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The outcome of micro vascular reconstruction of the lower limb after resection of primary bone tumors

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***Abstract*---**Background: Surgical and medical care for patients with bone and soft tissue tumors of the extremities continues to improve with advancement of chemotherapeutic strategies, surgical techniques, and understanding of pathogenesis. Aim and Objective: To Analysis of the results of lower limb preservation after neoplastic resection to reproduce an advisory algorithm for surgical decision making to achieve optimal functional results.Methods: This retrospective study was performed in the microsurgery unit Assiut university hospital between 2013 and 2019, involved (40) patients with primary malignant bone tumors and benign aggressive bone tumors who had wide local resection and reconstruction by vascularized fibula (osteoseptocutaneous flap). Results: The highest mean time of union rate was 5.75±2.06 for GCT. The least mean time of union rate was 3.86±1.21 forChondrosarcoma. the least Mean±SD of function was 2.83±0.75 in chondrosarcoma while the highest Mean±SD of emotional acceptance was 4±0.82 in Ewing sarcoma. The Mean±SD of pain were equal in both Ewing sarcoma and GCT. Conclusions: Benign aggressive tumors & primary malignant bone tumors now become not a rare tumor. Free vascularized fibular graft

is one of several methods of bone reconstruction after bone tumor resection. Using as a means of reconstruction. Transferred fibulae (biological graft) have ability to hypertrophy to a diameter close to that of reconstructed bone. Limb salvage surgery becomes the choice treatment of primary malignant bone tumor resection encouraged by development in chemotherapy & new surgical techniques.

***Keywords*---**outcome, microvascular reconstruction, lower limb, resection, bone tumors.

Introduction

Surgical and medical care for patients with bone and soft tissue tumors of the extremities continues to improve with advancement of chemotherapeutic strategies, surgical techniques, and understanding of pathogenesis (1). The long-term functional and psychosocial disability reported by survivors of bone malignancies is among the highest of all cancer survivors, comparable to that reported by survivors of brain cancer (2). Clearly, more research is needed to understand the factors which contribute to patient outcomes after treatment of sarcomas of the extremities. This information could guide physician and patient discussions in the perioperative period. Goals in treatment differ depending on whether a patient's tumor is benign or malignant. For malignant tumors of the extremities, treatment goals focus on both local oncologic control and optimizing function of the affected limb. Surgery, often aided by adjuvant therapy, is the cornerstone in treatment for these patients. Limb-salvage (LS) surgery for malignant extremity tumors show rates of local disease control and disease-free survival which are comparable to those observed after limb amputation (LA) (3).

Limb-salvage surgery has a potential advantage over amputation in allowing the patient to retain a functional native limb. Treatment goals for benign extremity tumors are to reduce pain, optimize function, and prevent local recurrence (4). Since benign bone and soft-tissue tumors are relatively rare, research involving surgery for benign extremity neoplasms is largely limited to case series on focused patient populations (5). Currently, 90-95% of patients with primary malignant bone and soft tissue tumors involving the extremities can be treated safely with wide resection and limb-salvage surgery with a low risk of recurrence and the same disease-free survival rate as amputation surgery (6). Limb salvage optimizes patient satisfaction since it provides immediate mobility, stability, weight bearing, and improved quality of life in addition to the cosmetic appearance and emotional acceptance (6). Despite these advances, however, discussions persist regarding the indications and criteria, and whether limb salvage provides superior functional results and quality of life for cancer patients (7). In this study, we aim to review and update the current criteria, and discuss its role in the quality of life of cancer patient.

Aim and Objective: To analysis of the results of lower limb preservation after neoplastic resection to reproduce an advisory algorithm for surgical decision making to achieve optimal functional results.

Patients and Methods

This retrospective study was performed in the microsurgery unit Assiut university hospital between 2013 and 2019, involved (40) patients with primary malignant bone tumors and benign aggressive bone tumors who had wide local resection and reconstruction by vascularized fibula (osteoseptocutaneous flap). The study those cases were followed up for at least 24 months before end this study. Inclusion criteria: Pathology: primary bone tumors of long bones of lower limb, procedure: wide local resection of tumor and reconstructed by micro vascular technique (successful transferred vascularized fibula graft), age: 11-48 years old, side: both sides, gender: male and female, proper biopsy, site: long bones of lower limb, pathological fracture of healed primary bone tumor, follow up: 2 years at least.

