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Original Research

Early Postoperative Outcomes of Extremity Tumors During the COVID-19 Era in a Developing Country – Is Limb Salvage a Viable Option?

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Background: With advancements in surgical techniques and adjuvant therapies, limb salvage (LS) has replaced amputation as the dominant treatment model for malignancies involving the extremities. But the COVID-19 pandemic has drastically affected cancer care especially in developing countries, with treatment delays possibly leading to a rise in amputations. Due to a lack of consensus regarding the ideal course of treatment for tumors involving the extremities in the current situation, the present study aimed to evaluate perioperative and short- term functional outcomes following LS surgery during the COVID-19 pandemic.
Methods: A single-institutional series of 45 patients who underwent surgical resection for extremity tumors and followed for at least 6 weeks after operation were included. We analyzed patients according to whether one had LS or major amputation during surgery, and compared intraoperative blood loss, operative duration, perioperative complication rates, COVID-19 infection rates, and Musculoskeletal Tumor Society (MSTS) scores during last follow-up, between the two groups.
Results: The LS group (n=21) had significantly longer operative duration (323 min vs. 214 min, p=.004) but higher MSTS scores (81% vs. 49%, p=.001) than the amputation group (n=24). Intraoperative blood loss (1113 mL vs. 779 mL, p=.46), superficial infection rates (14% vs. 8%, p=.12), and COVID-19 infection rates (14% vs. 29%, p=.23) were similar between the two groups.
Conclusion: The authors conclude that LS surgery can be a viable option for treating tumors involving the extremities especially in developing countries in the COVID-19 era.

Introduction

Sarcomas are rare malignancies involving soft tissue or bone with incidence of approximately 2 per 100,000 people-year, and most commonly affecting the lower extremities [1, 2]. Historically, extremity sarcoma was managed with amputation to control the gross disease [3]. But in a randomized trial comparing limb salvage (LS) with radiotherapy to amputation, no benefit for the latter was found [4]. With further surgical advancements as well as adjuvant therapies, LS has become standard treatment paradigm for cancers involving the extremities [5, 6]. But since March 2020 when the COVID-19 pandemic has been declared, healthcare systems especially in developing

countries continue to suspend hospital admissions to allow for surges and prevent viral spread [7]. Delaying surgery for stable tumors, changing chemotherapy schedules, and avoiding frequent hospital visits were precautions recommended to avoid nosocomial COVID-19 among cancer patients [8]. Such patients, including those with sarcoma, were found to be more susceptible to COVID-19 infection and also, risk contracting the severe form of the disease [9-11].

Because of resulting shortage of critical care resources to strengthen COVID-19 care, holistic, evidence-based cancer management has been compromised especially in developing countries [12]. Owing to a lack of consensus regarding the ideal management of tumors in the COVID-19 era, many patients with extremity malignancies often get neglected, leading to a rise in amputations [13]. The present paper aims to further evaluate the role of LS for extremity tumors in the COVID-19 era, by analyzing perioperative and short-term functional outcomes in a series of patients who underwent either LS or amputation in a Philippine tertiary center during the novel pandemic.

Materials and Methods

A review of our institutional database identified 68 patients diagnosed with biopsy-proven, non-benign tumor of the extremity, and treated at the East Avenue Medical Center in Quezon City, Philippines from April 1, 2020 to December 31, 2021. Institutional review board approval was obtained (IERB Protocol No. 2022-84). For the analysis, the present study excluded those: a) treated conservatively; b) with benign tumors; c) with cardiovascular, renal, or endocrine comorbidities, and

d) with follow-up fewer than 6 weeks. We decided to exclude cases with the aforementioned comorbidities to control for confounders. Of the 68 patients, 65 had malignant or intermediate tumors, of which 5 had less than 6 weeks of follow-up. Of the remaining 60 patients, 6 treated conservatively and 9 with various comorbidities were excluded, which left 45 patients for the analysis. All 45 patients had no CT-documented lung metastases and did not undergo systemic treatment prior to surgery. The COVID-19 situation in our hospital limited outpatient visits by cancer patients, leaving many of them without access to needed chemotherapy. Median follow-up after surgery is 8 weeks (range, 6 to 16 weeks).

