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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% v 31.7%; p<0.001), axial tumors (64.0% v 57.2%; p=0.01), and metastatic disease at diagnosis (35.5% v 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.

Keywords

Ewing sarcoma; pediatric cancers; adult; age; SEER

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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.

Patients and Methods

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 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 versus extra-skeletal); histology (EWS/Askin versus PNET); and stage (metastatic versus localized). In addition to the above, tumor size was evaluated when available. Size was dichotomized into ≥8 centimeters or < 8 centimeters 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 ≥ 40 (85.4%) and 2199 patients < 40 (91.7%). Data regarding tumor size was available for 229 patients ≥ 40 (59.8%) and 1235 patients < 40 (51.5%). A separate sensitivity analysis was also done

restricting patients to those diagnosed between 2000 — 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.

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.

Results

Patient Characteristics

2397 (86.2%) patients were < 40 years at diagnosis and 383 (13.8%) patients were ≥ 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% v 57.2%; $p=0.01$). Older patients also had higher rates of extra-skeletal primary tumors (66.1% v 31.7%; $p<0.001$) and were more likely to have metastatic disease at diagnosis (35.5% v 30.0%; $p=0.04$). Older patients also had smaller tumors: 43.2% had tumors ≥ 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 ≥ 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 — 2008. Differences persisted in tumor location ($p<0.001$) between the two age groups. Patients ≥ 40 years diagnosed in this time period continued to have higher rates of extra-skeletal primary tumors (66.2% v 38.4%; $p<0.001$) and smaller tumors (57.5% v 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 were similar to the overall cohort, but no longer significant (34.7% v 29.4%; $p = 0.1$).

Patient Outcomes

Overall survival was worse for patients diagnosed at ≥ 40 years old (Figure 1). In patients diagnosed at age ≥ 40, the five and ten 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%) versus 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 — 2008 also found that patients diagnosed at ≥ 40 years had inferior survival. In older patients, the five year Kaplan-Meier estimate of overall survival was 43.4% (95% CI 36.3 — 50.0) versus 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 ≥ 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 death in patients ≥ 40 years at diagnosis (Figure 2). A multivariable competing risk analysis controlling for the same variables described above was performed with and without tumor size. In the model that includes tumor size, patients ≥ 40 had a higher risk of death due to cancer with a subdistribution hazard ratio for death of 1.97 (95% CI 1.55 - 2.51; $p <0.001$). The same analysis without tumor size revealed a subdistribution hazard ratio for death of 1.81 (95% CI 1.49 — 2.20, $p<0.001$).

Discussion

This is the largest analysis of the rare subgroup of adults with EWS diagnosed at age ≥ 40. We found that even after adjusting for potential prognostic factors and competing risks, older patients had inferior survival. In addition, we observed that older patients were more likely to have extra-skeletal tumors, axial primary tumors, and tumors categorized as PNET rather than Ewing sarcoma. They were also more likely to have metastatic disease at the time of diagnosis. Racial differences were also noted with older patients more likely to be Black and less likely to be White, Hispanic/Latino.

Previous studies describing the clinical characteristics of adults ≥ 40 years at time of diagnosis have reached different conclusions. For example, a study by Bacci found no difference in tumor site or presence of metastases at diagnosis in this patient population.(4) Consistent with our results, other studies have found that patients ≥ 40 at diagnosis were more likely to have extra-skeletal tumors.(2, 4) Several studies looking at the clinical

characteristics we identified in this age group (metastatic at diagnosis, axial tumor location, and Black race) have found that these may confer inferior survival.(9, 10, 15-18) While the difference in survival between the two age groups persists in a multivariable analysis controlling for these variables, these findings may reflect underlying biologic differences that we are unable to control for in this analysis. For example, there may be differences in genetic translocations and/or chromosomal abnormalities between the two groups. It is also possible that differences in primary tumor location may lead to presentation at a later age. For example, older patients were more likely to have axial non-pelvic tumors, which may reflect sites that are more likely to present late. Tumors at these locations may present additional local control challenges that may have contributed to inferior outcomes observed in older adults.

