Collagen-fibrin patch (TachoSil®) in prevention of lymphoceles in gynecologic cancer

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Summary

Lymphoceles are a common post-surgical complication after lymphadenectomy in gynecologic malignancies. The careful sealing of lymphatic vessels to avoid the leaking of lymph fluid is usually standard in the effort to prevent lymphoceles. The current literature describes various additional methods that, however, did not show sufficient results. New evidence presented a possible new solution in the use of a collagen fibrin patch (TachoSil®) as a preventive measure. Objective of this study is to compare the effectiveness of TachoSil® – collagen fibrin patch – with standard techniques for the prevention of lymphoceles in patients with gynecologic malignancies.

Data of 17 patients were collected in a non-randomized observational study. All patients underwent a lymphadenectomy as treatment for their gynecologic cancer. 10 patients received the collagen-fibrin patch for prophylaxis, 7 patients did not. Ultrasound examination on day 4, 10 and 28 after surgery were performed to look for lymphoceles. Furthermore data on baseline characteristics, cancer characteristics, operation details and post-surgical complications were collected.

Lymphoceles developed in two patients of the case group and in no patients in the control group. One lymphocele was symptomatic. 80.0 % of the patients in the case group and 16.7 % of the patients in the control group suffered from a complication other than a lymphocele. Here, a significant difference between the two groups was found.

Although the discrepancy between our results and previous studies could be explained by the small size of the groups, new/ future studies with a larger sample size and longer follow-up time are needed to make significant statements on the possible benefit of collagen fibrin patches in the prevention of lymphoceles.
Samenvatting

Lymfoceles zijn een vaak voorkomende complicatie na lymfklieren verwijdering bij gynaecologische maligniteiten. Zorgvuldig sluiten van lymfevaten is de standaard therapie lekkage van lymfevloeistof en het ontstaan van een lymfocele te voorkomen. In de literatuur worden verschillende methoden beschreven echter zonder voldoende succes. Nieuwe onderzoeken laten een mogelijke preventie methode zien middels het gebruik van een collageen fibrine patch (TachoSil®). Doel van de studie is de effectiviteit van het collageen fibrine patch (TachoSil®) vergelijken met de standaard technieken.

De data van 17 patiënten is verzameld voor deze niet gerandomiseerde, observationele, pilot studie. Alle patiënten hebben een lymfklier verwijdering ondergaan als behandeling voor hun gynaecologische kanker. 10 patiënten hebben de collageen fibrine patch gekregen. 7 patiënten kregen de huidig geldende standaard therapie. Echo onderzoek werd uitgevoerd op de 4, 10 en 28 dag post operatie om het zetten naar lymfoceles. Verder is data verzameld over de baseline eigenschapen, het type kanker, details van de operatie en post operatieve complicaties.

Lymfoceles hebben zich ontwikkeld in twee patiënten van de case groep en in geen patiënt van de control groep. Een lymfocele gaf symptomen zo als pijn. Maar geen statistieke verschil kon gevonden worden. 80,0% patiënten van de case groep en 16,7% patiënten van de control groep onderliepen een andere complicatie dan een lymfocele met een significant verschil tussen de twee groepen.

Hoewel de discrepantie tussen onze resultaten en vroegere studies verklaard kan worden door het lage aantal aan patiënten van de groepen een nieuwe studie met een groter aantal patiënten en een langere follow-up tijd is nodig om een veel zegende uitspraak te kunnen maken over de benefit van het collageen fibrine patch in de preventie van lymfoceles.
Introduction

Every year about 19% of the 5.1 million new cancer patients worldwide are diagnosed with a gynecologic malignancy. In 2002, the estimated incidence of cervical cancers was 493,000, of ovarian cancers 204,000, of endometrial cancers 199,000 and of vaginal, vulvar and choriocarcinoma together 45,900 (1). Over the last decade, the number of vulvar cancer diagnoses has risen in several European countries (2-5). In England, the incidence rate increased by 18 % between 1990 and 2007 from 2.13 per 100,000 women to 2.51 per 100,000, with an even higher increase in the Netherlands of 70% in the period between 1989 and 2010, from 183 new cases to 315. In Germany, vulvar cancer diagnoses are responsible for a growing number of new gynecologic cancer diagnoses each year, the absolute numbers having increased from 1.328 in 1999 to 3.118 in 2011. The highest incidence of gynecological malignancies remains endometrial cancer with 11.129 cases, followed by ovarian cancers with 7.819, and 4.647 cervical cancers (6).

