ORIGINAL ARTICLE

Prophylactic Lymphedema Surgery in Lower Limb Soft Tissue Sarcomas: A Clinical Paradigm in a Promising Field

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ABSTRACT

Introduction: Oncological treatments, such as radiotherapy and surgery, are high-risk factors for the development of secondary lymphedema in the upper and lower limbs, as well as the genitalia. Prophylactic lymphedema surgery (PLS) has previously demonstrated promising results in reducing secondary lymphedema in breast cancer and urogenital cancer patients. We conducted a study to adapt this principle for patients with lower extremity sarcomas.

Material and Methods: Inclusion criteria included patients with tumors on the medial aspect of the thigh and leg, tumor size larger than 5 cm. Group A (19 patients) comprised a prospective cohort (2020-2023) in which a PLS protocol was executed. Lymphaticovenous anastomosis (LVA) was performed when lymphatic channels were interrupted due to tumor resection, intraoperatively verified by indocianine green (ICG). Lymph node transfer (LNT) was employed exclusively in cases involving preoperative radiotherapy and inguinal lymph node resection. Measurements were collected both preoperatively and at 1, 3, 6, and 12 months postoperatively. Group B (26 patients) constituted a retrospective cohort (2017-2020) without PLS reconstruction, where the prevalence of lymphedema was determined.

Results: In total, we enrolled 45 patients with soft tissue sarcomas located on the inner aspect of the thigh and leg (26 in the control group *vs.* 19 in the prophylactic group). In the control group, lymphedema was observed in 10 out of 27 patients (37.04%). In the prophylactic group, two patients exhibited signs of lower extremity lymphedema (2/19, 10.52%) with a median follow-up of 14.15 months (6 months - 33months), demonstrating statistically significant differences between the two groups (*p=0.02931*).

Conclusions: PLS for lower limb soft tissue sarcomas shows promising results, although it is premature to reach solid conclusions. Multicenter studies, standardization of criteria, larger sample sizes, and longer-term follow-up are imperative for further validation.

Keywords: Lymphedema, soft tissue sarcoma, secondary lymphedema, Lymphovenous anastomosis, vascularised lymph node transfer, supramicrosurgery.

INTRODUCTION

Soft tissue sarcomas (STS) are malignant mesenchymal tumors with surgery and chemo-radiotherapy as main treatments[1]. Despite the advantage of avoiding amputations on these patients, there is a high-rate incidence of secondary lymphedema derived from oncological treatments that can reach up to 42%[2]. It still burdens the QoL of these patients and implies a high long-term cost for the health system[3,4].

Physiopathologically, it can be explained because of surgical disruption of lymphatic vessels[5] and RT side effects, such as lymph nodes fibrosis and diminished lymphangiogenesis[6–8]. Lymphovenous anastomosis (LVA) and vascularised lymph node transfer (VLNT) are the main reconstructive/physiologic surgical treatments for secondary lymphedema. Many reports show that LVA´s have better results when they are performed in early stages[9]. Functional smooth muscle cells and no lymphosclerosis seems to be key factor[9,10]. On the other hand, VLNT show better results than LVA[11]. However, even though it has proved to be effective in all stages.

Many groups look a step ahead and have been working on preventive surgery for breast cancer related lymphedema (BCRL). They pursue to preserve lymph vessels (not nodes) that drain the upper limb (not the breast) and perform LVA immediately after axillary lymph node dissection (ALND)[12–14]. Other groups are working at the same time with these concepts for pelvic cancer related lymphedema[15], and recently for sarcoma lower limb related lymphedema[16].

We present here our preventive approach for sarcoma lower limb related lymphedema. The main differences in our approach include a 5 cm distance from the area of resection to perform the LVA in order to avoid RT effects and, the inclusion of prophylactic VLNT for patients where the tumor's location requires the removal of inguinal lymph nodes and preoperative RT.

