Making a Case for the Socioeconomic Determinacy of Survival in Osteosarcoma

Saminathan S. Nathan FRCS, John H. Healey FACS

Published online: 13 September 2012
© The Association of Bone and Joint Surgeons® 2012

Abstract

Background The literature on osteosarcoma survival generally focuses on tumor and treatment variables, although it is unclear whether and how ethnic and socioeconomic factors might influence survival.

Questions/purposes We therefore investigated the relative contribution of socioeconomic influences together with more traditional tumor-specific factors on osteosarcoma survival.

Methods We performed survival analyses on two national databases in two countries. Using multivariable analyses,

we compared these with corresponding institution-specific survival to determine if socioeconomic factors might impact osteosarcoma survival.

Results East Asian descent, state-specific treatment, female sex, treatment in the 1990s, low-grade disease, intracompartmental disease, small size, wide resections as opposed to forequarter or hindquarter amputations, and single primaries were good prognostic factors. Survival was better in the more affluent states. Males were affected at an older age than females. Blacks tended to have larger tumors, although their overall survival was similar to whites. East Asians were more likely to be treated in the 1990s with wide resections for smaller tumors and were located around states associated with good treatment. East Asians in Singapore and the United States had the same survival. Survival in East Asians in Singapore was similar to that of other races. The provision of health care for osteosarcoma varies greatly across the United States but is uniform in the socialized medical system in Singapore. Hence, the observed differences in the United States were likely the result of socioeconomic factors.

Conclusions Our analysis suggests ethnic and economic bias may influence survival in osteosarcoma and should receive greater attention in the collective literature on survival analyses.

Level of Evidence Level II, prognostic study. See the Guidelines for Authors for a complete description of levels of evidence.

The institution of one or more of the authors has received funding from the Biomet Oncology Fellowship (JHH), the Pearlman Limb Preservation Fund (JHH), and the National Medical Research Council of Singapore (SSN).

All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research* editors and board members are on file with the publication and can be viewed on request.

Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

This work was performed at the National University of Singapore, Singapore; and Memorial Sloan-Kettering Cancer Center, New York, NY, USA.

S. S. Nathan (✉)

Department of Orthopaedics, National University
of Singapore Yong Loo Lin School of Medicine,
Level 11, NUHS Tower Block, 1E Kent Ridge Road,
Singapore 119228, Singapore
e-mail: dosssn@nus.edu.sg

J. H. Healey

Orthopaedic Surgery Service, Department of Surgery,
Memorial Sloan-Kettering Cancer Center, Affiliated
with Weill Medical College of Cornell University,
New York, NY, USA

Introduction

The treatment of osteosarcoma has seen tremendous improvements in the 1970s and 1980s of the 20th century [4, 11, 13, 16, 17, 19]. Before 1972 the mainstay of

treatment for osteosarcoma had been surgery alone with dismal survival [16]; survival on the order of 17% to 20% was the norm [16, 17, 19]. With the advent of methotrexate for treating metastatic osteosarcoma published in 1972 [13], a new era began in which multimodality treatment involving multiagent chemotherapy and surgery redefined survival becoming the standard of care a decade later [11, 19]. Survival by the 1980s had reached 70% and was achieved in cooperative group studies worldwide [17, 19]. Multiagent chemotherapy with three of the four most active drugs (doxorubicin, platinum, high-dose methotrexate, and ifosfamide) became the standard in the 1990s [17].

However, over the last decade, it appears results of treatment have stagnated [1, 2, 24]. The disease-free survival rates have plateaued at approximately 60% to 70% globally in most single-institution series [1, 2, 17, 24]. One reason there has been so little recent progress in the treatment of osteosarcoma is that the disease is rare. Based on the National Cancer Institute US Cancer Statistics for 2000 (accessed November 18, 2004), there were only 360 cases of osteosarcoma in patients younger than 20 years of age (the age of peak incidence) compared with 186,839 cases of breast cancer and 187,415 cases of prostate cancer in the same time period [23]. There is a ceiling effect whereby it is difficult to document an improvement as a result of current success and small case numbers. This is compounded by heterogeneity in the disease presentation, histopathology, and epidemiology. The heterogeneity is reflected by a large number of demographic and tumor-related factors that independently predict survival to varying degrees: sex, decade of treatment, grade, compartmentalization, size, and number of primaries [1, 2, 11, 13, 16, 17, 19, 24]. The question arises as to whether socioeconomic factors might also influence survival, but the studies cited typically do not factor socioeconomic parameters in their analyses.

