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Pathologic fracture a poor prognostic factor in osteosarcoma: Misleading conclusions from meta-analyses?

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Abstract

Aim: Recently published meta-analyses have concluded that pathologic fracture is a negative prognostic factor in osteosarcoma. But several confounding variables were not accounted for in the index studies, thereby compromising internal validity.
Methods: A multivariable survival analysis of a retrospective cohort of 131 patients with conventional, high-grade osteosarcoma of the extremity long bones treated with neoadjuvant chemotherapy and surgical resection was performed.
Results: There were no significant differences in clinicopathologic variables between the 21 patients who suffered pathologic fracture and the 110 patients who did not in standard bivariable statistical tests. Hazard ratios for decreased overall and disease-free survival of patients with pathologic fracture failed to reach statistical significance in univariable Cox proportional hazard regression. Furthermore, pathologic fracture did not significantly affect patient outcome (hazard ratio for overall survival, 1.15 [95% CI 0.56–2.38], $P = 0.71$ or disease-free survival, 1.01 [95% CI 0.53–1.91], $P = 0.98$) after controlling for confounding factors not accounted for in prior meta-analyses, such as tumor size, chemotherapy response, and proximal tumor location.
Conclusions: Pathologic fracture is not a significant prognostic factor for extremity osteosarcoma after controlling for other established prognostic factors. Although a useful statistical method, meta-analysis can generate false conclusions if important confounding factors are ignored. Analysis of individual patient data, which would require collaboration among different groups, would circumvent this limitation of meta-analysis.

Keywords: Fractures; Spontaneous; Prognosis; Meta-analysis; Proximal; Osteosarcoma

Introduction

Although many studies have shown that pathologic fracture does not seem to affect the prognosis for osteosarcoma patients,[1–9] three recently published meta-analyses have once again raised the question of whether this event affects patient outcome.[10–12] Careful review of these meta-analyses discloses that critical prognostic variables (such as tumor site and size) were not accounted for, casting serious doubts on the validity of the reported findings.

Review of the inclusion/exclusion criteria also revealed that only one of these three meta-analyses explicitly excluded studies reporting on patients with non-extremity osteosarcoma or who received inadequate systemic chemotherapy. Since pathologic fracture is more apt to occur in patients with tumors located within the proximal extremities,[3,4,6,13] anatomic location within a long bone is another putative poor prognostic factor not accounted for in these meta-analyses.[3,4,6,13]

Therefore, this study was conducted to review the prognostic impact of pathologic fracture in a retrospective cohort of osteosarcoma patients, particularly in regard to other important prognostic factors, including location within long bones.

Abbreviations: AJCC, American Joint Committee on Cancer; MSTS, Musculoskeletal Tumor Society.

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Patients and methods

Patients

The Surgical Pathology files at Vanderbilt University Medical Center were searched for patients who had undergone surgical resection of conventional, high-grade osteosarcoma of the long bones of the extremities after receiving neoadjuvant chemotherapy. 131 patients who met these inclusion criteria were identified.

Pathology reports were reviewed to record the anatomic location and location within a long bone (proximal or distal metaphysis or diaphysis), size of the tumor, histologic diagnosis and grade, extent of tumor necrosis, American Joint Committee on Cancer (AJCC)[14] and Musculoskeletal Tumor Society (MSTS)[15] stage, status of surgical resection margins, and presence or absence of pathologic fracture (confirmed by reviewing pertinent radiographic studies). H&E-stained slides were reviewed to confirm the histologic grade, MSTS Stage, extent of chemotherapy effect, and resection margin status. Clinical data (patient age at diagnosis, sex, chemotherapy dates and regimens, dates of surgery, local recurrence, distant metastasis, and death, as well as cause of death) were abstracted from electronic medical records. Individuals who were censored had a median follow-up of 110 months (range, 11–339). There were 55 deaths not due to other known causes, with a median time to death of 24 months (range 4–127 months).

The study protocol was approved by the Vanderbilt University Institutional Review Board; a waiver of informed consent was obtained.[17,18]

Statistical analysis

Categorical variables were compared among study groups using Fisher's exact test. Continuous variables were compared using Student's t-test with unequal variances. Multivariate survival analysis was performed using Cox proportional hazard regression. Potential confounding variables included in the regression model included MSTS Stage, tumor size, chemotherapy response, tumor location within long bone (distal, proximal, or diaphyseal), and surgical resection margin status. For regression analysis, the presence of pathologic fracture (present/absent), good chemotherapy response (<90% or ≥90% tumor necrosis), and surgical resection margin status (negative/positive) were represented as binary variables. MSTS Stage, extremity long bone involved (femur, humerus, tibia, or fibula), and tumor location within a long bone (distal metaphysis, proximal metaphysis, or diaphyseal) were coded as categorical variables. Tumor size was entered as a continuous variable. All tests were two-sided with $\alpha = 0.05$. All statistical analyses were performed using Stata v13.1 (StataCorp, College Station, TX).

Results

Retrospective osteosarcoma cohort

Only patients with conventional, high-grade osteosarcoma of the long bones of the extremities were included. All patients received neoadjuvant chemotherapy and underwent surgical resection ($N = 131$). Clinicopathologic characteristics of patients with and without pathologic fracture are presented in Table 1. Of note, osteosarcomas associated with pathologic fracture were generally larger than those without (Fig. 1A), which is also reflected in a greater proportion of cases that were AJCC and MSTS Stage IIB (Fig. 1B) compared to osteosarcomas without fracture. However, none of these variables reached statistical significance in standard bivariable analyses. Similarly, fractures were nearly twice as frequent in proximally located tumors than those arising in the diaphysis or distal long bones (Fig. 1C). Again, this finding failed to reach statistical significance. Perhaps most importantly, osteosarcomas with fracture were

Table 1
Clinicopathologic characteristics of osteosarcoma patients with and without pathologic fracture.

	Fracture ($N = 21$)	No fracture ($N = 110$)	P[a]
Age	21.7 ± 13.9	21.0 ± 13.2	0.82
Sex			0.63
Male	11 (14%)	65 (86%)	
Female	10 (18%)	45 (82%)	
AJCC Stage			0.12
Stage IIA	6 (12%)	45 (88%)	
Stage IIB	8 (15%)	44 (85%)	
Stage IVA	4 (29%)	10 (71%)	
Stage IVB	3 (43%)	4 (57%)	
MSTS Stage			0.11
Stage IIa	1 (6%)	17 (94%)	
Stage IIb	14 (14%)	69 (86%)	
Stage III	7 (33%)	14 (67%)	
Bone			0.11
Femur	11 (16%)	56 (84%)	
Tibia	3 (8%)	37 (92%)	
Humerus	6 (32%)	13 (68%)	
Fibula	1 (20%)	4 (80%)	
Location within long bone			0.37
Proximal	11 (21%)	42 (79%)	
Distal	9 (12%)	64 (88%)	
Diaphyseal	1 (20%)	4 (80%)	
Surgical resection margin			0.67
Negative	19 (16%)	100 (84%)	
Positive	2 (20%)	8 (80%)	
Size (cm)	11.0 ± 6.9	9.7 ± 4.5	0.41
Chemotherapy response	74% ± 33%	85% ± 25%	0.17
Chemotherapy response			0.12
<90% tumor necrosis	10 (24%)	31 (76%)	
≥90% tumor necrosis	11 (12%)	79 (88%)	

Abbreviations: AJCC, American Joint Committee on Cancer; MSTS, Musculoskeletal Tumor Society.

[a] Statistical tests of association between categorical variables were performed using Fisher's exact test. Continuous variables were compared using Student's t-test with unequal variances.