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Early Clinical Outcome of Limb Salvage Surgery of Osteosarcoma in the Lower Extremity Using Liquid Nitrogen

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ABSTRACT

Background. Osteosarcoma in the lower extremity has become a challenge for orthopedic surgeons to manage because surgeons need to preserve the affected joint's functions and retain stability as physiologic as possible. Thus, limb salvage surgery may be the treatment of choice. One of the techniques using liquid nitrogen provides better functionality and efficacy in preventing recurrence. **Methods:** From October 2020 to October 2021, 7 patients with primary musculoskeletal sarcoma underwent limb salvage surgery (LSS) by wide resection of the tumor and reconstruction using recycled Autograft treated with liquid nitrogen. The resected bone was dipped in liquid nitrogen for 15 min and thawed at room temperature for 15 min. The recycled bone was re-implanted into its original site and stabilized with internal fixation, and some of them followed with arthroplasty. **Results:** Average age was 14.14 years old. The most common site was the distal femur which was found in 3 cases (42,8%). During the 6-months-follow-up period, all patients had a good function (mean functional MSTS score of 90%) with one case of local recurrence in the re-implanted bone and one case of infection. No metastasis was reported in any patient. **Conclusion:** Satisfying functional results were recorded in all subjects treated with cryosurgery in Dr. Mohammad Hoesin General Hospital Palembang with equal results with studies around the world.

1. Introduction

Osteosarcoma is the most case of a primary malignant bone tumor, with the population most at risk being children and adolescents, accounting for 2% of all childhood tumors.[1] Prior to 1970, treatment of osteosarcoma was primarily dependent on surgical resection, resulting in a five-year survival rate below 20%.[2] Advances in radiological imaging and the increased use of effective adjuvant treatments, both chemotherapy, and radiotherapy, have further increased the success of limb salvage surgery (LSS). The five-year survival rate of osteosarcoma has gradually increased to 60% from 20%, and the limb salvage rate has increased significantly in recent years.[3,4] The most common site of osteosarcoma in the lower extremity, particularly the femur, occurring in 42% of cases, with 75% of the tumor being in the distal part of the bone, and tibia which occurs in 19% of cases with 80% of tumors occurring in the proximal bone. In other words, almost 60% of osteosarcomas occur in the knee region.[5]

The LSS method aims to excise the tumor widely at the margins of vital tissue in the hope of preserving the affected extremity. If this cannot be reached, then an amputation will be the final straw. The decision for LSS was based on the site and size of the tumor, extramedullary spread, a manifestation of metastatic

disease, presence of tumor necrosis, age of the patient, and bone development. LSS principally consists of two steps, extensive resection of the bone tumor, then continue to the reconstruction of the defect. Reconstruction can be non-biological or biological. The non-biological reconstruction can be done using endoprosthesis, and the biological reconstruction can be achieved using vascularized fibula, recycled Autograft, or by the use of a combination of allograft/autograft and endoprosthesis.[6–9]

Reconstruction method using Autograft composite prosthesis treated with liquid nitrogen has been widely used in treating low-grade primary malignant bone tumors since its revelation in 2005.[10] This cryosurgery method was mainly developed in European and Middle Eastern countries, and there are still not many published reports on this procedure in Southeast Asia, especially in Indonesia.[11,12]

Along with innovative lower limb sarcoma surgical procedures, there is a growing need to evaluate functional outcomes and quality of life. Quality of life is an independent predictor of survival and response to therapy, especially among patients with bone cancer. Despite the intuitive speculation that patients with limb LSS surgical procedures should have better function and quality of life than patients with amputations, controversy remains about the differences in long-term outcomes in these patients. Currently, several disease-specific instruments have been used to evaluate the functional outcome of patients with tumors of the extremities. One popular example is the Musculoskeletal Tumor Society (MSTS) rating scale. The MSTS Rating Scale is a widely used functional instrument developed in 1983 and later modified by the MSTS in 1993. The LSS procedure provides an MSTS functional score on a scale from moderate to excellent in osteosarcoma patients.[13,14]

Furthermore, cryosurgery has several limitations if utilized on larger, more extensive high-grade malignant bone tumors involving soft tissue structures. Since its creation, complications like significant injury to the adjacent bone and soft tissue, skin necrosis, and nerve injury have been associated with the use of liquid nitrogen. Direct application of liquid nitrogen to soft tissues can cause cellular damage to muscle and adjacent neurovascular structures.

