

ORIGINAL ARTICLE

Prognostic factors and survival rate of osteosarcoma: A single-institution study

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Abstract

Aim: Osteosarcoma is a highly malignant primary bone tumor. The study aim to evaluate the prognostic factors influencing the survival rate in our center.

Methods: This was a retrospective cohort study of all patients treated between January 2005 and December 2010.

Results: We included 163 patients with an age range of 6–59 years (median = 19). The median follow-up was 47 months (range 36–84). The overall survival in patients who completed chemotherapy and surgery ($n = 117$) was 72% at 2 years and 44% at 5 years. Histologically, 99 (85%) had osteoblastic, 6 (5%) had chondroblastic and 3 (2.5%) had telangiectatic osteosarcoma. Limb salvage surgery was performed in 80 (49%) and 41 (25%) underwent amputation. However, 46 patients (28%) underwent no surgical intervention and incomplete chemotherapy. In total, 38/79 patients had a good chemotherapy response. There was a significantly better survival rate for limb salvage versus amputation. Independent prognostic factors for survival are compliance to treatment and presence of lung metastasis.

Conclusion: The overall survival of osteosarcoma patients was influenced by the presence of pulmonary metastases and compliance to treatment. Histological subtype, different chemotherapy regimens and histological necrosis after chemotherapy did not significantly influence survival. The patients who did not complete treatment had significantly poorer survival.

Key words: extremity, osteosarcoma, prognosis, survival analysis.

INTRODUCTION

Osteosarcoma is a primary malignant tumor derived from primitive bone-forming mesenchymal tissue and is characterized by the production of osteoid or immature

bone by malignant, proliferating spindle cells. Osteosarcoma is highly malignant and has a tendency to metastasize to the lung. The dramatic improvement in survival observed in the last two decades is primarily the result of efficient chemotherapy to combat micro-metastases. The modern treatment approach is multimodal in nature and includes neoadjuvant chemotherapy, surgery to control local disease and other adjuvant treatment. The 5-year survival rate using a multidisciplinary approach varies from 60 to 70%.^{1,2}

Multidisciplinary management of osteosarcoma has been practiced in the Musculoskeletal Oncology Unit of Hospital Universiti Sains Malaysia since 1997. Here we

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present a retrospective analysis of prognostic factors for survival in 163 patients managed from 2005 to 2010.

METHODS

This was a retrospective cohort study of all patients diagnosed as having osteosarcoma between January 2005 and December 2010 in our center. The patients with osteosarcoma were identified through a search of the computerized databases. As a part of the staging process, a routine hematological and biochemical investigation, magnetic resonance imaging of the primary tumor, whole-body bone scintigraphy and chest computed tomography were performed. The final diagnosis and subtype of the osteosarcoma were determined by pathologists after evaluating the final specimens obtained during limb salvage and amputation operations. For patients who did not undergo surgery, the diagnoses were made from biopsy specimens. The patients were staged according to Enneking's Staging System for musculoskeletal sarcoma.³

Surgery was performed after three cycles of chemotherapy. Repeat magnetic resonance imaging to evaluate the lesion to assess the response to chemotherapy and the changes in the extent of primary tumor was performed 2 weeks prior to surgery. Attempts for limb salvage were made for all patients. However, the final decision to salvage or ablate was taken during surgery based on feasibility for complete resection of the tumor en bloc with preservation of the neurovascular bundle and adequate muscle mass for final function.

Serial computed tomography scans of the chest and a whole-body Technetium-99m-MDP bone scan were performed at 6-month intervals for 2 years and yearly thereafter for 5 years. Optional local radiological assessments were performed based on symptoms. Patients with lung metastases who were candidates for surgical resection were treated with open thoracotomy and wedge resection of the pulmonary nodule.

