Gynecologic Oncology 170 (2023) 84–92

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Finding the sentinel lymph node in early cervical cancer: When is unusual not uncommon?

Anke Smits [a,d,*], Mieke ten Eikelder [a], Joelle Dhanis [b], William Moore [c], Dominic Blake [d], Petra Zusterzeel [a], Ali Kucukmetin [d], Nithya Ratnavelu [d], Stuart Rundle [d]

[a] Dept. of Obstetrics and Gynaecology, Radboud University Medical Center, 6525, GA, Nijmegen, the Netherlands
[b] Faculty of Medical Sciences, Radboud University, 6526, GA, Nijmegen, the Netherlands
[c] Faculty of Medical Sciences, Newcastle University, NE2 4HH Newcastle Upon Tyne, United Kingdom
[d] Dept. of Gynecological Oncology, Queen Elizabeth Hospital, NE9 6SX, Gateshead, United Kingdom

HIGHLIGHTS

- Abberant drainage sites reporesent a signficant portion of sentinel lymph nodes in cervical cancer
- A lower BMI is associated with increased rates of sentinel lymph nodes found in unusual locations.
- Nulliparity and tumor size >20 mm are also possible associated factors with unusual locations.

ARTICLE INFO

Article history:
Received 9 November 2022
Received in revised form 20 December 2022
Accepted 23 December 2022
Available online 17 January 2023

Keywords:
Cervical cancer
Sentinel lymph nodes
Unusual location
Aberrant drainage
BMI

ABSTRACT

Objective. To report our institutional experience with sentinel lymph node (SLN) detection using indocyanine green for cervical cancer, in terms of detection rates, detection of SLN at unusual locations, and factors associated with unusual SLN locations. In addition, we performed a systematic review of the literature to identify factors associated with unusual SLN localizations.

Methods. This is a retrospective cohort study of women with early-stage cervical cancer undergoing sentinel lymph node mapping between 2015 and 2019. Outcome measures were SLN detection rates, detection rates of unusual locations for SLN and risk factors for aberrant lymphatic drainage pathways. In addition, studies evaluating factors associated with unusual SLN locations in cervical cancer were assessed in a systematic review.

Results. A total of 100 patients were included. The unilateral SLN detection rate was 88%, whereas the bilateral detection rate was 75%. In 37% of all patients, SLN were found in unusual locations, and in 10% of patients SLN were solely found in unusual locations. Body mass index (BMI) was associated with finding SLN in unusual locations, with unusual nodes detected in 52% of patients with BMI <25 kg/m^2 and in 28% of patients with BMI ≥25 kg/m^2. The systematic review identified three studies, identifying lower BMI, nulliparity and tumor size of >20 mm as factors associated with finding SLN at unusual locations.

Conclusion. Aberrant drainage sites represent a significant proportion of SLN detected in cervical cancer. Factors associated with increased rates of unusual nodal locations are a lower BMI, with a possible association with nulliparity and tumor size of >20 mm.

1. Introduction

In recognition of the fact that the presence of lymph node metastasis is an important determinant for treatment, and a prognostic factor for survival in suspected early-stage cervical cancer, the International Federation of Gynaecology and Obstetrics (FIGO) have adopted lymph node status into the most recent stage description [1]. Lymph node involvement is seen in about 13% of suspected early stage cervical cancer (FIGO stage IA1- IIA1). Careful examination of pelvic lymph nodes is therefore not only crucial in determining the need for post-surgical adjuvant treatment consisting of chemoradiotherapy, but also for informing the patient of prognosis and risk of recurrence [2,3].

Standard surgery for apparent early-stage cervical cancer has traditionally included pelvic lymph node dissection (PLND) within strict

* Corresponding author at: Department of Obstetrics and Gynaecology, Radboud University Medical Centre, Geert Grooteplein Zuid 10, 6525GA Nijmegen, the Netherlands.
E-mail address: anke.smits@radboudumc.nl (A. Smits).

https://doi.org/10.1016/j.ygyno.2022.12.013
0090-8258/

anatomical boundaries to assess lymphatic spread [4,5]. In recent years, the sentinel lymph node (SLN) procedure has been established as an alternative method for the assessment of lymphatic spread in other gynecological cancers including vulvar and endometrial cancer [6–8]. In cervical cancer, despite a growing body of evidence, there is a reluctance to abandon PLND in favor of the SLN procedure alone due to the lack of clinical trials demonstrating its non-inferiority and oncologic safety, with pooled sensitivity rates of 90% and failure to map in 25–30% of patients [4,9].

Advantages of SLN dissection over PLND include decreased morbidity such as lymphoedema and lymphocyst formations, and a higher sensitivity for the detection of (micro)metastasis through ultrastaging [10,11]. Another benefit includes the detection of aberrant or "unusual" lymphatic drainage pathways and SLN that lie outside of the routinely dissected pelvic nodal basin, which occurs in around 10% of cases [12,13]. The lymphatic drainage system of the cervix and uterus is classically divided into an upper and a lower paracervical pathway (UPP and LPP) and the infundibulo-pelvic pathway (IPP). The upper paracervical pathway runs along the uterine artery, draining medial external and/or obturator lymph nodes and continuing to the lateral precaval and paraaortic areas [14]. The lower paracervical pathway (LPP) courses along the upper rim of the sacro-uterine ligament to the presacral area medial to the internal iliac artery with internal iliac and/or presacral draining nodes before continuing to the medial paraaortic and precaval areas. The IPP runs alongside the fallopian tube and upper broad ligament via the infundibulo-pelvic ligament [14]. However, aberrant or unusual drainage patterns are still considered uncommon, and not much is known about factors associated with detection of nodes at unusual locations.