All patients as well as operating room staff involved in the surgeries had negative RT-PCR COVID-19 tests prior to the procedures, with members of the surgical team additionally wearing Tyvek® coveralls (DuPontTM; Delaware, USA), N95 respirators (3MTM: Minnesota, USA), and facemasks. A patient was given prophylactic 1.5-g loading dose of intravenous (IV) cefuroxime (CEFRONE®; NCPC Hebei Huamin Pharmaceutical Co. Ltd.; Shijiazhuang, China) right after induction of anesthesia, continued at 750-mg doses every 12 hours after the surgery until removal of wound suction catheter. Additionally, 1 g of tranexamic acid (TXA) (CYCLOXID®; Jiangsu Ruinian Qianjin Pharmaceutical Co. Ltd.; Jiangsu, China) may be given by IV infusion prior to skin incision [14], although the decision to administer TXA was based on the surgeon’s preference and not on prospectively selected criteria. During or after the surgery, 250-mL aliquots of packed red blood cells were transfused as needed. Deep fascia, subcutaneous tissue, and skin were apposed with careful obliteration of soft tissue dead spaces during the surgical wound closure, and closed suction drainage as well as compressive bandaging were applied. Early assisted mobilization and range of motion exercises were encouraged following the operation, with amputees also referred to our Rehabilitation Medicine Service for preparation of prostheses. Surgical sites were inspected by the second day after surgery, and patients were sent home upon completion of the IV cefuroxime regimen when there are no signs of deep infection in the surgical site, serum hemoglobin has been optimized to at least 100 mg/dL, and repeated RT-PCR COVID-19 tests yielded negative results. For surgical site surveillance, wounds were inspected at 2 weeks after surgery then at 6 weeks in conjunction with radiographic surveillance. Musculoskeletal Tumor Society (MSTS) scores for each patient were recorded during outpatient follow-up, to monitor functional outcomes [15].

Data collected from the patients' medical charts included: a) surgical resection strategy as well as method of limb reconstruction, if applicable; b) total intraoperative blood loss, in milliliters (mL); c) operative duration, in minutes (min); d) development of perioperative complications; e) repeated RT-PCR COVID-19 test results; and e) MSTS scores during final follow-up. Patient-, disease-, and treatment-related variables were also recorded to describe baseline characteristics. We decided to compare LS with major amputation performed in the same COVID-19 period, especially since the need or preference of many cancer surgeons to delay surgical treatment for extremity malignancies has increased the rate of major amputations during the pandemic [13]. We grouped the patients according to whether one underwent LS surgery or major amputation, and compared the two groups by analyzing the mean volumes of intraoperative blood loss, operative duration, MSTS scores during last follow-up, perioperative complication rates and lastly, COVID-19 infection rates. Mann-Whitney U and Fisher's exact tests were used to analyze means and proportions, respectively. All statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA), with a two-tailed p-value of less than .05 considered significant.

Results

Baseline characteristics

We categorized patient-, disease-, and treatment- related variables according to whether one underwent LS surgery or major amputation during tumor resection (Table 1).