Methods: Patients were evaluated pre-operatively as follow

a. History taking and clinical examination including: Personal history: Patient name, age & sex, address, phone number and occupation. History of present illness: Complain (pain, swelling or pathological fracture), site, characters and onset, course of progression (rapid, gradual or stationary), relation to activity (stiffness, limping or deformity), associated with (weight loss, fever, neurological manifestation) and if trauma precipitate the pain. Family history: Any similar positive oncological disease or other oncological disease. Past history: Medical for chronic disease or surgical history for any previous operation Special habits of medical importance.
b. Examination: General examination and local examination including: Swelling, single or multiple, bone or soft, superficial or deep, Site and tenderness and surface, skin mobility, examination the joint, (effusion, range of motion, distal pulsations and sensation) and extremity edema.
c. Laboratory investigation: Routine laboratory investigations were done to all patients include: Blood count, ESR, liver function test and renal function test.
d. Pre-operative staging: Plain x-ray of the affected site, C-T scan, MRI and plain chest x-ray and C.T scan.
e. Biopsy: Biopsy was done for all cases. Team work, according of patient presentation, history of disease, lab investigation, physical imaging studies and biopsy result, after well discussed a case in weekly meeting conference take decision if lesion was operable and the patient was candidate for limb salvage procedure with FVFG.

Chemotherapy: All cases of osteosarcoma and Ewing sarcoma received pre-operative chemotherapy at South Egypt Cancer Institute or oncology department at assiut university hospital. Second MRI was done before surgery to check tumor response (radiological response).

Operation technique: Anesthesia. General anesthesia was routinely used in this situation may be combined with epidural analgesia according to assessment of anesthesia team, Patient position. Supine position was used in all cases. Surgical approach: Two surgical teams operating simultaneously or consecutively.

Resection of the tumor: The resection was performed under tourniquet whenever possible. Skin flaps were carefully designed to include the biopsy site(s), any previous operative scares and to allow direct exposure of the major neurovascular bundles. After isolation of the major neurovascular bundles, the tumor was excised with a wide margin including the biopsy track and surrounding muscle. Bone resection was performed at a distance of at least 3 cm from the intramedullary extent of the tumor as determined by preoperative MRI studies.

Harvesting of the fibula: Pre-operatively, the contralateral leg was carefully evaluated for obvious congenital anomalies, scars or old fractures. The dorsalis pedis and the posterior tibial pulses were palpable or at least audible at the ankle in all legs and arteriography was not performed in any patient. The skin flap was used to monitor the circulation of the flap post-operatively, and to provide tension free closure of the recipient site especially if large skin area was excised with the biopsy site or if there was later partial skin necrosis resulting from elevation of large flaps during tumor resection.

Microvascular anastomosis: Using the operating microscope and 10/0 suture, the peroneal artery and one or two vennae commitant were sutured to the prepared artery and veins in the recipient site. Intra-venous Dextran 40 was started as 100 ml initial bolus before releasing the vascular clamps, then as 0.5 ml/kg/hour continuos infusion throughout the operation and thereafter. Great attention was paid for the arrangement of the vascular pedicle to avoid tension or kinks at the anastomoses sites. The wound was then temporarily closed and the flap was observed for at least 20 minutes, after that, the wound was re-opened for second look and final check the patency of the anastomoses.

Wound closure: The recipient site was closed after insertion of two suction drains. Great care was taken for tension free closure especially at the site of anastomosis. The wound of the recipient site was dressed for open care using vaseline gauze and local antibiotic ointment. No compression or encircling bandages were used. The reconstructed limb was elevated so that the foot raised above the level of the heart. The donor site was closed after suturing the flexor halucis longus to the interosseous membrane under appropriate tension. Split thickness skin graft was used for coverage of the area of the harvested skin flap.

G- Post-operative management: All patients were given parenteral antibiotics for seven days post operatively, five to seven days stay in intensive care .so, after satisfied on viability of osteocutaneous flap and general health shift patient to ordinary ward to continue observation and medication, discharge after two weeks when progress normal health without any complication The resection specimen in all cases was sent to laboratory to assess the following; To confirm the description of histopathological lesion and assess surgical margin. Assess response to chemotherapy (% cellular necrosis) and on which take the decision of adjuvant chemotherapy dose and sorts, Regular visit checkup, general examination, local examination, incisional site infection, Check for any nodule or local pain, plain x-ray; Check fixation, stability fibular implant. Assess degree of union and callus formation, and detect degree of hypertrophy and chest CT scan routine done each 3 months in 1st year and done each 6 months in second 2 years.