Lymph node involvement is an adverse prognostic factor for all of these malignancies, and is a basis for therapeutic decision making (7-9). Magnetic resonance imaging and sentinel node biopsy show good results in the staging procedure (7,10-13). Lymph node dissection increases the survival even of low grade tumors (9, 14), therefore, lymphadenectomy is currently part of the routine therapy for women with possible lymph node metastases (7-9, 13).

Lymphadenectomy, like other surgical procedures, entails risks such as bleeding and injuries to adjacent structures (15). The ureter and the obturator nerve are prone to injury during pelvic lymphadenectomies (16). Another important but often overlooked postoperative complication after pelvic lymph node dissection is the formation of symptomatic lymphocele (16). Lymphoceles are defined as enclosed lymph fluid collections within and above the spaces created by node removal (17). Different studies show incidences of symptomatic lymphoceles from 5.8% up to 34.5% (15, 17-19). This range of results may be attributable to differences in anatomical location of lymph node dissection, the nature of the malignancies, the use of different diagnostic methods and also due to diverse definitions of lymphoceles. Achouri et al. (18) reported an incidence of 34.5% for symptomatic lymphocele in patients with cervical, endometrial and ovarian cancer, while the incidence per diagnosis differed between 64.7% for cervical cancer, 47.2% in ovarian cancer and 8.3% in endometrial cancer. Hinten et al. (20) found lymphocele rates of 29.2% after groin lymphadenectomy in vulvar cancer patients. Furthermore, the number of asymptomatic lymphoceles is even higher. Incidence rates of asymptomatic lymphoceles that were detected via computer tomography or ultrasound differ from 20.2% up to 56% (19,21).

Lymphocele development

Several risk factors for the post-surgical development of a lymphocele have been reported and studied. Lymphoceles are usually first detected two weeks after dissection (22). Symptomatic lymphoceles in particular seem to develop early (19), though lymphoceles can grow up to 2 years after the lymph node dissection (23). Higher numbers of removed lymph nodes are...
associated with a higher risk of postoperative complications, of these lymphocele is the most common (16, 24).

However, the research of Gaulthier et al. (25) showed that the extent of lymph node dissection and lymph node involvement, as well as neoadjuvant chemotherapy and a high BMI could not be identified as independent risk factors. The only independent risk factor they found in patients with ovarian cancer undergoing lymph node dissection was supraradical surgery, a procedure involving standard hysterectomy, bilateral adnexectomy, appendectomy and removal of pelvic and lumbo-aortic nodes, plus extensive peritomectomies, and possible resection of bowel or other metastases (26). Gaulthier et al. (25) concluded that supraradical surgery hinders the absorption capability of the peritoneum, leading to the increased rate of lymphoceles in these patients.

Another proposed risk factor is the performance of open surgery rather than a laparoscopic approach. Through analysis of various possible risk factors, Mundhenk et al. (27) examined 302 men, operated by the same surgeon, who had undergone pelvic lymph node dissection as a staging procedure for prostate cancer. They found a significantly higher rate of lymphocele development among those men receiving open surgery as compared to those having laparoscopic pelvic lymph node dissection (8.0% vs 0.8%, respectively). Interestingly they had a significantly higher number of symptomatic lymphoceles in slim patients, though no explanation could be given for this finding (27).

Another risk factor was proposed by Musch et al. (16), after finding a correlation between the development of lymphoceles and the operating surgeon. Even with the same amount of dissected lymph nodes, they showed an outcome difference for different surgeons. They hypothesized that the outcome is influenced not only by the level of thoroughness of different surgeons, but also other as yet unknown individual factors can affect lymphocele formation (16).

