Survival analysis of osteosarcoma patients: A 15-year experience

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Abstract

Introduction: Management of osteosarcoma has evolved considerably for the past two decades and there have been changes of practices especially pertaining to chemotherapy regime. This is a review of our cases in the past 15 years.

Method: This is a retrospective survival analysis study of 128 patients treated at University Malaya Medical Centre (UMMC) from 1997 to 2011.

Results: There were 80 (62.5%) male and 48 (37.5%) female patients with the median age being 15 (5–59). Majority had osteosarcoma of extremities (94.5%). More than 60% patients developed metastasis throughout the course of treatment with 39% presenting with lung metastasis. Osteoblastic osteosarcoma was the commonest subtype (65.6%). Of the 109 patients treated surgically, 84 patients (65.6%) underwent limb salvage surgery while the rest underwent amputation. Seventy-one per cent of patients completed treatment with local recurrence rate of 22.7%. The 5-year and 10-year survival rates were 56.31% (95% CI: 46.20, 65.24) and 22.33% (95% CI: 14.86, 30.76), respectively. The 5-year event-free survival was 52.94% (95% CI: 41.83, 62.87). In multivariate analysis, the independent prognostic factors were presence of metastasis and completion of treatment for both 5-year and 10-year overall survival. Good histological response was only significant for multivariate analysis at 5 years. Patients with metastasis had a hazard ratio of 20.4 at 5 years and 3.26 at 10 years.

Conclusion: Overall survival rate for osteosarcoma patients at our centre was comparably higher than other centres in the region. Two independent risk factors for survival are metastatic status and completion of treatment. A standardized chemotherapy regime is essential for long-term survival.

Keywords
chemotherapy, metastasis, osteosarcoma, survival outcome

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Introduction

Survival of patients diagnosed with osteosarcoma has improved significantly over the past two decades with survival rate being reported to be from 55% to 80%. However, the rates in many centres within the Asia-Pacific region are reported to be 27% to 48%, which is not as high as the Caucasian population. Faisham et al. and Pruk sakorn et al. attributed the low survival rate to patients' non-compliance to treatment regime. While Puri et al. attributed the poor survival to late presentation and large volume of tumour. The treatment protocol for osteosarcoma usually includes a neoadjuvant chemotherapy, followed by surgery and subsequent adjuvant chemotherapy. Standardized chemotherapy regimen for osteosarcoma was slowly evolving and it took significant amount of time to be established over the last two decades. There was difference in treatment modalities and practices, especially in the...
types of chemotherapy used. Most international collaborations have demonstrated that most effective chemotherapy regimens incorporate high dose methotrexate as one of the agents.1,3,10,11

Most of the outcome data in osteosarcoma is mainly from Caucasian population and there is little outcome study in different ethnic groups.10 As one of the national referrals centre for sarcoma cases, we have the advantage of treating large group of patients with standardized chemotherapy protocols and surgical principles by the same multidisciplinary team. The aim of this study was to review a group of patients diagnosed with osteosarcoma in our centre, and we were keen to investigate the survival rate and determine prognostic factors associated with their survival in this group.

Material and methods

This is a retrospective cohort study of all osteosarcoma patients treated at our centre from January 1997 to December 2011. These patients were identified retrospectively via the medical records and prospectively maintained patients database. Patient’s demographic details such as age, sex, disease profile, treatment received and outcomes were recorded. The disease profile included location of the tumour, metastatic status, histological subtype and the size of tumour. In terms of treatment profile, the type of surgery and whether patients received complete treatment consisting of both neoadjuvant and adjuvant chemotherapy, followed by surgery, were recorded. The updated patients database also recorded the duration of time to recurrence, progression of disease and death in years. All patients were thoroughly assessed for local disease and distant metastasis. Staging studies included plain radiographs, magnetic resonance imaging scan of the affected area, computed tomography (CT) scan of the thorax and total body scintigraphy (bone scan).

Patients received chemotherapy as per existing hospital protocol. Patients at the age of up to 16 years old were treated by the paediatric oncology unit, and patients older than 16 years old were taken care by the adult oncology unit. Both units used a methotrexate-based chemotherapy regimen. The current first-line chemotherapy regimen for osteosarcoma is doxorubicin, cisplatin and methotrexate, which were given during a period of six cycles, with each cycle lasting 35 days, based on the EUROMAS-1 study.10 For each cycle, intravenous infusions of doxorubicin 37.5 mg/m² and cisplatin 60 mg/m² were administered at day 1 and 2. Intravenous infusion of methotrexate 12,000 mg/m² was administered at day 22 and 29. Neoadjuvant chemotherapy was administered for two cycles in the paediatric group (up to 16 year old) and three cycles in the adult group (older than 16 year old) before the definitive surgery, followed by the remaining cycles as adjuvant chemotherapy postoperatively. Surgical treatment including metastatic lesion was performed to achieve clear oncologic margins. In cases of tumour recurrence, a second-line treatment of chemotherapy using etoposide and ifosfamide was given in a 21-day cycle.12 Intravenous infusions of etoposide 100 mg/m² and ifosfamide 1600 mg/m² were administered at day 1 to 5 of every cycle for a total of six cycles. Intravenous infusion of mesna 1600 mg/m² was given concomitantly at day 1 to 5 to reduce chemotherapy side effects. Chemotherapy-induced necrosis was assessed according to the scale of Huvos et al., where grade I denoted 0–50% necrosis; grade II: 51–90% necrosis; grade III: 91–99% necrosis; grade IV: 100% necrosis.13 Good responder included grade III and IV, and both good and poor responders received the similar chemotherapy regimens after the surgery.

