Clinical Outcome and Survival of Osteosarcoma Patients in Cipto Mangunkusumo Hospital: Limb Salvage Surgery versus Amputation

Achmad F. Kamal[1], Heru Widyawarman[2], Kurniadi Husodo[2], Errol U. Hutagalung[1], Wulyo Rajabto[3]

[1] Department of Orthopaedic and Traumatology, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2] Resident, Department of Orthopaedic and Traumatology, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[3] Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Achmad Fauzi Kamal, MD, PhD. Department of Orthopaedic and Traumatology, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro No. 71, Jakarta 10430, Indonesia. email: fauzi.kamal@ui.ac.id.

ABSTRAK

Tujuan: *menganalisis luaran dan kesintasan pasien-pasien osteosarkoma yang menjalani limb salvage surgery (LSS) dan amputasi di Rumah Sakit Cipto Mangunkusumo, serta faktor-faktor yang mempengaruhi luaran fungsional dan prognosis.* ***Metode:*** *ini adalah studi kohort retrospektif pasien osteosarcoma pada RS Cipto Mangunkusumo yang menjalani operasi penyelamatan ekstremitas (LSS), amputasi, LSS + amputasi, dan menolak operasi dari tahun 1995-2014. Pemilihan jenis tindakan dilakukan berdasarkan usia, stadium, lokasi, keterlibatan neurovaskular, tipe Huvos, kebutuhan fungsional, pilihan pasien, dan keadaan umum pasien. Luaran fungsional dinilai dengan skor Musculoskeletal Tumor Society (MSTS) dengan nilai maksimal 30.* ***Hasil:*** *subjek penelitian meliputi 80 laki-laki dan 52 perempuan berusia 4 hingga 61 tahun. Tindakan yang dilakukan meliputi limb salvage surgery (LSS) (n=37), amputasi (n=42), LSS + amputasi (n=2), dan menolak pembedahan (n=51). Angka kesintasan 5 tahun kumulatif adalah 14.6%. Angka kesintasan 5 tahun masing-masing kelompok; LSS, amputasi, kombinasi LSS dan amputasi, dan menolak tindakan masing-masing adalah 34,8%; 15,9%, 0%, dan 0%. Pasien ukuran tumor ≤8 cm cenderung menjalani LSS dibandingkan amputasi (60,7% vs 39,3%, p=0,046). Angka bebas rekurensi lokal 5 tahun untuk LSS dan amputasi masing-masing adalah 96,2% dan 86,5% (p=0,586). LSS menunjukkan skor fungsional MSTS yang lebih tinggi dibandingkan dengan amputasi (25,0% vs 18,5%, p=0,011).* ***Kesimpulan:*** *kesintasan LSS lebih baik daripada amputasi pada pasien osteosarkoma yang dirawat di Rumah Sakit Cipto Mangunkusumo. Luaran fungsional skor MSTS pasien LSS lebih baik daripada amputasi.*

Kata kunci: *osteosarkoma, limb salvage surgery, amputasi.*

ABSTRACT

Aim: *to analyze the outcome and survival rate of osteosarcoma patients in our hospital as well as the factors affecting prognosis and functional outcome.* ***Methods:*** *this is a retrospective cohort study of osteosarcoma patients in Cipto Mangunkusumo Hospital underwent limb salvage surgery (LSS), amputation, LSS + amputation, and*

