Limb Salvage Surgery for Treatment of Primary Bone Tumors: Comparing Three Modes of Reconstruction

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ABSTRACT

Fifty-six patients who underwent limb salvage surgery for a primary aggressive and malignant bone tumor and had reconstruction with either a large segment allograft, fibular autograft, or the Ilizarov fixator were evaluated for complications, functional outcome, surgeries performed, and oncologic outcome. Review of complications showed an average of 0.65, 0.75, and 0.67 complications per patient for the allograft, fibular autograft, and Ilizarov groups respectively. On the other hand, functional outcomes were similar with average ISOLS scores of 25.43, 24.8, and 25.13 for the three groups. Surgeries for management of complications were most frequent for allografts (0.81 surg/patient) and least for the Ilizarov group (0.50 surg/patient). However, total surgeries after the index operation for whatever indication were highest for the Ilizarov group (1.25 surg/patient) and least for the fibular autografts (0.6 surg/patient). Analysis of data showed no statistically significant differences between groups in any of the parameters when compared to each other.

INTRODUCTION

Limb saving surgery, rather than amputation, has become the standard treatment for patients with both aggressive and malignant primary bone tumors of the extremities[62]. In the past decade the debate is not whether the extremity can be preserved or not, but how the limb preservation surgery can be refined and further improved. There are two stages in limb preservation surgery: tumor excision followed by reconstruction of the bony defect to restore skeletal continuity[83]. Numerous reconstructive methods have been described[1,4,19,29,32,40,51,55,63,64,66,72,81,88]; most methods falling under one or a combination of the following[74]: allografts or bone transplants[27,87], fibular autografts[13,17,21,61,85], metallic tumor mega-prostheses[18], and bone regenerating techniques most commonly via the methods of Ilizarov[89].

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Since 1993, the Musculoskeletal Tumor Unit (MuST Unit) of the Department of Orthopedics, University of the Philippines-Philippine General Hospital has been performing an increasing number of limb salvage surgeries on Filipinos with aggressive and malignant extremity bone tumors. In many affluent countries, tumor prostheses remain the most popular mode of reconstruction[14]. However, the high cost of such implants precludes their routine use in our setting, leaving the following as our most viable reconstructive options: large segment allografts, fibular autografts, and bone regeneration using the Ilizarov fixator.

An increasing number of studies describe the results of reconstruction with large segment allografts[15,28,44,53,56,57,58,] fibular autografts[9,8,35,41,42,45,52,59,86], and more recently the Ilizarov method[3]. But is there a preferred method? What are the advantages and disadvantages of each method? Is one method better suited for certain types of patients or tumors? There has been to date, no comparative study of these different procedures. Ours is the first ever attempt in the English Orthopaedic Literature to compare allografts, autografts, and the Ilizarov procedure as reconstructive methods in limb saving surgery.

OBJECTIVES

General Objective:

To further improve the service we provide for patients with aggressive and malignant bone tumors.

Specific Objectives:

To compare the complications and functional outcomes of limb salvage patients undergoing the three methods of reconstruction, namely allografts, autografts, and the Ilizarov technique; and to describe the demographics and oncologic outcomes for the above modes of reconstruction.

MATERIALS AND METHODS

The study covered all patients who underwent limb salvage surgery at the UP-PGH by the UP-MuST Unit between January 1993 and December 2000. The latter date was chosen as a cut-off date so that we would have a patient follow-up of at least eighteen months.

These patients were identified through several entry points: (1) the Tumor Registry of the Tumor Service of the Department of Orthopedics, UP-PGH, (2) admissions log-book of the Orthopaedic Ward, PGH, and (3) from the personal files of the senior author.

Inclusion criteria:

- Patients with primary aggressive or malignant bone tumors
- Limb salvage surgery performed at the UP-PGH by the UP-MuST Unit
- Surgery involved the excision and reconstruction of a segment of diseased bone using any one of the three methods: large segment allografts, fibular autografts, or the Ilizarov technique of bone regeneration
- Patients should have been followed up for at least eighteen months or until death if less than eighteen months

Exclusion criteria:

- Patients with soft tissue sarcoma with bony involvement or patients with metastatic bone lesions
- Patients with tumors of the axial skeleton
- Patients who had combinations of two or more types of reconstruction.

