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ONCOLOGY

Closed incision negative pressure wound therapy versus conventional dressings following soft-tissue sarcoma excision: a prospective, randomized controlled trial

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Aims

The primary objective of this study was to compare the postoperative infection rate between negative pressure wound therapy (NPWT) and conventional dressings for closed incisions following soft-tissue sarcoma (STS) surgery. Secondary objectives were to compare rates of adverse wound events and functional scores.

Methods

In this prospective, single-centre, randomized controlled trial (RCT), patients were randomized to either NPWT or conventional sterile occlusive dressings. A total of 17 patients, with a mean age of 54 years (21 to 81), were successfully recruited and none were lost to follow-up. Wound reviews were undertaken to identify any surgical site infection (SSI) or adverse wound events within 30 days. The Toronto Extremity Salvage Score (TESS) and Musculoskeletal Tumor Society (MSTS) score were recorded as patient-reported outcome measures (PROMs).

Results

There were two out of seven patients in the control group (28.6%), and two out of ten patients in the intervention group (20%) who were diagnosed with a SSI ($p > 0.999$), while one additional adverse wound event was identified in the control group ($p = 0.593$). No significant differences in PROMs were identified between the groups at either 30 days (TESS, $p = 0.987$; MSTS, $p = 0.951$) or six-month (TESS, $p = 0.400$) follow-up. However, neoadjuvant radiotherapy was significantly associated with a SSI within 30 days of surgery, across all patients ($p = 0.029$). The mean preoperative modified Glasgow Prognostic Score (mGPS) was also significantly higher among patients who developed a postoperative adverse wound event ($p = 0.028$), including a SSI ($p = 0.008$), across both groups.

Conclusion

This is the first RCT comparing NPWT with conventional dressings following musculoskeletal tumour surgery. Postoperative wound complications are common in this group of patients and we observed an overall SSI rate of 23.5%. We propose proceeding to a multicentre trial, which will help more clearly define the role of closed incision NPWT in STS surgery.

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Introduction

The preferred management of soft-tissue sarcomas (STSs) in the limbs has changed in recent decades from primary amputation to limb-preservation with clear resection margins and the use of adjuvant/neoadjuvant treatments, such as radiotherapy or chemotherapy, where necessary.[1] Amputations are undertaken in around 5% to 15% of cases, and generally after previous attempts at limb salvage have failed.[2,3] Wound complications, such as infection, dehiscence, haematoma or

seroma formation, and necrosis, are relatively common following STS surgery.[4,5] Contributing factors may include tumour location and characteristics (such as lower limb and proximity to skin), residual dead space, disruption of vascular supply or lymphatic drainage, and the cytotoxic effects of radiotherapy or chemotherapy.[6-8]

The development of negative pressure wound therapy (NPWT) in the late 1990s has enhanced the care of complex wounds,[9,10] including open fractures with soft-tissue defects, contaminated wounds, skin grafts, and, more recently, closed incisions at increased risk of complications.[11,12] Accordingly, the applications of NPWT dressings at our institution were expanded in recent years to include patients who were considered to have high-risk wounds following sarcoma resection, even if primary closure had been achieved. Where possible, primary wound closure is undertaken following STS excision, but this can be challenging in cases where extensive dead space and skin loss occurs as a result of large resections. Reconstruction with local flaps or microsurgery involving free tissue transfer is indicated in larger defects.[13]

Although NPWT has generated considerable interest for a variety of indications in recent years,[11] it remains unclear whether it is significantly more effective at reducing postoperative complication rates than conventional dressings for primarily closed wounds. An international multidisciplinary consensus statement in 2016 concluded that closed-incision NPWT should be considered for patients at increased risk of developing wound complications, those undergoing high-risk procedures, and operations where a SSI may be associated with severe consequences.[14] Sarcoma patients generally fulfil all of these categories, but there are comparatively few studies on the use of NPWT in this group of patients. While an earlier retrospective case-matched study at our institution indicated a lower SSI rate in patients treated with closed incision NPWT than conventional dressings,[15] we highlighted the need for prospective evidence.

