

Osteosarcoma: A Meta-Analysis and Review of the Literature

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Abstract

Over the past 30 years, treatment advances and the addition of neoadjuvant chemotherapy have led to improved 5-year survival in patients with osteosarcoma. More recent literature suggests the overall prognosis remains highly variable, with little improvement since the introduction of neoadjuvant chemotherapy. Tumor necrosis is an important predictor of patient prognosis. Necrosis of more than 90% correlates with overall survival (OS) approaching 75%.

We reviewed the history of osteosarcoma treatment and survival and performed a meta-analysis of the 2000–2011 literature. Forty articles were included in the study. Five-year OS was 63% (95% confidence interval, 60%–66%) in studies that included patients with metastatic and nonmetastatic disease and 71% (95% confidence interval, 67%–76%) in studies that included only patients with nonmetastatic disease. Fifty percent of the patients in the studies of those with nonmetastatic osteosarcoma achieved 90% necrosis on histology. Five-year OS and number of patients achieving 90% necrosis are consistent with previous reports. Research is needed to improve treatment regimens and patient outcomes.

Osteosarcoma, a primary malignant tumor of the skeleton, is characterized by direct formation of immature bone or osteoid tissue by tumor cells. The World Health Organization histologic classification of bone tumors divides osteosarcoma into central and surface tumors and recognizes a number of subtypes within each group.¹ The present review refers only to the classic central high-grade primary osteosarcoma of bone, which represents about 90% of all osteosarcoma cases. Classic osteosarcoma represents about 15% of all biopsy-analyzed primary bone tumors.¹ It is the third most common type of neoplasia, preceded by leukemia and lymphoma among older children and adolescents aged 12 to 18 years.² High-grade primary osteosarcoma is the most common primary skeletal tumor of childhood and adolescence, with

an overall annual incidence of 5.6 cases per million children under age 15 years.^{3–5} Peak incidence is in the second decade of life, and males are affected slightly more often than females.^{2,6} The period of highest incidence coincides with the growth spurt of the long bones. Osteosarcoma preferentially affects the metaphysis of long bones, the 3 main sites being distal femur, tibia, and proximal humerus.²

Historical Perspective

For most of the 20th century, the 5-year survival rate for classic primary osteosarcoma was under 20%.⁷ In the 1970s, the first revolution in osteosarcoma treatment arrived with the introduction of adjuvant chemotherapy, which increased survival rates to 50%.^{8–10} During this expansion of research, several chemotherapeutics (eg, vincristine, bleomycin, dactinomycin) were discarded for poor effectiveness, and others (eg, cisplatin, ifosfamide) were added to doxorubicin and methotrexate, improving 5-year disease-free survival to about 70% in patients with nonmetastatic osteosarcoma. In another significant advance, adjuvant chemotherapy was supplemented with intensive preoperative chemotherapy, resulting in 5-year tumor-free survival that has ranged from 50% to 75% for high-grade osteosarcoma.^{5,11,12} Adding neoadjuvant chemotherapy and histologic response has allowed for evaluation of surgical margins and early treatment of microscopic disease. Thus, effective limb-sparing procedures can be performed, and the incidence of amputation has decreased from 90% to between 10% and 20%.^{13,14} However, statistical improvements in survival associated with neoadjuvant treatment may simply delay time of recurrence and metastasis.¹⁵ In addition, though chemotherapy has improved survival in osteogenic sarcoma, many have written that this improvement appears to reflect mainly the increase in the intensity of the chemotherapy used, which also leads to a higher propensity for side effects.¹⁶

Despite research and advances in chemotherapy regimens, the prognosis of patients with osteosarcoma remains highly variable and often dismal. Mirabello and colleagues¹⁷ examined osteosarcoma incidence and survival rates between 1973 and 2004 and found that, with the introduction of neoadjuvant chemotherapy, survival rates improved significantly between 1973 and 1983 and between 1984 and 1993, but there was little improvement between 1993 and 2004.

