Original Article

Demographic Determinants of Survival in Osteosarcoma

Saminathan S Nathan, [1]*FAMS*, John H Healey, [2]*FACS*,

Abstract

Introduction: Osteosarcoma treatment has experienced a renaissance in the last 3 decades with the institution of multimodality treatment involving multiagent chemotherapy and surgery. Yet globally, treatment success has stagnated at about 70% survival at 5 years in most single institution series. We performed survival analyses on 2 national databases in 2 countries and compared these with corresponding institution specific survival. Materials and Methods: All patients with the diagnostic code of non-metastatic intramedullary osteosarcoma in the long bones of the upper and lower limbs less than 30 years of age were selected from the Surveillance Epidemiology and End Result (SEER) database to ensure uniformity with respect to disease and treatment. We studied the factors: ethnicity, gender, age, grade, histology, size, site, surgery, compartmentalisation, number of primaries and venue of treatment for their contribution to survival. In addition, the data were stratified into 3 decades (seventies, eighties and nineties) to account for variations due to the evolution of treatment paradigms and imaging modalities. Results: Institution-specific survival was predictably better than national survival in the 4 databases. One thousand patients were selected from the SEER database. Oriental descent, state-specific treatment, female gender, treatment in the nineties, low-grade disease, intra-compartmental disease, small size, wide resections as opposed to forequarter or hindquarter amputations, and single primaries were good prognostic factors on univariate analysis as well as multivariate analysis ($P < 0.05$). Survival was better in the more affluent states ($P < 0.05$). Males were affected at an older age than females ($P = 0.004$). Blacks tended to have larger tumours although their overall survival was similar to whites. Orientals were more likely to be treated in the nineties with wide resections for smaller tumours and were located around states associated with good treatment. Orientals in Singapore and the United States had the same survival ($P = 0.45$). Survival in Orientals in Singapore was not significantly different from other races. The standard of healthcare for osteosarcoma varies greatly across the United States but is uniform in Singapore. Hence the observed differences in the United States were likely due to socioeconomic factors. Conclusion: This analysis confirms the importance of a number of prognostic variables in osteosarcoma and suggests the possibility of an ethnic and economic bias for good survival.

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Key words: Cancer, Ethnicity, Race, Sarcoma, Socioeconomic

Introduction

The treatment of osteosarcoma has seen tremendous improvements over the last 3 decades of the twentieth century.[1-5] Over the last decade it appears that results of treatment have stagnated.[6-8]

Before 1972, the mainstay of treatment for osteosarcoma had been surgery alone with dismal results.[3] Survival in the order of 17% to 20% was the norm. With the advent of methotrexate in the treatment of metastatic osteosarcoma, a new era began in which multimodality treatment involving multiagent chemotherapy and surgery redefined survival becoming the standard of care a decade later.[2,5] Survival by this time had reached 70% and was achieved in cooperative group studies worldwide. Multiagent chemotherapy with 3 of the 4 most active drugs (doxorubicin, platinum, high dose methotrexate and ifosfamide) became the standard in the nineties.[4] The disease-free success rates have plateaued at about 60% to 70% globally in most single institution series.[4,6-8]

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One reason that there has been so little recent progress in the treatment of osteosarcoma is that this disease is rare. Based on the National Cancer Institute United States Cancer Statistics for 2000 (accessed 18 November 2004), there were only 360 cases of osteosarcoma in patients under 20 years of age (the age of peak incidence) compared to 186,839 cases of breast cancer and 187,415 cases of prostate cancer in the same time period.[9] There is a ceiling effect whereby it is difficult to document an improvement due to current success and small case numbers. This is compounded by heterogeneity in the disease presentation, histopathology and epidemiology. Published series about osteosarcoma lack the power to detect variations in outcome based on demographic factors. We evaluated the contribution of demographic factors to survival from the Surveillance, Epidemiology and End Result (SEER) database that has tabulated the incidence of cancer since 1972.[10] This was compared with the Singapore Cancer Registry database to account for methodical bias in an international setting. The presence of any significantly different risk factor would be valuable in determining any bias that may be inherent in various published series.

Materials and Methods

Permission was obtained from the National Cancer Institute for the use of SEER data.[10] All patients 30 years of age or younger with the diagnosis of non-metastatic osteosarcoma in the intramedullary portion of long bones of the upper and lower limbs were chosen for analysis. This search criterion was used to ensure that the group would be an epidemiologically homogenous cohort—one that constitutes about 70% to 83% of classic osteosarcoma in the most prevalent age group.[10-12] This was compared to data from the Singapore Cancer Registry and institution-specific databases of the authors.

