A RETROSPECTIVE REVIEW:
LONG-TERM OUTCOMES AND PREDICTORS AFFECTING LONG-TERM OUTCOMES IN OSTEOSARCOMA PATIENTS IN THE GROOTE SCHUUR HOSPITAL PATIENT POPULATION

by
Heide Hart

Student Number: 1446289
Supervisor: Dr Jeannette Parkes

In fulfilment of the requirements for the degree

MMed Radiation Oncology Faculty of
Health Sciences UNIVERSITY OF CAPE TOWN
The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.
DECLARATION

I, ...Heide Hart..., hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signed by candidate

Signature: ... Signature Removed

Date: 24th August 2016
Abstract:

Background: Predictive factors for long-term outcomes in osteosarcoma patients are still controversial. There is no literature available regarding these factors in a patient population in a developing country.

Objectives: To determine the outcome of treatment of osteosarcoma patients treated at Groote Schuur Hospital from 1990-2012 in terms of local control (LRC), disease free survival (DFS) and overall survival (OS) and to determine the value of suggested predictive factors in this population.

Patients and methods: Retrospective review of all patients diagnosed and treated with osteosarcoma at Groote Schuur Hospital between 1990 and 2012, considering OS, DFS and LC. This review assesses the significance of suggested predictive factors from other studies, namely, HIV status, age at diagnosis, site of primary disease, type of chemotherapy used, response to chemotherapy and type of surgery in terms of OS, DFS and LC.

Results: Forty-three patients with histologically confirmed osteosarcoma were treated at Groote Schuur Hospital between 1990 and 2012. Median 5 year OS was 57.8%. On univariate analysis, the site of disease was the only statistically significant predictive factor for prognosis.

Conclusion: On univariate analysis, patients with axial disease have a worse predicted prognosis than those with primary disease in their extremities. The long-term outcome in our local clinical setting correlates favourably with the available international data. Due to the limited number of patients in the review, further research into HIV status, age, type of chemotherapy, type of surgery and their predictive value for prognosis in our patients with osteosarcoma is warranted.
Introduction:

Osteosarcomas are uncommon tumours but they are the commonest primary bone tumour diagnosed, with a bimodal age distribution. A peak incidence occurs in childhood and adolescence and another peak occurs in elderly patients. The majority of osteosarcomas are found in the long bones of the extremities, but they can also be found in the axial skeleton and extraskeletally. Since the advent of adjuvant chemotherapy in the mid 1970's and more recently, of neoadjuvant chemotherapy, there has been an improved overall survival seen in these patients. Since the 1980's, international data suggests 5 year overall survival rates of between 60 and 70% in patients with non-metastatic osteosarcoma of the extremities. Standard of care for osteosarcoma at present includes multi-drug chemotherapy followed by surgery and adjuvant chemotherapy. Radiotherapy is only used for irresectable or incompletely resected disease. Many studies have looked at predictive factors for prognosis, but the results remain conflicted. The suggested factors include: age at diagnosis, site of primary disease, type of surgery and response to neoadjuvant chemotherapy. Very little is available in the literature on HIV status and its effect on long-term outcomes in these patients.

We do not have accurate incidence data of osteosarcoma in South Africa nor data on the long-term outcome of patients. No data has previously been collected locally regarding predictive factors for prognosis.

We aimed to collect South African demographic data on osteosarcoma, including predictive factors. Furthermore we wanted to establish whether our patients have similar characteristics to the available international data.

Patients and methods:

Records of osteosarcoma patients seen at Groote Schuur Hospital between 1 Jan, 1990 and 31 Dec, 2012 were included in the review process after approval by the Human Research Ethics Committee of the University of Cape Town. The electronic patient registry at Groote Schuur Hospital was used to identify the patients.

A total of 42 patients were included in the initial analysis, but 5 were excluded due to defaulting any treatment other than their initial visit, leaving the remaining 37 patients as the patient population included in this case series. Patient demographics, treatment and follow-up data was collected and this included: age at diagnosis, race, gender, HIV status at diagnosis, date of diagnosis, site of primary tumour, metastatic status, chemotherapy received, date of surgery, type of surgery and histologic response to chemotherapy. Necrosis of 90% or more was used as the cut-off value, based on the Huvos grading system. As the size of the primary tumours was not documented in many folders and due to a recent change of radiological system, this information could not be obtained. Other data collected included follow-up imaging and date of development of recurrence or metastases.

