

ORIGINAL RESEARCH

Incidence and clinical course of lymphoceles following pelvic sentinel lymph node removal in endometrial cancer

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Abstract

Background: To assess the incidence and clinical course of pelvic lymphoceles following removal of sentinel lymph nodes (SLN) in endometrial cancer (EC). **Methods:** Between October 2014 and September 2021 consecutive women with a uterine confined EC deemed suitable for robotic surgery and detection of pelvic SLNs at a tertiary academic centre were screened for inclusion. A previously described SLN algorithm with detection of SLNs along parallel pelvic pathways, was adhered to. Follow-up, including a vaginal ultrasonography to detect pelvic lymphoceles, was scheduled every six months until two years post-surgery. The incidence, clinical course of pelvic lymphoceles, and any necessary intervention up to 12 and 24 months, were investigated. **Results:** A total of 449 women were included. After exclusions of women lost to, or having a remote hospital follow-up, 361 (at 12 months) and 276 (at 24 months) women were included. In ten women, a pelvic lymphocele was identified during the study period where a surgical fenestration was necessary in one patient, and one was treated with antibiotics. The remainder had either asymptomatic or spontaneously resolving lymphoceles. The development of a lymphocele was positively associated with increased Body Mass Index (BMI) ($p = 0.005$). However, neither adjuvant treatment, age, or the quantity of sentinel lymph nodes (SLNs) removed demonstrated a significant association ($p = 0.756$, $p = 0.971$ and $p = 0.463$ respectively). **Conclusions:** The overall risk of pelvic lymphocele development post SLN biopsy in women with EC was 2.7%. Eighty percent were either asymptomatic or had a spontaneously resolving lymphocele and the overall risk for intervention was 0.5%. Lymphocele development was associated with BMI but neither with the number of removed SLNs, age or adjuvant treatment. These results support the detection of SLNs in EC regardless of preoperative risk group. **Clinical Trial Registration:** NCT03680833, retrospectively registered.

Keywords

Lymphocele; Sentinel lymph node; Endometrial cancer

1. Introduction

To maintain awareness of nodal status while minimising the extent of surgical intervention and perioperative complications, sentinel lymph node (SLN) mapping has been widely implemented in the surgical staging of women with endometrial cancer (EC). US National Comprehensive Cancer Network (NCCN) guidelines endorse SLN detection for all cases of uterine-confined disease, regardless of preoperative risk classification [1]. Since 2020, Swedish national guidelines have aligned with these principles, additionally stipulating that EC surgeries involving SLN should be centralised at University Hospitals [2]. The European Society of Gynaecological Oncology, European Society for Radiotherapy and Oncology, and the European Society of Pathology (ESGO-ESTRO-ESP) guidelines recognise the proportion of SLN procedures as a

quality metric in EC surgery [3].

Despite these advancements, some discord remains among professionals regarding the use of SLN detection, particularly in cases of presumed low-risk EC. This hesitance is often justified by concerns over surgical and lymphatic complications associated with a perceived low risk of nodal metastases, a perspective primarily derived from historical non-SLN data [4, 5]. Reported complications from full pelvic lymphadenectomy (PLND) include organ injury, intraoperative bleeding or lymphocele formation (up to 34.5%), as well as lower-limb lymphedema [6, 7]. As many as 40.9% of women with EC who undergo PLND may experience long-term lymphatic complications, primarily lower-limb lymphedema, which negatively impacts quality of life [8, 9].

Most studies assessing the risk of lymphoceles post-PLND or SLN procedures are typically retrospective and/or symptom-

based, potentially leading to an underestimation of incidence rates. Lymph node status is vital for guiding adjuvant treatment, and recent research utilising ultra-sectioning (US) and immunohistochemistry (IHC) has revealed a higher incidence of nodal spread in women classified as low risk for EC than previously reported [10]. This finding underscores the importance of SLN detection in this patient demographic, particularly when the risk of lymphatic complications is low [11–14]. A prior study from our institution demonstrated that SLN-only procedures resulted in a significantly lower incidence of lower-limb lymphedema compared to pelvic and paraaortic lymphadenectomy (1.3% vs. 18.1%, $p = 0.0003$) [15].

The aim of this study was to prospectively investigate the incidence, clinical course, and interventions related to pelvic lymphoceles up to 24 months post-surgery following an SLN-only procedure in a consecutive cohort of women with EC.

2. Material and methods

The study was conducted at a tertiary academic centre in Sweden with a regional assignment for gynaecological cancer surgery including all women with EC. Between October 2014 and September 2021 consecutive women with a uterine confined EC, deemed suitable for robot assisted surgery and for adjuvant treatment, were approached for a prospective “SLN only” study in endometrial cancer ([clinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03680833), NCT03680833). Until June 2019, the study included women with an estimated low-grade endometrioid EC without a deep myometrial invasion, thereafter all risk groups of EC. Inclusion/exclusion criteria are outlined in the online study protocol.