The various ethnic types as indicated in the SEER database were reclassified for the purpose of this study into 4 groups: Black, White, Oriental and Others (Table 1). Data were analysed both in terms of these 4 groups as well as between Orientals and Others (Fig. 1). Data among the Orientals were compared between the 2 countries. There were 12 centres throughout the United States from which SEER data were recorded between 1973 and 2000. These were reclassified into 10 states and assessed for survival. States that were found to have significantly different survival were compared with those that had significantly better survival. The states were ranked by mean per capita income between 1973 and 2000 as recorded by the US Department of Commerce[13] to analyse economic influence on survival. By definition, states that ranked above 25 of the 50 United States were considered relatively affluent. Similarly, survival data was stratified into 3 categories according to the affluence of these states with 3 states in the upper income level, 4 in the middle income level and 3 in the lower income level.

Table 1. Reclassification of Subjects Based on Race and Ethnicity

Study Classification	Database Classification	Number
Oriental	Chinese	17
	Filipino	28
	Japanese	15
	Kampuchean	2
	Korean	6
	Vietnamese	4
Black	Black	133
White	White	742
Others	American Indian/ Alaska Native	17
	Hawaiian	15
	Samoan	2
	Others	19

Gender was recorded in the database as male or female. Age was categorised into 3 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 seventies), between 1981 and 1990 (the eighties) and 1991 and 2000 (the nineties) to account for the era-dependent treatment philosophies in osteosarcoma and improvement in imaging modalities which evolved stepwise over these 3 decades. The 4-part system for grade was reclassified into high or low-grade consistent with the World Health Organization, International Union Against Cancer (UICC), 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. Site of disease was analysed 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).[14] The number of primaries that the patient sustained at the time of diagnosis of osteosarcoma was reclassified as single versus multiple primaries. Survival in number of months and status at last review was available from the database.

Univariate analysis was performed using the method of Kaplan and Meier with log rank analysis of significance. Patients with missing data, as was the case for grade, surgery, compartmentalisation and size, especially in patients from the seventies, were excluded from univariate analysis. Their specific frequencies are quantified in the results section.

