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Extraskeletal versus Skeletal Ewing Sarcoma in the adult population: Controversies in care

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ABSTRACT

Background and Objectives: A lack of consensus exists on the prognosis of extraskeletal Ewing sarcoma (EES) relative to its skeletal (ES) counterpart in adults. This study sought to characterize outcome differences between the two diagnoses.

Methods: From 2004 to 2014, the NCDB identified 2,660 Ewing Sarcoma patients. Cox proportional hazards regression analysis was used to identify risk factors for overall survival (OS).

Results: EES patients were older, more likely to be female, and have smaller tumors. Among patients with ES, 4.0% received no treatment, 2.5% received local therapy only (surgery and/or radiation), 16.8% received chemotherapy only, while 52.2% received combination therapy (local and chemotherapy), and 17.0% recieived triple therapy (surgery, radiation and chemotherapy). Among patients with EES, 4.3% recived no treatment, 5.6% received local therapy only, 15.6% received chemotherapy only, while 47.0% received combination therapy, and 21.6% received triple therapy. No difference in OS was observed between the two groups ($P = 0.816$). Factors independently associated with OS for ES included age ($HR = 1.26$, $P = 0.01$), Charlson-Deyo Score (CDS) ≥ 2 ($HR = 3.66$, $P < 0.001$), combination therapy ($HR = 0.39$, $P < 0.001$) and triple therapy ($HR = 0.34$, $P < 0.001$). For EES, factors for OS were age ($HR = 1.52$, $P < 0.001$), CDS ≥ 2 ($HR = 1.90$, $P = 0.02$), combination therapy ($HR = 0.44$, $P < 0.001$), triple therapy ($HR = 0.34$, $P < 0.001$) and PNET histology ($HR = 1.33$, $P = 0.02$).

Conclusions: Demographic, histological, and treatment characteristics differ between adult patients diagnosed with ES and ESS. However, survival and independent predictors of survival are consistent between the two diagnoses.

1. Introduction

Ewing Sarcomas are malignant tumors of the bone and soft tissue [1,2]. The majority of cases originate from a skeletal primary site in children; however, 20–30% of cases have been shown to originate from extraskeletal sites [3]. The median age at diagnosis for extraskeletal cases is older than that of skeletal cases, thus making Extraskeletal Ewing Sarcoma (EES) of particular importance in the adult population. Recently, consensus for treating EES has shifted from Rhabdomyosarcoma protocols (RMS) to Skeletal Ewing Sarcoma protocols (ES) involving a combination of surgery, radiation, and chemotherapy. ES protocols have demonstrated documented improvements in patient outcomes [4–6].

Despite the consensus that EES patients benefit from ES treatment protocols, there is a lack of agreement on whether the two diseases carry a similar prognosis. Studies have been conducted comparing demographics, tumor characteristics, and patient outcomes between the two diseases, but they have yielded conflicting results [4,7,8]. Additionally, the majority of these studies were performed within pediatric populations, so reported differences between ES and EES cohorts may be less certain. As such, it remains unknown whether survival in the two diseases is correlated with the same treatment and prognostic factors [3,9]. Though ES protocols have been proven to be superior to RMS protocols in EES, there is no clinical evidence to suggest that ES protocols are the optimal approach in the treatment of EES.

Using the National Cancer Database (NCDB), the current study

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sought to compare outcomes and prognostic factors between adult ES and EES cases in order to inform decision-making in the management of Ewing tumors. We hypothesized that outcomes and prognostic factors would differ significantly between ES and EES tumors due to physiological differences in their primary sites. These differences may provide clinical evidence to be used in refining EES treatment protocols to optimize patient outcomes.

2. Materials and methods

2.1. Data sources and patient population

This retrospective cohort study was performed using data from the American College of Surgeons (ACS) NCDB. The NCDB includes data from over 1500 Commission on Cancer-accredited (CoC) cancer centers in the United States. It is sponsored by the ACS and the American Cancer Society. Patients whose tumor histology was consistent with Ewing Sarcoma diagnosed from 2004 to 2014 were identified using International Classification of Disease-Oncology Version 3 (ICD-*O*-3) histology codes "9260" (Ewing Tumor) and "9364" (Peripheral Neuroectodermal Tumor). All patients with ICD-*O*-3 site codes "40.0–41.9" (Bones, Joints, and Articular Cartilage), "47.0–47.9" (Peripheral Nerves and Autonomic Nervous System), and "49.0–49.9" (Connective, Subcutaneous, and Other Soft Tissues) were included in our analysis. All other site codes were excluded due to limited incidence. Statistical comparisons based on ICD site code were made between skeletal (40.0–41.9) and extraskeletal (47.0–47.9, 49.0–49.9) cohorts.