All patients were followed up at the clinic every 3 months for the first 2 years and 6 monthly subsequently up to 5 years, after which they will be seen annually for lifetime. Disease surveillance at the clinic included biplanar plain radiograph of the affected part and chest radiograph. A CT scan of the thorax was done every 6 months for those with known lung metastasis.

A survival probability across the group was calculated and plotted using the Kaplan–Meier product limit to estimate death and event-free duration. The median for overall survival time and event-free survival was calculated using the Kaplan–Meier survival curve. The comparison among categorical predictive factors was calculated using the log rank test. Univariate Cox hazard regression analysis was done for all independent variables to determine the predictive factors and to get the preliminary idea for variable selection in final model. Based on this analysis, variables with p values less than 0.25 were included into multiple Cox regression analysis. All selected variables were inserted into the Preliminary Final Model using Enter method.

Results

Total of 128 patients were treated at our centre between January 1997 and December 2011, with a median age of 15 years (range 5–59 years old) comprising of 80 (62.5%) male and 48 (37.5%) female patients. The patients were grouped according to age ≤16 years (children), 17–39 years (adolescent and young adult) and ≥40 years (adults).14 Of these, 81 patients were below 16 years (63.3%), 44 patients in the adolescent and young adult group (34.4%), with only 3 patients aged 40 and above (2.3%). This is consistent with the bimodal distribution of osteosarcoma in children and adults groups.

Six patients (4.7%) had axially located osteosarcoma at the ribs and pelvis. The remaining 121 patients (94.5%) had osteosarcoma located at the extremities with femur (51.2%, n = 64) was the commonest location, followed by tibia (24.8%, n = 32). Of the 128 patients analysed, more than 60% (n = 78) developed lung metastasis throughout the
course of treatment, with 50 patients (39.1%) had lung metastasis at the time of diagnosis. Nine per cent \((n = 12)\) had metastasis detected during treatment, while 12.5\% \((n = 16)\) had metastasis after completion of treatment. Eleven patients (8.6\%) had associated distant metastasis with the lung metastasis, and we noticed no patients had distant metastasis without lung metastasis.

We had more patients in Enneking stage III (48.4\%, \(n = 62\)) than patients staged at Enneking IIB (33.6\%, \(n = 43\)). This findings is consistent with more patients (46.1\%, \(n = 59\)) presented with large tumour size (>10 cm) at presentation. In our population, majority of patients presented late with large tumour and metastasis, thus higher grading in Enneking classification. Of the 128 patients, only 6 patients (4.7\%) presented with pathological fractures.

Osteoblastic osteosarcoma was the commonest histological subtype of osteosarcoma in our centre (65.6\%, \(n = 84\)) followed by other subtype chondroblastic (12.5\%, \(n = 16\)), giant-cell rich (5.4\%, \(n = 7\)), parosteal (2.3\%, \(n = 3\)) and fibroblastic (1.7\%, \(n = 2\)). The remaining 16 patients (12.5\%) were diagnosed with classical osteosarcoma, with no histological subtype recorded in the final histopathological report. Parosteal osteosarcoma was excluded from further analysis as this subtype is mainly treated with wide surgical resection. Chemotherapy-induced percentage of necrosis was only available in 91 patients. Of the 91 patients, 47.3\% \((n = 43)\) of the patients showed good response characterized by tumour necrosis of more than 90\% (grade III). This chemotherapy response is similar to a study done by Sami et al., which found 51.3\% had nearly complete response with grade III necrosis.\(^{15}\)

Large number of patients (84.8\%, \(n = 106\)) underwent surgical treatment as part of their management. Of the 106 patients who underwent surgery, 81 patients (76.4\%) underwent limb salvage surgery while the rest underwent amputation (23.6\%, \(n = 25\)). Only 19 patients (15.2\%) did not receive surgical treatment due to advanced disease, inoperable tumour and refusal for surgical treatment. Majority of patients (72.8\%, \(n = 91\)) completed the full treatment of chemotherapy and surgery. The remaining patients (27.2\%, \(n = 34\)) did not complete the prescribed treatment mainly due to progression of disease during the treatment period, refusal to continue chemotherapy or undergo surgery, went for alternative medicine, and loss to follow-up. The overall local recurrence in patients who underwent surgery \((n = 106)\) was 27.4\% \((n = 29)\). While the percentage of local recurrence in patients who completed the full treatment \((n = 91)\) was 8.9\% \((n = 8)\). In this study, we did not look at the surgical margins of the resected specimens and its association with the overall local recurrence. The surgical margins require more time for data collection, and this will be analysed and reported in a separate paper in the future.