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The long-term outcome for patients with metastatic disease is poor. Investigators have found that 11% to 20% of patients have pulmonary metastasis at initial diagnosis. About half of patients without pulmonary metastases develop them later in the disease course.¹⁸ Survival rates for patients with metastasis at initial presentation have ranged from 10% to 40%.¹⁹ Recurrent disease still occurs in 30% to 40% of patients, and more than 70% of them die of the tumor.¹⁵ The survivors of osteosar-

coma are then at increased risk for chronic medical conditions and adverse health status because of the osteosarcoma-related treatments.²⁰

Prognostic Factors

It is important to understand and exploit the influences of different prognostic factors in treating patients with osteosarcoma.⁷ These factors are important in establishing the best

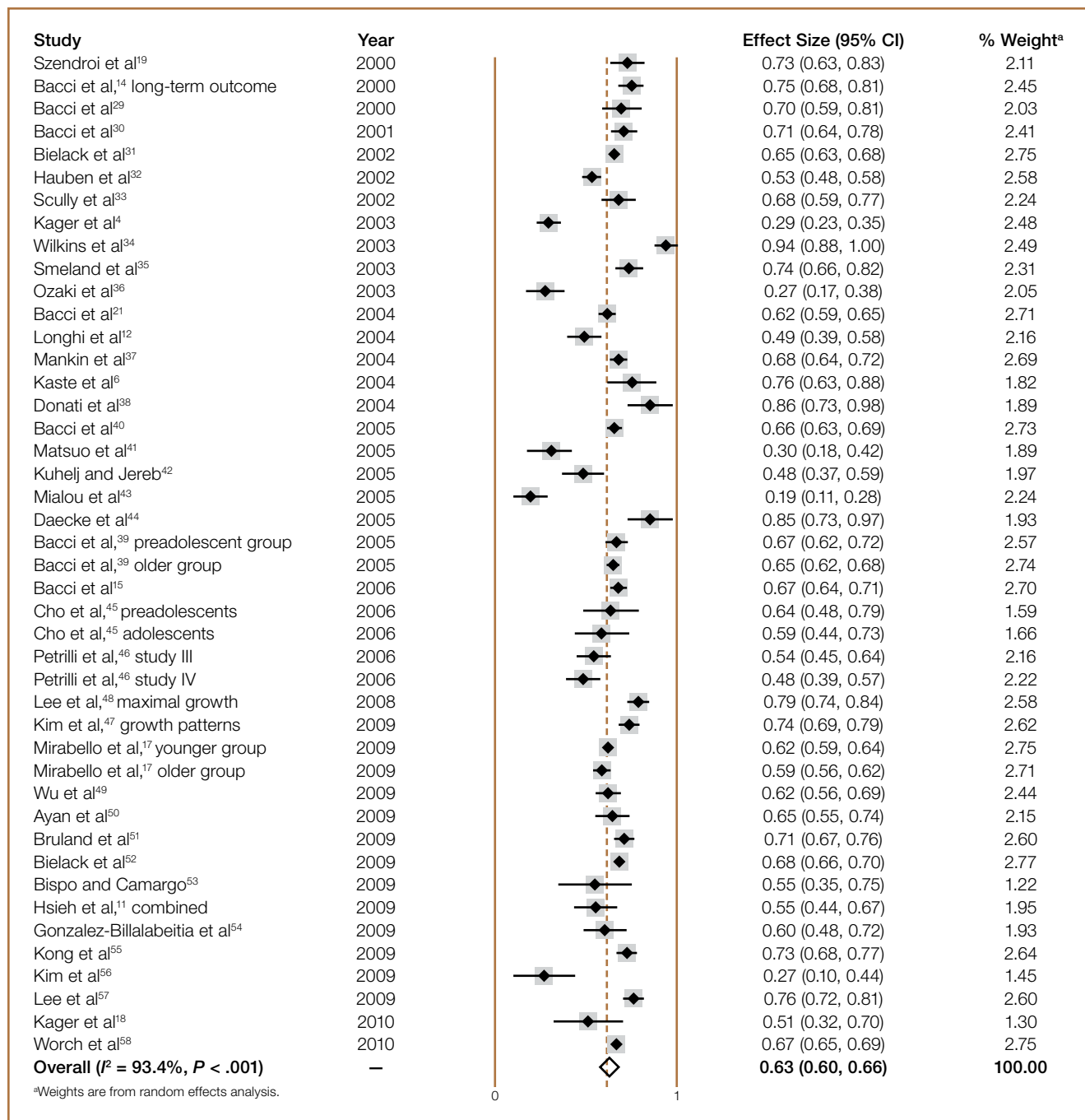


Figure 1. Five-year overall survival for studies that included patients with metastatic and nonmetastatic osteosarcoma is represented by black diamond. Gray box represents weight of study. Black bar represents 95% confidence interval. Each study's weight (far right of graph) is based on number of patients included in study. Abbreviation: CI, confidence interval.