Enrolled women were scheduled for a robotic hysterectomy, bilateral salpingo-oophorectomy, and detection of pelvic SLNs. All women had a preoperative computerized tomography (CT) scan of the thorax and abdomen. Women in whom postoperative adjuvant oncologic treatment was administered; pelvic external beam radiotherapy and 4–6 cycles of Carboplatin/Paclitaxel in all node-positive women, and chemotherapy only in node negative women with non-endometrioid EC, underwent an additional CT scan following completion of treatment. The SLN-procedure was performed according to a previously published anatomically based surgical algorithm with a strict definition of SLNs; detection of SLNs along parallel pathways (usually to the obturator fossa and external iliac positions) within the upper paracervical pathway (UPP) in all women, and in addition detection of SLN along the lower (presacral) paracervical (LPP) pathway in women with a non-endometrioid histology [5]. A da Vinci® Si or Xi Surgical robot with the FireFly® application was used (Intuitive Surgical, Sunnyvale, CA, USA). A standardised chart depicting the anatomical positions of SLNs was completed intraoperatively by the console surgeon for the estimation of the number of SLNs as perceived by the surgeon (online study protocol). SLNs were processed by IHC and US according to a standardised protocol (online study protocol). The number of SLNs estimated by the pathologist was extracted from the histology report.

Follow-up, including a vaginal ultrasonography, was scheduled at six months intervals until two years post-surgery and performed by a surgeon subspecialized in Gynecologic Oncol-

ogy. A 6–9 MHz vaginal probe by various manufacturers was utilised. A sonolucent or partially echogenic rounded structure without internal doppler flow located at either of the pelvic sidewalls or presacrally was considered to be a lymphocele. In women in whom a postoperative CT scan was performed, the presence of a lymphocele was noted. The study was approved by the Institutional Review Board (Skåne University Hospital, Dnr 2013/163 and 2018/541). Written informed consent was obtained from all enrolled women. Data was continuously entered into a secured Excel database. Descriptive data is presented with numbers and percentage. Statistical analyses were performed in the R statistical environment (version 4.2.3), using multivariable binary logistic regression (<https://www.R-project.org/>). A p -value of 0.05 or lower was considered statistically significant.

3. Results

A pelvic lymphocele was detected in 10 women (2.7%), 80% were asymptomatic or resolved spontaneously resulting in a 0.5% overall risk of requiring a medical or surgical intervention due to lymphocele formation.

A total of 449 women were assessed for eligibility. After excluding women who were lost to follow-up ($n = 53$) or had an incomplete follow-up ($n = 35$) (postoperative controls performed at other hospitals), data from 361 women was included in the final analysis. Demographic and clinical data is presented in Table 1. The bilateral indocyanine green (ICG)-defined mapping rate (at least one SLN per hemipelvis) allowing for reinjection of tracer was 88.3%. The median number of SLNs as perceived by the pathologist was 6 (1–18). No intraoperative complications related to the detection and removal of SLNs occurred. A total of 33 (9.1%) women had nodal metastases including isolated tumor cells (ITC) in their SLNs.

Between 0–12 months after surgery, seven women were diagnosed with pelvic lymphoceles; one of these women had bilateral lymphoceles. The median number of removed SLNs was similar in women with or without lymphocele formation (6 (2–11) vs. 5 (1–18)). Women who developed a lymphocele had a median age of 69 years (range 50–80 years) and a median BMI of 36 kg/m² (range 26–60 kg/m²). In comparison, women without a lymphocele were slightly older, with a median age of 71 years (range 32–92 years), and had a lower median BMI of 29 kg/m² (range 18–58 kg/m²). One woman with a lymphocele received adjuvant treatment, compared with 48 women in the group without a lymphocele. Recurrence occurred in twenty-two women (6.1%); none of these cases occurred in the lymphocele group.

Three women had symptomatic lymphoceles, and intervention was necessary in two of these women (0.5%); one woman was diagnosed with an infected lymphocele 10 days post-surgery that resolved after administration of intravenous antibiotics, and one woman underwent a surgical fenestration at six months post-surgery due to obturator nerve impairment that resolved after surgery. An additional three women were diagnosed with lymphoceles between 13- and 24-months post-surgery, none of whom required intervention. The median size of the lymphocele in women with symptoms was 50 mm (15–

TABLE 1. Demographic and clinical data on 361 women with endometrial cancer operated with robotic hysterectomy and a pelvic sentinel node biopsy.

