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Outcome for Adolescent and Young Adult Patients With Osteosarcoma:

A Report From the Children's Oncology Group

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Abstract

BACKGROUND—There are conflicting data regarding age as a prognostic factor in osteosarcoma. The authors conducted a study evaluating the impact of age on prognosis in children and young adults with osteosarcoma enrolled on North American cooperative group trials.

METHODS—Patients with high-grade osteosarcoma of any site enrolled on North American cooperative group trials CCG-7943, POG-9754, INT-0133, and AOST0121 were included in this study. Primary tumor site, age, sex, ethnicity, histologic response, and presence of metastatic disease at diagnosis were evaluated for their impact on overall survival (OS) and event-free survival (EFS).

RESULTS—A total of 1054 patients were eligible and had complete data available for the study. Age was not significantly associated with any other presenting covariate analyzed except sex. Age 18 or older was associated with a statistically significant poorer EFS ($P = .019$) and OS ($P = .043$). The 10-year EFS and OS in patients <10, 10 to 17, and ≥18 years old were 55%, 55%, 37% and 68%, 60%, 41%, respectively. The poorer EFS in patients ≥18 years old was because of an increased rate of relapse. Presence of metastatic disease at diagnosis, poor histologic response, and

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pelvic tumor site were also associated with a poorer prognosis. In multivariate analysis, age continued to be associated with poorer EFS (P = .019) and OS (P = .049).

CONCLUSIONS—In osteosarcoma, age 18 to 30 years is associated with a statistically significant poorer outcome because of an increased rate of relapse. Poorer outcome in adolescent and young adult patients is not explained by tumor location, histologic response, or metastatic disease at presentation.

Keywords

osteosarcoma; adolescent; young adult; prognosis; outcome

INTRODUCTION

The failure to adequately improve outcomes for adolescent and young adult (AYA) patients with cancer is increasingly recognized as a significant problem in oncology.[1,2] Consequently, for each cancer with a worse outcome in AYA patients, it is a research priority to identify the biologic, clinical, and social factors responsible for this disparity in prognosis.[1] Before embarking on a detailed analysis of this sort for a particular cancer, one must first fully understand whether there is a significant relationship between AYA age and outcome.

Bone sarcomas are among the tumors most commonly diagnosed in the AYA population and have a peak incidence between 15 and 39 years, the age range commonly accepted to define the AYA population.[2] In Ewing sarcoma, increasing age has consistently been demonstrated to be associated with a poorer prognosis.[3,4] Rhabdomyosarcoma and nonrhabdomyosarcoma soft tissue sarcomas have likewise been demonstrated to have a worse outcome in older patients.[5,6] Whether AYA age constitutes a significant risk for a poorer outcome in osteosarcoma is not clear. Whereas some prior studies have demonstrated a poorer prognosis in older patients,[7,8] others have demonstrated a poorer prognosis in younger patients,[9] and some show no association between age and prognosis.[10,11] Using data from the most recent North American Cooperative Group trials conducted by the Children's Cancer Study Group (CCG), the Pediatric Oncology Group (POG), and the Children's Oncology Group, we assessed the relationship between AYA age and prognosis in osteosarcoma.

MATERIALS AND METHODS

Patients

Patients enrolled on any of the 4 recent prospective North American Cooperative Group trials for newly diagnosed osteosarcoma, CCG-7943, POG-9754, intergroup study INT-0133, and AOST0121, were eligible for this study. The eligibility criteria for INT-0133 and CCG-7943 have previously been described.[12,13] Patients were eligible for AOST0121 if they had high-grade metastatic osteosarcoma with either bone metastases, bilateral lung metastases, or unilateral lung metastases with at least 4 nodules. Patients were eligible for POG-9754 if they had resectable, nonmetastatic high-grade osteosarcoma. Because of the eligibility criteria of these 4 trials, patients with both metastatic and nonmetastatic osteosarcoma and patients with both resectable and unresectable osteosarcoma are included

in this study (Table 1). For all trials, patients were excluded if they had received prior chemotherapy or radiation or if the osteosarcoma arose in a previously irradiated bone or in bone affected by Paget disease. Age of enrollment for all trials was younger than 31 years.

CCG-7943, POG-9754, INT-0133, and AOST0121 were approved by the institutional review boards at each of the participating institutions. The patient or the patients' legal guardians consented to treatment, and the patients assented themselves if age appropriate.

Treatment

All patients, with the exception of those enrolled on CCG-7943, received chemotherapy including at least high-dose methotrexate, doxorubicin, and cisplatin (MAP). Additional agents were administered with the MAP backbone in each trial. Patients enrolled on INT-0133 received MAP with muramyl tripeptide and/or ifosfamide as previously described.[13,14] All patients enrolled on AOST0121 received ifosfamide and etoposide in addition to MAP, and patients with ERBB2-positive tumors also were treated with trastuzumab. POG-9754 was a pilot study with 3 arms, each with a unique method of dose intensification. All patients enrolled on pilot 1 received MAP, and those patients on pilot 1 who were slow responders to neoadjuvant chemotherapy received additional doxorubicin to a cumulative dose of 600 mg/m^2 (administered with dexrazoxane). All patients enrolled on pilots 2 and 3 received ifosfamide in addition to MAP. Patients enrolled on pilot 2 who were slow responders to neoadjuvant chemotherapy received additional doxorubicin to a cumulative dose of 600 mg/m^2 (administered with dexrazoxane). Patients enrolled on pilot 3 who were slow responders to neoadjuvant chemotherapy received higher-dose ifosfamide. Patients enrolled on CCG-7943 were treated with a topotecan window, followed by alternating cycles of ifosfamide, carboplatin, and etoposide and doxorubicin and cisplatin as previously described.[12] All protocols indicated patients with resectable disease were to undergo resection with the intent of removing all local and metastatic tumor.

