Gynecologic Oncology 170 (2023) 273–281

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Lymphocele following lymph node dissection in cervical and endometrial cancer: A systematic review and meta-analysis

A. Jansen [a], A. de Jong [a], J.P. Hoogendam [a], I.G.T. Baeten [a], I.M. Jürgenliemk-Schulz [b], R.P. Zweemer [a], C.G. Gerestein [a,*]

[a] Department of Gynecologic Oncology, Division of Imaging and Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[b] Department of Radiation Oncology, Division of Imaging and Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

HIGHLIGHTS

- The pooled proportion for the overall lymphocele is more than four times as high (14%) as for symptomatic lymphoceles (3%).
- Laparotomic surgical approach and additional para-aortic lymph node dissection were risk factors for developing lymphoceles.
- Decreased number of lymph nodes was also a risk factor for developing lymphoceles.

ARTICLE INFO

Article history:
Received 5 October 2022
Received in revised form 31 December 2022
Accepted 17 January 2023
Available online xxxx

Keywords:
Lymphocele
Endometrial neosplasms
Uterine cervical neoplasms
Lymph node excision
Systematic review
Meta-analysis

ABSTRACT

Objectives. The purpose of this systematic review and meta-analysis was to evaluate the proportion and risk factors of lymphoceles and symptomatic lymphoceles after PLND in early-stage cervical and early-stage high or high-intermediate risk endometrial cancer.

Methods. Studies reporting on the proportion of lymphocele after PLND were conducted in PubMed, Embase and Cochrane Library. Retrieved studies were screened on title/abstract and full text by two reviewers independently. Quality assessment was conducted using the Newcastle Ottowa Scale and the Cochrane risk-of-bias tool. Proportion of lymphocele and possible risk factors were pooled through random-effects meta-analyses.

Results. From the 233 studies retrieved, 24 studies were included. The pooled proportion of lymphocele was 14% and of symptomatic lymphocele was 3%. Routinely performing diagnostics was associated with a significantly higher proportion of lymphocele compared to diagnostics performed on indication (21% versus 4%, $p < 0.01$). Laparotomic surgical approach led to a significantly higher proportion of lymphoceles than laparoscopic surgical approach (18% versus 7%, $p = 0.05$). The proportion of lymphocele was significantly higher when >15% of the study population underwent additional paraaortic lymph node dissection (PAOLND) opposed to <15% (15% versus 3%, $p < 0.01$). A mean number of lymph nodes dissected of <21 resulted in a significantly higher pooled proportion of lymphoceles opposed to when the mean number was 21 or higher (19% versus 5%, $p = 0.02$). Other risk factors analysed were BMI, lymph node metastasis, adjuvant radiotherapy and follow up. There was no sufficient data to detect significant risk factors for the development of symptomatic lymphoceles.

Conclusion. The pooled proportion of lymphocele was 14% of which symptomatic lymphoceles occurred in 3%. Significant risk factors for the total proportion of lymphoceles were laparotomic approach, decreased number of lymph nodes dissected and additional PAOLND.

* Corresponding author at: Department of Gynecological Oncology, Division of Imaging and Oncology, University Medical Centre Utrecht, F05.126, PO Box 85500, Utrecht 3508 GA, the Netherlands.
E-mail address: C.G.Gerestein-2@umcutrecht.nl (C.G. Gerestein).

https://doi.org/10.1016/j.ygyno.2023.01.022

Contents

1. Introduction

In the treatment of early-stage cervical cancer and early-stage high or high-intermediate risk endometrial cancer, pelvic lymph node dissection (PLND) is widely used to identify lymph node metastasis and determine the need for adjuvant therapy [1,2]. PLND is associated with postoperative morbidity, such as pelvic lymphocele and lower extremity lymphedema [3].

A lymphocele is defined as lymphatic-filled cystic lesion [4]. The peak incidence for lymphoceles is found at three to eight weeks after surgery, yet some develop after one year [5]. Where most asymptomatic and small uninfected lymphoceles regress spontaneously [5,6], large or symptomatic lymphoceles are an indication for treatment. Symptomatic lymphoceles present with pelvic pain, infection, lower urinary tract symptoms, leg edema, deep vein thrombosis and other symptoms related to compression of adjacent structures [5–7]. Additionally, symptomatic lymphoceles are associated with prolonged hospitalization and may cause a delay in onset of adjuvant therapy [8]. Certain risk factors for the development of (symptomatic) pelvic lymphoceles after PLND are reported, such as body mass index (BMI), prophylactic use of subcutaneous heparin, surgical approach (i.e. laparotomy or laparoscopy), number of lymph nodes dissected, presence of lymph node metastasis and adjuvant radiotherapy [6].

In literature, the incidence of lymphocele after PLND for patients with gynecological malignancies varies from 1% to 58%. For symptomatic lymphoceles the incidence varies from 5% to 18% [6]. The majority is asymptomatic and found during routine follow-up [9,10].

The aim of this systematic review and meta-analysis is to provide an updated overview of the incidence and risk factors for lymphoceles after PLND in early-stage cervical cancer and high- or high-intermediate risk endometrial cancer.

2. Methods

2.1. Systematic search

We systematically searched PubMed, Embase and Cochrane library databases for relevant data on lymphocele after PLND in patients with early-stage cervical cancer and high- or high-intermediate risk endometrial cancer [1,2]. We conducted the search on August the 14th 2022 using the following terms: “lymphocele”, “lymphocyst”, “lymph node dissection”, “lymphadenectomy”, “uterine neoplasms”, “endometrial cancer” and “cervical cancer”. Synonyms and alternative spellings were included, as well as the corresponding MeSH and Emtree terms.

2.2. Eligibility criteria

All studies were screened on title and abstract by two independent reviewers (AJ and AdJ). Discrepancies were resolved by consensus discussion and a third reviewer (CGG). The inclusion criteria for the individual studies required that a PLND had been performed on patients with clinically FIGO stage IA1-IB2 or IIA1 cervical cancer or FIGO stage I-II endometrial cancer [11,12]. Furthermore, studies had to report the proportion of identified lymphoceles. Studies were excluded if the full-text version was irretrievable, were not written in English, did not report original data, were case-reports or non-human studies. Full-text screening of the potential eligible studies was performed by two independent authors.

2.3. Quality assessment

We used the Newcastle Ottowa Scale (NOS) to assess study quality for case-control and cohort studies [13]. The NOS evaluates the risks of bias using nine domains within three categories. Each domain was

assigned with low risk, high risk or not applicable. Points were given for each domain assigned with low risk and a total score was calculated, with a maximum score of 9. A study score of 8 or 9 was considered as low risk of bias, 6 or 7 as moderate risk of bias and 5 or lower as high risk of bias. Studies with a score of 5 or lower were excluded from this review.

The Cochrane risk-of-bias tool for randomized trials version 2 (RoB2) was used to assess the quality of randomized controlled trials (RCT) [14]. This tool evaluates the risk of bias on five different domains: randomization, deviations from intervention, missing outcome data, measurement of outcome, and selection of reported result. All domains were assigned with either low risk, some concerns, or high risk. If all domains were assigned with low risk, an overall low risk of bias was considered. If one domain was assigned with some concerns, an overall score of moderate risk was considered. If two domains were assigned with some concerns or if one domain was assigned with high risk, an overall high risk of bias was considered. Studies with an overall high risk of bias were excluded from this review. The Risk-of-bias VISualization (robvis) tool was used to create the traffic light plots to visually summarize the quality assessment [15].