A previous study by Rubiansyah et al. in 2021 at RSMH hospital found good results for inducing osteosarcoma necrosis with histopathology results showing 50-90% and 91-00 % (Huvos grade II-III) post cryosurgery. (Primadika Rubiansyah, 2021) In this study, we will continue this study to evaluate the outcomes, specifically using MSTS scores, recurrence, infection, metastases, and survival rates of osteosarcoma patients who underwent LSS using the cryosurgery technique at Dr. Mohammad Hoesin General Hospital Palembang, Indonesia.

2. Methods

We continued the previous study in Dr. Mohammad Hoesin General Hospital by reviewing osteosarcoma data from musculoskeletal oncology medical registries, medical records, and follow-up records in the outpatient clinic between October 2020 to October 2021. After confirmation of histopathological diagnosis and appropriate staging investigations, all patients with osteosarcoma underwent appropriate neoadjuvant chemotherapy as per hospital protocol. Response to chemotherapy was assessed pre-operatively clinically as well as by radiographs and magnetic resonance imaging (MRI) of the affected part. The wide resection margin in this patient was 1 cm away from the intramedullary extent. Resected bone was stripped of soft tissues, including the periosteum. Intramedullary reaming, as well as curettage of any surface tumor tissue on the resected bone, was carried out. Liquid nitrogen was poured into a stainless-steel cylindrical container. The resected bone was dipped in liquid nitrogen for 15 minutes and then thawed at room temperature for 15 minutes. The recycled excised bone was re-implanted at the original site and stabilized by appropriate internal fixation using plating, nailing, arthroplasty, or a combination of both. Part of the malignant bone was sent to the pathological anatomy department for biopsy.

We have three different sites of osteosarcoma in our

patient's series. There were 3 patients who had malignant tumor growth in the distal femur region, one case who had the tumor in the mid-shaft of the femur, 2 patients who got the bone sarcoma in the proximal tibia region, and one case of osteosarcoma in the distal part of the tibia. Figure 1 shows one of four cases of the patients with osteosarcoma in the distal femur from the preoperative state until the final reconstruction state intraoperatively. Figure 2 shows one case of the patients with osteosarcoma in the distal part of the tibia near the ankle joint from the preoperative state until the final reconstruction state intraoperatively. Figure 3 shows one case of the patients with osteosarcoma in the mid-shaft of the femur from the preoperative state until the final reconstruction state intraoperatively. Lastly, Figure 4 shows one of two cases of the patients with osteosarcoma in the proximal part of the tibia from the preoperative state until the final reconstruction state intraoperatively.

Table 1. MSTS table

No.	Pain	Function	Emotional	Support	Walking	Galt
5	No pain	No restriction	Enthused	None	Unlimited	Normal
4	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate
3	Modest/non-disabling	Recreational restriction	Satisfied	Brace	Limited	Minor cosmetic
2	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate
1	Moderate/disabling	Partial restriction	Accepts	One cane or crush	Inside only	Major cosmetic
0	Severe disabling	Total restriction	Dislikes	Two canes or crutches	Not independently	Major handicap

Functional status was evaluated using the Musculoskeletal Tumor Society Scoring System (MSTS) (Table 1). The scale consists of six items, including pain, function, emotional acceptance, use of external support, walking ability, and gait. Change. Each item is rated on a scale of 0 to 5. The total score ranges from 0 to 30, with higher scores indicating better functioning. The MSTS score in the poor category <50%, less 50%-59%, 60%-69% sufficient, 60%-74% good, and very good if >75% of the maximum score. Local recurrence was assessed by physical, radiologic, and histopathology examinations. Metastasis was confirmed by chest X-ray or computed tomography scan and/or bone scintigraphy. We also followed up on the infection around the operated limb by physical examination