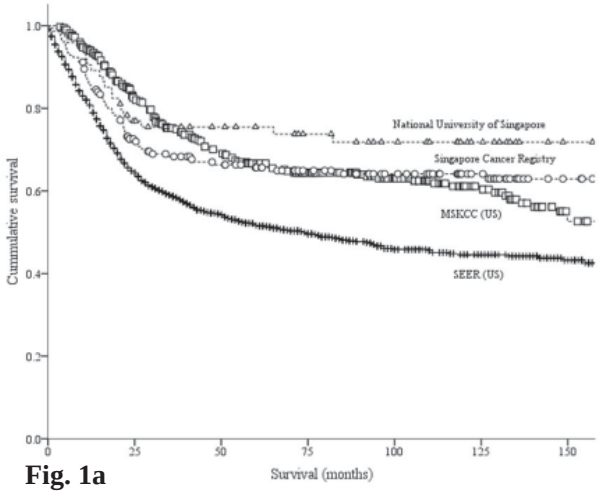

Fig. 1a

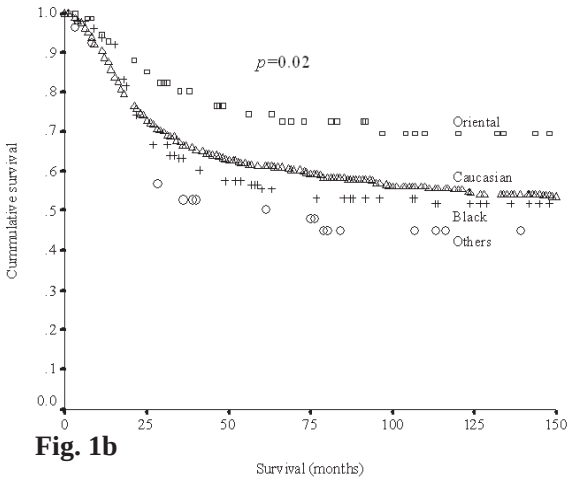

Fig. 1b

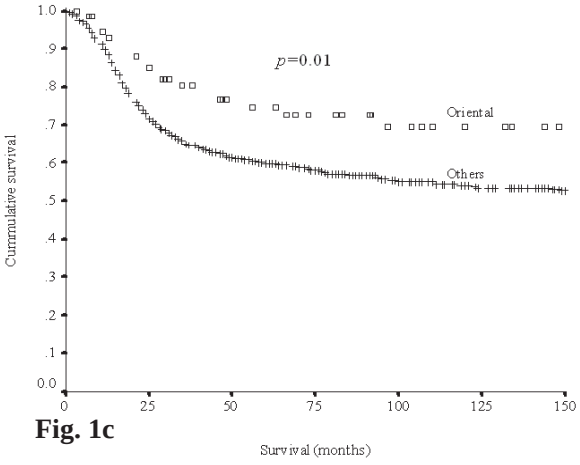

Fig. 1c

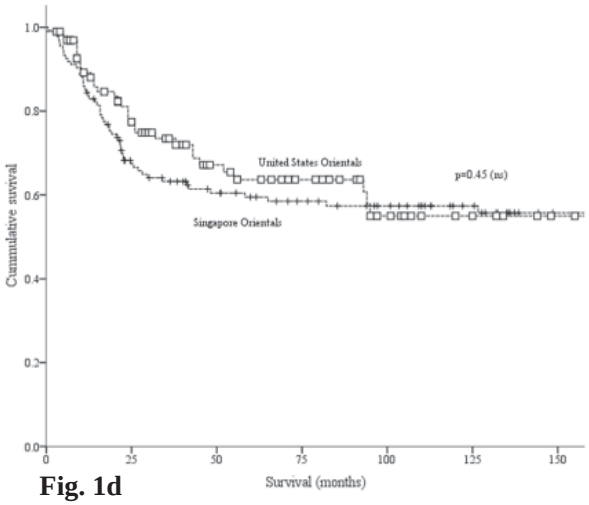

Fig. 1d

Fig. 1(a). Survival in the compared databases were fairly typical with institution-specific survival (viz National University of Singapore and Memorial Sloan-Kettering Cancer Center in the United States) registering better survival than nationwide databases (viz Singapore Cancer Registry and Surveillance Epidemiology and End Results in the United States). Patients of Oriental descent have the best survival in the SEER database. This is seen when patients of Oriental descent are compared both to individual groups (b) and all others (c). Nevertheless, when the Orientals in Singapore and those in the United States were compared, there was no statistical difference in survival between them (d).

Cox regression multivariate analysis was performed on all variables found to be significant by univariate analysis. (Table 2). Student's t-test was used as a test for significance in continuous variables and the chi-squared 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). All statistical analysis was performed using SPSS version 11.5 for Windows NT (Chicago, IL). Data, where relevant, are presented as mean ± standard deviation. Statistical significance was defined as $P < 0.05$.

Results

Comparable patients with high grade osteosarcoma who had undergone chemotherapy were identified from the SEER database, Singapore Cancer Registry, National University of Singapore and Memorial Sloan-Kettering Cancer Center. 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. There was no statistically significant difference in survival between the Singapore Cancer Registry survival and either of the 2 institutional databases ($P > 0.1$) and these were all statistically different from the SEER ($P < 0.0001$) (Fig. 1a). Survival amongst Orientals in the United States as recorded by the SEER (n = 98) and that amongst the Orientals in Singapore as

Table 2. Summary of Significant Prognostic Variables on Univariate Analysis

Factor	Number of Patients	Multivariate Analysis (*P* value)[2]	Five-year Survival (%)	Ten-year Survival (%)
Complete data model				
Gender				
Female	435	0.01	64	59
Male	565	1	59	52
Race				
Oriental	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				
Standard results	783	0.02	64	59
Poor 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
Incomplete data model*				
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
Compartmentalisation				
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

*Despite being incomplete, the remaining data were all significant in a separate model incorporating complete and incomplete data. Female gender, Oriental descent, favourable venues, latter decades of treatment and single primaries were independently predictive of good survival.

recorded by the Singapore Cancer Registry (n = 135) was not statistically different ($P = 0.45$).

Between 1973 and 2000, there were 2363 patients with intramedullary osteosarcoma recorded in the SEER database. Of these, there were 1000 patients with non-metastatic intramedullary osteosarcoma of the long bones in the upper and lower extremities in patients aged 30 years and younger. Overall, survival was 61% at 5 years and 55% at 10 years in this cohort.

The patients were aged (15 ± 6) years. There were 435 females of (15 ± 6) years of age and 565 males of (16 ± 5) years of age. This age difference was statistically significant ($P = 0.004$).

There were 172 (17%) patients in the first decade, 663 (66%) in the second and 165 (17%) patients in their third decade of life. Ethnicity comprised 6 categories reclassified as Orientals, 5 categories reclassified as Others, Blacks and Whites. Accordingly there were 742 (74%) Whites, 133 (13%) Blacks, 72 (7%) Orientals and 53 (5%) Others (Table 1). 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. Tumour 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 4 (2%) small cell osteosarcoma. The majority of osteosarcoma 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 done 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. Compartmentalisation 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 1 primary in 972 (97%) cases, 2 primaries in 27 (3%) cases and 3 primaries in 1 (0.1%) case (Table 2). Primaries were reclassified as single (1 primary) versus multiple (2 or 3 primaries) for subsequent analysis.

