, sex, tumor size, timing of radiation therapy, and use of chemotherapy between fracture and nonfracture patients.

Conclusions: These dose–volume toxicity relationships provide RT optimization goals to guide future efforts for reducing pathologic fracture rates. Prophylactic femoral intramedullary nailing may also reduce fracture risk for susceptible patients. © 2012 Elsevier Inc.

Keywords: Sarcoma, Predictive factors, Femoral fracture, Intramedullary nailing

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Introduction

The standard of care for lower extremity soft tissue sarcoma (STS) is limb-sparing surgery and radiation therapy (RT), with this treatment achieving local control rates of up to 95% (1–3). With excellent local control, concerns about long-term toxicity are becoming increasingly important. Radiation-associated fractures have been described in studies reporting fractures of the humerus, ulna, femur, patella, tibia, fibula, and metatarsal, with the majority occurring at the femur (1, 4–11). Femoral fractures can be devastating and often involve delays of osseous union beyond 12 months, requiring surgical intervention in cases of nonunion and total endoprosthetic replacement or limb amputation when nonunion persists (10–12).

Because of morbidities after radiation-associated femoral fractures, it is imperative to understand the treatment factors contributing to this risk. Common risk factors include age, sex, periosteal excision, and chemotherapy, with fracture rates up to 47% in patients with these risk factors (7, 8, 11). Yet, the literature on bone dose–volume toxicity relationships is sparse (6), and no study to our knowledge has examined these relationships at specific high-risk fracture regions within the femur. Intramedullary (IM) nailing has also been suggested as an attractive prophylactic measure (8, 10, 11). Therefore, this study aimed to identify clinical and dosimetric predictors for radiation-associated femoral fractures in patients with proximal lower extremity STS and to review our policy of prophylactic femoral IM nail stabilization in patients at high-risk for fracture.

Methods and Materials

Patients

After obtaining institutional review board approval, we identified 223 patients with extremity STS treated between January 1, 1985, and December 31, 2006, at the University of Michigan's Multidisciplinary Sarcoma Clinic. Cases were identified via the Department of Radiation Oncology record system and reviewed for those appropriate for this study. These included only patients who underwent both surgical resection and external-beam RT for STS of the proximal lower extremity. Those treated with either surgery or chemotherapy alone were not included. Patients were excluded if they had metastatic disease at the time of diagnosis, if their margin status was unknown, or if they first presented to the University of Michigan for recurrent disease. Any patient who received brachytherapy was excluded. B\y use of these criteria, 131 patients were identified. Local control results have been published elsewhere (13). Five (4%) patients sustained nontraumatic pathologic femoral fractures in the irradiated field. Complete three-dimensional (3D) treatment planning data was retrievable for 4 fracture patients(3 with femoral neck fractures and 1 with subtrochanteric fracture) and 59 nonfracture patients who received similar treatment. These patients were used for the dosimetric portion of this study. The clinical predictive factors of all 5 fracture patients were compared with those of all 126 nonfracture patients. These included age, sex, tumor size, timing of RT (adjuvant, neoadjuvant, both), periosteal excision with prophylactic femoral IM nailing, and chemotherapy use.

Planning and treatment

All patients underwent surgical resection, and 30 had secondary reexcision to achieve negative margins. One hundred fourteen patients received adjuvant RT after surgery, 10 patients received neoadjuvant RT, and 7 patients received both neoadjuvant and adjuvant RT. For adjuvant therapy, the initial target was treated to 45 Gy and included the tumor bed plus 5-cm proximal and distal margins, in addition to a 2-cm circumferential margin except when limited anatomically by compartments. This was followed by a boost to the tumor bed plus 2-cm margins in all directions. For neoadjuvant therapy, the target consisted of the gross tumor and similar margins treated to 45 to 50.4 Gy. Efforts were made to avoid circumferential bone irradiation and to spare at least half of the adjacent joints. All patients were treated with a fractionation schedule of 1.8 to 2.0 Gy per day. Four patients received two courses of treatment for recurrent disease. Almost two thirds of patients were treated using 3D conformal planning, and approximately one third of the patients were treated with two-dimensional planning. Intensity-modulated RT was used for 2 patients. All planning was completed using UMPLAN, an in-house treatment planning system.

Bone dosimetry

Femoral bone structures were autocontoured using thresholds of 150 to 3,000 and manually edited on sequential axial computed tomography slices. For the purposes of this study, the femoral neck was contoured from the lateral border of the femoral head to the intertrochanteric line. The intertrochanteric region of the femur was contoured from the tip of the greater trochanter superiorly to the bottom of the lesser trochanter inferiorly, and the subtrochanteric region from the bottom of the lesser trochanter superiorly to 5 cm inferiorly. The body of the femur was then contoured from the inferior border of the subtrochanteric region to the most inferior beam field edge. Femoral structure definitions are shown in Fig. 1.

Cumulative dose–volume histogram (DVH) data for all femoral structures were computed. From the DVHs for each patient, the mean dose and volume of bone (V_d) receiving specified doses ($\geq$30 Gy, 45 Gy, 60 Gy) were identified. Because we observed noticeable differences between fracture and nonfracture patients at higher dose ranges and the majority of patients were treated to 63 Gy, the dose–volume covariates were chosen to represent approximately 50%, 75%, and 100% of the prescribed dose, respectively.

Statistical analysis

Comparisons of the clinical characteristics were conducted by fracture status for the entire sample ($n = 131$). Dose metric comparisons were limited to the subset of cases with retrievable 3D treatment plans ($n = 63$). Comparisons between continuous and categoric covariates were conducted using the two-sample t test and Fischer's exact test, respectively. We considered p values at or below 5% to be statistically significant. Because of the small number of events, only univariate analysis was performed. All available clinical characteristics were also compared between those with and without retrievable 3D treatment planning information to detect selection bias. No significant differences were detected, indicating no evidence for systemic bias in the selection of the treatment planning subset.