Radiographic evaluation: The union, hypertrophy and other complication, can be evaluated by series of radiograph and C.T over regular interval. Functional assessment of upper limb: Evaluating the function of the surgical management by FVFG, reconstructed the defect after musculoskeletal tumors resected, and to permit the meaningful comparison between the FVFG reconstruction and alternative procedures in management, as well as, to develop meaningful surgical judgment. Evaluating system nowadays, using the modified musculoskeletal tumors society rating score (MTSRS) based on analysis of factors (use of external supports, walking ability and gait pain , function ,and emotional acceptance) are evaluated on a scale of zero to five, specific values (0, 1, 3, or 5) are equated with certain levels of achievement or performance (34,99).

Statistical analysis: The data were tested for normality using the Kolmogorov-Smirnov test and for homogeneity variances prior to further statistical analysis. Categorical variables were described by number and percent (N %), where continuous variables described by mean and standard deviation (Mean, SD, Median). Chi-square test used to compare between categorical variables where compare between continuous variables by t-test (ANOVA and Paired-samples T Test). A two-tailed $p < 0.05$ was considered statistically significant. All analyses were performed with the IBM SPSS 20.0 software. Ethical consideration: Reviewing the proposal was carried out before starting data collection via the Ethical review Committee of Assiut University, Privacy and confidentiality of all the data were assured.

Results

In our study all cases of Ewing sarcoma were less than 20 years old (4 cases), all cases of GCT in age of 20 to 30 years old, most cases of Osteosarcoma were less than 20 years old (75%, 18 cases) and 6 cases in age of 20 to 30 years old (25%) while 4 cases of chondrosarcoma were more than 30 years old (57.1%) and 3 cases were less than 20 years old (42.9%). Table 1

Table 1: Distribution of the studied patient regarding pathology, sex and age

	Pathology										P. value
	Osteosarcoma (n=24)		Ewing sarcoma (n=4)		GCT (n=4)		Chondrosarcoma (n=7)		Adamantinoma (n=1)		
	No.	%	No.	%	No.	%	No.	%	No.	%	
Sex											
Male	13	54.2	1	25	2	50	3	42.9	1	100	0.679
Female	11	45.8	3	75	2	50	4	57.1	0	0	
Age											
< 20 years	18	75	4	100	0	0	3	42.9	0	0	0.000**
20 - 30 years	6	25	0	0	4	100	0	0	0	0	
> 30 years	0	0	0	0	0	0	4	57.1	1	100	

Mean±SD	18.25±4.83	14.5±2.65	22.75±1.71	28±13.54	35±0	0.004**

Used chi square test;
* Statistically significant difference (p<0.05); ** statistically significant difference (p<0.01)

In our study most cases of osteosarcoma (18 cases), Ewing sarcoma (3 cases) and GCT (3 cases) (75% of each type)were fixed by plating while 3 cases only of chondrosarcoma (42.2%) were fixed by plating. ILN was used only in 5 cases of osteosarcoma (20.8%) and 4 cases chondrosarcoma (57%). Table 2

Table 2: Distribution of the studied patient regarding fixation method

	Pathology										P. value
	Osteosarcoma (n=24)		Ewing sarcoma (n=4)		GCT (n=4)		Chondrosarcoma (n=7)		Adamantinoma (n=1)		
	No.	%	No.	%	No.	%	No.	%	No.	%	
Fixation method											
Plating	18	75	3	75	3	75	3	42.9	0	0	0.016*
ILN	5	20.8	0	0	0	0	4	57	0	0	
Ex Fix	1	4.2	1	25	1	25	0	0	1	100	

Used chi square test;
* Statistically significant difference (p<0.05); ** statistically significant difference (p<0.01)

Table show high percentage (75%) of reconstruction with GCT scarified joint may be related to site or grade. 66.7 % Reconstruction with osteosarcoma scarified joint. 33.3 % preserved joint with reconstruction in osteosarcoma. 42.9 % preserve joint with reconstruction in chondrosarcoma while 50 % Ewing sarcoma preserve joint. Table 3