**Lymphocele impact**

Fortunately, most lymphoceles resolve spontaneously (28). However, some cause symptoms related to their size and location, i.e. through compression of adjacent structures. While most symptoms are light, limited to solely a pressure sensation (25, 29), lymphoceles can range from being asymptomatic to causing dramatic consequences, necessitating a medical intervention. For example, the formation of symptomatic lymphocele seems to be linked to increased thromboembolic events due to the compression of pelvic vessels (16). Hydronephrosis, edema, constipation or pain could appear by compression of the ureters, veins, bowels or nerves, respectively. Even urination frequency can be altered by the compression of the bladder (18, 30). Infected lymphoceles can cause abdominal pain and may lead to abscess formation (29).

Additionally, delayed chemotherapy due to lymphoceles has been described (21, 25). This delay, as well as morbidity associated with symptomatic lymphoceles, lead to the need of drainage and even further treatment and therefore causing additional morbidity and hospitalization of the patient (16).

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Lymphocele treatment

Treatment options for lymphoceles are limited. Aspiration of the lymph fluid is the simplest therapy but seldom leads to a cure for the patient (31). The evidence in the literature shows better results after placement of a drainage catheter (28, 32). Drainage seems to have an even higher success rate in combination with sclerotherapy, up to 80% to 100%. However the drainage period with sclerotherapy lasts up to 60 days (23).

In a large scale retrospective study, Radosa et al. (29) showed a success rate of 93.1% and a complication rate of 15.7% after laparoscopic fenestration as first line treatment of lymphoceles.

Lymphocele prevention

Until now several surgical techniques have been evaluated to date for the prospective prevention of lymphocele formation. These include leaving the peritoneum open at the end of the surgical procedure to allow lymph to flow into the peritoneal cavity, drainage catheter placement at the end of the surgical procedure, or leaving the vaginal pouch open to evacuate the leaking lymph (33-35). However recent studies have questioned those methods (27,36). Moreover, drainage seems to be a risk factor for lymph edema in inguinal lymphadenectomy (37).

Other studies proposed the prevention of lymphocele formation by omentoplasty, vessel sealing and medical glues. In omentoplasty an omental flap is created and placed on the side of the lymphadenectomy, thereby allowing the omentum to absorb the lymph (38). The sealing of lymphatic vessels with an electrothermal bipolar vessel sealing device, ultrasound advanced energy and ligaclips has been investigated with different rates of success (21,39,40). Application of medications as glue for leaking vessels has also been attempted as a prevention method. While fibrin glue showed insufficient results in the prevention of lymphoceles, n-butyl cyanoacrylate glue demonstrated effectiveness (41-43). Thus, despite efforts to find new ways to prevent lymphoceles, a widely agreed upon solution has not yet been found.

A possible new Lymphocele prevention measure: collagen-fibrin patch

The collagen-fibrin patch TachoSil® has proven to be effective as a hemostatic agent for gynecologic and obstetric surgery (44). It is coated with human fibrinogen and human thrombin that activate the natural coagulation cascade, thereby forming a fibrin clot. The patch binds to the covered area, and in addition absorbs fluids. These properties also make it interesting for the reduction of lymph fluid leakage (45). Studies indicated its usefulness in lymphocele prevention in endometrial cancer patients, with both laparoscopic surgery as well as in lymphadenectomy performed during laparotomy (19.2% vs. 51.7% and 23.3% vs. 57.1% respectively) (46, 47). Additionally Buda et al. (48) show a reduction in drainage volume and lymphocele formation in patients with vulvar cancer who underwent inguinal lymph node dissection and receive TachoSil® compared to the control group, 25.0% vs 62.5 %, respectively. Moreover, in male prostate cancer patients who underwent lymphadenectomy
and in patients undergoing kidney transplantation, a significant decrease of lymphocele development was found after TachoSil® application (10% vs. 30%, and 7.5% vs. 24.21% respectively) (49,50).

