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Authors:

1- Joe Lee, M.D. Department of Orthopaedic Surgery, University of California Irvine.

2- Bang H. Hoang, M.D. Department of Orthopaedic Surgery, Chao Family Comprehensive Cancer Center, University of California Irvine.

3- Argyrios Ziogas, Ph.D. Department of Epidemiology, School of Medicine, and the Genetic Epidemiology Research Institute, University of California Irvine.

4- Jason A. Zell, D.O., M.P.H. Division of Hematology/Oncology, Department of Medicine, Chao Family Comprehensive Cancer Center, Department of Epidemiology, School of Medicine, and the Genetic Epidemiology Research Institute, University of California Irvine.

Corresponding Author:

Jason A. Zell, DO, MPH, Department of Epidemiology, University of California, Irvine, 224 Irvine Hall, Irvine, CA 92697-7550; Phone: (949) 824-7401; Fax no: (949) 824-1343; email: jzell@uci.edu

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CONDENSED ABSTRACT

The California Cancer Registry is used to examine the epidemiology of Ewing sarcoma from 1989-2007, and to identify relevant prognostic factors for survival.

ABSTRACT

Background: Ewing sarcoma is a high-grade malignancy that most often occurs in children. Because its occurrence in adults has been historically low, few studies have been published on the epidemiology of Ewing sarcoma in this group of patients. Using data from a large, population-based cancer registry, we designed the present study to examine the outcome of children and adult patients with Ewing sarcoma and relevant prognostic factors.

Methods: A retrospective analysis of Ewing sarcoma patient cases in the California Cancer Registry database was performed to identify incident patient cases diagnosed between 1989-2007. Comparisons were made to examine differences in demographics, disease characteristics, treatment, and survival. Survival analyses were performed using Kaplan-Meier method with Log Rank tests and Cox proportional hazards models.

Results: 725 incident patient cases of Ewing sarcoma were identified, including 372 (51.3%) children and 353 (48.7%) adults. Hispanic race was associated with young age (P=0.001) and lower socioeconomic status (SES) (P=0.0001). Pelvic involvement was associated with large tumor size (>8cm) (P<0.0001), an increased incidence of metastasis (P<0.0002), and poorer survival (P<0.0001). After adjusting for clinically relevant factors, statistically significant lower overall survival was seen with adults (HR=1.71, 95% CI 1.35-2.17), Hispanics (HR=1.33, 95% CI 1.01-1.75), metastatic disease (HR=2.74, 95% CI 2.14-3.49), large tumor size (HR=1.65, 95% CI 1.17-2.34), no surgical treatment, and low SES.

Conclusion: We determined that adult age, Hispanic race, metastatic disease, large tumor size, and low SES are poor prognostic factors for overall survival among Ewing sarcoma patient cases.

Keywords: Ewing sarcoma, epidemiology, survival, cancer

INTRODUCTION

Ewing sarcoma refers histologically to a collection of small round cell tumors and clinically manifests with a variety of presentations.[1,2] Despite the substantial amount of work achieved in the last few decades to improve the treatment and survival for Ewing sarcoma

patients, little is known about the epidemiology of the disease.[3,4] This is especially true when studying adult patients, as Ewing sarcoma has historically been seen mostly in children and adolescents. Our current understanding about the epidemiology of Ewing sarcoma comes mainly from relatively small retrospective series.[1,3,5-7] The population based studies that have been done focused on pediatric patients, or report only on incidence and survival, without analyses on outcome or prognostic factors.[4,8-11]

In 1985, population-based cancer reporting became required in the state of California. This established the California Cancer Registry (CCR), which is now recognized as one of the leading cancer registries in the world.[12-15] The size and diversity of the California population make the CCR particularly valuable to study the epidemiology of rare diseases such as Ewing sarcoma. Using the CCR, we designed the present study to examine the outcome of children and adult patients with Ewing sarcoma and to determine the relevant prognostic factors for survival.

MATERIALS AND METHODS

Study Population

We performed a retrospective, case-only analysis of Ewing sarcoma patient cases in the CCR database. CCR is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, and is the largest contiguous-area population-based cancer registry in the world;[15] standardized data collection and quality control procedures have been in place since 1988.[12-16] Case reporting is estimated at 99% for the entire state of California,[15] with follow-up completion rate greater than 95% for most tumors.[15] Data were abstracted from medical and laboratory records by trained tumor registrars.[14] Tumor site and histology were coded according to World Health Organization criteria in International Classification of Diseases

(ICD) for Oncology.[16] Patient cases were identified and extracted from the CCR by using the ICD-O-3 histology code 9260 for Ewing sarcoma. We then excluded patient cases with the following unknown or missing variables: nonspecific or unknown SEER extent of disease classification and patients whose diagnosis dates and follow-up dates were inconsistent.

Data were obtained on 725 incident Ewing sarcoma patient cases during 1989-2007 in CCR. Patient cases were identified through high-quality reporting sources (hospital inpatient/outpatient centers, oncology treatment centers, laboratories, private practitioners, or nursing home/convalescent home/hospice facilities). Recorded data included demographic information, presence of metastasis, treatment during the first course of therapy, socioeconomic status (SES), and vital status. Adults were defined as patient cases age 18 and over at diagnosis. SES is denoted as a single index variable in CCR using statewide measures of education, income, and occupation from census data, as described previously by Yost et al.[17] The SES index used is based on principle component analysis of census block level CCR data linked to census data assessing the following areas: education level, median household income, proportion below 200% poverty level, median house value, median rent, percent employed, and percent with blue-collar employment.[17-21] Of note, "proportion below 200% poverty level" was used due to its greater sensitivity and is defined as all those in poverty plus those who have income above poverty but less than 2 times their poverty threshold.[22] Essentially, each aspect mentioned serves as a proxy for SES and is weighted together to derive at a score. Scores were divided into five categories, with the higher scores representing higher SES. Quintiles for the SES score were analyzed.

