Survival trends in osteosarcoma of humerus

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Management of osteosarcoma has evolved during the last 50 years. A review of 53 cases of osteosarcoma affecting the humerus included in the Scottish Bone Tumour registry from 1950 to 2000 is presented. Survival trends and the various factors influencing survival during this period are analysed. Patients were chronologically divided into two cohorts, one presenting before 1975 (18 patients) and the other presenting after 1975 (35 patients). The second half of the study period (1975 onwards) was characterized by availability of new treatment modalities like limb salvage and chemotherapy. A distinct improvement in survival was noted during the second half of the study (35% 5 years survival post 1975 vs. 18% pre 1975, $P = 0.007$). Survival and metastasis appeared to depend on multiple factors. Chemotherapy in isolation did not significantly affect survival. Limb salvage surgery did not have an adverse effect on survival rates. This improvement in survival could be due to a change in the natural history of the disease along with advances in diagnostics and therapeutics.

Keywords: osteosarcoma, humerus, survival, chemotherapy, limb salvage.

INTRODUCTION

Osteosarcoma is the most common malignant bone tumour (Vander Griend 1996). Humerus is the third most common site of occurrence of osteosarcoma (Marcove *et al*. 1970; Marcove & Rosen 1980; Glasser *et al*. 1992). Surgical excision remains the mainstay of therapy. Historically, before the advent of chemotherapy, osteosarcomas of the extremities with no metastasis at diagnosis had a survival of only 15% to 20% (Dahlin & Coventry 1967; Marcove *et al*. 1970). Studies in the 1970s reported an improved 2-year survival rate of up to 85% using adjuvant chemotherapy (Cortes *et al*. 1974; Sutow *et al*. 1975; Rosen *et al*. 1983). Whether this change in survival is the effect of chemotherapy or is in fact due to change in natural history of the disease is controversial (Carter & Friedman 1978; Taylor *et al*. 1978). Improved diagnostic accuracy with better imaging and staging prior to surgery with more aggressive and improved surgical techniques might have contributed to change in survival pattern.

Preoperative (neoadjuvant) chemotherapy was introduced in the mid-1970s. The proposed benefits of this included, allowing more time for the preparation of custom-made endoprosthesis, early treatment of presumed micrometastatic disease, the opportunity to evaluate the histological effects of preoperative chemotherapy on the primary tumour and the opportunity to tailor the postoperative chemotherapy according to the histological response of the tumour to preoperative chemotherapy (Rosen *et al*. 1979). Recent studies using chemotherapy in adjuvant and neoadjuvant forms have shown promising results in improving disease-free survival and recurrence rate in non-metastatic osteosarcoma (Bacci *et al*. 1991, 2000), although the prognosis continues to be poor in

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Table 1. Table summarizing tumour location and treatment of patients during the two periods of the study; period 1 (1950–1974) and period 2 (1975–2000) respectively

	Number of patients							
				Surgery				
	Proximal 1/3	Mid 1/3	Distal 1/3	Biopsy only	Amputation/ disarticulation	Limb salvage	Chemotherapy	Radiotherapy
Period 1 (1950–1974)	16	1	1	9	8	1	0	14
Period 2 (1975–2000)	24	7	4	13	11	11	26	22
Total	40	8	5	22	19	12	26	36

patients with high grade osteosarcoma of the extremities and metastasis at presentation (Bacci *et al*. 2003a). Neo-adjuvant chemotherapy now enables limb salvage surgery even in cases with pathological fractures without causing an increased risk of death or local recurrence (Bacci *et al*. 2003b).

The purpose of this paper is to review osteosarcoma of the humerus over the past 50 years taking into account the change in management strategies that have occurred during this period. We have analysed survival trends of osteosarcoma of the humerus, in particular studying the effect of introduction of chemotherapy and limb salvage in the management of these tumours. In addition, we have also examined the effect of other factors relating to tumour, patient and treatment that affect survival and recurrence.