refused surgery from year 1995 to 2014. The surgical decision was based on patient's age, staging, location, neurovascular involvement, Huvos type, functional demand, patient preference, and general condition. Functional outcome was assessed using the Musculoskeletal Tumor Society (MSTS) score with the maximum score of 30. ***Results:*** *subjects consisted of 80 male and 52 female aged 4 to 61 year-old. They underwent limb salvage surgery (LSS) (n=37), amputation (n=42), LSS + amputation (n=2), and refused surgery (n=51). Overall 5-year cumulative survival rate was 14.6%. The 5-year survival rate for each group; LSS, amputation, combined LSS and amputation, and refused surgery was 34.8%; 15.9%; 0%; and 0%, respectively. Patients with tumor size ≤8 cm tend to underwent LSS compared to amputations (60.7% vs 39.3%, p=0.046). Local recurrence-free survival for LSS and amputation was 96.2% and 86.5% respectively (p=0.586). MSTS score was higher in LSS than amputation group (25.0 vs 18.5, p=0.011).* ***Conclusion:*** *LSS had higher survival rate than amputation in osteosarcoma patients who were treated in Cipto Mangunkusumo Hospital. MSTS functional score in the LSS group was higher than amputation group.*

Keywords: *osteosarcoma, limb-salvage surgery, amputation.*

INTRODUCTION

Osteosarcoma is a malignant bone tumor derived from primitive mesenchyme cells and consists of malignant cells that produce bone and osteoid matrix.[1-3] It is the most common malignant bone tumor of non-hematopoietic origin, which is frequently found at the metaphyseal long bones such as the distal femur, proximal tibia, and proximal humerus during the second decade of life.[1-3]

Incidence of osteosarcoma in all population is approximately 4-5 per 1,000,000 population.[3] It is higher in adolescents to 8-11 per one million population per year at the age of 15-19 years.[4-5] In the United States, osteosarcoma are the most common primary malignancy of bone, representing approximately 56% of malignant bone tumors in children.[6-7] Osteosarcoma is also the most common primary malignant bone tumor in Cipto Mangunkusumo Hospital (CMH) Jakarta, Indonesia. Kamal et al.[8] reported 16.8 osteosarcoma new cases per year (total number 219 patients) who came to CMH from 1995 to 2008.

Because of the rapid and aggressive nature of this tumor, the standard management for osteosarcoma is limb amputation.[9-10] However, over the past 3 decades, since the development of effective chemotherapy agents has reduced the incidence of metastasis, the prognosis for patients with osteosarcoma has changed dramatically.[11-12] Multiple studies have shown the results of limb-salvage operation compared to amputation.[13-14] Simon et al.[15] and Rougraff et al.[16] have reported that the survival of patients with either limb salvage or amputation is no different, although there is a higher rate of local recurrence in patients with limb salvage. It is generally accepted that, if the surgery is carried out in an appropriate oncological manner, there is no detriment to the survival of patients treated with limb salvage in a variety of techniques.[17-18]

The aim of limb salvage surgery (LSS) is to widely resect the local tumor and to preserve normal soft tissue as much as possible, thus provide a well-functioning, tumor-free, and painless limb. Many options of LSS have been developed, including resection arthrodesis, resection and reconstruction using bone graft (autograft, allograft, extracorporeally irradiated autograft or endoprosthetic composite), endoprosthesis reconstruction, Ilizarov lengthening technique, rotation plasty, etc.[13-14,18-19]

In this study, we analyze the outcome and survival rate of osteosarcoma patients as well as the factors affecting prognosis in Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

METHODS

This is a retrospective cohort study using secondary data from musculoskeletal oncology registries, medical records, and follow up care in outpatient clinic or home visit treated in Cipto Mangunkusumo Hospital, Jakarta, Indonesia, from 1995 to 2014. All lesions were clinically, radiologically, and histologically confirmed as

osteosarcoma.

For each patient, we recorded gender, age, presenting symptom and its duration, tumour size, location, haemoglobin, serum alkaline phosphatase (SAP), type of biopsy performed, histologic type of osteosarcoma, Huvos grade and treatment performed. We evaluated the presence of local recurrence, metastasis, musculoskeletal tumor society (MSTS) functional outcome score, and survival after treatment.