Cause of death was recorded according to ICD criteria in effect at the time of death. Death from all causes was used to define overall survival (OS). Ewing specific survival (ESS)

was defined as death from Ewing sarcoma, alone. Hospital registrars contacted patient cases annually, and CCR staff annually reviewed state death certificates to identify deceased registry patient cases. The last date of follow-up was either the date of death or the last date of contact. In 2006-2007, complete followup was available for 681 (94%) patients.

Statistical Analysis

The clinical characteristics, including age, gender, race/ethnicity, presence of metastasis, tumor size, anatomic tumor site, SES quintile and treatment were analyzed with Pearson's chi-squared test or Fisher's exact test for categorical and dichotomous variables, and the non-parametric Kruskall-Wallis test for comparison of continuous variables (age) for more than two groups. Life-tables and Kaplan Meier curves were generated for each category, and curves were compared with the Log-Rank test. Multivariate survival analysis was utilized to calculate overall survival and Ewing-specific survival using Cox proportional hazards ratios. All statistical analyses were conducted using SAS 9.1 statistical software (SAS Institute, Inc., Cary, NC). Statistical significance was assumed for a two-tailed P-value less than 0.05.

Ethical Considerations

This study involved analysis of existing data from CCR database with no subject intervention. No identifiers were linked to subjects. This study was approved by the University of California Irvine Institutional Review Board (IRB) under the category "exempt status" (IRB#2008-6181).

RESULTS

Demographic Data

725 patient cases of Ewing sarcoma were identified between 1989-2007. The demographic and clinicopathologic data are shown in Table 1. The median age was 17, with 372 (51.3%) children and 353 (48.7%) adults (age 18 and older). Male to female ratio of patient cases was 3 to 2. Distribution by race/ethnicity revealed 414 Whites (57.1%), 241 Hispanics (33.2%), 20 Blacks (2.76%), 44 (6.1%) Asians/Pacific Islanders, and 6 Other (0.8%). Due to the relatively small number of patient cases, Blacks, Asians/Pacific Islanders, and Other were combined into one group labeled Others for the purposes of statistical analyses. When comparing the breakdown by race/ethnicity between children and adults, a significantly greater proportion of children were Hispanic (39.3%), as compared to the adult group (26.9%), (P=0.001).

Statistically significant differences in socioeconomic status (SES) were observed across the major ethnic groups. While a large proportion of Whites and Others patient cases belonged to the highest SES category (29.5% and 18.6%, respectively), significantly fewer Hispanic patient cases belonged to this SES category (4.6%), (P<0.0001). A significantly larger proportion of Hispanic patient cases belonged to the lowest SES category, compared with other ethnic groups (42.3% Hispanic vs. 7% White and 24.3% Other, P<0.0001). SES was not found to be significantly associated with rate of radiation therapy (P=0.23), chemotherapy (P=0.52), surgical intervention (P=0.25), metastatic disease (P=0.55), large tumor size (P=0.11), adult age (P=0.36), or location (P=0.11).

Clinicopathologic Characteristics

Among all patients, 528 (72.8%) presented with local disease, compared with 197 (27.2%) patients with metastasis. Tumor size was known for 406 patient cases (56.0%), with 164 (22.6%) patient cases having tumor size <8cm, and 242 (33.4%) patient cases having tumor size equal to or greater than 8cm. Patient cases with metastatic disease had a higher proportion of large tumors (8cm and greater) than did patient cases without metastatic disease (76.8% vs. 54.3%, P<0.0001). Furthermore, a greater proportion of Whites had tumor size smaller than 8cm, as compared with Others and Hispanics (46.6% vs. 31.8% and 33.6%, respectively, P=0.02). Large tumors was not associated with rate of low SES, chemotherapy, radiation therapy, or surgical intervention. Location of disease at initial presentation was as follows: 34 (4.9%) head/neck, 121 (17.4%) chest/abdomen, 301 (43.3%) extremities, 61 (8.8%) spine, and 178 (25.6%) pelvis, which includes the sacrum according to CCR site coding. There were 544 (75%) patient cases with skeletal involvement and 181 (25%) with non-skeletal involvement. Patient cases with pelvic involvement had a statistically higher frequency of metastasis at diagnosis compared to patient cases with extremity or other location involvement (36.5% vs. 19.6% and 25.9%, respectively; P=0.0002). Pelvic involvement also had a higher rate of large tumor size than did patient cases of extremity or other location involvement (73.0% vs. 60.5% and 45.1%, respectively, P<0.0001).

Treatment profile for all patients included 339 (46.7%) who did not receive radiation, and 386 (53.2%) who did receive radiation. Similar rate of radiation therapy was seen across the major racial/ethnic groups (45.7% Others vs 56.5% White vs 49.8% Hispanic, P=0.1). There was no significant difference in rate of surgical intervention (P=0.12), metastatic disease (P=0.09), SES (P=0.23), or tumor size (P=0.5) between patient cases that received radiation and those that did not. However, radiation was given more commonly to patient cases with pelvic

and axial involvement, compared to extremity involvement (58.43% and 57.41% vs 48.5%, respectively, P=0.048). The majority of patient cases received chemotherapy, 664 (93%), with only 50 (7.0%) patient cases that did not. When comparing the two age groups, a significantly greater proportion of the adult group did not receive chemotherapy (12.7% adults vs. 1.6% children, P<0.0001). Across the race/ethnic groups, a greater proportion of Others did not receive chemotherapy (14.5% vs. 6.2% White and 6.3% Hispanic, P=0.04). For patient cases that received chemotherapy compared with those that did not receive chemotherapy, no significant difference was found in the rate of surgical intervention (56.65% vs 52.08%, respectively, P=0.54), SES (P=0.52), tumor size (P=0.32), or tumor location (P=0.30). However, there was a significantly lower rate of radiation therapy (24% vs 56%, P<0.0001) and metastatic disease (12% vs 28.2%, P=0.01) among patient cases that did not receive chemotherapy versus those that did receive chemotherapy, respectively.