The primary objective of this study was to compare the postoperative infection rate between NPWT and conventional dressings for closed incisions following STS excision. Secondary objectives were to compare rates of adverse events (such as wound dehiscence, seroma, or haematoma formation) and functional scores. In addition, we sought to evaluate recruitment rate and patient engagement, to determine the feasibility of a multicentre randomized controlled trial (RCT).

Methods

Patients referred to the musculoskeletal oncology service at Glasgow Royal Infirmary were screened for possible recruitment to the NPWT in Soft Tissue Sarcoma Surgery trial (NCT02901405).[16] This single-centre, parallel, randomized controlled trial was performed in accordance with the provisions of the Declaration of Helsinki[17] and ethical approval was obtained from the West of Scotland Research Ethics Committee (16/WS/0146). Patients between 16 and 85 years old were eligible for inclusion if they presented with a STS, scheduled for wide local excision or planned marginal resection, in which primary wound closure was achievable. Exclusion criteria comprised previous surgery, post-radiation sarcomas, active infection in the planned surgical field, the presence of an endoprosthesis, combined cases with plastic surgeons involving reconstructive techniques (such as skin grafts or flap coverage), amputations, disseminated malignancy on preoperative radiology investigations, or any known contact dermatitis to medical adhesives. Patients were provided with an information leaflet and written, informed consent was obtained from all participants in the trial. All patient data were anonymized and blinded prior to analysis.

Allocation for the trial was determined using a computer-generated random number sequence, and administered by a sealed envelope or by contact through an independent trial coordinator (DWS). The envelopes were block randomized using a computer programme in blocks of four, with strata of lower limb and upper limb/trunk to ensure these potential confounders were distributed evenly, due to existing evidence that upper limb wounds have a lower complication rate than lower limb wounds.[7,8] Randomization was allocated by an individual who was not involved in recruitment or intervention within the trial.

Surgery was undertaken by fellowship-trained orthopaedic surgeons specialising in musculoskeletal oncology (AM, SG). All patients underwent preoperative MRI as part of the sarcoma multidisciplinary team (MDT) protocol. Following tumour excision, wounds were closed in layers with Vicryl (Ethicon, Johnson & Johnson, USA) and either skin clips or a subcuticular suture with knots tied under the skin using Monocryl (Ethicon), as per the operating surgeon's choice. The existing evidence from multiple studies indicates that there are no significant differences in adverse wound events between these skin closure methods.[18,19] Concealment was in place until the end of each surgical procedure, when a sealed envelope was opened by theatre staff to reveal the wound dressing allocation. Patients randomized to the control group received a sterile occlusive dressing (Tegaderm+ Pad Film Dressing with Non-Adherent Pad; 3M, USA), while patients randomized to the intervention group received a sterile negative pressure dressing (ActiV.A.C. Therapy System; KCI USA, USA).

In order to minimize harm, routine postoperative wound review was undertaken by the responsible clinician(s) for each patient. However, the diagnosis of any SSI according to Health Protection Agency criteria was made by a blinded investigator after the wound dressing was removed, within 30 days of surgery. Although treating clinicians and patients were not blinded to the primary outcome, assessors were blinded to the assignment. All patients were asked to complete Toronto Extremity Salvage Score (TESS)[20] and Musculoskeletal Tumor Society[21] (MSTS) questionnaires, to calculate