We therefore asked whether socioeconomic factors in addition to traditional tumor and treatment variables could be responsible for the variation in survival statistics in the United States.

Materials and Methods

We obtained permission from the National Cancer Institute for the use of Surveillance Epidemiology and End Results (SEER) data [22]. All patients 30 years of age or younger with the diagnosis of nonmetastatic osteosarcoma in the intramedullary portion of long bones of the upper and lower limbs were chosen for analysis. We used this search criterion to ensure that the group would be an epidemiologically homogenous cohort, one that constitutes approximately 70% to 83% of classic osteosarcoma in the

most prevalent age group [9, 12, 22]. Between 1973 and 2000 there were 2363 patients with intramedullary osteosarcoma recorded in the SEER database. Of these there were 1000 patients with nonmetastatic intramedullary osteosarcomas of the long bones in the upper and lower extremities in patients aged 30 years and younger.

We reclassified the various ethnic types as indicated in the SEER database for the purpose of this study into four groups: black, white, East Asian, and others. Data were analyzed both in terms of these four groups as well as between East Asians and others (Fig. 1). We compared data among the East Asians between the two countries. There were 12 centers throughout the United States from which SEER data were recorded between 1973 and 2000. These were reclassified into 10 states and assessed for survival. We compared states that had statistically lower survival with those that had higher survival. The states were ranked by mean per-capita income between 1973 and 2000 as recorded by the US Department of Commerce [3] to determine economic influence on survival. By definition, states that ranked above 25 of the 50 United States were considered relatively affluent. Similarly, survival data were stratified into three categories according to the affluence of these states with three states in the upper income level (designated rich), four in the middle income level (middle), and three in the lower income level (poor).

We recorded sex in the database as male or female. Age was categorized into three decades comprising patients in the first, second, and third decades of life. The decade of treatment was reclassified as treatment between 1973 and 1980 (the 1970s), between 1981 and 1990 (the 1980s), and 1991 and 2000 (the 1990s) to account for the era-dependent treatment philosophies in osteosarcoma and improvement in imaging modalities, which evolved gradually over these three decades. We reclassified the four-part system for grade into high or low grade consistent with the World Health Organization, International Union Against Cancer, American Joint Committee on Cancer, and the Musculoskeletal Tumor Society staging systems. Histological subtype was recorded as indicated in the database as small cell, telangiectatic, fibroblastic, and chondroblastic osteosarcoma and osteosarcoma not otherwise specified. We recorded site of disease as upper and lower extremity disease. Surgery was classified as wide resections, radical limb-preserving resections, amputations, and major amputations involving the limb girdle. Size was classified as per American Joint Committee on Cancer criterion of 8 cm or less (small) and greater than 8 cm (large) [7]. The number of primaries that the patient sustained at the time of diagnosis of osteosarcoma was reclassified as single versus multiple primaries.

There were 172 (17%) patients in the first decade, 663 (66%) in the second, and 165 (17%) patients in their third decade of life. Ethnically, there were 742 (74%) whites,

Fig. 1A–D (A) Survival in the compared databases was fairly typical with institution-specific survival (viz National University of Singapore and Memorial Sloan-Kettering Cancer Center [MSKCC] in the United States) registering better survival than nationwide databases (viz Singapore Cancer Registry and Surveillance Epidemiology and End Results [SEER] in the United States). Patients of East Asian

descent have the best survival in the SEER database. This is seen when patients of East Asian descent are compared both with individual groups (**B**) and all others (**C**). Nevertheless, when the East Asians in Singapore and those in the United States were compared, there was no statistical difference in survival between the two (**D**).