Overall survival, (defined in this review as time of diagnosis to time of death); local control and disease free survival, (both defined as the time from surgery to either local recurrence or diagnosis of metastases), were determined. This data was depicted on Kaplan Meier curves. The patients lost to follow-up and those who survived without disease recurrence were censored. To compare groups the log-rank test was used, with values less than p=0.05 being considered statistically significant. The data from each predictive factor was analysed according to the above stated methods. Only univariate analysis was done, due to small patient numbers. Prism version 6.01 software was used for the statistical analysis.
Results:

Thirty-seven patients were included in this case series. Of these 8(21.6%) had metastatic disease at presentation, 4(10.8%) did not have metastatic disease but were inoperable at presentation, due to the site of disease. 25(67.5%) patients had non-metastatic disease at presentation and underwent comprehensive treatment.

The 5-year overall survival for the total population (n=37) was 57.8% [95% CI 31.7% - 76.9%], with the median overall survival not yet reached at the time of analysis. The 5-year local control rate (n=25) was 75.8% [95% CI 50.5% - 89.3%] and the 5-year disease-free-survival (n=25) was 48.165% [95% CI 25.2% - 67.9%]. The median DFS was defined at 50 months. (Figure 1)

Recurrent or metastatic disease was detected on imaging and clinical examination. No histological confirmation was obtained in the majority of cases.

Patient characteristics:
The demographic data of the study population is included in Table 1. Of note, patients under 13 years of age were not included in this retrospective review, as they were treated at the children’s hospital and not at Groote Schuur Hospital. At presentation 30(81%) patients were
performance status 1, 2(5%) patients were performance status 2 and 1 patient was performance status 3-4. For 4 patients performance status was not documented. The median time of follow-up for the patient population was 39 months.

Figure 2: Flow diagram depicting patient identification, presentation and treatment
<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Ratio: 1.18:1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>n=20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>n=17</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Range: 14-58yrs</td>
<td>Median: 23yrs</td>
<td>Mean: 28yrs</td>
</tr>
<tr>
<td>Female</td>
<td>13-85yrs</td>
<td>21yrs</td>
<td>26yrs</td>
</tr>
<tr>
<td>Total population</td>
<td>13-85yrs</td>
<td>23yrs</td>
<td>27yrs</td>
</tr>
<tr>
<td><strong>Race:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African</td>
<td>n=11</td>
<td>29.7%</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>n=12</td>
<td>32.4%</td>
<td></td>
</tr>
<tr>
<td>Coloured</td>
<td>n=14</td>
<td>37.8%</td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td>n=0</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>n=0</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td><strong>HIV status at presentation:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>n=4</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>n=11</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>n=22</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td><strong>Metastatic disease at presentation:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>n=8</td>
<td>21.6%</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>n=25</td>
<td>67.5%</td>
<td></td>
</tr>
<tr>
<td>No, but inoperable primary</td>
<td>n=4</td>
<td>10.8%</td>
<td></td>
</tr>
<tr>
<td><strong>Site of primary disease:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trunk</td>
<td>n=4</td>
<td>10.8%</td>
<td></td>
</tr>
<tr>
<td>Pelvis</td>
<td>n=2</td>
<td>5.4%</td>
<td></td>
</tr>
<tr>
<td>Upper long bones</td>
<td>n=5</td>
<td>13.5%</td>
<td></td>
</tr>
<tr>
<td>Upper short bones</td>
<td>n=0</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Lower long bones</td>
<td>n=14</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Lower short bones</td>
<td>n=12</td>
<td>32.4%</td>
<td></td>
</tr>
</tbody>
</table>
Histology:

<table>
<thead>
<tr>
<th>Type of Osteosarcoma</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional subtype</td>
<td>n=15</td>
<td>40.5%</td>
</tr>
<tr>
<td>Osteoblastic</td>
<td>n=8</td>
<td></td>
</tr>
<tr>
<td>Chondroblastic</td>
<td>n=5</td>
<td></td>
</tr>
<tr>
<td>Fibroblastic</td>
<td>n=1</td>
<td></td>
</tr>
<tr>
<td>Telangiectatic</td>
<td>n=1</td>
<td></td>
</tr>
<tr>
<td>Surface Osteosarcomas</td>
<td>n=2</td>
<td>5%</td>
</tr>
<tr>
<td>Periosteal</td>
<td>n=1</td>
<td></td>
</tr>
<tr>
<td>Parosteal</td>
<td>n=1</td>
<td></td>
</tr>
<tr>
<td>Osteosarcoma, NOS</td>
<td>n=20</td>
<td>54%</td>
</tr>
</tbody>
</table>