The 5-year overall survival rate was 56.31\% (95% CI: 46.20, 65.24) with a median time for an event being 3 years (Figure 1). Factors that significantly affecting the survival outcome were metastatic status, percentage of necrosis, tumour size, Enneking stage, local recurrence, completion of treatment and whether or not patient received surgical treatment (Figure 2). Whereas the gender, age groups, location of tumour, pathological fracture and histological subtypes did not affect the survival outcome (Table 1). Patients who had metastasis at any point from presentation and throughout the course of treatment had a hazard ratio (HR) of 6.20 (95% CI: 2.47, 15.54; \(p < 0.001\)). Patients who responded well to neoadjuvant chemotherapy with necrosis more than 90\% had a positive predictive value with a HR of 0.39 (95% CI: 0.20, 0.73; \(p = 0.004\)) compared to the poor responder group. Tumour size larger than 10 cm had a HR of 2.06 (95% CI: 1.16, 3.64; \(p = 0.013\)) compared to tumour size smaller than 10 cm. Patients staged in Enneking stage III had a HR of 2.61 (95% CI: 1.42, 4.80; \(p = 0.002\)) compared to those in stage IIB. Completion of treatment also gave a positive predictive value for survival outcome with a HR of 0.23 (95% CI: 0.14, 0.37; \(p < 0.001\)). Both surgical treatments be it amputation or limb salvage surgeries, had a positive predictive value with HR of 0.33 (95% CI: 0.16, 0.67; \(p = 0.002\)) and 0.19 (95% CI: 0.10, 0.34; \(p < 0.001\)) respectively, compared to conservative treatment. Further analysis with multivariate cox regression, we found that the significant predictive factors for 5-year survival for osteosarcoma patients were their metastatic status, good response to chemotherapy and completion of treatment (Table 2). Metastatic status had a HR of 20.4 (95% CI: 2.50, 166.09; \(p = 0.005\)), good response to chemotherapy had a HR of 0.32 (95% CI: 0.14, 0.72; \(p = 0.006\)) and patients who completed treatment had a HR of 0.10 (95% CI: 0.02, 0.65; \(p = 0.016\)).
Figure 2. Kaplan–Meier curve for cumulative survival estimates among osteosarcoma patients.
The Kaplan–Meier analysis has estimated a 10-year survival rate of 22.33% (95% CI: 14.86, 30.76) with a median time to overall event being 3 years (95% CI: 1.52, 4.48) in our cohort (Figure 3). The metastasis status of patients has the biggest impact on the difference in our 10-year survival rate, with survival rate of 43.75% (95% CI: 26.46, 59.81) in patients with no metastasis compared to only 8.2% (95% CI: 3.02, 16.73) in patients with metastasis (p < 0.001) (Table 3). Patients with metastasis had a HR of 3.53 times of death (95% CI: 2.11, 5.89; p < 0.001) compared to patients without metastasis. Patients who were staged as Enneking stage III had a HR of 2.25 times to experience death (95% CI: 1.44, 3.50; p < 0.001) compared to those in stage IIB. Patients with tumour size of more than 10 cm had a HR of 2.13 times to experience death (95% CI 1.37, 3.30; p = 0.001) compared to patients with tumour sized less than 10 cm. Local recurrence had a negative outcome predictive factor with HR of 1.98 to experience death (95% CI: 1.24, 3.17; p = 0.005) compared to patients without local recurrence. On the other hand, good response to chemotherapy had a HR of 0.58 times to experience death (95% CI: 0.36, 0.91; p = 0.019) compared to the poor responders. Patients who completed their treatment with chemotherapy regimen and surgery were 72% less likely to experience death compared to those who did not complete both treatments. Patients who underwent surgery had a more positive outlook for survival outcome compared to those who did not undergo surgery. HR for patients who underwent amputation and limb salvage surgeries were 0.41 (95% CI: 0.21, 0.78; p = 0.007) and 0.31 (95% CI: 0.18, 0.53; p < 0.001) respectively, to experience death compared to patients who underwent conservative treatment. Further analysis using