	Total N=45	
	LS (n=21)	Amputation (n=24)
Age (years)*	46 (12 to 66)	34 (6 to 69)
Gender**		
Men	8 (46)	12 (50)
Women	13 (54)	12 (50)
Tissue involvement**		
Bone	13 (62)	11 (46)
Soft tissue	8 (38)	13 (54)
Limb involvement**		
Upper extremity	2 (10)	9 (38)
Lower extremity	19 (90)	15 (62)
Tumor diagnosis**		
Spindle cell sarcoma	0 (0)	5 (21)
Osteosarcoma	3 (14)	9 (38)
Giant cell tumor of bone	7 (33)	2 (8)
Undifferentiated pleiomorphic sarcoma	0 (0)	2 (8)
Rhabdomyosarcoma	0 (0)	1 (4)
Malignant melanoma	2 (10)	1 (4)
Liposarcoma	2 (10)	0 (0)
Squamous cell carcinoma	0 (0)	2 (8)
Leiomyosarcoma	1 (5)	0 (0)
Angiosarcoma	0 (0)	1 (4)
Synovial sarcoma	0 (0)	1 (4)
Metastatic bone disease from primary carcinoma	6 (28)	0 (0)
Operative duration (minutes)*	323 (88 to 900)	214 (47 to 378)
Intraoperative blood loss (milliliters)*	1113 (300 to 3800)	779 (100 to 2210)
COVID-19 infection**	3 (14)	7 (29)
MSTS scores (%)*	81 (27 to 97)	49 (20 to 97)
Perioperative complications**	3 (14)	2 (8)

Table 1. Patient Characteristics.

*Presented as the mean with the range in parentheses; **Presented as the number with the percentage in parentheses

There were 8 (46%) men and 13 (54%) women in the LS group, with a mean age of 46 years (range, 12 to 66). While in the amputation group, there were 12 (50%) men and women, with a mean age of 34 years (range, 6 to 69). A larger number of patients who underwent LS had bone tumors (13, or 62%), while majority of patients in the amputation group had soft tissue tumors (13, or 54%). Majority of tumors for both LS (19, or 90%) and amputation (15, or 62%) groups involved the lower extremities. Most of the cases in the LS group were giant cell tumor of bone (7, or 33%) and metastatic bone disease (6, or 28%), while majority in the amputation group were osteosarcoma (9, or 38%) and spindle cell sarcoma (5, or 21%). Due to out-of-pocket payment constraints among the patients, immunohistochemical analyses to subcategorize spindle cell sarcomas in our series have not been pursued.

COVID-19 infection

Seven (29%) of the 24 patients who underwent major amputation tested positive for COVID-19, all of which were mild [16]. Similarly, 3 (14%) patients in the LS group developed mild COVID-19. All the patients who developed COVID-19 underwent isolation at the hospital's regular COVID-19 unit prior to the surgeries, and recovered with negative RT-PCR COVID-19 tests following supportive care (Table 2).

Case No.	Group	Age/Sex	Diagnosis	Complication	Management	Outcome
3	LS	50/F	GCT of bone	Superficial SSI	Oral antibiotics	Improved
14	LS	50/M	Leiomyosarcoma	Superficial SSI	Oral antibiotics	Improved
8	Amputation	63/M	Spindle cell sarcoma	Superficial SSI	Oral antibiotics	Improved
10	Amputation	13/M	Rhabdomyosarcoma	Superficial SSI	Oral antibiotics	Improved
27	LS	52/M	Spindle cell sarcoma	Superficial SSI	Oral antibiotics	Improved
3	Amputation	24/F	GCT of bone	Mild COVID-19	Supportive care	Recovered
7	Amputation	61/M	UPS	Mild COVID-19	Supportive care	Recovered
8	Amputation	63/M	Spindle cell sarcoma	Mild COVID-19	Supportive care	Recovered
30	Amputation	17/F	Osteosarcoma	Mild COVID-19	Supportive care	Recovered
12	LS	56/F	Metastatic bone disease	Mild COVID-19	Supportive care	Recovered
35	Amputation	50/F	Osteosarcoma	Mild COVID-19	Supportive care	Recovered
4	Amputation	34/F	GCT of bone	Mild COVID-19	Supportive care	Recovered
24	LS	54/F	Metastatic bone disease	Mild COVID-19	Supportive care	Recovered
28	LS	50/M	Squamous cell CA	Mild COVID-19	Supportive care	Recovered
37	Amputation	17/F	Osteosarcoma	Mild COVID-19	Supportive care	Recovered

Table 2. List of Perioperative Complications.