SEER includes PNET and Ewing sarcoma as two histologic members of the Ewing sarcoma family of tumors. While the distinction between PNET and Ewing sarcoma is based on extent of neural differentiation, many clinicians refer to soft tissue tumors as PNET and bone tumors as Ewing sarcoma. Since older adults had a higher incidence of both soft tissue tumors and tumors classified as PNET, it is possible that our findings reflect this widely used nomenclature rather than a true increase in neural differentiation of tumors arising in older adults. An independent histologic review would be required to assess this finding further.

A greater proportion of cases were diagnosed in older patients in more recent years. This finding likely does not reflect a true increase in the incidence of the disease in older patients. Instead, we hypothesize that this finding may reflect the increased availability of molecular diagnostic techniques that allow previously unclassified tumors to be classified as EWS. Expanded use of molecular diagnostic techniques may aid in the diagnosis of challenging and atypical cases arising outside of the typical age range for EWS. Additional epidemiologic studies will be needed to determine whether the incidence of EWS is increasing, particularly in older patients.

Our finding that patients diagnosed at age ≥ 40 years had inferior survival is consistent with many studies that have looked at age as a prognostic factor in Ewing sarcoma.(7-10, 15) The Kaplan-Meier curves suggest that much of the difference in survival between the two age groups occurs in the first 24 months when patients are either undergoing active treatment or have recently completed treatment. This could represent differences in treatment strategies between the groups or could suggest biologic differences with older patients having more aggressive tumors that are less responsive to treatment. Unfortunately, little treatment information exists in SEER, so it is difficult to evaluate this difference, including potential differences in time to therapy initiation, cumulative doses and dose intensity of chemotherapy received, and clinical trial participation. One might hypothesize that pediatric EWS patients are more likely to be treated with intensive, multi-modality therapies on pediatric clinical trials. As EWS is much less common in patients ≥ 40 years, these patients may have received non-standard treatment protocols, which could have adversely affected their outcome. Supporting this hypothesis are several studies which found that older age is not prognostic when adult patients are treated on pediatric protocols.(2, 4, 5)

While the SEER database offers clinical characteristic and outcome data on a large group of patients, it is limited in treatment information as mentioned above. In addition, information on tumor size was available in <60% of our patient population making our finding that older patients were more likely to have small tumors difficult to interpret. We should also note that while we and other investigators have chosen to use a cut point of 40 years to identify this subset of patients, this is an arbitrary definition that we adopted to meet our aim of describing this unique subset of older patients. While clear differences are noted between

these two groups, the exact age threshold at which those differences occur is still unknown, though under investigation by our group.

In conclusion, we find that there are significant differences in clinical presentation and outcomes for patients diagnosed at age ≥ 40 years. The differences in clinical presentation provide evidence that there are probable biologic differences in the tumor and/or in the hosts who develop these tumors at a later age. The differences in outcomes may reflect biologic differences and/or important differences in treatment approach between these two groups. This work supports the idea that there are biologically different subsets of EWS that could benefit from tailored treatment strategies. Future studies should investigate the biology underlying these observed differences, identify the optimal prognostic threshold for age and begin to adjust treatment strategies according to individualized risk.