Research question

To date there is no published evidence of the efficiency of a collagen-fibrin patch as a lymphocele prophylaxis in all gynecologic malignancies. Furthermore it has not been studied in Germany. Therefore the objective of this study is to compare the effectiveness of the TachoSil®, collagen-fibrin patch with standard techniques for the prevention of lymphoceles in patients with gynecologic malignancies in a German hospital specialized in Gynecologic Oncology.

Material and Method

Study design and definition of cases

An observational non-randomized prospective pilot study was conducted to follow up patients who received a collagen-fibrin patch (TachoSil®) as prevention against lymphocele as part of their cancer treatment. Between January and May 2015, 17 patients with different gynecological cancers were scheduled for lymphadenectomy, of whom the first 10 received the prophylaxis patch and thereby constituted the case group, while the following represented the control group. This study was realized in the Clinic of Gynecology, Obstetrics and Gynecological Oncology of the University Hospital for Gynecology, Pius-Hospital Oldenburg, Medical Campus University Oldenburg, Germany.

A lymphocele was defined as lymph fluid accumulations with fibrotic lining or visible walls of a few millimeter thickness, within and above the spaces created by the node removal (Figure 1). Simple lymph fluid accumulations were not recognized as lymphoceles, as long as they did not show walls. A symptomatic lymphocele was defined as one presenting with symptoms such as pain or pressure sensation in the pelvic or inguinal area, or with signs of infection, impaired micturition or bowel movements. A complicated lymphocele was defined as any presenting with severe compression of the surrounding structures or thrombotic events.

Inclusion criteria

Patients with endometrial, cervical, ovarian or vulvar cancer, who were scheduled for inguinal, femoral, pelvic and/or para-aortic lymphadenectomy, without previous lymphadenectomy or lymph disease were included (Figure 2).
Exclusion criteria and end points

Patients who were previously diagnosed with a lymph disease. Furthermore, participants who missed an ultrasound examination, or who had undergone previous lymphadenectomy were excluded (Figure 2).

Surgical details

No changes were made to care standards for lymphadenectomy performance. All surgical interventions were performed by the same experienced gynecological oncologist, and were done either by laparotomy, laparoscopy or open groin dissection, according to the disease of the patient, previous abdominal or pelvic surgery, presence of dense and severe adhesions and extent of the disease.

Pelvic lymphadenectomy included the removal of lymphatic tissue, by monopolar and bipolar coagulation, from any one or several of the following sites, according to the primary tumor and macroscopic aspect of suspicious of affected lymph nodes:

- From the external iliac, internal iliac, and common iliac veins in case of uterine cancer;
- Iliac and obturator in cases of cervix cancer;
- Iliac and para-aortal in cases of ovarian cancer;
- And inguinal for vulvar cancer.
In selected cases other regions, including the femoral region, were dissected. Special attention was paid to the sealing or ligating of the lymphatic vessels in all cases. A draining catheter was not placed in any of the cases.

In cases where TachoSil® was applied during the procedure, the package was opened shortly after lymph node dissection and moistened with saline solution of 0.9% sodium chloride. It was then placed with the yellow, active side onto the area of lymph node dissection and pressed down for 3 minutes with the help of a surgical gauze (Figure 3). Pressing time was carefully stopped. During laparoscopic surgery, TachoSil® was folded in the form of an accordion in order to be inserted through the trocar. This method was also used for pre-rolled laparoscopy-specific TachoSil® sheets, which were also unrolled and folded as an accordion before insertion. This accordion form was found to be easier to unfold in comparison with unfolding the TachoSil® intra-abdominally. Moistening was done after unfolding TachoSil® intra-abdominally during laparoscopic procedures with the help of a flush-suction device. Afterwards, TachoSil® was carefully pressed on the area of lymph node dissection with the help of a gauze.