Table 3: Distribution of the studied patient regarding arthrodesis

	Pathology										P. value
	Osteosarcoma (n=24)		Ewing sarcoma (n=4)		GCT (n=4)		Chondrosarcoma (n=7)		Adamantinoma (n=1)		
	No.	%	No.	%	No.	%	No.	%	No.	%	
Arthrodesis											
No	8	33.3	2	50	1	25	3	42.9	1	100	0.651
Yes	16	66.7	2	50	3	75	4	57.1	0	0	

Used chi square test;

The most common complications were superficial wound infection (17.5%), exposed metal (15%) and broken metal (12.5%). Superficial wound infection was successfully managed by local care and secondary closure. Deep infection required repeat surgery for debridement. Nervepalsy (2cases of osteosarcoma) (peroneal nerve palsy and sural) Table 4

Table 4: Distribution of the studied patient regarding complication

	Pathology										P. value
	Osteosarcoma (n=24)		Ewing sarcoma (n=4)		GCT (n=4)		Chondrosarcoma (n=7)		Adamantinoma (n=1)		
	No.	%	No.	%	No.	%	No.	%	No.	%	
Complications											
Broken metal	4	16.7	1	25	0	0	0	0	0	0	0.353
Exposed metal	3	12.5	1	25	1	25	0	0	0	0	
Superficial wound infection	4	16.7	0	0	1	25	0	0	0	0	
Deep infection	1	4.2	0	0	1	25	1	14.3	0	0	
Stress fracture	2	8.3	1	25	0	0	0	0	0	0	
nonunion	0	0	0	0	1	25	0	0	0	0	
Nerve palsy	2	4.2	0	0	0	0	0	0	0	0	
Raw area	1	4.2	0	0	0	0	0	0	0	0	
Compartment syndrome	0	0	0	0	0	0	1	14.3	0	0	

Used chi square test;

Table 5: Distribution of the studied patient regarding recurrence

	Pathology										P. value
	Osteosarcoma (n=24)		Ewing sarcoma (n=4)		GCT (n=4)		Chondrosarcoma (n=7)		Adamantinoma (n=1)		
	No.	%	No.	%	No.	%	No.	%	No.	%	
Recurrence											
No recurrence	19	79.1	4	100	3	75	5	71.1	1	100	0.198
Recurrence	5	20.9	0	0	1	25	2	28.5	0	0	

Used One-way ANOVA test;

30 patients continue disease free 75%, 9 patients died from disease (2 cases before graft union and 2 cases before weight bearing) and one case (chondrosarcoma) live with disease till the end of study (24 month follow up). Table 6

Table 6: Distribution of the studied patient regarding fate of case at the end of study

Fate of case	Pathology										P. value
	Osteosarcoma (n=24)		Ewing sarcoma (n=4)		GCT (n=4)		Chondrosarcoma (n=7)		Adamantinoma (n=1)		
	No.	%	No.	%	No.	%	No.	%	No.	%	
CDF	18	75	3	75	4	100	4	57.1	1	100	0.279
DOD	6	25	1	25	0	0	2	28.5	0	0	
LWD	0	0	0	0	0	0	1	14.3	0	0	

Used chi square test;

The highest mean time of union rate was 5.75±2.06 for GCT. The least mean time of union rate was 3.86±1.21 forChondrosarcoma. Table 7

Table 7: Distribution of the studied patient regarding union time

	Pathology					P. value
	Osteosarcoma (n=24)	Ewing sarcoma (n=4)	GCT (n=4)	Chondrosarcoma (n=7)	Adamantinoma (n=1)	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Union (m)	4.23±1.41	4.75±0.96	5.75±2.06	3.86±1.21	4±0	0.282

Used One-way ANOVA test;

This table shows comparison between MTSRS at 12 months and at the end of study (at least 24 months). Table 8

Table 8: Distribution of the studied patient regarding modified tumor society rating system

	Pathology					P. value
	Osteosarcoma (n=24)	Ewing sarcoma (n=4)	GCT (n=4)	Chondrosarcoma (n=7)	Adamantinoma (n=1)	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
MTSRS 12mos	22.29±1.79	23.75±4.43	22.5±3.32	19.33±6.35	21±0	0.303
MTSRS final	23.24±1.76	25.5±2.65	23.5±3.32	21.83±1.94	30±0	0.006**