Statistical Analysis

The parameters age, sex, race, tumor site, presence of metastatic disease at diagnosis, histologic necrosis, and tumor margins were analyzed for their impact on event-free survival (EFS) and overall survival (OS) or postsurgical EFS, as described below. Age was analyzed as a categorical variable using the categories <10, 10 to 17, and ≥18 years. The association of each of the other parameters with age was evaluated using the exact conditional test of proportions.[15]

EFS was taken to be the time from study enrollment until disease progression, diagnosis of a second malignant neoplasm (SMN), death, or last patient contact, whichever occurred first. Patients who experienced disease progression, SMN, or death were considered to have experienced an EFS event; otherwise the patient was considered as censored at last contact. The cumulative incidence of each EFS event was estimated as a function of time since enrollment by the method of competing risks.[16] The risk of each EFS event type across groups was compared using the test of Gray.[17] OS was taken to be the time from enrollment to death or last patient contact, whichever occurred first. Patients who died were considered to have experienced a death event; otherwise the patient was considered as censored at last

contact. Survival curves were estimated by the method of Kaplan and Meier.[18] The risk of death was compared across groups using the log-rank test.[18] The conventional level of .05 was used to designate a comparison as statistically significant. A multivariate analysis using the proportional hazards regression model was performed.[18] EFS and OS analyses of age used tests stratified by metastatic status and study (because of the varied eligibility criteria and treatments among the 4 studies).

To determine the relationship between histologic response, age, and risk for EFS event, a secondary analysis was performed. This analysis was restricted to patients with localized osteosarcoma who underwent surgery after enrollment and before an EFS event and who had histologic response grading data available. For CCG-7943, POG-9754, and AOST0121, histologic response was reported as a numerical value. For INT-0133, histologic response was graded and reported as no effect, >50% viable tumor, 5% to 50% viable tumor, <5% viable tumor, and no viable tumor. Therefore, for all patients in the study, histologic response was categorized as good if there was ≥95% necrosis and poor if there was <95% necrosis in the resection specimen. The outcome measure used was postsurgical EFS. Postsurgical EFS was defined similarly to EFS, with the exception that the date of surgery (rather than the date of enrollment) was the starting date for post-surgical EFS. To assess the effects of age and necrosis on outcome, a stratified log-rank test[18] was performed with age stratified by histologic response. Similarly, the analysis of margins used postsurgical EFS and was restricted to patients with localized osteosarcoma who underwent surgery within 20 weeks of enrollment and had data reported regarding margins.

INT-0133 was opened May 1993 and closed November 1997. Data current to September 2005 were used for analysis. CCG-7943 was opened August 1995 and closed November 1998. Data current to July 2003 were used for analysis. POG-9754 was opened September 1999 and closed February 2002. Data current to July 2008 were used for analysis. AOST0121 was opened July 2001 and closed November 2005. Data current to July 2008 were used for analysis.

RESULTS

Patients

A total of 1175 patients were enrolled on the 4 North American Cooperative Group Trials; 121 patients were excluded from this study because they had been declared ineligible for the trial into which they were enrolled (n = 32) or because they had inconsistent or missing data (n = 89). After these exclusions, 1054 patients comprised the analytic population; 745 patients were from INT-0133 (70.7%), 28 patients were from CCG-7943 (2.7%), 79 patients were from AOST0121 (7.5%), and 202 patients were from POG-9754 (19.2%). Of the 878 patients with localized disease, 728 patients met criteria to be included in the analysis of margins, and 768 met criteria to be included in the analysis of chemotherapy response.

Patients in the study group were aged 1 to 30 years with a mean of 13.9 years. The majority of patients (71%) were 10 to 17 years of age at the time of enrollment onto 1 of the cooperative group trials (Table 2). One hundred seventy-six patients (17%) were <10 years old, and 129 patients (12%) were ≥18 years old at the time of enrollment. Ages of patients in

the oldest group ranged from 18 to 30 years with a mean of 21.5 years. One hundred seventy-six patients (17%) had metastatic disease at the time of diagnosis. Sex was the only parameter significantly associated with age (Table 2). Males were more likely than females to be ≥18 year old at the time of enrollment. The association between age and sex in the study population is similar to that seen in all patients diagnosed with osteosarcoma in the United States.[19]

OS and EFS

The 5- and 10-year EFS (with 95% confidence intervals [CIs]) for the entire study population was 56% (53.1%-59.2%) and 53% (49.5%-56.4%), respectively. The 5- and 10-year OS for the entire study population was 69% (65.4%-71.4%) and 59% (54.9%-63.1%), respectively (Fig. 1). The 5-year EFS and OS for the patients with localized osteosarcoma was 63% (59.3%-65.8%) and 74% (71.2%-77.3%), respectively. The 5-year EFS and OS for the patients with metastatic osteosarcoma was 23% (16.9%-30.2%) and 36% (27.4%-44.4%), respectively.