The sizes of the administered TachoSil® were the large patch measuring 9.5 cm x 4.8 cm and the medium patch measuring 4.8 cm x 4.8 cm. Application of TachoSil® was individualized by the treating surgeon. The individual dosages ranged from 1-4 units 9.5 cm x 4.8 cm. For smaller wounds, e.g. in minimally invasive surgery, the medium size, sometimes the pre-rolled patch (based on a patch of 4.8 cm x 4.8 cm) was used.

**Examination and imaging**

All patients had anamnesis taken and underwent clinical examination at day 4, 10 and 28 after surgery, with a range of +/- 2 days to evaluate symptoms such as pain or pressure sensation, or complications which could be related to a lymphocele. Patients were asked to rate their pain on a visual analog scale (VAS) from 0 till 10, where 0 was stated as no pain and 10 as the worst pain (51-53) (Appendix). Their body mass index was also calculated. The external wound area was examined to identify infections, and an ultrasound examination was performed according to the executed surgery, either trans-inguinal or trans-abdominal and/or trans-vaginal, looking for lymph fluid accumulation or lymphocele (Figure 4, 5). Every lymphocele was measured for size and documented.

**Data**

The following data were collected for analysis:

1) Baseline characteristics of patients: age, body mass index (weight, height)
2) Characteristics of the primary tumor: type of cancer, and cancer stage- based on the International Federation of Gynecology and Obstetrics (FIGO) staging systems.
3) Surgical details: total operation duration and surgical approach, number and types of dissected lymph nodes and lymph metastasis;
4) Lymphoceles and post-surgical symptoms related to lymphoceles and other complications

Statistical analysis
Data were analyzed using the statistical program IBM SPSS Statistics 21. Continuous variables are expressed as absolute numbers, while categorical variables are expressed as a median. The Fishers exact test was used for analyzing categorical variables. A p-value of < 0.05 was considered as statistical significant.

Ethical aspects
Written informed consent was obtained from all participating patients. The lymphadenectomy and the use of TachoSil® are accredited procedures for patients with gynecologic malignancies. Approval from the Committee of the Medical Master program of the University of Groningen to conduct the study was given.

Results
Baseline characteristics
The baseline characteristics of the two study groups are presented in Table 1. The median age was 70 years in the case group and 58 years in the control group. The median BMI was 29.06. 30.73, for case and control group respectively. Vulvar cancer was more frequent in the case group (5 vs 0). Half of patients (50%) in the case group and 42.8% in the control group had a Stage I FIGO tumor. Patients in the case group had a high amount of lymph metastasis (range 0-3 vs 0-1 in the control group). In relation to surgical approach, more cases underwent inguinal lymph node dissection (50% vs. 16.7%). The median operation duration was shorter in the case group (239 vs. 399 minutes). Fewer lymph nodes were dissected in the case group (median of 21 vs. 27). There were no statistically significant differences between the groups for any of the analyzed variables. One patient did not return for follow-up examination.