Type of surgery performed:

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation</td>
<td>n=13</td>
<td>35%</td>
</tr>
<tr>
<td>Limb-sparing Surgery</td>
<td>n=16</td>
<td>43%</td>
</tr>
<tr>
<td>Unknown or no surgery</td>
<td>n=8</td>
<td>21.6%</td>
</tr>
</tbody>
</table>

HIV Status:

We studied whether a patient’s HIV status affected their prognosis, as there is almost no available data on this topic. Unfortunately, due to limited patient numbers and not all patients having an HIV test at baseline, our results are not statistically significant. Nonetheless, they provide us with some data in this specific subset of patients. In terms of LRC, DFS and OS, HIV positive patients have a median local recurrence free survival of 20 months (p=0.1341), disease free survival of 20 months (p=0.3403) and an overall survival that was not yet reached at the time of analysis (p=0.2027). Of the four patients who were HIV positive at diagnosis, 2 had irresectable pulmonary metastatic disease upfront and received palliative chemotherapy, another one developed severe neutropenic sepsis on second line chemotherapy and opted to discontinue treatment and the last patient was well when lost to follow up.

In both the HIV negative and unknown status group, the median time for local recurrence had also not yet been reached at the time of analysis. The HIV negative group had a DFS of 38 months and an overall survival of 57 months. This appears to be longer than the HIV positive group. (See figure 2).
Site of primary disease:

The patients who had primary disease in the axial skeleton did worse than patients who had primary disease in the extremities. This was statistically significant for LRC, DFS and OS. Patients with their primary tumour in the pelvis had a median OS of 17 months, those with a primary elsewhere in the trunk, 25.5 months and those with their primary in the lower limb short bones (defined as the tibia) had a median OS of 57 months. The patients who had primary tumours in the upper limb extremities (in this case series only in the humerus) or in the lower limb long bones (including the femur only) had the best median OS which in this study had not yet been reached at the time of analysis (p=0.0261). These results are reflected in the DFS and LRC where patients who had axial primaries had worse long-term outcome in comparison to patients with an extremity primary. The median DFS was: non-pelvic trunk: 11 months, pelvis: 8 months, lower limb long bone (the femur): 33 months, lower limb short bones (the tibia): 50 months and the upper limb long bone (the humerus): the results were not yet reached at the time of the analysis (p=0.0236). The median LRC was: pelvis: 9 months and for all other sites it had not yet been reached at the time of the analysis (p=0.0225). (See figure 3)

Type of surgery:

28 patients had surgical excision of the primary tumour. 5 of these had metastatic disease at presentation. The remaining 9 patients were lost to follow-up prior to surgery or had irresectable axial skeleton disease. It appears that patients who had limb-sparing surgery had a better long-term outcome when compared to patients who had amputations for LRC, DFS and OS: Patients who had an amputation had a median OS of 58 months whereas for patients who had limb-sparing surgery the median survival had not been reached at the time of analysis (p=0.2695). The log-rank hazard ratio (HR) was not statistically significant but tended to favour patients in the limb-sparing arm, HR=0.3805 (95% CI=0.057-2.208).

The median DFS was 50 months in both arms. This was not statistically significant (p=0.8689). The HR=0.9012 (95% CI=0.2490-3.221). Median LRC was not yet reached at the time of analysis.
analysis for both limb-sparing surgery and amputation (p=0.1111), HR=0.1929 [95% CI=0.025-1.460].