In terms of surgical intervention, 318 (44.4%) did not receive any surgery. Among patients who did receive surgery, 105 (14.7%) underwent local excision or destruction, 159 (22.2%) had radical resection or limb salvage procedure, and 60 (8.4%) underwent amputation. 69 (9.6%) patients had surgery that was not otherwise specified, and in 5 (0.7%) patient cases, it is unknown if any surgical intervention was done.

Cause of Death Analysis

321 (44.3%) of the 725 Ewing sarcoma patient cases died. 72.3% of these deaths (n=232) were due to Ewing sarcoma related causes. Cause of death was unknown for 40 of the 321 patient cases (12.5%). There was no significant difference in cause of death between the differenct race/ethnicity groups (P=0.233).

Univariate Survival Analysis

For all patients, 5 year OS was 53.8% and 10 year OS was 48.3%. Five year ESS was 63.5% and 10 year was 59.9%. Compared with children, adults had significantly decreased overall survival (OS) as well as Ewing-specific survival (ESS) (P<0.0001, and P=0.0006, respectively). ESS curves by age are shown in Figure 1. A subset analysis was done on adult patients by eliminating patients age 0-19 years. Among the adult age groups 20-39, 40-49, 50-59, 60-69, and 70+, there was no significant difference in survival (p=0.466). Furthermore, there was no difference in survival between male and female patient cases. When the major ethnic groups were examined, Hispanics had the poorest OS (P=0.03). For ESS however, this survival difference was not significant (P=0.24). ESS curves by race are shown in Figure 2. Among the SES categories, the lowest SES had the poorest OS and ESS (P=0.002 and P=0.005, respectively). ESS among different SES groups is shown in Figure 3.

Patient cases that presented with metastatic disease had significantly poorer survival than those with local disease (P<0.0001). Comparisons were made with regard to location of disease, and patient cases with pelvic involvement were found to have the poorest OS and ESS (P<0.0001). This is illustrated in Figure 4. Patient cases with tumor size equal to or greater than 8cm had poorer OS and ESS than patient cases with tumor size smaller than 8cm (P<0.0001). There was no significant difference in OS and ESS between axial versus non-axial patient cases, or between skeletal versus non-skeletal patient cases (P=0.05 and P=0.49, respectively).

There was no difference in survival found between patient cases that received chemotherapy or radiation, and those that did not (OS P =0.18 and P=0.35, ESS P=0.54 and P=0.31, respectively). Patient cases that did not receive any surgery had the poorest OS and

ESS, compared to patient cases that did receive surgery (P<0.0001). Three treatment groups were formed consisting of patient cases that received surgery without radiation, surgery with radiation, and radiation without surgery. Survival among these groups were compared and the groups that received surgery without radiation and surgery with radiation were found to have significantly better survival than the group that received radiation without surgery (OS P=0.0002, ESS P=0.0004). There was no difference in survival between the the group that received surgery without radiation and the group that received surgery with radiation (OS P=0.5646, ESS P=0.8832).

Survival in different time periods was examined by categorizing patient cases into three groups based on their year of diagnosis: 1989-1994, 1995-2000, and 2001-2007. We restricted the analysis to events that occurred in the first 72 months in order to adjust for the shorter follow up times for patient cases diagnosed more recently. Five year survival improved during the most recent time period, with ESS being 61.5% for 1989-1994, 60.5% for 1995-2000, and 71.4% for 2001-2007. For patient cases diagnosed 2001 and after, ESS was significantly better than those diagnosed before 2001 (P=0.02). For the earlier time periods, a significantly higher rate of radiation therapy was given (1989-1994: 60%, 1995-2000: 56.1%, 2001-2007: 44.4%, P=0.002). Metastatic disease was also seen at a significantly higher rate during the earlier time periods (1989-1994: 32.7%, 1995-2000: 32%, 2001-2007: 17.5%, P<0.0001).

Multivariate Survival Analysis

The variables adult age, gender, race/ethnicity, location of disease, metastasis, SES, chemotherapy, radiation therapy, tumor size, surgery status, year for diagnosis (before and after 2001) were included in multivariate Cox regression model for OS and ESS. Again, we restricted

the analysis to events that occurred in the first 72 months in order to adjust for the shorter follow up times for patient cases diagnosed more recently. Statistical power was diminished for ESS analysis, as 68% of patient cases were censored. However, the pattern of censoring remained similar between all comparison groups. The results are summarized in Table 2. After adjusting for each of the above variables, adults had a significant increased risk of death compared to children (HR=1.71, 95% CI 1.35-2.17; $P<0.0001$, for OS; HR=1.64, 95% CI 1.24-2.16; $P=0.0005$, for ESS). Among the racial/ethnic groups, Hispanic patient cases had a significant increased risk of death for OS but not for ESS (HR=1.33, 95% CI 1.01-1.75; P=0.04, for OS; HR=1.2, 95% CI 0.86-1.67; P=0.29, for ESS). Patients with metastatic disease and large tumor size (8cm) had significantly decreased OS and ESS. When compared to patient cases that did not receive surgery, patient cases that received local or radical excision, and limb salvage procedures had a significantly decreased risk of death. Patient cases with local excision had HR=0.53 and 0.45 (95% CI 0.35-0.79 and 0.27-0.75) for OS and ESS, respectively; and patient cases with radical excision or limb salvage had HR=0.65 (95% CI 0.47-0.91) for OS and HR=0.54 (95% CI 0.35-0.82) for ESS. Interestingly, in multivariate analysis radiation therapy was significantly associated with better ESS (HR=0.75, 95% CI 0.57-0.99, P=0.04), but not OS (HR=0.82, 95% CI 0.65-1.03, P=0.09).