treatment for the individual. Thus, more aggressive treatments can be started in patients with prognostic factors that pose a higher risk of relapse.²¹ A number of clinical and pathologic features (eg, tumor site, size, subtype; patient sex and age; high alkaline phosphatase or high lactate dehydrogenase [LDH] values; multidrug resistance; genetic variations) have prognostic significance but often with contradictory results because of lack of uniformity in patient analyses and methods.¹⁵

Survival for patients with primary osteosarcoma has been analyzed with respect to tumor size and location.⁷ Studies have found higher survival rates for patients with smaller tumors (<10 cm) and more distal tumor locations.⁷ These superior survival rates may be the result of earlier detection of tumors and more options for surgical resection of smaller, distal tumors.

Serum LDH levels have helped in risk stratification of patients. High LDH often occurred at time of relapse, and relapse with high LDH correlated with poor prognosis. Meyers and colleagues²² found that 5-year disease-free survival was 72% for patients with normal LDH at presentation and 54% for patients with elevated LDH at presentation.

Several studies have shown that percentage of tumor necrosis on histology is strongly correlated with good prognosis.²¹ Most groups now define a good histologic response as less than 10% viable tumor cells at time of surgery, and a poor response as more than 10%.²³ Results of the Pediatric Oncology Group (POG) protocol for localized osteosarcoma (POG 9351), or Children's Cancer Group (CCG) 7921, found 45% of patients had favorable responses (>90% necrosis) after preoperative chemotherapy.²⁴ However, several clinicians have recently questioned this finding.

Overall, the prognosis for classic osteosarcoma of the extremity remains highly variable, and there has been little im-

provement over the past 20 years. The prognosis for younger patients, patients with spinal disease, and patients with metastatic disease remains poor. Although some prognostic factors have been identified and shown to predict a good outcome, it seems few patients have these positive factors. In this article, we describe the literature review and meta-analysis we performed to better define recent survival trends for patients with primary osteosarcoma.

Methods

The MEDLINE, PubMed, and Cochrane databases were searched for eligible studies published in English between 2000 and 2011—a decade of recently reported research. We applied the search strategy [“osteosarcoma” OR “osteogenic sarcoma”] AND [“prognosis” OR “treatment” OR “survival”] and selected reports that specifically addressed factors predicting survival in patients with osteosarcoma—reports that were limited to primary osteosarcoma of the pelvis or extremity and provided 5-year overall survival (OS) data. Abstracts of the selected articles were independently reviewed, and the inclusion and exclusion criteria were applied. We excluded basic science studies and those without pediatric patients, those without primary osteosarcoma, those with periosteal or parosteal osteosarcoma, and those that did not report 5-year OS data.

Statistical Analysis

Number or proportion of patients (whichever was reported) with 5-year OS and number or proportion of patients with 90% necrosis were extracted from each study. For each trial, proportion of patients with 5-year OS and 95% confidence intervals (CIs) and proportion of patients achieving 90% necrosis and 95% CIs were determined. We also calculated proportion of patients with 5-year OS and proportion of patients with 90%

