

**A Retrospective assessment of Osteosarcoma patients treated at
National Cancer Institute Sri Lanka**

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Abstract

Background

Osteosarcoma is the most common bone cancer in adolescent. In Sri Lanka outcome of osteosarcoma in adult population still not analyzed. National Cancer Institute of Sri Lanka (NCISL) is the leading cancer treatment center in Sri Lanka, so by analyzing the outcome of osteosarcoma at NCISL reveal the outcome in Sri Lanka.

Patients and methods

Osteosarcoma patients, who's age 13 years and above, who registered at NCISL during the year 2008 to 2011 were retrospectively analyzed. Totally 97 patients were identified. However 10 patients were referred to other peripheral centers and 7 patients clinic records were missed, therefore 80 patients were analyzed. The objectives were to identify clinical presentation, percentage of patients who abandoning treatment, percentage of limb sparing surgery, event free survival, progression free survival and overall survival.

Results

The mean age at presentation in this cohort was 27 years (SD 27), range from 13 years to 61 years. Sixty six percentage (53/80) were males and 34% (27/80) were females. Primary site at presentation for majority of the patients was limb (90%). Around seventeen percentage of them had metastasis at presentation, and major site of metastasis was lung (13.8%). Around 30% (24/80) of the patients defaulted their treatment within first 3 cycle of neo adjuvant chemotherapy, 5 patients were defaulted after neo adjuvant chemo and a patient defaulted during adjuvant chemo. All most all patients had treatment delay more than two weeks during the cause of the treatment. Totally 43 patients had primary site management. In which 40 (93%) patients had only surgery and 3 (6.9%) of them had both surgery and radiotherapy. Twenty three (53%) of the extremity osteosarcoma patients had limb sparing surgery and 19 (44%) of them undergone amputation. Twenty five (58.1%) of them had good pathological response rate to neo-adjuvant chemotherapy and 18 (41.9%) of them had bad pathological response rate. Seventeen (21.3%) patients had progressive disease during treatment, 13 (16.3%) of them had lung metastasis. Two and five year event free survival was 45% and 11% respectively. Progression free survival for 2 and 5 years were 45% and 12.5% respectively. Overall survival of 2 and 5 years were 46% and 10%.

Conclusion

Socio demographic data and clinical presentations almost similar with international data. However abandoning treatment and treatment delays are the significant problem in our patients. Surprisingly more than half of the patients undergone limb sparing surgery. Although survival rates were significantly low in the study population, inadequate data in clinic records and non-following survivors are giving hope to have more survival rate.

Introduction

Osteosarcoma is the second most common malignant primary bone tumor after multiple myeloma in adults <1,2>. It is the third most common cancer in teenagers after lymphoma and brain tumors. It comprises 2.5% of all malignancies and is more common in males than females. Localized osteosarcoma of adolescent generally has a good outcome with 5 year survival 60% to 80% and more likely curable if resectable <3>. However metastatic osteosarcoma has bad outcome with 5 year survival 15% to 30%, if lung metastasis is 40 %, < 3>. Great advances have been made in the treatment of osteosarcoma during the few decades. In the 1960s the only treatment available was amputation, and a small number of patients survived 2 years or more after diagnosis. Now multi-modal treatment is well accepted. Chemotherapy given before and after surgery cure many cases with osteosarcoma. It can also allow some people who previously would have needed to have a limb amputation to have limb sparing surgery instead. Ideally the patients should be treated under the supervision of a bone sarcoma multidisciplinary team. <21,22>

Although studies have shown similar survival for limb sparing surgery and amputation, the limb sparing surgery is amenable depend on site of tumors, size and extent of the tumor. In Sri Lanka most widely used surgical methods are wide local excision with limb sparing or amputation. Internal prosthesis for limb salvage surgery and rotationplasty or reconstructive surgeries are most costly and not always freely available in Government sectors in Sri Lanka. Even the cost of prosthetic limb for amputated patients is really high in Sri Lanka and really hard to find money for it for the poor patients. A loss of a limb can have significant psychological, financial, social implications. The biggest problem has been for teenagers, who worry about social effects of their operation. Emotional issues may be the major cause for the wide number of defaulting treatment in Sri Lanka. Psycho social support and encouragement are needed for all of them. Inoperable tumors and those who medically not fit for surgery are treated by radiotherapy. All the patients following active treatment need long term follow-up to find local and systemic recurrence. At NCISL these patients are followed up with clinical examination and chest X rays or CT scan if suspect systemic recurrence.