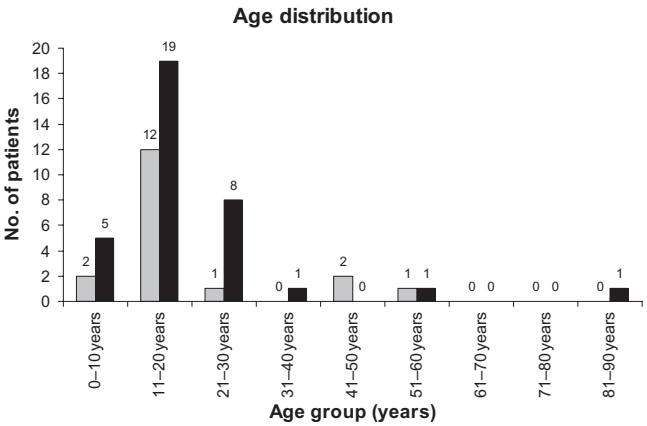

Figure 1. Age distribution of osteosarcoma of humerus: this bar chart depicts the number of patients in various age groups in period 1 (1950–1974) and period 2 (1975–2000) diagnosed with osteosarcoma of the humerus. During both periods the tumour commonly affected patients in their second decade. □, Period 1 (1950–1974); ■, period 2 (1975–2000).

MATERIALS AND METHODS

The Scottish bone tumour registry contains records of patients with bone tumours diagnosed and treated in various hospitals in Scotland. They include case histories, radiographs, treatment details, histopathology and follow-up. Records of all patients who were diagnosed as having osteosarcoma of the humerus and included in the registry between 1950 and 2000 were reviewed. Demographic details, case histories, treatment and survival of these patients were included in the analysis. Time from first presentation at the primary care centre to the time a histological diagnosis was made was defined as time to diagnosis. Survival was calculated from the time a histological diagnosis was made.

For the purposes of the study, we divided the series into two groups, those who presented before 1975 (period 1 – who were treated primarily with surgery and/or radiotherapy) and those 1975 onwards (period 2 – when chemotherapy was introduced in the management of these tumours). The survival of patients between the two groups was compared.

The software package SPSS (SPSS, Chicago, Illinois) was used to produce a series of Kaplan Meier curves and log-rank tests of significance ($P < 0.05$ is significant) on the survival rates of osteosarcoma affecting the humerus.

RESULTS

During the period 1950–2000, 53 cases of osteosarcomas involving the humerus were included in the registry. Of these, 40 cases involved the proximal third, eight cases the middle third and five cases, the distal third of the humerus (Table 1). The tumour affected most patients in the second decade (Fig. 1). Twelve patients presented with pathological fractures. Pain and swelling of the affected region was the most common presenting symptom. There were 36 males and 17 females.

Period 1 (1950–1974)

Eighteen patients presented with osteosarcoma of the humerus during this period. Sixteen (89%) of these involved the proximal humerus and one each involved the shaft and the distal humerus. Four patients presented with

pathological fracture. There was no difference in the side involved. Patients were diagnosed at an average of 7.3 weeks from the onset of symptoms (1–20 weeks). Diagnosis was made in all cases by incision biopsy. Seventeen patients had conventional osteosarcoma and one had parosteal osteosarcoma.

Treatment during this period was primarily by radiotherapy and/or surgery. Fifteen patients had radiotherapy (14 proximal humeri and one shaft of humerus). The type of radiation and the number of doses varied through the period. Eight patients had radical excision (two shoulder disarticulations and six forequarter amputations). Margins were clear in all cases. Only one patient was treated by limb salvage using a fibular graft following tumour excision. Sixteen (89%) patients developed pulmonary metastasis at an average of 15 months following diagnosis (1–85 months). None of the patients developed local recurrence following radical excision.

Period 2 (1975–2000)

There were 35 patients diagnosed as having osteosarcoma of the humerus during this period. Twenty-four (68.6%) of these involved the proximal humerus, seven (20%) involved the shaft of the humerus and four (11.4%) involved the distal humerus. Eight (22.9%) patients presented with pathological fractures. Fifteen patients had involvement of the right side. Diagnosis was by incision biopsy in all cases. Patients were diagnosed at an average of 13.6 weeks following onset of symptoms (1–104 weeks). Twenty-night patients had conventional osteosarcoma, three patients had parosteal osteosarcoma, one patient had periosteal osteosarcoma and two had telangiectatic osteosarcoma.