In this study we report our institutional experience with SLN detection in presumed early-stage cervical cancer (FIGO stage IA1 – IIA1) using indocyanine green with near infra-red fluorescence imaging (ICG-NIR), in terms of detection rates and a description of unusual locations of SLN. In addition, we assessed risk factors for aberrant lymphatic drainage and set this in a context of a systematic review of the literature to identify factors associated with unusual SLN localizations.

2. Methods

2.1. Institutional study

2.1.1. Study population

Patients undergoing the ICG-NIR SLN procedure as part of their primary surgery for FIGO stage (2009) IA1 with LVSI to IIA1 cervical cancer between October 2015 and October 2019 at the Northern Gynecological Oncology Centre, Gateshead, United Kingdom, were included. All cases of FIGO stage IA2 disease or above were squamous cell carcinomas, adenosquamous cancers or adenocarcinomas. FIGO stage IA1 disease with the above histological subtypes were included if LVSI was present, or in case of rare histology (small cell cancer). Definitive surgical management included radical hysterectomy (laparoscopic or open according to standard practice at the time of the procedure); extra-fascial (simple) laparoscopic hysterectomy; laparoscopically assisted radical trachelectomy and LLETZ (large loop excision of the transformation zone). Lymph node assessment included SLN mapping and excision followed by systematic pelvic lymphadenectomy and excision of any enlarged nodes. Selected patients with stage IA1–2, and small volume 1B1 tumors who declined lymphadenectomy, underwent only the sentinel lymph node procedure following detailed pre-operative counselling [15]. Ethical approval was not required as this was a secondary analysis of an audit of practice and service evaluation.

2.1.2. Sentinel node location

SLN location was documented at the time of the operation according to the notation previously described by Jewel et al. [16]. Usual locations for SLN were defined as those lying within the anatomical boundaries of the systematic pelvic lymphadenectomy: bifurcation of the common iliac artery cranially (including nodes on the bifurcation), the deep circumflex iliac vein caudally, the obturator nerve inferiorly, and the obliterated umbilical artery medially. This included nodes found at external iliac, internal iliac or obturator stations. Unusual SLN locations were described as those of common iliac (cranial to the bifurcation of the common iliac artery), pre-sacral or para-aortic distribution as these stations would not normally be contained within the lymphadenectomy specimen within our surgical practice.

2.1.3. Sentinel node technique

The ICG-NIR SLN procedure in cervical cancer was introduced at our institution in 2015. All patients had 1 ml of 0.25 mg/ml ICG (Pulsion medical system, Feldkirchen, Germany) injected into the cervix in 4 equal aliquots at 3- and 9- o'clock at a depth of 5 mm and 20 mm prior to the start of surgery. After access to the peritoneal cavity was attained, a systematic intraperitoneal inspection of the pelvic nodal basin, pre-sacral area and approach to the para-aortic basin was performed to identify visible fluorescent lymphatic channels and nodes. The retroperitoneum was opened bilaterally and SLN within the iliac and inter-iliac distribution were identified. If fluorescence was noted in the pre-sacral, common iliac or para-aortic basins on initial inspection, these regions were explored surgically, and nodes were retrieved irrespective of the presence of fluorescent nodes in the pelvic nodal basin. When no fluorescent signal was seen in either hemipelvis, a further 1 ml ICG was injected at the cervix according to the surgeon's discretion. All fluorescent lymph nodes were taken. Fluorescence imaging was undertaken using the Pinpoint (endoscopic) or Portable Handheld Imager (SPY-PHI) fluorescent Imaging Technology (Stryker).

2.1.4. Data collection

Patient data was collected retrospectively for ongoing audit of practice and service evaluation following the introduction of ICG-SLN technique in cervical cancer. Patient's demographic and clinical characteristics were collected from patient's medical records. Baseline characteristics included age at diagnosis, previous medical history (including cardiovascular disease, diabetes, pulmonary disease and other), Eastern Cooperative Oncology Group (ECOG) performance status, body mass index (BMI), and smoking status. Clinical characteristics included histological subtype, grade, presence of lymphovascular space invasion (LVSI), LLETZ, and clinical FIGO stage (2009). Surgical characteristics including SLN detection (unilateral and bilateral), and their localization were collected. Sentinel nodes could be resected from multiple locations per patient. Pathological handling of the excised SLN developed through the study period from standard section only to routine ultrastaging according to accepted international practice. Operative morbidity was graded according to the Clavien-Dindo classification system and included intra-operative complications such as total blood loss, injuries to vessels, nerves, bladder and ureters, and post-operative complications including fever, infection, urinary tract infection, wound problems and ileus [17]. Transient self-limiting urinary retention was reported separately.

2.1.5. Outcomes

The primary outcomes were the overall and bilateral detection rates of SLN, the amount of SLN per pelvic sidewall and the localization of SLN, including the number of unusual localizations. Secondary outcomes were baseline and clinicopathological factors associated with detection rates and resection of unusual locations of SLN. Diagnostic accuracy in terms of sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) was calculated for SLN detecting lymph node metastasis.

2.1.6. Statistical analyses

Continuous variables were presented as means with standard deviations or medians and interquartile range, as appropriate. Categorical outcomes were presented as frequencies and proportions. Categorical data was analyzed using Pearson Chi-squared tests and Fisher's exact tests. Continuous data was analyzed using non-parametric tests (Mann-Whitney *U* test). Statistical tests were two-tailed and considered significant at $p < 0.05$). Data were analyzed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA) [18].