Age was classified in groups of decades. Presenting symptoms were mass, pain, mass and pain, and bleeding. Duration of symptoms were measured in months. Tumor size was divided in 2 groups (<8 cm and >8 cm). Type of biopsy were divided into fine-needle aspiration biopsy (FNAB), core neddle biopsy, open biopsy, or combination between those. Types of patient management were divided into operative (LSS or amputation or both), chemotherapy only, and refused treatment. Local recurrence was detected by physical, radiologic, and histopathology examinations. Metastasis was detected by chest X-ray, computed tomography (CT) scan, and/or bone scintigraphy. Osteosarcoma patients who did not complete the profile data and the follow up of their condition were excluded.

Statistical analysis was performed using Statistical Program for Social Sciences (SPSS) software version 20. Chi-square analysis was performed to evaluate the tumor and patients' demographics and its correlation to the presence of local recurrence, metastases, complications, and mortality rate. Kaplan-Meier curve was used to describe the survival in the univariate analysis, its correlation with types of surgery, time to event analysis where as time to local recurrence were analyzed by log rank test. A p-value of 0.05 was considered as statistically significant.

This study had been approved by Research Ethics Committee, Faculty of Medicine Universitas Indonesia, Cipto Mangunkusumo Hospital number 247/H2.F1/ETIK/2014.

RESULTS

During January 1995 to June 2014 period, there were 132 consecutive osteosarcoma patients who were included in the study. Seventy six (57.6%) patients were in relatively young age group (11 - 20 year-old) with median of 17.5 year-old (interquartile range 14.0 - 23.0 year-old). Male and female patients were 80 (60.6%) and 52 (39.4%) respectively. The most common complaint was mass (79.5%) with median duration of 4.0 months (interquartile range 3.0-7.8 months), poor general condition (62.1%), relatively low hemoglobin level (median 11.6; interquartile range 9.7-13.3) and elevated level of alkaline phosphatase (56.2%). Patients with tumor size smaller than 8 cm tend to undergo LSS (60.7%) compared to amputation (60.7% vs 39.3%, p=0.046) (**Table 1**).

Overall local recurrence-free survival for osteosarcoma patient was 93.4%. Five year local recurrence-free survival for LSS and amputation showed 96.2% versus 86.5% (p=0.586), respectively (**Table 2**). MSTS score in LSS group was significantly higher than amputation group (25.0 versus 18.5, p=0.011). However, no statistically significant difference was found between two surgical techniques to the MSTS score category (**Table 3**). The mortality rate in amputation group was higher compared to the LSS group (p = 0.038) (**Table 4**).

Overall, the proportion of 5-year cumulative survival rate was 14.6%, where as the LSS, amputation, combined LSS and amputation, and refused treatment had 5 year survival rate of 34.8%; 15.9%; 0%; and 0%, respectively. LSS group had the highest survival rate (**Figure 1**).

Table 1. Characteristics of osteosarcoma patients in Cipto Mangunkusumo Hospital

Characteristics	N=132
Age, years, median (IQR)	17,5 (14,0–23,0)
Age groups, years, n (%)	
- 0 -10	12 (9.1)
- 11-20	76 (57.6)
- 21- 30	22 (16.7)
- 31- 40	11 (8.3)
- >40	11 (8.3)
Gender	
- Male	80 (60.6)
- Female	52 (39.4)

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Characteristics	N=132
Symptom, n (%)	
- Mass	105 (79.5)
- Pain	18 (13.6)
- Mass and pain	7 (5.3)
- Bleeding	2 (1.5)
Symptom duration, months, median (IQR)	4 (3.0-78)
General condition, n (%)	
- Poor	82 (62.1)
- Moderate	24 (18.2)
- Good	26 (19.7)
Hemoglobin, mg/dL, median (IQR)	11.6 (9.7-13.3)
Alkaline phosphatase, IU/L, median (IQR)	334 (185-666)
- Normal	57 (43.8%)
- Elevated (>270)	73 (56.2%)
Tumor size, cm, median (IQR)	12.0 (8.0-20.0)
- <8 cm, n (%)	41 (31.1)
- >8 cm, n (%)	91 (68.9)
Tumor location, n (%)	
- Femur distal	52 (42.4)
- Femur proximal	4 (3.0)
- Knee/patella	4 (3.0)
- Tibia distal	5 (3.8)
- Tibia proximal	42 (31.8)
- Fibula distal	1 (0.8)
- Fibula proximal	2 (1.5)
- Humerus distal	3 (2.3)
- Humerus proximal	7 (5.3)
- Radius distal	1 (0.8)
- Radius proximal	1 (0.8)
- Forearm	1 (0.8)
- Clavicle	2 (1.5)
- Pelvis/ischium/ilium/sacrum	2 (1.5)
- Rib	3 (2.3)
- Foot/ankle	2 (1.5)

