Clinics in Surgery

Research Article
Published: 23 Jul, 2020

Postoperative Seromas after Soft-Tissue Sarcoma Resection: Natural History and Progression

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Abstract

Introduction: Following wide surgical excision of deep soft-tissue sarcomas, particularly those that are large and underwent preoperative radiation, patients may develop a seroma despite prolonged surgical drain placement. This study aimed to evaluate the natural history of these fluid collections to better counsel patients regarding expectations.

Materials and Methods: We reviewed data on 48 patients with seromas after extremity soft-tissue sarcoma resection to determine the natural history of these seromas and which patient and treatment factors are associated with seroma resolution, which was assessed using advanced imaging. Kaplan-Meier and univariate analyses determined predictors of time to resolution. Alpha=0.05.

Results: Twenty patients had complete seroma resolution at a mean (standard error) 50 (7.0) months postoperatively. Complete resolution occurred at higher rates among men (56%) *vs.* women (24%); patients who did not undergo postoperative radiation (49%) *vs.* those who did (11%); and patients with initial seroma size <85 cm^3 (61%) *vs.* ≥ 85 cm^3 (17%) (all, $p<0.05$). Factors associated with shorter mean (standard error) time to resolution were upper-extremity involvement (6.2 [2.7] months) *vs.* lower-extremity involvement (52 [7.2] months); and initial seroma size <85cm^3 (14[1.7] months) *vs.* ≥ 85 cm^3 (76 [7.5] months) (both, $p<0.05$).

Discussion: Most seromas after extremity soft-tissue sarcoma resection shrank over time. Male sex, lack of postoperative radiation, and initial seroma size <85 cm^3 were associated with complete resolution. Initial seroma size <85 cm^3 were associated with faster resolution.

Keywords: Complication; Fluid collection; Radiation; Sarcoma; Seroma

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Received Date: *02 Jun 2020*
Accepted Date: *03 Jul 2020*
Published Date: *23 Jul 2020*

Citation:
El Abiad JM, Bridgham KM, Toci GR, Morris CD, Sacks JM, Fayad LM, et al. Postoperative Seromas after Soft-Tissue Sarcoma Resection: Natural History and Progression. Clin Surg. 2020; 5: 2875.

Introduction

Soft-tissue sarcomas are rare, accounting for approximately 1% of solid malignancies in adults [1]. Treatment is typically multidisciplinary, consisting of wide surgical resection with or without radiation and/or chemotherapy. After resection, the development of a seroma at the surgical site is common, occurring in 9% to 36% of patients despite postoperative drain placement [2-5]. Seromas are fluid collections composed of blood plasma ultra filtrates, and may be associated with preoperative radiation, large-volume resection, diabetes mellitus, and wound healing complications [6-13]. Several theories have been described to explain their pathogenesis, including persistent postoperative lymphatic leakage or crushing and shearing strains leading to fluid collections within the surgical field [14,15]. On Magnetic resonance imaging (MRI), seromas in the surgical bed appear as hypointense on T1-weighted images and uniformly hyperintense on T2-weighted and short tau inversion recovery images, often with a rim of hypointensity corresponding to the presence of hemosiderin around the periphery. Occasionally, seromas have complex heterogeneous signal related to the presence of prior blood products [16]. After administration of intravenous contrast medium, these fluid collections show peripheral enhancement only, without central enhancement. The characteristics of seromas on MRI have been further described on diffusion-weighted imaging and dynamic contrast-enhanced MRI, with additional features that differentiate seromas from recurrent tumors (Figure 1) and from postoperative hematomas [17]. Treatment can

be non operative or can involve drain placement, needle aspiration, or surgical irrigation and debridement. However, the natural course of seromas after soft-tissue sarcoma resection is incompletely characterized.

Although seromas do not directly cause increased risk of death, their prolonged presence may cause patient anxiety, especially when they are located in the area undergoing surveillance after wide resection of a previous malignant neoplasm. Anecdotally, in the era of electronic records, patients may express concern upon seeing their imaging interpretation include a seroma, prior to their surveillance clinical encounter. Further, large post operative fluid collections lead to functional impairment in some patients. Patients often ask what to expect regarding the resolution of postoperative seromas. To our knowledge, few data exist regarding the natural history, progression, and long-term outcomes of seromas after resection of extremity soft-tissue sarcomas. Only two studies describe the rate of change in seroma volume over time; however, these studies do not describe time to resolution or factors associated with resolution [2,4]. Therefore, counseling patients on the progression of seromas is challenging. Our aims were to investigate:

1. The natural history of seromas after extremity soft-tissue sarcoma resection

2. The associations of clinical, operative, and postoperative factors with the resolution of seromas.

Materials and Methods

This retrospective cohort study was approved by our institutional review board. We retrospectively reviewed records for all patients who developed seromas after resection of an extremity soft-tissue sarcoma between 2007 and 2017, as identified by imaging reports or retrospective review of cross-sectional imaging studies. Of the 571 adults who underwent extremity soft-tissue sarcoma resection during this period, 56 patients (9.8%) were identified with adjudicated postoperative seromas. Seromas were identified manually on postoperative MRI or computed tomography (CT) by two independent reviewers, and radiology reports were cross-referenced to ensure seromas were not missed on the initial scan. Seroma size was tracked over time. Discrepancies between sizes were resolved by consensus agreement.

We excluded patients with preoperative seromas, soft-tissue sarcomas in locations other than the extremities, fluid collections with imaging or aspiration characteristics that were suggestive of a hematoma, and patients <18 years old. We also excluded patients with <6 months of radiographic follow-up unless previous seroma resolution was confirmed. Forty-eight patients met our inclusion criteria and were included in our analysis. Medical records were reviewed for patient characteristics. Surgical factors were reviewed, as well as wound closure technique, flap placement, and perioperative drain use. Local recurrence of the soft-tissue sarcoma and seroma treatment methods were also recorded.

Demographic characteristics

Of the 48 patients included in our study, 21 (44%) were women. The mean (± standard deviation) patient age at time of surgery was 55 ± 16 years. The mean follow up time was 2.3 ± 1.2 years.

Treatment

In addition to resection, 7 patients underwent systemic chemotherapy and local preoperative or postoperative radiation for their soft-tissue sarcomas. Six patients underwent intervention for their seromas, including irrigation and debridement; drain placement, or needle aspiration.

Seroma assessment

Seromas were identified on surveillance MRI postoperatively as well-defined fluid collections arising in the soft-tissue sarcoma resection bed. Seromas appeared uniformly hypointense on T1-weighted images and hyperintense on T2-weighted or short tau inversion recovery images, and are distinguishable from hematomas. On post-contrast imaging, seromas showed peripheral enhancement only, without central enhancement. In patients with >1 seroma, the largest was selected and followed over time. Seroma volume was calculated according to approximated measurements in the transverse, anteroposterior, and craniocaudal dimensions.

Statistical analyses

Kaplan-Meier and univariate analyses were used to determine significant associations with time to resolution of postoperative seromas. Chi-squared analysis was then used to determine the difference in the proportion of seromas that completely resolved. Statistical significance was set at $p<0.05$.

Because of the skewed nature of our cohort, the median was used to convert continuous variables into categorical variables. The median age of the cohort was 54 years (range, 25 to 82). Therefore, we used the age of 55 years as a binary threshold. The median resection volume was 783 cm^3 (range, 23.6 to 10,500), and the median initial size of seromas was 85 cm^3 (range, 1.1 to 1257). Therefore, we used 780 cm^3 and 85 cm^3 as the binary thresholds, respectively. Body mass index (BMI) was dichotomized as obese (>30) or non-obese (≤ 30), and tumor location was categorized as upper or lower extremity. Because of our small sample size and proportion of patients with seroma resolution, calculation of time to seroma resolution was based on the mean value because calculation of median was not possible.

Results

Natural history of seromas

Seromas resolved in 20 patients with and without intervention at a mean of 50 months (95% confidence interval, 36 to 64; standard error [SE]=7.0) postoperatively. Although most resolved after 6 months, one patient had resolution of their seroma at 2.5 months, and two patients had resolution of their seroma at 4 months. In the 46 patients for whom initial seroma size was documented, serial monitoring of seroma size (volume) over time showed that 2 patients (4%) experienced a decrease of 25% to 49%, 7 patients (15%) experience a decrease of 50% to 74%, and 35 patients (76%) experience a decrease of 75% or more. Overall, 8 patients had an increase in the size of their seromas, 4 of whom had spontaneous regression of their seromas over time, while 2 required intervention (irrigation and debridement and drain placement) and then regressed. Thus, only 2 patients in our cohort had seromas that did not regress at latest follow-up.