Patients older than 12 years received neoadjuvant chemotherapy according to the modified EOI (European Osteosarcoma Intergroup) protocol, consisting of a 2-h infusion of cisplatin 100 mg/m² (total of three divided doses) administered on day 1 to day 3 and doxorubicin 25 mg/m² administered over 24 h via i.v. infusion on days 1–3. The above protocol was used for chemo-naïve non-metastatic and metastatic osseous osteosarcomas. In the neoadjuvant setting, three cycles of the above regimen were offered before limb salvage surgery, and the remaining three cycles of the same chemotherapy were administered 4 weeks following

surgery. The response to preoperative chemotherapy was assessed according to the histological response of the tumor. Patients who were good responders had equal to or greater than 90% tumor necrosis, whereas patients who were poor responders had less than 90% tumor necrosis based on histopathological reports.⁴ In cases with a favorable (>90% tumor necrosis) histological response, similar chemotherapy regimens were continued. Patients with an unfavorable histopathological response (<90% necrosis) received an alternate treatment regimen consisting of ifosfamide and etoposide. The regimen consisted of ifosfamide 3 g/m² administered via a 3-h i.v. infusion on days 1 to 4 and etoposide 75 mg/m² administered via a 1-h infusion on days 1 to 4. The above regimen was repeated every 4 weeks for three cycles. The appropriate antiemetic medication and G-CSF (Granulocyte-colony stimulating factor) prophylaxis were offered with the above chemotherapy. For salvage chemotherapy, high-dose (HD) methotrexate-based chemotherapy was offered after the failure of second-line chemotherapy.^{5,6} However, patients younger than 12 years old received the Memorial Sloan Kettering T10 chemotherapy regimen protocol using a combination of chemotherapeutic agents administered in three phases for 1 year.⁷ Pediatric patients who were scheduled for limb salvage surgery received four cycles of chemotherapy prior to surgery. Each cycle comprised HD methotrexate 12 mg/m², vincristine 1.5 mg/m², adriamycin 30 mg/m² and cisplatin 100 mg/m². Chemotherapy was continued postoperatively and included HD methotrexate, vincristine, bleomycin, cyclophosphamide and dactinomycin. Those who responded well clinically and histologically (greater than 90% necrosis) continued to receive HD methotrexate and other chemotherapy drugs, including vincristine, adriamycin, bleomycin, cyclophosphamide and dactinomycin, whereas those who did not respond well were considered as methotrexate resistant and received only bleomycin, cyclophosphamide, dactinomycin, adriamycin and cisplatin over the next 30 weeks. The final survival was confirmed from Malaysia National Registry Data (Birth and Death Division) for those who were unavailable during the recall process.

We analyzed the survival data using STATA 11.2 (StataCorp. 2009 Stata Statistical Software: Release 11. College Station TX: Stata Corp LP). The survival parameters were described using frequencies and percentages and the survival rate at 2 and 5 years was calculated. Differences in the survival functions between levels in predictors were tested using the log-rank test.

We plotted the Kaplan–Meier survival curves to depict the survival function over time between levels of the predictor.⁸ To identify the significant prognostic factors at the multivariable analysis, we used the Cox proportional hazard regression. The proportional hazard assumption was checked using “est phtest” in Stata. In all of our analyses, *P*-values (two sided) of less than 0.05 were deemed statistically significant.

RESULTS

A total of 163 osteosarcoma patients were included in this study, including 107 men (66%) and 56 women (34%), with a mean age at diagnosis of 19 years (6–59 years). Twelve (7%) patients with maxillofacial, pelvic and soft-tissue osteosarcoma, and another seven who defaulted follow-up and were inaccessible at the time of review, were excluded from this study. The median follow-up was 47 months (ranging from 36 to 84 months). The overall survival and disease-free survival analysis for all subjects is depicted in the left half of Table 1 and the sub-analysis of survival of those completing treatment (*n* = 117) is depicted on the right half. The survival parameters for both groups are also shown in the same table.