133 (13%) blacks, 72 (7%) East Asians, and 53 (5%) others. There were 247 (25%) patients treated between 1973 and 1980, 321 (32%) patients treated between 1981 and 1990, and 432 (43%) patients treated between 1991 and 2000. Tumor grade was recorded in 398 (40%) patients. There were 51 (13%) patients with low-grade and 347 (87%) patients with high-grade disease. The histologic subtype was recorded in 177 (18%) patients. There were 96 (54%) chondroblastic, 48 (27%) fibroblastic, 29 (16%) telangiectatic, and four (2%) small cell osteosarcoma. The majority of osteosarcomas at 823 (82%) were not otherwise specified. The lower limb was involved in 871 (87%) patients and the upper limb in 129 (13%) patients. Operations were classified in 302 (30%) patients. Wide resections were performed in 57 (19%) patients, limb-preserving

radical resections in 150 (50%) patients, amputations in 83 (27%) patients, and limb girdle implicated major amputations in 12 (4%) patients. Compartmentalization was recorded in 359 (36%) patients. Osteosarcomas were intracompartmental in 112 (31%) and extracompartmental in 247 (69%). Size was recorded in 244 (24%) cases. Size was small in 131 (54%) patients and large in 113 (46%) patients. Patients had one primary in 972 (97%) cases, two primaries in 27 (3%) cases, and three primaries in 1 (0.1%) case (Table 1). Primaries were reclassified as single (one primary) versus multiple (two or three primaries) for subsequent analysis. Although the authors recognize the controversy posed by the contentious definition of a multiple primary versus metastasis, we believe it is necessary to accept the definition at face value to reduce a systematic

Table 1. Summary of significant prognostic variables on univariate analysis*

Factor	Number of patients	Multivariate analysis (p value)	Five-year survival (%)	Ten-year survival (%)
Demographic data				
Sex				
Female	435	0.01	64	59
Male	565	1	59	52
Race				
East Asian	72	0.05	75	69
Black	133	0.7	56	52
White	742	1	61	55
Others	53	0.3	51	45
Venue of reporting				
Good results	783	0.02	64	59
Bad results	217	1	50	44
Decade				
1973–1980	247	0.0001	48	46
1981–1990	321	0.0001	58	51
1991–2000	432	1	72	67
Number of primaries				
Single	972	0.02	61	56
Multiple	28	1	51	41
Pathologic data				
Grade				
Low	51	0.01	79	76
High	347	1	64	57
Surgery				
Wide excision	57	1	86	77
Radical resection	150	0.32	75	64
Amputation	83	0.10	67	61
Major amputation	12	0.02	42	42
Compartmentalization				
Intracompartmental	112	0.05	80	71
Extracompartmental	247	1	66	56
Size				
8 cm or less	131	0.05	76	63
More than 8 cm	113	1	61	49

* Female sex, East Asian descent, favorable venues, latter decades of treatment, and single primaries were independently predictive of good survival. We performed a subset analysis of pathologic data, which supported the internal validity of the SEER data set; SEER = Surveillance, Epidemiology and End Results.

bias and allow for multivariate analysis to correct for this poor prognostic variable.

We recognized that although tumor and treatment findings from the SEER could be compared with the available literature, findings of a socioeconomic nature could be validated with a similar cancer registry outside the United States. The two national registries in turn would need to be validated with institution-based databases in the respective countries to ensure that, at least in terms of treatment

outcomes, the two countries were comparable. Therefore, the SEER data were compared with data from the Singapore Cancer Registry (cross-sectional survey) and the authors' institution-specific databases (retrospectively collected). These four databases were independent of each other and anonymized. Comparable patients with high-grade osteosarcoma who had undergone chemotherapy were identified. Accordingly there were 1389 patients identified in the SEER database, 182 in the Singapore

Cancer Registry, 405 in the Memorial Sloan-Kettering database, and 74 in the National University of Singapore database.