2.4. Data collection

To collect the data, a data extraction sheet was created in advance. The following data were collected of each study: 1) author and publication details; 2) inclusion period; 3) study design; 4) sample size of study population; 5) type of disease; 6) type of diagnostic procedure (i.e. routine or indication); 7) median or mean BMI; 8) type of surgical approach (i.e. laparotomy, laparoscopy, robot-assisted laparoscopy); 9) type of lymph node dissection (i.e. PLND with or without paraaortic lymph node dissection (PAOLND)); 10) median or mean number of lymph nodes dissected; 11) percentage of patients with lymph node metastasis; 12) percentage of patients who received adjuvant radiotherapy; 13) lymphocele events; 14) symptomatic lymphocele events; and 15) median or mean follow-up duration in months.

The primary outcome of interest was the proportion of pelvic lymphocele after PLND for cervical and endometrial cancer. Pelvic lymphocele was subdivided in asymptomatic and symptomatic lymphocele. Symptomatic lymphocele was defined as a lymphocele with symptoms related to compression of adjacent structures, pelvic pain and/or infection, lower urinary tract symptoms, leg edema or occurrence of deep vein thrombosis. Secondary outcomes were the proportions of lymphocele with respect to follow-up rate, detection by routine diagnostics or diagnostics on indication, and possible risk factors.

2.5. Statistical analysis

The individual proportions and 95% confidence intervals were calculated for all studies. To determine cut-off value of subgroups the mean or median was calculated. The proportions of the individual studies were pooled using a random-effects model and transformed using the Freeman-Tukey Double arcsine transformation. I^2 index and chi-squared test were performed to assess heterogeneity. Forest plots were created to visually summarize the results. We used a randomized effect model to test for subgroup differences. *P*-values between subgroups were calculated using the Chi-square test to determine whether a statistically significant association was found. A P-value ≤0.05 was deemed significant. Mixed effect meta-regression was conducted to further study covariates (e.g. BMI) and their association with the outcome of interest, e.g. lymphocele prevalence [16]. Covariate data was derived from the baseline data from each included study. The obtained regression coefficient and *p*-value from the meta-regression quantifies the strength and statistical significance of this association (continues covariate) of the difference between subgroups (categorical covariate). All meta-analyses were performed using the statistical software R version 4.1.2 (2021-11-01, R Foundation for Statistical Computing, Vienna, Austria) attached with the 'meta' package version 5.2.0, created by G. Schwarzer, and the 'metafor' package version 3.0.2, created by W. Viechtbauer.

3. Results

3.1. Systematic search and quality assessment

Fig. 1 shows an overview of the systematic search. We retrieved 233 studies, of which 125 studies were excluded based on title and abstract screening and 78 studies were excluded based on full-text screening (Supplement 1). Studies were excluded when inclusion criteria were not met ($n = 32$), full text was irretrievable ($n = 23$) or not written in English ($n = 15$). A subsequent 30 studies underwent quality assessment, whereof six case-control and cohort studies had a NOS of 5 or lower and were excluded due to their high risk of bias (Supplement 2). Five out of the six studies described single-armed cohort studies, which were excluded by the NOS tool due to missing data of a control arm (Supplement 3). In the sixth study, quality issues were raised due to missing or unreported data. Of the remaining studies, ten studies were assessed as having a low risk of bias [3,17–25] and 14 studies were assessed as having a moderate risk of bias [5,7,26–33] (Supplement 4). A total of 24 studies were included in the quantitative analysis, of which the characteristics are shown in Table 1.

3.2. Overall lymphocele incidence

A total of 2258 patients (24 studies) with endometrial or cervical cancer who underwent PLND were included in the meta-analysis. Pelvic lymphocele was diagnosed in 329 patients (15%). The incidence varied from 1% to 57% between the individual studies, with a pooled proportion of 14% (95%CI: 9%-.

20%) for developing a pelvic lymphocele as postoperative complication of PLND (Fig. 2). A meta-regression analysis showed no significant association between the proportion of patients with a lymphocele and the median follow-up rate ($p = 0.28$).

3.3. Asymptomatic lymphocele

A total of 1126 patients (13 studies) were investigated on the presence of asymptomatic lymphocele. Transvaginal and/or transabdominal ultrasound (11 studies) and CT-scan (2 studies) were used within the individual studies to diagnose lymphoceles. The incidence of asymptomatic lymphoceles varied from 0% to 46%, with a pooled proportion of 16% (95%CI: 8%–26%) (Supplement 5).

3.4. Symptomatic lymphocele

A total of 1326 patients (16 studies) were investigated on the presence of a symptomatic lymphocele. The incidence of symptomatic lymphoceles varied from 0% to 32% within the individual studies and corresponded to a pooled proportion of 3% (95%CI: 1%–6%) (Supplement 6).

3.5. Routine diagnostics versus diagnostics performed on indication

A total of 1291 patients (14 studies) underwent routine diagnostics to detect lymphoceles. Interval between surgery and first diagnostic measures for lymphocele detection varied from one day to one year. This corresponded to a pooled proportion of lymphoceles of 21% (95% CI: 13%–30%). A total of 493 patients (7 studies) underwent additional diagnostics based on indication to detect lymphoceles. This corresponded to a pooled proportion of lymphoceles of 4% (95%CI: 0%–12%). The difference in proportions between the two types of diagnostic procedures was found to be significant ($p < 0.01$) (Supplement 7).