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Characteristics	N=132
Stage (Enneking), n (%)	
- Stage IIB	101 (78.2)
- Stage III	31 (25.7)
Huvos Type, n (%)	
- Huvos I	9 (33.3)
- Huvos II	7 (25.9)
- Huvos III	9 (33.3)
- Huvos IV	2 (7.4)
- Responsive	11 (40.7)
- Unresponsive	16 (59.3)
Histological type, n (%)	
- Conventional	121 (91.7)
- Giant cell rich	6 (4.5)
- Small cell	4 (3.0)
- Periosteal	1 (0.8)
Biopsy type, n (%)	
- FNAB	104 (78.8)
- Open biopsy	16 (12.1)
- Core biopsy	12 (9.1)
Type of surgery, n (%)	
- Limb salvage surgery (LSS)	37 (28.0)
- Amputation	42 (31.8)
- LSS + amputation	2 (1.5)
- Refused treatment	51 (38.6)

DISCUSSION

Conventional osteosarcoma is more common in men than women by a ratio of 3 : 2. The tumor most commonly affect patients within the 2nd decade of life and more than 60% in patients less than 25 years old. The incidence of osteosarcoma is also increased at the 6th decade of life, so the disease has a bimodal distribution.[3,20,21]

Table 2. Local recurrence-free survival and average time-to-local recurrence

	5-year local recurrence-free (95% CI)	p value	Average time-to-local recurrence (95% CI)
Overall	93.4 (83.6–103.2)	0.586	168.3 (151.5–185.887)
LSS	96.2 (88.4–104.0)		164.3 (154.2–174.4)
Amputation	86.5 (66.9–106.1)		158.6 (123.5–193.7)

Table 3. Functional outcome according to the type of surgery

	Types of surgery		p value
	LSS	Amputation	
MSTS Score, median (IQR)	25.0 (20.0-26.0)	18.5 (11.8–23.3)	0.011
MSTS score percentage, %, median (IQR)	83.3 (66.7–86.7)	61.7 (39.2–77.5)	0.011
MSTS score category, n (%)			
- Poor	0 (0.0)	1 (100.0)	0.212
- Fair	1 (33.3)	2 (66.7)	
- Good	5 (55.6)	4 (44.4)	
- Very good	11 (78.6)	3 (21.4)	
- Poor – Fair	1 (25.0)	3 (75.0)	0.128
- Good – Excellent	16 (69.6)	7 (30.4)	

Table 4. Mortality in relation to treatment, metastasis, and complication

Parameter	No. (%) of patients		p value
	Dead	Alive	
Treatment, n (%)			
- LSS	20 (54.1)	17 (45.9)	0.038
- Amputation	32 (76.2)	10 (23.8)	
Metastasis, n (%)			
- Yes	55 (98.2)	1 (1.8)	0.001
- No	47 (61.8)	29 (38.2)	
Complication, n (%)			
- Yes	5 (55.6)	4 (44.4)	0.118
- No	97 (78.9)	26 (21.1)	

Osteosarcoma can occur in all bones, with the predilection site of metaphyseal region of the long bones (91%). Distal femur and proximal tibia are the most common locations followed by proximal humerus, sometimes found in the diaphysis of long bones, but rarely found in the flat bones.[1,3,4,20]

In our study, male and female ratio is 1.54 : 1 with peak incidence in the second decade of life followed by the third decade. Distal femur and proximal tibia are the most common locations of osteosarcoma. Our result is similar with other study reported by Picci et al.[22] during 21 years of follow-up at one institution. The author also reported that osteosarcoma is more common in male patients, mostly in second and third decade of life with conventional osteosarcoma as the most common type and the most common location is in distal femur and proximal tibia. Tan et al.[23] also reported similar results.