In the multivariate OS and ESS model, pelvic involvement was not independently associated with risk of death compared with other locations. This was also true for chemotherapy. In terms of SES, the lowest SES category showed a significantly increased risk of death compared to the other SES categories. Patient cases diagnosed 2001-2007 appeared to have improved ESS, with HR=0.72 (95% CI 0.51-1.00). But this was not significant with P=0.053.

DISCUSSION

Using data from the CCR during a 19-year period, we have described the epidemiology of Ewing sarcoma with a particular focus on outcomes after diagnosis. To our knowledge, our work represents the only population-based study examining survival and prognostic factors in pediatric and adult patients. The results reinforce old beliefs about Ewing sarcoma, while revealing many new findings. We have observed that adult age, Hispanic race, low SES, pelvic primary tumor, lack of surgical intervention, large tumor size (≥8cm), and metastatic disease are associated with poor OS. In multivariate analysis, only pelvic primary tumor lost statistical significance, while all other factors continued to be independent poor prognostic indicators for OS. For ESS, the survival difference for Hispanic race was not significant.

The effect of age on survival has long been a subject of debate, with different studies reporting conflicting results. In earlier small series, survival in adults was found to be dramatically worse than what was reported for children.[1,5] However, in more recent studies, age was not found to be a predictor of poor outcome as adults fared similarly to children when treated with chemotherapy.[1,7,23,24] Martin et. al described the clinical course of 59 adult patients with Ewing sarcoma and found metastasis at initial presentation to be the only predictor of long term survival.[1] In one of the largest series using a collaborative European study group done by Cotterill et. al, poor prognostic factors were concluded to be age, primary site, and metastasis at diagnosis.[25] Interestingly, they found that pelvic primaries had a high association with metastatic disease, and that age was directly related with pelvic primaries and tumor volume. However, the multivariate analysis model was performed on subgroups that excluded patients with metastatic disease. As such, the independent effects of age among all Ewing sarcoma patients were not

assessed in that study. Instead, many issues that were not studied, such as access to care, delay in presentation, and level of care, may explain why adults fared worse than children. Other possible reasons why adults have fared worse than children may be that less aggressive treatments are given. In our study group, we found that when compared to children, fewer adult patient case had treatment with chemotherapy. Furthermore, older patients may have many comorbidities that complicate treatments and outcomes. Unfortunately, the CCR does not record data on patient comorbidities, and our multivariate analysis cannot adjust for those factors. The CCR also does not clearly distinguish the level of care given to patients, i.e. whether or not patients received their treatments from cancer centers. In many instances, children are still able to obtain access to quality health care regardless of their SES, whereas this may not be the case for adults. We did however attempt to control for most of the clinicopathologic and treatment factors as well as SES in our multivariate model, and found that the adult and children groups had similar SES, location of disease, rate of metastasis, large tumor size, surgery, and radiation. Even with these similar characteristics, adults continued to have poorer survival characteristics. Figure 1 shows how adult patient cases still had poorer survival even after stratifying for disease stage at presentation (i.e., metastatic vs. non-metastatic stage). It is also important to note that there was no significant difference in survival among the different adult age groups, as the possibility of a small subset of older adults driving down the OS for all adults was considered. This raises the question of whether or not the disease affecting adults is truly the same as that affecting children. It may be possible that the biology of the disease differs between the age groups, that the disease is more aggressive in adults, or that adults do not respond as favorably to the current treatment regimens due to inherent biologic differences, or co-morbidities. Further

investigation into the histological characteristics of Ewing sarcoma in adult patient cases and how they differ from pediatric patient cases is needed and should be the aim of future studies.

In comparison to other studies, we also detected a significant association between pelvic involvement, large tumor size, and metastatic disease.[1-3,6,25] In our multivariate analysis, metastatic disease and large tumor size remained independent risk factors for death, while pelvic involvement did not. Thus, we have observed that pelvic primary involvement is not an independent risk factor, but rather is associated with poor survival due to its significantly high correlation with metastatic disease and large tumor size.

The diversity of the California population afforded us the opportunity to study Ewing sarcoma as it relates to race/ethnicity. In accordance with past findings, Ewing sarcoma occured most commonly in Whites and Hispanics, and less so in Asians and Blacks.[8-11] Whites represented about 42.7% of California's population in 1995-1997, but accounted for 57.1% of the Ewing sarcoma cases during the study period in the CCR; Hispanics represented 36.2% and were 33.2% of the cases; Asians and Blacks represented 19.1% and were only 8.9% of the cases.[26] Reviews of the SEER database by Gurney et al. and Esiashvili et al. found age adjusted incidence rate to be 3 and 2.9 per million, respectively, for patients of white race/ethnicity. Incident rate for Blacks were 6 times less than that of Whites.[8,9] Wilkinson et al. examined the CCR and found the age adjusted incident rate to be 1.6 per million for Hispanics, and 2.5 per million for Whites.[11] In our study group, we also found that Hispanic race was an independent risk factor for decreased OS, but not ESS. Significantly poorer survival in Hispanic patients was also found in a review of the SEER database examing pediatric Ewing sarcoma patients, although the authors of that study cited a small number of Hispanic patient cases.[10] It is possible that the difference in survival reflects differences in competing risks, where Hispanics may suffer

death from other causes disproportionately to other race/ethnic groups. However, cause of death was examined across the race/ethnicity groups and significant correlations were not seen (P=0.233). Also, according to census data from 1995-1997, overall life expectancy for Hispanics in California was actually higher than that for Whites, being 82.5 vs 77.3 years, respectively.[27] In our multivariate model examining ESS, 68% of the data were censored. This lowered our statistical power substantially and may explain why Hispanic race did not remain a significant prognostic factor for ESS, but was significant for OS. As mentioned, the CCR does not contain data on co-morbidities; nor does it include information on genetic, occupational, or environmental factors. These unaccounted differences may have led to the apparent discrepancy in survival between the race/ethnic groups. Another contribution to the poor survival seen in Hispanic patient cases was the significant association with large tumor size and low SES, which were found to be an independent risk factor for OS and ESS. The issues of race/ethnicity remain extremely complicated, reflecting countless other aspects that together affect the prognosis of each patient. Lastly, the possibility of inherent differences in the disease process, as with adult patient cases, is also raised and warrants further investigation.