Once the patients were identified at the above entry points, all their charts, records, and imaging modalities were retrieved from the Records Section of the PGH and the Tumor Service x-ray files. Patients were grouped according to the method of reconstruction and the following data collected: age, sex, bone and joints involved, pre-operative tumor dimensions, surgery performed, length of resected bone or bone gap, final histopathology, and events during the post-operative course (including complications and number of surgeries after the index operation).

Data were then collected on these patients regarding their functional and oncologic status. Patients who were not seen in the last three months were contacted through telephone, through their referring doctors, or by letters sent to their last known address. In some cases where patients did not respond, research assistants of the Tumor Service located and evaluated them at their residences.

Prior to comparison of the different methods of reconstruction, patient characteristics in each of the groups were tabulated and statistical analysis was done in search for possible bias. Comparison of the three groups was made on the following parameters: (1) complications, (2) functional evaluation, and (3) number of surgeries beyond the index operation. Data for the oncologic outcome were also integrated but were not statistically analyzed.

Complications

Records were scrutinized for all complications that occurred during the post-operative and follow-up period. It was also noted when the complications set in, and what interventions were used to remedy them, and whether these interventions were surgical or not. Complications could be included as data even if follow-up for a specific patient was less than eighteen months.

Functional Evaluation

Functional status (at least eighteen months postoperative) was assessed by either the author/s or a research assistant. Evaluation was based on the modified scoring system of the International Society of Limb Salvage (ISOLS) which assigned 5 points to each of six criteria. Three of the criteria were for any extremity, including pain, level of activity, and patient acceptance. Another three were either for the upper extremity: hand positioning, manual dexterity and lifting ability; or the lower extremity: supports, walking ability, and gait. In a few cases, our patients could not return for follow up but had complete chart entries; the latter were used to approximate the patient's functional score.

Number of Surgeries

All surgeries done after the index surgery were noted and were classified as those performed for management of a complication and those that were for other indications including those for continuing management for the specific mode of reconstruction.

Oncologic Outcome

This refers to both local and systemic recurrence, the patients current status being defined as one of the following: died of disease (DOD), died of causes other than disease (DOC), alive with no evidence of disease (ANED), and alive with evidence of disease (AWED).

Patients who were shifted from one mode of reconstruction to another were included in the analysis of data for both modes of reconstruction in terms of complications and surgeries performed, but were only evaluated for function if the ISOLS were taken at least eighteen months after surgery for that particular form of reconstruction.

Analysis of Data

Statistical analysis was done using the Epi-info software developed by the Center of Disease Control in the U.S. The complication rates, functional outcomes, and number of surgeries were compared among three groups using Bartlett's modification of the analysis of variance (ANOVA). The incidences of the three most common complications (that is, infections, fractures, and nonunion) were compared between groups as proportions and were analyzed using Chi-square. A result was considered significant if p value were < 0.05. Data for survival and recurrences were noted but were not statistically analyzed.

RESULTS

A total of sixty-nine patients with primary aggressive and malignant bone tumors underwent limb salvage surgery at our institution from January of 1993 to December of 2000. Of the sixty-nine patients, thirteen patients were excluded. One patient was noted to have poor resection margins post-op and underwent hip disarticulation two months after limb salvage. Two patients underwent a combination of reconstructive procedures: one with large segment allografts combined with vascularized fibular grafts while the other had a vascularized fibular graft with application of an Ilizarov fixator. Six patients died very soon post-operatively with no demonstrable complication related to the surgery nor any functional score available. Four candidates for the study were lost to follow, giving us a low drop out rate at 5.8%.