2.2. Systematic review on unusual nodes

2.2.1. Search strategy and selection criteria

This review was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [19]. Eligible for inclusion were studies evaluating factors associated with unusual SLN locations in cervical cancer. Eligible study designs included: randomized controlled trials, controlled clinical trials, case-control studies, cohort studies and cross-sectional studies, retrospective analyses of prospective trials were also eligible. Studies were considered if they assessed factors associated with unusual SLN locations. Participants included adult women undergoing surgery for primary cervical cancer. Different tracing methods including ICG, blue dye and technetium-99 (Tc99) were included. A systematic search was performed of PubMed, Medline, EMBASE (Ovid) and PsycINFO databases. The complete search strategy included keywords and MeSH terms related to the review topic (Appendix A). Reference lists of eligible studies were assessed to identify additional studies for inclusion.

2.2.2. Selection and assessment of studies

Two reviewers (MtE and JD) independently assessed publication title and abstract of all identified studies according to the inclusion criteria. Potentially relevant studies were retrieved in full text and further assessed for eligibility by both reviewers. Any disparities were resolved by discussion with a third independent reviewer (AS). The following variables were extracted by both reviewers: type of study, country, year of publication, population, and age, type of cancer, stage, histology, treatment, type of tracer, injection site, detection rates, lymph node locations, number of SLN, prevalence of unusual nodes and lymph node metastasis, factors associated with SLN in unusual locations and factors not associated with SNL in unusual nodes.

Study bias was assessed by two reviews (AS and MtE) using the Risk of Bias tool for Randomized Trials (RoB 2) and Risk Of Bias In Non-Randomized Studies of Interventions (ROBINS-I) for non-randomized cohort studies presented by the Cochrane Collaboration [20]. This assessment tool assesses bias due to confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurements and the selection of reported results.

Table 1
Baseline and clinical characteristics.

	Study population $N = 100$ (%)
Age (median, range)	39 (24–82)
PMH	
- None	36 (36%)
- Cardiovascular	7 (7%)
- Diabetes mellitus	2 (2%)
- Pulmonary	11 (11%)
- Other	43 (43%)
Unknown	1 (1%)
ECOG performance status	
- 0	78 (78%)
- 1	6 (6%)
Unknown	16 (16%)
BMI	
- Underweight (<18.5)	2 (2%)
- Normal (18.5–24.9)	34 (34%)
- Overweight (25–29.9)	31 (31%)
- Obese (>30)	28 (28%)
- Unknown	5 (5%)
Smoking	
- Yes	29 (29%)
- No	58 (58%)
- Stopped	13 (13%)
Histology	
- Squamous	59 (59%)
- Adeno	37 (37%)
- Adenosquamous	3 (3%)
- Other	1 (1%)
Grade	
- 1	17 (17%)
- 2	43 (43%)
- 3	28 (28%)
- Unknown	12 (12%)
LVSI	
- Yes	36 (36%)
- No	60 (60%)
- Unknown	4 (4%)
LLETZ prior to surgery	
- None	18 (18%)
- 1	58 (58%)
- 2	23 (23%)
- 3	1 (1%)
Preoperative FIGO stage (2009)	
- IA1	2 (2%)
- IA2	5 (5%)
- IB1	90 (90%)
o Tumor size <20 mm*	66 (66%)
o Tumor size >20 mm*	22 (22%)
o Unknown	2 (2%)
- IB2	1 (1%)
- 2A1	2 (%)

BMI: body mass index; ECOG: European Cooperative Oncology Group; LLETZ: large loop excision of transformation zone; LVSI: lymphovascular space invasion; PMH: previous medical history: * on final pathology.

3. Results

3.1. Institutional study

3.1.1. Patient population

A total of 100 patients were included in the study. Baseline and clinical characteristics are illustrated in Table 1. Median age of the population was 39 years (range 24–82). At least one co-morbidity was reported in 65% of patients and 78% were of ECOG performance status 0 (Table 1). More than half of patients were overweight (BMI 25–29.9 kg/m^2) (31%) or obese (BMI > 30 kg/m^2) (28%). A total of 59 patients (59%) were diagnosed with squamous cell carcinoma and LVSI was present in 36 patients. The majority had FIGO stage IB1 disease; the patient with stage IB2 had an exophytic squamous cancer of >4 cm, with no evidence local or metastatic spread on MRI and PET-CT and underwent surgery after extensive counselling.

3.1.2. Surgical management of the primary tumor

Surgical management of the primary tumor was by radical hysterectomy in 72 patients, radical trachelectomy in six patients and by extra-fascial hysterectomy in seven patients. Fifteen patients were managed with LLETZ procedure with complete excision of the tumor (Table 2). There were eight intra-operative complications, with obturator nerve injury in 1 patient for which a repair was needed, two patients with transient obturator nerve neuropraxia ($N = 2$), bladder injury ($N = 1$), ureteric injury (N = 1), vascular injury (N = 1) and surgical emphysema (N = 2).

Table 2
Surgical characteristics.

	Study population N = 100
Type of operation	
- Laparoscopic radical hysterectomy	67 (67%)
- Open radical hysterectomy	5 (5%)
- Laparoscopic extrafascial hysterectomy	7 (7%)
- Laparoscopic radical trachelectomy	6 (6%)
- Lymphadenectomy only +/− LLETZ	15 (15%)
EBL (median, SD)	50 (111)
Intraoperative complications	
- Yes	8 (8%)
- No	92 (92%)
Post-operative complications	
- Yes	27 (27%)
- No	73 (73%)
Individual postoperative complications	
- Infection	17%
o Urinary tract infection	6%
o Wound	4%
o Fever e.c.i.	5%
o Other	2%
- Ileus	3%
- Hypophosphatemia	1%
- Pulmonary embolism	1%
- Nerve injury (post-op leg weakness)	5%
- Return to theatre	1%
Lymph node dissection	
- Only SLN performed	14 (14%)
- SLN not found, only PLND	12 (12%)
- PLND and SLN	74 (74%)
SLN locations (N = 88)	
- Common only	54 (61%)
- Common and unusual	24 (27%)
- Unusual only	9 (10%)
- Node location not specified	1 (2%)
Positive lymph node	
- Yes	8 (8%)
o SLN only	6 (6%)
▪ Micrometastasis (>0.2–2 mm)	2 (2%)
▪ Macrometastasis	4 (4%)
o PLND (no metastasis in SLN)	2 (2%)
▪ Macrometastasis	2 (2%)
- No	92 (92%)

EBL: estimate blood loss; e.c.i.: e causa ignota (without source); LLETZ: large loop excision of transformation zone; PLND: pelvic lymph node dissection; SLN: sentinel lymph node.