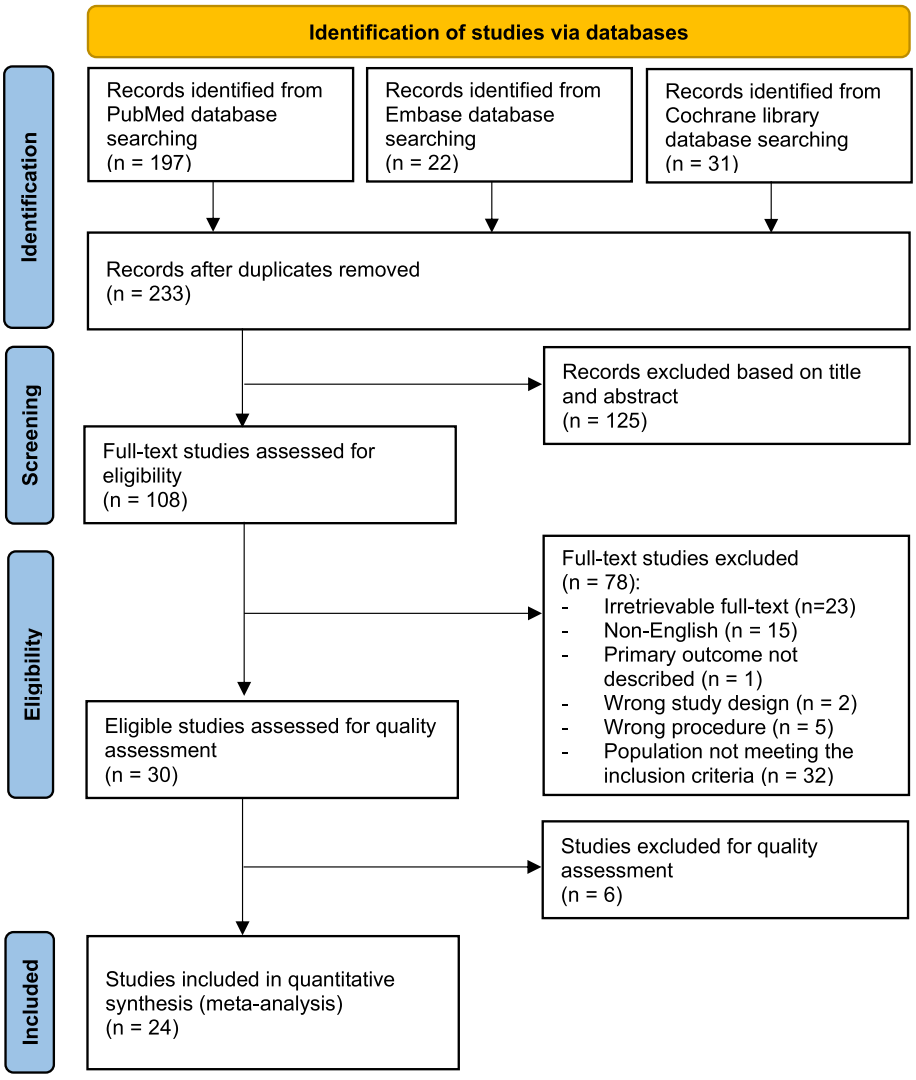

Fig. 1. PRISMA flow diagram of the systematic search.

Performing routine diagnostics did not result in a higher proportion of symptomatic lymphoceles (Supplement 8).

3.6. Risk factors overall lymphocele

Table 2 shows the pooled proportion of lymphoceles in the subgroup meta-analyses by surgical approach, percentage of patients with adjuvant radiotherapy, percentage of patients with metastatic lymph nodes, number of lymph nodes dissected, BMI and percentage of patients with additional PAOLND. Additional subgroup analysis between type of cancer and geographical regions has been conducted but will not be further discussed due to no significant associations.

3.6.1. Surgical approach

A total of 1087 patients (14 studies) underwent laparotomic PLND. This corresponded to a pooled proportion of lymphoceles of 18% (95% CI: 11%–28%). A total of 713 patients from 12 studies underwent laparoscopic PLND. This corresponded to a pooled proportion of lymphoceles of 7% (95%CI: 2%–15%). Lymphoceles occurred significantly less often in de laparoscopy group ($p = 0.05$) (Table 2).

3.6.2. Adjuvant radiotherapy

We divided the studies that reported the percentage of patients with adjuvant radiotherapy in two subgroups using the median percentage of 21%. Subgroup analysis did not provide a significant difference between the two subgroups ($p = 0.30$) (Table 2). Additionally meta-regression analysis did not provide a significant association between radiotherapy and the incidence of lymphocele ($p = 0.14$).

3.6.3. Lymph node metastasis

Percentage of patients with metastatic lymph nodes were described in 12 studies. We divided the subgroups using the median of 10%. Studies of which the percentage of patients with metastatic lymph nodes was 10% or more showed a pooled proportion of lymphoceles of 17% (95%CI: 7%–30%) in contrast studies <10% metastastic lymph nodes corresponded to a pooled proportion of lymphoceles of 5% (95%CI: 0%–16%). ($p = 0.13$) (Table 2) Meta-regression analysis also did not result in a statistically significant association ($p = 0.32$).

3.6.4. Number of lymph nodes dissected

Mean number of lymph nodes dissected was reported in 18 studies. The mean number of lymph nodes dissected varied from 16 to 32. Subgroup analysis with the median number of lymph nodes dissected

Table 1
Table showing the characteristics of included studies.

No.	Author	Region	Year	Inclusion period	Study design	Disease	Diagnosis	Surgery	Surgical approach	N total	N lymphocele	Follow-up duration**
1	Kakubari et al. [24]	Asia	2022	2010–2016	Retrospective	CC, EC	Routine	PLND	LT, LS	196	29	59 (LT) and 36 (LS)
2	Wrobel et al. [22]	Europe	2021	2013–2014	Prospective	CC, EC	Routine	PLND	LT	50	22	12
3	Wedin et al. [17]	Europe	2020	2014–2018	Prospective	EC	Routine	PLND, PAOLND	LT, LS, RALS	116*	16	12
4	Togami et al. [3]	Asia	2020	2007–2017	Retrospective	EC	NA	PLND	LT, LS	230*	22	NA
5	Togami et al. [16]	Asia	2018	2007–2017	Retrospective	CC	NA	PLND	LT, LS, RALS	112*	22	NA
6	Tinelli et al. [33]	Europe	2016	2009–2015	Retrospective	EC	Indication	PLND, PAOLND	LS	110	1	38,5
7	Hao et al. [27]	Asia	2016	2011–2013	Prospective	CC	Routine	PLND	LS	45	2	23
8	Bifulco et al. [28]	Europe	2014	2011–2012	Prospective	CC, EC	Routine	PLND	LT	41*	15	3
9	Tinelli et al. [29]	Europe	2013	2010–2012	Prospective	EC	Routine	PLND	LS	29*	15	3
10	Tinelli et al. [30]	Europe	2012	2008–2010	Prospective	EC	Routine	PLND	LT	28*	16	3
11	Ghezzi et al. [7]	Europe	2012	2002–2010	Prospective	EC	Routine	PLND	LT, LS	261	21	83 (LT) and 27 (LS)
12	Gallotta et al. [23]	Europe	2010	2008–2009	Prospective	CC, EC	Routine	PLND	LS	30	9	NA
13	Camanni et al. [34]	Europe	2010	2005–2007	Retrospective	EC	Indication	PLND	LS	34*	1	1
14	Park et al. [18]	Asia	2010	1998–2007	Retrospective	CC	Routine	PLND	LT, LS	145*	30	NA
15	Hilaris et al. [25]	Europe	2009	2004–2008	Prospective	CC, EC	Indication	PLND, PAOLND	LS	25	2	1
16	Ko et al. [19]	North America	2008	2004–2007	Retrospective	CC	Indication	PLND	LT, RALS	48	1	NA
17	Han et al. [35]	Asia	2008	2000–2006	Retrospective	EC	NA	PLND, PAOLND	LT	132	9	NA
18	Hertel et al. [36]	Europe	2006	1995–2005	Prospective	CC	Indication	PLND, PAOLND	LS	100	1	29
19	Larciprete et al. [20]	Europe	2006	1999–2003	Retrospective	CC	Indication	PLND, PAOLND	LT, LS	42	1	NA
20	Kim et al. [5]	Asia	2004	1999–2003	Retrospective	CC, EC	Indication	PLND, PAOLND	LT	134*	24	NA
21	Srisomboon et al. [31]	Asia	2002	1999–2000	Prospective	CC	Routine	PLND	LT	100	8	2,8
22	Logmans et al. [21]	Europe	1999	1992–1994	Prospective	CC	Routine	PLND	LT	10*	0	12
23	Franchi et al. [32]	Europe	1997	1991–1995	Prospective	CC, EC	Routine	PLND	LT	120	58	1,8
24	Patsner [26]	North America	1995	1987–1994	Prospective	CC	Routine	PLND	LT	120	4	1,4

EC: endometrial cancer, CC: cervical cancer, PLND: pelvic lymph node dissection, PAOLND: paraaortic lymph node dissection, LT: laparotomy, LS: laparoscopy, RALS: robot-assisted laparoscopy.
* = population within larger cohort meeting the inclusion criteria. ** = mean/median follow-up duration in months.