3. Results

Descriptive characteristics of all subjects can be seen in Table 2. From October 2020 to October 2021, 7 patients (5 females, 2 males) underwent limb salvage surgery (LSS) by wide resection of the tumor and reconstruction with recycled tumor-bearing Autograft sterilized using liquid nitrogen combined with plating and internal fixation, and some of them followed with arthroplasty. The median age of the group was 14.14 ± 3,1, with the youngest being 9 years and the oldest being 19 years. All of them had 2B Enneking-grade Osteosarcoma.

All patients were being followed-up 6 months after surgery. On the latest follow-up, one patient (14,3%) experienced recurrence, and one patient (14,3%) had an infection at the surgical site. No patients had metastatic disease. The mean functional score for the study group was 27.14 ± 2.7 or 90% ± 0.1 in

percentage. The functional evaluation was performed using the modified system of the Musculoskeletal Tumour Society based on parameters including pain, functional activities, emotional acceptance, the use of external support, walking ability, and gait.

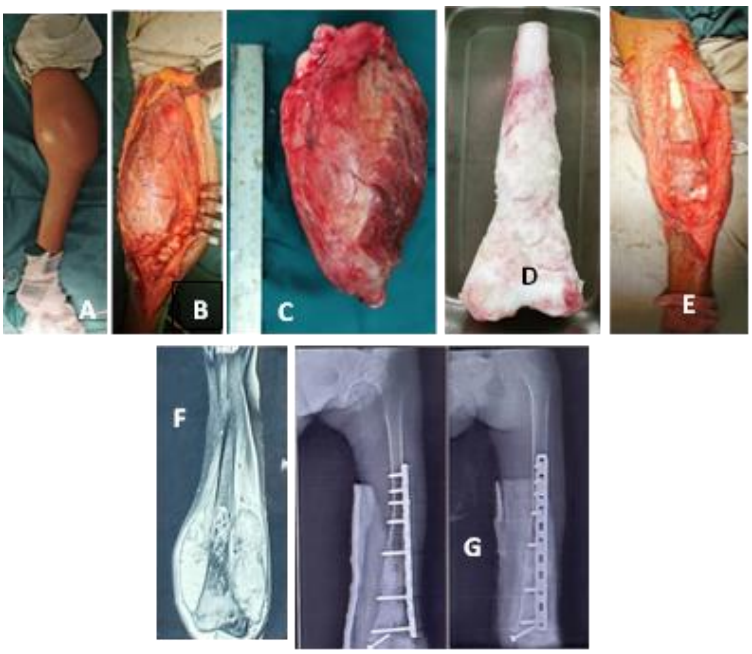

Figure 1. A. Clinical photo of a 9-year-old female with osteosarcoma involving distal femur; B. Intraoperative view of the tumor. C. Post-resection of the tumor. D. Post-submersion in liquid nitrogen. E. Clinical view post internal fixation. F. CT-imaging of preoperative state. G. X-ray imaging post internal fixation.

Figure 2. a clinical photo of a 14-year-old female with osteosarcoma involving the distal part of the tibia. b Intraoperative view of the tumor. C. Post-resection of the tumor. D. Post-submersion in liquid nitrogen. E. Post internal fixation. F. CT-imaging of preoperative state. G. X-ray imaging post internal fixation.