Twenty-seven patients had a post-operative complication, which were all classified as Clavien-Dindo 1–2. After radical hysterectomy, 24 patients experienced transient urinary retention.

3.1.3. Sentinel lymph nodes procedures

The overall SLN detection rate per patient was 88%, and 75% of patients had a successful bilateral SLN procedure. Of 88 patients who successfully mapped a SLN in either hemipelvis, 74 underwent a formal bilateral pelvic node dissection after the sentinel node procedure (Table 2). Baseline and clinical characteristics were assessed for associations with detection rates of SLN. Increasing age as a continuous variable was significantly associated with not finding a SLN ($P = 0.001$). Other baseline and clinical characteristics such as BMI, tumor size, histology, previous number of LLETZ, surgical approach, surgical year and nodal metastasis were not associated with detection rates (data not shown).

A total of 286 SLN were detected, with an average of 3 nodes per patient (IQR 2). Localizations of nodes are shown in Fig. 1. Twenty-six percent of SLN (46/178), were located outside of the anatomical pelvic nodal basin including pre-sacral ($N = 6$), common iliac ($N = 30$) and para-aortic ($N = 10$) locations. Overall, 33/88 patients (38%) had SLN located in unusual locations, and of these 9/88 (10%) had SLN found in unusual locations only. Six patients had a metastatic nodal disease in the SLN (6/88; 7%), they were located at the external iliac ($N = 4$), obturator fossa (N = 1) and common iliac stations (N = 1) (Fig. 1). In these patients, the SLN were the only nodes that were positive for metastases. Two patients had a positive non-SLN (2/74, 2.7%). Both patients had squamous cell carcinoma, FIGO 2009 stage IB1, with LVSI. All non-SLN positive nodes contained macro-metastases of >2 mm and in one sample there was extra-capsular extension. Within the group who underwent both SLN and PLND ($N = 74$), five patients had a lymph node metastasis (SLN metastasis $N = 3$, PLND metastasis $N = 2$). In three patients, a SLN metastasis was confirmed intra-operatively by pathological review, resulting in the abandonment of a consecutive PLND. This resulted in sensitivity and NPV rates of respectively 75% and 97.1%.

Recurrence occurred in four patients (4%) after laparoscopic surgery, and was found in the vaginal vault (N = 2), para-aortic node ($N = 1$) and in both the vaginal vault and obturator node (N = 1). In all patients a SLN mapping and a PLND had been performed, except for one patient where the SLN was not detected. Two patients with a nodal recurrence had SLN detected in unusual locations only (common iliac areas), for which ultrastaging was not performed. In one patient with an isolated vaginal vault recurrence, SLN were detected in the external iliac area, while in the other patient the SLN failed to map.

Analyses showed that lower BMI was significantly associated with detection of SLN in unusual locations ($P = 0.016$), with unusual nodes detected in 52% of patients with BMI <25 kg/m^2 and in 28% of overweight and obese patients (BMI ≥25 kg/m^2). Other baseline and clinical characteristics such as age, tumor size, surgical approach, year and type of surgery did not show a significant association (data not shown).

3.2. Systematic review

Ninety-four studies were identified by the search strategy described above. Following exclusions (Fig. 2), three studies were included in the final analysis [21–23]. Table 3 shows the characteristics of the included studies. Two of the included studies were retrospective analyses of prospective multicenter trials [21,23], one was a multicenter prospective study [22]. A total of 616 patients with cervical cancer were included. The number of patients per study ranged from 139 to 304.

The average age of included patients varied between 42 and 44 years. Balaya et al. and Bats et al. included only early-stage cervical cancer (FIGO 2009 stage IA1–2, IB1 and IIA1). The most frequent histologic type of cervical cancer was squamous cell carcinoma in all studies (66% to 76%) [21,23]. Patent blue dye and/or technetium were used in all studies as the labelling technique with injection of tracers occurring into the four cardinal points of the cervix [21–23].

External iliac and interiliac stations (including the obturator fossa) were defined as common sites in all studies. Para-aortic, common iliac, internal iliac (which included presacral and parametrial station) were defined as unusual locations. Most lymph nodes were found in the common (external iliac and interiliac) areas with rates varying between 76% and 83% [21,23]. The average SLN found per patient varied from 2.7 to 3.8 [21,23]. Studies reported that 25% to 38% of all included patients had at least one lymph node in an unusual area whereas 5%–11% had SLN in unusual areas only. The percentage of patients with positives nodes varied between 16% and 23%, with 12–14% of positive nodes found in unusual locations of which most were found in the para-aortic, parametrial and common iliac areas.