Clinical factors

The lower extremity was the most common site of the tumor (n=46) (Table 1). Of tumors in the lower extremity, only 1 was in the adductor compartment. The mean initial size of seromas was 231 ± 324 cm^3.

Operative factors

Wide resection of the primary sarcoma was performed in all 48 cases, and the mean tumor resection volume was 1545 ± 2333

Table 1: Characteristics of 48 patients who developed seromas after resection of soft-tissue sarcoma.

Characteristic	N (%)
Female sex	21 (44)
Body mass index (kg/m^2)†	30±7.2*
History of smoking	19 (40)
Seroma location	
Upper extremity	2 (4)
Lower extremity	46 (96)
Surgical	
Resection size (cm^3)‡	1545 ± 2333*
Complex closure	20 (42)
Flap use	10 (21)
Drain use	28 (58)
Intervention	
Preoperative radiation	42 (88)
Postoperative radiation	9 (19)
Chemotherapy	7 (15)
Intervention for seroma	6 (13)
Needle aspiration	2 (4.2)
Drain placement	1 (2)
Irrigation and debridement	3 (6)
Initial seroma size (cm^3)‡	231 ± 324*
Wound healing complication	6 (13)

*Data presented as mean ± standard deviation
†Data on body mass index were available for 39 patients
‡Data on resection size and initial size for seroma were available for 46 patients

cm^3. Twenty patients underwent complex wound closure or flap coverage, and 10 patients underwent flap reconstruction. A surgical drain was placed at the end of surgery in 28 patients. These were removed when drainage was less than 30 cubic centimeters over a 24-h period. Wound healing complications, including wound dehiscence and surgical site infections, occurred in 6 patients. Most patients (n=42) had undergone preoperative radiation; whereas, only 9 patients underwent postoperative radiation, and 7 patients received chemotherapy. A total of 6 patients underwent local intervention for the postoperative seroma (Table 1).

Factors associated with seroma resolution

Univariate analysis indicated that significantly larger proportions of seromas resolved in men (56%) than in women (24%) (p=0.027); in patients who did not undergo postoperative radiation (49%) than in those who did (11%) (p=0.039); and in patients with an initial seroma size <85 cm^3 (61%) than in those with seromas ≥ 85 cm^3 (17%) (p=0.003). Factors associated with shorter mean (SE) time to resolution were upper extremity involvement (6.2 [2.8] months) *vs.* lower extremity (52 [7.2] months) (p=0.011) and initial seroma size <85 cm^3 (14 [1.7] months) *vs.* ≥ 85 cm^3 (76 [7.5] months) (p=0.004) (Table 2).

Discussion

Although studies have suggested factors associated with seroma formation, few data have been published regarding factors influencing the natural history and progression of postoperative seromas in this population [2,4]. We conducted a single-center retrospective review using our institute's cancer registry to study

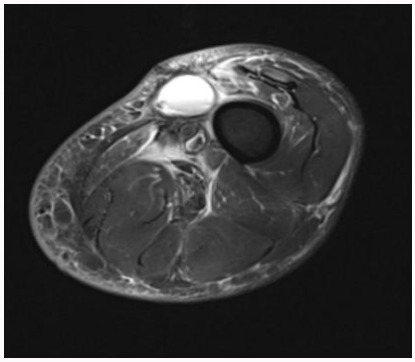

Figure 1: Axial fat-saturated T2-weighted magnetic resonance image showing 3.1 cm × 2.2 cm seroma in the anterior thigh compartment.

the natural history of seromas and factors affecting their resolution after extremity soft-tissue sarcoma resection. The overall resolution rate of seromas in our study was 42% (20/48 patients), at a mean of 50 months postoperatively. Most patients (96%) had a decrease of at least 75% in the size of their seroma by the end of follow-up. Factors associated with a higher rate of seroma resolution were male sex, lack of postoperative radiation, and initial seroma size <85 cm^3. Factors associated with shorter mean time to seroma resolution were upper extremity involvement and initial seroma size <85 cm^3.

Seromas are a common postoperative finding, observed in 9% to 36% of patients after limb salvage surgery for soft-tissue sarcomas [2-5]. Radiation is used routinely for large, high-grade sarcomas to decrease the risk of local recurrence, although preoperative radiation is associated with postoperative wound healing complications and the formation of postoperative seromas [10,18-26]. Tumor size, diabetes mellitus, and the proximity of the tumor to the skin are also associated with the development of postoperative wound complications [26]. Although studies have suggested factors associated with seroma formation, few data have been published regarding factors influencing the natural history and progression of postoperative seromas in this population [2,4].