| Variables               | % Survival rate (95% CI) | Median survival time (95% CI) | Log rank statistic | p Value |
|-------------------------|--------------------------|------------------------------|--------------------|---------|
| Gender                  |                          |                              |                    |         |
| Male                    | 56.45 (43.25, 67.70)     | 2 (0.91, 3.09)               | 0.33               | 0.562   |
| Female                  | 56.10 (39.71, 69.64)     | 4 (–, –)                     |                    |         |
| Age                     |                          |                              |                    |         |
| 16 and below            | 57.75 (45.43, 68.24)     | 2 (–, –)                     | 3.50               | 0.061   |
| 17–39                   | 53.33 (34.28, 69.14)     | 4 (0.51, 3.49)               |                    |         |
| 40 and above            | 50.00 (0.60, 91.04)      | 4 (0.00, 10.40)              | 0.32               | 0.570   |
| Primary site            |                          |                              |                    |         |
| Axial                   | 50.00 (11.09, 80.37)     | 3 (–, –)                     | 0.20               | 0.657   |
| Extremity               | 56.70 (46.26, 65.86)     | 3 (–, –)                     |                    |         |
| Metastasis              |                          |                              |                    |         |
| Yes                     | 40.98 (28.64, 52.92)     | 2 (1.40, 2.61)               | 23.47              | <0.001  |
| No                      | 90.63 (73.69, 96.88)     | 4 (–, –)                     |                    |         |
| Pathological fracture   |                          |                              |                    |         |
| Yes                     | 66.67 (19.46, 90.44)     | 3 (–, –)                     | 1.35               | 0.245   |
| No                      | 55.67 (45.24, 64.89)     | 3 (1.65, 4.35)               |                    |         |
| Histological subtype    |                          |                              |                    |         |
| Osteoblastic            | 54.55 (41.82, 65.61)     | 2 (0.65, 3.35)               | 1.23               | 0.267   |
| Others                  | 60.71 (40.39, 75.98)     | – (–, –)                     |                    |         |
| Histological response   |                          |                              |                    |         |
| >90%                    | 75.00 (58.52, 85.69)     | 2 (1.40, 2.60)               | 10.91              | 0.001   |
| <90%                    | 39.53 (25.11, 53.63)     | – (–, –)                     |                    |         |
| Tumour size             |                          |                              |                    |         |
| >10 cm                  | 45.45 (30.46, 59.27)     | 2 (1.26, 2.74)               |                    |         |
| <10 cm                  | 65.00 (48.18, 77.56)     | – (–, –)                     | 7.82               | 0.005   |
| Enneking stage          |                          |                              |                    |         |
| IIB                     | 68.29 (51.74, 80.19)     | – (–, –)                     | 12.30              | <0.001  |
| III                     | 46.67 (31.72, 60.30)     | 2 (1.24, 2.76)               |                    |         |
| Local recurrence        |                          |                              |                    |         |
| Yes                     | 38.46 (20.41, 56.30)     | 2 (1.25, 2.75)               | 4.02               | 0.045   |
| No                      | 67.69 (54.88, 77.59)     | – (–, –)                     |                    |         |
| Completed treatment     |                          |                              |                    |         |
| Yes                     | 58.14 (47.01, 67.73)     | – (–, –)                     | 48.36              | <0.001  |
| No                      | 20.00 (3.09, 47.47)      | 0 (–, –)                     |                    |         |
| Primary surgery         |                          |                              |                    |         |
| Amputation              | 50.00 (25.93, 70.05)     | 2 (0.00, 4.45)               | 4.52               | 0.033   |
| Salvage                 | 58.75 (47.18, 68.62)     | – (–, –)                     |                    |         |
| Conservative            | 25.00 (0.89, 66.53)      | 0 (–, –)                     | 10.44              | 0.001   |
the multivariate cox regression, we only found metastasis status and completion of treatment as the most statistically significant predictive factors. The HR was 3.26 (95% CI: 1.44, 7.40; \( p = 0.005 \)) for patients with metastasis and 0.10 (95% CI: 0.02, 0.63; \( p = 0.014 \)) for patients who have completed treatment (Table 4).

The 5-year event-free survival in our study was 52.94% (95% CI: 41.83, 62.87) with a median time for event being 1 year (95% CI: 0.29, 1.72) (Figure 4). The log rank test showed factors that significantly affecting the event free survival were presence of metastasis, histological response, tumour size, Enneking staging, local recurrence status, completion of treatment, and surgical treatment (Table 5). All these significant factors in event free survival were similar to the significant factors affecting the 5-year and 10-year overall survival in our previous analysis.

**Discussion**

The results showed that the 5-year overall survival rate was 56.3% with a 5-year event free survival rate at 52.9%. This finding is similar to most studies conducted within the Asia-Pacific region with reported 5-year overall survival rates between 27% and 67%.4–9,16,14,17 Study by Hung et al. reported fairly better rate at 67% for overall 5-year survival. The 10-year overall survival rate in this study was 22.3% which is similar to our study, and none of the aforementioned studies in Asia-Pacific region performed this 10-year survival analysis.16 The 5-year overall survival rates were much higher for western regions with rates ranging 60% to 68%.1–3 Bielack et al. reported a high 10-year overall survival of 59.8%, with event free survival rates of 52.3% and 48.9% at 5 and 10 years.1 The 5-year overall survival rate of our patients was similar compared to other centres in this region but lower than the reported western literature.