Figure 4: Kaplan Meier survival curves for disease site: LRC (p=0.0225), DFS (p=0.0236), OS (p=0.0261)

**Chemotherapy and response to chemotherapy:**

The majority of patients received multimodality treatment. Patients who were deemed non-metastatic at presentation either received neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy or they had surgery prior to presentation to the Department of Radiation Oncology and received adjuvant chemotherapy. The majority of patients received a dual-drug chemotherapy regime of cisplatin 100mg/m² D1 and adriamycin 25mg/m² D1-3. Of the 37 patients analysed, 34 patients received chemotherapy. 26 received cisplatin-adriamycin neoadjuvantly, 7 patients received adjuvant chemotherapy only and 1 received high-dose methotrexate (HDMTX) alternating with cisplatin and adriamycin. All long-term outcome results obtained from this analysis were not statistically significant and were difficult to interpret, due to the small patient numbers and the diversity of chemotherapy regimens used.

In terms of histological response to chemotherapy, 19 patients had their response assessed after receiving 3 cycles of neoadjuvant cisplatin-adriamycin. 21% of patients had a good response, with necrosis ≥ 90% and 79% had a poor response, with necrosis < 90%. Amongst the patients that had a poor response, 1 was lost to follow-up post-surgery, 10 completed
another two cycles of the cisplatin-adriamycin regimen followed by a change in chemotherapy with two cycles high dose methotrexate. 4 patients completed another 3 cycles of the cisplatin-adriamycin regimen and did not change chemotherapy. Long-term outcome results for poorly-responding patients whose chemotherapy regimen was changed, was not statistically significant: the median LRC time was not yet reached at the time of analysis for both groups (p=0.8203) and the median DFS for the chemotherapy changed arm was 72.5 months versus 41.5 months for the chemotherapy unchanged arm (p=0.8064). The median OS was not reached at the time of analysis for both arms (p=0.8268). (See figure 4)

Discussion:

According to the SEER Program, osteosarcomas present with a bimodal age distribution, with a peak between 15 and 25 years of age and another later in life (> 60yrs). Our patient population had the highest incidence in patients younger than 25 years, in the 13-25 year age group. (See Table 1) We only had one patient over the age of 60 years. A specific analysis including age at diagnosis as a potential predictive factor was therefore not included in this article. The most common histological subtype of osteosarcoma diagnosed (90% of patients), according to the World Health Organization, is the conventional subtype.

However, the majority of patients were not sub-classified on initial histology report and have therefore been included in the series as “osteosarcoma not otherwise specified”. We have not included a discussion on stage of disease at diagnosis, as patients were classified as “non-metastatic” vs. “metastatic” and “operable” vs. irresectable”. Our 5-year overall survival rates were similar to patients in international studies that received the two-drug regimen of cisplatin and adriamycin. The 5-year local control rate amongst our patients was high compared to the disease-free and overall survival rates and this could be attributed to a higher amputation rate than seen internationally. The higher amputation
rate may indicate a higher proportion of patients presenting with locally advanced disease.

According to international data, the 5-year DFS and OS rates are not very different, reflecting that second-line therapies are not generally found to be effective.\(^3, 13\) In our centre, a combination of ifosfamide and etoposide is used at recurrence. In our case series, a difference was shown between the DFS and the OS which would indicate successful salvage treatment. However, it is worth noting that this series includes a small group of patients that had indeterminate lung nodules at diagnosis which were assumed to be metastases. These patients may have been incorrectly staged upfront as having metastatic disease, without histological confirmation and therefore it is possible that these results do not indicate successful salvage but rather patients whose indeterminate lung nodules were not metastases. These patients were excluded from the DFS analysis, which only included non-metastatic patients. Furthermore, DFS in this review was calculated from the date of surgery i.e. the patient was free of disease and the OS was calculated from the date of diagnosis, which in the majority of cases was prior to surgery. The entire cohort was included in the overall survival analysis.

Most of the patients included in this case series received 3 cycles of neo-adjuvant cisplatin-adriamycin, followed by either another three cycles of cisplatin-adriamycin after surgery or in the case of some of the younger poor responders, two cycles of cisplatin-adriamycin followed by two cycles of high dose methotrexate. In the poorly responding patients \((n=15)\), with necrosis < 90\%, there was no statistically significant difference in the long-term outcome of patients who changed regimen when compared to patients who continued with their chemotherapy unchanged. This has been shown in international literature too. Historically, it was thought that there might be some benefit, in changing chemotherapy post-operatively in younger poorly responding patients \((< 40\,\text{years})\). However, in the recent results presented at EMSOS of the phase III randomized-controlled trial, EURAMOS1, results indicate that there is no benefit to changing the chemotherapy regimen in poorly responding patients and that it may be more toxic to do so. It is worth noting that, unlike our patients who were treated with cisplatin and adriamycin alone upfront, all patients in this trial received methotrexate, cisplatin and adriamycin with or without interferon.\(^7, 14\)

The site of primary disease varies in different age groups. This was not apparent in our patient population, probably due to our limited number of patients and the fact that the majority of our patients were in the < 25 year old age group. It has been shown that patients with their primary disease in the short bones of the upper limbs have the best prognosis, followed by disease of the other bones of the extremities.\(^1, 9, 11\) This is reflected in our results.