Treatment was by chemotherapy in 26 (74.3%) patients. The drugs used and their dosages were individually tailored. Twenty-two (62.9%) patients had radiotherapy, of which 16 patients also received chemotherapy. The type of radiation and the number of doses varied between patients. Eleven (31.4%) patients had radical excision (five proximal humeral tumours, four shaft tumours, two distal humeral tumours). Of these, five patients had disarticulation of the shoulder joint and six patients had forequarter amputation. Margins were clear in all cases. One patient who had a shoulder disarticulation developed local recurrence of the tumour. Eleven (31.4%) patients underwent limb salvage surgery, of which eight had additional chemotherapy and all had additional radiotherapy. Twenty-two (62.9%) patients developed pulmonary metastasis at an average of 10.5 months following diagnosis. Of these, seven (20%) had metastasis at the time of diagnosis.

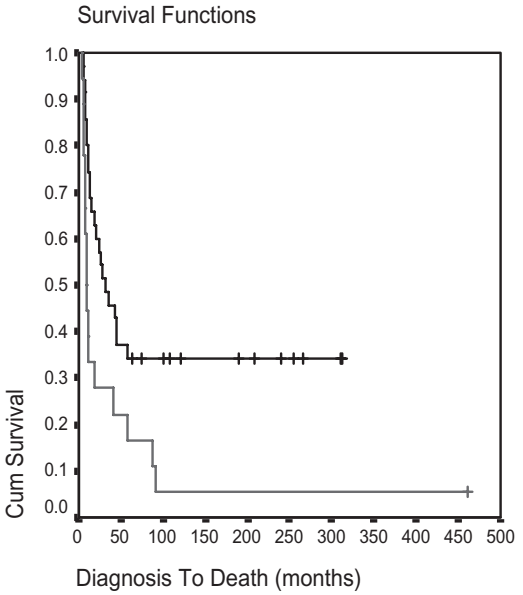

Figure 2. Survival of patients (in months) from diagnosis. The figure shows an improved survival of patients during the period post 1975, compared with those diagnosed and treated during the period 1950–1974 (35% vs. 18% 5-year survival rate respectively, $P = 0.0070$). Period: —, post 1975; +, post 1975-censored.: —, pre-1974; +, pre 1974-censored.

ANALYSIS OF SURVIVAL

Survival vs. period of diagnosis (Fig. 2)

There is a clear difference in the survival curves, with those patients in period 2 having a 35% chance of survival after 5 years. Those diagnosed during period 1 have only an 18% chance of survival after 5 years. This is a statistically significant difference ($P = 0.0070$) and reflects the impact that the introduction of neoadjuvant chemotherapy and limb salvage surgery, in the mid-1970s, had on patient survival.

Survival vs. gender (Fig. 3)

Again the graphs indicate a clear distinction between the two survival curves with female survival at almost 50% after 5 years, compared with just 15% for males. This is also a statistically significant difference ($P = 0.0126$), although it must be noted that males made up two-thirds of the total patients analysed ($n = 36$).

Survival vs. age group (Fig. 4)

The clear separation of curves shows 5-year survival for those aged 20 and above being almost 40%, and about a 20% chance of survival at 5 years for those in the 10–20