We reported a significant drop in the 10-year overall survival rate (22.3%) as compared to the 5-year survival rate (56.3%). This large drop is likely due to the inclusion of patients treated from 1996 to 2006 in the survival analysis. The main difference between this groups of patients (1996–2006) with the more recent patients after year 2006, was the chemotherapy regimen used, as there was no standardized chemotherapy protocol implemented in our centre for the management of osteosarcoma prior to year 2006. Although all the regimens used were methotrexate based, there were a few different combinations, such as vincristine-cyclophosphamide-doxorubicin-methotrexate, and methotrexate-doxorubicin-cisplatin regimens. The chemotherapy regimen was only standardized for osteosarcoma patients after 2006 when the orthopaedic oncology unit was established, using methotrexate-doxorubicin-cisplatin based on the EUROMAS-1 study. Therefore, the 10-year overall survival analysis for this study includes both patients who received non-standardized chemotherapy regime prior to year 2006 and standardized EUROMAS-1 protocol after year 2006. However, regardless of the chemotherapy regimens used prior to year 2006, our study has shown that it is more important to complete the chemotherapy treatment with combination of surgery as both have significant impact for a better long-term survival.

Different sarcoma centres decide the type of chemotherapy regimen differently (Table 6). Study by Faisham et al.
grouped patients into two groups consisting of those who were less and over 12 years of age. The older age group received a modified EOI (European Osteosarcoma Inter-group) protocol consisting of cisplatin and doxorubicin as neoadjuvant. Patients who responded well to chemotherapy received similar chemotherapy regimen while it was changed to ifosfamide and etoposide for those who responded poorly. Patients in the younger age group received chemotherapy based on the Memorial Sloan Kettering T10 protocol, comprising vincristine, cisplatin, doxorubicin and methotrexate for neoadjuvant treatment. Postoperatively, patients received a combination of methotrexate-vincristine-bleomycin-cyclophosphamide-dactinomycin as adjuvant treatment.6 Other study by Pruksakorn et al. divided their osteosarcoma patients into two groups, aged above and below 15 years old. The younger age group received doxorubicin and carboplatin for both neoadjuvant and adjuvant treatment. Older patients received doxorubicin and cisplatin regimen as first-line treatment.7 In Europe, the Germany-Austria-Swiss Osteosarcoma Group used a chemotherapy protocol comprising of high dose methotrexate, cisplatin, doxorubicin, bleomycin, cyclophosphamide and dactinomycin in varying combination for neo-adjuvant and adjuvant treatment.1 Whereas for the Scandinavian Sarcoma group, osteosarcoma patients were treated using methotrexate, doxorubicin and cisplatin both in the neoadjuvant and adjuvant therapies.3 These two large studies showed a high 5-year overall survival rate between 65% and 70%. A study by Ferrari et al. reviewed the latest chemotherapy regimens and described the standard treatment based on EUROMAS-1, OS2006 and ISG/OS-1 studies and concluded that the methotrexate-doxorubicin-