MATERIAL AND METHODS

Clinical paradigm

Two patient cohorts were established: Group A (19 patients), a prospective cohort of lower limb STS patients comprising patients recruited between June 2020 and March 2023, all of whom exhibited risk factors for developing lymphedema and underwent a prophylactic lymphedema surgery (PLS) protocol. Group B (26 patients), a retrospective cohort (January 2017- December 2020), in which no lymphatic reconstruction was performed. In the retrospective cohort, imaging studies and tumor size were thoroughly reviewed to ensure the formation of two comparable cohorts. Inclusion criteria were patients at high-risk of lymphedema development (medial aspect of the leg or thigh, tumor size larger than 5 cm and radiotherapy[17]). Exclusion criteria were those patients with lymphedema development or groin lymph node dissection previous to the tumor diagnosis/resection or ICG allergy. Our main objective was to determine the lymphedema prevalence in our cohort of patients.

In Group A, lymphatic vessels injury was verified intraoperatively after tumor excision. A PLS protocol was executed: lymphaticovenous anastomosis (LVA) was performed when lymphatic channels were interrupted due to tumor resection, intraoperatively verified by indocianine green (ICG). Lymph node transfer (LNT) was employed exclusively in cases involving preoperative radiotherapy and inguinal lymph node resection because of the location of the tumor. Measurements were collected both preoperatively and at 1, 3, 6, and 12 months postoperatively. Clinical follow-up included bilateral lower limb measurements (1-month, 3-months, 6-months, and 1-year postoperatively) taken by the same two examiners, and leg volume (calculated according to the Sitzia method[18]). We measure both limbs in the foot dorsum, and from malleolus up to the groin. To be able to compare one patient with another we employed the lower extremity lymphedema index (LEL-Index)[19]. An ICG lymphography was performed preoperatively, intraoperatively after tumor resection, and one year postoperatively. The 1-year lymphography imaging results were classified according to Yamamoto´s dermal backflow staging system (linear, splash, stardust, and diffuse patterns)[20].

For more restrictive results, we consider as lymphedema development diagnosis: the report of clinical signs of lymphedema (heaviness or swelling), increase in volume more

than 10% respecting the healthy leg or LEL-index>250. The compliance with any of these criteria implies lymphedema diagnosis according to our study.

Group B (26 patients) constituted a retrospective cohort (January 2017-December 2020). In these patients, tumor excision was performed according to the standard, without PLS reconstruction. A cross-sectional survey was conducted to study the prevalence of lymphedema using a Self-Report Lower-Extremity Lymphedema Screening Questionnaire[21] and the classification of the International Society of Lymphology[22]. We record demographic data including gender, age, body mass index (BMI), toxic habits; but also, more specific data including tumor type, surgery date, sentinel node biopsy or groin lymph node dissection, postoperative complications and, adjuvant treatments.

Group A: Surgical technique

Preoperatively:

We mark the tumor resection area (tumor and oncological margins) with black pen. Then, we perform an indocyanine green lymphography (ICG-L) of both legs to study the patient´s basal lymphatics status. We mark the lymph vessels course in the leg with a green pen and confirm if they enter the tumor resection area.

Intraoperatively:

After tumor resection, we perform an ICG-L of the resection field with the microscope to confirm that lymph vessels have been disrupted. We clip them to prevent lymph drainage in order to avoid lymphorrea and lymphocele. We make another incision 5 cm distal to the tumor resection area following the previous marked way of the lymph vessels to perform a preventive LVA. LVA could be done in end-to-side (E-S) or end-to-end (E-E) manner depending on intrinsic intraoperative conditions. We confirm patency of the LVA with ICG-L with the microscope.

In cases where tumor resection includes lymph nodes from the groin area and the patient had received preoperative RT, we indicate VLNT. The VLNT were isotopic, carried out initially to occlude space, reduce retraction, and underlying vascular compression and in the long term, to promote lymphangiogenesis and lymphatic flow from the limb, in accordance with the experimental study of Jila et al[23]. After tumor resection, in addition

to lymphatic reconstruction, coverage of the defect was performed if it was necessary. The algorithm of treatment is presented in Figure 1.