Figure 5 Ultrasound picture of lymph fluid accumulation in the pelvis and hyperechogenic area showing the still air filled TachoSil patch; By C. Wencker with permission of the patient
Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Case group n=10</th>
<th>Control group n= 7</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; yrs., median (range)</td>
<td>70 (29-82)</td>
<td>63 (42-75)</td>
<td>1.0</td>
</tr>
<tr>
<td>BMI; median (range)</td>
<td>29.06 (20.2-35.92)</td>
<td>30.73 (19.59-38.22)</td>
<td>1.0</td>
</tr>
<tr>
<td>Type of cancer; n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cervix</td>
<td>3 (30)</td>
<td>2 (33.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>ovarian</td>
<td>1 (10)</td>
<td>2 (33.3)</td>
<td></td>
</tr>
<tr>
<td>endometrium</td>
<td>1 (10)</td>
<td>2 (33.3)</td>
<td></td>
</tr>
<tr>
<td>vulvar</td>
<td>5 (50)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>FIGO stage; n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>5 (50)</td>
<td>3 (50)</td>
<td>1.0</td>
</tr>
<tr>
<td>II</td>
<td>2 (20)</td>
<td>1 (16.7)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>3 (30)</td>
<td>2 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Lymph metastasis; median (range)</td>
<td>0.0 (0-3)</td>
<td>0.0 (0-1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Surgical approach; n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>laparoscopy</td>
<td>2 (20)</td>
<td>1 (16.7)</td>
<td>0.44</td>
</tr>
<tr>
<td>laparotomy</td>
<td>3 (30)</td>
<td>4 (66.7)</td>
<td></td>
</tr>
<tr>
<td>inguinal</td>
<td>5 (50)</td>
<td>1 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Operation duration; min (range)</td>
<td>239 (148-400)</td>
<td>399 (64-463)</td>
<td>0.5</td>
</tr>
<tr>
<td>Total dissected lymph nodes; median (range)</td>
<td>21 (15-55)</td>
<td>27 (5-44)</td>
<td>0.62</td>
</tr>
<tr>
<td>Type of dissected lymph nodes; median (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inguinal</td>
<td>13 (0-24)</td>
<td>2.5 (0-7)</td>
<td>0.21</td>
</tr>
<tr>
<td>pelvic</td>
<td>7.5 (0-46)</td>
<td>16.5 (0-37)</td>
<td>0.22</td>
</tr>
<tr>
<td>para-aortal</td>
<td>0 (0-7)</td>
<td>3 (0-14)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Table 1: BMI = Body mass index, min = minutes, yrs. = years, FIGO = International Federation of Gynecology and Obstetrics staging systems. p<0.05 means statistically significant

Lymphocele development

Only two patients of the case group developed lymphoceles compared to no patient in the control group (20% vs 0%). Both lymphoceles were documented for the first time at the evaluation 28 days after surgery, one measuring 12.24 cm and the other 5.26 cm in diameter. The smaller one was an infected inguinal lymphocele requiring drainage and antibiotic management with the only related symptom being pain having a VAS score range upon till 8, but no significant difference could be calculated concerning the development of a lymphocele between the two groups (Table 2).
Table 2 Total and symptomatic post-surgery lymphocele

<table>
<thead>
<tr>
<th>Post-surgery lymphocele</th>
<th>Case group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 10</td>
<td>n = 6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td></td>
</tr>
<tr>
<td>Time of examination; n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>day 4;</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>N/A</td>
</tr>
<tr>
<td>day 10</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>day 28</td>
<td>2 (20)</td>
<td>0 (0)</td>
<td>0.5</td>
</tr>
<tr>
<td>Symptomatic lymphocele; n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pain</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>1.0</td>
</tr>
<tr>
<td>infection</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>thrombosis</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

N/A = not applicable, p<0.05 means statistically significant.

In Table 3, the characteristics of the two patients who developed a lymphocele are described. The median values were 76.5 years old and a BMI of 29.06. One patient was diagnosed with ovarian and the other with vulvar cancer, both staged FIGO II. They had a median of 2.5 lymph metastasis and a median of 18 lymph nodes dissected in a median operation duration of 232 minutes. One had an open inguinal lymphadenectomy done and the other a laparotomy to dissect the lymph nodes.

Table 3. Characteristics of the patients who developed a lymphocele

<table>
<thead>
<tr>
<th>n=2</th>
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<tbody>
<tr>
<td>Age; yrs., median (range)</td>
</tr>
<tr>
<td>BMI; median (range)</td>
</tr>
<tr>
<td>Type of cancer; n (%)</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
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<tr>
<td>FIGO staging; n (%)</td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Lymph metastasis; median (range)</td>
</tr>
<tr>
<td>Surgical approach; n (%)</td>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Operation duration; min (range)</td>
</tr>
<tr>
<td>Total dissected lymph nodes; median (range)</td>
</tr>
</tbody>
</table>

Table 3: yrs. = years. BMI = Body mass index. min = minutes. FIGO = International Federation of Gynecology and Obstetrics staging systems

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Complications
In the case study group, eight patients (80%) experienced at least one complication other than a lymphocele compared to only one patient in the control group. A significant difference with a p-value (p=0.035) was found between the two groups. According to the type of cancer, all patients with vulvar cancer and four with cervix cancer had complications (Table 4).