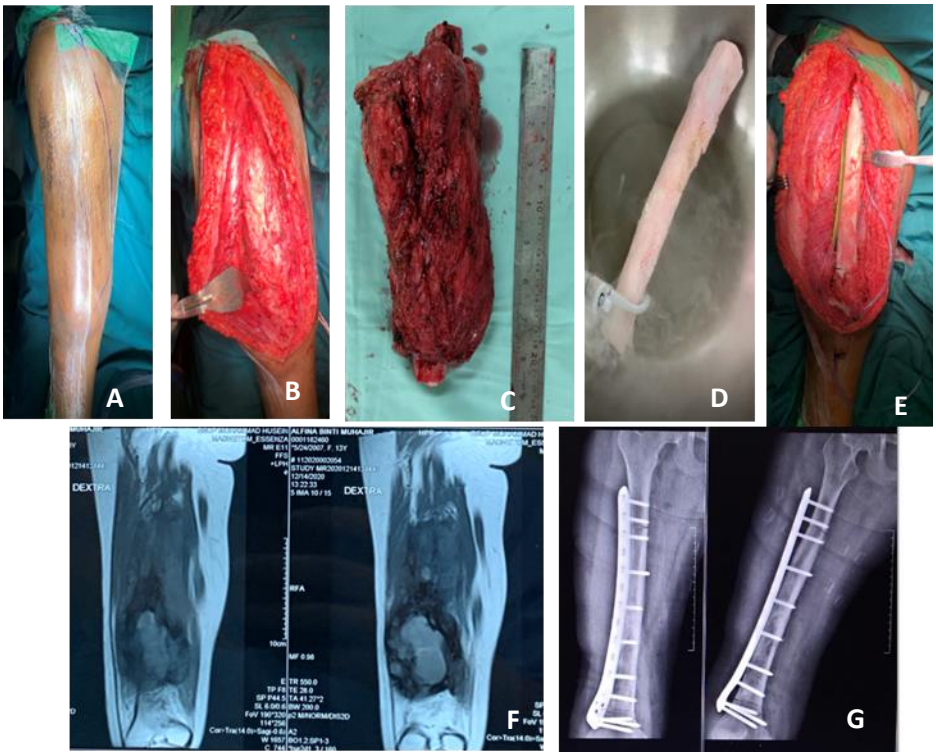

Figure 3. A clinical photo of a 13-year-old female with osteosarcoma involving the mid-shaft of the femur. B Intraoperative view of the tumor. C. Post-resection of the tumor. D. Post-submersion in liquid nitrogen. E. Post internal fixation. F. CT-imaging of preoperative state. G. X-ray imaging post internal fixation

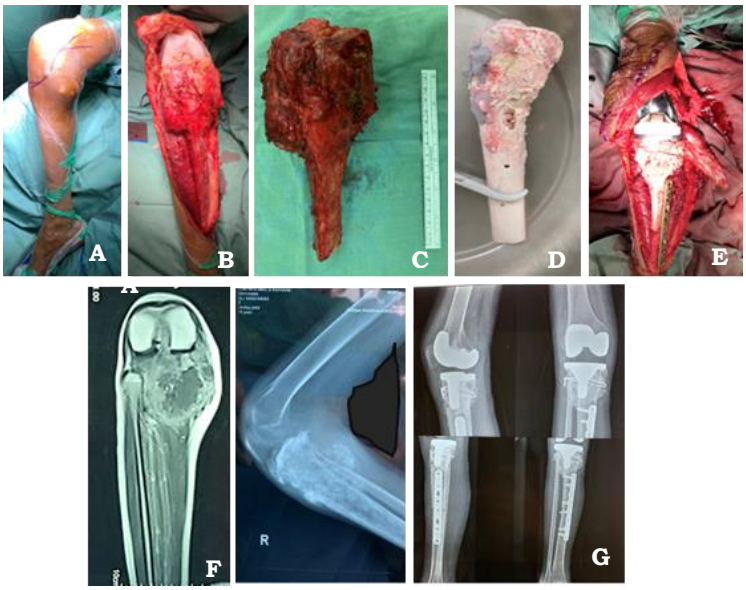

Figure 4. A. clinical photo of a 15-year-old female with osteosarcoma involving the proximal part of the tibia with knee joint involvement. B. Intraoperative view of the tumor. C. Post-resection of the tumor. D. Post-submersion in liquid nitrogen. E. Post internal fixation and total knee replacement; F. Radioimaging of preoperative state. G. X-ray imaging post internal fixation and TKR.