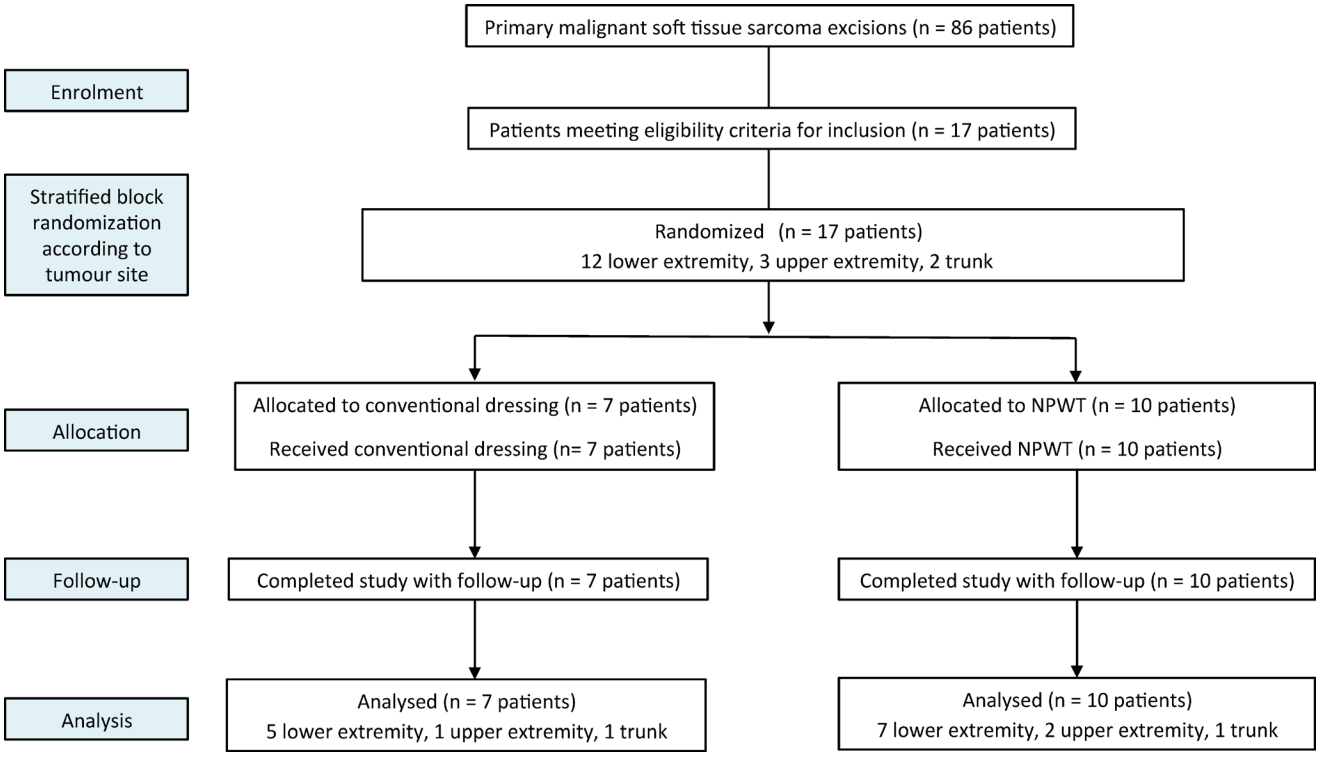

Fig. 1

Consolidated Standards of Reporting Trials (CONSORT) diagram, showing the flow of patients through the Negative Pressure Wound Therapy (NPWT) in Soft Tissue Sarcoma Surgery trial (NCT02901405).

patient-reported outcome measures (PROMs) at 30 days and six months postoperatively.

Patients. Between August 2016 and January 2020, 86 patients (42 female, 44 male) with a mean age of 58 years (19 to 93) underwent surgery for a primary malignant STS at our institution. There were 52 cases in the lower limb (60.5%), 27 in the upper limb (31.4%), and seven in the trunk (8.1%). Wide local excision or planned marginal resection was undertaken in 76 patients (88.4%), with radical surgery performed in only ten cases where an amputation was required (11.6%); four below-knee, three above-knee, one below-elbow, and two hip disarticulations. Two patients required endoprosthetic reconstruction of the femur and one required femoral fixation with an intramedullary nail.