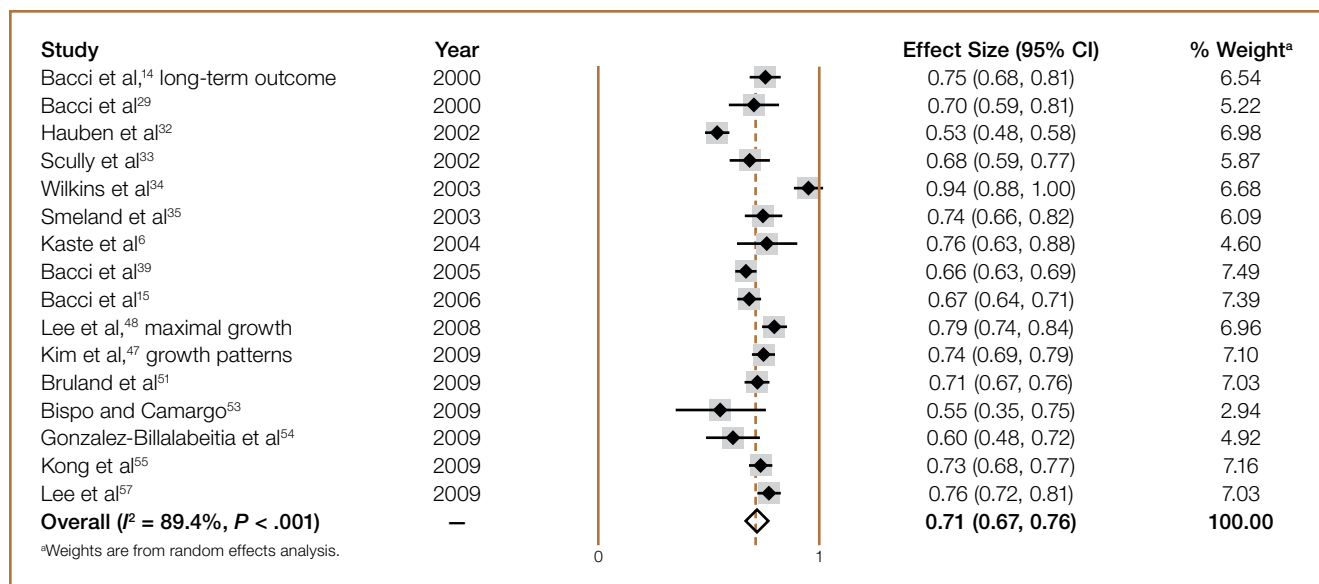


Figure 2. Five-year overall survival for studies that included only patients with nonmetastatic osteosarcoma. Abbreviation: CI, confidence interval.