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References

1. Pizzo, PA.; Poplack, DG. Principles and practice of pediatric oncology. 6th ed. Wolters Kluwer/ Lippincott Williams & Wilkins Health; Philadelphia: 2011.
2. Pieper S, Ranft A, Braun-Munzinger G, Jurgens H, Paulussen M, Dirksen U. Ewing's tumors over the age of 40: a retrospective analysis of 47 patients treated according to the International Clinical Trials EICESS 92 and EURO-E.W.I.N.G. 99. Onkologie. 2008; 31(12):657–63. Epub 2008/12/09. [PubMed: 19060503]
3. Martin RC 2nd, Brennan MF. Adult soft tissue Ewing sarcoma or primitive neuroectodermal tumors: predictors of survival? Arch Surg. 2003; 138(3):281–5. Epub 2003/03/04. [PubMed: 12611575]
4. Bacci G, Balladelli A, Forni C, Ferrari S, Longhi A, Bacchini P, et al. Adjuvant and neoadjuvant chemotherapy for Ewing sarcoma family tumors in patients aged between 40 and 60: report of 35 cases and comparison of results with 586 younger patients treated with the same protocols in the same years. Cancer. 2007; 109(4):780–6. Epub 2007/01/16. [PubMed: 17219445]
5. Bacci G, Ferrari S, Comandone A, Zanone A, Ruggieri P, Longhi A, et al. Neoadjuvant chemotherapy for Ewing's sarcoma of bone in patients older than thirty-nine years. Acta Oncol. 2000; 39(1):111–6. Epub 2001/02/07. [PubMed: 10752664]
6. Verrill MW, Judson IR, Wiltshaw E, Thomas JM, Harmer CL, Fisher C. The use of paediatric chemotherapy protocols at full dose is both a rational and feasible treatment strategy in adults with Ewing's family tumours. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 1997; 8(11):1099–105. Epub 1998/01/14. [PubMed: 9426329]
7. Gupta AA, Pappo A, Saunders N, Hopyan S, Ferguson P, Wunder J, et al. Clinical outcome of children and adults with localized Ewing sarcoma: impact of chemotherapy dose and timing of local therapy. Cancer. 2010; 116(13):3189–94. Epub 2010/06/22. [PubMed: 20564643]
8. Baldini EH, Demetri GD, Fletcher CD, Foran J, Marcus KC, Singer S. Adults with Ewing's sarcoma/primitive neuroectodermal tumor: adverse effect of older age and primary extraosseous disease on outcome. Annals of surgery. 1999; 230(1):79–86. Epub 1999/07/10. [PubMed: 10400040]
9. Cotterill SJ, Ahrens S, Paulussen M, Jurgens HF, Voute PA, Gadner H, et al. Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2000; 18(17):3108–14. Epub 2000/08/30. [PubMed: 10963639]
10. Lee J, Hoang BH, Ziogas A, Zell JA. Analysis of prognostic factors in Ewing sarcoma using a population-based cancer registry. Cancer. 2010; 116(8):1964–73. Epub 2010/02/13. [PubMed: 20151425]

11. Surveillance, E.; End Results (SEER) Program. Research Data (1973-2008). National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch; (www.seer.cancer.gov)based on the November 2010 submission
12. Hayes FA, Thompson EI, Meyer WH, Kun L, Parham D, Rao B, et al. Therapy for localized Ewing's sarcoma of bone. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1989; 7(2):208–13. Epub 1989/02/01. [PubMed: 2915236]
13. Fine JPGR. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999; 94:496–509.
14. Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD. A note on competing risks in survival data analysis. British journal of cancer. 2004; 91(7):1229–35. Epub 2004/08/12. [PubMed: 15305188]
15. Grier HE, Krailo MD, Tarbell NJ, Link MP, Fryer CJ, Pritchard DJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. The New England journal of medicine. 2003; 348(8):694–701. Epub 2003/02/21. [PubMed: 12594313]
16. Jawad MU, Cheung MC, Min ES, Schneiderbauer MM, Koniaris LG, Scully SP. Ewing sarcoma demonstrates racial disparities in incidence-related and sex-related differences in outcome: an analysis of 1631 cases from the SEER database, 1973-2005. Cancer. 2009; 115(15):3526–36. Epub 2009/06/24. [PubMed: 19548262]
17. Rodriguez-Galindo C, Liu T, Krasin MJ, Wu J, Billups CA, Daw NC, et al. Analysis of prognostic factors in ewing sarcoma family of tumors: review of St. Jude Children's Research Hospital studies. Cancer. 2007; 110(2):375–84. Epub 2007/06/15. [PubMed: 17569105]
18. Worch J, Matthay KK, Neuhaus J, Goldsby R, DuBois SG. Ethnic and racial differences in patients with Ewing sarcoma. Cancer. 2010; 116(4):983–8. Epub 2010/01/07. [PubMed: 20052725]