In total, 17 patients (19.8%), with a mean age of 54 years (21 to 81), met the eligibility criteria for recruitment to the trial, as presented in Figure 1, with demographic details presented in Table I. All patients meeting the eligibility criteria were successfully recruited, and completed their treatment. No crossover between the control and intervention groups occurred, although any patients requiring further surgery were subsequently treated with NPWT if the presence of a wound complication had already been determined. The mean follow-up was 25 months (8 to 42), with no patients lost to follow-up. In the NPWT group, two patients died from metastatic disease at 16 and 23 months respectively, while all patients in the control group were alive at latest follow-up (p = 0.485, Fisher's exact test).

Statistical analysis. Data were analyzed using statistical software (SPSS v. 25; IBM, USA). Categorical data and frequencies, such as the incidence of SSIs or adverse wound events between the control and intervention groups, were compared using Fisher's exact test. An independent-samples *t*-test was used to examine any differences in parametric continuous data, such as PROMs, between the groups. For all statistical tests, a p-value < 0.05 was considered significant.

Results

There was no statistically significant difference observed in any of the measured outcomes (Table II) between patients receiving NPWT and conventional dressings. Two out of seven patients in the control group (28.6%), and two out of ten patients in the intervention group (20%) were diagnosed with a SSI within 30 days of surgery (p > 0.999, Fisher's exact test), representing an overall SSI rate of 23.5%. Other than complications directly associated with SSI (such as cellulitis or persistent discharge), only one further adverse wound event (Table III) was identified in the control group (p = 0.593, Fisher's exact test). This was a non-infected seroma, which was treated with ultrasound-guided needle drainage, and required no further intervention. The patient subsequently received

Table I. Demographic data.

Variable	Conventional dressing	NPWT	p-value
Patients, n (M:F)	7 (4:3)	10 (4:6)	0.486
Mean age at surgery, yrs (SD; range)	50 (20.9; 21 to 81)	56 (13.7; 33 to 71)	0.484*
Mean follow-up, mths (SD; range)	27.9 (10.3; 9 to 38)	24 (10.7; 8 to 42)	0.464*
Mean preoperative mGPS (SD; range)	0.29 (0.76; 0 to 2)	0.1 (0.32; 0 to 1)	0.494*
Mean tumour diameter on preoperative MRI, mm (SD; range)	120.6 (60.3; 42 to 200)	95.2 (46.5; 35 to 190)	0.341*
Mean wound length, mm (SD; range)	303 (85.7; 175 to 380)	265.5 (91.2; 170 to 450)	0.458*
ASA grade, n			0.301†
1	1	3	
2	4	7	
3	2	0	
Specific comorbidities, n			
Smoker/history of smoking	5	4	0.335†
Diabetes mellitus	2	1	0.537†
Cardiovascular disease	3	2	0.593†
History of any other malignancy	0	2	0.485†
Radiotherapy, n (%)			
Neoadjuvant	3 (42.9)	5 (50)	> 0.999†
Adjuvant	2 (28.6)	3 (30)	> 0.999†
Tumour site, n			
Lower limb	5	7	> 0.999†
Upper limb	1	2	> 0.999†
Trunk	1	1	> 0.999†
Tissue diagnosis, n			
Fibroblastic sarcomas			
Myxofibrosarcoma	1	1	-
Undifferentiated pleomorphic sarcoma	1	3	-
Fibromyxoid sarcoma	1	2	-
Liposarcomas			
Myxoid liposarcoma	1	3	-
Pleomorphic liposarcoma	1	0	-
Spindle cell sarcoma	2	0	-
Malignant peripheral nerve sheath tumour	0	1	-

*Independent-samples *t*-test.
†Fisher's exact test.
mGPS, modified Glasgow Prognostic Score; NPWT, negative pressure wound therapy; SD, standard deviation.