Survival in months and status at last review were available from the database. Univariate analysis was performed using the method of Kaplan and Meier with log rank analysis to determine differences between survival curves. Patients with missing data, as was the case for grade, surgery, compartmentalization, and size, especially in patients from the 1970s, were excluded from univariate analysis. Data were stratified into three decades (1970s, 1980s, and 1990s) to account for variations resulting from the evolution of treatment paradigms and imaging modalities. Cox regression multivariate analysis was performed on all variables significant by univariate analysis (Table 1). Student's *t*-test was used as a test for significance in continuous variables represented by means with SD and the chi-square test was used as a test for significance in categorical variables. Data were captured in a database generated in Microsoft Excel Version 10 for Windows NT (Redmond, WA, USA). All statistical analysis was performed using SPSS Version 11.5 for Windows NT (Chicago, IL, USA). Data, where relevant, are presented as mean $\pm$ SD.

Results

We found no difference ($p > 0.1$) in survival between the Singapore Cancer Registry and either of the two institutional databases although the survival from all three differed ($p < 0.001$) from that for the SEER (Fig. 1A).

Overall survival was 61% at 5 years and 55% at 10 years in the SEER-derived cohort. Survival was skewed by two states that had worse ($p < 0.001$) survival compared with the remaining eight. There were no differences in survival among the eight states in question. Between these two groups the states with poor survival had 5- and 10-year survival rates of 50 and 44 months, respectively, versus 60 and 59 months among the eight others. Within the two states associated with a poor prognosis, survival in the 1980s was worse than that in the 1970s and 1990s contributing to the absence of a difference in survival across the three decades. In the remaining eight states, survival improved ($p < 0.001$) across the three decades. There was no apparent bias resulting from grade of disease or surgical procedures performed to account for this difference.

When the 10 states were ranked by mean per-capita income between 1969 and 2003, one of four states in the nonaffluent half and one of six in the affluent half of the United States were associated with a poor prognosis. Survival in the three most affluent states (66% and 58% survival at 5 and 10 years, respectively) was better

($p < 0.048$) than that in the three least affluent states (56% and 52% survival at 5 and 10 years, respectively). There was no difference in survival between the middle four states and that in the most or least affluent states.

Patients of East Asian descent had better survival ($p = 0.01$) than the other ethnic groups (Fig. 1B). Five- and 10-year survival rates were 75% and 69% as opposed to 60% and 54%, respectively, among all others (Fig. 1C). We found four possible confounding variables exist among East Asians (Table 2). Compared with whites, East Asian patients tended to have smaller tumors ($p = 0.06$), which were resectable by limb preservation procedures ($p = 0.25$) and were more commonly treated in the 1990s ($p = 0.07$). The majority of East Asians were treated in states associated with good survival ($p < 0.001$) and were over-represented in states with better per-capita income (Fig. 2). Nevertheless, even after correcting for these factors, East Asian ethnicity remained a favorable predictor of survival compared with the index ethnic category of whites. This survival advantage with a hazard ratio of 0.62 matched the survival advantage of having one versus multiple primaries (hazard ratio, 0.57). Survival among East Asians in the United States as recorded by the SEER ($n = 98$) and that among the East Asians in Singapore (Fig. 1D) as recorded by the Singapore Cancer Registry ($n = 135$) were similar ($p = 0.45$).

Discussion

We were curious if there could be socioeconomic factors responsible for some of the variability in survivorship analysis in osteosarcoma. Our survivorship analysis incorporated the more traditional tumor and treatment-related variables with socioeconomic and demographic variables.