A different chemotherapy protocol was used for 20% (23/117) of patients, as they were younger than 12 years old. Distal femur lesions were observed in 45% of patients, followed by proximal tibia lesions in 28% and proximal humerus lesions in 12%. Histologically, 99 (85%) patients had osteoblastic osteosarcoma, followed by 6 patients (5%) with chondroblastic osteosarcoma and 3 (3%) patients with telangiectatic osteosarcoma. Limb salvage surgeries were performed for control of local disease in 80 patients and amputations in 41 patients. One patient who underwent limb salvage surgery and three patients who had amputation surgery did not complete chemotherapy. There were 28% (46/163) of patients who did not undergo any surgical intervention and did not complete the course of chemotherapy. These groups of patients were evaluated differently for survival.

The overall survival rate of the 163 patients was 58% at 2 years and 35% at 5 years. The overall survival of the 117 patients who completed chemotherapy and surgical treatment was 72% at 2 years and 44% at 5 years. There was no significant difference in the survival rate between men and women (*P* = 0.079). Male patients had survival rates of 70 and 40% at 2 and 5 years, respectively, compared with 76 and 53%, respectively, for female patients. There was also no significant differ-

ence in survival between patients older than and younger than 40 years of age (*P* = 0.515). No significant difference was observed among the subtypes of osteosarcoma (*P* = 0.791). Osteoblastic osteosarcoma patients had respective 2- and 5-year survival rates of 70 and 45%, whereas the other histology subtypes had survival rates of 95 and 41%. There was no difference in survival between patients <12 and ≥12 years of age who received different types of chemotherapy. The survival rate of the limb salvage group was 85% at 2 years and 58% at 5 years. By contrast, the amputation group demonstrated poor survival rates of 45 and 14% at 2 and 5 years, respectively, and this was statistically significant if compared with limb salvage group. Patients who underwent no surgical intervention and did not complete the chemotherapy course had the worst outcome, with a survival rate of 24% at 2 years and 13% at 5 years. The median survival of this group was 9 months. This group had a significantly worse outcome when compared with patients who had completed treatment (Figs 1,2). Seventy-nine patients were evaluated for chemotherapy response. In this group, 48% (38/79) of patients had a good chemotherapeutic response, with survival rates of 92 and 66% at 2 and 5 years, respectively, whereas 52% (41/79) were poor responders with survival rates of 71 and 42% at 2 and 5 years, respectively.

Local recurrence developed in nine patients (7%). All but one patient with local recurrence had a poor response to chemotherapy. At the time of review, one patient survived without disease following secondary amputation, three patients survived with multiple pulmonary metastases and five patients succumbed to the disease. The survival rate of patients with local recurrence was 67% at 2 years and 22% at 5 years.

Lung metastases were seen in 55/163 (33%) at the time of presentation and subsequently developed in 86/163 patients by the end of study: 64% at the initial presentation, 17% during treatment and 17% after the completion of first-line chemotherapy and surgery. Patients without pulmonary metastases who completed treatment had better survival rates (85 and 61% at 2 and 5 years, respectively) compared with patients with pulmonary metastases (60 and 29% at 2 and 5 years, respectively). Pulmonary metastases at the time of diagnosis were associated with poor survival rates of 53 and 24% at 2 and 5 years, respectively. Patients who had pulmonary metastasis during treatment had survival rates of 64 and 29% at 2 and 5 years, respectively. Patients with pulmonary metastases after treatment also had better survival rates of 73 and 40% at 2 and 5 years,

