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Characteristics and outcomes of patients with Ewing sarcoma over 40 years of age at diagnosis

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ABSTRACT

Background: The peak incidence of Ewing sarcoma (EWS) is in adolescence, with little known about patients who are ≥40 years at diagnosis. We describe the clinical characteristics and survival of this rare group. *Methods*: This retrospective cohort study utilized the Surveillance Epidemiology and End Results database. 2780 patients were identified; including 383 patients diagnosed ≥40 years. Patient characteristics between age groups were compared using chi-squared tests. Survival from diagnosis to death was estimated via Kaplan–Meier methods, compared with log-rank tests, and modeled using multivariable Cox methods. A competing risks analysis was performed to evaluate death due to cancer. *Results*: Patients ≥40 years of age were more likely to have extra-skeletal tumors (66.1% vs. 31.7%; $p < 0.001$), axial tumors (64.0% vs. 57.2%; $p = 0.01$), and metastatic disease at diagnosis (35.5% vs. 30.0%; $p = 0.04$) compared to younger patients. Five-year survival for those age ≥40 and age <40 were 40.6% and 54.3%, respectively ($p < 0.0001$). A Cox multivariable model controlling for differences between groups confirmed inferior survival for older patients (hazard ratio for death of 2.04; 95% CI 1.63–2.54; $p < 0.0001$); though treatment data were unavailable and not controlled for in the model. A competing risks analysis confirmed increased risk of cancer-related death in older patients. *Conclusion*: Patients ≥40 years at diagnosis with EWS are more likely to have extra-skeletal tumors, metastatic disease, and axial primary tumors suggesting a difference in tumor biology. Independent of differences in these characteristics, older patients also have a lower survival rate.

1. Introduction

Ewing sarcoma (EWS) is the second most frequent primary malignant bone cancer of young people, following osteosarcoma. It can arise in almost any age group, however more than half of patients are adolescent at the time of diagnosis, with a median age of 15 [1]. Little is known about the rare subset of patients who are ≥40 years at initial diagnosis.

Previous studies describing this rare subgroup of adults with EWS have reached different conclusions. For example, a recent article evaluated 47 patients whose diagnosis of EWS was made over the age of 40 and found the 3-year event-free and overall survival to be similar to patients diagnosed at <40 years treated on the same chemotherapy protocols [2]. Other studies evaluating outcomes in adult patients with localized EWS also found no significant difference in survival when compared to younger patients [3–6]. These results are in contrast to a large body of literature suggesting that older patients have inferior outcomes compared with younger patients [7–10].

We therefore sought to evaluate patient characteristics and outcomes in the rare subset of patients diagnosed with EWS at ≥40 years compared to younger patients. This age cut-point was chosen as it aligns with many of the published articles in EWS who define older adults as ≥40 years. In order to identify and study a larger number of patients, we utilized the US National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database.

2. Patients and methods

2.1. Patients and variables

This retrospective cohort study utilized patients from the SEER database from 1973 to 2008 [11]. Data from the SEER system provide coverage that represents ~26% of the US population. The population covered by SEER tends to be more urban and have a higher proportion of foreign-born people, but is otherwise comparable to the general US population. The SEER program provides data on cancer incidence, patient demographics, primary tumor site, tumor morphology, stage

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at diagnosis, and survival. We identified 3676 patients with a histologic diagnosis of EWS, Askin tumor, or peripheral primitive neuroectodermal tumor (PNET). We excluded 798 patients because their tumor arose within the central nervous system and 98 patients because they had secondary EWS. The remaining 2780 patients form the analytic cohort for the current study.

Patients were dichotomized based on their age at diagnosis into either age ≥ 40 years or age < 40 years. Patient and tumor variables evaluated included: sex; race/ethnicity (White, non-Hispanic/Latino; Black; Asian/Pacific Islander; or White, Hispanic/Latino); tumor site (head/neck, upper extremity, lower extremity, pelvis, chest/thorax, abdominal, spinal column, unknown); tissue origin (skeletal vs. extra-skeletal); histology (EWS/Askin vs. PNET); and stage (metastatic vs. localized). In addition to the above, tumor size was evaluated when available. Size was dichotomized into $\geq$8 cm or <8 cm in maximal dimension based on prior literature suggesting this was a prognostic cut point [12]. Year of diagnosis (divided into 5-year increments) was also evaluated to account for changes in treatment and supportive care over time. Anatomic site and histology codes are documented in SEER using the International Classification of Childhood Cancer and/or the International Classification of Disease for Oncology, third revision (ICD-O-3) codes. Complete information was available for all variables with the exception of stage and tumor size. Information on stage was available for 327 patients aged $\geq$40 (85.4%) and 2199 patients <40 (91.7%). Data regarding tumor size was available for 229 patients $\geq$40 (59.8%) and 1235 patients <40 (51.5%). A separate sensitivity analysis was also done restricting patients to those diagnosed between 2000 and 2008 to reflect current diagnostic methods and treatment protocols.