Osteosarcoma patients usually come to the hospital because of pain that is initially mild and intermittent, but progressively becomes more intense and persistent. Another common complaint is a lump in the extremities that swells rapidly and painful. Tumor at the area near the joints often disturbs joint function. Pathological fractures can occur in 5-10% of osteosarcoma patients.[2,3] The other common symptoms are weight loss, fever, and malaise.[1,3,4]

Laboratory tests are needed to assess patient's general condition but cannot be the basis of diagnosis.[4] Increase in SAP (serum alkaline phosphatase) usually occurs in osteosarcoma. SAP level evaluation to show osteoblast activity are done regularly. The level of bone-specific

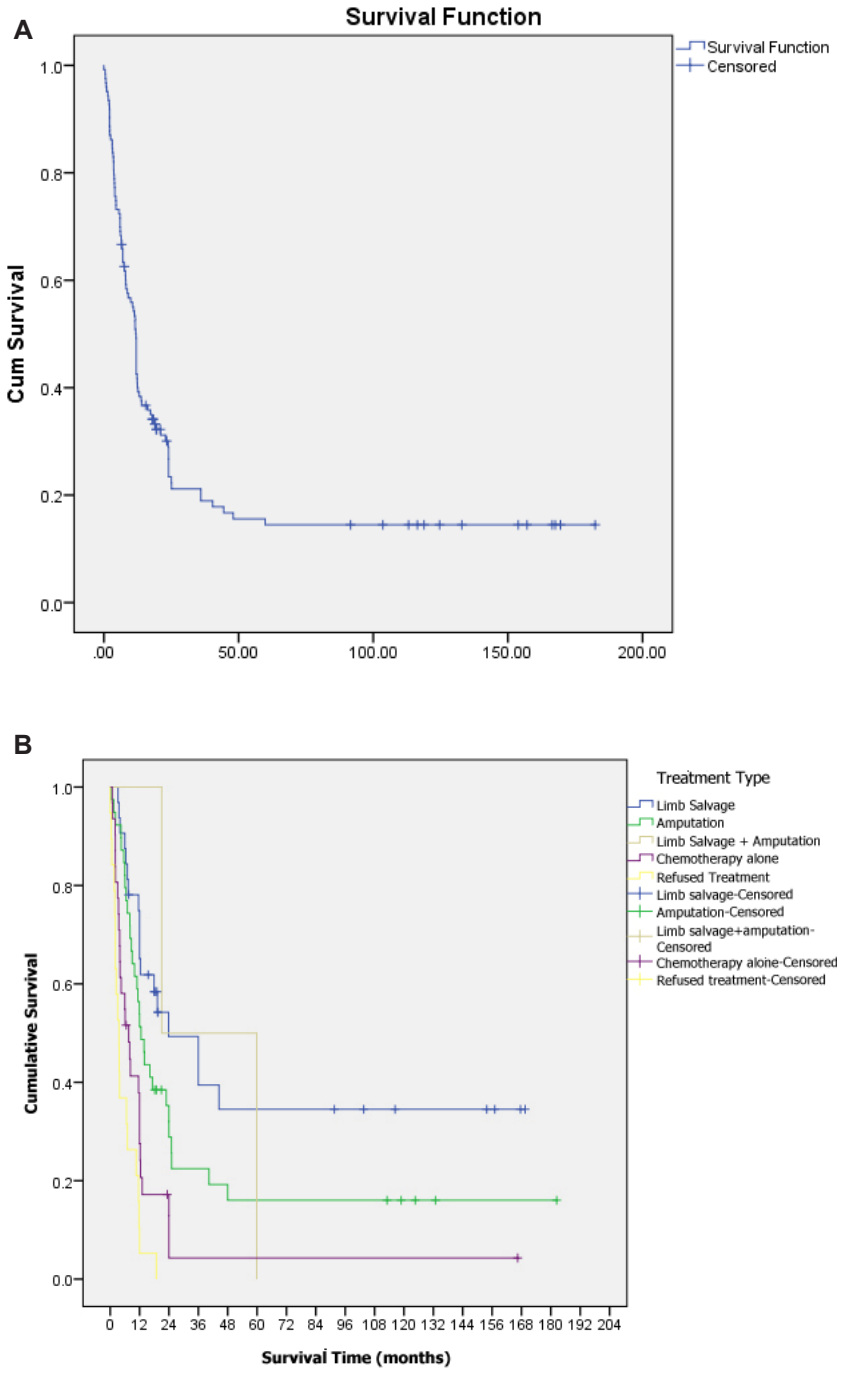

Figure 1. (a) Overall survival curve for osteosarcoma patients. Survival curve was based on Kaplan-Meier method. (b) Comparison of survival curves according to the type of management of LSS, amputation, combined LSS and amputation, chemotherapy alone, and refused treatment.

alkaline phosphatase (BSAP), although not specific for osteosarcoma should be used as a reference for a follow-up marker of metastasis and recurrence.[3,21] In our study, SAP values were divided into normal (43.2%) and increased (55.3%).

In the management of osteosarcoma, biopsy plays a very important role for diagnosis. A biopsy can be done with FNAB, core biopsy, or open biopsy. FNAB is a technique which is simple, relatively safe and cheaper than the open biopsy with 70-90% diagnostic accuracy in determining the malignant primary bone lesions. FNAB can also be done in the outpatient clinic,

thus saving time and cost of hospitalization. Neoadjuvant chemotherapy can also be given after FNAB. Another advantage is it only cause little interference or damage to soft tissue and bone with minimal risk of pathologic fractures.[27-30] In our hospital, open biopsy in bone tumor is only performed if the result of FNAB or core biopsy was inconclusive or inconsistent with the clinical and radiological findings.