Clinical Assessment

We administer alprostadil 40 mg iv every 12 hours for five days after surgery to prevent anastomotic occlusion, according with Koshima et al protocol[24]. In the first two days, the patient maintains absolute bed rest with raised limb, and then he can start mobilization if there were no other limitations.

Statistical Analysis

Statistical analysis used IBM-SPSS v.26 (IBM, Armonk, NY, USA). Two-tailed tests set $p<0.05$ with Greenhouse-Geisser corrections. Continuous variables summarized as means and standard deviations, compared with two-way repeated measures ANOVA for time and measurements. Qualitative variables described by frequencies and cases, compared using the Chi-Squared test.

RESULTS

In total, we enrolled 45 patients with soft tissue sarcomas located on the inner aspect of the thigh and leg: 19 in the prophylactic group (Group A) *vs* 26 in the control group (Group B) (Table 1). The average age was 59.8 years (SD 15.5), and an average body mass index (BMI) of 27.5 (SD 6.3). The most common tumor location was the groin and the thigh (78.3%) and 21.7% were on the knee and the leg. Three patients were smokers (6.7%). The mean maximum diameter of the tumor was 12.6 cm (SD 6.9). No resection of large vessels or substitution with prostheses was performed. In all cases, perivascular resection could be performed, preserving those structures.

In the control group (Group B), lymphedema was observed in 10 out of 26 patients (38.5%). In the prophylactic group (Group A), two patients exhibited signs of lower extremity lymphedema (2/19, 10.52%), demonstrating statistically significant differences between the two groups ($p=0.03$). In the statistical analysis, we identified an odds ratio (OR) of 5.625. It means that the odds of developing lymphedema are 5.625 times higher in the control group (Group B) when compared to the PLS group (Group A). The identified differences are not attributed to inter-group variability because no statistically significant differences were found between both groups.

In the prophylactic group (Group A), a total of 22 patients were recruited. Two of them were excluded because they were upper extremities. One patient was excluded because the LVA could not be performed, although their data were taken into account for the demographic study. A total of 19 patients who underwent lower limb sarcoma resection and lymphedema prophylactic surgery reconstruction were recorded (Table 2). All patients received prophylactic lymphedema surgery (PLS). In addition, direct closure was performed on 10.5% of patients and a local flap coverage on 21% of patients (Table 1). The rest of patients (68.4%) underwent a coverage with microsurgical free flap (Figure 2).

When we talk about group A (PLS reconstruction) LVAs were performed in all patients, an average of 1.37 (range 1-3 per patient). End-to-end (E-E) anastomoses was performed in most of the patients (73.68%), four end-to-side (E-S) anastomoses were performed (21%) and in one of the patients, it was not possible to perform the anastomosis due to sclerosis and a small caliber of the lumen (5.55%). Four VLNT were performed in groin-tumor-resection patients with preoperative RT. Postoperative radiotherapy was received by 58% of patients (range 50-68Gy). In the immediate postoperative period, there were two microvascular failures (10.53%) that required new free flaps coverage. LVAs were in another surgical field (at least at 5 cm), any of them were affected by the surgical review of the flaps. Two patients had a hematoma (minor complication, 10.53% of patients) and underwent debridement without major impact on the patient. We observed additional minor complications in the immediate postoperative period lasting less than a month, including: seroma (5.26%), immediate postoperative infection (10.53%), recurrent lymphangitis (5.26%) and lymphorrhea (10.53%). In Group B, only major complications that required further surgical intervention were recorded in the immediate postoperative period. In these patients, 3 abscesses (11.5%), two serohematomas (7.7%), and two surgical dehiscences (7.7%) were identified, without statistically significant differences. In both groups, the patients were discharged after a mean of 11.9 days (SD 16.25).