Female gender was a good prognostic parameter (Fig. 2). Sixty-four percent and 59% of females were alive at 5 and 10 years versus 59% and 52% of males ($P = 0.04$). Although this difference was marginal it was found to be independently significant on multivariate analysis.

In the seventies, the concepts of multimodality treatment involving chemotherapy and surgery began to develop. In the eighties, these concepts were gradually adopted by centres involved in the care of patients with osteosarcoma. In the nineties, multiagent chemotherapy and surgery became the standard of care. Concurrently, imaging modalities continued to improve. It was important to account for this evolution of care in survivorship risk analysis (Fig. 3). Our

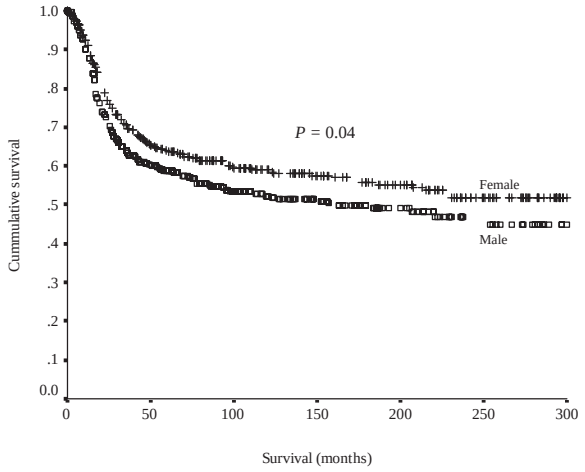

Fig. 2. Females did better than males. Although marginal on univariate analysis this was borne out by multivariate analysis.

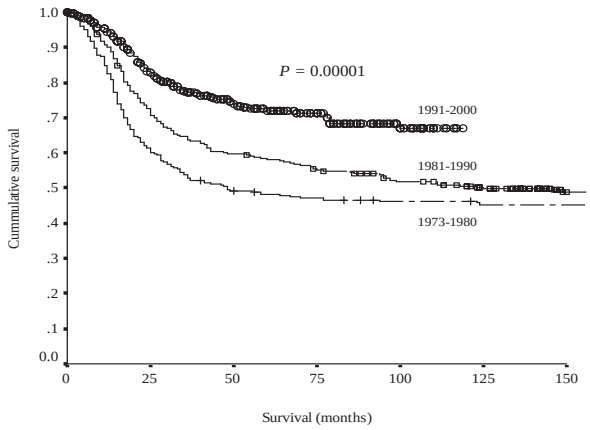

Fig. 3. Patients survived progressively better over the 3 decades from the seventies to the nineties. Classification in this manner allowed for the data to be analysed along the lines of known changes in management paradigms. In the seventies, surgery was the mainstay of treatment. In the eighties, a heterogenous mix of patients occurred while the concepts of chemotherapy coupled with surgical resection were adopted. In the nineties, the management combining chemotherapy and surgery was considered standard. Together with this, imaging modalities had also advanced allowing better delineation of tumours which in turn translates to better local control of disease.

analysis shows that survival gradually improved over the 3 decades in line with this evolution ($P = 0.00001$). This remained significant on multivariate analysis and was a potential confounding variable for the subsequent analysis.

Survival was remarkably skewed by 2 states that had significantly worse survival compared to the remaining 8 ($P = 0.0002$). There were no differences in survival among the 8 states in question. Between these 2 groups the states with poor survival had 5- and 10-year survival rates of 50 and 44 months versus 60 and 59 months among the 8 others (Fig. 4). Interestingly, within the 2 states associated with

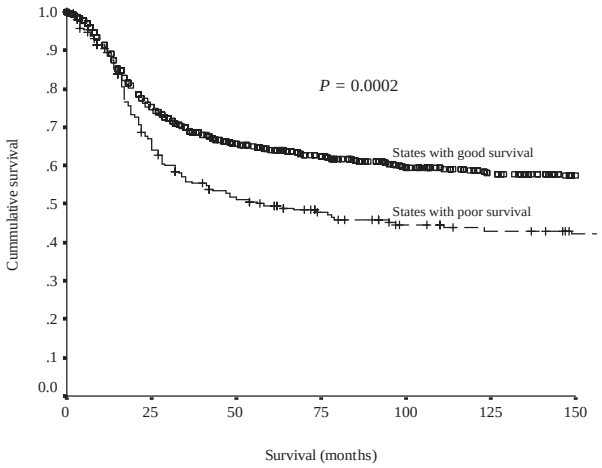

Fig. 4. Patients recorded by 2 states performed significantly worse than in the other 8 states. On multivariate analysis, this factor remained significant. Of note, treatment in the eighties in states with poor survival was actually worse compared to the seventies and nineties making survival differences through the 3 decades insignificant.