Table 1 Detailed prognostic parameters and survival outcomes

Survival parameters	All cases (163 patients)			Completed treatment (117 patients)			Univariate analysis (log-rank)	Univariate analysis (log-rank)
	Case number	2-year survival	5-year survival	Case number	2-year survival	5-year survival		
Survival								
Overall	163	95 (58%)	57 (34%)	117	84 (72%)	51 (44%)	—	—
DFS	163	43 (26%)	38 (23%)	117	43 (37%)	38 (33%)	—	—
Completed treatment [§]								
No	46	11 (24%)	6 (13%)	—	—	—		
Yes	117	84 (72%)	51 (44%)	117	84 (72%)	51 (44%)	0.079	0.079
Gender								
Male	107	62 (58%)	35 (33%)	79	55 (70%)	31 (39%)	0.477	0.477
Female	56	33 (59%)	22 (40%)	38	29 (76%)	20 (53%)	0.655	0.655
Age group 1								
<40 years	156	90 (58%)	54 (35%)	112	80 (71%)	48 (43%)	0.004	0.004
≥40 years	7	5 (71%)	3 (43%)	5	4 (80%)	3 (60%)	0.785	0.785
Age group 2								
<12 years	26	20 (77%)	14 (54%)	23	18 (78%)	12 (52%)	0.328	0.328
≥12 years	137	75 (55%)	43 (32%)	94	66 (70%)	39 (42%)	<0.001	<0.001
Histology subtype [†]								
Osteoblastic	99	67 (68%)	43 (43%)	96	67 (70%)	43 (45%)	0.661	0.661
All others	18	17 (94.4%)	7 (39%)	17	16 (94%)	7 (41%)	0.004	0.004
Pathological Fracture								
No	146	87 (60%)	54 (37%)	106	76 (72%)	48 (45%)	0.328	0.328
Yes	17	8 (47%)	3 (18%)	11	8 (73%)	3 (27%)	<0.001	<0.001
Surgery								
No	42	10 (24%)	5 (12%)	—	—	—	0.661	0.661
Yes	121	85 (70%)	52 (43%)	117	84 (72%)	51 (44%)	0.004	0.004
LSS	80	68 (85%)	47 (59%)	79	67 (85%)	46 (58%)	<0.001	<0.001
Amputation	41	17 (42%)	5 (12%)	38	17 (45%)	5 (13%)	0.165	0.165
Local recurrence								
No	154	89 (58%)	55 (36%)	108	78 (72%)	49 (45%)	0.004	0.004
Yes	9	6 (67%)	2 (22%)	9	6 (67%)	2 (22%)	<0.001	<0.001
Chemotherapy response [‡]								
Greater than 90%	38	35 (92%)	25 (66%)	38	35 (92%)	25 (66%)	0.004	0.004
Less than 90%	41	29 (71%)	17 (42%)	41	29 (71%)	17 (42%)	<0.001	<0.001
Lung Metastasis								
No	77	54 (70%)	37 (48%)	54	46 (85%)	33 (61%)	0.122	0.122
Yes	86	41 (48%)	20 (23%)	63	38 (60%)	18 (29%)	0.016	0.016
At presentation	55	21 (38%)	10 (18%)	34	18 (53%)	8 (24%)		
During Rx	16	9 (56%)	4 (25%)	14	9 (64%)	4 (29%)		
After completion	15	11 (73%)	6 (40%)	15	11 (73%)	6 (40%)		
Other metastasis								
No	151	88 (58%)	54 (36%)	106	77 (73%)	48 (45%)	0.122	0.122
Yes	12	7 (58%)	3 (25%)	11	7 (64%)	3 (27%)	0.016	0.016

[†]Only some patients had histopathological results available for analysis. [‡]Not all patients were evaluated for chemotherapy responses. [§]Patients with completed treatment were reanalyzed. DFS, disease-free survival; LSS, limb salvage surgery.

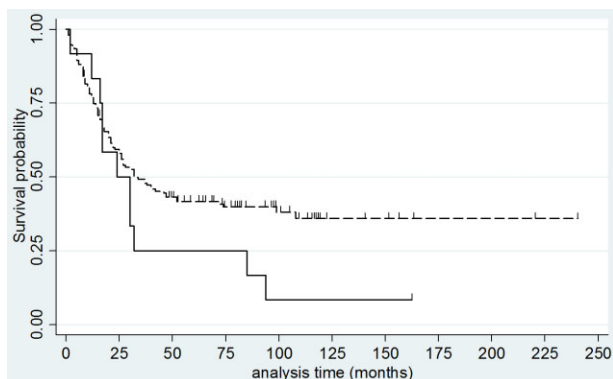


Figure 1 Kaplan–Meier describing the survival function in patients who completed treatment and surgical resection of the primary tumor and those who did not complete treatment. —, had metastasis; ----, no metastasis. Ticks – censored.

