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Clinical Features and Outcomes in Patients with Ewing Sarcoma and Regional Lymph Node Involvement

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Abstract

Background—A minority of patients with Ewing sarcoma present with regional lymph node involvement. We investigated if patient characteristics and outcomes differ between patients with Ewing sarcoma with and without regional node involvement.

Procedure—Patients < 40 years of age with Ewing sarcoma or peripheral primitive neuroectodermal tumor (PNET) reported to the SEER database from 1973 to 2008 were evaluated based on the presence (n=91) or absence (n=1361) of regional node involvement. Patient characteristics were analyzed using Fisher exact tests. Overall survival was estimated by Kaplan-Meier methods and evaluated using log-rank tests and Cox models.

Results—Patients with regional node involvement were more likely to have extraskeletal primary tumors (65.9% vs. 31.2%; $p < 0.001$) and axial tumors (71.1% vs. 59.6%; $p = 0.03$) compared to patients without regional node involvement. The incidence of regional node involvement was 12.4% for patients with extraskeletal primary tumors compared to 3.2% for patients with skeletal tumors. Five-year overall survival from diagnosis was inferior for patients with regional node involvement compared to those without regional node involvement (45.9% vs. 60.3%; $p < 0.001$). On multivariate analysis, regional node involvement was predictive of inferior overall survival independent of age, metastatic status, tumor site, and soft tissue origin (hazard ratio 1.59; 95% CI 1.16–2.19).

Conclusions—Patients with extraskeletal Ewing sarcoma should undergo evaluation for regional node involvement. If validated, our findings indicate that regional node involvement may be an independent adverse prognostic factor in Ewing sarcoma, and potentially useful in risk-stratifying patients with otherwise localized disease.

Introduction

Ewing sarcoma is an aggressive malignancy of bone and soft tissues with a peak incidence in adolescence. Recognized prognostic factors in this disease include tumor stage, size, site, and age at diagnosis [1–9]. The metastatic pattern is typically hematogenous, with lung, bone, and bone marrow being the most common metastatic sites. Dissemination to regional lymph nodes is conventionally thought to be uncommon, though the incidence of regional node involvement has been poorly defined in previous studies [10]. Contemporary treatment protocols typically consider patients with regional lymph involvement to have localized disease, though the impact of regional node involvement on outcomes in this disease has

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also been poorly studied. Studies in another childhood sarcoma, rhabdomyosarcoma, have shown that regional lymph node status may be important for risk stratifying patients [11–13]. This issue has not been systematically evaluated in prior studies of Ewing sarcoma.

Given this lack of previous studies, it is uncertain if the clinical characteristics and outcomes differ for patients with and without regional lymph node involvement. We hypothesized that patients with Ewing sarcoma and regional lymph node involvement might have different baseline tumor characteristics at time of diagnosis and outcomes compared to patients without regional node involvement. Using data from the Surveillance, Epidemiology and End Results Program (SEER), we examined this hypothesis in a cohort of patients diagnosed with Ewing sarcoma and reported regional node status.

Methods

Patients and Variables

We gathered patient information from the US National Cancer Institute's SEER database, which included data from 1973–2008. The SEER system is used in regions that represent approximately 26% of the US population. The SEER program provides data on cancer incidence, patient demographics, primary tumor site, tumor morphology, stage at diagnosis, limited treatment data, and survival data.

Patients with histologically confirmed Ewing sarcoma, Askin tumor, or peripheral primitive neuroectodermal tumor (PNET) diagnosed between 0 and 39 years of age were eligible for the study. This age range was chosen to capture the majority of typical cases of Ewing sarcoma. From 1973–2008, the SEER database included 2,383 cases of Ewing sarcoma or PNET in patients < 40 years of age. We excluded patients with unknown regional lymph node involvement (n=931), as this was the primary predictor variable of interest. The remaining 1,452 patients formed the analytic cohort for this study.