Variables analyzed included patient demographics, tumor characteristics and treatment method. Age was divided into two categories, those between 18 and 30 years and those older than 30, in order to create two similarly sized cohorts for comparison. The Charlson/Deyo Comorbidity Score encapsulated the number and severity of a patient's comorbidities. Tumor size was defined as its largest diameter. Tumor differentiation, stage, and surgical margin status were determined using the final pathology report. Metastatic status at diagnosis was assessed using the Collaborative Status Data Collection System (CS). Surgical approach was categorized using site-specific codes assigned in ICD-*O*-3. Summary of therapy was classified into five groups: no therapy, local therapy only (only surgery or radiation), chemotherapy only, combination therapy (chemotherapy and local therapy), and triple therapy (surgery, radiation, and chemotherapy).

2.2. Statistical analysis

Continuous variables were summarized by medians and interquartile ranges (IQR) and groups were compared using the Mann—Whitney two-sample test. Categorical variables were described by frequencies and compared using Pearson's chi-squared test. Unknown and missing variables were included as their own group. Notably, tumor stage and grade were unknown in a significant number of patients and included as such in order to avoid bias. A sensitivity analysis was performed to address the impact of their inclusion.

Overall survival (OS) was calculated from the time of diagnosis to the date of last patient contact. Patient vital status at the date of last contact was used to determine whether the patient had died or was lost to follow-up. Patients lost to follow-up were censored from the analysis. Kaplan-Meier methods and log-rank tests were used to evaluate the equivalence of survival functions for the ES and EES cohorts. Cox proportional hazards models were used to evaluate independent predictors of survival. All P-values were derived using two-tailed tests. The alpha value for statistical significance was set to 0.05 and proportionality assumptions were verified graphically using logarithmic methods [10]. Statistical analysis was performed using Stata/MP 14.2 for Windows (StataCorp, College Station, TX). This study was approved by the Johns Hopkins Medicine Institutional Review Board.

3. Results

3.1. Baseline patient characteristics

A total of 2,661 patients were identified who met inclusion criteria; 1,682 (63.2%) had ES tumors while 978 (36.8%) had EES tumors. Demographic and histological characteristics for the two patient cohorts are summarized in Table 1. Patients with EES were older (median = 30 years vs. 25 years), more likely to be older than 30 years of age (49.5% vs. 33.8%; $P < 0.001$), and more likely to be female (45.2% vs. 33.1%; $P < 0.001$). There was no difference in race, median income quartile, or urban/rural status between the two patient groups. Patients with EES were more likely to present with concomitant comorbidity as defined by the Charlson-Deyo Score (10.3% vs. 5.6%; $P < 0.001$).

3.2. Tumor characteristics

Tumor characteristics between the two groups were significantly different (Table 1). EES tumors were more likely to be of Primitive Neuroectodermal Tumor (PNET) histology (25.5% vs. 2.4%; $P < 0.001$) and more likely to be well differentiated (1.1% vs. 0.2%; $P < 0.001$). There was no difference in average tumor size (ES median = 110 mm vs. EES median = 100 mm) or prevalence of tumors greater than 10 cm between the two cohorts. Additionally, there was no difference in metastatic status at the time of diagnosis. EES patients were more likely to have Stage I disease and less likely to be have Stage IV disease (20.7% vs. 12.2% and 24.4% and 27.9%, respectively; $P < 0.001$). There was no difference in patient vital status at the time of last contact between cohorts.

3.3. Treatment characteristics

Treatment approach between ES and EES cohorts were significantly different ($P < 0.001$) with ES patients receiving more combination therapy (52.2% vs. 47.0%; $P < 0.001$) and EES patients receiving more triple therapy (21.5% vs. 17.0%; $P < 0.001$). Additionally, a higher proportion of EES patients received local therapy only compared to the ES cohort (5.6% vs. 2.5%; $P < 0.001$). ES patients were less likely to receive surgery (48.1% vs. 36.2%; $P < 0.001$) while EES patients were less likely to receive radiation (53.6% vs. 60.6%; $P = 0.002$) or chemotherapy (15.9% vs. 20.0%; $P = 0.02$, Table 2). Of the patients who underwent surgery, the surgical margin status between the ES and EES cohort was not significantly different (64.3% negative margin vs. 65.6% negative margin; $P = 0.74$, Table 2). EES patients were more likely to be treated at either an Academic Program or a Comprehensive Cancer Center (17.8% vs. 11.8%, 10.0 vs. 6.4%; $P < 0.001$).

3.4. Clinical outcomes

Despite differences in patient, tumor and therapy characteristics between the ES and EES cohorts, no differences in clinical outcomes were observed. Differences in thirty-day mortality, ninety-day mortality, and 30-day readmission rate were not statistically significant between the cohorts (Table 2, all $p > 0.05$). Kaplan-Meier estimates of overall survival are illustrated in Fig. 1. Median survival for the skeletal cohort was 47.5 months (95%CI: 42.2–55.1)