Readers should be aware of the limitations of our study. First, the SEER database had missing data. This is inherent to most large databases. The comparisons of the tumor and treatment variables may only be valid if we assume that the absent data are comprised of a balanced distribution that matches that of the collected data. This is not unreasonable given the high rate of null reporting (60%–76%) in the four categories highlighted here. In addition, by excluding absent data in univariate analysis, only significant variables are entered into multivariate analysis. In multivariate analysis, only a comparison between recorded data was made; null data were included for multivariate modeling but not actually used for comparison of factors. In this manner, bias resulting from deficits in reporting is minimized. Furthermore, demographic data were complete for this large study so conclusions regarding these variables can be made with much greater confidence. Nevertheless,

Table 2. Race stratified for the major prognostic factors studied in this article*

Factor	Race							
	East Asian		Black		White		Others	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Sex								
Female	33	(46)	53	(40)	331	(45)	18	(34)
Male	39	(54)	80	(60)	411	(55)	35	(66)
Age (years)								
1–10	14	(19)	27	(20)	124	(17)	7	(13)
11–20	50	(69)	87	(65)	486	(65)	40	(76)
21–30	8	(11)	19	(14)	132	(18)	6	(11)
Venue								
Good results	70	<u>(97)</u>	91	(68)	583	(79)	39	(74)
Bad results	2	(3)	42	(32)	159	(21)	14	(26)
Decade								
1973–1980	11	(15)	32	(24)	188	(25)	16	(30)
1981–1990	22	(31)	49	(37)	236	(32)	14	(26)
1991–2000	39	<u>(54)</u>	52	(39)	318	(43)	23	(43)
Grade								
Low	2	(6)	4	(7)	43	(15)	2	(9)
High	31	(94)	52	(93)	244	(85)	20	(91)
Histology								
Small cell	1	(1)	0	(0)	3	(0)	0	(0)
Telangiectatic	4	(6)	4	(3)	21	(3)	0	(0)
Fibroblastic	3	(4)	8	(6)	35	(5)	2	(4)
Chondroblastic	8	(11)	13	(10)	69	(9)	6	(11)
Not otherwise specified	56	(78)	108	(81)	614	(83)	45	(85)
Site								
Upper limb	10	(14)	18	(14)	97	(13)	4	(8)
Lower limb	62	(86)	115	(86)	645	(87)	49	(92)
Surgery								
Wide excision	7	<u>(25)</u>	7	(17)	40	(19)	3	(17)
Radical resection	15	<u>(54)</u>	20	(48)	106	(50)	9	(50)
Amputation	5	(18)	13	(31)	61	(29)	4	(22)
Major amputation	1	(4)	2	(5)	7	(3)	2	(11)
Compartmentalization								
Intracompartmental	14	(38)	20	(38)	72	(28)	6	(43)
Extracompartmental	23	(62)	33	(62)	183	(72)	8	(57)
Size								
8 cm or less	17	<u>(77)</u>	13	(39)	94	(53)	7	(54)
More than 8 cm	5	(23)	20	(61)	82	(47)	6	(46)
Number of primaries								
Single	70	(97)	124	(93)	728	(98)	50	(94)
Multiple	2	(3)	9	(7)	14	(2)	3	(6)

* There were relatively more East Asian patients treated in the 1990s who had limb-preserving surgery for small tumors in states with standard survival results (underlined) that could have accounted for their better performance.

the conclusions about the tumor and treatment variables should be viewed with caution. Second, we are comparing two immigrant East Asian populations in two

demographically isolated areas. It would be critical that there are not any wide variations in the populations themselves as a result of these geographic locations. Our analysis

Fig. 2 The East Asians were overrepresented in the category of rich and middle categories of affluence as well as the good categories of survival.

(Fig. 1A) suggests the two populations are comparable from the perspective of survival outcomes.

Our study is noteworthy for its large patient cohort spanning three critical decades in the evolution of osteosarcoma treatment in two countries. We found the survival of East Asian descent is greater than that for patients of other ethnicities. Furthermore, survival improved in most states in the United States, whereas in some states it remained the same over the three decades. Thus, our data suggest ethnic and socioeconomic factors may relate to survival.