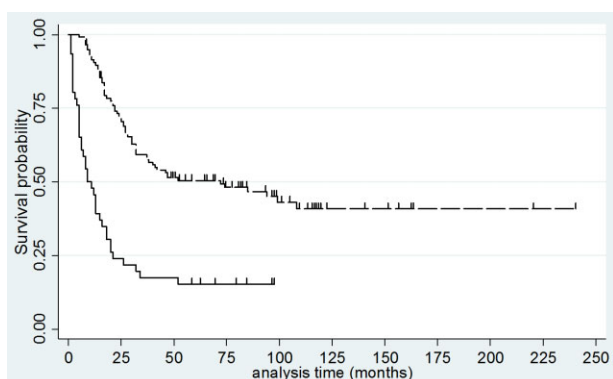


Figure 2 Kaplan–Meier describing the survival function in patients who underwent limb salvage surgery and those who underwent limb amputation. —, not complied; ----, complied. Ticks – censored.

respectively (Fig. 3). Three patients underwent surgical resection of the nodule, and all survived at 5 years.

Eleven patients (9%) had bone metastases without pulmonary metastases, and their survival rate was 64% at 2 years and 27% at 5 years. A total of 17 patients presented with pathological fracture but 6 patients did not complete treatment. The 11 patients who completed treatment had a 27% survival rate at 5 years, and none had local recurrence irrespective of the modalities of surgical treatment. The overall results and final univariate analysis are summarized in Table 1.

Results from the multivariable analysis are presented in Table 2. Compliance to treatment (i.e. undergoing surgery and completing chemotherapy), age categorized

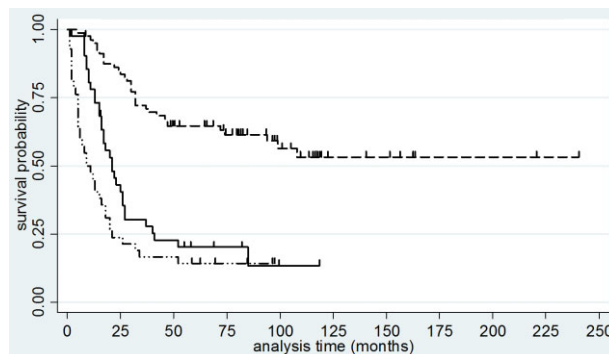


Figure 3 Kaplan–Meier describing the survival function in patients who developed lung metastases at initial presentation, during the treatment course or after the completion of treatment. ----, no surgery done; —, limb salvage surgery; ·····, amputation. Ticks – censored.

at 12 years old and the presence of lung metastasis are the three independent prognostic factors for survival in our analysis. Conversely, sex is not a significant prognostic factor and other type metastasis is barely nonsignificant in the adjusted analysis. Patients who did not comply with treatment have 4.22 times higher risk, those at or above 12 years of age have 2.12 times higher risk, and patients with lung metastasis have 2.37 times higher risk of death when adjusted for other important confounding variables.

DISCUSSION

This study included all 163 consecutive patients managed in our institution over a period of 5 years, 117 of whom completed planned treatment. This analysis will provide an additional perspective to discuss with patients, particularly as the acceptance of treatment is still low in developing countries.

Overall survival for all subjects in this study was slightly lower than in other studies, but when sub-analysis of those who completed the treatment was performed, the results were comparable to other studies in this region.^{9–11} The overall survival of patients who completed treatment was 44% at 5 years, whereas it was 58% at 5 years for the limb salvage group. A study conducted in Singapore on 47 patients with extremity osteosarcoma treated with the limb salvage technique reported a 2-year survival rate of 64%. In a study from Hong Kong, limb salvage surgery in conjunction with neoadjuvant chemotherapy resulted in a survival rate of 63% at 2 years.¹¹ Ogihara *et al.* reported 60% survival

Table 2 Survival predictor in the patients with osteosarcoma – multivariate analysis