In group A, as for chronic complications, one patient (5.26%) had recurrent episodes of lymphangitis that required hospitalization for intravenous antibiotic treatment during first six months after surgery. The mean follow-up time was 14.15 months (SD 8.84).

Regarding volumetric measurements, in group A we have 36 lower extremities with healthy and STS leg measurements (Table 2). The overall survival rate after 14 months of follow-up was 89.5%.

As previously mentioned, while between Group A and B, we found statistically significant differences in the prevalence of lymphedema, within Group A, when comparing volumetric measurements of the healthy leg with the affected leg, no statistically significant differences were observed (*p value=0.319*), nor in terms of the evolution over time of both legs (*p value=0.665*). Mean volume in the healthy leg group was 7028.46 mL, whereas mean volume in the STS leg group was 7496.25 mL (467.69 mL difference). This difference represents less than a 10% difference in volumes between both extremities (less than 702.84). LEL-index mean in healthy leg group were 200.82, whereas the STS leg LEL-index was 212.42, and both groups maintain under the limit of 250[19] (Table 3).

1-year lymphography imaging was performed on 11 patients (Figure 3). Table 4 summarizes the predominant patterns at one-year post-surgery according to Yamamoto´s dermal backflow staging system[20]. The predominant pattern around the LVA was selected at 5 minutes after the contrast injection. The rest of the leg below the anastomosis maintained a linear pattern.

The diagnostic criteria for lymphedema are ambiguous, as demonstrated in this series of patients. When we individualize the volume means over time in each patient, and comparing the healthy and the STS leg, we found 5 patients with lymphedema (26.32%). However, when standardized with the LEL-index, we found that only 2 of the patients maintain the lymphedema diagnosis (10.52%) (Table 5).

The same incongruence applies when comparing the volumes at one year, we found that one of the legs have a difference greater than 10% compared to the healthy leg (9.09%). Regarding the LEL-index, we found two patients with an index >250 (18.18%).

DISCUSSION

With any new intervention in oncology patients, the primary concern is to prevent the spread of the disease to other parts of the body. As the main route of dissemination for soft tissue sarcomas is through the bloodstream[25], LVAs are considered safe despite being performed in patients with active oncological disease.

We believe that primary prevention and early intervention are the most effective approaches. That's why we address the issue as soon as direct disruption of lymph vessels occurs. LVA can be performed in different ways: telescopic [12,26] or intima-to-intima[27]. We prefer an intima-to-intima LVA, because of lower risk of thrombosis [27]. We performed more E-E than E-S anastomosis, even though our preference is for the latter[28] because it is more technically demanding.

VLNT can be performed isotopic or heterotopic[29]. We chose isotopic VLNT, when sarcoma resection involves inguinal area and neoadjuvant radiotherapy has been previously done, so gaining the advantages of the isotopic transfer while avoiding the deleterious effect of radiotherapy for lymph nodes. Donor-site lymphedema has been reported from 1.1 to 2.3%[30–32].

During the treatment of patients in Group A, and with the goal of achieving like-to-like reconstruction, the following procedures were performed: LVAs were used to facilitate drainage into the venous system, addressing the disrupted lymphatic system distally following tumor resection. Additionally, in cases of inguinal tumors where tumor excision required inguinal clearance and preoperative neoadjuvant treatment had been administered, VLNT was conducted to stimulate lymphangiogenesis at the inguinal level.

Reverse mapping (RM) allows us to avoid/diminish the risk of lymphedema development in the donor-site[33]. To highlight this fact, in all 19 patients we performed RM and confirm after resection with ICG-L under the microscope, the disruption of the lymphatics, and clip them to minimize the risk of lymphorrhagia and lymphocele [34]. There were no cases of lymphorrhagia or lymphocele in group A.

Another great advancement from the last years was the indocyanine green-lymphography (ICG-L). ICG-L can stratify different patterns, helping us to plan preoperatively, reduce

surgical time and allow us to test LVA patency intraoperatively[35–37]. Furthermore, it has also been used to test LVA patency postoperatively[38].