Characteristics	n (%) or median (range) as appropriate
Age	69 (32–92)
BMI	30 (18–60)
Parity	2 (0–6)
Time for SLN (experienced surgeon, min)	21 (6–55)
Estimated blood loss (mL)	70 (0–1200)
Conversion to laparotomy	2 (0.55%)
Postoperative histology	
Endometrioid adenocarcinoma FIGO I–II	314 (87.0%)
Endometrioid adenocarcinoma FIGO III	14 (3.9%)
Serous adenocarcinoma	18 (5.0%)
Clear cell adenocarcinoma	6 (1.7%)
Carcinosarcoma	4 (1.1%)
Other	5 (1.4%)
Stage (FIGO 2009)	
I	331 (91.7%)
II	7 (1.9%)
IIIA–B	3 (0.8%)
IIIC	19 (5.3%)
IVA–b	1 (0.3%)
Presence of nodal metastases including ITC	33 (9.1%)
Uterine stage (irrespective of nodal status)	
IA	280 (77.6%)
IB	73 (20.2%)
II	8 (2.2%)
Low risk/high	
Preoperatively assessed	259/102 (71.9%/28.1%)
Postoperatively assessed	232/129 (64.4%/35.6%)

BMI: Body Mass Index; SLN: sentinel lymph node; FIGO: International Federation of Gynecology and Obstetrics; ITC: isolated tumor cells.

210 mm) compared with 25 mm (12–90 mm) in women with no symptoms. Lymphoceles in this patient cohort were identified through a combination of imaging modalities. Six were initially detected during a vaginal ultrasound examination; four of the six were subsequently verified by CT scan. Four were identified directly through a primary CT or magnetic resonance imaging (MRI). Anatomically, two lymphoceles were located at the common iliac area, with the remaining nine situated more caudally; a specific distinction between the obturator fossa and

interiliac area was not made. Seven women, presented with unilateral lymphoceles on the left pelvic side wall. One woman had a lymphocele on the right-side wall, and one woman was diagnosed with bilateral lymphoceles. The side distinction was not provided for one woman. In six women the lymphocele resolved spontaneously.

To assess potential risk factors for lymphocele development, a multivariable logistic regression analysis was performed. This analysis evaluated the effects of BMI, age, the number of SLNs removed, and adjuvant treatment. After adjusting for age, the number of SLN removed, and the presence of adjuvant treatment, BMI was determined to be the only independent factor that significantly increased the risk for lymphocele development in this patient group. The analysis yielded an adjusted odds ratio (aOR) for BMI of 1.11, 95% confidence interval (CI) 1.03–1.20, $p = 0.005$. Conversely, the effect of adjuvant treatment was found to be inconclusive due to a low statistical power (aOR = 0.71, 95% CI 0.04–4.09, $p = 0.756$). This lack of statistical power resulted from only one patient in the lymphocele group having received adjuvant treatment (Table 2).

TABLE 2. Adjusted odds ratio for predictors of lymphocele using multivariable logistic regression analysis.

Characteristic	OR	95% CI	<i>p</i> -value
BMI	1.11	1.03–1.20	0.005
Number of Lymph Nodes removed	1.07	0.88–1.26	0.463
Received Adjuvant Treatment	0.71	0.04–4.09	0.756
Patient age	1.00	0.94–1.06	0.971

CI: Confidence Interval; OR: Odds Ratio; BMI: Body Mass Index.

4. Discussion

This prospective study, utilising serial vaginal ultrasonography up to 24 months following sentinel lymph node biopsy in women with endometrial cancer, identified an overall incidence of pelvic lymphoceles of 2.7%. Notably, only 0.5% of all patients required any form of intervention, supporting SLN detection in EC irrespective of preoperative risk assessment.

Our results are comparable to a retrospective study by Diniz *et al.* [16] who found an incidence of 3.4% and a symptomatic rate of 1.1% among 178 patients. Terada *et al.* [12] and Gonçalves *et al.* [17] reported no lymphoceles in their respective cohorts of 201 and 113 patients following SLN removal in patient with EC. The incidence of symptomatic lymphoceles in the present study (0.8%, 3 of 361 women) was comparable to that reported by Diniz *et al.* [16] (1.1%, 2 of 178 women who underwent SLN mapping only). The median age in the present study was higher (69 years versus 59 years, respectively), while the median BMI was similar (30 kg/m² versus 29 kg/m², respectively). Established risk factors for lymphatic complications include a greater number of resected lymph nodes, smoking, the presence of metas-