3.2.1. Factors associated with unusual locations

All studies assessed factors associated with SLN found at unusual locations. Balaya et al. reported that BMI < 25, nulliparity and tumor size <20 mm were found to be significantly associated with finding more unusual nodes in multivariate analyses [21]. Age, previous surgery, histology and stage did not show a significant association. BMI, parity and tumor size were not evaluated by the other two studies [22,23]. Bats et al. assesses whether pre-operative scintigraphy and tracer type were

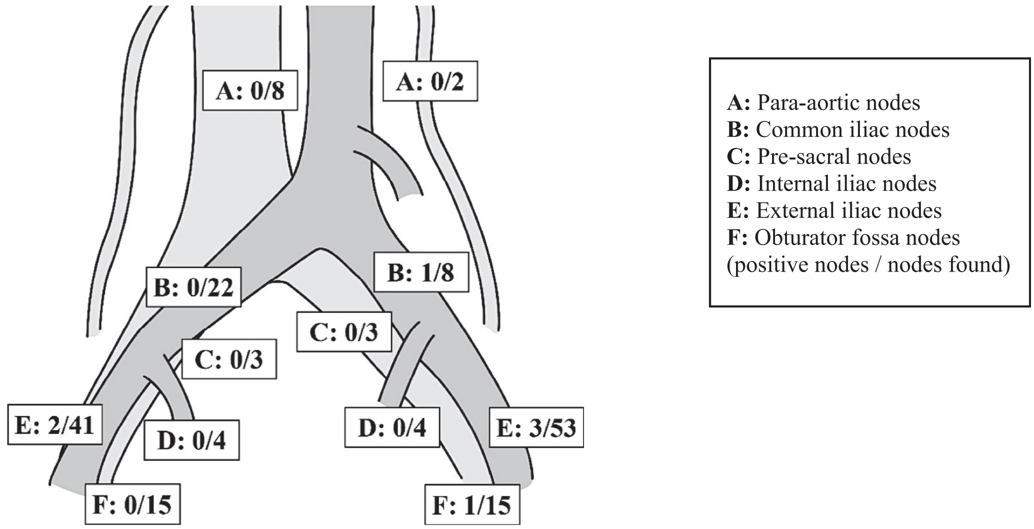

Fig. 1. Localizations of sentinel lymph nodes.

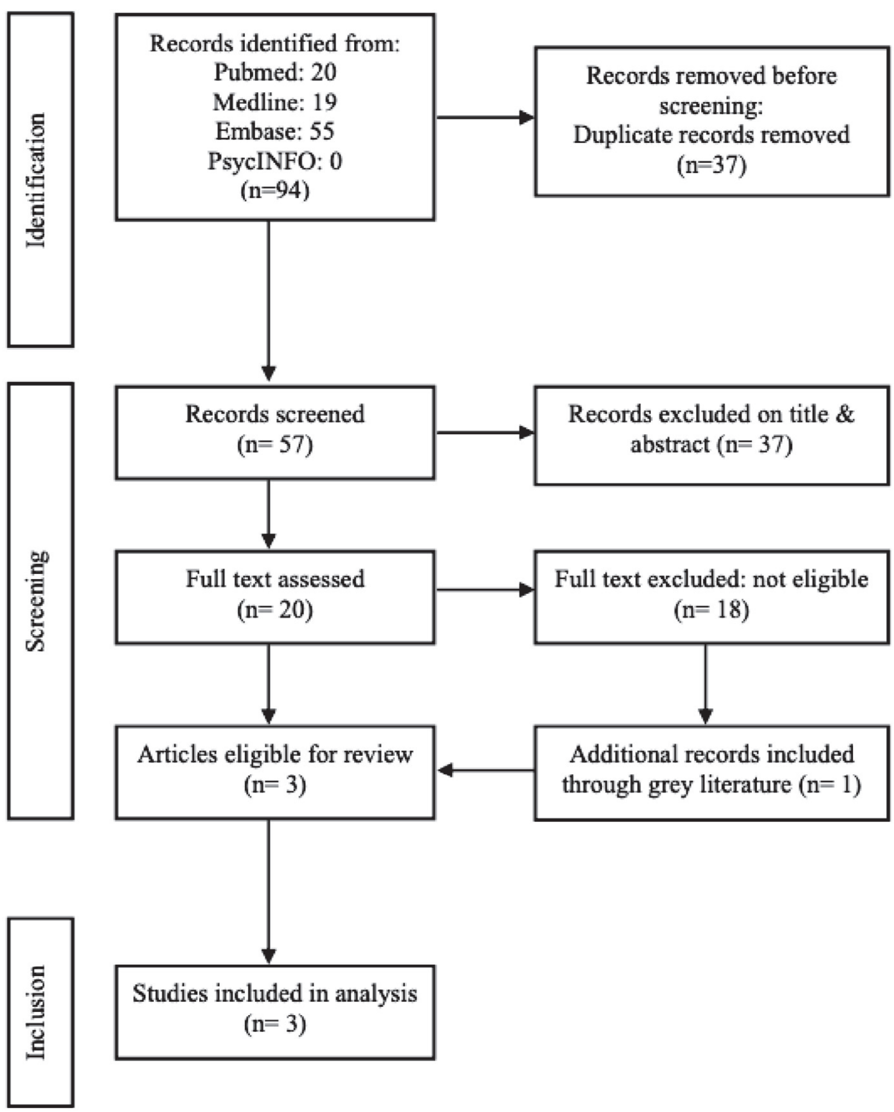

Fig. 2. PRISMA flowchart of selection of studies.

Table 3
Characteristics of included studies.