The definition of lymph node involvement was determined using all available relevant SEER data fields. These included the regional node data field, Evidence of Disease (EOD) 2, 4, and 10 coding schemes, Collaborative Staging (CS) lymph node status, and American Joint Committee on Cancer Staging (AJCCS) coding systems. EOD and CS codes are specific to patients diagnosed within certain time intervals: EOD 2 1973 – 1982; EOD 4 1983 – 1987; EOD 10 1988 – 2003; CS 2004 - present. The regional node data field was available for patients diagnosed in 1988 and later. AJCCS data were available for those diagnosed 2004 and later. The regional node field is determined by pathology report. For all other fields, the presence or absence of lymph nodes is entered into the SEER database based on pathology, imaging, and physical exam findings. Data regarding which findings were used for each patient in these other fields are not available in SEER. For a given patient with data available in multiple fields, each field was compared to others available for every patient to evaluate internal consistency. Patients were excluded for conflicting data (n=3) or presence of distant nodes without specifically confirmed regional nodes (n=75). These 78 patients are accounted for in the number of excluded patients listed above as having unknown regional node involvement.

Patient characteristics and clinical presentation were evaluated according to the presence or absence of regional lymph node involvement. Predictor variables of interest included: sex; stage (metastatic vs. localized); age (analyzed as a continuous variable); year of diagnosis (in sequential 5-year blocks); race (white vs. non-white); histology (PNET vs. Ewing sarcoma); tissue origin (skeletal vs. extraskeletal); primary tumor site (axial vs. appendicular and also pelvic vs. non-pelvic); and tumor size (< 8 vs. ≥ 8 cm in maximal dimension). Anatomic site codes were classified according to the ICD-O coding scheme. Patients were

classified as extraskeletal or skeletal Ewing sarcoma based on ICD-10-CM coding used by the SEER database as previously reported [14].

Data on treatment received were also collected but not analyzed. Data regarding the use of surgery as local control and for management of regional nodes were inconsistent and not felt to be reliable for further analysis. The SEER database does not provide information regarding lymph node-directed radiation therapy, only whether it was used at any site or not. Other treatment details, including the use of chemotherapy, were not available. We concluded that the availability of only general treatment information was not relevant to our specific research question. Therefore, treatment differences based on the presence of absence of regional node involvement were not evaluated in the current study.

Statistical Methods

Patient and tumor categorical characteristics were evaluated for differences between patients with and without regional lymph node involvement using the Fisher exact test. A two-sample t-test was used to compare patient age between groups.

Overall survival from the time of diagnosis was estimated by Kaplan-Meier methods and potential differences between patients with and without regional node involvement were evaluated using the log-rank test. Overall survival was expressed as Kaplan-Meier estimates with 95% confidence interval (CI). The median follow-up time for the analyzed cohort was 148 months. Cox proportional hazard models were used to assess the effect of regional node involvement on overall survival while controlling for other known prognostic factors. The proportional hazards assumption was evaluated using time-dependent covariates, with proportional hazards assumption considered satisfied if $p \geq 0.05$ for the time-dependent covariate. The SEER database was accessed using SEER*Stat version 7.0.2. All statistical analyses were performed using SAS, version 9 and STATA, version 11.

Results

Patient Characteristics

Of the 1,452 patients in the analytic cohort, 91 (6.3%) had regional node involvement and 1361 (93.7%) did not have regional node involvement. The clinical characteristics of patients in these two groups are shown in Table I.

Significant differences in clinical presentation were noted between patients with and without regional node involvement. Patients with regional node involvement were more likely to have extraskeletal primary tumors (65.9% vs. 31.2%; $p < 0.001$) compared to patients without regional node involvement. The corresponding incidence of regional node involvement was 12.4% among patients with extraskeletal primary tumors compared to 3.2% among patients with skeletal tumors. Patients with regional node involvement were also more likely to have a histological classification of PNET rather than Ewing sarcoma (49.5% vs. 21.6%; $p < 0.001$), have an axial primary tumor (71.1% vs. 59.6%; $p = 0.03$), be diagnosed in more recent years (83.6% diagnosed ≥ 1994 vs. 75.8% diagnosed ≥ 1994 ; $p = 0.009$), and have metastatic disease at the time of diagnosis (36% vs. 22%; $p = 0.004$). The incidence of regional node involvement was 9.9% for patients with metastatic disease compared to 5.2% among patients with otherwise localized tumors. There were no statistically significant differences in age, sex, race, or tumor size between patients with and without regional node involvement.

