Archives of Gynecology and Obstetrics (2019) 299:1467–1474
https://doi.org/10.1007/s00404-019-05113-z

GYNECOLOGIC ONCOLOGY

Efficacy of a collagen-fibrin sealant patch (TachoSil®) as adjuvant treatment in the inguinofemoral lymphadenectomy for vulvar cancer: a double-blind randomized-controlled trial

Silvia Baggio[1] · Antonio Simone Laganà[2] · Simone Garzon[1] · Matteo Scollo[1] · Ricciarda Raffaelli[1] · Saverio Tateo[3] · Fabio Ghezzi[2] · Massimo Franchi[1]

Received: 29 October 2018 / Accepted: 4 March 2019 / Published online: 11 March 2019

Abstract

Purpose To evaluate the effect of a collagen-fibrin sealant patch (TachoSil®) in preventing postoperative complications after inguinofemoral lymphadenectomy for vulvar cancer.

Methods Double-blind randomized-controlled trial on consecutive patients undergoing bilateral inguinofemoral lymphadenectomy for vulvar cancer. Intraoperatively, inguinofemoral areas were randomized: one was treated with TachoSil®, while the contralateral had standard closure without collagen-fibrin sealant patch. Surgical outcomes, amount of drainage volume, duration of drain placement, and any postoperative complication (vulvar wound dehiscence, inguinal wound dehiscence, cellulitis, lymphangitis, lymphoceles, and hematoma) were recorded. Leg measurements were taken preoperatively and during postoperative follow-up until 6 months to evaluate lymphedema.

Results A total of 19 patients were enrolled and 38 inguinofemoral dissections were performed. There was no significant difference between the investigational and control arm in the amount of drainage volume ($p=0.976$), and duration of drain placement ($p=0.793$). The postoperative complications, excluding lymphedema, were 10/19 (53%) in investigational arm and 9/19 (47%) in control arm ($p=0.74$). At the end of follow-up, the prevalence of grade 1 lymphedema was 44.4% and 50% in investigational and control arm, respectively ($p=0.744$); grade 2 and 3 lymphedema had a prevalence of 33.3% in both arms ($p=1$).

Conclusion Application of TachoSil® does not seem to improve postoperative lymphorrhagia nor to reduce the incidence of postoperative complications in patients undergoing inguinofemoral lymphadenectomy for vulvar cancer. Considering this point, it would be useful to identify additional strategies in inguinofemoral dissection for the prevention of these complications.

Keywords Vulvar cancer · Inguinofemoral lymphadenectomy · Postoperative morbidity · Collagen-fibrin sealant patch · TachoSil® · Lymphedema

Introduction

Vulvar cancer is the fourth most common cancer of the genital tract, and accounts for approximately 5% of all gynecological cancers [1]. Vulvar cancer is frequently diagnosed at early stages and it is usually treated only with surgery; adjuvant therapy is added when necessary [2, 3]. When sentinel lymph-node mapping is not feasible, inguinofemoral groin dissection is required despite a reported morbidity rate up to 70% [4], with an associated significant reduction of quality of life (QoL) [5]. Complications of the inguinofemoral lymphadenectomy range from seroma and hematoma formation, to wound infection, wound dehiscence, wound

✉ Simone Garzon
simone.garzon@univr.it

[1] Department of Obstetrics and Gynecology, AOUI Verona, University of Verona, Piazzale A. Stefani 1, 37126 Verona, Italy

[2] Department of Obstetrics and Gynecology, "Filippo Del Ponte" Hospital, University of Insubria, Varese, Italy

[3] Department of Obstetrics and Gynecology, "Santa Chiara" Hospital, Trento, Italy

necrosis, lymphocyst formation, and chronic lymphedema [6, 7]. Approximately, 30% to 63.5% of women with inguinofemoral dissection (as well as primary groin node radiation) develop mild-to-severe lymphedema [8, 9], which has been shown as the most frequent complication reported to affect QoL [10]. Various strategies have been tested to reduce complications in case of inguinofemoral lymphadenectomy, with limited success. These include avoidance of electro-cauterization, ultrasound coagulation, modified incision lines, suction drainage devices, video endoscopic surgery, and omentoplasty.

TachoSil® (Fibrin sealant patch; human fibrinogen 5.5 mg and human thrombin 2.0 IU/cm^2; Takeda, Austria, GmbH), a sterile fixed combination of a collagen matrix coated with coagulation factors, has already shown its efficacy in achieving hemostasis after liver and kidney surgery [11], in preventing leakage after lung surgery [12] and in reducing lymphatic fluid production after mediastinal [13] and axillary [14–16] lymph-node dissection.