Age as a Prognostic Factor

The 10-year EFS in patients aged <10, 10 to 17, and ≥18 years was 55% (46.6%-62.7%), 55% (51.0%-58.9%), and 37% (24.1%-49.6%), respectively. The 10-year OS in patients aged <10, 10 to 17, and ≥18 years was 68% (58.7%-75.5%), 60% (54.6%-64.4%), and 41% (25.3%-55.7%), respectively. The hazard ratio (HR) for death for age ≥18 years compared with those aged <10 years was 1.7 (95% CI, 1.15-2.54; overall $P = .021$; Table 3). When stratified according to the presence of metastatic disease and study, age ≥18 years continued to be associated with a statistically significant poorer EFS (overall $P = .019$) and OS (overall $P = .043$; Fig. 2).

Poorer EFS and OS for patients aged ≥18 years is also seen when the analysis is restricted to patients with localized osteosarcoma (overall $P = .032$ for EFS and overall $P = .016$ for OS; Fig. 3). In patients with metastatic disease at presentation, AYA age is not associated with an increased risk of death (overall $P = .88$) or an EFS event (overall $P = .19$).

In patients with localized disease, the risk of relapse as the first EFS event is significantly (overall $P = .043$) higher in patients aged ≥18 years, whereas the risks of death and SMN as a first EFS event are not increased (Fig. 4). The same trend is observed in the entire study population, but the increased risk of relapse does not reach statistical significance (overall $P = .100$).

Additional Prognostic Factors

Metastases—Patients with metastatic disease at the time of diagnosis had a significantly worse EFS ($P < .001$) and OS ($P < .001$) than those with localized disease (Table 3).

Histologic response—Of the 768 patients included in the analysis of histologic response, 415 (54%) had a poor histologic response. Patients with a poor histologic response had a significantly worse postsurgical EFS and postsurgical OS ($P < .001$). After stratifying for histologic response and study, increasing age was associated significantly with increased

risk of a postsurgical EFS event (P = .042; Fig. 5). The log-rank test for the effect of age on postsurgical OS stratified by histologic response and study has a 2-sided P value of .047.

Site—Ninety-six percent of patients in the study had the primary tumor located in the extremity, 2% had the primary tumor located in the pelvis, and 2% had the primary tumor located in a nonextremity, nonpelvic location (other). Patients with pelvic tumors had a significantly higher risk of an EFS event (P < .001) and death (P < .001) than patients with tumors of the extremity or other site. A detailed report regarding these patients with osteosarcoma of the pelvis is to be published separately. The 18 patients with other primary sites included 10 (56%) patients with a primary jaw tumor, 4 (22%) with a primary rib tumor, and 3 (17%) with a primary vertebral tumor. The EFS and OS of patients with other tumor sites were similar to those seen in patients with extremity tumor site.

Margin of resection after definitive surgery—Fifty-seven (8%) of the 728 patients who met criteria for analysis of margins had a primary tumor surgical resection specimen with positive margins. The HR for death for positive margins was 1.61 (95% CI, 1.01-2.56; P = .043; Table 3).

Race—Fourteen percent of the study population was black, 12% was Hispanic, 66% was white, 7% was classified as other race, and 5 patients (<1%) were of unknown race. There was no association between race and outcome (Table 3).

Sex—Five hundred ninety-three (56%) of the patients were male, and 461 (44%) of the patients were female. The HR for death for male sex was 1.26 (95% CI, 1.01-1.56; P = .038; Table 3).

Relative Risk Regression Analysis

The relative risk regression analysis was conducted including the parameters study, tumor site, metastasis, and age. Age ≥18 years remained a significant predictor of survival, with an HR compared with age <10 years of 1.55 (95% CI, 1.04-2.31) and an HR compared with age 10 to 17 years of 1.42 (95% CI, 1.05-1.92). Tumor site and presence of metastatic disease were also significant predictors of OS in the multivariate analysis (Table 4). In the relative risk regression analysis for EFS, age ≥18 years approached statistical significance, with an HR compared with age <10 years of 1.38 (95% CI, 0.99-1.93) and an HR compared with age 10 to 17 years of 1.46 (95% CI, 1.12-1.90).

DISCUSSION

In this patient population, AYA age of 18 to 30 years is associated with a significantly increased risk of relapse or death. The effect of AYA age 18 to 30 years on outcome is greatest in patients with localized disease. Secondary analyses that stratified the population according to histologic response similarly demonstrated a significantly increased risk of death and EFS event in patients aged 18 to 30 years. Such analyses, however, were conducted on groups with a limited sample size. AYA age was not associated with an increased risk of an EFS event or of death in patients with metastatic disease, probably because prognosis is so poor in the group of metastatic patients included in this study.