Patient Outcomes

Overall survival was inferior for patients with regional node involvement compared to patients without regional node involvement (Figure 1). In patients with otherwise localized disease, the 5-year estimates of overall survival for patients with regional node involvement were 52.5% (95% CI 36.9–66%) compared to 67.9% (95% CI 64.5–71.1%) for patients without regional node involvement (Figure 1A; $p = 0.004$). The negative impact of regional node involvement on overall survival was also seen in the entire cohort that included patients with and without distant metastasis. Five-year estimates of overall survival for the entire cohort of patients with regional node involvement were 45.9% (95% CI 33.9–57.1%) compared to 60.3% (95% CI 57.2–63.2%) for patients without regional node involvement (Figure 1B; $p < 0.001$). In the cohort of patients with distant metastasis at initial diagnosis, the presence of regional node involvement did not impact overall survival.

In order to evaluate the independent impact of regional node involvement on overall survival, we constructed a Cox proportional hazards model that controlled for known prognostic factors. Age and tumor site were included as covariates in the model. Metastatic status and extraskeletal vs. skeletal tissue origin failed the proportional hazards assumption and were therefore stratified within the model. After controlling for these four variables, the hazard ratio for death for patients with regional node involvement was 1.59 (95% CI 1.16–2.19; $p = 0.004$) compared to the reference group without regional node involvement.

In order to evaluate the robustness of this model, a series of sensitivity analyses were performed. Tumor size data were available for only 59.2% of analyzed patients. A sensitivity analysis that also controlled for tumor size was performed and yielded similar results to the primary model without tumor size (hazard ratio for death in patients with regional nodes: 2.08 with 95% CI 1.41–3.06). A separate sensitivity analysis controlling for year of diagnosis was also performed and yielded similar results to the primary model (hazard ratio for death in patients with regional nodes: 1.55 with 95% CI 1.13–2.14). Given the changes in both diagnostic and treatment modalities over time, we also performed a separate sensitivity analysis of our original model using data only from patients diagnosed from 1994–2008 and again obtained similar results (hazard ratio for death in patients with regional nodes: 1.73 with 95% CI 1.20–2.50). We also performed a separate sensitivity analysis repeating our original model using only patients aged five through 30 years at the time of diagnosis. We obtained similar results to those seen in our original model (hazard ratio for death in patients with regional nodes: 1.48 with 95% CI 1.02–2.16).

Discussion

In this study, we found significant differences in patient and tumor characteristics between patients with and without regional lymph node involvement. We also found that patients with regional node involvement had inferior overall survival compared to patients without regional node involvement. We identified regional node involvement as a new independent adverse prognostic factor. The main impact of regional node involvement on outcome was among patients with otherwise localized disease. Regional node involvement was prognostically informative independent of other recognized prognostic factors in this disease, including age, metastatic status, and primary tumor site.

We demonstrated that patient and tumor characteristics differ based on the presence or absence of regional node involvement. We observed a significantly higher rate of regional node involvement in patients with extraskeletal primary tumors. This finding implies that when the diagnosis of extraskeletal Ewing sarcoma is made, a careful investigation for regional lymph nodes should be performed. In addition, patients with regional node involvement were more likely to be metastatic, have PNET histology, arise in axial

locations, and be diagnosed more recently. It is perhaps not surprising that patients with distant metastasis have higher rates of regional node involvement as this has been previously shown in patients with rhabdomyosarcoma [15]. This result suggests that a metastatic phenotype in Ewing sarcoma allows for both hematogenous and lymphatic dissemination. The findings of increased rates of axial tumors and PNET histology in patients with regional lymph node involvement are consistent with previous results showing that extraskelatal tumors are more likely to have these characteristics [14]. The increased number of cases reported in more recent years likely reflects newer imaging technology, including FDG-PET scans, that may allow for improved detection of regional lymph nodes [16,17].