This fibrin sealant patch has already been evaluated in the prevention of postoperative complications after inguinofemoral lymphadenectomy for gynecological and not gynecological lower limb malignancies, but results are controversial [7, 17, 18]. Considering this point, the purpose of this double-blind randomized-controlled trial was to investigate TachoSil® efficacy in the improvement of postoperative lymphorrhagia (amount of drainage volume and duration of drain placement) and in the prevention of postoperative complications (vulvar wound dehiscence, inguinal wound dehiscence, cellulitis, lymphangitis, lymphoceles, hematoma, lymphedema) in patients undergoing bilateral inguinofemoral lymphadenectomy and radical vulvectomy for vulvar cancer.

Materials and methods

The study protocol was opened for enrollment on May 2016 and ended on August 2017. All patients with histologic diagnosis of vulvar cancer had preoperative evaluation with record of the size, location, and extension of the vulvar neoplasm, and clinical and ultrasonographic assessment of groin region. Further staging with computer tomography of thorax/abdomen and pelvis was performed in those patients with clinical suspicion of metastatic disease and/or advanced stage disease. History and personal data such as age, body mass index (BMI), previous surgery, saphenous vein treatment (saphenectomy, or its ligation), concomitant diseases, and chronic therapy were recorded. Patients underwent standard preoperative biochemical exams, including full blood count, liver and kidney function tests, electrolytes, coagulation profile, and neoplastic markers. We considered eligible for this randomized-controlled trial all consecutive patients with histologically confirmed vulvar cancer classified as T1b or T2 lesion [International Federation of Gynecology and Obstetrics (FIGO) TNM classification], with no suspicious lymph nodes at preoperative evaluation, undergoing radical vulvectomy with bilateral inguinofemoral lymphadenectomy. Although the cases are early vulvar cancers, in this study we did not perform sentinel lymph-node mapping, because the appropriate organizational context as well as the appropriate training level required for a procedure that is technically challenging were not available [19].

In included patients, ankles, mid-calves, and mid-thighs circumferences were recorded preoperatively. Enrolled patients underwent bilateral inguinofemoral lymphadenectomy, radical vulvectomy, and vulvar–perineal reconstruction with cutaneous flaps. All inguinofemoral dissections were performed, as described by Zhang et al. [4], by the same surgical team and senior surgeon.

To eliminate the inter-subject variability, the non-stratified 1:1 ratio randomization involved, intraoperatively, the two inguinofemoral regions of each patient. One of the two inguinofemoral areas was randomly assigned to be treated with TachoSil®, while the contralateral had a standard closure without fibrin sealant patch. A computer-generated randomization schedule was used (www.randomization.com) and kept by one investigator (S.G.). Only the surgeon (M.F.) was unmasked about the inguinofemoral region treated, whereas patients and investigators (clinical evaluation in postoperative period, follow-ups, and statistical analysis) were masked to treatment allocation. The inguinofemoral area with the fibrin sealant patch applied was considered part of the investigational arm (IA), while the contralateral (not treated) was part of the control arm (CA). Only one patch of TachoSil® was applied, with the yellow active side onto the wound surface, after that blood and other fluids were cleaned. The patch had to extend around the inguinal lymphadenectomy area and maintained in place for at least 3 min. A closed suction Jackson–Pratt drain was placed for each side and was removed when the output was < 50 ml over 24 h. No patient underwent pelvic lymphadenectomy based on the unsuspected lymph-node involvement at the preoperative evaluation for both inguinofemoral and pelvic regions.

All patients had postoperative thromboembolic prophylaxis with low-molecular-weight heparin (50 units/kg/q24 h) and elastic compression until complete mobilization. Antibiotics prophylaxis was administered preoperatively and postoperatively until the removal of the drain.

We assessed and recorded data about surgical procedure, histopathological evaluation, amount of drainage volume, duration of drain placement, and postoperative complications (vulvar wound dehiscence, inguinal wound dehiscence, cellulitis, lymphangitis, lymphoceles, and hematoma). Definitive FIGO stage and adjuvant therapies were also

recorded. The lower extremity lymphedema was assessed with serial circumferential measurements at each follow-up of the ankle, mid-calf, and mid-thigh. Follow-up was conducted until the sixth postoperative month, with evaluations performed at the time of drain removal, at the sixth week and at the third and sixth postoperative month. Lymphedema was then graded according to the circumferential increase compared to the preoperative value. Lymphedema was categorized as grade 1 if the circumference was higher than the base value, but < 3 cm; grade 2 if the increase was between 3 and 5 cm; grade 3 with an increase greater than 5 cm [20, 21].

All the collected data were recorded in a database created by investigators masked to the laterality of the patch. The randomization list was revealed to the investigators only at the end of the study, when all the results were collected, to allow the final considerations. The study ended when all the enrolled patients, consistent with the sample size, completed the follow-up as reported in the study design.