Several other publications have investigated prognostic factors in osteosarcoma including age. Results have varied, with some studies showing a poorer prognosis in older patients,[7] others demonstrating a poorer prognosis in younger patients,[9] and still others reporting a lack of association between age and prognosis.[10,11] One important methodological consideration contributing to variable results is the manner in which age has been converted to a categorical variable. Studies using age > and <40 years have found no association between age and outcome.[10,11] Age has been dichotomized at a younger cutoff to assess the impact of preadolescence and postadolescence on outcome, with disparate results.[7,9,20] Of note, few prior studies have used categorical age values relevant to the question of prognosis in the AYA population. One other study used similar age groupings as were used here. Although the results do not reach statistical significance, the disease-free survival appeared to be worse in patient aged >21 years.[21] Potential reasons for disparate findings of these studies include differences in patient populations, treatment eras, treatment regimens, and other prognostic factors evaluated in the analysis.

This study has several possible limitations. Because the composition of the patient population is defined by the eligibility criteria of the 4 North American cooperative group trials onto which patients were enrolled, the patient population included in this study may not be representative of osteosarcoma populations as a whole. However, in an analysis restricted to localized osteosarcoma, age retained its prognostic significance. Furthermore, the age distribution of the study population is similar to that seen in the Surveillance, Epidemiology, and End Results database of the National Cancer Institute, with the exception of a slightly smaller proportion of patients aged 20 to 35 years. It is possible that outcome is worse in the 18- to 30-year-olds in this study because of a selection bias that older patients with more advanced or aggressive osteosarcoma were more likely to seek out treatment at pediatric sites and/or enrollment on a pediatric cooperative group trial without a similar trend for younger patients.

Because of a lack of prospectively collected data, we were not able to evaluate the impact of treatment delivery or tumor size on prognosis. Other studies have demonstrated that larger tumor size is a significant predictor of poor outcome in osteosarcoma.[9-11,22] Age and tumor size are highly correlated variables in osteosarcoma[22,23] and rhabdomyosarcoma.[24] When relative tumor size has been carefully evaluated in osteosarcoma, it typically does not have a significant impact on prognosis[22,23] suggesting a complex relationship between age and tumor size in this disease. Although it is possible that older age is a proxy for larger tumor size in our study, it is just as likely that larger size has been a proxy for older age in prior studies. Future prospective studies should acquire sufficient data regarding absolute and relative tumor size to permit detailed analysis of the relationship between age, tumor size, and prognosis.

The factors potentially responsible for poorer outcomes in AYA patients with cancer are multiple and include delayed diagnosis, tumor biology, decreased rates of participation in clinical trials, worse compliance with chemotherapy schedules, distinct chemotherapy metabolism, and increased toxicity resulting in delays in chemotherapy administration. Among patients enrolled in INT-0133, comprising 70% of the patient population analyzed for this study, there was no evidence of a statistically significant difference in toxicity-

related treatment delays or dose reductions between the 3 age groups. There was not an increased rate of metastatic disease in 18- to 30-year-olds, suggesting that delayed diagnosis may not be the cause of worse outcome in this patient group. Unfavorable tumor biology and distinct chemotherapy metabolism in 18- to 30-year-olds with osteosarcoma are factors deserving of dedicated investigation in future studies.

Similar to previous reports, we found pelvic site, the presence of metastatic disease at diagnosis, positive tumor margins, and a poor histologic response to chemotherapy to be significant predictors of a poor prognosis.[9,11,21] Male sex was identified as a significant predictor of poor outcome on univariate analysis. But male sex was associated with age ≥18 years, and only age ≥18 years remained a statistically significant predictor of outcome after regression analysis was performed.

On the basis of the results of this study, it is reasonable to proceed with a detailed evaluation of the biologic, clinical, research, and social factors that may contribute to inferior outcomes in AYA patients aged between 18 and 30 years with osteosarcoma. However, the conduct of this research must take into account the existence of other prognostic factors (metastases, tumor site, and response to chemotherapy) with a larger magnitude of effect.