Survival (date of diagnosis to date of death or last follow-up) was determined from the vital status field (alive or dead) in SEER. Follow-up time was calculated from survival time fields in SEER. The last date of follow-up was October 28, 2011. Cause of death was determined using the SEER cause-specific death classification and other cause of death classification fields, which denote if a patient died from their malignancy or from another unspecified cause. These cause of death classifications are based on ICD-8, ICD-9, and ICD-10 codes entered into the SEER database.

2.2. Statistical methods

Patient and tumor categorical characteristics were compared between age groups using chi-squared tests. A multinomial logistic model was fit for the multilevel categorical variable race/ethnicity to identify differences between the groups. Overall survival was estimated via Kaplan–Meier methods and potential differences between patients based on age group were evaluated using the log rank test. Survival was expressed as Kaplan–Meier estimates with a 95% confidence interval (CI). The median follow-up time for the analyzed cohort was 90 months (range 0–429 months).

A Cox proportional hazards model was constructed to assess the effect of age group on overall survival while controlling for potential prognostic factors. Covariates included sex, race, tumor location, tumor size, and year of diagnosis. Models constructed using stage or tissue origin as covariates failed the proportional hazards assumption as assessed using time-dependent covariates. Therefore, the final models stratify by stage and tissue origin to control for differences in these variables between the two age groups.

A competing risks analysis using the Fine and Gray method controlling for the same variables was used to determine the subdistribution hazard ratio for death (with 95% CI) due to cancer, rather than other causes, between the age groups [13,14].

The SEER database was accessed using SEER*Stat version 7.0.5. All statistical analyses were performed using SAS, version 9.2 and STATA, version 12.

3. Results

3.1. Patient characteristics

2397 (86.2%) patients were <40 years at diagnosis and 383 (13.8%) patients were $\geq$40 years at diagnosis. The clinical and tumor characteristics of both groups are shown in Table 1. Primary tumor location differed significantly according to age group ($p < 0.001$). At least part of this finding was due to higher rates of axial primary tumors in older patients (64.0% vs. 57.2%; $p = 0.01$). Older patients also had higher rates of extra-skeletal primary tumors (66.1% vs. 31.7%; $p < 0.001$) and were more likely to have metastatic disease at diagnosis (35.5% vs. 30.0%; $p = 0.04$). Older patients also had smaller tumors: 43.2% had tumors $\geq$8 cm in maximal diameter compared to 52.2% of younger patients ($p = 0.01$). Global differences were noted in race/ethnicity between age groups ($p < 0.001$) and this finding was driven by the observation that older patients were more likely to be Black and less likely to be White, Hispanic/Latino. We also examined year of diagnosis in 5-year increments between age groups. A greater proportion of incident cases were found in more recent years in those $\geq$40 years as compared to those <40 years at diagnosis ($p < 0.0001$). There were no statistically significant differences in sex or proportion with pelvic primary tumors between the two groups.

A sensitivity analysis was performed only with patients diagnosed between 2000 and 2008. Differences persisted in tumor location ($p < 0.001$) between the two age groups. Patients $\geq$40 years diagnosed in this time period continued to have higher rates of extra-skeletal primary tumors (66.2% vs. 38.4%; $p < 0.001$) and smaller tumors (57.5% vs. 47.0%; $p = 0.02$). In addition, the ethnic/racial differences noted above persisted with older patients being more likely to be Black and less likely to be White, Hispanic/Latino ($p < 0.001$). The point estimate for the rates of metastases at diagnosis between the two groups in this time period was similar to the overall cohort, but no longer significant (34.7% vs. 29.4%; $p = 0.1$).

3.2. Patient outcomes

Overall survival was worse for patients diagnosed at $\geq$40 years old (Fig. 1). In patients diagnosed at age $\geq$40, the 5 and 10 year Kaplan–Meier estimates of overall survival were 40.6% (95% CI 35.1–46.0) and 33.9% (95% CI 28.0–39.8%) vs. 54.3% (95% CI 52.1–56.4%) and 48.7% (95% CI 46.3–51.0%) in patients who were diagnosed at <40 years ($p < 0.0001$). A sensitivity analysis in patients diagnosed between years 2000 and 2008 also found that patients diagnosed at $\geq$40 years had inferior survival. In older patients, the 5-year Kaplan–Meier estimate of overall survival was 43.4% (95% CI 36.3–50.0) vs. 59.6% (95% CI 56.3–62.8) in patients who were diagnosed in <40 years ($p < 0.0001$).

A multivariable model was used to assess the effect of age group on overall survival while controlling for potential prognostic factors (stage, tumor site, sex, race/ethnicity, tissue origin, tumor size, histology, and year of diagnosis). Since tumor size data were available in <60% of patients, two models were constructed, one with size as a covariate and one without size as a covariate. The model that included tumor size confirmed that patients $\geq$40 years had inferior survival with a hazard ratio for death of 2.04 (95% CI 1.63–2.54; $p < 0.0001$). The model that did not include tumor size yielded similar results with a hazard ratio for death of 1.92 (95% CI 1.63–2.27; $p < 0.0001$).

Older patients are more likely to die from causes other than cancer due to co-morbidities. To account for this, the cumulative incidence of death due to cancer was estimated. This univariate analysis indicated a higher cumulative incidence of cancer-related