Table II. Comparison of postoperative outcomes between control and intervention groups

Outcome	Conventional dressing	NPWT	p-value
SSI within 30 days, n (%)	2 (28.6)	2 (20)	> 0.999*
Median ASA grade in patients diagnosed with SSI	2	2	> 0.999*
Mean wound length in patients diagnosed with SSI, mm (SD; range)	345 (49.5; 310 to 380)	335 (162.6; 220 to 450)	0.941†
Any postoperative adverse wound event, n (%)	3 (42.9)	2 (20)	0.593*
Mean MSTS at 30 days (SD)	24.75 (5.19)	24.50 (6.99)	0.951†
Mean TESS at 30 days (SD)	87.26 (16.53)	87.42 (14.35)	0.987†
Mean TESS at 6 months (SD)	68.49 (32.27)	81.62 (13.62)	0.400†
Cancer recurrence, n (%)‡	1 (14.3)	3 (30)	0.603*

*Fisher's exact test.
†Independent-samples *t*-test.
‡One patient in the conventional dressing group developed a local recurrence with no metastases; one patient in the NPWT group developed a local recurrence with distant metastases; two patients in the NPWT group developed metastatic disease with no local recurrence.
ASA, American Society of Anesthesiologists; MSTS, Musculoskeletal Tumor Society score; NPWT, negative pressure wound therapy; SD, standard deviation; SSI, surgical site infection; TESS, Toronto Extremity Salvage Score.

adjuvant radiotherapy, with no recurrence at 35 months follow-up.

There was a statistically significant association between the use of neoadjuvant radiotherapy and a SSI within 30 days of surgery, across patients in both groups (p = 0.029, Fisher's exact test). While all postoperative wound infections occurred in the lower limb (specifically around the thigh), the association was not statistically significant within our sample size (p = 0.261, Fisher's exact test). In addition, there was no relationship identified between

Table III. Details of postoperative adverse wound events

Case	Age/sex	Study group	ASA	Preoperative mGPS	Tumour site	Adverse wound event	Management
1	58 F	Control	2	2	Posterior thigh	SSI with seroma	Wound debridement and irrigation at 41 days postoperatively*
2	81 F	Control	2	0	Anterior thigh	SSI	Oral antibiotics; no further surgery
3	49 M	Control	3	0	Anterior thigh	Seroma, not infected	Ultrasound-guided drainage at 20 days postoperatively; no further surgery
4	71 M	NPWT	3	1	Anterior thigh	SSI	Oral antibiotics; no further surgery
5	44 F	NPWT	1	0	Medial thigh	SSI with seroma	Wound debridement and irrigation at 21 days postoperatively

*Patients who required any further surgery for an adverse wound infection subsequently received NPWT.
ASA, American Society of Anesthesiologists; mGPS, modified Glasgow Prognostic Score; NPWT, negative pressure wound therapy; SSI, surgical site infection.

postoperative adverse wound events and cancer recurrence (p = 0.538, Fisher's exact test).

The mean preoperative modified Glasgow Prognostic Score (mGPS)[22] was significantly higher among individuals who developed a postoperative adverse wound event (p = 0.028, independent-samples *t*-test), including an SSI (p = 0.008, independent-samples *t*-test), across patients in both groups. However, no relationship was found between mean preoperative mGPS and cancer recurrence (p = 0.762, independent-samples *t*-test) or mortality (p = 0.374, independent-samples *t*-test). Furthermore, there was no statistically significant association between tumour diameter and postoperative adverse wound events (p = 0.664, independent-samples *t*-test), including a SSI (p = 0.380, independent-samples *t*-test), across patients in both groups.

The mean TESS was 87.26 (SD 16.53) in the control group and 87.42 (SD 14.35) in the intervention group at 30 days follow-up (p = 0.987, independent-samples *t*-test), while the mean MSTS was 24.75 (SD 5.19) in the control group and 24.50 (SD 6.99) in the intervention group at 30 days follow-up (p = 0.951, independent-samples *t*-test). At six-month review, the mean TESS was 68.49 (SD 32.27) in the control group and 81.62 (SD 13.62) in the intervention group (p = 0.400, independent-samples *t*-test).