Statistical analysis

The primary outcome was the amount of drainage volume. Secondary endpoint measures were duration of drainage placement and the incidence of postoperative complications in IA and CA (vulvar wound dehiscence, inguinal wound dehiscence, cellulitis, lymphangitis, lymphoceles, hematoma, and lymphedema).

With an expected reduction of total drainage volume of at least 300 ml for IA (Tachosil® application) compared to CA, and an expected standard deviation of 550 ml [17], considering no drop-out, a sample size of 19 items for each arm would achieve 90% of power (α error: 0.05; β error: 0.1) to find a reduction of total drainage volume of at least 150 ml in IA compared to CA. Statistical analyses were performed using SPSS for Windows V.21.0 (IBM Corporation, Armonk, NY). Kolmogorov–Smirnov test was used to determine if the data were Gaussian distributed. Since all the quantitative data were normally distributed, they were presented as mean ± standard deviation (SD), while qualitative variables were expressed as numbers and percentages. Comparison of quantitative variables between the two arms was performed using the *t* test, while the comparison of qualitative variables with the Chi-square test. p value < 0.05 was defined as statistically significant.

Ethics and methodological standards

The design, analysis, interpretation of data, drafting, and revisions conform the Helsinki Declaration, the Committee on Publication Ethics (COPE) guidelines (https://publicationethics.org/), the CONSORT (CONsolidated Standards of Reporting Trials), and SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statements, available through the EQUATOR (enhancing the quality and transparency of health research) network (www.equator-network.org). The trial was approved by the independent Institutional Review Board (IRB) of the study center and was registered on the European Union Clinical Trials Register (registration number: EudraCT 2011-006059-13). Each patient enrolled in the study signed informed consent for all the procedures and to allow data collection and analysis for research purpose. The study was not advertised, and no remuneration was offered to the patients to enter or continue the study. An independent data safety and monitoring committee evaluated the results.

Results

In the study period, 23 patients were eligible for diagnosis of vulvar carcinoma with planned radical vulvectomy and bilateral inguinofemoral lymphadenectomy. Considering inclusion and exclusion criteria, 19 out of 23 patients (82.6%) were enrolled in the study (Table 1). Since the two inguinofemoral regions were treated differently, 38 was the total number of lymphadenectomies analyzed, with 19 cases for both IA and CA. Flow of participants through the trial is reported in the CONSORT diagram (Fig. 1).

The mean age of patients was 69.8 ± 11.7 years and the mean BMI was 26.7 ± 4.6 kg/m^2. At the preoperative evaluation, no suspected lymph nodes were reported as consistent with eligible criteria, and vulvar cancer was classified as T1b in 14 women and T2 in 5 women (4 cases with the involvement of 1/3 lower vagina and 1 case with the involvement of 1/3 lower urethra).

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Total bilirubin ≤ 1.5	Previous radio-chemotherapy treatment on pelvis
Platelet count > 100,000/ml	History of primary or secondary lymphedema of the lower extremities
Creatinine ≤ 2.0 mg/dl	Superficial phlebitis of the lower extremities
	Non-healing ulcer of the lower extremities
	Chronic infection of the lower extremities
	Sensitivity or anaphylaxis to excipients of TachoSil®