poor prognosis, survival in the eighties was worse than that in the seventies and nineties making the difference in survival across the 3 decades statistically insignificant. In the remaining 8 states, survival improved predictably across the 3 decades ($P = 0.00001$). There was no apparent bias due to 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, it was noted that there was 1 of 4 states in the non-affluent half and 1 of 6 in the affluent half of the United States associated with poor prognosis. This difference was not significant. Survival in the 3 most affluent states (66% and 58% survival at 5 and 10 years) was better than that in the 3 least affluent states (56% and 52% survival at 5 and 10 years) and this difference was significant ($P < 0.05$). There was no significant difference in survival between the middle 4 states and that in the most or least affluent states.

Low-grade disease was a significant ($P = 0.03$) positive predictor of survival among the 40% of patients for whom it was recorded (Fig. 5). In multivariate analysis, comparison was between low- and high-grade disease alone which was significant (Table 2). It was noted that when low-grade disease was analysed with respect to the decade of treatment, patients treated in the seventies had low survival rates (56% at 5 and 10 years) and this progressively improved over the 3 decades (5- and 10-year survival rates 80% and 73% in the eighties and 5- and 10-year survival rates were 87% and 87% in the nineties). There was a significant difference in survival in low-grade disease treated in the seventies and

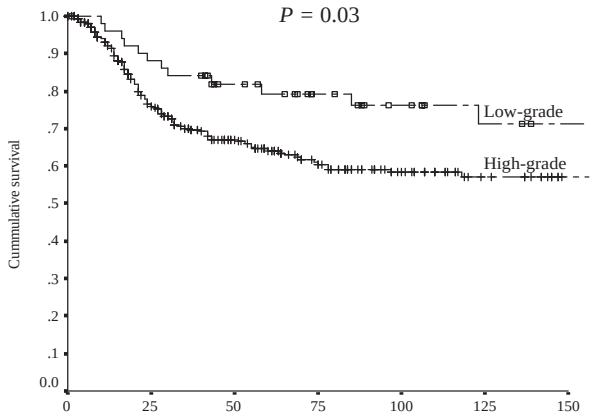

Fig. 5a

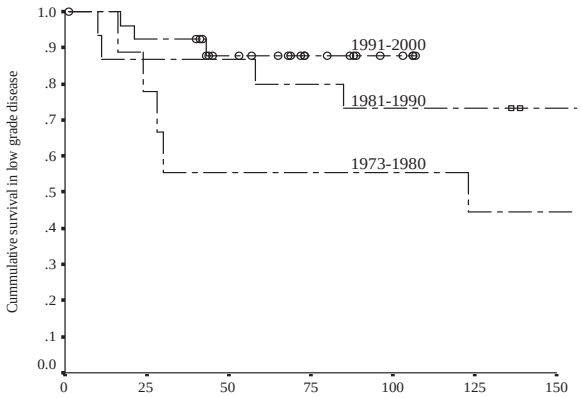

Fig. 5b

Fig. 5(a). Patients with higher grade of disease faired poorly compared to those with low-grade disease. Low- and high-grade osteosarcomas are fundamentally different with respect to prognosis and hence the utility of chemotherapy. Their inclusion here was to account for the low incidence of dedifferentiation and to account for significance in multivariate analysis. The patients with low-grade disease have a remarkably poor survival rate approaching 70% at 10 years. This is unusual considering that surgery should not have changed over the years and that there is no adjuvant treatment for low-grade disease. When stratified for decade of treatment (b), we demonstrate that patients with low-grade disease performed progressively better in recent times. This is likely due to the evolution of local imaging modalities (e.g. magnetic resonance imaging) that would translate to better local control.

nineties ($P = 0.04$).