<table>
<thead>
<tr>
<th>Patients with complication; n (%)</th>
<th>Case Group n (%)</th>
<th>Control group n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of cancer; n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cervix</td>
<td>3</td>
<td>1</td>
<td>0.035</td>
</tr>
<tr>
<td>ovarian</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>endometrium</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>vulvar</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

p<0.05 means statistically significant.

The more frequent complications were wound dehiscence and lymph edema with an occurrence of five (50%) and four (40%) times all found in the case group. In the control group one hydronephrosis was found. There were no statistically significant differences concerning the type of complications (Table 6).

<table>
<thead>
<tr>
<th>Other complications; n (%)</th>
<th>Case group (n=10)</th>
<th>control group (n=6)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound infection</td>
<td>3 (30)</td>
<td>0 (0)</td>
<td>0.25</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>5 (50)</td>
<td>0 (0)</td>
<td>0.93</td>
</tr>
<tr>
<td>Numbness in the wound area</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Pain due to nerve damage</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>0 (0)</td>
<td>1 (10)</td>
<td>0.37</td>
</tr>
<tr>
<td>Lymph edema</td>
<td>4 (40)</td>
<td>0 (0)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

p<0.05 means statistically significant.
Discussion

The terms lymph cyst and lymphocele are used synonymously since their first description in the English literature in 1958 by Grays et al. (54, 55). Lymphoceles, however, usually have a fibrotic lining in place of an epithelial lining (56), hence the term lymphocele is preferred in the literature. Lymph node dissection is still part the standard of care in advanced gynecologic malignancies (9, 13). Complications such as the development of a lymphocele are widely known. Therefore many different prevention techniques have been considered in the literature (36, 38-40). A lymphocele might compress various surrounding structures and cause a range of symptoms and complications, some with consequences such as discontinuation of cancer treatment (18,21,25,30). Therefore, lymphocele development should be prevented through adequate surgical technique or the use of prophylactic measures, including prophylactic substances such as collagen fibrin patches.

TachoSil® is such a collagen fibrin patch coated with human fibrin and thrombin and is commonly used as a hemostatic agent in surgery for bleedings that are difficult to control (44). In recent years, these properties have also been tested for other purposes (45). In the study of Tinelli at al. (46) a group of patients suffering from endometrium cancer, in which TachoSil® was applied after laparoscopic lymphadenectomy, was matched with a group of patients who had the same amount of lymphoceles removed. They found a smaller incidence of lymphocele in the TachoSil® group, similar to that in their previous study, where they removed the lymph nodes from endometrium cancer patients by laparotomy (47).

To date, the efficiency of collagen-fibrin patches as lymphocele prophylaxis has not been studied in endometrial, cervical, ovarian and vulvar cancer patients together. Therefore, the objective of this study was to compare the effectiveness of TachoSil® -collagen-fibrin patch with standard techniques for lymphocele prevention in patients with gynecologic malignancies.

Collagen-fibrin patch (TachoSil®) in prevention of lymphoceles in gynecologic cancer - Corinna Wencker
In this study, ten cancer patients who had undergone lymphadenectomy and received a collagen-fibrin patch (TachoSil®) as a prevention method against lymphocele, and seven control cancer patients were followed up. This study was realized between January and May 2015, in the Clinic of Gynecology, Obstetrics and Gynecological Oncology of the University Hospital for Gynecology, Pius-Hospital Oldenburg, Medical Campus University Oldenburg, Germany. One patient was lost to no show.

The age of the participants ranged between 29 and 82 years of age and they were overweight. Most of them presented with FIGO stage I vulva, ovarian, endometrial or cervix cancer. Number of dissected lymph nodes ranged from 5 to 55, with a range up to 3 lymph metastasis. The median duration of operation was 275 minutes, with 47.5% of patients having received laparotomy. There were no statistically significant differences among baseline characteristics between the groups.