General Data

A total of fifty-six patients were included in the study. Patients' ages ranged from seven to sixty five with a mean age of 30.2 years. There were twenty-nine females and twenty-seven males. Tumor histologies were as follows: Thirty-three giant cell tumors (58.9%), sixteen osteosarcomas (28.6%), two chondrosarcomas (3.6%), and one each (1.8%) of chondroblastoma, osteochondroma, primitive neuroectodermal tumor, Ewing's sarcoma, and adamantinoma.(Figure 1)

Twenty two patients (39.3%) had involvement of the distal femur; sixteen (28.6%) of the proximal tibia; five (8.9%) of the proximal humerus; three (5.4%) of the distal radius; two (3.6%) each of the proximal and midshaft of the femur and the distal tibia; and one patient (1.8%) each with involvement of the midshaft of the humerus, the talus, the fibula, and the metatarsal. (Figure 2)

Twenty-six underwent primary reconstruction using large segment allografts, twenty had fibular autografts, and twelve had application of the Ilizarov. Two patients who had large segment allografts developed complications and were shifted to an Ilizarov fixator. Both patients were evaluated for complications in both forms of reconstruction; however, function was evaluated only for the reconstruction that they have had for at least eighteen months of follow-up – one patient being evaluated as an Ilizarov and the other as a large segment allograft.

Allografts

Among the patients who underwent reconstruction using large segment allografts, there were fifteen females and eleven males. Eighteen patients had giant cell tumors (69.23%), six had osteosarcomas (23.08%), and two had chondrosarcomas (7.69%). Excluding those that had passed