	Country and year	Study design	Population and age	Stage and type cancer	Approach, tracer and injection site	Total SLN and lymph node location	Nodal metastasis	Unusual node prevalence	Factors associated with unusual nodes
Balaya [21]	France 2019	Retrospective analysis of two multicenter prospective trials	$N = 326$ Median age 42 years	Cervical cancer FIGO stage 2009 IA1* – IA2: 35 (11.1%) IB1: 273 (86.9%) IIA: 6 (1.9%) SCC: 216 (66.3%) AC: 87 (28.1%) Other: 7 (2.3%)	Minimal invasive: 299 (92%) Laparotomy: 26 (8%) Patent blue and Tc99	$N = 1104$ Inter/external iliac: 918 (83.2%) Common: 102 (9.2%) Para-aortic: 17 (1.5%) Promontory: 18 (1.6%) Parametrial: 43 (3.9%) Other: 6 (0.3%)	53/326 (16.3%)	$N = 168$ (16.8%) unusual nodes. 80 patients (24.5%) with at least one unusual node.	- Nulliparity - Tumor size (>20 mm) - BMI <25 NS: age, menopausal status, previous surgery, stage, histology, LLETZ, surgical approach, positive nodes, LVSI, parametrial invasion, vaginal invasion, positive margins.
Bats [22]	France 2013	Multicenter prospective study	$N = 139$ Median age 43 years	Cervical cancer FIGO stage 2009 IA1*: 5 (3.6%) IA2: 12 (8.6%) IB1: 121 (87.1%) IIA: 1 (0.7%) SSC: 103 (74.1%) AC: 34 (24.4%) ASC: 2 (1.4%)	Not specified Patent blue and Tc99	$N = 454$ External iliac and interiliac: 366 (80.6%) Common iliac: 38 (8.4%) Internal iliac: 6 (1.3%) Paraaortic: 15 (3.3%) Parametrium: 29 (6.4%)	23/139 (16.5%)	$N = 28$ (6.2%) unusual nodes. 52 patients (38.2%) had at least one unusual node. 7 patients (5.1%) with only unusual nodes	Mean number of radioactive SLN in unusual places was significantly higher than mean number of SLN detected with patent blue dye. NS: scintigraphy or type of tracer.
Marnitz [23]	Germany2006	Retrospective analysis of multicenter prospective trial	$N = 151$ Mean age 44 years	FIGO stage 2009 IA: 21 (13.9%) IB: 95 (62.9%) IIA: 14 (9.3%) IIB: 18 (11.9%) IIIB: 2 (1.3%) IVA: 1 (0.7%) SCC: 114 (75.5%) AC: 37 (24.5%)	Laparotomy: 91 (60.3%) Laparoscopy: 60 (39.7%) Tc99 and patent blue dye; patent blue dye or Tc99	$N = 406$ External iliac: 20 (5%) Interiliac: 288 (71%) Common iliac: 20 (5%) Internal iliac: 33 (8%) Para-aortic: 17 (4%) Parametrium: 29 (7%)	34/151 (23%)	$N = 99$ (24.4%) unusual nodes. Patients not specified.	NS: histology and stage. Usage of combined Tc99 + blue dye and patent blue dye were associated with para-aortic nodes.

AC: adenocarcinoma; BMI: body mass index; FIGO: International Federation of Gynaecology and Obstetrics; NS: not significant; SCC: squamous cell carcinoma; SLN: sentinel lymph node; Tc99: Technetium-99; * = LVSI positive.

associated with detection of unusual nodes. They found that Tc99 was associated with higher average SLN sampled from unusual locations. However, unexpected location did not differ between lymphoscintigraphy and intraoperative detection [20]. Marnitz et al. found that the combination of blue dye and radioactive tracer was associated with a higher number of SLN in unusual locations compared to a single marker in univariate analysis but found no associations with histology nor stage [15].

3.2.2. Quality of evidence

All included studies were retrospective analyses of multicenter prospective trials, with Balaya et al. including patients from a randomized controlled trial and a multicenter prospective trial [21–23]. The other studies were non-randomized and were single-arm intervention trials, leading to a high risk of bias associated with non-randomization, and selective reporting (Table 4). An evaluation of bias was performed using the ROBINS-1 tool and is illustrated in Table 4 for all included studies, as Balaya et al. also included data from a non-randomized trial. With regards to confounding factors, only one study corrected for possible confounders in the statistical analysis [21]. There was some heterogeneity among studies regarding the selection of patients in terms of stage and inclusion criteria. Balaya and Bats et al. had a similar study population in terms of stage and histology, while Marnitz et al. also included (locally) advanced stages. Other quality indicators including classification of interventions, deviations from intended interventions and measurement of outcomes were of low risk of bias in all studies.

4. Discussion

Replacing systematic PLND in apparently early-stage cervical cancer in favor of the SLN procedure and its more favorable morbidity profile has been reported by some centers [24]. Existing evidence relating to oncologic outcomes is dominated by retrospective studies with considerable heterogeneity in technique, study population and the conduct of both the procedure and subsequent pathological handing of the SLN. Outcomes of prospective trials that include survival outcomes, such as the SENTIX and SENTICOL III are therefore highly anticipated [25,26]. Pooled sensitivity rates for SLN procedure in cervical cancer have been reported to be as high as 90% in a large systematic review and meta-analysis, however this careful review also highlighted potential factors associated with lower sensitivity rates, such as larger tumor size tumors >2 cm (73.9%) [9]. Until such time that these factors are more clearly understood, surgeons should exercise care in implementing an SLN only technique for the assessment of pelvic lymph node status in these patients, as this may result in considerable under-treatment of patients.

A reluctance to abandon PLND for SLN procedures in early cervical cancer, however, does not argue against the adoption of the technique into routine practice. In our institutional study, unusually located SLN were detected in 38% of patients. The prevalence of unusually located SLN in cervical cancer has previously been reviewed by Ouldamer et al.. They reported on 27 studies that included 1301 patients and found 16.3% of SLN were found at unusual locations, with 6.6% being found along the common iliac, 1.3% sacral, 4.3% parametrial and 2.0% in the para-aortic area. All included studies used blue dye and/or

Table 4
Quality of evidence.