Cancer registry data from the CCR is particularly useful for analysis of different treatment groups and outcomes. When treatment groups based on surgical intervention and radiation therapy were examined, the groups with surgical intervention had significantly better survival. Rate of surgical intervention was not found to be related to SES or large tumor size. In our multivariate model, surgical intervention consisting of excision and limb salvage procedures was found to be significantly associated with improved survival when compared with no surgery. These findings should be considered when developing treatment protocols and supports the role of surgical intervention. In particular, limb-sparing surgery should be recognized as a viable

option. Limb-sparing surgery has been shown to result in significantly improved daily function of patients when compared to amputation[28,29]

Radiation therapy was not found to be significantly associated with improved survival in our univariate analysis. After adjusting for all of the available clinicopathologic factors, including year of diagnosis 2001 and after, our multivariate model did find improved ESS but not OS. Although there was also no association with race, SES, rate of surgery, metastasis, large tumor size, or adult age, a significant selection bias likely exists for patients receiving radiation therapy. As we have found, a significant association existed between patients who received radiation therapy and pelvic primary location, which in turn is related to higher rates of metastasis, large tumor size, and poor survival. Historically, radiation therapy was commonly reserved for complex or inoperable tumors, and for palliative treatment.[30] By adjusting for time, the bias created by less developed radiation therapy protocols in the past was minimized.

Although chemotherapy was not found to be significantly associated with improved survival, only 7.5% of the patient cases did not receive chemotherapy. Also, of the group of patients that did not receive chemotherapy, 6 (12%) were lost to follow. It may be that there was not enough power to make a meaningful comparison, and that this variable may be confounded by selection bias as well. Patient cases that did not receive chemotherapy were found to have significantly lower rates metastatic disease and radiation therapy. These findings may indicate that patients who did not receive chemotherapy had less aggressive disease and better local control with surgery alone.

The SES descriptor used here has been associated with survival in patients with a variety of solid tumor types: breast, pancreas, colorectal, melanoma, and lung cancer.[17,18,20,21,31] It was not found to be related to adult age, tumor location, rate of large tumor size, metastasis,

chemotherapy, radiation therapy, or surgical intervention. Yet it was found to be an independent risk factor for poor survival in patients with Ewing sarcoma. SES may reflect many factors, such as access to care and even quality of care. Our data demonstrate that significant healthcare disparities exist, and further research efforts that may lead to policy changes in order to eliminate such disparities are needed.

As previously mentioned, the CCR does not contain data on patient comorbidities. In respect to our study limitations, it is important to identify other information that is not included in the CCR. Information on radiation dose and duration, chemotherapy regimen, and surgical margins is not included in the CCR. Patient medical history including medications, tobacco or alcohol use, employment, environmental exposures, and family history were also not recorded in the CCR. Other relevant details that may have helped to clarify our analysis that is not in the CCR include whether or not the patient was treated at a cancer center, and if the treating surgeon was specialty trained in oncology.[13-15]

CONCLUSION

We examined 725 Ewing sarcoma patient cases recorded in the CCR from 1989 to 2007, and observed that adult age, low SES, tumor size equal to or greater than 8cm, and metastatic disease were independent risk factors for poor OS and ESS. Hispanic race/ethnicity was associated with low SES and young age, and additionally was found to be an independent risk factor for poor OS, but not ESS. Patient cases with pelvic involvement were more likely to have metastatic disease and large tumor size. Surgery, including limb salvage procedures, was found to be significantly associated with improved OS and ESS. In multivariate analysis, radiation therapy was found to be significantly associated with improved ESS, but not OS. These findings

raise many questions regarding our basic understanding of Ewing sarcoma. Future research with particular attention to the histopathologic characterization of Ewing sarcoma is warranted.

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Table 1. Patient Characteristics and Univariate Analysis for Ewing Sarcoma Patient Cases 1989-2007

	Children	Adults	Chi-squared	Overall Survival P value	Ewing Specific Survival P value
Sex			0.21	0.93	0.21
Male	217 (58.3)	222 (62.9)			
Female	155 (41.7)	131 (37.1)			
Race/Ethnicity			0.001	0.03	0.24
White	197 (53.0)	217 (61.5)			
Hispanic	146 (39.3)	95 (26.9)		Worse Survival	Worse Survival
Other	29 (7.8)	41 (11.6)			
SES			0.36	0.002	0.005
Lowest	81 (21.8)	67 (19.0)		Worse Survival	Worse Survival
Second Lowest	75 (20.2)	73 (20.7)			
Middle	78 (21.0)	83 (23.5)			
High	70 (18.8)	52 (14.7)			
Highest	68 (18.3)	78 (22.1)			
Stage			0.18	<0.0001	<0.0001
Local disease	279 (75.0)	249 (70.5)			
Metastasis	93 (25.0)	104 (29.5)		Worse Survival	Worse Survival
Tumor Size			0.16	<0.0001	<0.0001
<8cm	87 (43.9)	77 (37.0)			
8cm and greater	111 (56.1)	131 (63.0)			
Anatomic Site			0.08	<0.0001	<0.0001
Extremities	166 (46.2)	135 (40.2)			
Pelvis	95 (26.5)	83 (24.7)		Worse Survival	Worse Survival
Other	98 (27.3)	118 (35.1)			
Radiation			0.89	0.35	0.31
No	173 (46.5)	166 (47.0)			
Yes	199 (53.5)	187 (53.0)			
Chemotherapy			<0.0001	0.18	0.54
No	6 (1.6)	44 (12.7)			
Yes	363 (98.4)	301 (87.3)			
Surgery			0.4	<0.0001	<0.0001
None	161 (43.5)	157 (45.4)		Worse Survival	Worse Survival
Local	47 (12.7)	58 (16.8)			
Rad. Exc./Limb salvage	92 (24.9)	67 (19.4)			
Amputation	33 (8.9)	27 (7.8)			
Surgery NOS	35 (9.5)	34 (9.8)			
Unknown	2 (0.5)	3 (0.9)			