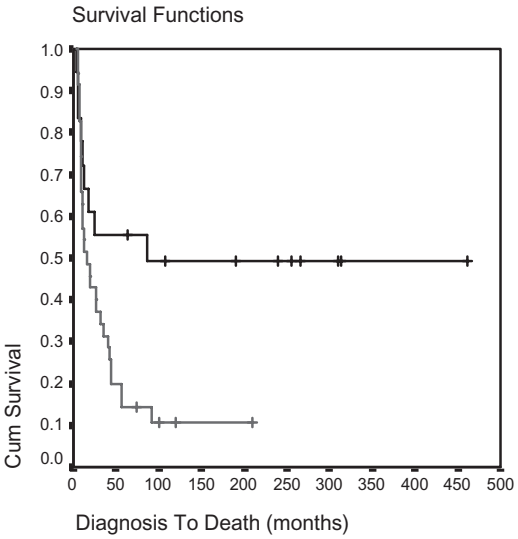

Figure 3. Survival curves for males and females. This graph shows an improved 5-year survival rate of females (50%) compared with males (15%), $P = 0.0126$. Sex: —, female; +, female-censored.: —, male; +, male-censored.

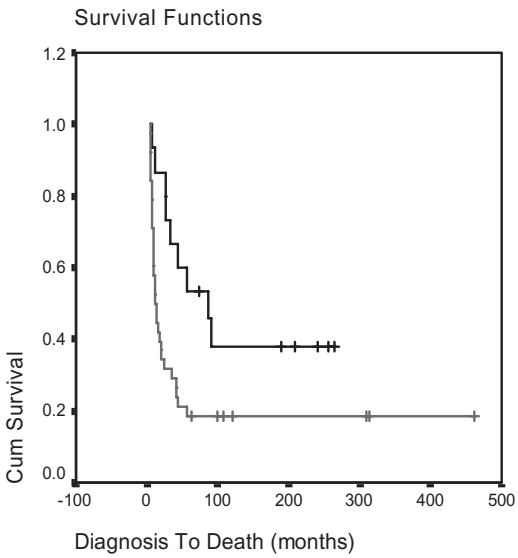

Figure 4. Figure showing survival curves for patients affected by osteosarcoma of humerus before the age of 20 years compared with those after this age. There was a significant improved survival ($P = 0.0169$) in patients over the age of 20 (40%) compared with those below this age (20%) at 5 years. Age: —, >20 years; +, 20 years-censored.: —, 0–20 years; +, 0–20 years-censored.

age bracket (the most common), the difference is statistically significant ($P = 0.0169$).

Survival vs. final diagnosis

When looking at survival against final diagnosis of tumour the log-rank test indicates a statistically significant difference ($P = 0.0165$) between the four tumour types. Both osteosarcoma parosteal and osteosarcoma periosteal have a 100% survival rate after 5 years while telangiectatic osteosarcoma has a 0% survival rate. Few conclusions can be drawn from these curves as they represent so few of the tumours ($n = 4$, 1 and 2 respectively). Conventional osteosarcomas can be looked at with a little more conviction as they made up 87% of the total group ($n = 46$) and showed a 22% chance of survival after 5 years. Moreover, by looking more closely at the two time periods, final diagnosis of tumour was a more statistically significant factor in the second period than it was in the first period ($P = 0.0690$), indicating that the chance of survival was more dependent on the diagnosis in period 2 ($P = 0.0423$).

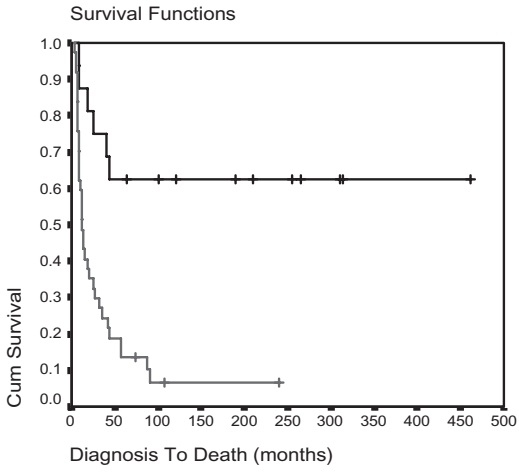

Figure 5. Figure depicting the impact of radiotherapy on survival of patients with osteosarcoma of the humerus. Patient who did not have radiotherapy have an improved 5-year survival (63%) compared with those who had radiotherapy (15%), $P = 0.001$. Radiotherapy: —, no; +, no-censored.: —, yes; +, yes-censored.

