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ORIGINAL ARTICLE – SARCOMA

Femoral Fracture in Primary Soft-Tissue Sarcoma of the Thigh and Groin Treated with Intensity-Modulated Radiation Therapy: Observed versus Expected Risk

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ABSTRACT

Purpose. This study was designed to compare the observed risk of femoral fracture in primary soft-tissue sarcoma (STS) of the thigh/groin treated with intensity-modulated radiation therapy (IMRT) to expected risk calculated using the Princess Margaret Hospital (PMH) nomogram.

Methods. Expected femoral fracture risk was calculated by using the PMH nomogram. Cumulative risk of fracture was estimated by using Kaplan–Meier statistics. Prognostic factors were assessed with univariate and multivariate analysis using Cox's stepwise regression.

Results. Between February 2002 and December 2010, 92 consecutive eligible patients were assessed. Median follow-up was 73 months (106 months in surviving patients). IMRT was delivered preoperatively (50 Gy) in 13 (14%) patients and postoperatively in 79 (86%) patients (median dose, 63 Gy; range, 59.4–66.6 Gy). The observed crude risk of fractures was 6.5% compared with 25.6% expected risk from the nomogram; the cumulative risk of fracture using IMRT at 5 years was 6.7% (95% CI 2.8–16.0%). The median time to fracture was 23 months (range, 6.9–88.6). Significant predictors of fracture on univariate analysis were age ≥ 60 years ($p = 0.03$), tumor location in the anterior thigh ($p = 0.008$), and periosteal stripping to > 20 cm ($p < 0.0001$). On multivariate analysis, age

≥ 60 years and periosteal stripping > 20 cm retained significance ($p = 0.04$ and $p = 0.009$, respectively).

Conclusions. In this study, the cumulative risk of femur fracture in patients treated with IMRT (6.7%) is less than the expected risk using the PMH nomogram (25.6%). Established predictors of femur fracture, such as gender, tumor size, and dose of RT, seem to have less impact on fracture risk when using IMRT.

The overall rate of radiation-associated bone fracture in soft-tissue sarcoma (STS) of the extremity is approximately 4–6%.[1–3] Most of these fractures occur in patients with lower extremity lesions, particularly the thigh.[4] Even within the thigh, there is a higher rate of fracture in anterior compartment tumors compared with medial or posterior compartments.[3,5] The dose of radiation also influences the rate of femoral fracture; a 9% rate was reported for lower extremity STS treated to > 60 Gy compared with 1% for those treated to 50 Gy.[4]

One potential means of reducing fracture risk in STS is intensity-modulated radiation therapy (IMRT), which can spare at least a portion of the circumference of a long bone from receiving the full dose of radiation.[6] In a previous report from Memorial Sloan Kettering Cancer Center (MSKCC), the rate of bone fracture using adjuvant IMRT for primary STS of the extremity was 4.8%.[7] Determining the true impact of IMRT on the rate of fracture, however, is challenging. First, several factors, apart from radiation techniques, influence the risk of fracture, such as patient age, gender, tumor size, location, and the extent of

periosteal stripping.[2,3] Second, these radiation-related fractures tend to manifest long after treatment, with a median time to fracture of close to 40 months.[4,7]

Investigators from Princess Margaret Hospital (PMH) incorporated the above risk factors for femur fracture into a predictive nomogram.[10] We sought to examine the impact of IMRT on fracture risk by comparing the *observed risk* of femoral fracture in primary STS treated with limb-sparing surgery and IMRT to the *expected risk* using the PMH nomogram. Using this nomogram rather than simply comparing fracture rates with other reports in the literature accounts for the influence of various factors and thus allows for more accurate estimation of the true impact of IMRT on fracture rate. The IMRT cohort was limited to patients whose median follow-up (surviving patients) exceeded 8 years.

METHODS

Patients

The prospective database at our institution was reviewed to identify patients with primary nonmetastatic soft tissue sarcoma (STS) of the thigh/groin who underwent both limb-sparing surgery and adjuvant IMRT at MSKCC between February 2002 and December 2010. Patients receiving prophylactic internal fixation were excluded. This retrospective analysis was approved by our Institutional Review Board.

Radiation Therapy

Treatment plans were generated using our in-house treatment-planning system (Top Module, New York, NY, USA). Details regarding treatment planning and delivery have been previously described.[6] In brief, when expanding the target gross tumor volume (GTV) for preoperative IMRT or tumor bed for postoperative IMRT to the clinical target volume (CTV), nearby bone is excluded. Typical expansion from CTV to planning target volume (PTV) was 1 cm. Routine portal imaging was performed on a weekly basis. The median dose of preoperative IMRT was 50 Gy and for postoperative IMRT was 63 Gy. For patients who subsequently developed fractures, the location of the fracture was digitized into the patient's original treatment plan and dosimetric factors associated with the fracture were assessed.