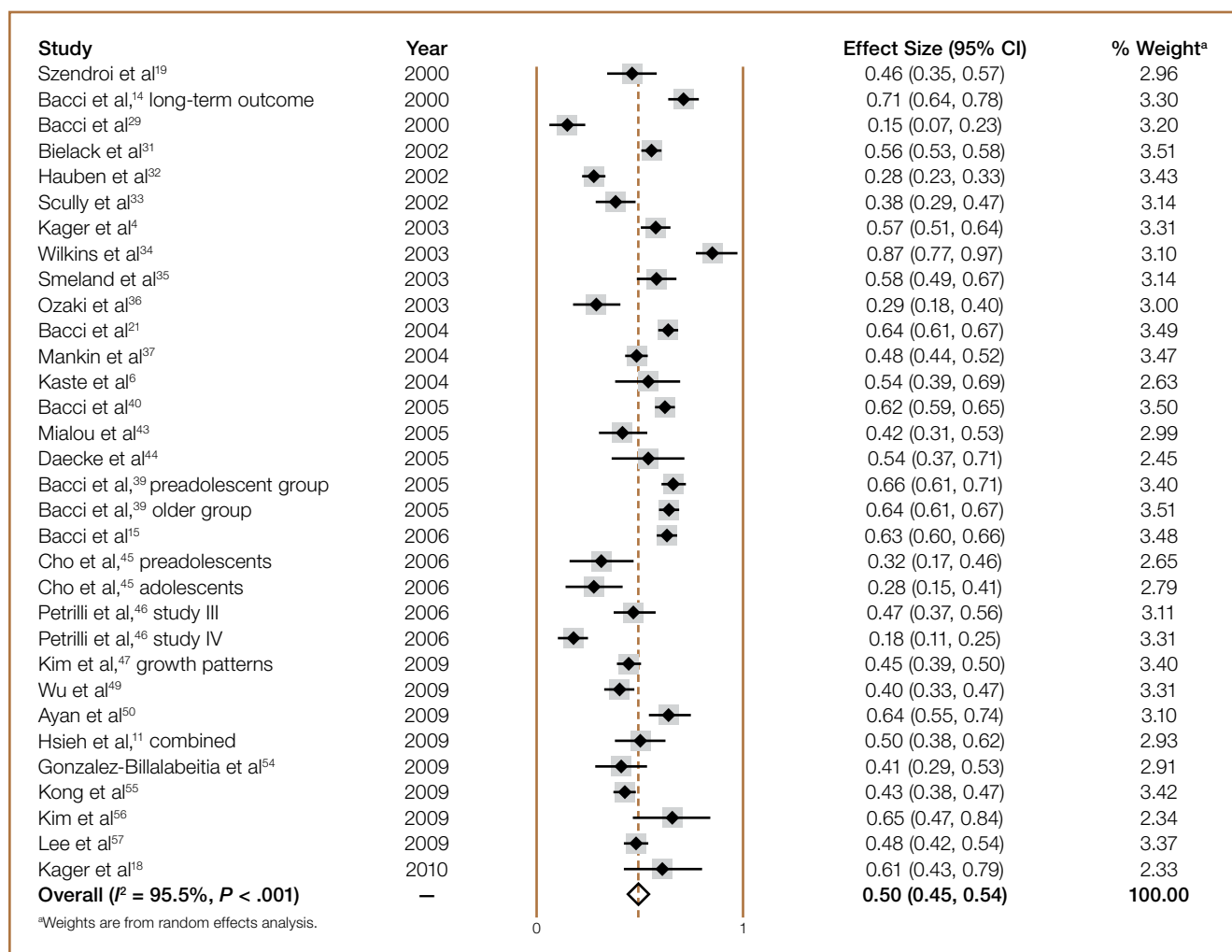


Figure 3. Proportion of patients achieving 90% necrosis for studies that included patients with metastatic and nonmetastatic osteosarcoma. Abbreviation: CI, confidence interval.

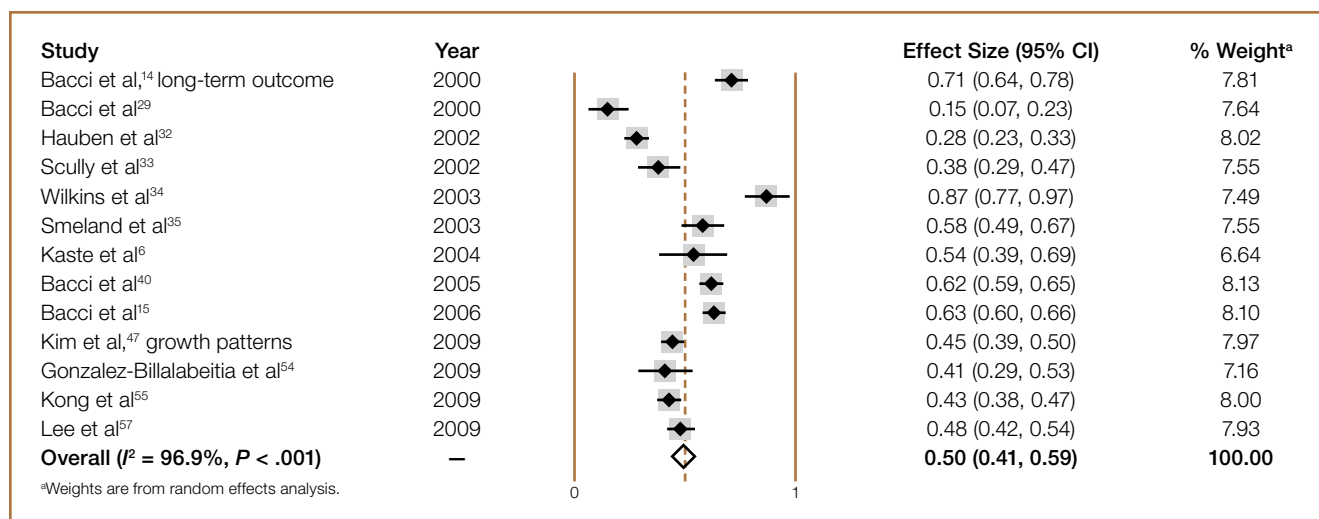


Figure 4. Proportion of patients achieving 90% necrosis for studies that included only patients with nonmetastatic osteosarcoma. Abbreviation: CI, confidence interval.

necrosis with corresponding 95% CIs of studies that included patients with nonmetastatic disease.