Patients who had wide excision for high-grade osteosarcoma survived significantly longer than those who had major amputations involving limb girdles ($P = 0.004$). This was significant on multivariate analysis (Fig. 6). There was no significant difference in survival between wide excisions, radical resections and amputations in 30% of cases for whom surgery was recorded. In patients who had major amputations, survival remained constant at 42% over 10 years. In contrast, patients in all other categories had survival rates that gradually deteriorated over 10 years (Table 2). Major amputations, unlike limb salvage procedures, had durable outcomes. In addition, when stratified for treatment

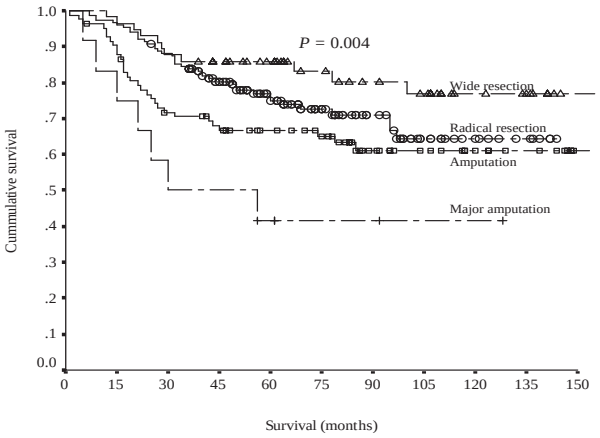

Fig. 6. Patients with wide resections fared the best in this cohort while those for whom major amputations (i.e. forequarter and hindquarter) were done did poorly. The other patients clustered between these two.

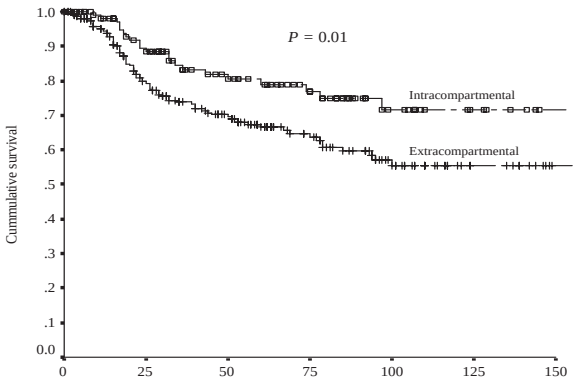

Fig. 7. Patients with extracompartmental disease faired poorly next to those with intracompartmental disease. This was independently prognostic of survival even when controlled for size.

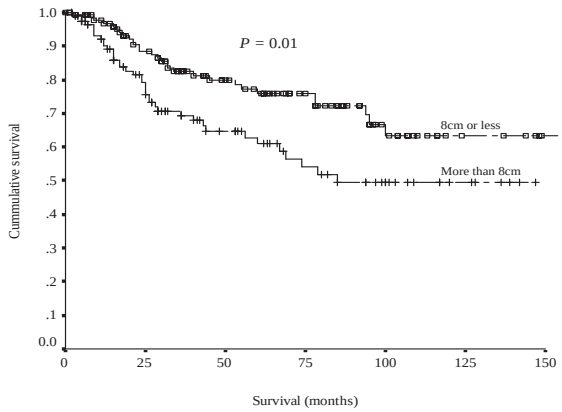

Fig. 8. Patients with large tumours faired poorly next to those with small tumours.

decade, there were significantly more limb preserving procedures in the nineties than there were in the eighties ($P = 0.02$). Limb preservation procedures were performed in 38 of 67 patients in the eighties and 169 of 235 patients in the nineties. Data from the seventies were not captured

Table 3. Race Stratified for the Major Prognostic Factors

	Race							
	Oriental		Black		White		Others	
	n	%	n	%	n	%	n	%
Gender								
Female	33	(46)	53	(40)	331	(45)	18	(34)
Male	39	(54)	80	(60)	411	(55)	35	(66)
Age (years)								
1 to 10	14	(19)	27	(20)	124	(17)	7	(13)
11 to 20	50	(69)	87	(65)	486	(65)	40	(76)
21 to 30	8	(11)	19	(14)	132	(18)	6	(11)
Venue								
Standard results	70	(97)	91	(68)	583	(79)	39	(74)
Poor 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	(54)	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	(25)	7	(17)	40	(19)	3	(17)
Radical resection	15	(54)	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)
Compartmentalisation								
Intracompartmental	14	(38)	20	(38)	72	(28)	6	(43)
Extracompartmental	23	(62)	33	(62)	183	(72)	8	(57)
Size								
8 cm or less	17	(77)	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)

Note: There were relatively more Oriental patients treated in the nineties who had limb preserving surgery for small tumours in states with standard survival results (underlined) that could have accounted for their better performance.