It is important to note that, as depicted in Table 1, Group A or PLS displays prolonged hospital stays and extended surgical durations, with statistically significant disparities. Nevertheless, it is worth considering that the long-term costs associated with disease progression may outweigh these factors. Squitieri et al evaluated cost-effectiveness of prophylactic LVA for BCRL. They showed a $7,646.65 reduction in costs per patient[4], due to the reduction of long-term complications for the patient.

Wagner et al., recently published a study of prophylactic LVA for STS compared with a prior retrospective cohort[16]. Lymphedema Quality of Life Inventory (LyQLI) affected 45% of the control group, while just 12.5% in the study group[16]. However, their approach of performing LVA on the dorsum of the foot, despite dealing with patients with lymphatic competent valves, is questionable to us. We chose a location 5 cm distal to the edge of resection to perform the LVA in order to avoid RT effects. It also was an advantaged when required flap revision, because it did not interfere with the prophylactic reconstruction.

Given the incongruence of different lymphedema diagnostic criteria and following current trends, we prefer the result of the LEL-index as it helps us control possible biases. However, we present both results (comparison of raw measurements and LEL-index) to show the greatest transparency possible in terms of results. The results are summarized in Table 5. Given the fluctuation in leg volume over time as shown in Figure 4, we consider the measurement at one-year to be more representative than the average of measurements.

We have 10.52% lymphedema incidence (2/19 cases), with a LEL-index means in accordance with stage II by the Campisi classification. These should be carefully analyzed as some of the measurements may be biased for example: the differences of volume that could be due to muscle hypotrophy/hypertrophy (bed rest, crutches, wheelchair), flap donor site (for example ALT in contralateral limb) and tumor resection. LEL-index measures help us to partially correct these possible biases.

In figure 4, it is shown the volume evolution of both legs (healthy and STS leg) in 1-year patients follow-up. It shows a symmetric increase in volume after 6-months in both legs that could be explained by the atrophy of the legs in the immediate postoperative period. However, it is curios how the STS leg have a slightly higher volume than the control, although non-statistical (*p= 0.171 Greenhouse-Geisser test*) or clinically relevant differences at one year of follow-up were found.

Finally, the weaknesses of the study should be mentioned. In the case of group B, the absence of definitive diagnostic procedures necessitated reliance on self-reported surveys and the International Society of Lymphology scale for diagnosis. To enhance the rigor of our findings, a decision was made to exclude patients in group B presenting with stage I lymphedema, i.e., those reporting the possibility of reversibility of the condition. Nevertheless, it is noteworthy that the difference lymphedema prevalence between both groups is above 30%, with persistently substantial statistical distinctions. Finally, the Group A management with two different approaches, VLNT and LVAs, makes it difficult to determine which of the two treatments benefits patients and to what extent. Therefore, the statistical analysis was repeated, excluding cases of VLNT (4 cases), resulting in incidences of secondary lymphedema of 12.5% vs. 38.5%, but without statistically significant differences due to the reduced study power (*p=0.059*).

In summary, we see promising results of combining heterotopic LVA and postradiotherapy VLNT, as primary prevention techniques for lower limb lymphedema in high-risk patients with soft tissue sarcomas.

CONCLUSION

Prophylaxis/preventive lymphedema surgery mixes many interesting concepts like timing (primary *vs* secondary), indication (LVA *vs* VLNT, both), technique (telescopic *vs* intima-to-intima), location (isotopic *vs* heterotopic), lymph axiality-based flap transfer, RT effects, RM, and others, making it difficult to find consensus on a unique approach.

There are new lines of research to be pursued in this field to prove these concepts. Although it is a cutting-edge approach, it needs stronger evidence to become a daily practice. Our particular prophylactic lower limb lymphedema approach for soft tissue sarcomas attempts to tailor it according to each individual.

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