Justification

Assessment of osteosarcoma patients at NCISL will help in planning, implementing and evaluating the management of the cancer in Sri Lanka. As the cancer mainly affecting teenagers, its cause major emotional and psycho social impact on them. The adolescence are the backbone of future generation of our country, so it's a vital think to give a proper care to them. And the age group tend to default their treatment because of long treatment cause, side effects of chemotherapy and fear of losing limb. They need proper council ling and financial support for prosthesis. Proper counselling system and psycho social support still not developed well in Sri Lanka, so addressing the issue by evaluating number of patents who abandoning treatment will help for future planning and implementation.

Literature Review

Osteosarcoma is the most common malignant bone tumor in adolescent. It arises from primary mesenchymal bone forming cells. Most osteosarcoma arises as solitary lesion within the fastest growing areas of the long bones. The top three affected areas are the distal femur, proximal tibia and proximal humerus , but virtually any bone can be affected. The percentage of commonly affected areas is Femur 42%, Tibia 19%, Humerous 10%, Skull and Jaw 8%, Pelvis 8%. The incidence of osteosarcoma slightly higher in males. The incidence increase steadily with age rising more dramatically in adolescence in correspondence with the adolescent growth spurt<5>. In the united states the incidence of osteosarcoma is 400 cases per year, in the UK its 530 per year<19>, in Sri Lanka aroud 25 to 30 cases per year <20>.

Dramatic improvement in survival has been achieved between 1975 and 2010. Five year survival rate increases from 56% to approximately 66% in adolescence. In a retrospective study by Kim et, al showed that initial tumor size appears to be associated with histologic response and is an important prognostic factor in osteosarcoma <10>. Patients with at least 90% necrosis in the primary tumor after induction chemo have a better prognosis than those with less necrosis. Patients with less necrosis, <90%, in the primary tumor after initial chemo have a higher rate of recurrence

within the first 2 years than do patients with a more favorable amount of necrosis, >90%. <12>. Less necrosis should not be interpreted to mean that chemo has been ineffective; cure rates for patients with little or no necrosis after induction chemo are much higher than cure rates for patients who receive no chemo. A review of two consecutive prospective trials performed by the children's oncology group showed that histologic necrosis in the primary tumor after initial chemo was affected by the duration and intensity of the initial period of chemotherapy<13>. Presently understanding of outcome and prognosis for osteosarcoma is driven by not only histological response to chemotherapy agents but also by serum markers and clinical staging,<6>. Patients with an elevated ALP at diagnosis are more likely to have pulmonary metastasis. In patients without metastasis, those with an elevated LDH are less likely to do well than are those with a normal LDH,<6>. Buet al conducted a meta-analysis of eight published studies to determine whether P16 (INK4a) a prognostic factor for patients with osteosarcoma, shows that a high level of expression of P16(INK4a) significantly associated with favourable overall survival<7>.Expression of MiR-14a significantly associated with tumor size and distant metastasis. High expression of MiR-148a was associated with poor overall survival and poor disease specific survival,<8>.

Osteosarcoma should manage by multidisciplinary team. Oncologic outcomes are optimized when the biopsy is performed by the same surgeon who will be responsible for the definitive tumor resection,<13,14>.Treatment strategies for high grade osteosarcoma with multidrug chemotherapy and resection result in 3-year event free survival of 60-70%<15>.The most common factors predicting survival are presence of metastasis,histological response preoperative chemotherapy and complete surgical resection<15>. Internationally accepted osteosarcoma protocol is the control arm of EURAMOS-1. Which comprising pre-operative of two 5-week cycles of cisplatin 120g/m², doxorubicin 75mg/m²,methotrexate 12g/m² x 2(MAP) and post-operative two further cycle of MAP and two cycle of just MA. In experimental arm of EURAMOS-1 study added ifosfamide and etoposide (MAPIE)post operatively. .However EURAMOS-1 result do not support the addition of ifosfamide and etoposide to postoperative chemotherapy in patients with poorly responding osteosarcoma<15>.Four types of surgery are done for primary sites, which are Wide local excision, Lymb-sparing surgery,

amputation, Rotationplasty. With advances in surgical techniques limb salvage has become the surgery of choice in extremity bone sarcoma,<16,17>. Osteosarcoma is relatively resistant to radiation therapy<9>. Complete resection of primary tumor and any skip lesions with adequate margins is essential for cure. Radiation therapy was found to improve local control, disease specific survival and overall survival in a retrospective study of cranio-facial bones that had positive, uncertain margins after surgical resections,<9>. For patients with axial skeletal primaries who either do not undergo surgery for their primary tumor or who undergo surgery that results in positive margins,radiation therapy may improve survival<4,11>.