From 132 patients in this study, only 81 patients underwent surgery with 28.0%, 31.8%, and 1.5% patients underwent LSS, amputation, and both procedures, respectively. The remainder of patients who refused surgery were further classified into receiving chemotherapy only (23.5%) and refused all treatment (15.2%). Patients who only received chemotherapy came to the our hospital with enormous size of tumour that were indicated for amputation but refused it or due to advanced condition. They who refused any therapy possibly due to various factors such as socio-economic, health insurance, and beliefs. Many still believe that chemotherapy may worsen patient's condition and many are still afraid to undergo surgery. In general, these two groups (chemotherapy alone and refused any therapy) mostly came from patients that seek treatment before 2005. However after that era, our government provided national health insurance system for all Indonesian resients and made them easier to gain health services in any level hospital. Therefore, many patients came to the health care center early.

In our study, tumor size and staging of cancer are the important factors which determine type of surgery. Patients with tumor size smaller than 8 cm tended to undergo LSS. Osteosarcoma patients with stage IIB who underwent the LSS were less than those underwent amputation (52.6%). However, those with stage III tended to undergo amputation (58.8%) compared to LSS. Several important factors to be considered for amputation are: large size tumor, neurovascular involvement, the presence of ulcer, hemorrhage from the tumor, and pathologic fracture. Although in several cases of pathologic fracture, LSS could be performed as long as the neoadjuvant chemotherapy gave good response.