($n = 22$) did not result in a statistically significant association between ($p = 0.06$). (Supplement 15) However, a secondary meta-regression provided a statistically significant association between the mean number of lymph nodes dissected and the proportion of lymphoceles ($p = 0.03$). Indicating a lower proportion of lymphoceles with an increased number of lymph nodes dissected. Subgroup analysis with a cut-off point of 21 dissected lymph nodes resulted in a significant association between a lower proportion of lymphoceles and an increased number of lymph nodes dissected (5% vs 19%, $p = 0.02$, see Table 2). Additional subgroup analysis was carried out with cut-off points between 17 and 23. The subgroup analysis with a cut-off point of 17–21 all resulted in a significant association between lower proportion of lymphoceles and an increased number of lymph nodes dissected.

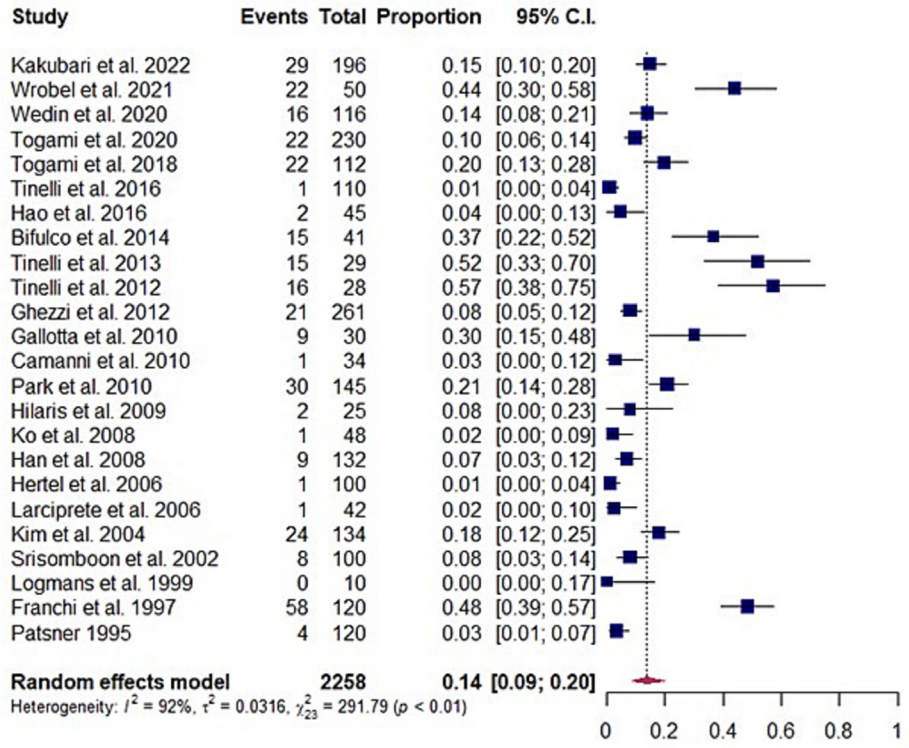

Fig. 2. Forest plot showing the proportion of lymphoceles in all studies included.

Table 2
Table showing the association between risk factors and incidence of lymphocele in subgroup analysis.

Risk factor	No of studies	No of patients included	Pooled proportion of lymphocele (95% CI)	Heterogeneity I^2 (%)	Subgroup differences (p value)	Supplement
Surgical approach				93	0.05	Supplement 9
Laparotomy	14 (5, 7, 18, 19, 20, 21, 22, 24, 26, 28, 30, 31, 32, 35)	1087	0.18 (0.11–0.28)			
Laparoscopy	12 (7, 18, 19, 20, 23, 24, 25, 27, 29, 33, 34, 36)	713	0.07 (0.02–0.15)			
Adjuvant radiotherapy (%)				93	0.30	Supplement 11
≥ *21%*	4 (7, 24, 25, 32)	512	0.18 (0.06–0.36)			
< *21%*	4 (17, 19, 24, 27)	299	0.08 (0.00–0.22)			
Metastatic lymph nodes (%)				92	0.13	Supplement 13
≥ *10%*	7 (17, 20, 25, 29, 31, 32, 35)	564	0.17 (0.07–0.30)			
< *10%*	5 (19, 21, 24, 27, 33)	409	0.05 (0.00–0.16)			
Lymph nodes dissected (*n*)				90	0.02	Supplement 16
≥ *21*	10 (17, 20, 21, 24, 25, 26, 27, 31, 33, 34)	776	0.05 (0.01–0.12)			
< *21*	8 (7, 19, 20, 23, 29, 30, 32, 36)	638	0.19 (0.09–0.30)			
BMI (kg/m^2)				90	0.27	Supplement 18
≥ *25*	10 (7, 17, 19, 22, 23, 25, 28, 29, 30, 33)	607	0.15 (0.07–0.26)			
< *25*	6 (7, 20, 24, 25, 27, 36)	514	0.07 (0.01–0.19)			
Additional PAOLND (%)				83	<0.01	Supplement 20
≥ *15%*	3 (5, 17, 25)	275	0.14 (0.09–0.21)			
< *15%*	3 (20, 35, 36)	274	0.03 (0.01–0.07)			

3.6.5. BMI

Subgroup and meta-regression analysis did not show a significant difference in proportion of lymphoceles related to BMI.

3.6.6. PAOLND

The percentage of patients who underwent PAOLND in addition to PLND was reported in six studies. We divided the studies who reported the percentage of patients with PAOLND in two subgroups using the median percentage of 15%. A total of 275 patients (three studies) of which the percentage of patients with additional PAOLND was 15% or more were investigated on the incidence of lymphoceles. This corresponded to a pooled proportion of lymphoceles of 14% (95%CI: 9%–21%). A total of 274 patients from three studies of which the percentage of patients with additional PAOLND was <15% were investigated on the incidence of lymphoceles. This corresponded to a pooled proportion of lymphoceles of 3% (95%CI: 1%–7%). A subgroup analysis resulted in a statistically significant association between the two subgroups ($p < 0.01$) (Table 2). A secondary meta-regression analysis also provided a statistically significant association between the percentage of patients who had undergone additional PAOLND and the proportion of lymphoceles ($p < 0.01$). This indicated that the proportion of lymphoceles is higher when PLND is combined with PAOLND.

3.7. Risk factors symptomatic lymphocele

Table 3 shows the pooled proportion of symptomatic lymphoceles in the subgroup meta-analysis. Subgroup analysis showed no statistically significant association between laparotomic or laparoscopic approach for symptomatic lymphoceles ($p = 0.70$) (Table 3). Only one study in the laparoscopic subgroup described results of robot-assisted laparoscopic PLND. This study reported one patient (6%) with a symptomatic lymphocele.

Furthermore, subgroup and meta-regression analysis on adjuvant radiotherapy, lymph node metastasis, number of lymph nodes dissected, BMI and additional PAOLND did not show any significant difference in proportion of symptomatic lymphoceles (Table 3).

Table 3
Table showing the association between risk factors and incidence of symptomatic lymphocele in subgroup analysis.