Osteosarcoma patients who presented with lung metastasis can be cured by means of complete surgical resection, this procedure should be performing at the time of primary tumor resection. Xiao et al conducted a literature review intended to find outcome of various chemotherapy regimens in the treatment of metastatic, relapsed, and refractory osteosarcoma.They recommended the use of second line chemotherapy that is based on the combined ifosfamide- etoposide regimen,<12>.

Pediatric sarcoma in Central America studied 30% of sarcoma patients are abandoned treatment before completion. In the study more patients were abandon treatment if the tumor situated in the extremities and more likely to abandon treatment in the first three months rather than later in treatment. <18>. Abandoning treatment is the major problem in developing countries. All osteosarcoma patients following completion of active treatment need long term follow up. To monitor for recurrence, patients should assess with signs, symptoms, blood work and radio graphic scans. The patients may have long term side effects of treatment, including psycho social, cardiological ,nephrological and neurological. When the patients have been without therapy for 5 or more years, they are considered long term survivors<22>.

Objectives

General Objective

To determine survival and curability of osteosarcoma patients registered at National Cancer Institute Sri Lanka.

Specific objectives

- To determine the percentage of patients who defaulted the treatment and to ensure the validity of psychosocial support.
- To determine the pathological response rate for neoadjuvant chemotherapy and comparability between pathological response rate and recurrence rate.
- To determine the percentage of patients who underwent limb sparing surgery
- To assess event free survival of osteosarcoma.

Materials and Methods

This is a retrospective,descriptive study conducted at the National Cancer Institute Sri Lanka(NCISL). This is the most leading cancer center in Sri Lanka.

Study population

Ninety seven osteosarcoma patients who were newly registered from January 2008 to December 2011 were identified from the data base and the relevant clinic records were traced from the clinics as well as the record room. However 10 patients were referred to other peripheral centers for further management and 7 patients' clinic records were missed from record rooms.Therefor the total analysable population was 80.

Data collection

Data was extracted from the patient clinic records using a data extraction form(Annexure I).Extracted data were socio demographic data(Age,Sex),disease details at presentation(primary site, metastatic site,), treatment details; primary site management; Details of progressive disease or metastatic disease during treatment. Follow up details (detail of recurrence, time of recurrence after treatment).

Inclusion criteria

All osteosarcoma patients, who were 13 years old or above and treated at

National Cancer Institute Sri Lanka in the year 2008 to 2011.

Exclusion criteria

All osteosarcoma patients under 13 years old.

Statistical analysis

All osteosarcoma patients under inclusion criteria during the study period and whose relevant records were available were analyzed. Survivals were calculated using the Kaplan Meier charts and level of significance was estimated by the log rank test. The difference between 2 variables were calculated using the Pearson's Chi square test and fisher's exact test. The level of significance was considered 0.5.

Ethical Consideration

Prior to commencement of the study ethical clearance was obtained from the Ethical Review Board of the Faculty of Medicine, University of Colombo. Patient's records were assessed during non-clinic hours. This ensured the security of the patient records as well as absolutely no inconvenience was caused to patients.

Results

Demographic data-

Mean age of Osteosarcoma patients in the cohort was 27.4 years with a range of 13 to 61 years. Majority of the patients were in the age group of 13 to 25 year old, which was 65%. Furthermore the disease significantly higher in males than their counterpart. Fifty three (66.3%) of them were males and 27(33.8%) of them were females in the cohort.