Used One-way ANOVA test;
* Statistically significant difference ($p<0.05$); ** statistically significant difference ($p<0.01$)

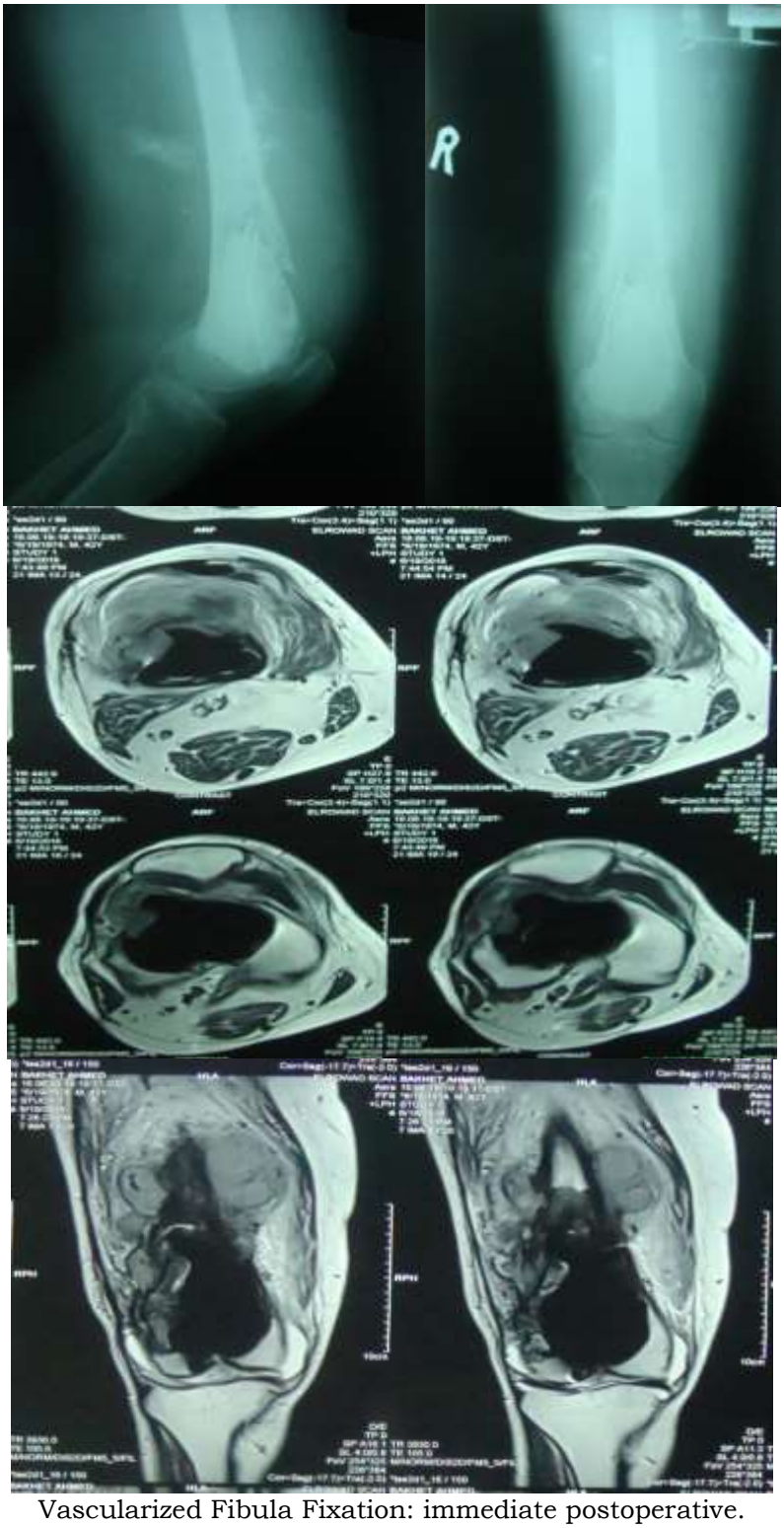
In our study the least Mean±SD of function was 2.83±0.75 in chondrosarcoma while the highest Mean±SD of emotional acceptance was 4±0.82 in Ewing sarcoma. The Mean±SD of pain were equal in both Ewing sarcoma and GCT. Table 9