A number of demographic and tumor-related factors independently predicting survival, namely, sex, decade of treatment, grade, compartmentalization, size, and number of primaries, influences survival to varying degrees [1, 2, 11, 13, 16, 17, 19, 24]. The SEER registry lends further credence to those findings. Surgical procedures have been examined as prognostic variables [6, 17, 20]. Our data support the consensus that there is no difference in survival between limb salvage surgery and amputations. Furthermore, we show that patients who undergo a major amputation involving a limb girdle have poor survival. These amputations are usually for the larger, less resectable tumors and so selection bias influences the results. Furthermore, the data should be viewed with caution because there was no information on margins. Nonetheless, major amputations were the only category with stable, durable outcomes (42% survival at 5 and 10 years). The continued deterioration of results in patients who had limb-preserving surgery suggests long-term survival data are needed to judge the outcomes of this procedure.

The treatment of osteosarcoma in Singapore is uniform given the small country size and availability of largely socialized health care heavily funded by the government

and the limited but consolidated experience of these patients. Hence, there was no difference in survival between the institution-specific data and the national data in Singapore. Contrast this with the situation in the United States where there is a large difference between institutional and national data, yet East Asians in both countries had similar survival (Fig. 1D). Because Singapore national survival data were similar to Memorial Sloan-Kettering Cancer Center and National University of Singapore data, we surmise that East Asians in the United States had superior survival. East Asians had a higher proportion of smaller tumors and hence possibly were being diagnosed earlier. These tumors were small enough that limb salvage surgery could be performed and they were more commonly operated on in the 1990s and in states where treatment was associated with better survival results. However, even when demographic factors were accounted for in multivariate analysis, it was found that East Asians were inherently better survivors. A number of possibilities exist including racial differences in drug metabolism and efficacy. For example, there is a high prevalence of alcohol dehydrogenase and glucose-6-phosphatase deficiency in East Asians [14, 21]. Alcohol dehydrogenase has been implicated in the metabolism of cyclophosphamide [18]. Ethanol may potentiate doxorubicin toxicity [5, 15]. Alterations in enzymatic pathways may mean that in these patients, drugs are not as efficiently metabolized and have a higher bioavailability. There is insufficient information to examine the many hypotheses that are generated from these data.

In summary our data support the present literature in identifying various prognostic factors for patient survival with osteosarcoma. Ethnicity may have an impact on survival. This suggests that demographics are a confounding variable in survivorship analyses that require further analysis in clinical series [8, 10]. It also highlights that research into varied fields such as ethnic differences in medical care delivery and drug metabolism have the potential to improve the management and outcome of osteosarcoma.

Acknowledgments We express our gratitude to Elyn R. Riedel, Department of Biostatistics and Epidemiology, Memorial Sloan-Kettering Cancer Center, for her invaluable assistance in statistical analysis.

References

1. Bacci G, Briccoli A, Ferrari S, Longhi A, Mercuri M, Capanna R, Donati D, Lari S, Forni C, DePaolis M. Neoadjuvant chemotherapy for osteosarcoma of the extremity: long-term results of the Rizzoli's 4th protocol. *Eur J Cancer*. 2001;37:2030–2039.
2. Bacci G, Ferrari S, Longhi A, Picci P, Mercuri M, Alvegard TA, Saeter G, Donati D, Manfrini M, Lari S, Briccoli A, Forni C; Italian Sarcoma Group/Scandinavian Sarcoma Group. High dose ifosfamide