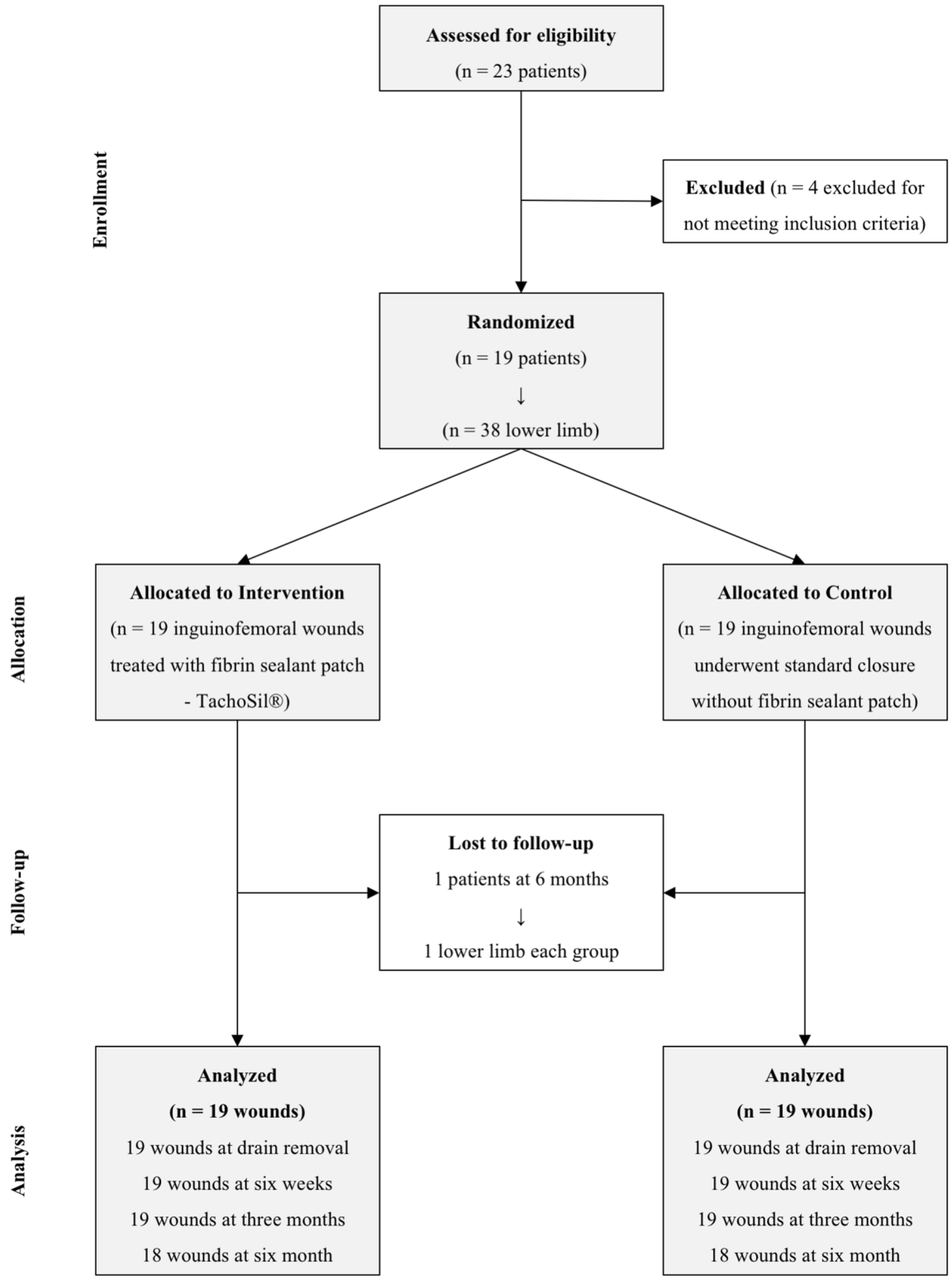

Fig. 1 CONSORT diagram shows flow of participants through the trial

No significant differences were observed between the IA and the CA regarding previous saphenectomy or ligature of the saphenous vein ($p = 0.55$). The median number of lymph nodes removed was 7 (range 1–16) in the TachoSil® arm and 8 (range 4–19) in the control arm ($p = 0.25$), with a mean weight of 34.2 ± 15.6 g in the IA and 40.0 ± 18.1 g in the CA ($p = 0.24$). There were no intraoperative complications.

Postoperatively, the definitive tumor stage (FIGO classification) ranged between stage IB and IIIC. The primary vulvar lesion had a mean size of 3.63 ± 2.12 cm based on histopathology. In 12 women with T1b and one woman with T2 vulvar cancer, all the lymph nodes were negative at the histopathological evaluation, confirming IB stage for the 12 women and II stage for the other one. Three cases were classified as IIIA stage: in two women one positive lymph node with metastasis ≥ 5 mm was reported, and in one woman, two positive lymph nodes with metastasis < 5 mm were identified. In two women, the definitive histopathological evaluation identified, respectively, three and four lymph nodes with metastasis, and they were classified as IIIB. Only in one case the extracapsular spread of the tumor was identified in one lymph node among a total of four positive lymph nodes, and the case was classified as IIIC. Bilateral positive lymph nodes were identified in one out of six women, while, in the other patients, the histopathological evaluation identified lymph nodes with metastasis monolaterally. Three cases were in the IA and two cases were in the CA ($p = 1$).

After surgery and definitive histopathological evaluation, a total of seven patients (36.8%) required adjuvant radiotherapy: six patients for lymph-node involvement and one woman for positive margins at the site of primary vulvar lesion excision. At the end of the study, no patients underwent reoperation for recurrent vulvar cancer.

A close suction system drain was used bilaterally in all patients and we found no statistically significant difference between the two arms in overall postoperative drainage volumes, with a mean of 751.4 ± 581.0 ml in IA and a mean of 749.1 ± 585.1 ml in CA ($p = 0.976$). The duration of drain placement was comparable between IA and CA, with a mean of 15.2 ± 4.7 days in the IA compared to a mean of 15.0 ± 5.0 in CA ($p = 0.793$). The day of maximum drainage was the 28th and 27th day for the IA and the CA, respectively ($p = 0.67$).