Table 9: Distribution of the studied patient regarding functional assessment items

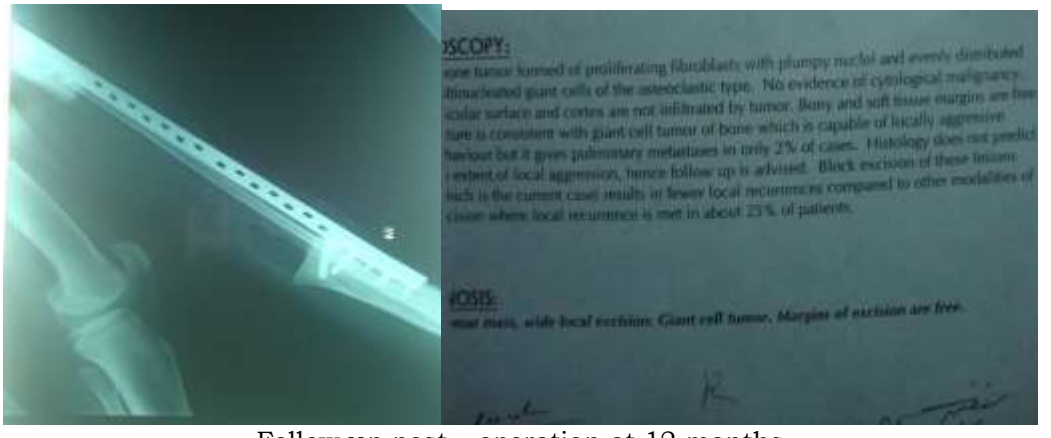
	Pathology					P. value
	Osteosarcoma (n=24)	Ewing sarcoma (n=4)	GCT (n=4)	Chondrosarcoma (n=7)	Adamantinoma (n=1)	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Pain	4.57±0.6	4.75±0.5	4.75±0.5	4±0.63	5±0	0.176
Function	3.29±0.46	3.75±0.5	3±0.82	2.83±0.75	5±0	0.008**
Emotional acceptance	3.86±0.57	4±0.82	3.75±0.5	3.33±0.52	5±0	0.096
External support	4.24±0.54	4.75±0.5	4.25±0.96	4.5±0.55	5±0	0.387
Walking ability	4.19±0.51	4.5±0.58	4±0.82	4.17±0.41	5±0	0.431
Gait	3.33±0.48	3.5±0.58	3.75±0.5	3.17±0.41	5±0	0.013*

Used One-way ANOVA test;
* Statistically significant difference ($p<0.05$); ** statistically significant difference ($p<0.01$)

GCT: 42 years male with Rt distal femur tumor.



Vascularized Fibula Fixation: immediate postoperative.



Follow up post – operation at 12 months

Follow up post – operation at 36 months

Discussion

Nowadays, limb sparing surgeries are the main line of treatment for most tumors of extremities irrespective of their grade and stage. These have proved to be cost-effect compared to amputation (8). Limb salvage surgery has become the standard of care in about 90% of patients especially if treated in specialized centers. The procedure involves transfer of a living piece of the patients own bone, which has no immunologic reaction and proceeds to heal following the biology of normal fracture healing. Common primary malignant bone tumors and benign n aggressive tumors in children, adolescent and young adults (≤ 30 years old) include osteosarcoma, Ewing sarcoma and Giant cell tumors about 87.5% of primary bone tumors distributed among children, adolescent and young adults. So, primary bone tumors affect in essential age group in society. In this field, the data of this study harmonize to other data calculated all over the world.

Many thesis as in our study said there no specific sex predilection in distribution of primary bone tumors among sex of patients (9) (male and female 20 cases for each). Thesis is short term outcome of vascularized fibular graft after primary bone tumors resection, follow up period at least 24 months. according this study (table 2), osteosarcoma (60%) had significant higher incidence, while chondrosarcoma (17.5%) of malignant primary bone tumors among distribution of primary malignant bone tumors in group which studied and GCT and Ewing sarcoma (10%)for each other. The data of this study confirm that epidemiological variations of malignant primary bone tumors, which appear related to different in populations factors that may contribute with its. This is slightly agree with Global health 2018, distribution cancers in populations based on registries data cancer in Beijin but the Ewing sarcoma had the lowest incidence (10).