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REFERENCES

1. Adolescent and Young Adult Oncology Progress Review Group. Closing the gap: research and care imperatives for adolescents and young adults with cancer. NIH Pub. No. 06-6067. National Institutes of Health; Bethesda, MD: 2006. Available at: http://planning. cancer.gov/library/AYAO_PRG_Report_2006_FINAL.pdf
2. Bleyer A, Barr R, Hayes-Lattin B, Thomas D, Ellis C, Anderson B. The distinctive biology of cancer in adolescents and young adults. Nat Rev Cancer. 2008; 8:288–298. [PubMed: 18354417]
3. Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med. 2003; 348:694–701. [PubMed: 12594313]
4. Craft A, Cotterill S, Malcolm A, et al. Ifosfamide-containing chemotherapy in Ewing's sarcoma: the Second United Kingdom Children's Cancer Study Group and the Medical Research Council Ewing's Tumor Study. J Clin Oncol. 1998; 16:3628–3633. [PubMed: 9817284]
5. Sultan I, Qaddoumi I, Yaser S, Rodriguez-Galindo C, Ferrari A. Comparing adult and pediatric rhabdomyosarcoma in the Surveillance, Epidemiology and End Results program, 1973 to 2005: an analysis of 2,600 patients. J Clin Oncol. 2009; 27:3391–3397. [PubMed: 19398574]
6. Sultan I, Rodriguez-Galindo C, Saab R, Yasir S, Casanova M, Ferrari A. Comparing children and adults with synovial sarcoma in the Surveillance, Epidemiology, and End Results program, 1983 to 2005: an analysis of 1268 patients. Cancer. 2009; 115:3537–3547. [PubMed: 19514087]
7. Ferrari S, Bertoni F, Mercuri M, et al. Predictive factors of disease-free survival for non-metastatic osteosarcoma of the extremity: an analysis of 300 patients treated at the Rizzoli Institute. Ann Oncol. 2001; 12:1145–1150. [PubMed: 11583198]
8. Pakos EE, Nearchou AD, Grimer RJ, et al. Prognostic factors and outcomes for osteosarcoma: an international collaboration. Eur J Cancer. 2009; 45:2367–2375. [PubMed: 19349163]

9. Bacci G, Longhi A, Versari M, Mercuri M, Briccoli A, Picci P. Prognostic factors for osteosarcoma of the extremity treated with neoadjuvant chemotherapy: 15-year experience in 789 patients treated at a single institution. Cancer. 2006; 106:1154–1161. [PubMed: 16421923]
10. Harting MT, Lally KP, Andrassy RJ, et al. Age as a prognostic factor for patients with osteosarcoma: an analysis of 438 patients. J Cancer Res Clin Oncol. 2010; 136:561–570. [PubMed: 19784847]
11. Bielack SS, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. J Clin Oncol. 2002; 20:776–790. [PubMed: 11821461]
12. Seibel NL, Krailo M, Chen Z, et al. Upfront window trial of topotecan in previously untreated children and adolescents with poor prognosis metastatic osteosarcoma: Children's Cancer Group (CCG) 7943. Cancer. 2007; 109:1646–1653. [PubMed: 17334983]
13. Meyers PA, Schwartz CL, Krailo M, et al. Osteosarcoma: a randomized, prospective trial of the addition of ifosfamide and/or muramyl tripeptide to cisplatin, doxorubicin, and high-dose methotrexate. J Clin Oncol. 2005; 23:2004–2011. [PubMed: 15774791]
14. Meyers PA, Schwartz CL, Krailo MD, et al. Osteosarcoma: the addition of muramyl tripeptide to chemotherapy improves overall survival—a report from the Children's Oncology Group. J Clin Oncol. 2008; 26:633–638. [PubMed: 18235123]
15. Bishop, S.; Feinberg, SE.; Holland, YMM. Discrete Multivariate Analysis. MIT Press; Cambridge, MA: 1975.
16. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999; 18:695–706. [PubMed: 10204198]
17. Gray R. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat. 1988; 16:1141–1154.
18. Kalbfleisch, JD.; Prentice, RL. The Statistical Analysis of Failure Time Data. 2nd ed.. John Wiley and Sons; New York, NY: 2002.
19. Cancer Epidemiology in Older Adolescents and Young Adults 15 to 29 Years of Age, Including SEER Incidence and Survival: 1975-2000. National Cancer Institute; Bethesda, MD: 2006.
20. Bacci G, Longhi A, Bertoni F, et al. Primary high-grade osteosarcoma: comparison between preadolescent and older patients. J Pediatr Hematol Oncol. 2005; 27:129–134. [PubMed: 15750443]
21. Meyers PA, Heller G, Healey J, et al. Chemotherapy for nonmetastatic osteogenic sarcoma: the Memorial Sloan-Kettering experience. J Clin Oncol. 1992; 10:5–15. [PubMed: 1370176]
22. Kaste SC, Liu T, Billups CA, Daw NC, Pratt CB, Meyer WH. Tumor size as a predictor of outcome in pediatric non-metastatic osteosarcoma of the extremity. Pediatr Blood Cancer. 2004; 43:723–728. [PubMed: 15390310]
23. Bieling P, Rehan N, Winkler P, et al. Tumor size and prognosis in aggressively treated osteosarcoma. J Clin Oncol. 1996; 14:848–858. [PubMed: 8622033]
24. Ferrari A, Miceli R, Meazza C, et al. Soft tissue sarcomas of childhood and adolescence: the prognostic role of tumor size in relation to patient body size. J Clin Oncol. 2009; 27:371–376. [PubMed: 19064986]