Risk factor	No of studies	No of patients included	Pooled proportion of symptomatic lymphocele (95% CI)	Heterogeneity, I^2 (%)	Subgroup differences (p value)	Supplement
Surgical approach				73	0.70	Supplement
Laparotomic	11 (7, 19, 20, 21, 22, 24, 26, 28, 30, 31, 32)	752	0.04 (0.01–0.08)			10
Laparoscopic	9 (7, 18, 19, 20, 23, 24, 25, 29, 33)	444	0.03 (0.00–0.07)			
Adjuvant radiotherapy (%)				80	0.60	Supplement
≥ *21%*	4 (7, 24, 25, 32)	512	0.04 (0.00–0.10)			12
< *21%*	3 (17, 19, 24)	254	0.02 (0.00–0.08)			
Metastatic lymph nodes (%)				79	0.28	Supplement
≥ *10%*	6 (17, 20, 25, 29, 31, 32)	432	0.01 (0.00–0.05)			14
< *10%*	4 (19, 21, 24, 33)	364	0.04 (0.00–0.10)			
Lymph nodes dissected (*n*)				75	0.24	Supplement
≥ *21*	8 (17, 20, 21, 24, 25, 26, 31, 33)	697	0.02 (0.00–0.05)			17
< *21*	7 (7, 19, 20, 23, 29, 30, 32)	538	0.05 (0.02–0.10)			
BMI (kg/m^2)				85	0.81	Supplement
≥ *25*	10 (7, 17, 19, 22, 23, 25, 28, 29, 30, 33)	607	0.07 (0.02–0.14)			19
< *25*	4 (7, 20, 24, 25)	369	0.05 (0.00–0.16)			
Additional PAOLND (%)				18	0.14	Supplement
≥ *15%*	2 (17, 25)	141	0.00 (0.00–0.01)			21
< *15%*	1 (20)	42	0.02 (0.00–0.10)			

4. Discussion

The pooled proportion of pelvic lymphoceles after PLND for cervical and endometrial cancer was 14%; the pooled proportion rate of symptomatic lymphoceles was 3%. The pooled proportion for the overall lymphocele was more than four times as high as for symptomatic lymphoceles. Meta-analysis did not show an association between follow up duration and the incidence of lymphocele. Routine diagnostics resulted in a higher proportion of lymphocele likely by diagnosing non clinically relevant lymphoceles. Significant risk factors for lymphocele were surgery laparotomic approach, decreased lymph nodes dissected and additional PAOLND.

Symptomatic lymphoceles are clinically more relevant since they can lead to significant morbidity and often need a therapeutic intervention [34]. Symptomatic lymphoceles could cause prolonged hospitalization and a delay in onset of adjuvant oncological therapy [8,9]. The primary treatment for symptomatic lymphocele is percutaneous catheter drainage [10]. Alternative treatment includes percutaneous fine needle aspiration, sclerotherapy and surgical marsupialization. Percutaneous catheter drainage in combination with antibiotics showed to be an effective therapeutic strategy with high success rate for treating infected lymphoceles [35].

Routinely performed diagnostics identified more lymphoceles opposed to diagnostics performed on indication only. Between routine diagnostics and diagnostics performed only on indication there was no significant association found for the proportion of symptomatic lymphocele. In practice, diagnostics on indication are often performed, which is sufficient to detect symptomatic lymphoceles. Since lymphoceles are underreported when performing diagnostics on indication, we advise physicians to be more aware of this complication and perform diagnostics when patients develop symptoms related to compression of adjacent structures, pelvic pain and/or infection, lower urinary tract symptoms, leg edema or deep vein thrombosis postoperatively after PLND.

Most of the included studies used transvaginal ultrasound as measurement of lymphocele. Ultrasound is often implemented as the first choice of imaging in practice and is therefore a representative measurement of the studied outcome. One study described how features of symptomatic and asymptomatic differ on ultrasound, which makes it possible to diagnose if or which lymphocele causes symptoms [36]. In practice, the distinction between asymptomatic and symptomatic lymphocele is mainly made based on physical examination and anamnesis. Furthermore, accuracy of ultrasound depends on the experience of the sonographer and may impact the results. There is no clear definition of what sufficient expertise is and how to compare the accuracy of different sonographers. Therefore, expertise of the sonographer may cause between-study variance. Due to lack of data, we were not able to correlate our results with other imaging modalities (i.e. computed tomography and magnetic resonance imaging).

In this meta-analysis we showed laparotomy as surgical approach to be associated with an increased risk of lymphocele. The lower incidence of lymphoceles in laparoscopic surgery could be associated with less tissue damage, reduced peritoneum handling and tissue bleeding, less contamination and less postoperative adhesions compared to laparotomic surgery [7,37–40].

PAOLND was found to be a risk factor for developing lymphoceles in this meta-analysis. It should be noted that this analysis was carried out on a small subgroup and additional PAOLND is only carried out in around 83 patients. In addition, by lack of insight into original data of these studies, it is not possible to look at the incidence of lymphocele per patient which has undergone PAOLND. The small subanalysis and the fact that analysis is carried out over the entire group may cause bias by inhomogeneity. A possible explanation of PAOLND as a risk factor for lymphocele could be the extended damage of the lymph drainage and storage system by removing lymph nodes in multiple subsequent areas and in this way decreasing the number of adjacent lymph nodes to take over. Approved risk stratification by molecular classification and performing sentinel lymph node (SLN) procedure instead of PAOLND and PLND in endometrial and cervical cancer could decrease morbidity in these patients [2,41–44]. SLN detection is demonstrated to be a safe replacement for full lymphadenectomy in FIGO stage I-II endometrial cancer and adding full lymphadenectomy would not reduce the risk of recurrence [45–48]. An SLN procedure decreases the risk of lymphocele formation and in low-risk endometrial cancer it is associated with a lower incidence of leg edema [49–51].

Our results on BMI and lymph nodes dissected were remarkable compared to previous literature. Multiple previous studies identified high BMI as a risk factor for lymphocele and lymphedema formation [5,18,52–54], whereas we could not confirm such association. Also, this analysis showed an association between number of lymph nodes dissected lower than 21 and incidence of lymphocele. When looking at previous studies, a higher number of lymph nodes removed is a risk factor for lower extremity edema. Although it remains unclear to which degree the number of lymph nodes removed attributes to the formation of lymphocele, we would expect a similar association regarding lymphocele [5,53–55]. Despite the fact that our findings do not correspond to what is described in literature and we have to be careful in drawing conclusions, our results could be supported by the following two hypotheses. Firstly, operating more radically may result in diffuse lymph drainage problems, leading to lower extremity edema, but does not automatically mean that more local problem such as a lymphocele occur. Secondly, when a surgeon removes more lymph nodes, it could be that more collateral lymphatic pathways develop which could decrease the formation of lymphocele.

Possible surgical techniques and materials are described to prevent the development of lymphoceles: nonperitonization (i.e. leaving the peritoneum open after PLND), not inserting a drain postoperatively, and the use of fibrin application or synthetic glues [9,19,29,56–58]. Nonperitonization may reduce the incidence of lymphocele by allowing lymphatic fluid to drain into the abdominal cavity where it can be absorbed by the peritoneum and omentum [56,59]. A retrospective cohort study and prospective randomized study confirmed that the formation of lymphoceles was significantly lower when the peritoneum was left open. After nonperitonization, it is common to insert a drain into the peritoneum to release the excess of lymphatic fluid after lymph node dissection. Paradoxically, drainage of the peritoneum is associated with a higher risk of lymphocele formation. Charoenkwam et al. described a higher rate of overall and symptomatic lymphoceles formation in patients in whom drainage was applied compared to patients in whom only nonperitonization was performed [60]. Drainage may cause irritation of the peritoneum, which decreases the capacity of resorption. Fibrin applications (e.g. TachoSil) and synthetic glues (e.g. synthethic cyanoacrylic glue) were originally developed as an adjunct to control bleeding during surgery. Beside hemostatic properties, it is also described to have adhesive properties which may be beneficial regarding lymph fluid leaks and lymphocele formation. Fibrin application reduced the proportions of overall lymphocele and symptomatic lymphocele, as stated in a meta-analysis by Gasparri et al. [58] Bifulco et al. established a statistically lower incidence of lymphoceles when synthetic cyanocrylic glue was applied opposed to the control group [29]. Throughout the analysis it is notable that Tinelli et al. (2012), Tinelli et al. (2013), Franchi et al. and Wrobel et al. report higher proportions of lymphoceles, respectively 57%, 52%, 48% and 44%, as opposed to other individual studies within the analysis. These studies might pay more attention to the development of lymphocele as they all investigate prevention techniques such as the use of fibrin application and nonperitonization. Therefore, more cases of asymptomatic lymphoceles could be reported. This could have led to publication bias.