	Confounding	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of reported results
Balaya (21)	+	-	+	+	?	+	-
Bats (22)	-	-	+	+	?	+	-
Marnitz (13)	-	-	+	+	?	+	-

X Serious risk; - Moderate risk; + Low risk; ? No information

technetium tracing techniques [12]. Balaya et al. recently reported similar results following secondary analyses of the SENTICOL 1 and 2 studies [21]. In our population, 26% of SLN were found in unusual locations, and is the highest reported rate to date. From these patients, 10% had SLN in unusual locations only, mirroring findings by Balaya et al. [21]. Two systematic reviews recently confirmed that ICG is a comparable, if not superior tracer, compared to technetrium combined with blue dye in terms of SLN detection rates, which might partially explain the difference in unusual node detection rate [27,28]. Another possible explanation might be the infiltration method at 3 and 9 o'clock at different depths and consequently pick up by lymphatic channels, which differs from the SENTICOL protocols [21–23]. The recent study by Luhrs et al. with similar tracer and injection technique as the SENTICOL studies, reported atypical positioning of a SLN in 21.9% of cases of cervical cancer patients, with metastatic lymph nodes in 8.7% and 4.8% in the presacral area and common iliac area respectively [29].

The presence of a significant number of SLN located outside of the anatomical pelvic nodal basin is not unexpected. Several detailed descriptions of the lymphatic pathways that drain the cervix have been proposed and demonstrated, with the above detailed UPP/LPP/IPP pathways being the most cited [14]. However, other contradictory descriptions also exist [30–32]. What these studies show, however, is the complexity of the lymphatic relations of the female pelvis. It raises the question of whether we can regard the extra-pelvic nodal locations described as truly unusual or if they are actually part of a described and predictable lymphatic pathway. Furthermore, it has been proposed that additional factors such as natural anatomical variance, disease location and tumor lympho-angiogenesis may contribute to the development of aberrant pathways that further increase the likelihood of extra-pelvic SLN [33]. It is still debated whether detection of multiple SLN in the hemipelvis is due to multiple independent lymphatic pathways or an overflow of lymphatic tracer transport to the second echelon nodes, or both. However, an increasing number of studies advocate to aim for bilateral detection of at least one SLN in both the UPP and LPP in cervical cancer to decrease false-negative rates [14,29]. Lastly, the considerable variation in surgically based classification and nomenclature for localizations of resected nodes hinders specific comparisons. The description by Marnitz et al. is used in the SENTICOL and SENTIX protocols, separately distinguishing parametrial nodes, whilst in other studies this is regarded part of the parametrectomy [16,23].

A total of three studies were identified evaluating factors associated with unusual SLN locations. In common with our own findings, our review of existing literature found that a significant predictor for finding unusually located nodes was reported to be low BMI. Obesity is a relevant predictor of mapping failure and decreased overall detection rates in endometrial cancer [34]. This can be attributed to the suboptimal visualization of spaces during surgery and the thicker layer of retroperitoneal fat which may obscure channels. Other predictors of unusual SLN location in the literature were nulliparity and tumor size (>20 mm). Whilst future studies are needed to confirm these findings, it has been proposed that a larger tumor size and positive nodes may modify the tumor lymphatic drainage due to compression, obstruction of lymphatic vessels and possibly alteration of tracer diffusion [35]. In addition, complex mechanisms associated with uterine lymphatic vessel modification during pregnancy have been proposed to impact lymphatic drainage in cervical cancer [21,36]. Tracer methods were also associated with finding more SLN in unusual locations. Unfortunately, due to the relative novelty of the ICG technique, this has only been assessed by one study [37].

An important strength of this study is the concurrent systematic review of the literature to validate our findings. In addition, we are the first to assess risk factors for unusual drainage patterns with the use of ICG alone. The study is however limited by the study size, the retrospective data-collection and the change in pathological assessment during the study period. Although this represents a reflection of clinical practice, is it possible that SLN with micro-metastasis or isolated tumor cells were missed as ultrastaging was not performed on all sentinel nodes. In addition, despite having detected a relatively large proportion of nodes in unusual places, this did not result in improved detection rates. We, however, believe this due to the study size and recommend future clinical trials to include assessment of aberrant drainage pathways. Sensitivity and NPV have been reported for our study, but have to be interpreted with caution due to our study size.

As the oncologic safety of the SLN only technique is still being debated, our study supports the continued assessment of SLN set against the traditional PLND. Our study underlines the importance of recognizing the diverse pattern of lymphatic drainage that may exist in cervical cancer and the significant potential of finding oncologically important SLN in apparently unusual locations. Specifically, common iliac SLN, cranially to the bifurcation and therefore outside of the classical pelvic lymph node basin, comprised 65% of all SLN found at unusual locations. The common finding across all studies that low BMI is associated with a high rate of unusually located SLN is highly clinically relevant. This finding underlines the need for careful and diligent exploration of spaces associated with commonly described drainage pathways in all women, prior to declaring a successful completion of the SLN procedure. Whilst recognizing that this may be associated with increased operative risk in women with high BMI, methods to ensure that relevant pathways are closely observed are essential. Possibly, this may be achieved by following the lymphatic channels arising from the parametrium following injection as described by Balaya et al. [21]. This can be easily and safely implemented with only the small cost of a slightly longer procedural time, but equally mandates that the procedures are conducted by experienced and accredited oncologic surgeons, familiar with retroperitoneal anatomy.