Table 2. Subjects' characteristics

Variables	Total
Gender; n (%)	
Male	2 (28,6)
Female	5 (71,4)
Age; mean ± SD.	14.14 ± 3,1
Knee region affected; n (%)	
Distal femur	3 (42,8)
Femur shaft	1 (14.3)
Proximal tibia	2 (28,6)
Distal tibia	1 (14,3)
MSTS; mean ± S.D.	27.14 ± 2.7
Percentage of MSTS; mean ± SD.	90% ± 0.1
Infection; n (%)	
Yes	1 (14,3)
No	6 (85,7)
Enneking Stage (%)	
1A	0
1B	0
2A	7 (100)
2B	0
3	0
Recurrence; n (%)	
Yes	1 (14,3)
No	6 (85,7)
Metastasis; n (%)	
Yes	0
No	7 (100)

Table 3. All subjects detailed characteristic and functional outcomes using MSTS score

No.	Age	Sex	Site of sarcoma	MSTS						Total score (%)
				Pain	Function	Emotional Acceptance	Use of support	Walking ability	Gait	
1	19	M	Distal left femur	5	5	5	2	3	3	23 (76,7)
2	13	M	Distal right femur	5	5	5	4	4	4	27 (90)
3	15	F	Proximal right tibia	5	5	5	5	5	5	30 (100)
4	9	F	Distal left femur	5	5	5	3	4	4	26 (86,7)
5	13	F	Shaft right femur	5	4	4	4	4	4	25 (83,3)
6	14	F	Distal right tibia	5	5	5	5	5	4	29 (96,7)
7	16	F	Proximal right tibia	5	5	5	5	5	5	30 (100)

Further description of functional outcome based on MSTS score of each subject can be seen in Table 3. One patient has an excellent knee function but needs an external brace and limited walking and gait ability. Fortunately, there are no patients who have MSTS score below 75%, which means all the patients had very good functionality. Details of the results can be inferred in Table 2.

4. Discussion

We found that the average age of osteosarcoma in our patients was 14 years old. A global survey by

Mirabello et al. confirmed our finding that osteosarcoma incidence peaked in males at age 15– 19 and in females at age 10–14 all around the world (3.4 to 4.3 per million people).[15] Latest review by Sadykova et al. found a similar result that in the age range 0 to 14 years, the incidence of osteosarcoma in all races and sexes was an average of four cases per year per million people (3 to 4.5).[16]

Our study defined that female is the most common sex to be afflicted with osteosarcoma, which was 71,4% of our subjects. This finding is similar to a global survey by Mirabello et al., who found that although osteosarcoma incidence soared among females at age 0-14 years, male teenagers took the spot at the age of 15-24, with a ratio of 1,43:1.[15] Latest review by Sadykova et al. is line with our result that in adolescents, the incidence is higher among males (peak rate of 9–15 cases/million population) compared to females (peak rate of 6–10 cases/million population), which suggest that hormonal changes, bone growth, and puberty-associated development may be involved in osteosarcoma etiology.

Our study found that the distal femur is the most site affected, which occurred in 3 of 7 patients. In line with our study is a survey by Lee on 320 children in South Korea, which revealed that the distal femur (52.3%) was the most frequently affected site in osteosarcoma among children and adolescents, followed by the proximal tibia (19.5%) and proximal humerus (11.1%).[17] Taran et al. also found that the metaphyseal region of long bones was the favorite site where malignancy spurted, with 42% occurring in the femur, 19% in the tibia, and 10% in the humerus.[18]