We applied a random-effects model to compensate for the studies heterogeneity regarding the population and procedure. For every outcome, the pooled proportion of symptomatic lymphoceles was separately analysed as it is clinically more relevant. Also, a subgroup

analysis between routine diagnostics and diagnostics on indication was performed to determine whether it had impact on the proportions of lymphocele. Furthermore, quality assessment was performed to exclude studies with a high risk of bias. Still, results of this study should be interpreted within the limitations of the original studies. A quality assessment needed to be carried out to realize all criteria of a systematic review. Although quality assessment was performed using two different tools, the NOS tool showed limitations in assessing the quality of single-armed cohort studies. No other quality assessment tool covers single-armed cohort studies. Therefore, single-armed cohort studies were excluded in this meta-analysis due to missing data of a control arm. A major limitation of this study is the heterogeneity within the studies. In addition to heterogeneity within study populations of individual studies, inter-heterogeneity of the included studies also limited this meta-analysis. The total proportion of asymptomatic lymphoceles could be underreported as in a third of the patient's lymphoceles were detected after diagnostics on indication. The included studies provided limited data on BMI and number of dissected lymph nodes with substantial heterogeneity. Consequently, it was not possible to accurately evaluate whether BMI and number of dissected lymph nodes are possible risk factors for the development of lymphoceles in this analysis. Due to aggregation bias, meta-regression analysis based on aggregate data (e.g. average patient characteristics such as BMI and number of dissected lymph nodes) could reflect a logical fallacy in the interpretation of the observed data [61]. Therefore, these results at group level may be either an under- or overestimation between patient-level characteristics and the proportion of lymphoceles. Another pitfall of meta-regression analysis is the statistical power, which is lower when the analysis is conducted using a limited number of studies. Similarly, to minimize the risk of overfitting, we did not adjust for covariates due to the limited number of studies. In conclusion, clinicians should be cautious in drawing conclusions regarding risk factors because of shortcomings of this research. First, they have not been demonstrated at patient level, but in an overarching meta-analysis. Secondly, since routine diagnostics have not been performed in one third of the study population the incidence of lymphoceles is underreported. Thirdly, particularly in smaller subgroups, there is inevitable bias due to variation in diagnostic measures and inhomogeneity of the material and univariate analyses. However, this meta-analysis is the best attempt so far to provide insight into the incidence and risk factors of lymphocele after PLND in cervical and endometrial cancer patients. With the shift towards more minimal invasive surgery, procedures, and approaches, robot-assisted laparoscopy (RALS) is increasingly adopted. Only limited data was available regarding RALS, thus further research is needed to determine the incidence of lymphocele after RALS.

5. Conclusion

This systematic review and meta-analysis showed a total pooled proportion of lymphoceles after PLND in early-stage cervical and endometrial cancer of 14%. Symptomatic lymphoceles occur less frequently at 3%. Performing diagnostics routinely was associated with a higher proportion of lymphocele. Significant risk factors for developing lymphoceles were laparotomic approach, decreased number of lymph nodes dissected and additional PAOLND. Further research is needed to determine the incidence of lymphocele after minimally invasive robot-assisted laparoscopic staging and to identify risk factors for symptomatic lymphoceles.

Contributors

All authors declare to have contributed to the research protocol and interpretation and the writing of the article. Two authors (AJ and AdJ) carried out the abstract and title screening, full text screening, quality assessment and data analysis. Discrepancies were resolved by consensus discussion and a third reviewer (CGG).

Declaration of Competing Interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2023.01.022.

References

[1] N. Concin, X. Matias-Guiu, I. Vergote, D. Cibula, M.R. Mirza, S. Marnitz, et al., ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma, Int. J. Gynecol. Cancer 31 (1) (2021).

[2] N. Colombo, E. Preti, F. Landoni, S. Carinelli, A. Colombo, C. Marini, et al., Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 24 (2013) vi33–8.

[3] S. Togami, R. Kubo, T. Kawamura, S. Yanazume, M. Kamio, H. Kobayashi, Risk factors for lymphatic complications following lymphadenectomy in patients with endometrial cancer, Taiwan J. Obstet. Gynecol. 59 (3) (2020) 420–424.

[4] Common Terminology Criteria for Adverse Events (CTCAE), Version 5 [Internet], US Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 2017, Available from https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

[5] H.Y. Kim, J.W. Kim, S.H. Kim, Y.T. Kim, J.H. Kim, An analysis of the risk factors and management of lymphocele after pelvic lymphadenectomy in patients with gynecologic malignancies, Cancer Res. Treat Off. J. Korean Cancer Assoc. 36 (6) (2004) 377.

[6] V. Weinberger, D. Cibula, M. Zikan, Lymphocele: prevalence and management in gynecological malignancies, Exp. Rev. Anticancer. Ther. [Internet] 14 (3) (2014) 307–317, https://doi.org/10.1586/14737140.2014.866043.

[7] F. Ghezzi, S. Uccella, A. Cromi, G. Bogani, C. Robba, M. Serati, et al., Lymphoceles, Lymphorrhea, and lymphedema after laparoscopic and open endometrial cancer staging, Ann. Surg. Oncol. [Internet] 19 (1) (2012) 259–267, https://doi.org/10.1245/s10434-011-1854-5.

[8] Ş. Gezer, A. Pulur, İ. Yücesoy, Application of thrombin gel matrix for the prevention of lymphocele in patients with endometrial cancer: A prospective randomized trial, J. Gynecol. Obstet. Hum. Reprod. [Internet] 50 (7) (2021) 101994, Available from: https://www.sciencedirect.com/science/article/pii/S2468784720303640.

[9] M. Zikan, D. Fischerova, I. Pinkavova, J. Slama, V. Weinberger, L. Dusek, et al., A prospective study examining the incidence of asymptomatic and symptomatic lymphoceles following lymphadenectomy in patients with gynecological cancer, Gynecol. Oncol. 137 (2) (2015) 291–298.

[10] A.S. ten Hove, M.Y. Tjiong, I.A.J. Zijlstra, Treatment of symptomatic postoperative pelvic lymphoceles: A systematic review, Eur. J. Radiol. [Internet] 134 (2021) 109459, Available from: https://www.sciencedirect.com/science/article/pii/S0720048X20306495.

[11] S. Pecorelli, Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium, Int. J. Gynecol. Obstet. 105 (2) (2009) 103–104.