High SAP values is one of the factors that determine prognosis. Other prognostic factors include age ≤ 14 years, tumor volume > 200 mL, inadequate surgery, chemotherapy with a regimen of two drugs and poor histologic response to chemotherapy.[21,24-26] In this study, LSS group had higher survival rate than amputation group, with median survival time of 23.9 months. We believe that these results may be due to more complete chemotherapy in the group LSS. Other factors that influenced our patients' survival are improvement of reconstruction technique of LSS and biopsy type (FNAB). They also affect the increase in survival of patients.[31]

We found a 5-year survival rate of osteosarcoma patients 14.6%. However, 5-year survival rate in patients who underwent LSS was 34.8%. In other words, the LSS group had higher survival rate than amputation group. LSS group also had better result compared to chemotherapy alone or no treatment groups. It might be due to the patients who were performed LSS received more complete chemotherapy compared to amputation group or more complete management (chemotherapy and surgery) than last two groups. This result is in contrast to Tan et al.[23] who reported a 5-year survival rate of 61.8% and Foster et al.[32] in Canada who obtained 5-year survival rate of 62%. Great difference in survival rate may be influenced by several factors such as the poor general condition of patients, large tumor size, chemotherapy completeness, unresponsive to chemotherapy (Huvos grading), and complications.

Patients who underwent LSS have a local recurrence rate of 3.8%, lower than patients who underwent amputation which is 13.5%. This result is in contrast to a study by DiCaprio et al.[33] who reported the incidence of local recurrence were higher in LSS group compared to amputation. Picci et al.[34] reported that local recurrence in LSS and amputation were 7% and 2.4%, respectively.

Some patients showed poor response to chemotherapy as showed with Huvos histologic grading (55.6%), while the rest showed good response to chemotherapy (44.4%). These results differ from previous study that was reported by Bacci et al.[13] that showed histologic response to chemotherapy was good in 63% of patients.

Histological response to chemotherapy is worse in our hospital may be due to resistance of chemotherapy regiments, different regiment type (in pediatric type), or larger tumor size. However, it is still needed for further evaluation.

A number of patients died (80%) with 3.3% and 6.7% experienced local recurrence or complication, respectively. The percentage of patients in stage III with metastases who had good and excellent functional status (66.7%) were lower than patients in stage IIB (85.7%). Unfortuntely, most of patients died and only 21.6% survived. On the contrary, only 35.1% patients experienced metastasis compared to those who did not (64.9%). The mortality rate in the amputation group was significantly higher than the LSS group. High mortality rate was found in patients with metastases compared to those who did not. Thus, it is concluded that metastases greatly affects survival. This result is consistent with other studies which mentioned rate of local recurrence and metastasis are important prognostic factors.[35]

Metastasis to the lung is the most common. However, metastasis also occur to other bones (spine, acetabulum, cranium), lymph nodes, and heart. In our study, patients undergoing amputation were more likely to experience metastasis compared to LSS. This could be due to more patients in the amputation group did not receive complete chemotherapy. Only 16.6% of patients received complete chemotherapy. Ward et al.[18] reported tumor necrosis percentage of below 90% and inadequate chemotherapy were important risk factors associated with metastasis and death.

The functional outcome based on MSTS system score in LSS group was significantly higher compared to amputation group (83.3% versus 61.7%). Patients who did not experience local recurrence were likely to have good and excellent functional outcome, whereas those with local recurrence had worse score. These results are supported by previous studies that mentioned functional outcomes in patients with LSS procedure were better than amputation (without affecting the survival rate).[16,36-38] Aksnes et al.[39] reported that amputation was one of the factors associated with low physical function. Patients without metastasis and complications tend to have good and excellent functional scores.

CONCLUSION

In our study, tumor size and staging of osteosarcoma were the important factors which determine type of surgery. Combination of surgery and chemotherapy gave better survival than chemotherapy only. We confirmed that LSS had higher survival rate than amputation in patients received complete chemotherapy in Cipto Mangunkusumo Hospital. Survival rate was influenced by the type of surgery, general condition, tumor size, chemotherapy completeness and responsiveness (Huvos grading). MSTS functional score in the LSS group was better than those in amputation group. Patients who did not have metastasis and complication tended to have good and excellent functional scores.

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