Table 1 -Distribution of osteosarcoma population by demographic data (n=80)

Characteristic	n	%
Age at presentation (years)		
13-25 years	52	65%
26-50	17	21.3%
>50	11	13.7%
Mean 27.04 SD 14.63 Ranges 13-61		
Sex		
Male	53	66.3%
Female	27	33.8%

Primary site

Primary site at presentation for majority of the patients was in femur bone with 51(63.8%) and Tibia with 20(25%). 90.1%(72) of the patients primary site was lower limb. Other affected sites were upper limb humerus 3(3.8%),radius 2(2.5%),pelvis 1(1.3%) and head&heck 2(2.5%).

Table 2 – Distribution of patients according to Primary site

Site	Numbers(80)
Lower limb femur	51 (63.8%)
Lower limb tibia	20(25%)
Lower limb fibula	1(1.25%)
Upper Limb Humerus	3(3.8%)
Upper Limb Radius	2(2.5%)
Pelvis	1(1.25)
Head % Neck	2(2.5%)

Only 14(17.5%) patients had metastasis at presentation. 11(13.8%) of them presented with lung metastasis, 2(2.5%) of them presented with brain metastasis and one with bone metastasis.

Table 3 – Distribution of patients according to metastatic status

Site	OsteosarcomaN=80 (%)
No metastasis	66 (82.5%)
Metastasis	14(17.5%)
Lung metastasis	12 (15%)
Bone metastasis	1(1.25%)
Brain metastasis	1(1.25%)

Neoadjuvant Chemotherapy

From the 80 patients 51(63.8%) had completed neo-adjuvant chemotherapy. 24(30%) of them defaulted treatment after 1 to 3 cycles of chemotherapy. Five(6.25%) were died during neo-adjuvant course of treatment. In the cohort

7(8.75%) patients had defaulted treatment after finishing neoadjuvant chemotherapy. According to protocol the recommended duration of neoadjuvant chemotherapy for osteosarcoma is 10 weeks. But all most all patients were not completed the neoadjuvant chemotherapy in this recommended period. The minimum time period was 12 weeks, maximum was 18 weeks, and means 14.04 weeks (SD 1.649).

Table 4 –Time taken to complete neo adjuvant chemotherapy

Duration (weeks)	Number (%)
12	10(12.5%)
13	12 (15%)
14	12 (15%)
15	6(7.5%)
16	7(8.8%)
17	2(2.5%
18	2(2.5%

Primary site management.

Totally 43 patients had undergone primary site management. In which 40(93%) patients had only surgery and 3(6.9%) of them had both surgery and radiotherapy. 23(53%) of the extremity osteosarcoma patients had limb sparing surgery and 19(44%) of them undergone amputation.

Table 5 –Form of local treatment

Local treatment	Number43
Surgery	40 (93%)
Amputation	19 (44%)
Limbsparing/WLE	23(53%)
WLE	1(2.3%)
Surgery&Radiotherapy	3 (6.9%)

25(58.1%) patients had good pathological response rate to neu-adjuvant chemotherapy and 18(41.9%) of them had bad pathological response rate.

According to protocol the duration between pre and post local treatment should be 4 weeks. In our cohort all osteosarcoma patients who have had surgery as the local treatment had delays well beyond this recommended duration. The mean duration between chemotherapy cycles pre and post local treatment 8.05 weeks(SD2.17). This period ranged from 6 to 19 weeks.

Table 6 –Time between pre and post local treatment chemotherapy

Duration (weeks)	Number (%)
6	(8.8%)
7	11 (13.8%)
8	10 (12.5%)
9	10(12.5%)
10	1(1.25%)
12	1(1.25%)
19	1(1.25%)

Adjuvant chemotherapy

According to protocol in Osteosarcoma adjuvant chemotherapy should be completed in 19 weeks. However none of them completed treatment during this recommended time, mean duration of completion of adjuvant chemotherapy was 23 weeks (SD1.85), range from 20 to 27 weeks. One patient had defaulted during adjuvant chemotherapy.