[12] N. Bhatla, J.S. Berek, M. Cuello Fredes, L.A. Denny, S. Grenman, K. Karunaratne, et al., Revised FIGO staging for carcinoma of the cervix uteri, Int. J. Gynecol. Obstet. 145 (1) (2019) 129–135.

[13] J. Peterson, V. Welch, M. Losos, P. Tugwell, The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, Ottawa Ottawa Hosp. Res. Inst. 2 (1) (2011) 1–12.

[14] J.A.C. Sterne, J. Savović, M.J. Page, R.G. Elbers, N.S. Blencowe, I. Boutron, et al., RoB 2: a revised tool for assessing risk of bias in randomised trials, BMJ (2019) 366.

[15] L.A. McGuinness, J.P.T. Higgins, Risk-of-bias VISualization (robvis): an R package and shiny web app for visualizing risk-of-bias assessments, Res. Synth. Methods 12 (1) (2021 Jan) 55–61.

[16] J.P.T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M.J. Page, et al., Cochrane Handbook for Systematic Reviews of Interventions, John Wiley & Sons, 2019.

[17] S. Togami, T. Kawamura, M. Fukuda, S. Yanazume, M. Kamio, Kobayashi H. Risk factors for lymphatic complications following lymphadenectomy in patients with cervical cancer, Jpn. J. Clin. Oncol. [Internet] 48 (12) (2018 Dec 1) 1036–1040, https://doi.org/10.1093/jjco/hyy151.

[18] M. Wedin, K. Stålberg, J. Marcickiewicz, E. Ahlner, Å. Åkesson, G. Lindahl, et al., Incidence of lymphedema in the lower limbs and lymphocyst formation within one year of surgery for endometrial cancer: a prospective longitudinal multicenter study, Gynecol. Oncol. 159 (1) (2020) 201–208.

[19] N.Y. Park, W.J. Seong, G.O. Chong, D.G. Hong, Y.L. Cho, I.S. Park, et al., The effect of nonperitonization and laparoscopic lymphadenectomy for minimizing the incidence of lymphocyst formation after radical hysterectomy for cervical cancer, Int. J. Gynecol. Cancer 20 (3) (2010).

[20] E.M. Ko, M.G. Muto, R.S. Berkowitz, C.M. Feltmate, Robotic versus open radical hysterectomy: a comparative study at a single institution, Gynecol. Oncol. 111 (3) (2008) 425–430.

[21] G. Larciprete, B. Casalino, M.F. Segatore, S. Jarvis, V. Catarinella, E. Cirese, Pelvic lymphadenectomy for cervical cancer: extraperitoneal versus laparoscopic approach, Eur. J. Obstet. Gynecol. Reprod. Biol. 126 (2) (2006) 259–263.

[22] A. Logmans, R.H. Kruyt, H.G. de Bruin, P.H. Cox, M. Pillay, J.B. Trimbos, Lymphedema and Lymphocysts following lymphadenectomy may be prevented by Omentoplasty: a pilot study, Gynecol. Oncol. [Internet]. 75 (3) (1999) 323–327, Available from: https://www.sciencedirect.com/science/article/pii/S009082589995624X.