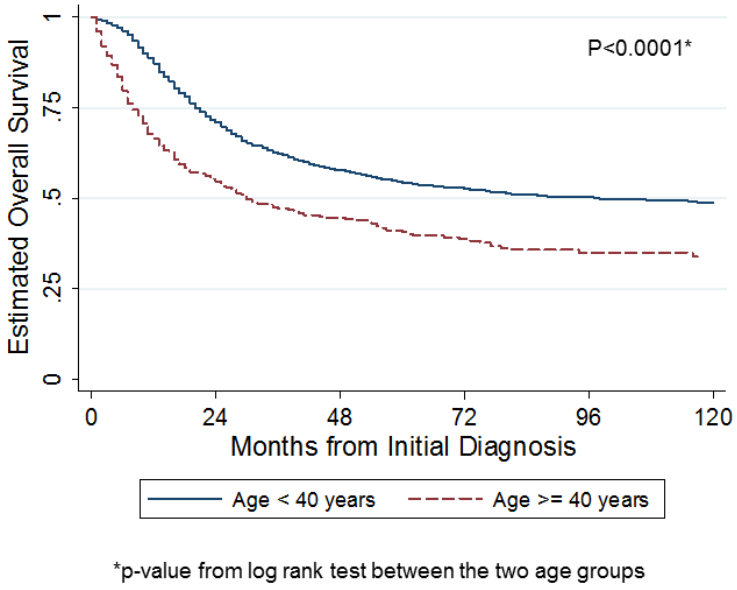

Figure 1a.
Kaplan-Meier estimates of overall survival from time of diagnosis according to age greater than or equal to 40 at diagnosis (n = 383) or age less than 40 at diagnosis (n = 2397).

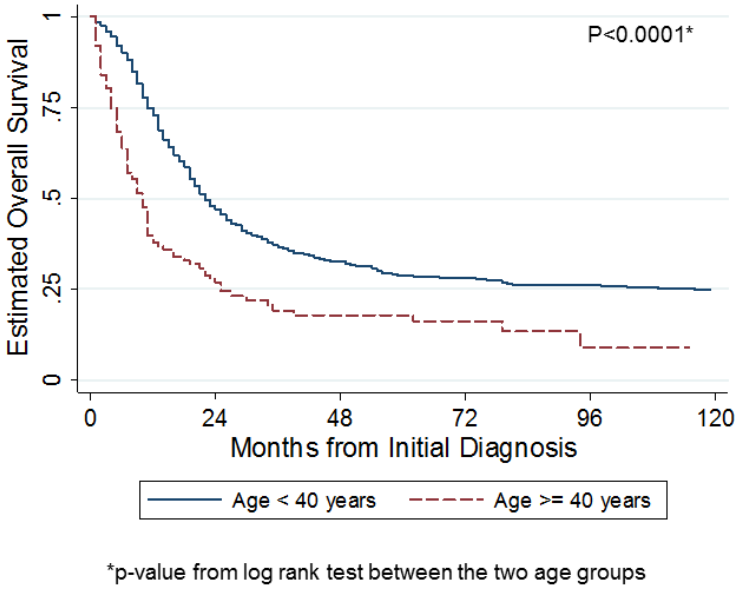

Figure 1b.

Kaplan-Meier estimates of overall survival from time of diagnosis according to age greater than or equal to 40 at diagnosis (n = 116) or age less than 40 at diagnosis (n = 659) in patients whose disease was metastatic at diagnosis.