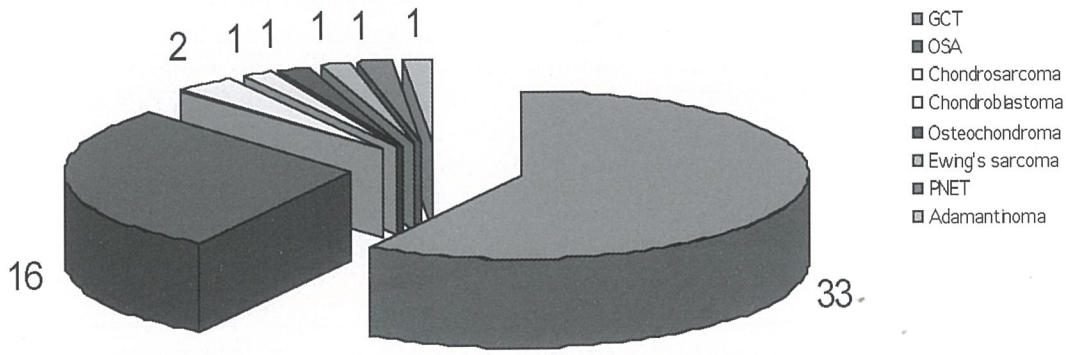

Figure 1. Percentage of the different types of tumors

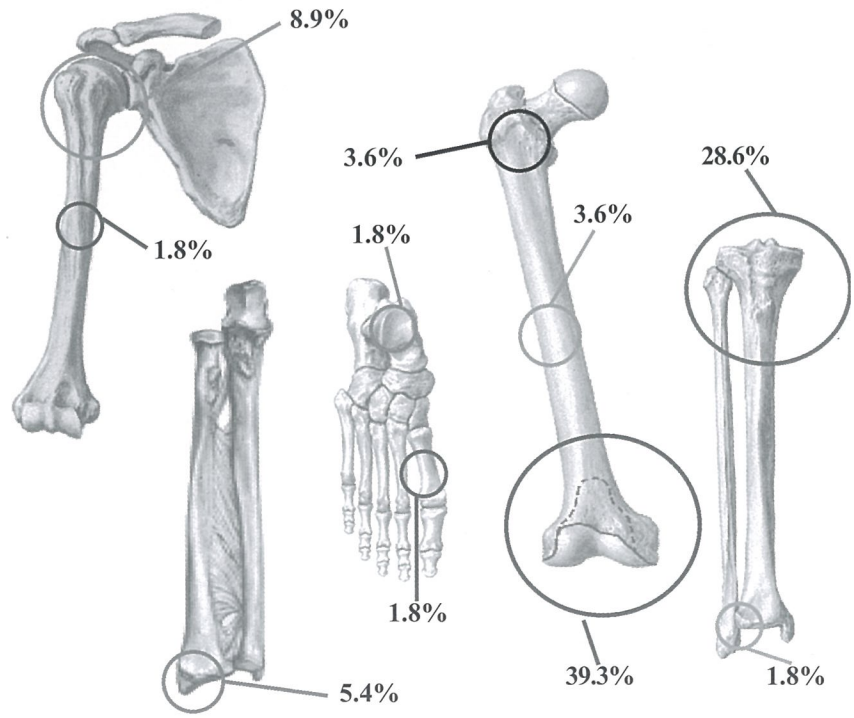

Figure 2. Bones involved and their respective percentages

away and those that had been amputated for infections, follow-up ranged from eighteen to eighty-nine months. Average follow-up was 43.7 months.

Complications. Fifteen of the patients (57.69%) developed seventeen complications within the follow-up period – an average of 0.65 complications per patient ($^{17}/_{26}$). Infection was the most common complication (30.8%); followed by fracture (15.4%) and then by non-union (7.7%). Delayed union, implant failure and hip dislocation occurred once each (3.8%).

Function. Only twenty-one out of twenty-five (one patient was evaluated functionally as an Ilizarov) patients were evaluated for function. The four patients who were not evaluated included three patients whosubsequently underwent amputations for infections before eighteen months post-op and one patient who could not follow-up for scoring (96.2% follow-up). ISOLS scores ranged from seventeen to thirty. Average score was 25.4 out of a possible 30 points (84.8% of normal function).

Surgeries. Fifteen of the seventeen complications (88.2%) required operative management with only two treated conservatively. A total of 21 surgeries were performed to manage these complications. Each patient averaged 0.85 surgeries ($^{22}/_{26}$) for whatever indication after the index operation.

Oncologic Outcome. Twenty-two patients (84.6%) are alive with no evidence of disease, two (7.7%) died of other causes, one is alive with evidence of disease and one died of the disease (3.8% each).

Fibular Autografts

Twenty patients underwent limb salvage using fibular autografts, nine females and eleven males. Nine patients had giant cell tumors (45%) and seven had osteosarcomas (35%). The other four patients had an osteochondroma, chondroblastoma, Ewing's sarcoma, and primitive neuroectodermal tumor (5% each) respectively. Excluding the patient who died four months post-op and another who subsequently had an above-knee amputation, follow-up ranged from twelve to one hundred eight months. Average follow-up was 35.2 months.

Complications. Thirteen out of twenty patients (65%) developed complications with a total of fifteen complications. The complication rate for each patient was 75% ($^{15}/_{20}$). Infection was the most common complication (35%), followed by non-union (10%). Fractures, delayed union, implant failure, leg length discrepancy, skin necrosis, and donor site foot drop occurred once (5%) each.

Function. Fifteen patients were evaluated for function. Not evaluated were two patients who eventually underwent amputation or disarticulation for infection, two patients who had passed away before eighteen months post-op, and one patient lost to follow-up (95% follow-up). ISOLS ranged from twelve to thirty with an average score of 24.8 out of a possible 30 (82.7% of normal function).

Surgeries. Only eleven of the fifteen complications (73.3%) required operative management, with each patient averaging 0.6 surgeries ($^{12}/_{20}$) after the index surgery – all for the treatment of complications.

Oncologic Outcome. Twelve patients (63.2%) are alive with no evidence of disease, five (26.3%) died of the disease, one is alive with evidence of disease and one died of other causes (5.3% each).