We found that 42% of patients who developed seromas after wide resection of extremity soft-tissue sarcomas had complete radiographic resolution of the seroma at a mean of 50 months after resection. The radiographic resolution rate of 42% may be increased with longer follow-up. Although mean follow-up was 28 months, many seromas did not completely resolve until sometime after that, on average. Poon-Chue et al. [4] performed a retrospective study of 8 patients who underwent soft-tissue sarcoma resection and found that, on the basis of postoperative MRI, most seromas (7/8) decreased or remained the same in size. However, the authors did not provide data or analysis on how many seromas resolved or time to resolution. In our analysis, the time to complete resolution is reported only for the subset of patients whose seromas resolved completely.

Most postoperative seromas were in the lower extremity. In their series of 8 patients with postoperative seromas, Poon-Chue et al. [4] found that all seromas were in the lower extremity. They hypothesized that postoperative seromas in the upper extremity were uncommon, possibly because of reduced gravitational effects on lymphatic and vascular drainage or the smaller soft tissue size and less subcutaneous fat in the upper extremity compared with the lower extremity [4]. Although our study was not designed to investigate reasons for this finding, we too found that seromas were rare in the upper extremity

Table 2: Univariate analysis of variables associated with proportion of and time to resolution of seromas after soft-tissue sarcoma resection in 48 patients.

Variables	N	Resolved (n=20)		Time to Resolution	
		N (%)	p value*	Mean (95% CI), mo	p value†
Age (yr)					
<55	25	12 (48)	0.353	18 (14-22)	0.419
≥ 55	23	8 (35)		57 (38-77)	
Sex					
Male	27	15 (56)	0.027	17 (13-21)	0.155
Female	21	5 (24)		67 (48-86)	
Body mass index (kg/m ^{2})‡					
≤ 30	22	8 (36)	0.163	53 (32-73)	0.344
>30	17	10 (59)		16 (11-22)	
Smoking					
No	29	12 (41)	0.96	48 (30-66)	0.743
Yes	19	8 (42)		23 (16-31)	
Resection size (cm ^{3})					
<780	23	9 (39)	0.522	49 (28-71)	0.554
≥ 780	23	11 (48)		22 (15-28)	
Location					
Upper extremity	2	2 (100)	0.087	6.2 (0.8-12)	0.011
Lower extremity	46	18 (39)		52 (38-66)	
Closure					
Simple	28	11 (39)	0.692	25 (19-31)	0.562
Complex	20	9 (45)		44 (23-66)	
Flap placement					
No	38	14 (37)	0.186	25 (20-30)	0.21
Yes	10	6 (60)		37 (11-63)	
Drain placement					
No	20	6 (30)	0.166	58 (36-80)	0.227
Yes	28	14 (50)		18 (13-22)	
Preoperative radiation					
No	6	1 (17)	0.184	23 (17-29)	0.253
Yes	42	19 (45)		47 (33-62)	
Postoperative radiation					
No	39	19 (49)	0.039	21 (16-26)	0.061
Yes	9	1 (11)		82 (62-101)	
Chemotherapy					
No	41	18 (44)	0.447	48 (33-63)	0.501
Yes	7	2 (29)		21 (14-29)	
Intervention					
No	42	18 (43)	0.658	47 (32-62)	0.631
Yes	6	2 (33)		20 (11-29)	
Initial seroma size (cm^3)¶					
<85	23	14 (61)	0.003	14 (11-18)	0.004
≥ 85	23	4 (17)		76 (61-91)	
Wound complications					
No	42	19 (45)	0.184	22 (17-27)	0.121
Yes	6	1 (17)		78 (54-103)	

CI: Confidence Interval

*From chi-squared analysis

†From univariate Cox proportional hazards regression

‡Of the 20 patients with seroma resolution, body mass index values were available for 18

¶Of the 20 patients with seroma resolution, data on initial seroma size (cm ^{3}) were available for 18

after soft-tissue sarcoma resection. Skibber et al. [27] also found that the lower extremity was the most common location of postoperative seromas. In our study, a higher proportion of seromas located in the upper extremity resolved and did so significantly faster than those in the lower extremity, despite being similar in size.

Although studies have shown that resection volume is associated with the risk of seroma formation, we are aware of no research on seroma size as a predictor of natural history and progression of seromas [9,13]. Initial volume of the seroma may be predictive of resolution. We found that a significantly smaller proportion of seromas ≥ 85 cm^3 resolved, and that they took longer to resolve compared with seromas <85 cm^3. However, the proportions of patients with 25%, 50%, and 75% decreases in seroma volume were similar between seromas of smaller and larger sizes.