As shown in Table 2, the overall complications rate was 53% (10/19) in the IA and was 47% (9/19) in the CA ($p = 0.74$). The saphenous vein was not spared in three cases in the IA and in four cases in the CA, and no association was found between saphenectomy and complications ($p = 0.90$). Considering the IA, all complications were investigated, and none was directly attributable to the use of TachoSil®. There were no reported allergic reactions or product-related toxicities, neither thromboembolic events nor other systemic complications. One patient with extensive bilateral inguinofemoral and vulvar wound breakdown was managed with reoperation; the other cases were treated with wound care and healing by secondary intention.

The overall prevalence of grade 2 lymphedema was 21.1% in the IA and 10.1% in the CA ($p = 0.76$), but considering grade 2 and 3 lymphedema together, they presented the same overall prevalence (33.3%) in the two arms ($p = 1$). Prevalence of lymphedema at six months was calculated considering 18 patients instead of 19, because one patient did not undergo the last two scheduled follow-ups. The prevalence of grade 2 or 3 lymphedema increased in both arms over time as shown in Table 3, starting from a percentage of 5% (IA) and 10% (CA) in the postoperative period, 26% at 6 weeks, 31–33% at 3 and 6 months, respectively. Among patients who developed grade 2 or 3 lymphedema, no new cases of lymphedema were observed after the 3-month follow-up. No significant differences were observed about the prevalence of grade 2 and 3 lymphedema between the two arms ($p = 0.547$). Similarly, grade 1 lymphedema did not show significantly different prevalence in the two arms ($p = 0.515$). Furthermore, comparing every limb measurement between IA and CA, we did not find any significant difference (see Table 4) except for the circumference of the mid-calf at 6 months, although, in this case, the best outcome was in the CA.

Table 2 Analysis of postoperative drainage and complications after inguinofemoral lymphadenectomy

	Investigational arm 19	Control arm 19	*p*
Lymphoceles	4 (21.1%)	3 (15.8%)	0.676
Lymphangitis	4 (21.1%)	6 (31.6%)	0.461
Inguinal wound breakdown	3 (15.8%)	2 (10.5%)	0.631
Vulvar wound breakdown	2 (10.5%)	3 (15.8%)	0.631
Hematomas	1 (5.3%)	0 (0%)	0.311
Cellulitis	2 (10.5%)	1 (5.3%)	0.548

Values are reported as number and percentage

Table 3 Analysis of postoperative lymphedema over time in investigational and control arms

Lymphedema	1 week	6 weeks	3 months	6 months
1° grade				
I	10 (52.6%)	10 (52.6%)	9 (47.4%)	8 (44.4%)
C	9 (47.4%)	10 (52.6%)	11 (57.9%)	9 (50.0%)
p	0.745	1	0.515	0.744
2° and 3° grade				
I	1 (5.3%)	5 (26.3%)	6 (31.6%)	6 (33.3%)
C	2 (10.5%)	5 (26.3%)	6 (31.6%)	6 (33.3%)
p	0.547	1	1	1

Values are reported as number and percentage considering the lower limb part with the highest increase of circumference measurements; investigational arm (I); control arm (C)

Table 4 Analysis of postoperative lymphedema in different body area in investigational and control arms

	Investigational arm	Control arm	*p*
Lymphedema[a]	1 (5.3%)	1 (5.3%)	1
Lymphedema 1°[a]	11 (57.9%)	11 (57.9%)	1
Lymphedema 2°[a]	4 (21.1%)	2 (10.1%)	0.761
Lymphedema 3°[a]	3 (15.8%)	5 (26.3%)	1
Δ Ankle PO, cm[b]	0.37 ± 0.76	0.42 ± 0.77	0.790
Δ Mid-Calf PO, cm[b]	0.42 ± 0.69	0.21 ± 0.54	0.163
Δ Mid-Thigh PO, cm[b]	0.63 ± 1.30	0.95 ± 1.93	0.344
Δ Ankle 6 w, cm[b]	1.26 ± 2.08	1.37 ± 2.61	0.650
Δ Mid-Calf 6 w, cm[b]	1.58 ± 2.46	0.84 ± 2.24	0.026
Δ Mid-Thigh 6 w, cm[b]	2.00 ± 3.33	2.26 ± 4.11	0.438
Δ Ankle 3 m, cm[b]	1.26 ± 1.73	1.37 ± 1.95	0.725
Δ Mid-Calf 3 m, cm[b]	1.74 ± 2.21	1.42 ± 2.24	0.343
Δ Mid-Thigh 3m, cm[b]	2.47 ± 4.21	2.74 ± 4.64	0.399
Δ Ankle 6 m, cm[b]	1.22 ± 1.67	1.44 ± 1.95	0.495
Δ Mid-Calf 6 m, cm[b]	1.89 ± 2.49	1.50 ± 2.38	0.248
Δ Mid-Thigh 6 m, cm[b]	2.17 ± 4.22	2.78 ± 5.31	0.232