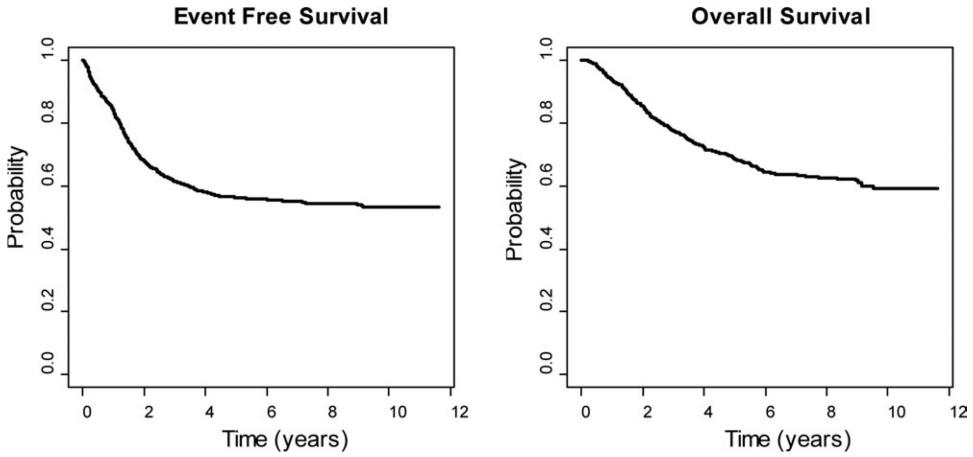

Figure 1.

Event-free and overall survival of all patients aged 1 to 30 years in the study population (n = 1054) are shown.

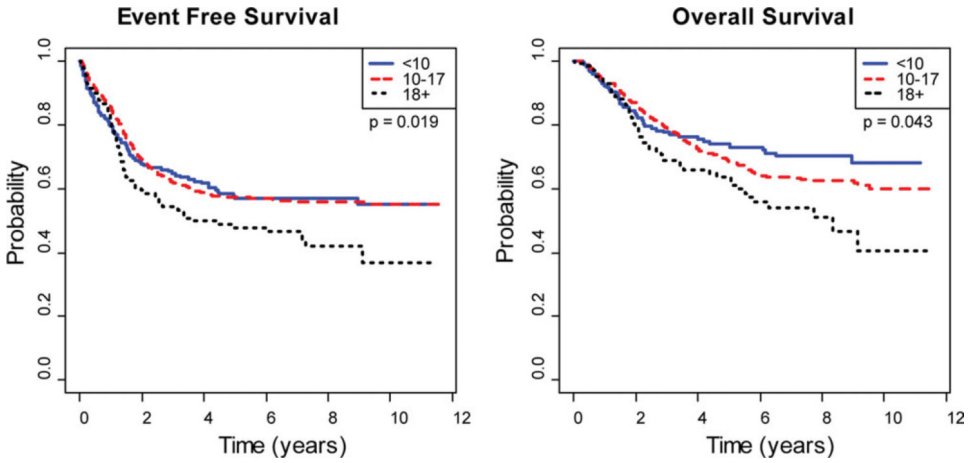

Figure 2.

Event-free and overall survival of all patients are shown by age at study enrollment, stratified by study and presence of metastatic disease at diagnosis.

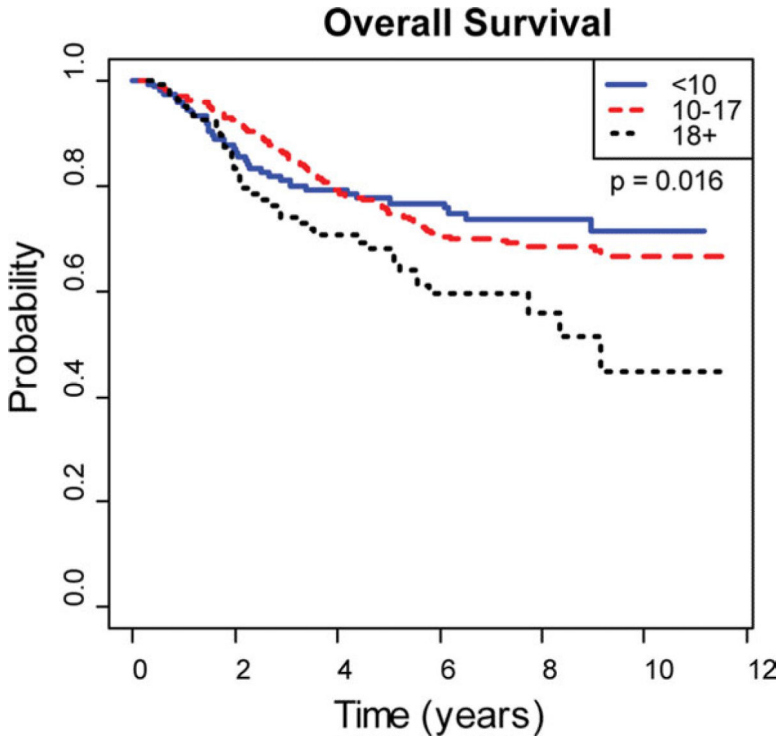

Figure 3.

Overall survival is shown by age of patients with localized osteosarcoma, stratified by study.