Bone Regeneration (Ilizarov)

Twelve patients underwent reconstruction using an Ilizarov fixator. Ten patients had the Ilizarov fixator used as the primary form of reconstruction with another two patients having large segment allografts shifted to Ilizarov after an infection. Of the ten patients, half were males and half were females. Six patients (60%) had giant cell tumors, three (30%) had osteosarcoma, and one had an adamantinoma (10%). Follow-up ranged from eighteen to sixty six months with an average follow-up of 36.83 months.

Complications. A total of twelve patients (including those converted from large segment allografts) were evaluated for complications – six (50%) of which developed complications. A total of eight complications were noted, an average of 0.67 ($^{8}/_{12}$) complications per patient. Early consolidation of the corticotomy site was the most common complication (25%). Infection, fracture, non-union, malalignment, and poor regenerate occurred once (8.3%) each.

Function. Eight out of a possible eleven patients (one patient converted from a large segment allograft) were evaluated for function. The rest of the three died before 18 months post-op (100% follow-up). ISOLS ranged from eighteen to twenty nine with an average score of 25.13 (83.77% of normal function).

Surgeries. Five out of eight complications required a subsequent operation, with a total number of six surgeries to remedy these complications. However, patients had an average of 1.25 surgeries ($^{16}/_{12}$) after the index operation, mostly as inherent part of continuing care.

Oncologic Outcome. Six of the patients (60%) are alive with no evidence of disease, three died of the disease (30%) and one (10%) is alive with evidence of disease.

Only four recurrences were noted out of the fifty-six patients. Two patients had giant cell tumors, one had an osteosarcoma, and the other one, an adamantinoma.

Analysis of Data. The average number of complications suffered by patients in each of the modes of reconstruction were compared using ANOVA and showed no significant difference among the three groups with a p value of 0.675. Functional scores were treated with the same statistical analysis and also yielded no significant difference among groups ($p = 0.9146$). The total number of surgeries were also similar among groups ($p = 0.1314$). Chi-square was used to evaluate the percentage of patients with a particular complication for each of the forms of reconstruction. The incidence of the three most common

complications; infection, fracture, and non-union, were similar between groups with p values of 0.1514, 0.7758, and 0.6986 respectively.

DISCUSSION

Limb salvage surgery has been shown to do as well, if not better than amputation in terms of long term survival[5,34], local recurrence[65,68], and functional outcome[7,12,36,43,50,80]. These benefits, however, come at the cost of higher rates of post-operative complications and re-operations. These problems, while dependent on many factors, are to a large extent influenced by the type of reconstruction performed. In the Philippines, the three most commonly used methods of reconstruction are large segment allografts, fibular autografts, and bone regeneration methods using the Ilizarov technique.

The use of allografts or bone transplant has been documented in the literature for over a century[22]. Despite concern about possible transmission of diseases[75], and possible graft rejection[10,11,23,24,31,54,70], the use of allografts for treatment of large bony defects remains to be an extremely popular option both in the local and international setting because of its relative affordability and biologic nature when compared to the very expensive tumor prosthesis[33].

Autografts have the fundamental advantage of being readily available and being from one's own body. In the case of vascularized grafts, the blood supply provides a biologically sound form of reconstruction which increases the chance for union[30]. Both foreign and local literature would claim excellent to good results in a large majority of patients[30].

The literature on the use of the Ilizarov fixator for reconstruction of a bone defect after resection of bone tumors are sporadic[82]. The use of the Ilizarov, especially for malignant lesions has not been popular because of the prolonged period of treatment. The duration of treatment was deemed unacceptable to patients with such potentially life-threatening illnesses. However, its relative affordability and availability make it the third most common form of reconstruction in the Philippines.

We posed the question: *Which method of reconstruction gives the best results?* To answer this question, we investigated patient outcomes in terms of (1) complication rates, (2) functional outcome, and (3) number of surgeries performed. These parameters are believed to be dependent on the type of reconstruction performed. Complications are the major source of suffering for these patients; with certain morbidities inherently possible only for a particular type of reconstruction. Furthermore, limb salvage surgery would only be successful if the patient ended up with good function. Lastly, the number of surgeries a patient has to undergo affects his quality of life and ability to go back to his pre-morbid state.