We assessed statistical heterogeneity among trials included in the meta-analysis using the Cochran Q test. Inconsistency was quantified with the I^2 statistic, which estimates percentage of total across-studies variation caused by heterogeneity rather than chance.²⁵ We considered I^2 higher than 50% as indicating substantial heterogeneity. When substantial heterogeneity was not found, the pooled estimate calculated on the basis of the fixed-effects model was reported using the inverse variance method. When substantial heterogeneity was found, the pooled estimate calculated on the basis of a random-effects model was reported using the DerSimonian and Laird²⁶ method, which takes both within- and between-study variations into account.

Publication bias was assessed through funnel plots and with Begg and Egger tests.^{27,28} Two-tailed $P < .05$ was considered statistically significant. All statistical analyses were performed with Stata/SE Version 11.0 (StataCorp).

Results

Our literature search yielded 597 articles. We cross-referenced these articles with the MEDLINE, PubMed, and Cochrane search results using the same keywords and discarded the duplicates. The abstracts of these articles were then reviewed in detail. The 40 articles^{4,6,11,12,14,15,17-19,21,29-58} that met our study inclusion criteria reported on studies that included patients with metastatic and nonmetastatic osteosarcoma. Because of the significant difference in OS of patients with metastatic disease, we also analyzed articles that included only patients with nonmetastatic disease. Sixteen articles^{6,14,15,29,32-35,39,47,48,51,53,54,55,57} were included in the analysis of patients with nonmetastatic disease.

Figure 1 shows 5-year OS for each of the 40 studies. For studies that compared survival of different groups of patients, the survival of each group is shown separately. For example, Bacci and colleagues³⁹ divided patients into adolescent and preadolescent groups and reported 5-year OS for each. In our analysis, we treated each group independently and reported their 5-year OS separately. For each study, 5-year OS, weight of study, and CI are included. Five-year OS ranged from 19% to 94%. Analysis was performed to determine 5-year OS for all studies based on weight given to each study. The random-effects model used for this analysis (heterogeneity test, $Q = 656.23$; $P < .001$; $I^2 = 93.4\%$) showed 5-year OS of 63% (95% CI, 60%-66%) for studies that included patients with metastatic and nonmetastatic osteosarcoma.

Figure 2 shows 5-year OS (range, 53%-94%) for each of the 16 studies that included only patients with nonmetastatic disease. The random-effects model used for this analysis (heterogeneity test, $Q = 142.08$; $P < .001$; $I^2 = 89.4\%$) showed 5-year OS of 71% (95% CI, 67%-76%) for studies that included only patients with nonmetastatic disease.

We then examined percentage of patients achieving 90% necrosis on histology in each study. Several studies included in the OS analysis did not report percentage necrosis, leaving 29 studies for the necrosis analysis. Of these 29 studies,

all 29 included patients with metastatic and nonmetastatic disease,^{4,6,11,14,15,18,19,21,29,31-36,37,39,40,43-47,49,50,54-57,59} and 13 included only patients with nonmetastatic disease.^{6,14,15,29,32-35,40,47,54,55,57} Again, because of the known difference in prognosis between patients with metastatic disease and patients with nonmetastatic disease, we performed separate analyses, one for the combined dataset of all 29 studies (Figure 3) and the other for the 13 nonmetastatic studies (Figure 4). Random-effects models showed 90% necrosis for 50% of patients in both analyses: studies that included patients with metastatic and nonmetastatic disease (95% CI, 45%-54%; heterogeneity test, $Q = 692.88$; $P < .001$; $I^2 = 95.5\%$) and nonmetastatic studies (95% CI, 41%-59%; heterogeneity test, $Q = 385.42$; $P < .001$; $I^2 = 96.9\%$).

We also performed a meta-regression analysis that included necrosis as a continuous variable for both the overall dataset and the nonmetastatic dataset. Five-year OS was plotted against percentage of patients achieving 90% tumor necrosis for each study. The results are plotted in Figure 5 (combined dataset).