tases, postoperative radiotherapy, higher BMI, and advanced age [6, 18, 19]. In the present study, only increased BMI was associated with lymphocele development. We found no association with the number of resected SLNs, the presence of metastases, adjuvant treatment, or advanced age. The absence of lymphoceles in the study by Terada *et al.* [12] may be explained by their lower mean age and BMI (56 years vs. 69 years and 25 kg/m² vs. 30 kg/m²) compared to our cohort. While Terada *et al.* [12] used a comparable follow-up method, including serial vaginal ultrasonography, Goncalves *et al.* [17] did not specify their detecting method and relied partly on telemonitoring due to the Covid pandemic. Diniz *et al.* [16] included pelvic and abdominal imaging examinations every 3–4 months for the first 2 years. Although this reduces the risk for interobserver variability. According to Swedish guidelines, the follow-up focuses instead on clinical control, thorough assessment of symptoms, and optional supplementary examinations for low-risk disease. CT or other advanced imaging is reserved for patients with a high risk of recurrence (based on risk stratification after surgery) or when symptoms/clinical findings strongly suggest a recurrence [2]. Comparing the rates of pelvic lymphoceles across different surgical studies is challenging due to a lack of standardization in methodology, including interobserver variability in diagnosis and whether detection is based on symptoms or routine imaging screening.

Several studies confirm that SLN-only procedures lead to a significant reduction in lymphatic complications compared to full lymphadenectomy, resulting in an overall low rate of lymphoceles. Most lymphoceles are incidental findings with no clinical impact although intervention rates of up to 50% have been reported [6, 12, 17–20]. In our cohort, 20% of women with a lymphocele (0.5% of all patients) needed intervention compared to 33.3% in the study by Diniz *et al.* [16].

Most lymphoceles developed caudally in the pelvic with the potential risk of symptoms arising from the obturator nerve. In the present study, the overall risk was low and only one woman (0.25%) needed intervention due to obturator nerve involvement. As shown in previous studies from our institution, this location is also the most probable site for harbouring SLN metastases, and it is therefore essential that an optimal SLN algorithm incorporates SLN detection in the obturator fossa [21].

The strengths of this study are the prospective design, serial ultrasound examination of all women regardless of symptoms, and strict adherence to a defined SLN algorithm including removal of SLNs from both the external iliac position and the obturator fossa. A primary weakness of this study is the high rate of women lost to follow-up, as many patients attended clinical controls at remote referring hospitals. This potential underestimation of the true lymphocele incidence introduces a reporting bias. Although surgical interventions for lymphoceles are performed exclusively at our institution, thereby making it probable that complicated cases were referred, the lack of certainty remains a notable limitation when interpreting the results. Furthermore, despite all patients being examined by experienced gynecologic oncologists, a limitation is the inherent interobserver variability in lymphocele diagnosis and the absence of a standardized reporting system. This variabil-

ity necessitates reliance on individual clinical experience and diagnostic criteria. To mitigate the risk of misdiagnosis, the finding was confirmed or primarily diagnosed by a CT or MRI in eight of ten patients.

Although most lymphoceles develop within 6 months post-surgery, three women developed a lymphocele between 12 and 24 months after the procedure. Although this was also reported by Goncalves *et al.* [17], adhesion-caused peritoneal fluid accumulation might have been misdiagnosed as a lymphocele in these women.

5. Conclusions

This study provides prospective 12- and 24-months data on a large cohort of women systematically screened using vaginal ultrasound regardless of symptoms. The development of a lymphocele was positively associated with increased BMI. The risk of nodal spread was 18 times higher than the risk of developing a pelvic lymphocele needing intervention which is reassuring in the context of detecting pelvic SLNs in women with an estimated low risk of pelvic metastases.

AVAILABILITY OF DATA AND MATERIALS

The data cannot be shared due to ethical restrictions.

AUTHOR CONTRIBUTIONS

CL—confirms she has full access to all data in the study and has the final responsibility for the decision to submit the manuscript; contributed to study design, data acquisition, analysis, and interpretation as well as writing and revising of the draft, and the final approval of the manuscript. DM—contributed to study design, data acquisition, analysis, and interpretation as well as writing and revising of the draft, and the final approval of the manuscript. MB—contributed to data acquisition, analysis, and interpretation as well as revising of the draft, and the final approval of the manuscript. BG—contributed to data acquisition, analysis, and interpretation as well as revising of the draft, and the final approval of the manuscript. All authors have given their written permission to publish the manuscript in its present form.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Review Board (Skåne University Hospital, Dnr 2013/163 and 2018/541). Written informed consent was obtained from all enrolled women.

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CONFLICT OF INTEREST

Celine Lönnerfors has received honoraria from Intuitive Surgical for proctoring and lectures in robot assisted surgery. Celine Lönnerfors has no other relevant financial interests, activities, relationships or affiliations. No disclaimers for any of the other co-authors or relatives of any of the authors.

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