[23] A. Wrobel, I. Winkler, T. Rechberger, K. Skorupska, P. Miotla, Does intraoperative application of TachoSil reduce the number of lymphoceles after pelvic lymphadenectomy? Ginekol. Pol. 93 (4) (2022) 278–283.
[24] V. Gallotta, F. Fanfani, C. Rossitto, G. Vizzielli, A. Testa, G. Scambia, et al., A randomized study comparing the use of the Ligaclip with bipolar energy to prevent lymphocele during laparoscopic pelvic lymphadenectomy for gynecologic cancer, Am. J. Obstet. Gynecol. 203 (5) (2010) 483–e1.
[25] R. Kakubari, E. Kobayashi, M. Kakuda, T. Iwamiya, T. Takiuchi, M. Kodama, et al., Postoperative lymphocyst formation after pelvic lymphadenectomy for gynecologic cancers: comparison between laparoscopy and laparotomy, Int. J. Clin. Oncol. 27 (3) (2022) 602–608.
[26] G.E. Hilaris, T. Tsoubis, V. Konstantopoulos, K. Pavlakis, Feasibility, safety, and cost outcomes of laparoscopic management of early endometrial and cervical malignancy, JSLS J. Soc. Laparoendosc. Surg. 13 (4) (2009) 489.
[27] B. Patsner, Closed-suction drainage versus no drainage following radical abdominal hysterectomy with pelvic lymphadenectomy for stage IB cervical cancer, Gynecol. Oncol. 57 (2) (1995) 232–234.
[28] M. Hao, Z. Wang, F. Wei, J. Wang, W. Wang, Y. Ping, Cavitron ultrasonic surgical aspirator in laparoscopic nerve-sparing radical hysterectomy: a pilot study, Int. J. Gynecol. Cancer 26 (3) (2016).
[29] G. Bifulco, P. Giampaolino, I. Morra, G.A. Tommaselli, F. Tarsitano, G. Chiacchio, et al., Synthetic cyanoacrylic glue in the prevention of post-operative lymphocele after pelvic lymphadenectomy in patients with uterine malignancies: a prospective, single-blind, preliminary study, Gynecol. Oncol. 134 (3) (2014) 556–560.
[30] A. Tinelli, O.A. Mynbaev, D.A. Tsin, G. Giorda, A. Malvasi, M. Guido, et al., 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 (5) (2013).
[31] A. Tinelli, G. Giorda, C. Manca, M. Pellegrino, R. Prudenzano, M. Guido, et al., Prevention of lymphocele in female pelvic lymphadenectomy by a collagen patch coated with the human coagulation factors: a pilot study, J. Surg. Oncol. 105 (8) (2012) 835–840.
[32] J. Srisomboon, C. Phongnarisorn, P. Suprasert, C. Cheewakriangkrai, S. Siriaree, K. Charoenkwan, A prospective randomized study comparing retroperitoneal drainage with no drainage and no peritonization following radical hysterectomy and pelvic lymphadenectomy for invasive cervical cancer, J. Obstet. Gynaecol. Res. 28 (3) (2002) 149–153.
[33] M. Franchi, F. Ghezzi, F. Zanaboni, C. Scarabelli, P. Beretta, N. Donadello, Nonclosure of peritoneum at radical abdominal hysterectomy and pelvic node dissection: a randomized study, Obstet. Gynecol. 90 (4) (1997) 622–627.
[34] S. Anne, M.Y. Tjiong, I.A.J. Zijlstra, Treatment of symptomatic postoperative pelvic lymphoceles: a systematic review, Eur. J. Radiol. 134 (2021) 109459.
[35] X. Ma, Y. Wang, A. Fan, M. Dong, X. Zhao, X. Zhang, et al., Risk factors, microbiology and management of infected lymphocyst after lymphadenectomy for gynecologic malignancies, Arch. Gynecol. Obstet. 298 (6) (2018) 1195–1203.
[36] V. Weinberger, D. Fischerova, I. Semeradova, J. Slama, D. Cibula, M. Zikan, Ultrasound characteristics of a symptomatic and asymptomatic lymphocele after pelvic and/or paraaortic lymphadenectomy, Taiwan J. Obstet. Gynecol. [Internet]. 58 (2) (2019) 266–272, Available from: https://www.sciencedirect.com/science/article/pii/S102845591930018X.
[37] D.E. Ott, Laparoscopy and adhesion formation, adhesions and laparoscopy, Seminars in Reproductive Medicine, Thieme Medical Publishers 2008, pp. 322–330.
[38] C.N. Gutt, T. Oniu, P. Schemmer, A. Mehrabi, M.W. Büchler, Fewer adhesions induced by laparoscopic surgery? Surg. Endosc. 18 (6) (2004) 898–906.
[39] F. Ghezzi, A. Cromi, M. Serati, S. Uccella, G. Formenti, G. Bogani, et al., Radiation-induced bowel complications: laparoscopic versus open staging of gynecologic malignancy, Ann. Surg. Oncol. 18 (3) (2011) 782–791.
[40] C. Atabekoglu, M. Sönmezer, M. Güngör, R. Aytaç, F. Ortaç, C. Ünlü, Tissue trauma in abdominal and laparoscopic-assisted vaginal hysterectomy, J. Am. Assoc. Gynecol. Laparosc. 11 (4) (2004) 467–472.
[41] E.J. Crosbie, S.J. Kitson, J.N. McAlpine, A. Mukhopadhyay, M.E. Powell, N. Singh, Endometrial cancer, Lancet [Internet]. 399 (10333) (2022) 1412–1428, Available from: https://www.sciencedirect.com/science/article/pii/S0140673622003233.
[42] S. Kommoss, M.K. McConechy, F. Kommoss, S. Leung, A. Bunz, J. Magrill, et al., Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series, Ann. Oncol. 29 (5) (2018) 1180–1188.
[43] A. León-Castillo, S.M. De Boer, M.E. Powell, L.R. Mileshkin, H.J. Mackay, A. Leary, et al., Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: impact on prognosis and benefit from adjuvant therapy, J. Clin. Oncol. 38 (29) (2020) 3388.
[44] C. Luna, P. Balcacer, P. Castillo, M. Huang, F. Alessandrino, Endometrial cancer from early to advanced-stage disease: an update for radiologists, Abdom. Radiol. 46 (11) (2021) 5325–5336.
[45] J. Persson, S. Salehi, M. Bollino, C. Lönnerfors, H. Falconer, B. Geppert, Pelvic sentinel lymph node detection in high-Risk endometrial Cancer (SHREC-trial)—the final step towards a paradigm shift in surgical staging, Eur. J. Cancer 116 (2019) 77–85.
[46] B. Hagen, M. Valla, G. Aune, M. Ravlo, A.B. Abusland, E. Araya, et al., Indocyanine green fluorescence imaging of lymph nodes during robotic-assisted laparoscopic operation for endometrial cancer. A prospective validation study using a sentinel lymph node surgical algorithm, Gynecol. Oncol. 143 (3) (2016) 479–483.
[47] M. Plante, O. Touhami, X.-B. Trinh, M.-C. Renaud, A. Sebastianelli, K. Grondin, et al., Sentinel node mapping with indocyanine green and endoscopic near-infrared fluorescence imaging in endometrial cancer. A pilot study and review of the literature, Gynecol. Oncol. 137 (3) (2015) 443–447.
[48] F. Martinelli, A. Ditto, G. Bogani, U.L.R. Maggiore, M. Signorelli, V. Chiappa, et al., Sentinel lymph node mapping in endometrial cancer: performance of hysteroscopic injection of tracers, Int. J. Gynecol. Cancer 30 (3) (2020).
[49] D. Cibula, R. Kocian, A. Plaikner, J. Jarkovsky, J. Klat, I. Zapardiel, et al., Sentinel lymph node mapping and intraoperative assessment in a prospective, international, multicentre, observational trial of patients with cervical cancer: the SENTIX trial, Eur. J. Cancer 137 (2020) 69–80.
[50] T.P. Diniz, E. Drizlionoks, C.C. Faloppa, J.N. Menezes, H. Mantoan, B.T. Gonçalves, et al., Impact of sentinel node mapping in decreasing the risk of lymphocele in endometrial cancer, Ann. Surg. Oncol. 28 (6) (2021) 3293–3299.
[51] B. Geppert, C. Lönnerfors, M. Bollino, J. Persson, Sentinel lymph node biopsy in endometrial cancer—feasibility, safety and lymphatic complications, Gynecol. Oncol. 148 (3) (2018) 491–498.
[52] K. Kuroda, Y. Yamamoto, M. Yanagisawa, A. Kawata, N. Akiba, K. Suzuki, et al., Risk factors and a prediction model for lower limb lymphedema following lymphadenectomy in gynecologic cancer: a hospital-based retrospective cohort study, BMC Womens Health 17 (1) (2017) 1–10.
[53] L.F. Rebegea, G. Stoleriu, N. Manolache, C. Serban, M. Craescu, M.-N. Lupu, et al., Associated risk factors of lower limb lymphedema after treatment of cervical and endometrial cancer, Exp. Ther. Med. 20 (6) (2020) 1.
[54] S.G. Jung, S.H. Im, M. Kim, M.C. Choi, W.D. Joo, S.H. Song, et al., The association between the number of retrieved pelvic lymph nodes and ipsilateral lower limb lymphedema in patients with gynecologic Cancer, J. Investig. Surg. 35 (5) (2022) 978–983.
[55] A. Achouri, C. Huchon, A.S. Bats, C. Bensaid, C. Nos, F. Lécuru, Complications of lymphadenectomy for gynecologic cancer, Eur. J. Surg. Oncol. J. Eur. Soc. Surg. Oncol. Br. Assoc. Surg. Oncol. 39 (1) (2013 Jan) 81–86.
[56] M. Suzuki, M. Ohwada, I. Sato, Pelvic lymphocysts following retroperitoneal lymphadenectomy: retroperitoneal partial “no-closure” for ovarian and endometrial cancers, J. Surg. Oncol. 68 (3) (1998) 149–152.
[57] P. Benedetti-Panici, F. Maneschi, G. Cutillo, G. D'andrea, V.S. di Palumbo, M. Conte, et al., A randomized study comparing retroperitoneal drainage with no drainage after lymphadenectomy in gynecologic malignancies, Gynecol. Oncol. [Internet]. 65 (3) (1997) 478–482, Available from: https://www.sciencedirect.com/science/article/pii/S0090825897946485.
[58] M.L. Gasparri, I. Ruscito, D. Bolla, P.B. Panici, M.D. Mueller, A. Papadia, The efficacy of fibrin sealant patches in reducing the incidence of lymphatic morbidity after radical lymphadenectomy: a meta-analysis, Int. J. Gynecol. Cancer 27 (6) (2017).
[59] A. Achouri, C. Huchon, A.-S. Bats, C. Bensaïd, C. Nos, F. Lécuru, Postoperative lymphocysts after lymphadenectomy for gynaecological malignancies: preventive techniques and prospects, Eur. J. Obstet Gynecol. Reprod. Biol. [Internet]. 161 (2) (2012) 125–129, Available from: https://www.sciencedirect.com/science/article/pii/S0301211511006750.
[60] K. Charoenkwan, C. Kietpeerakool, Retroperitoneal drainage versus no drainage after pelvic lymphadenectomy for the prevention of lymphocyst formation in patients with gynaecological malignancies, Cochrane Database Syst. Rev. 6 (2014).
[61] M. Geissbühler, C.A. Hincapié, S. Aghlmandi, M. Zwahlen, P. Jüni, B.R. da Costa, Most published meta-regression analyses based on aggregate data suffer from methodological pitfalls: a meta-epidemiological study, BMC Med. Res. Methodol. 21 (1) (2021) 1–9.