In our study, the majority (75.75%) of limb salvage, that in which joint was sacrifice approach, 66.7 % Reconstruction with osteosarcoma scarified joint, 25 % preserved joint with reconstruction in GCT. 42.9 % preserve joint with reconstruction in chondrosarcoma while 50 % Ewing sarcoma preserve joint. These related to many factors; main cause is related to bone tumor site, size, grade, cost of substituted joint prosthesis and surgeon experience. Free vascularized fibula graft intercalary reconstruction is indicated for osseous joint sparing reconstruction is performed mostly in the femur and tibia. Intercalary reconstruction required adequate remaining bone stock to allow stable fixation. If inadequate bone remains the procedure likely benefit from free vascularized fibular graft and joint sacrificed to allow sizing graft reconstruction and asses soft tissue coverage. Plate fixation allows stability for compression across the fibular graft-host junction which likely improves healing. Screw holes, which are thought to contribute to late graft fracture (11).

In these study the assessment of functional outcome of the tumor resection in lower limb with free vascularized fibulae , by comparison pain, functional activities, emotional acceptance and External support and Walking ability at end (12) months with the end of study (at least more than 24months). Which are verified statistical significant difference at the assessment witch had a scoring system which allocated in to 5 points, values of 0-to 5 were assigned based on established criteria. The values (0, 1, 3&5) were equated with certain levels of

achievement or performance. A score of (5) indicates normality and score (3) would suggest partial problems and a score of one significant disability. The result was expressed as the proportion of expected normal function for the patient.

The Mean±SD of Functional assessment of osteosarcoma with FVFG at 12 mos is (21.94±3.45) while at the end of study is 23.24±1.76 in which statistical significant difference ($p<0.05$) in comparison between (12) months & end of study. The least Mean±SD of function was 2.83±0.75 in chondrosarcoma while the highest Mean±SD of emotional acceptance was 4±0.82 in Ewing sarcoma.The Mean±SD of pain were equal in both Ewing sarcoma and GCT. Pain scored excellent at end of study, which at patient free from the pain. Mean values for external support and gait after (6) months sharply increased with time to reach good score at end of study. The explain of these fact, at that time union grafts & recipient bone start & progressed in consolidation.so, patients started walking & discarded from external support. Functional outcome assessment: were using modified musculoskeletal tumor society rating score (MTSRS) selected the items which are pain, function and emotional acceptance, the external support, walking ability and gait items for lower limb. Follow up at the end of 12 months post operatively, at the end of study at least equal 24 months. Reducing the number of criteria to clearly defined and easily measurable parameters also facilitates the recording of results. For this reason, we are of the opinion that the purposed modification of evaluation system represents a practicable alternative to the original method of (MTSRS) (12).

In" 2017 " M,Emor et al., (13) conducted study which were said," local recurrence occur in 4.8% in vascularized fibular grafts for reconstruction of extremity bone and defects after resection of bone and soft tissue tumors". Retrospective study of Nouri et al., (14) published by EL sevier Masson SAS." patients with average age of 29.6 years. The use of vascularized fibula alone and stabilization by external fixation were main shortcoming in this series; local recurrence was observed in two cases (15.3%) at 18 months of follow up". In our study; (20.9%) local recurrence for osteosarcoma, no recurrence for Ewing sarcoma (only 4 cases).While two cases of chondrosarcoma patients (28.5%) with local recurrence and one case in GCT (25%). Thirty patients continue disease free 75%, nine patients died from disease (2 cases before graft union and 2 cases before weight bearing, 6 cases of osteosarcoma) and one case (chondrosarcoma) live with disease till the end of study (24 month follow up).

Conclusion

Benign aggressive tumors & primary malignant bone tumors now become not a rare tumor. inspite that, the experience to deal with such complicated issue, still build up with time. Free vascularized fibular graft is one of several methods of bone reconstruction after bone tumor resection. Using as a means of reconstruction. Transferred fibulae (biological graft) has ability to hypertrophied to a diameter close to that of reconstructed bone. Limb salvage surgery become the choice treatment of primary malignant bone tumor resection encouraged by development in chemotherapy & new surgical techniques.

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