Calculation of Expected Fracture Risk

Expected risk of fracture was calculated using the PMH nomogram, which incorporates risk factors, including gender, age at index surgery (in years), compartment of thigh (anterior, posterior, adductor, or "other"), tumor size (in cm), tumor dose (< 60 Gy or ≥ 60 Gy), and extent of periosteal stripping (< 10 cm, 10–20 cm, or > 20 cm).[10] The probability of fracture (P_{frac}) was calculated using maximum likelihood estimates for each factor in the nomogram, using the equation

$$P_{\text{frac}} = 1/(1 + e^{-\Sigma(\text{MLE})}).$$

Assessment/Follow-Up

The status of all patients was checked at least once weekly while on treatment by the treating radiation oncologist. Follow-up evaluation included physical examination and imaging. All patient follow-up was prospectively performed at our institution. Toxicity was graded by using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, with the highest grade of any observed toxicity reported for each patient.

Statistics

All outcomes were measured from time of definitive surgery to time of event. Fracture-free interval was defined as the time from definitive surgery to highest fracture grade. Lower-grade fractures were noted but excluded from our analysis, because they were outside the treatment field. Patients were censored at the date of last follow-up or death. Outcomes were estimated by using the Kaplan–Meier method and cumulative incidence functions; confidence intervals at median follow-up times were calculated by using Wilson's interval with continuity correction. Log-rank test and Cox proportional hazards regression models were used for univariate and multivariate analysis. Receiver-operating characteristic (ROC) analysis was performed to calculate the area under the receiver operator curve (AUC) and test the predictive power of the PHM nomogram in the study population treated with IMRT. Statistical analysis was performed by using SPSS v22.0.0 (SPSS Inc.).

RESULTS

Patients

Between February 2002 and December 2010, 92 consecutive eligible patients were treated with limb-sparing surgery and IMRT. Median follow-up was 73 months (106 months in surviving patients). Patient characteristics are provided in Table 1. Of the patients treated, 36 (39%) were female. The average age was 58 years (range, 19–88). Thigh compartment was anterior in 43 (47%) patients, posterior in 28 (30%), medial in 17 (18%), and groin in 4

TABLE 1 Demographic and clinical characteristics of the studied cohort (n = 92)

	n (%)
Gender	
Female	36 (39.1%)
Male	56 (60.9%)
Age (year)	
< 60	51 (55.4%)
≥ 60	41 (44.5%)
Compartment	
Anterior	43 (46.7%)
Posterior	28 (30.4%)
Medial/groin	21 (22.8%)
Tumor size (cm)	
< 10	36 (39%)
≥ 10	56 (61%)
Extent of periosteal stripping (cm)	
< 10	76 (82.6%)
10–20	9 (9.8%)
> 20	7 (7.6%)
Radiation dose (Gy)	
> 60	76 (85.2%)
≤ 60	16 (17.4%)
Chemotherapy	
Yes	33 (35.9%)
No	59 (64.1%)

(4%). The median tumor maximum dimension was 11.1 cm (range, 2.5–31 cm), and 56 tumors (61%) were > 10 cm in size. Periosteal stripping was performed in 20 (22%) patients; the extent of periosteal stripping was < 10 cm in 4 patients, 10–20 cm in 9 patients, and > 20 cm in 7 patients (1 patient had a partial cortical resection). Preoperative IMRT to 50 Gy was delivered in 13 (14%) patients, and postoperative IMRT was delivered in 79 (86%) patients to a median dose of 63 Gy (range, 59.4–66.6 Gy). Neoadjuvant or adjuvant chemotherapy was administered in 33 (36%) patients.

Fractures

There were six (6.5%) Grade 3 femoral fractures. The median time to fracture was 23 months (range, 6.9–88.6 months). All six patients with Grade 3 fractures were older than age 50 years when treated for primary STS (median age, 61 years), and all had tumors located in the anterior compartment of the thigh. Of the six patients who experienced Grade 3 fractures, five patients (83.3%) were treated to a dose of > 60 Gy and had a tumor > 10 cm, four patients (66.7%) were female, two patients (33.3%)

underwent significant bone manipulation (both with > 20 cm of periosteal stripping), and two patients (33.3%) received adjuvant chemotherapy as part of initial definitive treatment. In five patients (83.3%), the fracture was an acute event requiring open reduction and internal fixation. The sixth patient started developing symptoms and signs of avascular necrosis of the femoral head 4 years after IMRT, ultimately leading to planned hip replacement 3 years later (7 years after IMRT).