Sample size for an equivalent multicentre, prospective RCT has been determined using a power calculation based on the primary outcome of SSI. A minimum clinical difference of 15% was based on the available literature and a previous internal departmental audit. A power calculation for this difference set at a 95% confidence interval, powered to 0.80, indicates a requirement of 77 patients per arm to reach a statistical significance of $p < 0.05$. In order to accommodate for the possibility of a small loss to follow-up, we would propose recruiting 85 patients per group. An interim analysis should be conducted using a *z*-test to compare proportions of SSI and adverse events between each group, with guidance to stop the trial if a statistically significant difference is found with respect to either of these parameters.

Discussion

This is the first RCT involving the use of NPWT in sarcoma patients. Although we observed a lower postoperative wound complication rate with NPWT than conventional dressings, our sample size was insufficient to determine whether this was statistically significant. A recent Cochrane Review across all types of surgery reported 'moderate-certainty evidence' that NPWT appears to result in lower SSI rates than conventional dressings, and 'low-certainty evidence' that there is no clear difference in postoperative wound dehiscence or mortality rates.[23] A meta-analysis of 14 articles by Semsarzadeh et al[24] determined a significant benefit of NPWT over conventional dressings in reducing the SSI rate for closed incisions, with a relative risk reduction rate of 29.4%.[24] A systematic review of 19 articles by De Vries et al[25] similarly determined that closed incision NPWT significantly reduced the risk of SSI in both clean and contaminated procedures, with an overall relative risk reduction rate of 52.44%. In stratified analyses, however, the effect was not statistically significant for trauma and orthopaedic procedures. A recent cost-utility analysis suggested that NPWT was unlikely to be cost-effective relative to conventional dressings following closed surgical incisions for lower limb trauma.[26] No equivalent data are available for patients undergoing musculoskeletal tumour surgery, and this would be a useful secondary outcome of a multicentre RCT.

Neoadjuvant radiotherapy and preoperative mGPS were the only statistically significant variables associated with postoperative SSI in our study, and were independent of the use of NPWT or conventional dressings. The mGPS was developed as an inflammation-based prognostic indicator for the survival of patients with cancer, independent of tumour site, as the host inflammatory response has been shown to have an important role in the progression of cancer.[22] Although the mGPS was not specifically developed as a prognostic marker for wound complications, existing evidence from colorectal surgery patients has strongly correlated preoperative CRP and albuminaemia with postoperative infections.[27] Radiotherapy is known to impair wound healing through a number of effects, including cell apoptosis, microvascular damage, and defective collagen deposition by irradiated fibroblasts.[28] Peat et al[4] reported that preoperative radiotherapy was a significant risk factor for wound complications (p = 0.04) following closed incisional surgery for soft tissue sarcomas. O'Sullivan et al[29] undertook a randomized trial comparing the effect of preoperative versus postoperative radiotherapy on wound complications following soft tissue

sarcoma resections. They found that wound complications were significantly more common in patients who received preoperative radiotherapy ($p = 0.01$), but that overall survival was nevertheless better in this group ($p = 0.048$). Following a multicentre RCT, it would be interesting to determine whether NPWT has any specific benefit for the subset of STS patients who receive neoadjuvant radiotherapy, or those with a higher preoperative mGPS, which may help to narrow the indications for when to use NPWT.

Tseng et al[30] examined the rate of major wound complications following STS surgery in patients who received preoperative radiotherapy at The University of Texas MD Anderson Cancer Centre. They found that wound complications were significantly more common in the lower limb ($p = 0.03$), but there was no difference in wound complications between patients who underwent primary closure and those who received reconstructive surgery (including rotational flaps, free tissue transfers, and skin grafting). Their study described a low threshold for the involvement of reconstructive surgeons, which is consistent with our practice, where an increasing proportion of sarcoma resections are undertaken with plastic surgeons as part of a MDT approach, in order to preserve function and reduce morbidity.