Oncologic result is only described but not evaluated in this paper. These results have been described in previous reports showing the local experience with osteosarcomas and giant cell tumors to be similar to that in foreign literature. Furthermore, survival and recurrence rate would depend more on the aggressiveness of the underlying tumor, its stage, its response to neo-adjuvant chemotherapy, and the feasibility of obtaining tumor-free resection margins[16,46,67] rather than the type of reconstruction used.

Demographic Data

Demographic data were compared among groups to make sure the groups were comparable, especially since the patients were not randomised. Statistics (ANOVA) showed comparable groups in terms of age, bone gap, and follow-up period.

Complications

The most common complications associated with the use of allografts for management of bone tumors are infection[25,48,75,76], non-union[53], fractures[8,73], and soft tissue necrosis[49]. Despite current recommendations on the prevention of these problems, they remain to be major obstacles to management. Our results show that infection remains to be a major problem in our setting. While the incidence of infection in limb salvage surgery with the use of large segment allografts would fall somewhere between 5-15% according to studies abroad, our data shows an incidence of 30.77%. Results also showed that fractures had an incidence of 15.38%, almost exactly approximating the findings of Berrey et al in a very large study on fractures in allografts[8]. A more recent study by Thompson et all showed a much higher incidence at 45.7%[73]. Incidences of non-union and implant failure are also within those observed on foreign studies.

Arai et al on complications of vascularized fibular grafts found fracture of the graft to be the most common complication, occurring in about 22% of vascularized fibulas[2]. Infections were considered uncommon at 7%. On the other hand, our data showed infection rates at 35% while fracture rates were at 5%. Infections are quite frequent owing to the relatively large dead space and relatively prolonged OR time for these cases. Other common complications such as delayed union, skin necrosis, and nerve palsy (foot drop) occurred at frequencies similar to those observed abroad[79].

Tsuchiya et al reported that fractures, infection, skin necrosis, equinus deformity, skin evagination, subluxation of the fibular head, and premature consolidation are the most common complications with the use of the Ilizarov fixator for bone tumor reconstruction. The incidence of premature consolidation were relatively high for our series. Infection rates are markedly lower in the Ilizarov group and is comparable to rates found in foreign literature on the use of the fixator. Non-union, malalignments and poor regenerate formation occurred as often as those for foreign studies[78].

In our patients, we analyzed complication rates (1) altogether, and according to (2) individual complication types. Fibular autografts had an incidence (75%) per patient, followed by the Ilizarov group (66.67%), and large segment allografts (65.38%). No significant difference among the three were noted (p=0.6750).

Incidences of specific complications such as infection, fractures, an non-union were also compared between groups. Analysis using chi-square showed no significant values, with p values of 0.1514, 0.7758, and 0.6986 for infections, fractures, and non-unions respectively.

Amputation after failure of treatment was noted to be most common with the use of large segment allografts (15.3% amputation rate) with no Ilizarov developing such

a complication. When infection sets in for patients with allograft, a formal debridement is most often required and patients tend to end up with amputations. This validates the observations of Quinn et al that despite proper and adequate management, there is only about a 57% chance that infection would be eradicated for these patients.

Functional Outcome

Studies have shown that function was apparently better for patients who underwent limb salvage using large segment allografts as opposed to amputation[84]. A Mayo clinic study on the functional outcome of patient who underwent vascularized fibular graft reconstruction by Hsu et al reported excellent results in 38% of patients. Most of the other patients had either good or fair results, with only 8% having poor results[37]. Tsuchiya et reported that for patients who underwent reconstruction using the Ilizarov, 60% would have excellent function with the rest having either good or fair results with no poor result noted[78].

Simon et al noted an average of 23 points (76.67% of normal function) using the ISOLS scoring system for patients who underwent limb salvage[68]. A German literature specifically on the use of vascularized fibular grafts showed an average of 73% return to normal function (ISOLS score of 22)[45].