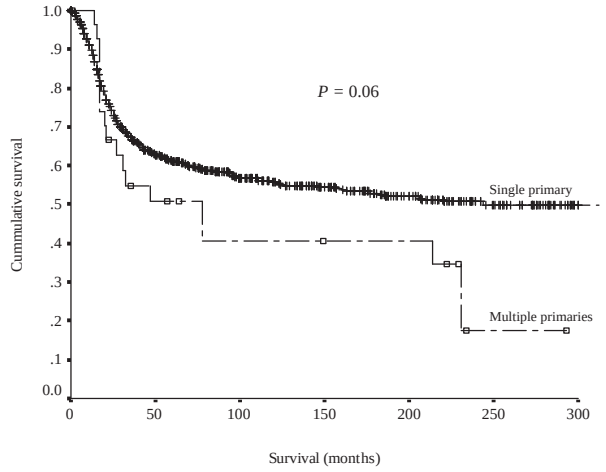

Fig. 9. Patients with single primaries fared better than those with multiple primaries. There was a high chance of a beta error—there were only 28 individuals with multiple primaries next to the 972 individuals with single primaries. Also, it was demonstrated in the larger database that number of primaries was a significant risk factor (data not shown). Hence, despite the statistically weak association, it was decided to include this factor in multivariate analysis.

in the database.

We found a significant difference in survival between intracompartmental and extracompartmental disease (P = 0.01) among the 36% of cases for whom compartment was recorded. This was significant on multivariate analysis (Fig. 7).

Small size was a good prognostic indicator (P = 0.01) compared to large size (Fig. 8). Multivariate analysis held size to be an independent predictor when small size was compared to large size among the 24% of cases for which size was recorded.

Patients of Oriental descent were noted to perform significantly better (P = 0.01) than the other ethnic groups in terms of survival (Fig. 1b). Five- and 10-year survival was 75% and 69% as opposed to 60% and 54% respectively among all others (Fig. 1c). When stratified for all parameters assessed in the study, we demonstrate that 4 possible confounding variables exist among Orientals (Table 3). Compared to the Whites, Oriental patients tended to have smaller tumours (P = 0.06), which were resectable by limb preservation procedures (P = 0.25) and were more commonly treated in the nineties (P = 0.07). The overwhelming majority of Orientals were treated in states associated with good survival (P = 0.00001). When these factors were considered in multivariate analysis, Oriental ethnicity had diminished significance (P = 0.07). Nevertheless, when the incomplete tumour and treatment data were excluded from multivariate analysis (i.e. grade, surgery, compartmentalisation and size), Oriental ethnicity remained significant (P = 0.04).

Discussion

This study is noteworthy for its large patient cohort spanning 3 critical decades in the evolution of osteosarcoma treatment in 2 countries. In this time, it is interesting to note that the survival benefit among patients of Oriental descent is significantly greater than that for patients of other ethnicities. Furthermore the finding that the standard of care for osteosarcoma had evolved in most states in the United States while in some states they had remained the same over the 3 decades is enlightening. From our review, this is the first study to highlight that osteosarcoma may have an ethnic and socioeconomic determinant of survival.[15,16]

The other demographic and tumour-related factors found to be independently significant for survival, namely, gender, decade of treatment, grade, compartmentalisation, size and number of primaries (Fig. 9) have been shown to be of various degrees of significance in previous studies.[1-8] This national registry lends further credence to those findings. Surgical procedures have been examined as prognostic variables. Our data support the consensus that there is no significant difference in survival between limb salvage surgery and amputations.[4,17-19] Furthermore, we show that patients who underwent a major amputation involving a limb girdle have poor survival. These amputations are usually for the larger, less resectable tumours and so selection bias influences the results. 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 that long-term survival data are needed to judge the outcomes of this procedure. It may be difficult in this context of a national database to determine the cause of death as being relevant to osteosarcoma and will remain cautious on these conclusions which are unlikely to be resolved given the present model of data collection.

The deficits in reported data present potential confounding bias. Missing data is inherent to most large databases and their treatment remains controversial. The comparisons of the tumour and treatment variables may only be valid if we assume that the absent data comprised a balanced distribution that matches that of the collected data. This is not unreasonable given the high rate of null reporting (60% to 76%) in the 4 categories highlighted above. In addition, by excluding the absent data in univariate analysis, only significant variables are entered into multivariate analysis. In multivariate analysis, only comparison between recorded data were made—null data were included for multivariate modeling but not actually used for comparison of factors. In this manner, bias due to deficits in reporting is minimised. Nevertheless, the conclusions about the tumour and treatment variables should be viewed with caution.