No evidence of publication bias was detected for 5-year OS or percentage necrosis for the analyses of the combined datasets by either Egger test or Begg test. For 5-year OS, P_s were .21 (Egger) and .19 (Begg); for percentage necrosis, P_s were .10 (Egger) and .62 (Begg). In addition, no evidence of publication bias was detected for the analyses of the nonmetastatic studies by either test. For 5-year OS, P_s were .55 (Egger) and .41 (Begg); for percentage necrosis, P_s were .42 (Egger) and .95 (Begg).

Discussion

Five-year OS was 63% (95% CI, 60%-66%) for studies that included patients with metastatic and nonmetastatic osteosarcoma and 71% (95% CI, 67%-76%) for studies that included only patients with nonmetastatic osteosarcoma. These percentages fall within the range found in the literature. Mankin and colleagues³⁷ reviewed 648 cases of patients with osteosarcoma treated at Massachusetts General Hospital in 2004; OS was

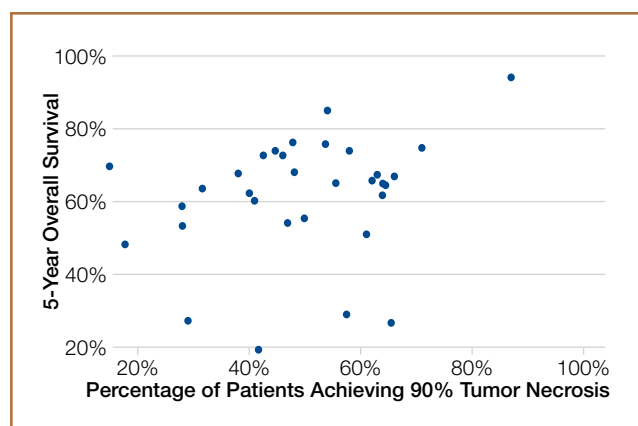


Figure 5. Association of 5-year overall survival with proportion of patients achieving 90% tumor necrosis in each study.

68%. In 2011, Sampo and colleagues⁶⁰ reported 10-year OS of 63% for patients with metastatic and nonmetastatic disease and 73% for patients with local disease at presentation. Five-year OS rates in the literature are consistently about 70%. Ferrari and colleagues⁶¹ reported 5-year OS of 73% and 74% for 230 patients treated with 2 different neoadjuvant chemotherapy regimens between 2001 and 2006. The consistency in 5-year OS suggests OS of pediatric patients with osteosarcoma has plateaued, and there has been no significant improvement in survival of patients with osteosarcoma over the past 30 years.

Histologic response to preoperative chemotherapy is strongly associated with survival in pediatric osteosarcoma. Bielack and colleagues³¹ reported 5-year OS of 75% to 80% for patients who responded well to preoperative chemotherapy (>90% tumor necrosis) and 45% to 55% for patients who responded poorly (<10% necrosis). In our meta-analysis of studies that included patients with nonmetastatic osteosarcoma, 50% achieved necrosis of more than 90%. Percentage of patients achieving necrosis of more than 90% has been about 45%, according to past reports. In 2012, Ferrari and colleagues⁶¹ reported that 45% of 230 patients treated with neoadjuvant chemotherapy achieved more than 90% tumor necrosis. Therefore, 5-year OS and percentage of patients achieving 90% necrosis are consistent with previous reports, though this also suggests these numbers have remained constant over the past several decades.

Despite its expansive scale, our study has several important limitations. Data were extracted from published studies, and individual patient data were not available, so we were not able to assess the effects of risk factors (eg, tumor size, location) on 5-year OS. We could not correlate the proportion of patients with 90% necrosis to 5-year OS, as studies did not report OS by necrosis strata. Also, because our numbers were derived from published studies, they may not accurately represent outcomes in the community as a whole. In addition, several successive studies may contain duplicate patient cases. We limited our search to studies published since 2000 to include patients recently diagnosed and treated for osteosarcoma; however, several studies published after 2000 also included patients diagnosed and treated before 2000. Several of these studies are from countries outside the United States and may have a significantly different incidence of osteosarcoma as well as treatment methods and survival rates.

Although this meta-analysis suggests 5-year OS remains about 70% for patients with primary nonmetastatic osteosarcoma, we cannot settle on this conclusion because of the many differences between the studies we included. Therefore, more studies of patients diagnosed and treated within the past 10 years are needed to confirm our beliefs about patient survival.

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This paper will be judged for the Resident Writer's Award.