The cumulative risk of fracture at 5 years was 6.7% (95% confidence interval [CI] 2.8–16.0%; Fig. 1). Significant predictors of fracture on univariate analysis were age ≥ 60 (p = 0.03), tumor location in the anterior compartment of the thigh (p = 0.008), and periosteal stripping > 20 cm (p < 0.0001). On multivariate analysis, age ≥ 60 years and periosteal stripping > 20 cm retained significance (p = 0.04 and p = 0.009, respectively). The risk of femur fracture among patient groups classified according to the assessed clinical and treatment variables is provided in Table 2.

The PMH nomogram was predictive of femoral fracture in the current cohort of patients treated with IMRT, with an ROC AUC of 0.866 (p = 0.003; Fig. 2). The expected risk calculated using the PMH nomogram was 25.6%, whereas the observed risk of fracture at 5 years was only 6.7%.

Dosimetric Analysis

The locations of all fractures noted in this population were digitized into the patient's original treatment plan, and dosimetric factors associated with the fracture were assessed. For the site of fracture, the median maximum dose (D_{max}) was 65.6 Gy (range, 62.9–74.1 Gy), and the median D_{mean} was 52.2 Gy (range, 46.3–65.7 Gy). For the
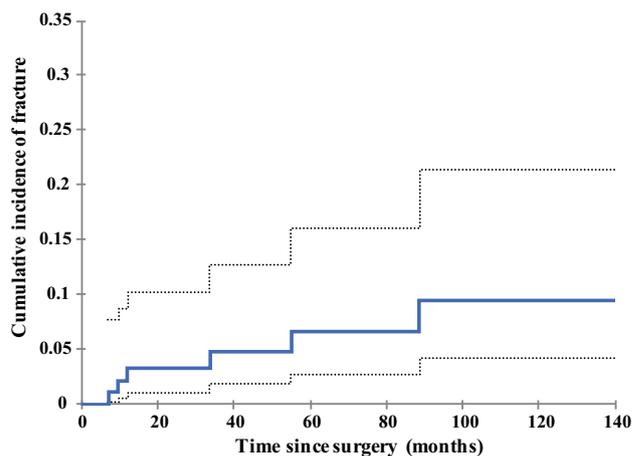

FIG. 1 Cumulative rate of Grade 3 fracture over time among patients with STS of the thigh treated by limb-sparing surgery and IMRT between February 2002 and December 2010 at MSKCC. Dotted lines indicate 95% CI bounds

TABLE 2 Risk of Grade 3 femur fracture at 5 years among patients classified according to clinical and treatment variables

	Crude risk	Cumulative risk over 5 years (%)	95% CI (%)	Univariate *p* value	Multivariate *p* value
Gender					
Female	4/36 (11.1%)	10.2	0.0–21.5	0.17	
Male	2/56 (3.6%)	4.1	0.0–9.6		
Age (year)					
< 60	1/51 (2.0%)	2.0	0.0–6.0	0.03	0.04
≥ 60	5/41 (12.2%)	13.4	0.5–26.3		
Compartment					
Anterior	6/43 (14.0%)	14.0	2.3–25.8	0.008	0.95
Other	0/49 (0.0%)	0.0	0.0–0.0		
Tumor size (cm)					
< 10	1*/36 (2.8%)	0.0	0.0–0.0	0.13	
≥ 10	5/56 (8.9%)	12.7	1.5–23.9		
Extent of periosteal stripping (cm)					
≤ 20	4/85 (4.7%)	4.7	0.0–9.9	<0.0001	0.009
> 20	2/7 (28.6%)	31.4	0.0–67.9		
Dose (Gy)					
≤ 60	1/16 (6.3%)	8.3	0.0–24.0	0.95	
> 60	5/76 (6.6%)	6.3	0.1–12.6		
Chemotherapy					
No chemotherapy	4/59 (6.8%)	6.6	0.0–13.9	0.99	
Chemotherapy	2/33 (6.1%)	6.3	0.0–14.7		

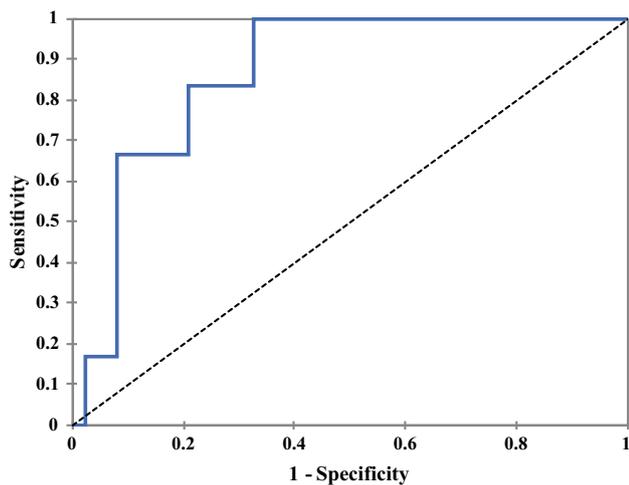*This patient developed fracture past 5 years (88.6 months)