Locally, functional outcome has been evaluated for all three forms of reconstruction considered in this study. In 1997, Wang, Caro, and Leung[84] noted and average return to normal function of 82.75% for the lower extremity and 81.6% for the upper extremity after reconstruction using vascularized fibular grafts. The second part of the series was completed at year 2000 when Wang and Escano[83] evaluated ISOLS scores of patients who underwent reconstruction using large segment allografts. Functional outcome was noted to be excellent in 50% of patients, good in 31%, and poor in 13%. The last leg is currently being investigated by Wang and Lopez. An average ISOLS score of 25.8 was noted for patients who underwent reconstruction using the Ilizarov fixator. This study therefore integrates these studies; data collection, however, was made independent from these studies. Furthermore, differences in inclusion and exclusion criteria make results of our study different from the above-mentioned literature.

Our data showed ISOLS scores of 25.43, 24.8, and 25.13 for large segment allografts, fibular autografts, and Ilizarov respectively. These scores are relatively higher than those noted in foreign literature. Although only by sheer speculation, this may be attributed to relatively higher expectations for patients in more affluent countries. Comparison of the scores by reconstruction groups using ANOVA showed no statistically significant differences in function achieved ($p=0.8154$). Although average score was lowest for fibular autografts, data included a score of twelve for a twenty four year old male with mental retardation. His condition may have significantly contributed to his inability to cope and may have skewed our data for that group.

Surgeries Performed

Surgeries mean extra cost for our patients and increased probability for complications with repeated anesthesia. Thus, the number of subsequent surgeries to manage the complication were investigated. Our data showed that despite having lower complication rates, the large segment allograft group required numerous surgeries to treat such complications (0.8 surg/patient). Deep infections associated with the use of allografts more often than not required several formal debridements, removal of the allograft, and even shifting to an Ilizarov fixator in some instances. The Ilizarov group required the least operative procedures to manage the complications (0.5 surg/patient). Infections in the Ilizarov group are usually managed with intravenous antibiotics and release of pin tracts, not requiring the extensive debridements performed to manage infected allografts.

Nonetheless, the Ilizarov group still required an average 1.25 of surgeries after the index operation. This is due to the inherent need for subsequent surgery for this form of reconstruction, even if there is no complication. Surgeries performed include docking procedures or removal of the fixator for patients who cannot tolerate it at the clinic. On the other hand, the fibular autograft group, despite relatively higher complication rates, showed only 0.6 subsequent operations after the index procedure, while allografts required 0.85. Nonetheless, statistical analysis using ANOVA again showed no significant differences in the amount of surgeries performed after the index operation between groups ($p = 0.1314$).

CONCLUSIONS

The following were concluded by the investigators of this study:

(1) There is no significant differences between the three modes of reconstruction in terms of number complications; although one must remember that certain complications specific to certain types of reconstruction
(2) There is no statistically significant difference in terms of rates of the three most common complications; that is, infection, fracture, and non-union among the three groups
(3) There is no significant difference in functional outcome for the three groups
(4) There is no significant difference in number of surgeries for whatever indication among groups
(5) The type of reconstruction chosen may depend on several factors, including the availability of resources and the expertise of the surgeon

LIMITATIONS

The following are the limitations of this study:

(1) Patients are of different tumor types, each histologic type with its own peculiarities
(2) Randomization was not performed for patients in this study and the choice of reconstruction was based on the availability of allografts, implants, and the particular preference and expertise of the surgeons
(3) Duration of follow-up may not have been enough to reveal long-term complications

RECOMMENDATIONS

Based on the results and limitations of this paper, the authors would like to recommend the following:

(1) Compare quality of life of the patients during the treatment period for each of the modes of reconstruction

(2) Compare the above parameters after patients have been sub-grouped into a particular tumor type in order to more accurately assess the implications on our patient's survival and disease-free interval

(3) Patients may be randomized into each of the groups to enable us to have almost equal patient number per group

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