- in combination with high dose methotrexate, Adriamycin and cisplatin in the neoadjuvant treatment of extremity osteosarcoma: preliminary results of an Italian Sarcoma Group/Scandinavian Sarcoma Group pilot study. *J Chemother.* 2002;14:198–206.
3. Bureau of Economic Analysis, US Department of Commerce; Per Capita Personal Income by State. Available at: <http://bber.unm.edu/econ/us-pci.htm>. 2004. Accessed November 25, 2004.
 4. Enneking WF. *Musculoskeletal Tumor Surgery*. ed 1. New York, NY, USA: Churchill Livingstone; 1983.
 5. Ganey PE, Thurman RG. Ethanol potentiates doxorubicin-induced inhibition of cell survival in cultured Chinese hamster ovary cells. *Cancer Res.* 1991;51:2036–2040.
 6. Gherlinzoni F, Picci P, Bacci G, Campanacci D. Limb sparing versus amputation in osteosarcoma. Correlation between local control, surgical margins and tumor necrosis: Istituto Rizzoli experience. *Ann Oncol.* 1992;3(Suppl 2):S23–S27.
 7. Greene FL. *AJCC Cancer Staging Manual*. ed. 6. New York, NY, USA: Springer-Verlag; 2002.
 8. Guo W, Xu W, Huvos AG, Healey JH, Feng C. Comparative frequency of bone sarcomas among different racial groups. *Chin Med J (Engl)*. 1999;112:1101–1104.
 9. Huvos AG. *Bone Tumors—Diagnosis, Treatment & Prognosis*. ed. 2. Philadelphia, PA, USA: WB Saunders Co; 1991.
 10. Huvos AG, Butler A, Bretsky SS. Osteogenic sarcoma in the American black. *Cancer.* 1983;52:1959–1965.
 11. Huvos AG, Rosen G, Marcove RC. Primary osteogenic sarcoma: pathologic aspects in 20 patients after treatment with chemotherapy en bloc resection, and prosthetic bone replacement. *Arch Pathol Lab Med.* 1977;101:14–18.
 12. Jaffe HL. *Tumors and Tumorous Conditions of the Bones and Joints*. Philadelphia, PA, USA: Lea & Febiger; 1958.
 13. Jaffe N. Recent advances in the chemotherapy of metastatic osteogenic sarcoma. *Cancer.* 1972;30:1627–1631.
 14. Lai HC, Lai MP, Leung KS. Glucose-6-phosphate dehydrogenase deficiency in Chinese. *J Clin Pathol.* 1968;21:44–47.
 15. Liu Y, Thurman RG. Potentiation of Adriamycin toxicity by ethanol in perfused rat liver. *J Pharmacol Exp Ther.* 1992;263:651–656.
 16. Marcove RC, Mike V, Hajek JV, Levin AG, Hutter RV. Osteogenic sarcoma under the age of twenty-one. A review of one hundred and forty-five operative cases. *J Bone Joint Surg Am.* 1970;52:411–423.
 17. Meyers PA, Heller G, Healey J, Huvos A, Lane J, Marcove R, Applewhite A, Vlamis V, Rosen G. Chemotherapy for nonmetastatic osteogenic sarcoma: the Memorial Sloan-Kettering experience. *J Clin Oncol.* 1992;10:5–15.
 18. Parekh HK, Sladek NE. NADPH-dependent enzyme-catalyzed reduction of aldophosphamide, the pivotal metabolite of cyclophosphamide. *Biochem Pharmacol.* 1993;46:1043–1052.
 19. Rosen G, Nirenberg A, Caparros B, Juergens H, Kosloff C, Mehta BM, Marcove RC, Huvos AG. Osteogenic sarcoma: eight-percent, three-year, disease-free survival with combination chemotherapy (T-7). *Natl Cancer Inst Monogr.* 1981;56:213–220.
 20. Simon MA, Aschliman MA, Thomas N, Mankin HJ. Limb-salvage treatment versus amputation for osteosarcoma of the distal end of the femur. *J Bone Joint Surg Am.* 1986;68:1331–1337.
 21. Teng YS. Human liver aldehyde dehydrogenase in Chinese and Asiatic Indians: gene deletion and its possible implications in alcohol metabolism. *Biochem Genet.* 1981;19:107–114.
 22. *The Surveillance, Epidemiology, and End Results (SEER) Program*. National Cancer Institute. Available at: <http://seer.cancer.gov>. 2004. Accessed November 18, 2004.
 23. *US Cancer Statistics Working Group. United States Cancer Statistics: 2000 Incidence and Mortality*. Atlanta, GA, USA: US Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2000.
 24. Zalupski MM, Rankin C, Ryan JR, Lucas DR, Muler J, Lanier KS, Budd GT, Biermann JS, Meyers FJ, Antman K. Adjuvant therapy of osteosarcoma—a Phase II trial: Southwest Oncology Group study 9139. *Cancer.* 2004;100:818–825.