Table 7 –Time taken for completion of adjuvant chemotherapy

Duration (weeks)	Number (%)
20	3(3.8%)
21	4 (5%)
22	8 (10%)
23	4(5%)
24	8(10%)
25	2(2.5%)
26	3(3.8%)
27	1(1.25%)

Progressive disease

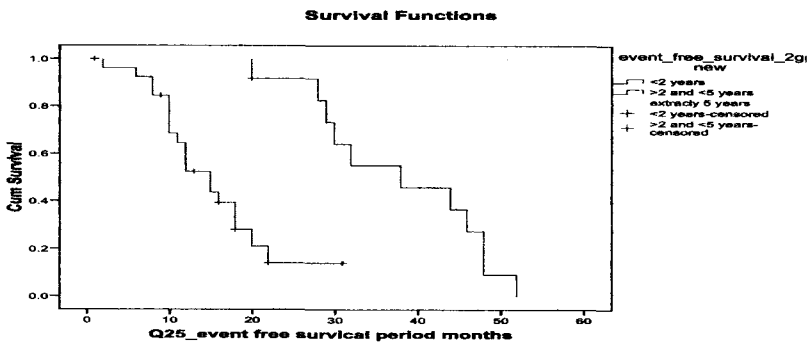
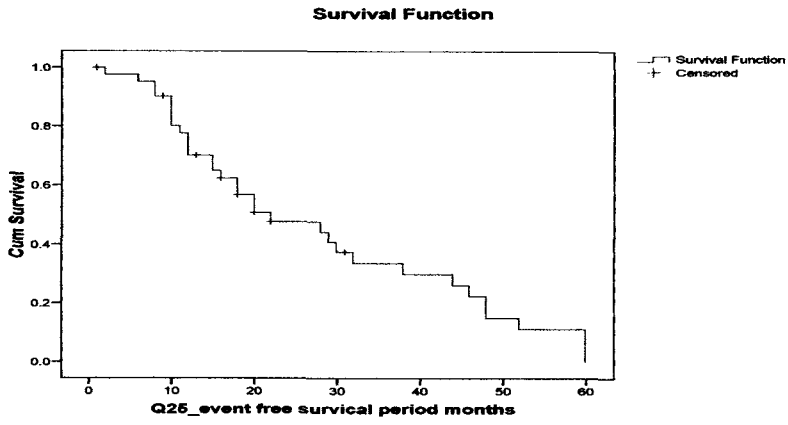
In the study population 17 (21.3%) patients had progressive disease during treatment. In which 15(18.75%) patients had metastasis during cause of the treatment. 13(16.3%) of them had lung metastasis and a patient had bone metastasis. A patient had multiple metastases during the cause of the treatment.

13(16.3%) patients had recurrence after completion of the treatment. The mean time taken to recur was 8.46 months (SD5.109), range from 3 to 20

months. 12(15%) patients who had progressive disease have had bad pathological response rate to neo-adjuvant chemotherapy and all most all patients had treatment delay during the course of treatment. In the cohort patients who had recurrence after treatment were slightly high in females than males, 8/13 and 5/13 respectively. But the difference was not statistically significant ($p > .05$). However there was a statistically significant impact on age group of the recurred patients ($p < 0.05$), 6/13 patients were age < 25 years old and 7/13 were 25 years old. In which 7/13 of this patients had bad pathological response rate to neo-adjuvant chemotherapy and 6/13 of this patients had good pathological response rate. However the impact of pathological response rate on recurrence of tumor in our cohort was not statistically significant.

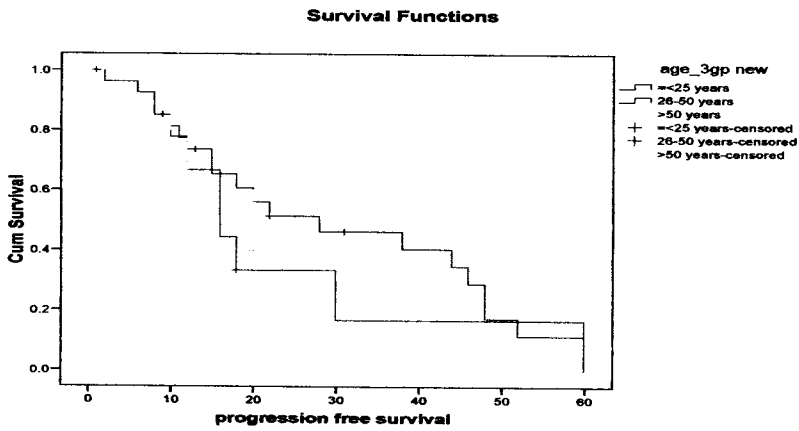
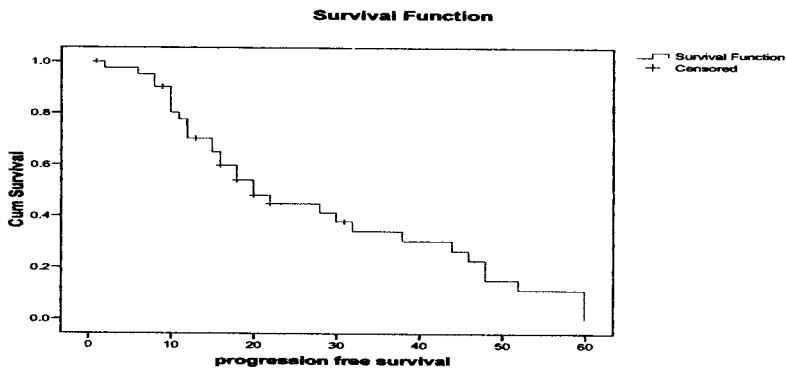
Event free survival