Most patients in our study underwent preoperative radiation, which is an established risk factor for wound complications after soft-tissue sarcoma resection [6-8,10-12]. We found no significant difference in the proportions of patients who developed seromas or the time to resolution of seromas according to preoperative radiation status. However, postoperative radiation was associated with persistence of seromas. This persistence may be influenced by radiation-induced physiologic changes, including decreased compliance of the soft tissues after surgery, potentially creating space for postoperative seromas to form and remain. Whereas preoperative radiation is strongly associated with development of seromas, postoperative radiation may be associated with progression of existing seromas.

Our study has several limitations. First, postoperative surveillance imaging intervals may not accurately reflect the time needed for a seroma to resolve. This may have led to overestimating the time until resolution. Second, most patients were diagnosed and followed using MRI or CT. Although 2 independent reviewers evaluated all imaging and approximated seroma measurements, few patients had histologic or cytologic analysis of their fluid collections. Third, although imaging findings and clinical follow-up were consistent for all patients, 11 patients later developed local sarcoma recurrence at the resection site. In these 11 patients, the imaging characteristics of the sarcoma recurrence were distinguishable from those of the seroma on MRI. Fourth, the small cohort size limited our ability to stratify patients for sub analysis, and only two seromas were localized to the upper extremity. Nonetheless, our study is one of the largest evaluations of postoperative seromas after soft-tissue sarcoma resection. Fifth, the low rate of complete resolution of seromas (43%) restricted the analysis of the time needed for resolution to using means rather than medians, despite concerns that the data may have been non-normally distributed. Because data regarding time to resolution in our series appear to be right-skewed, univariate analysis using log-rank may have overestimated the time needed for resolution of the postoperative seromas. Therefore, we were unable to perform multivariate analysis, potentially leading to confounding bias.

Conclusion

Seromas after wide resection of extremity soft-tissue sarcomas resolved completely in <50% of our patients, although most seromas decreased by at least 75% in volume during repeat surveillance. Our results show that male sex, upper extremity seroma location, lack of postoperative radiation, and initial seroma size <85 cm^3 are associated with earlier resolution of postoperative seromas in this patient population.

Acknowledgment

We thank Rachel Box, Jenni Weems, and Kerry Kennedy for their editorial assistance.