Patients who had limb-sparing surgery had a more favourable long-term outcome when compared to patients who had amputations. However, there is a selection bias in this patient population due to large and locally advanced tumours preferentially requiring amputation. Patients with neurovascular involvement, rapidly growing tumours on neoadjuvant chemotherapy and skin involvement by tumour are not good candidates for limb-sparing surgery. The number of limb-sparing surgeries compared to amputations varies from centre to centre as better imaging and greater surgical expertise is required to perform the former.

Higher rates of limb-sparing surgery are possible with timeous referral of patients. The rate of limb sparing surgery in the Western Cape from is approximately 82\%. This correlates favourably with international figures.\(^15\)

There is very limited data available on the effect of HIV status on prevalence and outcome in osteosarcoma. The data we collected was not complete for our entire case series, but we had the results of 18 patients, which is more than has been described in the literature to date. In South Africa, there is a national prevalence of HIV infection in adults of approximately
10.6%, which is consistent with our patient population.\(^{(10)}\) Despite a trend towards HIV positive patients doing worse, there was no statistically significant difference in long-term outcome in the HIV positive or negative groups in our retrospective audit. Further research is required to determine an accurate relationship between osteosarcoma and HIV infection, as our patient numbers were small.

**Conclusion:**

Osteosarcoma is a relatively rare cancer in which treatment has not changed significantly over the past thirty years. In our local setting, long-term outcome correlates with that found in the international literature. The site of a patient’s primary has been found to be a significant predictive factor for overall and disease free survival in all patients. Further research needs to be done into other predictive factors as the patient numbers in our case series were limited. This case series is also a retrospective review in a single institution, which may have contributed to bias in the patients’ results.

The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper. The research was approved by an ethics committee.

**References**

Literature Review:

The objectives of this literature review included obtaining demographic data on osteosarcoma patients and obtaining data on the long-term outcome of various treatment regimens used in these patients. Certain factors have been suggested in international studies to have predictive value including: age at diagnosis, site of primary disease, response to chemotherapy and type of surgery. The main objective of this literature review was to determine the validity of these factors and potentially any others in the available literature.

For the literature search strategy I used the UCT Health Sciences library databases, in particular Pubmed and ScienceDirect. I initially looked for randomized controlled trials in osteosarcoma, but found very few. I then used the following keywords to search for the articles: “Osteosarcoma” and “demographics” and “epidemiology” and “international” / “Southern Africa”; “osteosarcoma”, “prognostic factors” and “age”; “site of disease”; “response to chemotherapy”; “chemotherapy regimens”; “surgery”; “osteosarcoma” and “radiotherapy”; “osteosarcoma” and “outcomes”; “osteosarcoma” and “metastatic disease” and “outcomes”; “osteosarcoma” and “HIV”. Unfortunately most of the data obtained was retrospective and the majority of data on epidemiology was international and not from Southern Africa. I excluded any basic sciences data on osteosarcomas and data on chemotherapy in the metastatic setting. I did include data from a wide variety of age populations, as some centres only treat children and adolescents and some mainly adults.

Osteosarcomas are uncommon tumours but they are the most common bone tumours diagnosed. They make up less than 1% of all cancers diagnosed in the United States of America and international studies have incidence figures as low as 0.2% (1, 2). They are more common in paediatric patients but still make up less than 20% of all tumours in this patient population. (3) Unfortunately we do not have accurate, current data of the incidence of osteosarcoma in South Africa.