| Variables          | % Survival rate (95% CI) | Median survival time (95% CI) | Log rank statistic | p Value  |
|--------------------|--------------------------|-------------------------------|-------------------|---------|
| Gender             |                          |                               |                   |         |
| Male               | 24.19 (14.43, 35.33)     | 2 (0.91, 3.09)               | 0.03              | 0.869   |
| Female             | 19.51 (9.16, 32.72)      | 4 (1.09, 6.91)               |                   |         |
| Age                |                          |                               |                   |         |
| 16 and below       | 16.90 (9.29, 26.45)      | 5 (3.24, 6.76)               | 0.18              | 0.669   |
| 17–39              | 33.33 (17.53, 50.00)     | 2 (0.51, 3.49)               |                   |         |
| 40 and above       | 50.00 (0.60, 91.04)      | 4 (0.00, 10.40)              | 0.08              | 0.780   |
| Primary site       |                          |                               |                   |         |
| Axial              | 16.67 (0.77, 51.68)      | 3 (0.00, 7.80)               | 0.06              | 0.803   |
| Extremity          | 22.68 (14.95, 31.41)     | 3 (1.46, 4.54)               |                   |         |
| Metastasis         |                          |                               |                   |         |
| Yes                | 8.20 (3.02, 16.73)       | 2 (1.40, 2.61)               | 31.18             | <0.001  |
| No                 | 43.75 (26.46, 59.81)     | 9 (8.30, 9.70)               |                   |         |
| Pathological fracture |                        |                               |                   |         |
| Yes                | 33.33 (4.61, 67.56)      | 6 (0.00, 14.40)              | 1.43              | 0.232   |
| No                 | 21.65 (14.09, 30.28)     | 3 (1.52, 4.48)               |                   |         |
| Histological subtype |                      |                               |                   |         |
| Osteoblastic       | 22.73 (13.53, 33.38)     | 2 (0.65, 3.35)               | 0.02              | 0.885   |
| Others             | 10.71 (2.72, 25.06)      | 5 (2.28, 7.73)               |                   |         |
| Histological response |                      |                               |                   |         |
| >90%               | 27.50 (14.86, 41.72)     | 7 (5.40, 8.60)               | 6.84              | 0.009   |
| <90%               | 11.63 (4.26, 23.06)      | 2 (1.40, 2.60)               |                   |         |
| Tumour size        |                          |                               |                   |         |
| >10 cm             | 4.55 (0.83, 13.61)       | 2 (1.26, 2.74)               |                   |         |
| <10 cm             | 25.00 (12.98, 39.01)     | 7 (4.59, 9.41)               | 14.84             | <0.001  |
| Enneking stage     |                          |                               |                   |         |
| IIB                | 24.39 (12.65, 38.17)     | 7 (5.64, 8.36)               | 16.49             | <0.001  |
| III                | 8.89 (2.84, 19.31)       | 2 (1.24, 2.76)               |                   |         |
| Local recurrence   |                          |                               |                   |         |
| Yes                | 3.85 (0.28, 16.43)       | 2 (1.25, 2.75)               | 9.85              | 0.002   |
| No                 | 32.31 (21.38, 43.71)     | 7 (4.41, 9.59)               |                   |         |
| Completed treatment|                          |                               |                   |         |
| Yes                | 20.93 (13.08, 30.04)     | 6 (3.67, 8.33)               | 40.01             | <0.001  |
| No                 | 10.00 (0.57, 35.81)      | 0 (–, –)                     |                   |         |
| Primary surgery    |                          |                               |                   |         |
| Amputation         | 27.78 (10.11, 48.87)     | 2 (0.00, 4.45)               | 6.10              | 0.013   |
| Salvage            | 21.25 (13.09, 30.74)     | 6 (3.77, 8.24)               | 26.34             | <0.001  |
| Conservative       | 0 (–, –)                 | 0 (–, –)                     |                   |         |

Yasin et al. 7
cisplatin regimen should be included in both neo-adjuvant and adjuvant treatment. Based on the study by Ferrari et al., there was no improvement in overall survival and event free survival rates when those responding poorly to chemotherapy were given ifosfamide and etoposide instead, as adjuvant chemotherapy. The OS2006 study showed that ifosfamide and etoposide were acceptable treatment alternatives when doxorubicin and cisplatin was contraindicated. Based on the mentioned studies, the overall survival rate is seen to be closely related to the standardized chemotherapy regimen used, which explains the lower survival rate in certain parts of the Asia-Pacific region as compared to the western counterparts.

Presence of lung metastasis has consistently been shown to affect outcome for patients in many literatures. In this study, 39% patients (n = 50) presented with lung metastasis and 22% patients (n = 28) developed lung metastasis during and after treatment. The multivariate analysis for 5-year survival in this study showed that the presence of lung metastasis at presentation or during follow-up was an independent prognostic factor to poorer outcome with a very high HR of 20.6. This factor was also true for our 10-year survival analysis with a HR of 3.26. This finding is comparable with other studies on metastasis at presentation ranging from 33% to 54%. The higher percentage of lung metastasis either at presentation or during follow-up is associated with poorer outcome in 5-year and 10-year survival analysis. Our 10-year survival rate without lung metastasis was 43.8%, which is much lower than the rate reported by Bielack et al. In this study, we found none of the patients had distant metastasis without lung metastasis. There were eleven (8.6%) patients presented with lung metastasis together with distant metastasis. Study by Bielack et al. has reported 3.3% patients with lung and distant metastasis in their cohort. While Faisham et al. has reported 7.3% of their patients presented with distant metastasis. However, the status of lung metastasis for their patients was not reported. The likelihood of a distant metastasis without lung metastasis in osteosarcoma patient is very low due to the haematogenous route for metastasis in sarcoma cases. All circulations including from the primary tumour goes through the lung, making it the commonest site for metastasis. However, there are reports of extrapulmonary metastasis without lung metastasis. Study by Jeffree et al. reported that 5% among their 124 patients had only extrapulmonary metastasis. There was also a rare case of metastasis of osteosarcoma to the kidneys without the involvement of the lungs, reported. The metastatic lesion was detected 8 years after the diagnosis of a parosteal type distal femur osteosarcoma that was confirmed on histopathological examination of the resected tumour. This was reported in autopsy cases, which found 90% of patients with osteosarcoma would have lung metastasis and 10–12% with renal metastasis alone.