The current study provides, for the first time, evidence that patients with regional node involvement have inferior outcomes. Importantly, these results were confirmed even after controlling for other known prognostic factors in this disease including age, primary tumor site, metastatic status, and tissue origin. There may be other biologic or treatment differences that account for the observed increased mortality seen in patients with regional node involvement. Unfortunately, additional biological and treatment data are not available from the SEER database and these possibilities can not be further elucidated by the current study. Nevertheless, if confirmed, these outcome differences suggest another variable to employ in risk-stratifying patients with Ewing sarcoma, particularly among patients without evidence of distant metastatic disease. These results also suggest that patients with regional node involvement may require augmented treatment strategies, perhaps directed at the draining nodal basin. However, given the fact that management of nodal disease was not available in the SEER database, we are unable to make specific therapeutic recommendations for patients with regional node involvement.

We have confirmed that regional node involvement in Ewing sarcoma is relatively rare. In order to study this subset of patients, we utilized the SEER database to evaluate the largest group of Ewing sarcoma patients to date with known lymph node involvement. However, there are several limitations to analyzing data from a tumor registry. We were limited to the available data in the registry. As such, we were unable to report on important variables, such as time to tumor recurrence, management of regional nodes with surgery or radiation, or chemotherapy regimen utilized. In the absence of complete treatment details, it is unclear if regional node status will remain prognostic in the setting of contemporary therapy. Most importantly, lymph node involvement could not be confirmed and many patients were excluded due to unknown lymph node status (39.1% of patients with Ewing sarcoma in the SEER database). The patients with regional node involvement likely included patients identified by biopsy, imaging, and/or physical examination.

Based on our findings, we conclude that there are significant differences in clinical presentation and outcomes for patients with Ewing sarcoma with and without regional lymph node involvement. If our findings are validated in future studies, regional lymph node involvement may prove useful in risk stratification, particularly among patients with otherwise localized disease. Moreover, patients with extraskelatal Ewing sarcoma require special attention for the possible presence of regional nodes. Additional efforts should be directed at verifying our findings and subsequently determining optimal treatment strategies to maximize outcomes in patients with Ewing sarcoma and regional node involvement.

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Figure 1.

A) Kaplan-Meier estimates of overall survival from time of diagnosis according to the presence or absence of regional lymph node involvement in patients with Ewing sarcoma and no distant metastasis. B) Kaplan-Meier estimates of overall survival from time of diagnosis according to the presence or absence of regional lymph node involvement in all patients with Ewing sarcoma.

Table I

Patient characteristics according to the presence or absence of regional node involvement in 1,452 patients with Ewing sarcoma and known regional node status.

Characteristic	Regional Node Involvement n = 91 (6.3%)	No Regional Node Involvement n = 1361 (93.7%)	p-value
Mean age	18.3 years	17.0 years	0.15
Range	0–39 years	0–39 years	
Male	59.3%	59.0%	1.0
Race			0.86
White	91.1%	90.0%	
Non-White	8.8%	10.0%	
Stage			0.004
Distant Metastasis	36.0%	22.0%	
No Distant Metastasis	64.0%	78.0%	
Histology			<0.001
PNET	49.5%	21.6%	
Ewing sarcoma	50.5%	78.4%	
Tissue Origin			<0.001
Skeletal	34.1%	68.8%	
Extraskelatal	65.9%	31.2%	
Primary Site			0.03
Axial	71.1%	59.6%	
Non-axial	28.9%	41.4%	
Pelvic	22.2%	22.8%	
Non-pelvic	77.8%	77.2%	
Size			0.25
8cm	48.5%	56.1%	
Year of Diagnosis			0.009
1973–1978	2.2%	7.8%	
1979–1983	6.6%	7.4%	
1984–1988	0%	3.4%	
1989–1993	7.7%	5.2%	
1994–1998	17.6%	8.1%	
1999–2003	24.2%	25.7%	
2004–2008	41.8%	42.0%	