LS, limb salvage; GCT, giant cell tumor; UPS, undifferentiated pleiomorphic sarcoma; CA, carcinoma; SSI, surgical site infection; COVID,coronavirus disease

Following analysis, COVID-19 infection rates (29% vs. 14%, p=.23) were similar between the LS and amputation groups (Table 3). Mean inpatient postoperative duration for the LS group is 10 days (range, 2 to 17 days), while for the amputation group, 14 days (range, 1 to 19 days). There were no recorded pulmonary complications or mortalities from this COVID-19 cohort during the follow-up period.

Clinical outcomes

The mean operative duration by the LS and amputation groups were 323 min (range, 88 to 900) and 214 min (range, 47 to 378), respectively, while mean intraoperative blood loss were 1113 mL (range, 300 to 3800) and 779 mL (range, 100 to 2210), respectively (Table 1). Majority of tumors for both LS (19, or 90%) and amputation (15, or 62%) groups involved the lower extremities, and mean MSTS scores during final follow-up were 81% (range, 27 to 97) for the LS group and 49% (range, 20 to 97) for the amputation group (Table 1). In the perioperative period, 2 (8%) patients in the amputation group and 3 (14%) in the LS group developed superficial incisional surgical site infection (SSI) [17], which eventually improved following extended oral antibiotic therapy (Table 2).

Our study found statistically significant differences in operative duration (323 min vs. 214 min, p=.004) and MSTS scores (81% vs. 49%, p=.001), illustrating better functional outcomes following LS in the short-term period despite longer duration of surgeries. Intraoperative blood loss (1113 mL vs. 779 mL, p=.46) and superficial incisional SSI rates (14% vs. 8%, p=.12) were similar between the two groups (Table 3).

	N	Mean/ Proportion	P-value
Blood loss			0.46
LS	21	1113 mL	
Amputation	24	779 mL	
Operative duration			0.004
LS	21	323 min	
Amputation	24	214 min	
Superficial SSI			0.12
LS	21	14%	
Amputation	24	8%	
COVID-19 infection			0.23
LS	21	14%	
Amputation	24	29%	
MSTS scores			0.001
LS	21	81%	
Amputation	24	49%	

Table 3. Analysis of Outcomes.

LS, limb salvage; SSI, surgical site infection; COVID, coronavirus disease; MSTS, Musculoskeletal Tumor Society; mL, milliliters; min- minutes

Discussion

LS has become the standard treatment model for tumors involving the extremities [5, 6]. But due to the COVID-19 pandemic, several precautions have been recommended to prevent nosocomial COVID-19 among susceptible cancer patients as well as preserve critical care resources [8-12]. Consequently, holistic cancer care especially in developing countries has been compromised, with resulting neglect of most patients with extremity tumors leading to more amputations [13]. Owing

to a lack of consensus regarding the ideal management of extremity tumors in a time of pandemic, the present paper analyzed a series of patients who underwent surgery in a Philippine tertiary center and found LS to be a viable option for treating extremity tumors in the COVID-19 era. The present study is not without limitations. First, selection bias may be unavoidable considering our analysis being retrospective in nature. Second, our study may be limited by the short follow-up period. Longer-term outcomes, such as local recurrence and even function that can change over time, are just as important in deciding if LS is a viable option. It has been recognized that traditional clinical research using standard follow-up is extraordinarily difficult in the developing world, where resources are limited [18]. Moreover, given the precautions recommended in the time of COVID-19 pandemic, it became more challenging for patients with extremity tumors to pursue regular follow-up. Thus, similar to experiences of Young et al. [19], patients most commonly sought follow-up for removal of wound sutures or due to development of SSI. Lastly, multi-institutional studies involving larger cohorts may be necessary, in order to address the relatively small number of patients included in our analysis. The number of patients admitted for surgery in our institution must have been limited by earlier hospital memorandums to help preserve critical care resources by delaying elective surgeries.