Values are reported as number and percentage (a) or as mean ± SD (b); difference (Δ); postoperative (PO) during hospitalization; weeks (w)

Discussion

TachoSil® and other similar fibrin-based sealants have already been studied in different surgical fields as therapeutic strategies to reduce lymphadenectomy-related complications, such as lymphorrhagia, seroma, lymphoceles, and lymphedema with the reported conflicting results. Fibrin-based sealant was investigated in breast cancer patients undergoing axillary lymphadenectomy: one study reported fibrin sealant reducing overall lymphatic drainage amount and allowing earlier removal of closed suction drains [16]; conversely, the other studies reported no significant differences regarding the incidence and severity of lymphoceles, seromas, volume of axillary drainage, and drainage duration [22–24]. In endometrial cancer, TachoSil® was tested in laparoscopic pelvic lymphadenectomy with a reported significant lower total prevalence of lymphocele, although a non-significant difference in the prevalence of symptomatic ones [25–28]. Similarly, TachoSil® was investigated by Simonato et al. [29] in prostate cancer with pelvic lymphadenectomy, and was associated with a reduced drainage volume and lower incidence of lymphocele. Swan et al. [30], who investigated primarily melanoma, reported no advantage in using fibrin-based sealants during elective axillary and groin lymphadenectomy in terms of reducing drainage output or postoperative complication rate independently by the oncologic disease.

As far as the use of fibrin-based sealant in inguinofemoral lymphadenectomy for gynecologic malignancies is concerned, Buda et al. [17] investigated TachoSil® in vulvar and ovarian cancers reporting a significant lower daily drainage volume in the treatment group, and a lower incidence of lymphocyst requiring drainage, cellulitis, wound infection, and late lymphedema although without reaching statistical significance. Conversely, Carlson et al. [9] studied a fibrin-based sealant spray in inguinofemoral lymphadenectomy for vulvar cancer reporting no significant difference in duration of drains, drain output or incidence of inguinal infections, wound breakdowns, seromas, and lymphedema; furthermore, they reported a potential increased risk of vulvar wound complications. Based on these conflicting results, a recent meta-analysis concluded that the available evidence is not robust enough to advocate the use of fibrin-based sealants in inguinofemoral lymphadenectomy for malignant conditions, especially considering the additional cost for these products [18].

In wounds treated with TachoSil®, our study found that the overall postoperative drainage volume was not lower, nor the drain was removed earlier than in wounds closed without collagen-fibrin sealant patch. The median days of drainage placement were 15 days in both arms similar to results reported by a previous study [9], and the strict rule for drains removal (drainage < 50 ml over 24 h) increases the validity of these data and further confirms the similar drainage volume. Indeed, in other studies, the drainage had been left in place at least 1 week independently of the daily amount of drainage, so results are less comparable [17]. Overall, our results suggest that TachoSil® did not seem to be effective in improving postoperative lymphorrhagia.

Regarding postoperative complications, we found no significant differences between the two study groups, with comparable incidence of vulvar wound dehiscence, inguinal wound dehiscence, cellulitis, lymphangitis, lymphoceles, and hematoma. In addition, we found the same prevalence of grade 2 and 3 lymphedema (33.3%) in both IA and CA, and a prevalence of grade 1 lymphedema of 44.4% and 50% in IA and CA, respectively. Interestingly, we found that grade 1 lymphedema, which had the same incidence in the two arms, showed a lower prevalence at the 6th month compared to the 6th week follow-up after surgery. Based on these results, TachoSil® did not seem to be effective in reducing the incidence of postoperative complications after inguinofemoral lymphadenectomy for vulvar cancer, confirming what was previously reported by Carlson et al. [9]. One of the strengths of our study was the randomization of the inguinofemoral wounds, instead of the women. This allowed to avoid the multivariate analysis of BMI, tumor size, FIGO stage, or other patients' characteristics and TachoSil® application, because of the choice to randomize the inguinofemoral areas instead of the patients eliminates the inter-patient variability and reduces biases. Indeed, our results show different incidence and severity of

complications among patients (data not shown), but, when we consider the same woman case and control of itself, we found no significant variation between the investigated and the control side. This kind of randomization is a way to reduce inter-subject variability between cases and controls when population is small, reducing confounding factors: tumor is the same, patient is the same, surgeon performing lymphadenectomy is the same, and the only difference concerns the application of the fibrin-based sealant. Furthermore, our results are strengthened by the prospective double-blind study design and the inclusion of only vulvar cancers [17, 30]. Nevertheless, these conclusions are limited by the small-study population due to the strict inclusion/exclusion criteria and the rarity of vulvar cancer, as occurred in the previous studies [9, 17]. On that basis, the small-study population does not allow to exclude completely a potential effect of TachoSil® for all complications, although results of our study and previous studies suggest that it is improbable. About the primary outcome, we can exclude a reduction of total drainage volume higher than 150 ml after TachoSil® treatment with a power of 90%. About methodology, one potential further weakness concerns the choice to consider incremental increase in lower extremity circumference as a surrogate for lymphedema. There are many objective and subjective methods to evaluate lymphedema and we opted for the use of circumference measurements as they were easy to perform and reproducible [20, 21]. Volumetric measurements are much more specific, but also more expensive and time-consuming. Moreover, the 6-month follow-up may fail to detect patients who develop lymphedema later.