In distinction, demographic data were complete for this large study, so conclusions regarding these variables can be made with much greater confidence. The treatment of osteosarcoma in Singapore is uniform given the small country size and availability of largely socialised healthcare heavily funded by the government and the limited but consolidated experience of these patients. Hence there was no statistical 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 statistical difference between institutional and national data (P <0.0001). Yet, Orientals in both countries had virtually identical survival rates (Fig. 1d). Since Singapore's national survival data was similar to that of Memorial Sloan-Kettering Cancer Center and National University of Singapore, we may surmise that Orientals in the United States were receiving superior care. Orientals were noted to have a higher proportion of smaller tumours and hence possibly were being diagnosed earlier. These tumours were small enough that limb salvage surgery could be performed and they were more commonly operated on in the nineties 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 Orientals 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 Orientals.[20,21] Alcohol dehydrogenase has been implicated in the metabolism of cyclophosphamide.[22] Ethanol may potentiate doxorubicin toxicity.[23,24] Alterations in enzymatic pathways may mean that in these patients, drugs are not as efficiently metabolised and have a higher bioavailability. There is insufficient information to examine the many hypotheses that are generated from these data.

Conclusion

In summary, we provide results from an international comparison to the largest multi-institutional cancer database. It supports the present literature in its identification of various prognostic factors for patient survival with osteosarcoma. In addition, we offer the possibility that 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. It also highlights that research into varied fields such as ethnic differences in medical care delivery and drug metabolism has the potential to improve the management and outcome of osteosarcoma.

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REFERENCES

1. Jaffe N. Recent advances in the chemotherapy of metastatic osteogenic sarcoma. Cancer 1972;30:1627-31.
2. 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 Patho Lab Med 1977;101:14-8.
3. 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;52:411-23.
4. Meyers PA, Heller G, Healey J, Huvos A, Lane J, Marcove R, et al. Chemotherapy for nonmetastatic osteogenic sarcoma: the Memorial Sloan-Kettering experience. J Clin Oncol 1992;10:5-15.
5. Rosen G, Nirenberg A, Caparros B, Juergens H, Kosloff C, Mehta BM, et al. Osteogenic sarcoma: eight-percent, three-year, disease-free survival with combination chemotherapy (T-7). Natl Cancer Ins Monogr 1981;56:213-20.
6. Zalupski MM, Rankin C, Ryan JR, Lucas DR, Muler J, Lanier KS, et al. Adjuvant therapy of osteosarcoma--A Phase II trial: Southwest Oncology Group study 9139. Cancer 2004;100:818-25.
7. Bacci G, Ferrari S, Longhi A, Picci P, Mercuri M, Alvegard TA, et al. 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.
8. Bacci G, Briccoli A, Ferrari S, Longhi A, Mercuri M, Capanna R, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremity: long-term results of the Rizzoli's 4th protocol. Eur J Cancer 2001;37:2030-9.
9. United States Cancer Statistics: 2000 Incidence: National Cancer InstituteNorth American Association of Central Cancer Registries, 2000.
10. The Surveillance, Epidemiology, and End Results (SEER) Program. National Cancer Institute, 2004.
11. Huvos AG. Bone tumors - diagnosis, treatment & prognosis. 2nd ed. WB Saunders Company, 1991.
12. Jaffe HL. Tumors and tumorous conditions of the bones and joints. Lea and Febiger, 1958.
13. Bureau of Economic Analysis: U.S. Department of Commerce, 2004.
14. Greene FL. AJCC cancer staging manual. 6th ed. New York: Springer-Verlag Inc, 2002.
15. Huvos AG, Butler A, Bretsky SS. Osteogenic sarcoma in the American black. Cancer 1983;52:1959-65.
16. Guo W, Xu W, Huvos AG, Healey JH, Feng C. Comparative frequency of bone sarcomas among different racial groups. Chin Med J (Engl) 1999;112:1101-4.
17. 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;68:1331-7.

18. 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;3Suppl 2:S23-7.
19. Enneking WF. Musculoskeletal tumor surgery. 1st ed. Churchill Livingstone, 1983.
20. Teng YS. Human liver aldehyde dehydrogenase in Chinese and Asiatic Indians: gene deletion and its possible implications in alcohol metabolism. Biochem Genet 1981;19:107-14.
21. Lai HC, Lai MP, Leung KS. Glucose-6-phosphate dehydrogenase deficiency in Chinese. J Clin Pathol 1968;21:44-7.
22. Parekh HK, Sladek NE. NADPH-dependent enzyme-catalyzed reduction of aldophosphamide, the pivotal metabolite of cyclophosphamide. Biochem Pharmacol 1993;46:1043-52.
23. Ganey PE, Thurman RG. Ethanol potentiates doxorubicin-induced inhibition of cell survival in cultured Chinese hamster ovary cells. Cancer Res 1991;51:2036-40.
24. Liu Y, Thurman RG. Potentiation of adriamycin toxicity by ethanol in perfused rat liver. J Pharmacol Exp Ther 1992;263:651-6.