The percentage of lymphocele formation in the literature ranges from 20.2% to 56% (19,21), with low levels of lymphoceles in vulvar and endometrium carcinoma patients (18,20). Younger age and lower BMI might present a higher risk for lymphocele development (18,27). Previous studies showed a higher rate of lymphocele development among FIGO stage I (71.42%) compared to FIGO stage III (19.04%) cancers (57).

According to our results, the median number of dissected lymph nodes were 21 and 27 in the case and control group, respectively. Following lymphadenectomy, 20% of patients of the case group, one with vulvar cancer and one with cervical cancer, developed a lymphocele between 10 to 28 days after surgery, while there was no one in the control group with this complication. None of the patients suffering from endometrium cancer developed a lymphocele. The patients developing lymphoceles had a median age of 76 and a median BMI of 29.06, a FIGO-stage III cancer, and a median of 18 lymph nodes dissected, suggesting that extent of lymph node removal may not be a risk factor for lymphocele formation. One lymphocele measured 12.24 cm, and the other one with 5.26 cm in diameter. The smaller one was an infected inguinal lymphocele requiring puncture and antibiotic management, with pain being the only related symptom.

Our findings are similar to the study results of Ghezzi et al. (57), where the groups had a median of 17.5 lymph nodes removed. Moreover, the study of Achouri et al. (18) showed that additional para-aortal node removal did not increase the risk for the development of a lymphocele.

It is described that a laparoscopy decreases the risk for the development of a lymphocele as compared to a laparotomy (15, 27). Ghezzi et al. (57) presented lower incidences of lymphoceles in laparoscopic lymphadenectomies compared to open lymph node dissection (1.4% vs. 15.4%) in endometrium cancer patients. Consistent with these previous results, in the current study a lymphocele only developed after laparotomy and open groin dissection. However the duration of the surgery was not associated (median 232 minutes) with the development of a lymphocele.

There were no cases of severe adverse events during the time of the study, but other complications excluding lymphocele, were experienced by 80% (n=8) of patients from the case group. The distribution of complications between the different malignancies was divided such that 100% of the vulvar cancer patients and 80% of the cervix cancer suffered of at least one complication. The more frequent complications were wound dehiscence and lymph edema, with Collagen-fibrin patch (TachoSil®) in prevention of lymphoceles in gynecologic cancer - Corinna Wencker
an occurrence of 50% and 40%, respectively. In the control group, one hydronephrosis was found. Concerning the type of complication, there were no statistically significant differences between the two groups. This is consistent with prior evidence showing a high incidence of complications in patients treated with inguinal lymph node dissection for vulvar cancer (20), which is the standard treatment in patients with this malignancy in its late stage (9).

The weakness of this study is the limited number of patients and in particular the difficulty to have matched controls. Therefore, the discrepancy between our results and previous studies can be explained by the small size of the groups, especially for vulvar cancer patients receiving TachoSil®, as there was no control patients with vulvar cancer.

**Conclusion**

The burden of morbidity and the increased risk of infections and thromboembolic events associated with lymphoceles, as well as the possible interruption or postponement of adjuvant therapies due to lymphocele development are of great concern to patients undergoing standard treatment for gynecological cancers. The use of substances, such as collagen fibrin patches have been proposed as a safe prophylactic agents, albeit the results of the present study are inconclusive, though this could be explained by the limited sample size.

Moreover, since lymphoceles may potentially grow up to 2 years after the lymph node dissection, future studies with a larger sample size and longer follow-up time are needed to make significant statements on the possible benefit of collagen fibrin patches in the prevention of lymphoceles.
References


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(22) Tam KF, Lam KW, Chan KK, Ngan HY. Natural history of pelvic lymphocysts as observed by ultrasonography after bilateral pelvic lymphadenectomy. Ultrasound Obstet Gynecol 2008 Jul;32(1):87-90.


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Appendix

Figure 7: The visual analog scale (VAS) and Wong-Baker FACES Pain Rating scale, the VAS was used for the assessment of pain.