References

1. Burningham Z, Hashibe M, Spector L, Schiffman JD. The epidemiology of sarcoma. Clin Sarcoma Res. 2012;2:14.
2. Davies AM, Hall AD, Strouhal PD, Evans N, Grimer RJ. The MR imaging appearances and natural history of seromas following excision of soft tissue tumours. Eur Radiol. 2004;14(7):1196-202.
3. Panicek DM, Schwartz LH, Heelan RT, Caravelli JF. Non-neoplastic causes of high signal intensity at T2-weighted MR imaging after treatment for musculoskeletal neoplasm. Skeletal Radiol. 1995;24(3):185-90.
4. Poon-Chue A, Menendez L, Gerstner MM, Colletti P, Terk M. MRI evaluation of post-operative seromas in extremity soft tissue sarcomas. Skeletal Radiol. 1999;28(5):279-82.
5. Vanel D, Shapeero LG, Baere TD, Gilles R, Tardivon A, Genin J, et al. MR imaging in the follow-up of malignant and aggressive soft-tissue tumors: results of 511 examinations. Radiology. 1994;190(1):263-8.
6. Bujko K, Suit HD, Springfield DS, Convery K. Wound healing after preoperative radiation for sarcoma of soft tissues. Surg Gynecol Obstet. 1993;176(2):124-34.
7. Cheng EY, Dusenbery KE, Winters MR, Thompson RC. Soft tissue sarcomas: Preoperative *vs.* postoperative radiotherapy. J Surg Oncol. 1996;61(2):90-9.
8. Chmell MJ, Schwartz HS. Analysis of variables affecting wound healing after musculoskeletal sarcoma resections. J Surg Oncol. 1996;61(3):185-9.
9. Geller DS, Hornicek FJ, Mankin HJ, Raskin KA. Soft tissue sarcoma resection volume associated with wound-healing complications. Clin Orthop Relat Res. 2007;459:182-5.
10. O'Sullivan B, Davis AM, Turcotte R, Bell R, Catton C, Wunder J, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: A randomised trial. Lancet. 2002;359(9325):2235-41.
11. Peat BG, Bell RS, Davis A, O'Sullivan B, Manktelow RT, Bowen V, et al. Wound-healing complications after soft-tissue sarcoma surgery. Plast Reconstr Surg. 1994;93(5):980-7.
12. Prosnitz LR, Maguire P, Anderson JM, Jones EL, Dewhirst M, Powers BE, et al. The treatment of high-grade soft tissue sarcomas with preoperative thermoradiotherapy. Int Radiat Oncol Biol Phys. 1999;45(4):941-9.
13. Sanniec KJ, Swanson S, Casey WJ 3rd, Schwartz A, Bryant L, Rebecca AM. Predictive factors of wound complications after sarcoma resection requiring plastic surgeon involvement. Ann Plast. Surg. 2013;71(3):283-5.
14. Sitzmann JV, Dufresne C, Zuidema GD. The use of sclerotherapy for treatment of postmastectomy wound seromas. Surgery. 1983;93(2):345-7.
15. Sterling A, Butterfield WC, Bonner R Jr, Quigley W, Marjani M. Post-traumatic cysts of soft tissue. J Trauma. 1977;17(5):392-6.
16. James SL, Davies AM. Post-operative imaging of soft tissue sarcomas. Cancer Imaging. 2008;8(1):8-18.
17. Del Grande F, Subhawong T, Weber K, Aro M, Mugera C, Fayad LM. Detection of soft-tissue sarcoma recurrence: Added value of functional MR imaging techniques at 3.0 T Radiology. 2014;271(2):499-511.
18. Bedi M, King DM, Shivakoti M, Wang T, Zambrano EV, Charlson J, et al. Prognostic variables in patients with primary soft tissue sarcoma of the extremity and trunk treated with neoadjuvant radiotherapy or neoadjuvant sequential chemoradiotherapy. Radiat Oncol. 2013;8:60.
19. Brant TA, Parsons JT, Marcus RB, Spanier SS, Heare TC, Griend VD,

et al. Preoperative irradiation for soft tissue sarcomas of the trunk and extremities in adults. Int J Radiat Oncol Biol Phys. 1990;19(4):899-906.

20. Nielsen OS, Cummings B, O'Sullivan B, Catton C, Bell RS, Fornasier VL. Preoperative and postoperative irradiation of soft tissue sarcomas: Effect of radiation field size. Int J Radiat Oncol Biol Phys. 1991;21(6):1595-9.

21. Sampath S, Schultheiss TE, Hitchcock YJ, Randoll RL, Shierve DC, Wong JYC. Preoperative *vs.* postoperative radiotherapy in soft-tissue sarcoma: Multi-institutional analysis of 821 patients. Int J Radiat Oncol Biol Phys. 2011;81(2):498-505.

22. Zagars GK, Ballo MT, Pisters PW, Pollock RE, Patel SR, Benjamin RS. Preoperative *vs.* postoperative radiation therapy for soft tissue sarcoma: A retrospective comparative evaluation of disease outcome. Int J Radiat Oncol Biol Phys. 2003;56(2):482-8.

23. Baldini EH, Lapidus MR, Wang Q, Manola J, Orgill P, Pomahac B, et al. Predictors for major wound complications following preoperative radiotherapy and surgery for soft-tissue sarcoma of the extremities and trunk: Importance of tumor proximity to skin surface. Ann Surg Oncol. 2013;20(5):1494-9.

24. Cannon CP, Ballo MT, Zagars GK, Mirza AN, Lin PP, Lewis VO, et al. Complications of combined modality treatment of primary lower extremity soft-tissue sarcomas. Cancer. 2006;107(10):2455-61.

25. Kunisada T, Ngan SY, Powell G, Choong PFM. Wound complications following pre-operative radiotherapy for soft tissue sarcoma. Eur J Surg Oncol. 2002;28(1):75-9.

26. Ziegele M, King DM, Bedi M. Tumor volume is a better predictor of post-operative wound complications compared to tumor size in soft tissue sarcomas of the proximal lower extremity. Clin Sarcoma Res. 2016;6:1.

27. Skibber JM, Lotze MT, Seipp CA, Salcedo R, Rosenberg SR. Limb-sparing surgery for soft tissue sarcomas: wound related morbidity in patients undergoing wide local excision. Surgery. 1987;102(3):447-52.