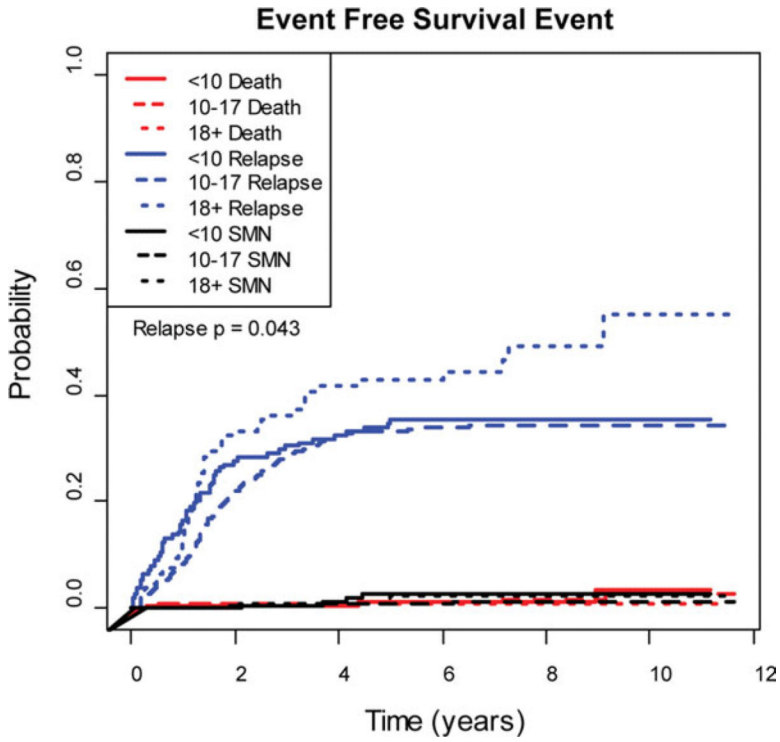

Figure 4.

Event-free survival is shown by event type and age, stratified by study. SMN, second malignant neoplasm.

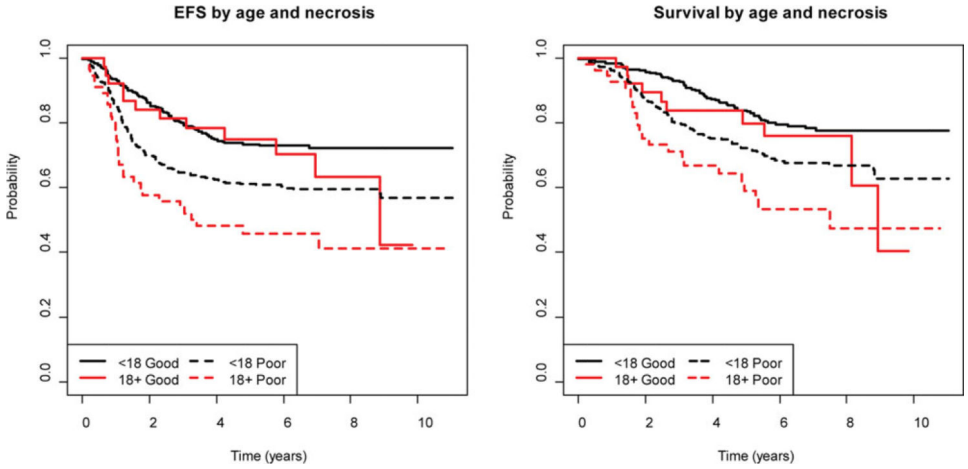

Figure 5.

Postsurgery event-free survival (EFS) and postsurgery overall survival are shown by age and necrosis. (Poor necrosis: <95% necrosis; good necrosis: ≥95% necrosis.)

Table 1

North American Cooperative Group Trials Onto Which Patients Included in This Study Were Enrolled

Study	Cooperative Group	Eligibility		Treatment Arms
		Metastatic Disease	Unresectable Disease	
INT-0133	CCG	Allowed	Allowed	MAP
	POG	No	No	MAP + MTPPE
				MAP + IFOS
				MAP + MTPPE + IFOS
CCG-7943	CCG	Required[a]	Allowed	TOPO + ICE + AP
POG-9754	POG	No	No	MAP
				MAP, high A
				MAP + IFOS
				MAPIE
AOST0121	COG	Required[b]	Allowed	MAP
				MAPIE + trastuzumab

Abbreviations: AP, doxorubicin and cisplatin; CCG, Children's Cancer Group; COG, Children's Oncology Group; high A, higher cumulative dose doxorubicin (up to 600 mg/m^2); ICE, ifosfamide, carboplatin, and etoposide; IFOS, ifosfamide; MAP, high-dose methotrexate, doxorubicin, and cisplatin; MAPIE, MAP plus ifosfamide and etoposide; MTPPE, muramyl tripeptide phosphatidyl ethanolamine; POG, Pediatric Oncology Group; TOPO, topotecan.

[a] Unresectable pulmonary metastases with ≥5 nodules and/or disease involving multiple bones or other organs.

[b] Bone metastases ± lung metastases, or bilateral lung metastases, or unilateral lung metastases with ≥4 nodules.