Survival vs. radiotherapy (Fig. 5)

One of the most interesting results the analysis has produced is the impact that radiotherapy has on survival of osteosarcoma of the humerus. As the graph clearly elucidates, those patients who did not have radiotherapy as a form of treatment have a far greater 5-year survival rate (approximately 63%) than those who did (approximately 15%). Again, this is a statistically significant difference (0.001) and possibly reflects the relationship between radiotherapy and metastases. Indeed, if we separate the two different groups, use of radiotherapy is a statistically significant factor in period 2 ($P = 0.0015$) when other treatment options became available, compared with period 1

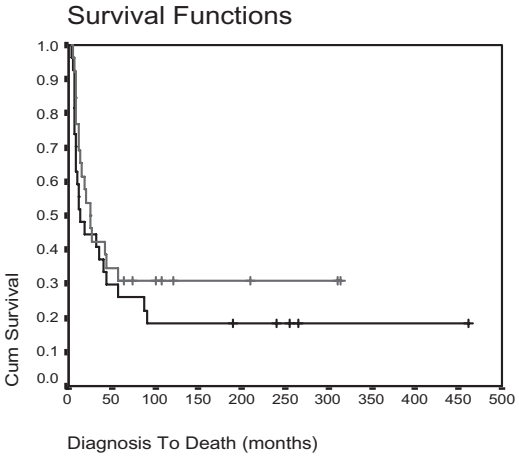

Figure 6. Figure depicting the influence of chemotherapy on the 5-year survival following osteosarcoma of the humerus. Patients receiving chemotherapy did not have a statistically significant difference in survival compared with those who did not ($P = 0.3120$). Chemotherapy: —, no; +, no-censored.: —, yes; +, yes-censored.

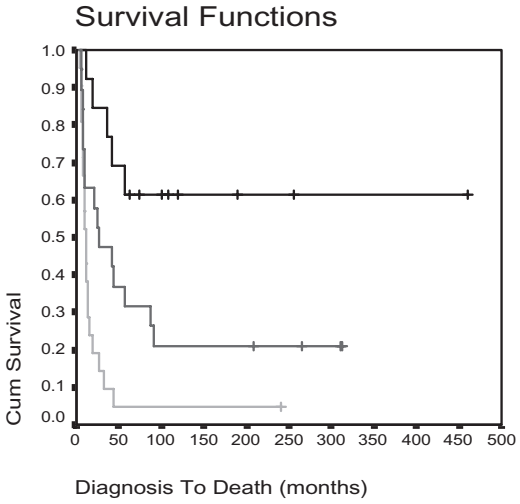

Figure 7. Survival curve of patients who have had no surgery, limb salvage surgery and amputation. This shows a significant difference between these three groups of patients ($P = 0.0001$), with those who have had limb salvage surgery having a 62% 5-year survival. 86% of patients who had no surgical intervention other than a diagnostic biopsy developed metastasis and had a survival of less than 10%. Surgery: —, none/biopsy; +, none/biopsy-censored.: —, limb salvage; +, limb salvage-censored.: —, amputation; +, amputation-censored.

where it was not a statistically significant factor ($P = 0.1536$)

Survival vs. chemotherapy (Fig. 6)

Despite the clear difference in the two survival curves shown above, there is no statistically significant difference in the 5-year survival rates between those who did receive chemotherapy as a form of treatment and those who did not ($P = 0.3120$). Those who did receive chemotherapy, though, had roughly a 30% chance of survival after 5 years compared with approximately an 18% chance for those who did not. This is to be expected after the aforementioned (*Survival vs. period of diagnosis*) statistically significant difference between period 1 and period 2 with the latter (characterized by the introduction of chemotherapy as a form of treatment) having a greater 5-year survival rate.

Survival vs. surgery (Fig. 7)

The data analysis distinctly shows the difference in survival rates depending on what type of surgery patients had. The results are statistically significant ($P = 0.0001$) with limb salvage surgery (introduced post 1975) giving around a 62% 5-year survival rate. In comparison, patients receiving amputation had just over a 30% chance of survival at 5 years and those receiving no surgery or biopsy only, with little or no chance (only one of 21 patients survived past 5 years). Indeed 86% ($n = 18$) of those who did not have surgery had metastases making their chance of 5 years survival less than 10%.