Bedi et al[31] reviewed 123 patients who underwent excision of lower limb STSs following neoadjuvant radiotherapy, determining that there were significantly fewer complications among 39 patients who received NPWT than 84 who received conventional dressings ($p < 0.001$), even after controlling for potential confounders ($p < 0.004$). In contrast to our study, they also included patients who required complex reconstructions, such as free flaps. Likewise, Sakellariou et al[32] found a significantly higher postoperative infection rate following musculoskeletal tumour surgery among 17 patients treated with conventional dressings, than 15 patients who received NPWT ($p = 0.028$). Both of these studies were retrospective in design and comprised broader selection criteria than the present study.

Chen et al[33] reported that NPWT was safe and effective in a series of five patients who required skin grafts following STS excision. Tumour diameter, proximity to skin, and proximal lower limb tumours are important factors which have been associated with an increased risk of wound complications.[5,6,8] There were no significant differences in any of these parameters between the control and intervention groups in the present study (Table I), and no significant association with adverse wound events, including SSI, within our sample size. Among all patients who underwent malignant soft tissue sarcoma surgery at our institution, both the predominance of lower limb tumours and amputation rate generally reflect the contemporary literature.[2,3,34]

The most common tissue diagnoses among patients recruited to this trial were fibroblastic sarcomas in nine patients (52.9%) and liposarcomas in five patients (29.4%). Among the 86 patients who underwent surgery at our institution for a primary malignant STS during the recruitment period, only six leiomyosarcomas (7%) were diagnosed (although none of these patients met the recruitment criteria for the trial), in contrast to 28 cases of fibroblastic sarcoma (32.6%) and 17 cases of liposarcoma (19.8%). These observed proportions do not represent epidemiological data,[35] but rather our practice as a tertiary service for musculoskeletal oncology surgery.

We recognize that this study has certain limitations. Due to strict inclusion criteria, there was a relatively low number of eligible patients over the recruitment period of 42 months. STSs comprise less than 1% of all diagnosed malignancies,[36] and only 19.8% of cases which underwent surgery at our institution were recruited to this RCT. This loss of potential recruits was predominantly due to cases involving reconstructive surgery or patients presenting with metastatic disease. The rationale for specific inclusion criteria was to reduce the risk of possible confounders. Broadening the selection criteria in a multicentre study would increase the sample size and may generate more pragmatic evidence; although this would be at greater risk of bias, patients could be prospectively stratified into groups, such as those requiring an endoprosthesis or combined cases with plastics.

Despite our limited sample size, there was good adherence to the trial, with no crossover between study groups and no loss to follow-up. Among numerous available PROMs, we selected the TESS and MSTS as validated instruments,[20,21] which are widely used in the assessment of patients following musculoskeletal tumour surgery. These showed no significant postoperative differences between the control and intervention groups, and this would appear to be consistent with the existing evidence on quality of life scores following closed incision NPWT, which is largely in the context of fracture surgery.[23,37]

The five-year survival rate for STSs is around 55%,[36] and despite surgical advances and a MDT approach to management of the disease, there is still significant morbidity associated with treatment.[38] Complications following musculoskeletal tumour surgery can often be devastating; consequently, reducing the rate of complications not only improves long-term outcomes, but also the patient's experience of cancer treatment. NPWT therefore continues to attract considerable interest among musculoskeletal oncologists and limb-salvage surgeons, particularly for the highest-risk patients.[39,40] Proceeding to a multicentre RCT will help more clearly define the role of closed incision NPWT in STS surgery.

Take home message

- Postoperative wound complications are common following soft-tissue sarcoma (STS) surgery, although we could not identify a significant difference in surgical site infections (SSIs), adverse wound events, or functional scores when comparing closed incision negative pressure wound therapy (NPWT) with conventional dressings.
- Neoadjuvant radiotherapy was significantly associated with a SSI across all patients, and the mean preoperative mGPS was also significantly higher among patients who developed a postoperative adverse wound event.
- A multicentre randomized controlled trial will help more clearly define the role of closed incision NPWT in STS surgery.

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