Our study found COVID-19 infection rates to be similar between the LS and amputation groups. To the best of our knowledge, outcomes for patients with extremity tumors and COVID-19 are relatively scarce. One single-institutional series of 10 patients with both sarcoma and COVID-19 involved 5 (50%) hospitalizations, 3 (60%) of which were eventual mortalities - 2 from COVID-19 and 1 from sarcoma [20]. Moreover, a larger multi-institutional registry analysis of 100 patients with a diagnosis of sarcoma and laboratory-confirmed COVID-19 found a hospitalization rate of 96%, of whom 18 (19%) died within 30 days from COVID-19 diagnosis. Patients with higher mortality rate had older age (OR=2.04, p=.016), higher Eastern Cooperative Oncology Group Performance Status scores (OR=12.2, p<.001), lung metastases (OR=2.77, p=.013), and received systemic treatment within 3 months of COVID-19 diagnosis (OR=2.65, p=.001) [21]. Our finding showed more favorable outcome with none of the 10 patients developing severe COVID-19, but all recovering with supportive care. This could have been due to exclusion of patients with associated comorbidities, as well as the absence of both systemic treatment and lung metastases in the cohort we included for the analysis.

We found extremity tumor surgery by LS to be safe in the COVID-19 era, having determined similar intraoperative blood loss and perioperative complication rates between the two groups. Moreover, findings illustrate better functional outcomes following LS in the short-term period despite longer duration of LS surgeries. Kumar et al. [22] evaluated feasibility of surgery for bone sarcomas during the COVID-19 lockdown in India, and found similar intraoperative blood loss (p=.905), type of anesthesia (p=.103), and operative duration (p=.9) to those of surgeries in the immediate 4 weeks before the lockdown. Moreover, 84% of major surgeries during the lockdown period were LS procedures [22]. Similar to our series, none of the patients who underwent surgery had evidence of severe COVID-19 infection at 15 days follow-up.

Believing the initial fear during the pandemic is gradually waning off, Garg et al. [23] proposed that cancer surgery can no longer be postponed indefinitely in the curative setting. They insisted that cancer patients cannot be denied surgery for as long as we learn to coexist with COVID-19, having recognized that various modifications are being made in hospital systems to minimize effect of COVID-19 on outcomes. Sud et al. [24] used healthcare resource costing to contextualize life-years gained from cancer surgery to equivalent volumes of COVID-19 hospitalizations, and found that average losses of 0.97 and 2.19 life-years gained per patient are already incurred with surgical delays of only 3 and 6 months, respectively. Thus, they recommend that surgical pathways be maintained at normal throughput, with attention to backlogs already accrued [24]. Moreover, Tiwari et al. [12] reviewed various guidelines proposed by different healthcare organizations and institutes regarding the modified care pathways for malignant bone neoplasms in the current pandemic and upon summary, proposed that curative surgery for high-grade malignant tumors should not be delayed and be given the highest priority. They recommend surgeries to be planned

carefully with preference for younger patients (<60 years) and American Society of Anesthesiology grade I or II. We consider our study's favorable outcomes to be possibly due to inclusion of relatively younger patients without systemic comorbidities for the analysis, and likewise, recommend curative LS surgery for similar patients without delay.

In conclusion, the authors conclude that LS can be a viable option, and not unnecessarily be delayed, when treating bone and soft tissue tumors involving the extremities especially in developing countries in the COVID-19 era. Our findings, however, must be considered preliminary. Longer-term outcomes such as local recurrence and even function, which can change over time, are just as important in deciding if LS is a viable option. Multi-institutional prospective comparative studies involving more tertiary centers and longer follow-up are therefore recommended.

Conflicts of Interest

The authors declare no conflict of interest.

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