Chart 1

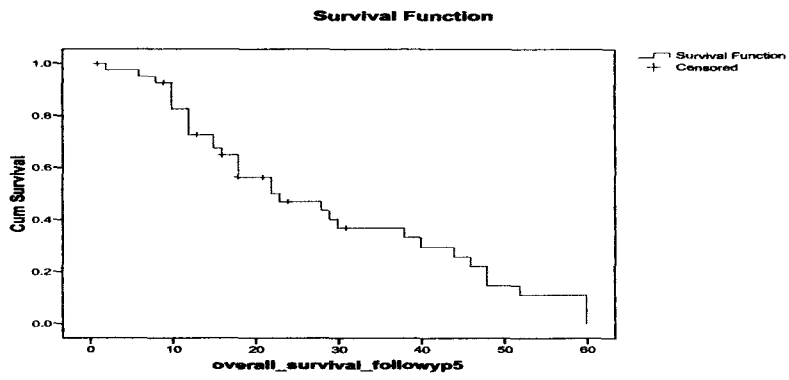


Progression free survival

Chart 3



Overall survival



Discussion

In the retrospective study 80 osteosarcoma patients were studied. Osteosarcoma annual incidence in Sri Lanka according to cancer incident data in 2010 about 25 cases (20). Our study population from the year 2008 to 2011 ensure that all most all of the patients were treated at National Cancer Institute Sri Lanka and they were included in our cohort.

Socio demographic data

In the study population the mean age of osteosarcoma was 27 years. The age is within the most commonly affected age group in International statistic data (19). Multiple studies have demonstrated that osteosarcoma has slight male predominance<19>. However in our cohort 53(66%)were males and 27(33.8%)were females, men were almost two time more commonly affected than women.

Primary site

Osteosarcoma most commonly occurs around knee joint. In our cohort also it was seen most commonly in lower end of femur and upper end of tibia, it was 51(63.8%) and 20(25%) respectively. The next common site was upper limb 5(6.3%). Furthermore extremity tumors were most commonly seen in younger people, 51(63.75%) patients were age <25.

Presentation

14(17.5%) patients in the study were presented with metastasis. However this was comparable with previous studies, which shows <20% of patients presented with metastatic state in adults<21,22 >. As expected the most common site of metastasis was lung, which was 11(13.8%). Other rare sites were bone and brain.

Abandon Treatment

About 24(30%) patients abandon their treatment during the cause of neu-adjuvant chemotherapy and all most all the patients abandon within first three cycle of chemotherapy. The cause of the significant number of defaulting treatment in our cohort known. However it may due to psycho social imbalance of adolescence cause fear about treatment and the side effect of chemotherapy. Moreover five patients had defaulted treatment after finishing neu-adjuvant chemotherapy and before surgery. It may due to the fear about losing limb or they may follow further treatment in other centers which may not registered in our clinic records. In addition one patient abandons treatment during adjuvant chemotherapy. The considerable amount of defaulted treatment emphasize the validity of proper counselling system and aid of psycho social support which lacking

at National cancer institute Sri Lanka.

Local treatment

In our cohort 40 patients had undergone surgery only to primary site, and three patients had both surgery and radiotherapy. In which 19(23.75%) extremity osteosarcoma patients had amputation and 23(28.8%) patients had limb sparing surgery. One mandible osteosarcoma patient had wide local excision. Interestingly considerable number of patients undergone limb sparing surgery.