Table 2. Multivariate Analysis (Cox Models) of Overall and Ewing-Specific Survival

	Overall Survival Analysis		Ewing's Specific Survival	
	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Age				
Children (<18yo)	1.00*	-	1.00*	-
Adult	1.71 (1.35-2.17)	<0.0001	1.64 (1.24-2.16)	0.0005
Sex				
Male	1.00*	-	1.00*	-
Female	1.00 (0.79-1.26)	0.99	0.91 (0.68-1.2)	0.5
Race/ethnicity				
White	1.00*	-	1.00*	-
Hispanic	1.33 (1.01-1.75)	0.04	1.2 (0.86-1.67)	0.29
Others	0.99 (0.65-1.49)	0.95	0.85 (0.5-1.43)	0.54
SES				
Lowest	1.00*	-	1.00*	-
Second lowest	0.54 (0.38-0.78)	0.001	0.55 (0.36-0.84)	0.005
Middle	0.57 (0.40-0.82)	0.002	0.41 (0.26-0.64)	<0.0001
High	0.75 (0.51-1.08)	0.12	0.65 (0.42-1.00)	0.05
Highest	0.67 (0.45-0.99)	0.04	0.61 (0.39-0.96)	0.03
Stage				
Local disease	1.00*	-	1.00*	-
Metastasis	2.74 (2.14-3.49)	<0.0001	2.85 (2.13-3.80)	<0.0001
Tumor size				
<8cm	1.00*	-	-	-
8cm and greater	1.65 (1.17-2.34)	0.005	1.61 (1.05-2.48)	0.03
Anatomic site				
Extremity	1.00*	-	1.00*	-
Pelvis	1.27 (0.95-1.68)	0.1	1.21 (0.87-1.69)	0.26
Other	0.85 (0.63-1.15)	0.3	0.85 (0.59-1.22)	0.37
Radiation				
No	1.00*	-	1.00*	-
Yes	0.82 (0.65-1.03)	0.09	0.75 (0.57-0.99)	0.04
Chemotherapy				
No	1.00*	-	1.00*	-
Yes	0.67 (0.42-1.07)	0.09	1.09 (0.55-2.15)	0.81
Surgery				
None	1.00*	-	1.00*	-
Local excision/destruction	0.53 (0.35-0.79)	0.002	0.45 (0.27-0.75)	0.002
Radical excision/limb salvage	0.65 (0.47-0.91)	0.012	0.54 (0.35-0.82)	0.004
Amputation	0.78 (0.51-1.21)	0.27	0.71 (0.42-1.20)	0.2
Surgery NOS	0.82 (0.57-1.19)	0.32	0.81 (0.53-1.25)	0.79
Year of diagnosis				
before 2001	1.00*	-	1.00*	-
2001 and after	0.95 (0.73-1.24)	0.7	0.7`2 (0.51-1.00)	0.053

Table/Figure legends

Table 1

Table 1. Differences in patient variables between children and adult groups were analyzed with Pearson's chi-squared test. OS and ESS were examined by each patient variable with associated P values.

Table 2

Table 2. * Reference group

Figure 1

Fig 1. Ewing specific survival of adults versus children, stratified by stage of disease.

Figure 2

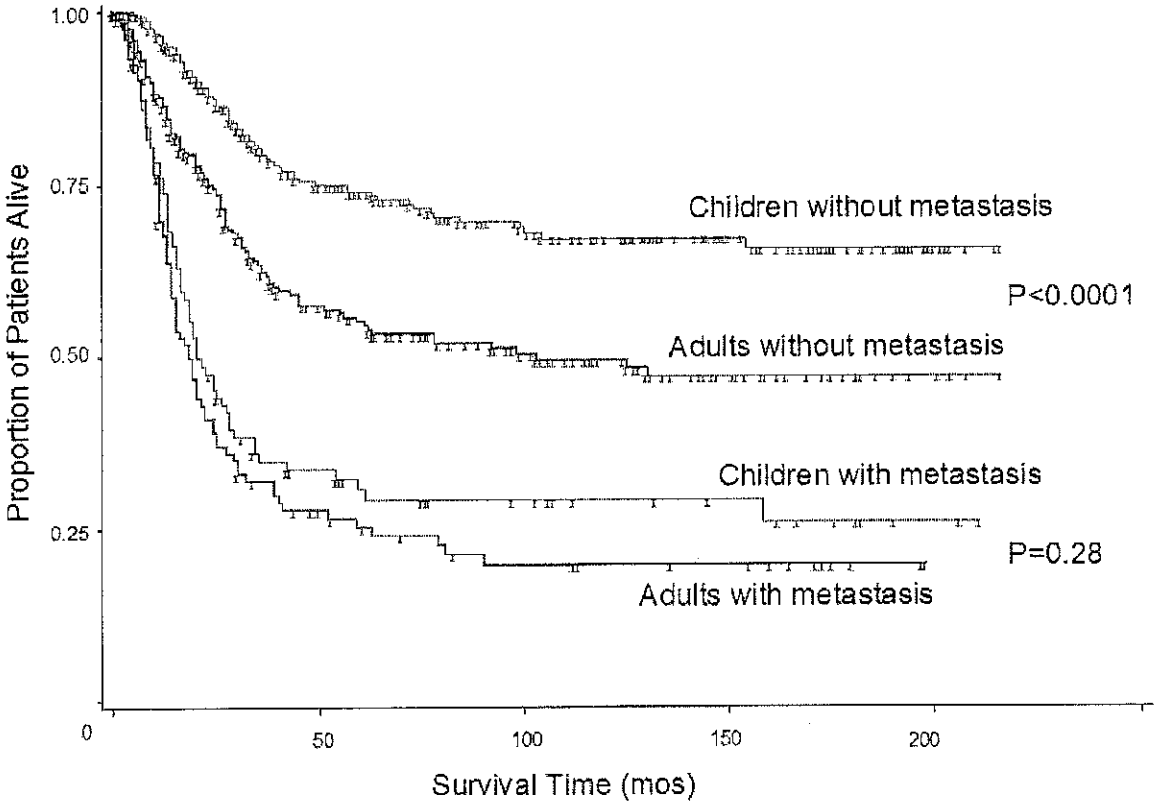
Fig 2. Ewing specific survival by race/ethnicity; P=0.24.