Gender and racial differences were seen in international incidence data. In children, there appeared to be a greater incidence of osteosarcomas in the Black and other populations versus Caucasian patients, but in adults the highest incidence appears to be in the Caucasian population. Males are affected more commonly by this malignancy than females. In terms of gender as a predictive factor for prognosis, female patients generally appear to have a better prognosis than males. In the SEER incidence data, there was no uniformity across various age groups regarding racial differences in patients and therefore its ability to be used as a predictor of prognosis is unclear when considering this data. (1, 4)

The risk factors predisposing to the development of osteosarcoma are not concrete, but there are some factors that appear to lead to a higher incidence of this disease. Osteosarcomas seem to be associated with hereditary syndromes, including Li-Fraumeni Syndrome, hereditary retinoblastoma, Rothmund-Thomson syndrome and Bloom and Werner Syndromes. Other suggested risk factors include: previous radiation treatment, exposure to alkylating agents, Pagets disease and other benign bone lesions. However, despite there being the suspicion that genetic and environment factors play a role in the development of this disease, there is more research required to confirm and further define these factors and the exact aetiology of osteosarcomas. (3, 4)

Osteosarcomas occur predominantly in children and adolescents below 20 years of age, with a peak between 13 and 16 years. A second peak occurs in a patient population over 60 years of age. It is surmised that this bimodal distribution relates to a growth spurt in adolescents and in the elderly, to pre-existing conditions like Paget’s disease. Patients’ age at diagnosis has been proven to be associated with prognosis in various malignancies including: breast cancer, thyroid cancer, renal cell cancer, colon cancer and rhabdomyosarcoma. With regards to osteosarcoma, current international data shows that there are large differences in incidence and survival by age, with elderly patients appearing to have a worse prognosis than younger patients. (1, 2, 4) However, this is a controversial topic, as previous trials done, specifically studying age as a prognostic factor did not yield statistically significant results in multivariate analyses. In a trial by Harting et al, it appears that having an age of 40 years or older is associated with a worse outcome, but this was only true on the univariate analysis. (5) Many studies and published articles have analysed the value of this predictive prognostic factor and most seem to agree that patients who are diagnosed at an older age tend to have a worse prognosis. The splitting of patients’ ages into various subgroups is also variable in the available data, but for the purposes of my research I have followed the split used by the SEER database from the United States of America; namely, 0-24 years, 25-60 years and 60-85 years. This topic requires further study. (1, 5-9)
The site of primary disease appears to vary in the different age groups. Also different sites of disease appear to be associated with different outcomes. In the United States of America, it has been shown that in younger patients, tumours occur more frequently in the metaphyses of long bones and that in elderly patients, primary tumours are more usually axial. Recent evidence shows that patients with local disease in the upper short bones have a better long-term survival than other patients. Those that have primary pelvic disease or are diagnosed with other primary axial tumours have the worst prognosis.(1) Localised disease at presentation also had a better prognosis than metastatic disease.(1, 7, 10) Tumour size at diagnosis is recognized by the WHO as a predictive factor for prognosis and has been shown to be a statistically significant prognostic variable in various retrospective audits performed. Unfortunately, as with many of the suggested predictive factors of prognosis in this disease, some articles still show that this too is inconclusive and further research is required to prove the value of this predictive factor in multivariate analyses.(7, 10)

HIV status and associated prognosis in osteosarcoma has not been looked at in the literature before. There was an article published by Marais et al from Grey’s Hospital in Kwa-Zulu Natal in 2013, but unfortunately they only included five patients who were HIV positive and three who were HIV negative with osteosarcoma. Therefore this topic requires further research.(11)

There are three major histological variants of intramedullary osteosarcoma recognised by the WHO: conventional osteosarcoma, which includes: chondroblastic, osteoblastic and fibroblastic subtypes; telangiectatic osteosarcoma and small cell osteosarcoma. There are also juxtacortical osteosarcomas which include the low-grade parosteal type, the intermediate-grade periosteal type and high-grade surface osteosarcomas.(4, 10) The most common histological subtype diagnosed is the conventional type. Approximately 50% of patients have the osteoblastic subtype. Previously it was thought that patients with types of intramedullary osteosarcoma other than the conventional subtype, had a worse prognosis, but with current aggressive multimodality treatment regimens, there is not much difference documented. However, some data suggests that patients with chondroblastic osteosarcoma, have a worse prognosis than the other subtypes of conventional osteosarcoma. The periosteal and parosteal subtypes of juxtacortical osteosarcoma have a more indolent course versus the intramedullary types.(4, 12)