Treatment Delay

In our cohort all most all patients were delayed to complete treatment than recommended time period. The mean delay for neoadjuvant chemotherapy and local site management was 4 weeks, and for adjuvant chemotherapy its 3 weeks. Most of the delayed treatment due to neutropenia sepsis, bone marrow suppression, surgical delays and may be unavailability of drugs.

Pathological response rate

Pathological response rate to neoadjuvant chemotherapy had impact on survival. In our cohort 25(58.1%) patients had good pathological response rate and 18(41.9%) patients had bad pathological response rate. The reason for the poor response rate to neoadjuvant chemotherapy not identified, but it may due to treatment delay as all of these patients had treatment delay more than 2 weeks.

Progressive disease

Almost one fifth (21%) of these patients had progressive disease during the cause of treatment. Fifteen (18%) of them had metastasis, 13 with lung metastasis, 1 with bone and 1 with multiple sites. Disease progression significantly high in our cohort and it caused statistically significant association with event free survival and overall survival.

Recurrence of disease

13(16.%) patients had recurrence of the disease after completion of chemotherapy. The mean time of recurrence was 8.46 months from completion of last chemotherapy (SD 5.109).The commonest site of recurrence was lung, two patients had local recurrence and one had brain recurrence. In the cohort 7/13 patients were >25 years age, this association was statistically significant ($p<.05$).

Survival

Two and year EFS in the study population were 45% and 11 % respectively. PFS for 2 and 5 years were 45% and 12.5% and OS were 46% and 10% respectively. The survival in our cohort was significantly lower than other multiple studies. A cooperative German-Austrian-Swiss Osteosarcoma study showed 5 year OS of 70% .Although our cohort shows poor survival, the studies survival was calculated from date of first registration at national cancer institute Sri lanka to last entry of event in patient records, so the patient who was not followed in our clinic may still survive. This may be the reason for the very low survival rates in our cohort. However pathological response rate for neo-adjuvant chemotherapy, progressive disease during treatment and recurrence of tumor and metastatic presentation were statistically significantly associate with EFS and OS($p<.05$). Influence of treatment delay on survival statistically could not assess because all most all the patients had treatment delay more than 2 weeks. Which may also the reason for the poor survival.

Conclusions

- In demographic data age of presentation is similar to international data, but in our cohort male sex is far more common than female sex.
- Clinical presentation, including status of metastases, similar to international data.
- Defaulting treatment is the major issue in our patient, significant number of patients are abandoning their treatment within first three cycle. Which emphasizes the important of implementation of proper counsel ling system, psycho social support and cost free aids of prosthesis for the patients in our country.
- Nearly 58% of the patients had good pathological response to neo adjuvant chemotherapy.
- 46% of the patients, who had good pathological response rate to neo adjuvant chemotherapy, had recurrence after treatment. However this association statistically not significant.
- More than 50% of patients, who had surgery undergone limb sparing surgery, however actual number of patients who undergone surgery relatively low due to defaulting the treatment.
- EFS,PFS and OS for 2 and 5 years in the cohort were 45%,11% and 45%,12.5% and 46%,10% respectively. The survival rate is noticeably lower than international data.

Limitation

This malignancy relatively rare and we excluded pediatric osteosarcomas; therefore the overall numbers of the subjects are less. In addition this study was a retrospective study done from available clinic data, therefore limitation of detail documentation in clinic notes impacts the study. For example, may be all the defaulted patients were not really abandon their treatment, they may got these treatment in other centers. However this could not assess properly because of inadequate patient contact details and no interconnected patients records within the health centers in Sri Lanka.

Recommendations

- Computerized patients registrations and documentation system would improve reliability and accuracy of data. In addition the system should be interconnected with all Government health sectors in Sri Lanka, which ease to trace patients records and follow up.
- Proper counselling system particularly for adolescents, psycho social support and cost free prosthesis for the patients are mandatory to improve outcome.
- Ensuring the availability of drugs and prompt supportive care. Which would improve to adhere with treatment on scheduled time and be reduce treatment delay.
- Establishing multidisciplinary team and tumor board would reduce delaying surgery and improve outcome.
- Implementing survivorship analyzing system would help to find out survivors, who not followed up in clinics.

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