Table 2

Characteristics of the Study Population and Association of Parameters With Age

Characteristic	All, n=1054	Age, No. (%)			*P* [a]
		<10 Years, n=176, 17%	10-17 Years, n=749, 71%	≥18 Years, n=129, 12%	
Sex					<.001[b]
Male	593 (56)	91 (52)	406 (54)	96 (74)	
Female	461 (44)	85 (48)	343 (46)	33 (26)	
Race					.059
Black	151 (14)	27 (15)	107 (14)	17 (13)	
Hispanic	125 (12)	28 (16)	90 (12)	7 (5)	
Other	78 (7)	17 (10)	51 (7)	10 (8)	
White	695 (66)	103 (59)	498 (67)	94 (73)	
Unknown	5 (1)	1 (< 1)	3 (< 1)	1 (1)	
Site					.066
Extremity	1010 (96)	171 (97)	720 (96)	119 (92)	
Pelvic	26 (2)	1 (1)	19 (3)	6 (5)	
Other	18 (2)	4 (2)	10 (1)	4 (3)	
Metastatic					.212
Yes	176 (17)	22 (13)	134 (18)	20 (16)	
No	878 (83)	154 (87)	615 (82)	109 (84)	
Study					N/A
INT-0133	745 (70)	130 (74)	528 (70)	87 (67)	
CCG-7943	28 (3)	6 (3)	17 (2)	5 (4)	
AOST0121	81 (8)	6 (3)	67 (9)	6 (5)	
POG-9754	202 (19)	34 (19)	137 (18)	31 (24)	
Response, n=768					.349
Good	353 (46)	65 (51)	249 (46)	39 (41)	
Poor	415 (54)	63 (49)	296 (54)	56 (59)	
Tumor margins, n=728					.893
Positive	62 (8)	12 (9)	42 (8)	8 (9)	
Negative	682 (92)	118 (91)	482 (92)	85 (91)	

Abbreviation: N/A, not applicable.

[a] *P* value associated with the test of the hypothesis that the row characteristic is independent of age.

[b] Statistically significant.

Table 3

Parameters and Their Association With Overall Survival by Univariate Analysis

Characteristic	Patients, No. (%)	5-Year EFS, %	HR [95% CI]	*P* [a]	5-Year OS, %	HR [95% CI]	*P* [b]
Age				.038[c]			.021[c]
<10 years	176 (17)	58			74		
10-17 years	749 (71)	57	0.99 [0.77-1.27]		68	1.20 [0.88-1.65]	
≥18 years	129 (12)	48	1.38 [1.00-1.92][c]		64	1.70 [1.15-2.54][c]	
Sex				.080			.038[c]
Female	595 (56)	59			71		
Male	461 (44)	54	1.18 [0.98-1.42]		67	1.26 [1.01-1.56][c]	
Race				.328			.484
White	695 (66)	57			69		
Black	151 (14)	56	1.11 [0.85-1.44]		67	1.05 [0.77-1.44]	
Hispanic	125 (12)	51	1.27 [0.96-1.67]		64	1.28 [0.93-1.77]	
Other	83 (8)	61	0.94 [0.65-1.35]		72	0.95 [0.62-1.46]	
Site				<.001[c]			<.001[c]
Extremity	1010 (96)	57			69		
Pelvic	26 (2)	23	3.64 [2.32-5.70][c]		38	3.78 [2.38-6.01][c]	
Other[d]	18 (2)	55	0.95 [0.47-1.91]		83	0.54 [0.17-1.68]	
Metastatic				<.001[c]			<.001[c]
No	878 (83)	63			74		
Yes	176 (17)	23	3.32 [2.87-4.33][c]		36	3.87 [3.05-4.91][c]	
Response, n=768				<.001[c]			<.001[c]
Good	353 (46)	73			83		
Poor	415 (54)	59	1.79 [1.39-2.29][c]		71	1.85 [1.39-2.47][c]	
Tumor margins, n=728				.112			.043[c]
Negative	671 (92)	66			66		

Characteristic	Patients, No. (%)	5-Year EFS, %	HR [95% CI]	*P* [a]	5-Year OS, %	HR [95% CI]	*P* [b]
Positive	57 (8)	58	1.40 [0.92-2.14]		63	1.61 [1.01-2.56][c]	

Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio.

[a] *P* value associated with the log-rank test of the hypothesis of equality of risk for EFS event across the levels of the characteristic identified in the row.

[b] *P* value associated with the log-rank test of the hypothesis of equality of risk for death across the levels of the characteristic identified in the row.

[c] Statistically significant.

[d] Unknown included in other.

Table 4

Parameters and Their Association With Overall Survival and Event-Free Survival by Regression Analysis

Survival	HR (95% CI)	*P*
Overall survival		
Age ≥18 years		.049
Versus <10 years	1.55 (1.04-2.31)	
Versus 10-17 years	1.42 (1.05-1.92)	
Site, pelvic		<.001
Versus extremity	3.08 (1.92-4.92)	
Versus other	6.1 (1.80-20.70)	
Metastasis (vs nonmetastatic)	3.26 (2.26-4.69)	<.001
Event-free survival		
Age ≥18 years		.019
Versus <10 years	1.38 (0.99-1.93)	
Versus 10-17 years	1.46 (1.12-1.90)	
Site, pelvic		<.001
Versus extremity	2.95 (1.87-4.66)	
Versus other	3.61 (1.58-8.24)	
Metastasis (vs nonmetastatic)	2.92 (2.11-4.05)	<.001

Abbrevations: CI, confidence interval; HR, hazard ratio.