In terms of treatment, 30-40 years ago, surgery alone or radiotherapy was administered in localised disease in osteosarcoma patients, as sole modality treatment. It was found that 80-90% of treated patients developed metastatic recurrence of their disease and the 2 year survival rates were as low as 15-20%. The hypothesis was made that the majority of patients have undetected micrometastases at diagnosis and the concept of adjuvant chemotherapy was introduced in the 1970’s. With the addition of adjuvant chemotherapy, the survival rates improved from 20% to 60% and adjuvant chemotherapy became the standard of care.(2, 13)

Later on, neoadjuvant chemotherapy was introduced. The benefit of the timing of this treatment included the early treatment of micrometastases, tumour shrinkage prior to surgery and the ability to predict a patient’s long-term prognosis. Patients with a poor response to neoadjuvant chemotherapy (< 90%) could also be changed to alternative regimens e.g. high dose methotrexate. Choosing neoadjuvant chemotherapy over adjuvant chemotherapy and changing the chemotherapy regimen post-surgery in poor responders, however, has not been proven to change long-term outcomes.(2) Current chemotherapy protocols being used to treat osteosarcomas include combinations of cisplatin, Adriamycin, ifosfamide, and high dose methotrexate. These drugs have all shown activity in the treatment of osteosarcoma. Studies done including etoposide have shown it to be less active. At least two agents are used concurrently as standard of care. Whether three agents should be used in younger patients is also controversial, but it does appear to slightly improve long-term outcomes when compared to a two-agent protocol.(13) However, there has been no proven statistical difference in patients who receive a three- versus four-drug regimen. There is also controversial data available regarding the changing of chemotherapy regimens post-operatively in poor responders, and the benefit of this. (13) In the recent results of the phase III randomized-controlled trial, EURAMOS1, presented at EMSOS, it is indicated that there is no benefit to changing the chemotherapy regimen in poorly responding patients and that it may be more toxic to do so.(14)

It appears that one of the most important predictive factors of prognosis is response to neoadjuvant chemotherapy. The degree of necrosis is measured and patients who have 95% or more necrosis after
three cycles of neoadjuvant chemotherapy have been found to have a better long-term survival than those with less than 95% necrosis.\(^{(2)}\) This figure of 95% however, is relatively subjective and some centres use 90% as their defining percentage. There have even been authors that document using 65% as their cut off. Either way it seems that patients with higher percentages of necrosis have a better prognosis when compared to those that have less necrosis in the tumour specimen, but these variable defining criteria have made it difficult to determine the true predictive value of chemotherapy-induced necrosis as a prognostic factor.

There also appears to be a correlation between the response to chemotherapy and the tumour histology. In a single centre study done in Italy, it appeared that the degree of necrosis was only a valid prognostic factor in patients with osteoblastic and telangiectatic osteosarcoma and there was no difference between patients’ long-term survival with chemotherapy-induced necrosis of 90-99%. This study was however only done in young patients with extremity osteosarcomas so these findings cannot be used as a general consensus. It also appeared that female patients had a better histological response versus male patients. Another study showed that a ‘good’ necrotic response was higher for patients with fibroblastic and telangiectatic osteosarcomas when compared to osteoblastic and chondroblastic osteosarcomas.\(^{(2, 7, 15)}\)

The majority of patients that do relapse, develop distant metastases alone. Initial poor responders to chemotherapy appear to have a much higher rate of systemic relapse without local recurrence when compared to patients who are good responders.\(^{(13)}\)

Current research is looking at ways to predict neoadjuvant chemotherapy response pre-surgery as this could assist in determining which patients may benefit from changing chemotherapy protocols. Dynamic enhanced contrast MRI scan has been considered, but this was found not to be specific for tumour necrosis. Now further research is being done into the use of PET-CT scans in this setting.\(^{(16, 17)}\)

Neoadjuvant chemotherapy may also allow for greater tumour shrinkage, which facilitates limb-sparing surgery as opposed to limb amputations. Other factors that may also play a role in allowing for higher rates of limb-sparing surgery include: improved imaging techniques, more specialized centres and an improvement in timeous referral patterns. In an Italian study published in 2005 the percentage of limb-sparing surgeries was 85.4% versus 10.2% for amputations.\(^{(15)}\) Other international studies show rates of limb-sparing surgery as high as 90%. The single centre studies reviewed generally have higher figures for limb sparing surgery when compared to multi-institutional trials which have rates of between 36 and 50%.\(^{(18)}\)