Our study also showed that patients who did not undergo surgery had a poorer outcome than those treated surgically. Most of these patients had advanced disease at presentation and the tumour was inoperable. In our study, the longest that such patient lived was up to 2 years. Wiromrat et al. has reported a 27.6% overall 5-year survival rate for their

| Variables | Regression coefficient (b) | Adjusted HR (95% CI) | Wald stats | p Value |
|-----------|---------------------------|----------------------|------------|--------|
| Metastasis | Yes                       | 1.18                 | 3.26 (1.44, 7.40) | 8.011   | 0.005  |
|           | No                        | 0.00                 | Ref.       |        |       |
| Histological response | >90% | -0.48                 | 0.62 (0.36, 1.07) | 3.011   | 0.083  |
|           | <90%                      | 0.00                 | Ref.       |        |       |
| Tumour size | <10 cm | 0.00                 | Ref.       |        |       |
|           | >10 cm                    | 0.28                 | 1.32 (0.75, 2.32) | 0.933   | 0.334  |
| Enneking stage | IIB | 0.00                 | 1.10 (0.55, 2.22) | 0.069   | 0.793  |
|           | III                       | 0.09                 | 1.21 (0.66, 2.24) | 0.382   | 0.537  |
| Local recurrence | Yes | 0.19                 | 1.37 (0.61, 3.08) | 0.575   | 0.448  |
|           | No                        | 0.00                 | Ref.       |        |       |
| Completed treatment | Yes | -2.29                | 0.10 (0.02, 0.63) | 6.039   | 0.014  |
|           | No                        | 0.00                 | Ref.       |        |       |
| Primary surgery | Amputation | 0.31               | 1.37 (0.61, 3.08) | 0.575   | 0.448  |
|           | Salvage                   | 0.00                 | Ref.       |        |       |

HR: hazard ratio.
patients who did not receive the standard osteosarcoma treatment of neoadjuvant chemotherapy, surgery and adjuvant chemotherapy. Twenty-two per cent of patients received chemotherapy alone, 25% underwent solely amputation and 25% underwent chemotherapy and amputation. Wiromrat found that patients who received chemotherapy alone without surgery had a poorer median survival time of 4.1 years.8 Thus the combination of treatment with chemotherapy and surgical resection is utmost important in the survival of osteosarcoma patients.

This is a retrospective cohort study in a single centre. The data collected in this study is based on the available medical records. Our 10-year survival rate is representative of patients who were treated before 2006, where the chemotherapy regime was not yet standardized, and the 10-year survival rate was significantly low. In order to determine the survival rate at 10 years on a standardized chemotherapy regime and to compare the different regimens used, future studies should be conducted with patients treated after 2006. We have decided to use the EUROMAS-1 protocol as a standard treatment since the establishment

| Variables                  | % Survival rate (95% CI) | Median survival time (95% CI) | Log rank statistic | p Value |
|----------------------------|--------------------------|------------------------------|--------------------|---------|
| Gender                     |                          |                              |                    |         |
| Male                       | 52.00 (37.43, 64.72)     | 1 (0.13, 1.87)               |                    |         |
| Female                     | 54.29 (36.61, 68.98)     | 2 (0.35, 3.46)               | 1.004              | 0.316   |
| Age                        |                          |                              |                    |         |
| 16 and below               | 49.15 (35.93, 61.09)     | 2 (1.24, 2.76)               |                    |         |
| 17–39                      | 62.50 (40.30, 78.42)     | 1 (–, –)                     | 0.671              | 0.413   |
| 40 and above               | 50.00 (0.60, 91.04)      | 3 (0.00, 7.80)               | 0.001              | 0.975   |
| Ethnicity                  |                          |                              |                    |         |
| Malay                      | 60.53 (43.29, 74.00)     | 1 (0.00, 2.19)               |                    |         |
| Chinese                    | 42.86 (26.43, 58.31)     | 1 (0.00, 2.09)               | 0.256              | 0.613   |
| Indian                     | 58.33 (27.01, 80.09)     | 2 (–, –)                     | 1.079              | 0.299   |
| Primary site               |                          |                              |                    |         |
| Axial                      | 66.67 (5.41, 94.52)      | 0 (–, –)                     |                    |         |
| Extremity                  | 52.44 (41.13, 62.56)     | 2 (0.28, 1.72)               | 0.090              | 0.764   |
| Metastasis                 |                          |                              |                    |         |
| Yes                        | 34.78 (21.52, 48.38)     | 1 (0.62, 1.39)               |                    |         |
| No                         | 83.33 (64.50, 92.70)     | *                            | 26.550             | <0.001  |
| Pathological fracture      |                          |                              |                    |         |
| Yes                        | 40.00 (5.20, 75.28)      | 1 (0.00, 2.60)               |                    |         |
| No                         | 53.75 (42.26, 63.92)     | 1 (0.23, 1.77)               | 0.01               | 0.953   |
| Histological subtype      |                          |                              |                    |         |
| Osteoblastic               | 50.94 (36.87, 63.39)     | 1 (0.15, 1.85)               |                    |         |
| Others                     | 54.17 (32.71, 71.43)     | 3 (1.03, 4.98)               | 1.27               | 0.259   |
| Histological response     |                          |                              |                    |         |
| >90%                       | 56.76 (39.43, 70.84)     | 4 (–, –)                     |                    |         |
| <90%                       | 46.88 (29.15, 62.77)     | 1 (0.49, 1.51)               | 4.66               | 0.031   |
| Tumour size                |                          |                              |                    |         |
| >10                        | 45.45 (28.18, 61.21)     | 1 (0.27, 1.73)               |                    |         |
| <10                        | 52.78 (35.47, 67.43)     | 3 (0.00, 6.85)               | 5.82               | 0.016   |
| Enneking stage             |                          |                              |                    |         |
| IIB                        | 64.71 (46.30, 78.18)     | *                            |                    |         |
| III                        | 40.54 (24.88, 55.65)     | 1 (0.54, 1.46)               | 10.01              | 0.002   |
| Local recurrence           |                          |                              |                    |         |
| Yes                        | 15.00 (3.73, 33.47)      | 1 (0.56, 1.44)               | 12.80              | <0.001  |
| No                         | 72.22 (58.22, 82.22)     | *                            |                    |         |
| Completed treatment        |                          |                              |                    |         |
| Yes                        | 53.42 (41.39, 64.05)     | 3 (0.85, 5.15)               | 38.58              | <0.001  |
| No                         | 20.00 (0.84, 58.19)      | 0 (–, –)                     |                    |         |
| Primary surgery            |                          |                              |                    |         |
| Amputation                 | 61.54 (30.83, 81.84)     | 1 (–, –)                     | 4.07               | 0.044   |
| Salvage                    | 51.47 (39.06, 62.55)     | 2 (1.15, 2.84)               | 17.66              | <0.001  |
| Conservative               | 33.33 (00.90, 77.41)     | 0 (–, –)                     |                    |         |