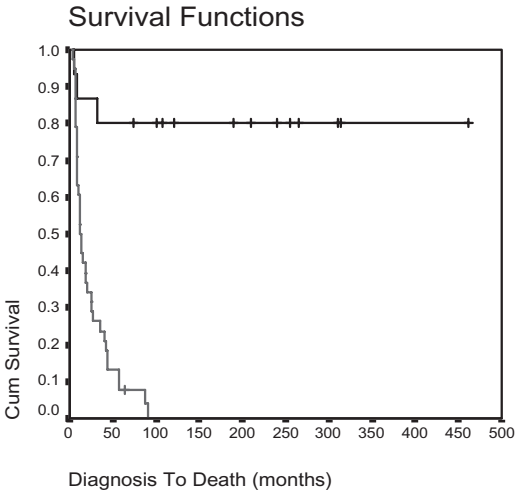

Figure 8. Survival curve of patients who had metastasis at the time of diagnoses compared with those who did not have them. Presence of metastasis significantly reduced the 5-year survival rate ($P = 0.000$). Metastasis: —, no; +, no-censored.: —, yes; +, yes-censored.

Survival vs. metastases (Fig. 8)

The graph demonstrates what is already known about all forms of cancer; survival rates are far greater if there are no

metastases. For osteosarcoma of the humerus, without metastasis, there is an 80% chance of survival at 5 years, compared with an 8% chance in the presence of metastasis. This is a statistically significant difference ($P = 0.000$).

Survival vs. other variables

A number of other variables were analysed against diagnosis to death, to determine if they had a statistically significant impact. Those which did not have a significant effect on survival and which have not been presented in more detail are 'region of bone involved', 'presence of pathological fracture', 'time to diagnosis' and 'side involved'.

ANALYSIS OF FACTORS INFLUENCING METASTASIS

Metastasis vs. age group

Our study illustrates that those in the >20 years age group have approximately a 55% chance of living without recurrence at 5 years compared with a 20% chance for those under 20. This is a statistically significant difference ($P = 0.0312$).

Metastasis vs. radiotherapy

Patients who did not receive radiotherapy as part of their treatment had a far greater chance of living metastasis free after 5 years (around 63%) compared with those who did receive it (18%). Again this is statistically significant, $P = 0.002$.

Metastasis vs. side (Fig. 9)

Another of the statistically significant differences ($P = 0.0100$) in relation to suffering metastases is that of which side of the body the original tumour was found. As the graph shows, those who had an original tumour on the left of the body had a 40% chance of living metastasis free at 5 years compared with those on the right side who had a 15% chance.

Metastasis vs. surgery (Fig. 10)

Like the survival rates, the type of surgery the patient received was a statistically significant factor influencing recurrence ($P = 0.034$). Indeed, the graph emphasizes that those who had no surgery had the least potential to be metastasis free after 5 years (16%) compared with those who did, with those having limb salvage surgery fairing best (55% chance of being metastasis free at years). Many of those patients who did not have surgery, though, presented with metastasis (as noted earlier) and this has a clear effect on their outcome.

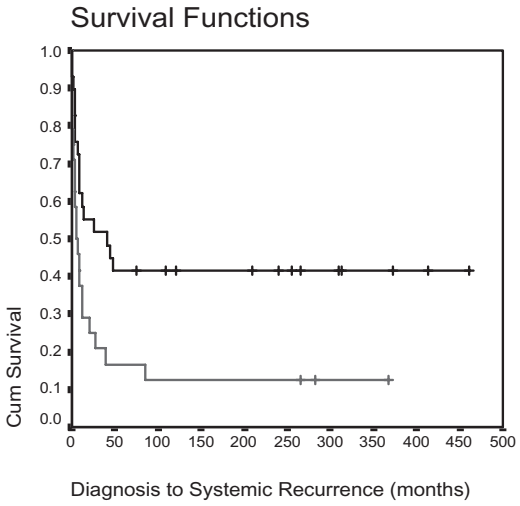

Figure 9. Graph depicting the influence of the side of the body affected by osteosarcoma of humerus in determining the metastasis free survival. Patients having osteosarcoma of the left humerus had a 40% chance of living metastasis free at 5 years ($P = 0.010$). Side involved: —, left; +, left-censored.: —, right; +, right-censored.