Conclusion

In conclusion, the overall high incidence of postoperative complications after inguinofemoral lymphadenectomy for vulvar cancer reported in this study highlights the importance of adopting techniques that are more respectful of the women psychophysical well-being. Besides the possible problems related to vulvectomy and its physical and psychological impact, the complications related to inguinofemoral lymphadenectomy are equally important. Unfortunately, this randomized-controlled trial shows that lymphorrhagia and complications after inguinofemoral lymphadenectomy for vulvar cancer do not seem to be improved by the use of a collagen-fibrin sealant patch (TachoSil®) in the inguinofemoral wound.

Author contributions Franchi M, Ghezzi F, Tateo S, and Baggio S: study conceptualization and protocol planning. Garzon S: randomization protocol and manuscript writing/editing. Franchi M: surgical procedures (unmasked). Baggio S, Scollo M, and Raffaelli R: clinical evaluations and follow-ups, data collection (masked). Laganà AS: final data analysis (masked) and manuscript writing/editing. Franchi M, Ghezzi F, and Tateo S: project administration and methodology validation. All the authors conform the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, contributed to the intellectual content of the study, and gave approval for the final version of the article.

Funding None.

Compliance with ethical standards

Conflict of interest The authors have no proprietary, financial, professional or other personal interest of any nature in any product, service, or company. The authors alone are responsible for the content and writing of the paper.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Siegel R, Naishadham D, Jemal A et al (2014) Cancer statistics, 2014. CA Cancer J Clin 64:9–29. https://doi.org/10.3322/caac.21208
2. Oonk MHM, Planchamp F, Baldwin P et al (2017) European society of gynaecological oncology guidelines for the management of patients with vulvar cancer. Int J Gynecol Cancer 27:832–837. https://doi.org/10.1097/IGC.0000000000000975
3. Bogani G, Cromi A, Serati M et al (2017) Predictors and patterns of local, regional, and distant failure in squamous cell carcinoma of the vulva. Am J Clin Oncol 40:235–240. https://doi.org/10.1097/COC.0000000000000138
4. Zhang SH, Sood AK, Sorosky JI et al (2000) Preservation of the saphenous vein during inguinal lymphadenectomy decreases morbidity in patients with carcinoma of the vulva. Cancer 89:1520–1525
5. Goker A, Guvenal T, Yanikkerem E et al (2011) Quality of life in women with gynecologic cancer in Turkey. Asian Pac J Cancer Prev APJCP 12:3121–3128
6. Benoit L, Boichot C, Cheynel N et al (2005) Preventing lymphedema and morbidity with an omentum flap after ilioinguinal lymph node dissection. Ann Surg Oncol 12:793–799. https://doi.org/10.1245/ASO.2005.09.022
7. Wills A, Obermair A (2013) A review of complications associated with the surgical treatment of vulvar cancer. Gynecol Oncol 131:467–479. https://doi.org/10.1016/j.ygyno.2013.07.082
8. Zweizig S, Korets S, Cain JM (2014) Key concepts in management of vulvar cancer. Best Pract Res Clin Obstet Gynaecol 28:959–966. https://doi.org/10.1016/j.bpobgyn.2014.07.001
9. Carlson JW, Kauderer J, Walker JL et al (2008) A randomized phase III trial of VH fibrin sealant to reduce lymphedema after inguinal lymph node dissection: a gynecologic oncology group study. Gynecol Oncol 110:76–82. https://doi.org/10.1016/j.ygyno.2008.03.005
10. Farrell R, Gebski V, Hacker NF (2014) Quality of life after complete lymphadenectomy for vulvar cancer: do women prefer