*Right censoring of patients from the statistical analysis.
of our orthopaedic oncology unit in 2006. Our updated database is more organized than prior to 2006 and we expect the 10-year survival rate after 2006 to reach plateau in the future.

**Conclusion**

Osteosarcoma patients treated in our centre from 1997 to 2011 had survival rate at 5 and 10 years, at 56.3% and 22.3%, respectively. The event-free survival at 5 years was 52.9%. These findings are comparable with many centres around this region. Furthermore, our survival rate was also not too far off from the survival rates in other centres in developed countries. From our analysis, the independent prognostic factors were presence of metastasis and completion of treatment. Chemotherapy responsiveness or percentage of necrosis was only significant in multivariate analysis for 5-year survival rate. Osteosarcoma patients presented with metastasis either at the time of diagnosis or during treatment period had a poorer survival rate. The long-term survival of our patients can be improved by educating the patients, giving them counselling on the importance of completing the prescribed treatment. Further improvement will include standardized chemotherapy regimen and surgical practices as decided by the multidisciplinary sarcoma board meeting. It is also important to have health education to the public on early detection of bone sarcoma to prevent delayed presentation with large tumour and systemic metastasis.

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| References | Chemotherapy regime | 5-year OS (%) | 10-year OS (%) | Significant risk factors |
|------------|----------------------|---------------|----------------|-------------------------|
| Yip et al.9 | CPT, DOX, HD-MTX, IFO, ETP | 43.0 | NA | Nil |
| Bielack et al.1 | CPT, DOX, HD-MTX, IFO, BLM, CTX | 65.3 | 59.8 | Tumour site and size, primary metastases, response to chemotherapy and surgical remission |
| Smeland et al.3 | CPT, DOX, HD-MTX | 74.0 | NA | Positive prognosticators were tumour volume <190 ml, 24-h serum methotrexate >4.5 mM and female gender |
| Wiromrat et al.8 | CPT, DOX, HD-MTX, ETP, IFO | 27.6 | NA | Patients who received chemotherapy only survived longer |
| Pruksakorn et al.7 | Age < 15 – CP, DOX | 37.9 | 33.6 | Presence of metastasis at initial examination, delayed and against treatment cooperation, and axial skeletal |
| Vasquez et al.18 | CPT, DOX, HD-MTX, IFO | 64.5 | NA | Negative prognosticators were initial elevation of ALP and poor histological response |
| Hung et al.16 | Before 2004 – HD-MTX, DOX, IFO, EPI, CPT | 67.7 | NA | Negative prognostic factors were patients diagnosed before 2004 and patients with metastasis |
| Faisham et al.6 | Age < 12 – VCR, CPT, DOX, HD-MTX, BLM, DACT | 34.0 | NA | Presence of pulmonary metastases and compliance to treatment |
| This study | CPT, DOX, HD-MTX | 56.3 | 22.3 | Independent risk factors were presence of metastasis and completion of treatment |

OS: overall survival; CPT: cisplatin; DOX: doxorubicin; HD-MTX: high dose methotrexate; IFO: ifosfamide; ETP: etoposide; BLM: bleomycin; CTX: cyclophosphamide; CP: carboplatin; ALP: alkaline phosphatase.
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