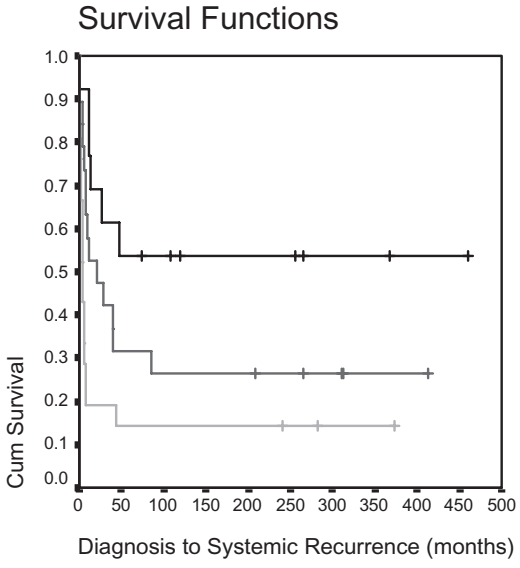

Figure 10. Graph demonstrating the relationship between type of surgery and development of metastasis. This shows a significant difference between the patients, who did not have surgery, who had an amputation and who were offered limb salvage surgery ($P = 0.034$). 16% of patients who did not have surgery were metastasis free at 5 years, while 55% of patients who had a limb salvage procedure were metastasis free at 5 years. Surgery: —, none/biopsy; +, none/biopsy-censored.: —, limb salvage; +, limb salvage-censored.: —, amputation; +, amputation-censored.

Other variables

A number of other variables were analysed against diagnosis to metastases to determine if they had a statistically significant impact. Those which did not have a significant effect on survival and which have not been presented in more detail are 'region of bone involved', 'chemotherapy', 'pathological fracture', 'time to diagnosis' and 'histology'.

DISCUSSION

'Osteosarcoma', also termed as 'osteogenic sarcoma', is characterized histologically by proliferating tumour cells which in most instances produce osteoid or immature bone. Numerous classification systems have been proposed based on location of the tumour, histological grading, type of matrix produced and radiographic appearance. Conventional osteosarcoma is the most common type of tumour encountered. Histologically, these tumours have been graded based on the degree of differentiation. Examples of high grade types are conventional and telangiectatic osteosarcoma. Periosteal osteosarcoma is an intermediate grade tumour and parosteal osteosarcoma is a low grade tumour. The histology of these tumours is known to vary widely in different areas of the same tumour (Bacci *et al*. 2003b). This tumour predominately affects patients in the second and third decades of life (Vander Griend 1996; Bramwell 2000; Klein & Siegal 2006). In our series, 40 (75.5%) patients were in the second and third decade of life. Forty-six (86.8%) patients had conventional osteosarcoma.

Survival in osteosarcomas depends on numerous factors like the age of the patient, type, grade and stage of tumour, methods of treatment and presence of metastasis. Prior to the 1970s, treatment primarily consisted of amputation with or without radiotherapy (Marcove *et al*. 1970). In our series, chemotherapy was introduced in the management of these tumours from 1975. Chemotherapy has been reported to decrease metastasis and improve survival enabling limb salvage surgery (Jaffe *et al*. 1983; Eckardt *et al*. 1985; Link *et al*. 1986). A total of 26 (74.3%) patients received chemotherapy in the second half of the study period. However, chemotherapy alone was not a statistically significant factor influencing survival. Histology of the tumour played a greater role in influencing survival. Metastasis was an important factor influencing survival with those having metastasis having poor survival as shown in other series (Saeter *et al*. 1995; Aksnes *et al*. 2006).