FIG. 2 Predictive power of the PMH femur fracture nomogram among patients with STS of the thigh treated by limb-sparing surgery and IMRT between February 2002 and December 2010 at MSKCC (blue line). AUC = 0.866, *p* = 0.003

irradiated femur, the median D_{max} was 65.9 Gy (range, 65.5–76 Gy), the median D_{mean} was 42.5 Gy (range, 31.2–60.2 Gy), and the median V_{40} (volume of femur irradiated to ≥ 40 Gy) was 0.63 (range, 0.38–0.916).

DISCUSSION

At a median follow-up of 73 months (106 months in surviving patients), the crude rate of femoral fracture was 6.5% in our cohort of 92 patients with primary thigh/groin STS treated by limb-sparing surgery and IMRT at our institution. The overall crude rate of femoral fracture with conventional RT ranges from as low as 2% in some series to as high as 22% in others.[3,4,6–12] This wide range in outcomes reflects the varied influence of several prognostic factors on the risk of femoral fractures, such as age, gender, tumor size, compartment within the thigh, extent of periosteal stripping, and radiation dose and technique on the risk of femoral fractures. This makes direct comparisons between the end outcomes in published series uninformative.

Therefore, we utilized the PMH nomogram, which incorporates several of these prognostic factors. In that study, in which all patients were treated with conventional radiation therapy (and none with IMRT), the crude rate of femoral fracture was 21.7% (22/101) with an estimated 5-year rate of 15%. The PMH nomogram was predictive of femoral fracture in the current cohort of patients treated with IMRT, with an ROC AUC of 0.866 (*p* = 0.003). More importantly, the calculated *expected risk* at 5 years was

25.6%, whereas the *observed risk* was only 6.7%, indicating that the use of IMRT was associated with a reduced risk of femoral fracture.

The association between a lower rate of femoral fracture and the use of IMRT is likely due to reduction in the radiation dose to the whole circumference of the femur. Bishop et al. reported that the rate of femoral fracture was 0% when none or part of the bone circumference was treated compared with 7% when the whole circumference was treated to doses of ≥ 50 Gy ($p < 0.001$).[8] When treating the whole circumference of femur to doses ≥ 50 Gy, combined with adjuvant chemotherapy and periosteal stripping/bone exposure, the femoral fracture rate increased to 37% at 10 years.

Among patients who developed fractures in our cohort, the median radiation dose (D_{mean}) to the femur was 42.5 Gy, and the median D_{max} was 65.9 Gy, which are both greater than the current widely used dose constraints of $D_{mean} < 37$ Gy and $D_{max} < 59$ Gy. This discordance with guidelines results from the fact that the study cohort was treated before the publication of the two studies on which recommendations are based, comparing RT dose/volume parameters between patients who developed fractures and those who did not. In the first study, the D_{mean} to the femur among patients who experienced fractures was 44 Gy versus 38 Gy among those who did not, and the D_{max} was 65 Gy versus 59 Gy.[13] In the second study, the D_{mean} was 57.6 Gy versus 22.9 Gy.[14] Our findings lend further credence and support to the importance of dose constraints for reducing the risk of femoral fracture. Because doses are lower when IMRT is delivered preoperatively, this approach is particularly appropriate for patients at high risk for fracture, such as those with anterior thigh tumors that require significant periosteal stripping.

Another important finding in this cohort treated exclusively with IMRT was that there were no observed instances of nonunion or complications secondary to fixation. This is in contrast to reports in the literature, where rates of nonunion ranging from 27 to 45% have been observed in patients who developed fractures after receiving conventional RT.[2,3,15]

This study is not without its limitations, due to its retrospective nature and the inherent biases present in such research. To limit these biases, we restricted our analysis to patients with primary STS of the thigh/groin who received all surgical and radiation treatment at our institution. Limiting reported fractures to those classified as Grade 3 makes this outcome clear and unequivocal, and comprehensive dosimetric information was available for all patients in the study cohort. We excluded patients treated after 2010 to allow more than adequate time to capture any potential fracture several years beyond the completion date of IMRT. After 2010, we implemented the above-mentioned dose constraints for weight-bearing bone to limit further the radiation dose to the femur. Whether such dose constraints will influence the rate of femoral fractures will be the subject of future investigation.

CONCLUSIONS

The use of IMRT was associated with a low crude rate (6.5%) of femoral fracture, despite the high dose of radiation delivered to the target volume. More importantly, the observed cumulative risk of femoral fracture in this cohort of patients treated with IMRT was less than the expected risk calculated using the PMH nomogram.

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