Predictor	Hazard ratio	Standard error	95% confidence interval		P-value
Female	1.09				
Male	1.00	0.24	0.70	1.67	0.708
Not complied	4.22				
Complied	1.00	0.93	2.74	6.49	<0.001
At or above 12 years old	2.12				
Less than 12 years old	1.00	0.75	1.07	4.23	0.032
Had lung metastasis	2.37				
No lung metastasis	1.00	0.51	1.55	3.62	<0.001
Had other metastasis	1.87				
No other metastasis	1.00	0.63	0.97	3.61	0.063

at 5 years among patients with osteosarcoma who were treated with limb salvage surgery.¹⁰ The group of patients who did not comply with treatment had poor survival, with a 24% survival rate at 2 years, and 13% at 5 years. An international collaboration has confirmed that patients who do not undergo surgery have a worse prognosis, reflecting the tendency for this group of patients to be considered inoperable or not suitable for surgery due to disseminated disease.¹² In our study, we included patients who did not complete or refused treatment even as their disease progressed. These patients were either from a lower socioeconomic group or had poor educational status. Traditional healers who advised against modern treatment also contributed to poor treatment compliance.

Effective neoadjuvant chemotherapy has revolutionized the management of patients with osteosarcoma. In the past, treatment with amputation alone resulted in a survival rate of 20% at 5 years. However, with the addition of chemotherapy, the survival rate has improved to 60%. The combination of chemotherapy and surgery should be the standard choice of treatment, including pre- and postoperative chemotherapy. However, the impact of combination chemotherapy on survival remains controversial. A previous case study of 407 patients demonstrated no survival benefit with a multi-agent regimen compared with a two-drug regimen.^{5,6} Another study also demonstrated that intensification of chemotherapy improved the histological response without a concomitant improvement in overall survival.¹³⁻¹⁶ In our center, because of poor patient compliance and intolerance to an HD methotrexate regimen among teenagers and adult patients, we used a modified EOI protocol, which was easy to administer and reproducible. We also confirmed that the survival outcome of intensification chemotherapy regimens for children

younger than 12 years of age was not significantly different compared with the modified EOI protocol in an older age group.

Limb-sparing surgery for patients with primary malignant sarcoma of the extremities is now well established.¹⁷ Ablation was often the only alternative approach for many of the patients who presented late with advanced disease or did not respond to neoadjuvant chemotherapy, which precluded limb salvage surgery. The survival of those treated with limb salvage surgery was better compared with those treated by amputation in this study at 58% compared with 13% at 5 years. The amputation group presented with either larger tumors or more extensive systemic metastases that preclude limb salvage surgery. Local recurrence developed in 8% of patients, which was comparable to other studies. In our study, local recurrence developed in patients who had a poor response to chemotherapy and resulted in a grave prognosis for the majority, even though they were treated with major amputation. Amputation conferred only a marginal benefit against local recurrence; however, it was generally the treatment of choice for large tumors and patients with a worse perceived prognosis. This fact explained why the amputation group had a poor survival rate and has been confirmed by other studies.¹²

Microscopic tumor spread was present in 80% of osteosarcoma patients at the time of diagnosis, and approximately 5% had established pulmonary metastases. At diagnosis, osteosarcoma is classically localized in 80% of cases, and pulmonary metastases are evident in 20%.^{12,18} However, pulmonary metastasis was more common in our study, at 34%, due to late presentation and late treatment onset. Pulmonary metastasis at initial diagnosis and multiple nodules were associated with poor prognosis in a previous

study.¹² Additionally, single pulmonary nodules, resectable nodules and late nodule occurrence have been shown to improve survival.¹² Our study confirmed these findings.

Conclusion

The overall survival of osteosarcoma patients is good. Limb salvage surgery is justified as a surgical treatment for osteosarcoma. Pathological fracture did not increase risk of local recurrence or impact survival. Patients who do not comply with treatment had worse survival. Older patients and patients with pulmonary metastases have a significantly increased risk of death in patients with osteosarcoma in our setting.

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