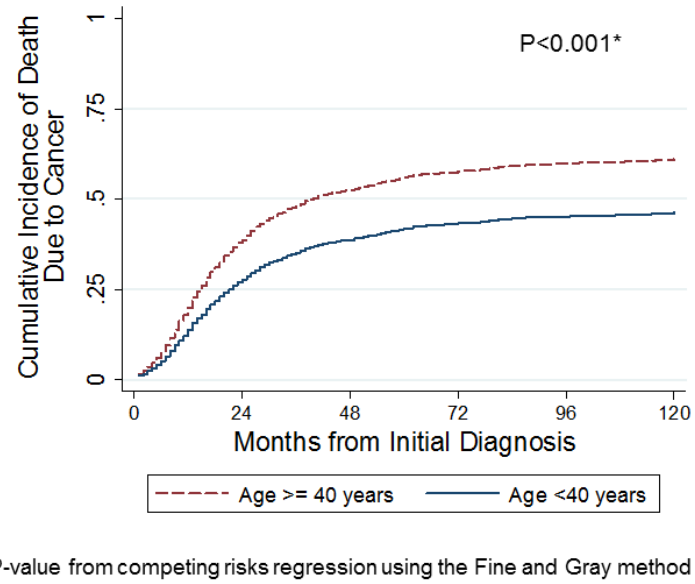

Figure 2.
Cumulative incidence of death from cancer according to age greater than or equal to 40 at diagnosis or age less than 40 at diagnosis in a competing risks model.

Table 1

Patient characteristics according to age greater than or equal to 40 or less than 40 at diagnosis in patients with Ewing sarcoma.

Characteristic	Age < 40 years	Age ≥ 40 years	p-value[a]
Total Number of Subjects, n (%)	2397 (86.2)	383 (13.8)	N/A
Sex, n (%)			
Male	1451 (60.5)	217 (56.7)	0.15
Age at Diagnosis in Years			
Mean	17.2	53.7	N/A
Range	0-39	40-92	
Race, n (%)			
White, Non-Hispanic	1698 (72.0)	287 (76.5)	<0.001
Black	76 (3.2)	24 (6.4)	
Asian/Pacific Islander	139 (5.9)	26 (6.9)	
White, Hispanic	446 (18.9)	38 (10.1)	
Primary Tumor Site, n (%)			
Head/Neck	150 (6.3)	33 (8.6)	<0.001
Upper extremity	269 (11.2)	21 (5.5)	
Lower extremity	624 (26.0)	61 (15.9)	
Pelvic	538 (22.4)	78 (20.4)	
Thoracic	393 (16.4)	67 (17.5)	
Abdominal	103 (4.3)	39 (10.2)	
Spinal Column	188 (7.8)	28 (7.3)	
Unknown	132 (5.5)	56 (14.6)	
Pelvic	538 (22.4)	78 (20.4)	
Non pelvic	1859 (77.6)	305 (79.6)	0.36
Axial	1372 (57.2)	245 (64.0)	
Non axial	1025 (42.8)	138 (36.0)	0.01
Tissue Origin, n (%)			
Skeletal	1638 (68.3)	130 (33.9)	
Extra-skeletal	759 (31.7)	253 (66.1)	<0.001
Stage, n (%)[b]			
Distant Metastasis	659 (30.0)	116 (35.5)	0.04
Size, n (%)[c]			
≥ 8 cm	645 (52.2)	99 (43.2)	0.01
Histology			
PNET	578 (24.1)	209 (54.6)	
Ewing Sarcoma	1819 (75.9)	174 (45.4)	<0.001

Characteristic	Age < 40 years	Age ≥ 40 years	p-value[a]
Diagnosis Year, n (%)			
<1980	182 (7.6)	4 (1.0)	<0.0001
1980 – 1984	169 (7.1)	5 (1.3)	
1985 – 1989	165 (6.9)	8 (2.1)	
1990 – 1994	290 (12.1)	28 (7.3)	
1995 – 1999	337 (14.1)	72 (18.8)	
2000 – 2004	698 (29.1)	147 (38.4)	
2005 – 2008	556 (23.2)	119 (31.1)	

[a]P-value between age groups by chi-squared.

[b]Based on stage data available for 85.4% of patients diagnosed at age 40 or above and 91.7% of patients diagnosed at age less than 40.

[c]Based on size data available for 59.8% of patients diagnosed at age 40 or above and 51.5% of patients diagnosed at age less than 40

Abbreviations: N/A, not applicable