Chemotherapy alone did not seem to be a significant factor influencing risk of recurrence either. In the first half of the study period prior to introduction of chemotherapy, 16 (89%) patients developed pulmonary metastasis following diagnosis of the primary lesion. There were no local recurrences in patients who had amputation.

In the second half of the study period (period 2), among the 26 patients who received chemotherapy, 18 (69%) patients developed pulmonary metastasis. Seven of these 18 patients had metastasis at the time of diagnosis of the tumour before the commencement of chemotherapy and only 11 (42.3% of those who received chemotherapy) developed metastasis after commencement of chemotherapy at an average of 13.5 months following diagnosis of the primary lesion (2–48 months). Although it appears as if the overall incidence of metastasis in patients who received chemotherapy in period 2 (42.3%) was lower than in period 1 (89%), it is possible that some of these patients in period 1 may have had metastasis on presentation which were not identified early, as diagnostic techniques were not sufficiently advanced. Among the nine patients who did not receive chemotherapy in period two, four (44.4%) developed pulmonary metastasis.

Among the 11 patients who had amputation in period 2, seven (63.6%) developed pulmonary metastasis. Four patients had pulmonary metastasis at the time of diagnosis and three developed pulmonary metastasis at 5, 7 and 12 months following diagnosis. All four patients who had pulmonary metastasis at the time of diagnosis received preoperative chemotherapy.

Also in this second group, 12 patients had limb salvage surgery of which six (50%) patients developed pulmonary metastasis (one at the time of diagnosis of the primary lesion). Chemotherapy was commenced preoperatively in seven patients and post-operatively in a further two patients. Five out of the six patients who had pulmonary metastasis received chemotherapy, this being started preoperatively in four patients. Hence, if we include those patients who had metastasis diagnosed at presentation, the overall rate of metastasis during the second period is significantly lower in patients who had limb salvage.

Considering the two groups as a whole, age, surgical procedure, side involved and radiotherapy seemed to influence recurrence, with the older patients and those who had surgery especially limb salvage surgery having a lower risk of developing metastasis. We feel this is due to a combined influence of various factors. We found that patients with a right sided tumour had a higher risk of developing metastasis, the significance of this finding is unclear as this has not been reported elsewhere.

A large number of variables have influenced both the survival and risk of developing metastasis following osteosarcoma of the humerus. It is likely that there has been an interaction between these variables, with some of

them playing a greater role in determining outcome. A multivariate analysis is necessary to clarify the relative importance of each of the variables. However, this was not performed due to the relatively small numbers of patients in our study spread out over a large period, which would prevent us drawing out any meaningful conclusions. These are rare tumours: only 53 patients over 50 years in a population of 5 million. Even specialist centres are no guarantee of adequate experience and international co-operation is the best way to extend and amplify our current, somewhat inadequate, knowledge.

As the study was retrospective, we did not have access to additional material for verification of metastasis or radiological grading of tumour in all cases. Modes of investigation, histological techniques used and grading system have changed during the last 50 years. The resulting stage shift is one of the drawbacks of performing historical studies, like ours and can influence classification and comparison of results. Further studies, exploring role of changes in investigations and staging systems, over the last 50 years, in influencing the results, are necessary to overcome this problem.

Another drawback of our study was that, chemotherapy and radiotherapy in most cases were provided in different hospitals and the regimen was individually tailored based on existing protocols. Hence, we did not have elaborate details of drugs and doses and could not provide a detailed analysis based on dose response.

CONCLUSION

Survival and metastasis in patients affected by osteosarcoma depends on multiple factors. There has been a significant improvement in survival in the last 25 years. Chemotherapy in isolation did not significantly affect survival or metastasis. Limb salvage surgery did not have an adverse effect on survival rates. This improvement in survival could be due to a change in the natural history of the disease along with advances in diagnostics and therapeutics. These being relatively rare tumours; pooling of data and sharing experience, between various international centres is necessary to improve our understanding of osteosarcoma.

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