MSTS functional scale was used to assess the functional outcome post-surgery. We found all 7 patients were subjected with excellent MSTS scores of more than 90%, averaging 27,14. The result is in line with Takeuchi et al., who found that the use of Autograft treated with liquid nitrogen had the mean MSTS score of 27.7 (range 18 to 30) among 12 osteosarcomas patients.[19] Abdelaal et al. found that the mean MSTS score of 24 children with osteosarcoma in lower limbs after 5 years was 25 (range 6-30).[20] Another positive finding by Van der Heijden et al. found that the mean MSTS score of patients with bone tumors who underwent LSS using liquid nitrogen was 26 (range 8-30) even after 8 years of follow-up. The study also claimed that the functionality was comparable with the likes of bone grafts or bone cement.[21] This promising result is in line with functional outcomes acquired by different LSS techniques, such as the mega prosthesis, of which the median MSTS score was 84% (53–100%).[22] A study by Kamal and Rubiansyah found that the median 1-year-follow-up MSTS score of patients with osteosarcoma around the knee who underwent mega prosthesis, extracorporeal irradiation, and resection arthrodesis was 78% (71-83%), 72% (64-77%), and 68% (61-70%) respectively.[6]

We found all 7 patients had 2B Enneking grades of osteosarcoma and underwent limb salvage surgery. This finding was in line with Yuan et al., who found that high-grade osteosarcoma should be managed with at least a combination of limb salvage injury and neoadjuvant therapy.[23] A similar report from Gede et al. also found that an intercompartment extension in osteosarcoma can be effectively managed with limb salvage surgery, specifically using liquid nitrogen, with a decent MSTS score and satisfaction.[24]

We found one local recurrence (14,3%) in our patients until the 6-month hallmark follow-up. Meller et al., in a retrospective cohort, concluded that cryosurgery is a safe, reliable, and can be considered adjuvant therapy with a recurrence rate of 3% in 440 patients with malignant bone tumors during two years of follow-up.[25] Other studies by Tsuchiya et al. reported a 7.1% local recurrence (2 patients) in their group of 28 patients, none of which was in the composite autograft group.[10] The latest 2017 study by Chen et al. found that cryosurgery may be the recommended treatment for benign-aggressive and malignant bone tumors with minimal bone loss or long-term functional complications.[26] However, one big data retrospective study by Van der Heijden et al. revealed that the 10-year-recurrence rate of using liquid nitrogen was 31% of 132 osteosarcomas patients.[21] These findings show that cryosurgery may be as effective in preventing bone

tumor recurrence as broad resection techniques for the therapeutic treatment of benign-aggressive, low-grade, and malignant bone tumors.[11,26]

We found no metastases in our case series. This can be explained when a malignant lesion is excised and the host is no longer exposed to the antigens present in the malignant cells. In the case of cryosurgery, the antigens present on the dead malignant cells are retained, enabling a host immune response that can lead to a systemic response against the malignant cells.[26,27] There have been scarce reports that metastatic tumors appeared after freezing of the primary tumor. A cohort retrospective study by Abdelaal et al. found that there was no metastasis among 24 children with osteosarcoma in lower limbs after 10 years.[20] One big data retrospective study by Van der Heijden et al. revealed that metastasis only occurred in two out of 132 osteosarcoma patients after 11 and 12 months of follow-up.[21]

Although impressed indifferent, we received one case (14,3%) of infection at the surgery site. This may be associated with the lack of antibiotics mixed in normal saline during the recycling process, but this needs further evaluation. Complications such as infection of the frozen bone have been reported in cryosurgery, according to a study by Van der Heijden et al. They found that the risk of infection was 3.9 times more likely to happen in the use of liquid nitrogen (95%CI=1.5-10, p=0.006). Tsuchiya et al. reported complications of deep infection in three and fractures in two patients in their group of 28 patients, but all were successfully managed.[10] Souna et al. in 2010 found no incidence of postoperative infection with cryosurgery in 15 patients with chondrosarcoma tumors.[28] A recent study by Chen et al. in 2017 found that cryosurgery was very safe against the incidence of postoperative infection, with an incidence rate of only 1.4% of 214 patients with bone tumors.[23]

5. Conclusion

Cryosurgery has become a reliable choice of surgery in the management of osteosarcoma in the lower extremity. Satisfying functional results were recorded in all subjects treated with cryosurgery in Mohammad Hoesin General Hospital Palembang with equal result to studies around the world. However, further long-term, big data study is needed to describe more reliable results on recurrence, infection, and metastasis.

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