A retrospective audit done in the Western Cape between 2000 and 2006 showed that our rates of limb-sparing surgery are approximately 82%.\(^{(19)}\) Presenting features which would exclude patients from limb-sparing surgery include skin involvement, major neurovascular involvement and rapidly progressing disease on neoadjuvant chemotherapy. The type of surgery performed on its own has been recognised as a predictive factor for prognosis in a retrospective audit done in the United States by Harting et al and in the study by Bacci et al. In both of these publications there appeared to be an association between chemotherapy-induced necrosis and limb salvage surgery.\(^{(4, 10, 15, 20)}\)

Radiotherapy in osteosarcoma is not standard of care treatment and conventional osteosarcoma is relatively resistant to radiotherapy. It has however, been shown to be of use for local control in patients in whom wide, local excision of the primary is not possible, in particular in truncal primaries. There is some evidence that higher doses delivered with proton beam radiotherapy and heavy ions may provide prolonged local control in these cases.\(^{(21)}\) It is also effective in improving local control in patients with microscopic residual.\(^{(22)}\) Primary radiotherapy is generally ineffective at obtaining local control and therefore whenever possible surgery is performed.\(^{(13)}\)

Various molecular markers have been considered in osteosarcoma but to date none of them have had any predictive value with regards to prognosis.\(^{(2)}\) Metastatic disease at presentation is a predictor of poor long-term outcomes when compared to patients with localised disease only. In international studies, less than 20% of patients have metastatic disease at presentation.\(^{(2, 7)}\) The most common sites for patients to present with metastases are the lungs followed by the bones. Patients with lung metastases alone have a better outcome than those with bone metastases and patients with lymph node or other organ metastases have the worst prognosis of all.\(^{(7)}\) When assessing metastases, resectability is the most important predictive factor for long-term survival. Response to neoadjuvant chemotherapy
can also assist in predicting prognosis. Younger patients, under the age of 20 years at diagnosis, diagnosed with metastatic disease also appear to have better long-term survival when compared to older patients.(2)

Local experience has not been well-documented. To date there have been two retrospective reviews published on osteosarcoma in South Africa, namely Ga-Rankuwa and Grey’s Hospital. Both studies looked at disease presentation in their units and the long-term outcomes of their patients. The conclusions were similar, stating that the patients in a Southern African setting present with advanced disease, which limits treatment options and is associated with poor long-term outcomes. Nothing has been documented regarding the viability of the suggested predictive factors for prognosis in an African population, nor did the data include any patients from the Western Cape.(18, 23)

The current standard of care treatment for non-metastatic osteosarcoma of the extremities consists of chemotherapy and surgery. International available data quotes 5 year overall survival figures for non-metastatic extremity osteosarcomas in the region of 60-70%, depending on the data considered (3, 20, 24). For tumours of the axial skeleton the cure rate is only about 30%.(20) Five year disease-free survival rates have been quoted as 55-70% depending on the institution considered, the age group of patients studied and the chemotherapy regimens used.(25, 26) Unfortunately, in many of the studies done in osteosarcoma, 5 year outcome data is quoted but the majority of patients are followed up for periods shorter than 5 years, making this data inaccurate.(25) No data obtained from patients in the Southern African setting contributed to these figures. It is controversial whether a two-drug chemotherapy regimen gives inferior long-term outcomes versus three- or four-drug regimens and one trial has shown that when compared to multi-drug regimens, the two-drug regimen, of cisplatin-adriamycin, had similar outcomes. However, the 5 year OS in this trial was only 55% and the 5 year DFS was only 44%.(27)

Therefore further future research is needed to clarify which chemotherapy regimen provides the best long-term outcomes. The available data regarding predictive factors for prognosis in osteosarcoma is controversial, but it seems that the majority of studies, even if the majority are only retrospective reviews, agree that the presence of metastases at diagnosis, poor response to chemotherapy and axial site of primary are associated with worse long-term outcomes. Age at diagnosis, type of chemotherapy and tumour size also appear to be predictive of prognosis and possibly the patient’s baseline serum ALP level. The association between HIV and osteosarcoma outcomes needs definite further research.(2, 7, 9, 11, 13, 25)

References