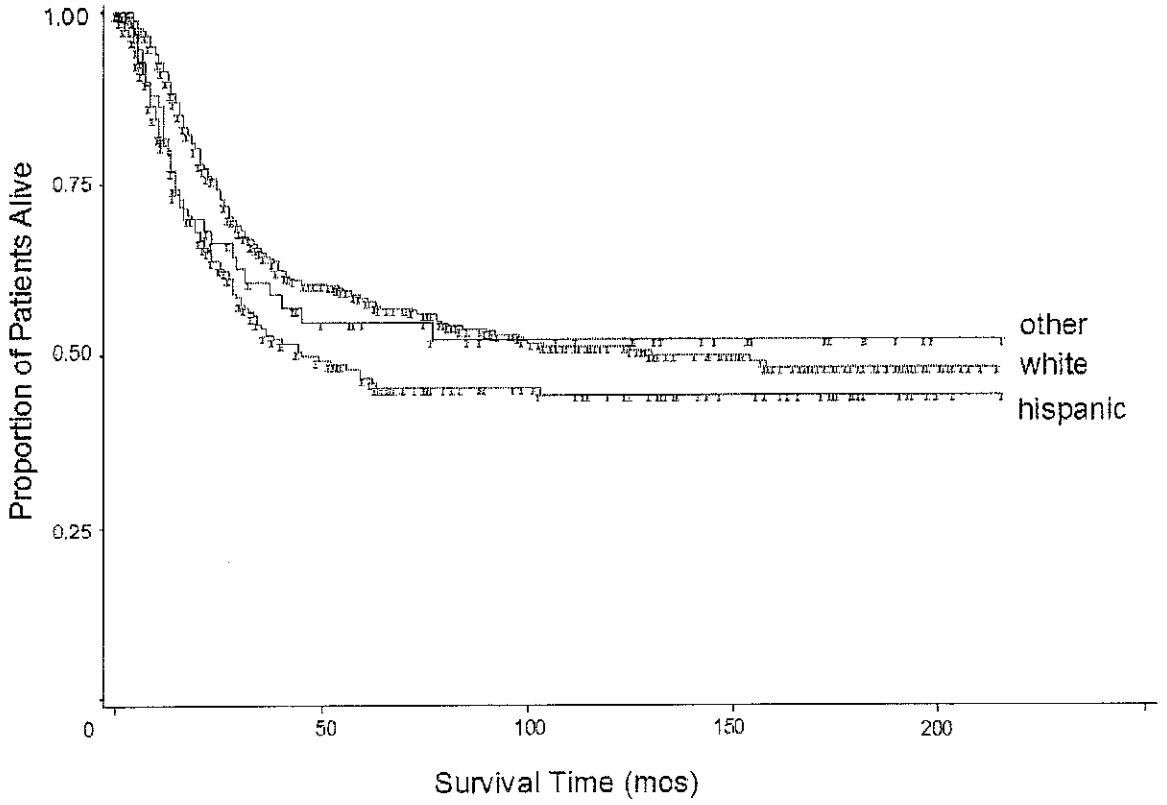
Figure 3

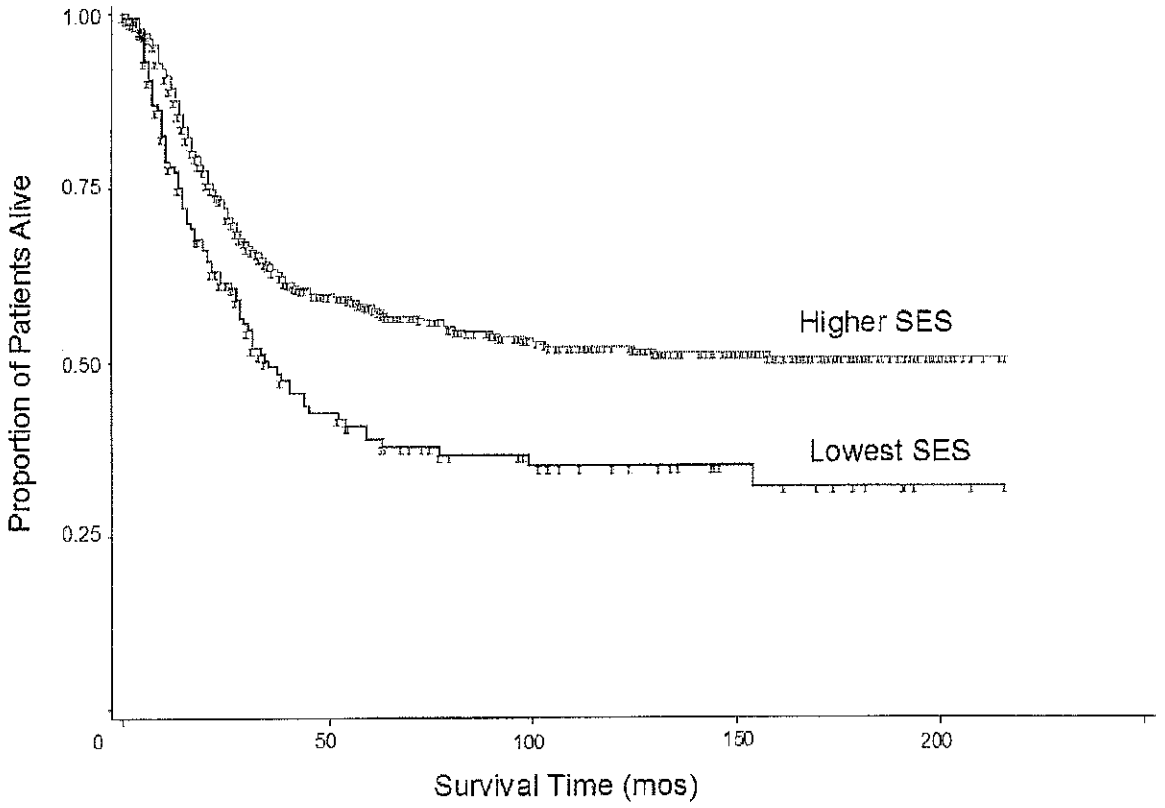
Fig 3. Ewing specific survival by socioeconomic status (SES). Lowest SES quintile compared with other quintiles; P=0.0003.

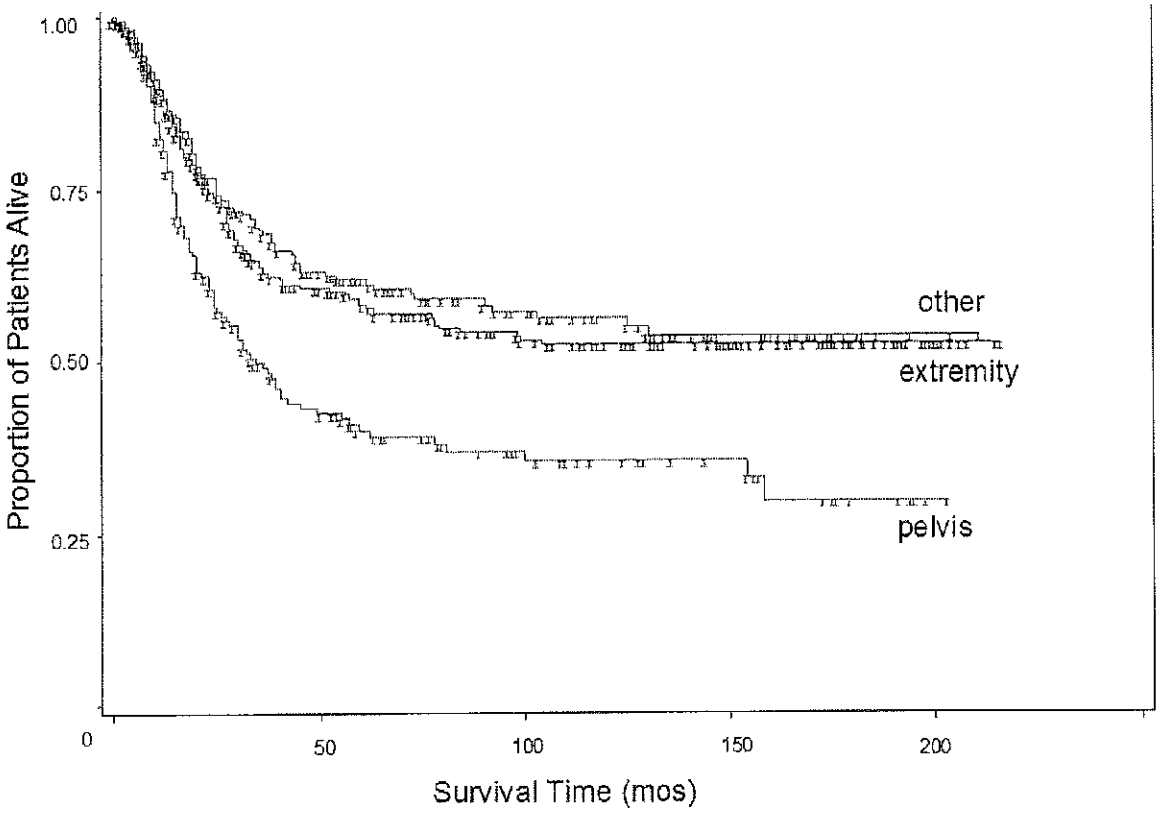
Figure 4

Fig 4. Ewing specific survival by anatomic site of disease; P=0.0001.


1.00
0.75
0.50
0.25
0
Proportion of Patients Alive
50
100
150
200
Survival Time (mos)
Children without metastasis
P<0.0001
Adults without metastasis
Children with metastasis
P=0.28
Adults with metastasis


1.00
0.75
0.50
0.25
0
50
100
150
200
Proportion of Patients Alive
Survival Time (mos)
other
white
hispanic


1.00
0.75
0.50
0.25
0
50
100
150
200
Proportion of Patients Alive
Survival Time (mos)
Higher SES
Lowest SES


1.00
0.75
0.50
0.25
0
Proportion of Patients Alive
50
100
150
200
Survival Time (mos)
other
extremity
pelvis