sentinel lymph node biopsy? Int J Gynecol Cancer 24:813–819. https://doi.org/10.1097/IGC.0000000000000101
11. Siemer S, Lahme S, Altziebler S et al (2007) Efficacy and safety of TachoSil ® as haemostatic treatment versus standard suturing in kidney tumour resection: a randomised prospective study. Eur Urol 52:1156–1163. https://doi.org/10.1016/j.eururo.2007.04.027
12. Anegg U, Lindenmann J, Matzi V et al (2007) Efficiency of fleece-bound sealing (TachoSil®) of air leaks in lung surgery: a prospective randomised trial. Eur J Cardiothorac Surg 31:198–202. https://doi.org/10.1016/j.ejcts.2006.11.033
13. Czerny M, Fleck T, Salat A et al (2004) Sealing of the mediastinum with a local hemostyptic agent reduces chest tube duration after complete mediastinal lymph node dissection for stage I and II non–small cell lung carcinoma. Ann Thorac Surg 77:1028–1032. https://doi.org/10.1016/j.athoracsur.2003.08.041
14. Gilly FN, Carry PY, Brachet A et al (1994) Effect of fibrin glue on lymphostasis during lymph node excisions. Prospective randomized study in 40 patients. Ann Chir 48:194–196
15. Moore M, Burak WE, Nelson E et al (2001) Fibrin sealant reduces the duration and amount of fluid drainage after axillary dissection: a randomized prospective clinical trial. J Am Coll Surg 192:591–599
16. Langer S, Guenther JM, DiFronzo LA (2003) Does fibrin sealant reduce drain output and allow earlier removal of drainage catheters in women undergoing operation for breast cancer? Am Surg 69:77–81
17. Buda A, Ghelardi A, Fruscio R et al (2016) The contribution of a collagen-fibrin patch (Tachosil) to prevent the postoperative lymphatic complications after groin lymphadenectomy: a double institution observational study. Eur J Obstet Gynecol Reprod Biol 197:156–158. https://doi.org/10.1016/j.ejogrb.2015.12.005
18. Weldrick C, Bashar K, O'Sullivan TA et al (2014) A comparison of fibrin sealant versus standard closure in the reduction of postoperative morbidity after groin dissection: A systematic review and meta-analysis. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol 40:1391–1398. https://doi.org/10.1016/j.ejso.2014.07.034
19. Covens A, Vella ET, Kennedy EB et al (2015) Sentinel lymph node biopsy in vulvar cancer: systematic review, meta-analysis and guideline recommendations. Gynecol Oncol 137:351–361. https://doi.org/10.1016/j.ygyno.2015.02.014
20. Marrs J (2007) Lymphedema and implications for oncology nursing practice. Clin J Oncol Nurs 11:19–21. https://doi.org/10.1188/07.CJON.19-21
21. Holcomb SS (2006) Identification and treatment of different types of lymphedema. Adv Skin Wound Care 19:103–108
22. Cipolla C, Fricano S, Vieni S et al (2010) Does the use of fibrin glue prevent seroma formation after axillary lymphadenectomy for breast cancer? A prospective randomized trial in 159 patients. J Surg Oncol 101:600–603. https://doi.org/10.1002/jso.21531
23. Vinchant M, Bonneau C, Lesavre M et al (2013) Interest of a thrombin and fibrinogen combipatch in preventing breast cancer seroma after lymph node dissection. Gynecol Obstet Fertil 41:583–587. https://doi.org/10.1016/j.gyobfe.2013.09.007
24. Lacoste C, Ouldamer L, Body G, Marret H (2013) Does the use of TachoSil allow to reduce the morbidity of axillary dissection? Gynecol Obstet Fertil 41:141–143. https://doi.org/10.1016/j.gyobfe.2012.12.012
25. Tinelli A, Giorda G, Manca C et al (2012) Prevention of lymphocele in female pelvic lymphadenectomy by a collagen patch coated with the human coagulation factors: a pilot study. J Surg Oncol 105:835–840. https://doi.org/10.1002/jso.22110
26. Grimm C, Polterauer S, Helmy S et al (2014) A collagen-fibrin patch (Tachosil®) for the prevention of symptomatic lymphoceles after pelvic lymphadenectomy in women with gynecologic malignancies: a randomized clinical trial. BMC Cancer 14:635–641. https://doi.org/10.1186/1471-2407-14-635
27. Tinelli A, Mynbaev OA, Tsin DA et al (2013) Lymphocele prevention after pelvic laparoscopic lymphadenectomy by a collagen patch coated with human coagulation factors: a matched case-control study. Int J Gynecol Cancer 23:956–963. https://doi.org/10.1097/IGC.0b013e31828eeea4
28. Ghezzi F, Uccella S, Cromi A et al (2012) Lymphoceles, lymphorrhea, and lymphedema after laparoscopic and open endometrial cancer staging. Ann Surg Oncol 19:259–267. https://doi.org/10.1245/s10434-011-1854-5
29. Simonato A, Varca V, Esposito M et al (2009) The use of a surgical patch in the prevention of lymphoceles after extraperitoneal pelvic lymphadenectomy for prostate cancer: a randomized prospective pilot study. J Urol 182:2285–2290. https://doi.org/10.1016/j.juro.2009.07.033
30. Swan MC, Oliver DW, Cassell OCS et al (2011) Randomized controlled trial of fibrin sealant to reduce postoperative drainage following elective lymph node dissection. Br J Surg 98:918–924. https://doi.org/10.1002/bjs.7462