5. Conclusion

Traditionally regarded unusual SLN locations represent a significant proportion of all SLN detected in cervical cancer. Our institutional study reports the highest proportion of unusual nodes reported to date. We have identified that in common with available data, lower BMI is associated with increased rates of SLN found in unusual locations. In addition, we identified nulliparity and tumor size >20 mm as possible associated factors, but these need to be confirmed by future studies further assessing SLN complementary to PLND. We hope that increased awareness and identification of these associated factors will improve the identification of SLN in unusual sites, and consequently improve SLN detection, sensitivity rates and consequently oncology safety.

Author's contributions

AS was responsible for the conceptualization, methodology, data curation, analysis and writing of the original draft. MtE was responsible for conceptualization, methodology, analysis and writing of the original draft. JD was responsible for analysis and writing of original draft. WM and DB was responsible for data curation, review and editing of the manuscript. PZ, AK and NR were responsible for review and editing of the manuscript. SR was responsible for conceptualization, writing and review of the manuscript.

Funding

There were no sources of funding.

Appendix A. Search strategy

"Uterine Cervical Neoplasms"[Mesh].

OR

Cervical cancer*[tiab] OR cervical carcinoma*[tiab] OR cervical malign*[tiab] OR cervix carcinoma*[tiab] OR cervix cancer*[tiab] OR cervix neoplasm*[tiab] OR cervical tumor*[tiab] OR cervical tumor*[tiab] OR cervix tumor*[tiab] OR cervix tumor*[tiab].

AND

"Sentinel Lymph Node"[Mesh].

OR

Sentinel[tiab] OR sentinel lymph[tiab] OR sentinel lymph node*[tiab] OR sentinel node*[tiab] OR sentinel gland*[tiab] OR SLN[tiab] OR SLNs[tiab].

AND

Uncommon location*[tiab] OR unexpected location*[tiab] OR Uncommon[tiab] OR Unexpected[tiab] OR unexpected lymph drainage [tiab] OR uncommon lymph drainage[tiab] OR unexpected lymphatic drainage[tiab] OR uncommon lymphatic drainage[tiab] OR unexpected drainage[tiab] OR uncommon drainage[tiab] OR topography[tiab] OR atypical topography[tiab] OR atypical lymph drainage[tiab] OR atypical lymphatic drainage[tiab] OR atypical[tiab] OR aberrant drain*[tiab] OR aberrant[tiab].

References

[1] 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. Gynaecol. Obstet. 145 (1) (2019) 129–135.

[2] M.L.G. Ten Eikelder, F. Hinten, A. Smits, M.A. Van der Aa, R.L.M. Bekkers, J. IntHout, et al., Does the new FIGO 2018 staging system allow better prognostic differentiation in early stage cervical cancer? A Dutch Nationwide cohort study, Cancers (Basel). 14 (13) (2022).

[3] Y.N. Lee, K.L. Wang, M.H. Lin, C.H. Liu, K.G. Wang, C.C. Lan, et al., Radical hysterectomy with pelvic lymph node dissection for treatment of cervical cancer: a clinical review of 954 cases, Gynecol. Oncol. 32 (2) (1989) 135–142.

[4] L. Dostalek, E. Avall-Lundqvist, C.L. Creutzberg, D. Kurdiani, J. Ponce, I. Dostalkova, et al., ESGO survey on current practice in the management of cervical cancer, Int. J. Gynecol. Cancer 28 (6) (2018) 1226–1231.

[5] D. Cibula, R. Potter, F. Planchamp, E. Avall-Lundqvist, D. Fischerova, C. Haie Meder, et al., The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology Guidelines for the management of patients with cervical cancer, Int. J. Gynecol. Cancer 28 (4) (2018) 641–655.

[6] W.J. Koh, N.R. Abu-Rustum, S. Bean, K. Bradley, S.M. Campos, K.R. Cho, et al., Uterine neoplasms, version 1.2018, NCCN clinical practice guidelines in oncology, J. Natl. Compr. Cancer Netw. 16 (2) (2018) 170–199.

[7] M.H.M. Oonk, F. Planchamp, P. Baldwin, M. Bidzinski, M. Brannstrom, F. Landoni, et al., European Society of Gynaecological Oncology Guidelines for the management of patients with vulvar cancer, Int. J. Gynecol. Cancer 27 (4) (2017) 832–837.

[8] 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) 12–39.

[9] S. Kadkhodayan, M. Hasanzadeh, G. Treglia, A. Azad, Z. Yousefi, L. Zarifmahmoudi, et al., Sentinel node biopsy for lymph nodal staging of uterine cervix cancer: a systematic review and meta-analysis of the pertinent literature, Eur. J. Surg. Oncol. 41 (1) (2015) 1–20.

[10] D. Cibula, N.R. Abu-Rustum, L. Dusek, J. Slama, M. Zikan, A. Zaal, et al., Bilateral ultrastaging of sentinel lymph node in cervical cancer: lowering the false-negative rate and improving the detection of micrometastasis, Gynecol. Oncol. 127 (3) (2012) 462–466.

[11] B. Guani, K. Mahiou, A. Crestani, D. Cibula, A. Buda, T. Gaillard, et al., Clinical impact of low-volume lymph node metastases in early-stage cervical cancer: a comprehensive meta-analysis, Gynecol. Oncol. 164 (2) (2022) 446–454.

[12] L. Ouldamer, H. Marret, O. Acker, I. Barillot, G. Body, Unusual localizations of sentinel lymph nodes in early stage cervical cancer: a review, Surg. Oncol. 21 (3) (2012) e153–e157.

[13] 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.

[14] B. Geppert, C. Lonnerfors, M. Bollino, A. Arechvo, J. Persson, A study on uterine lymphatic anatomy for standardization of pelvic sentinel lymph node detection in endometrial cancer, Gynecol. Oncol. 145 (2) (2017) 256–261.

[15] I. Biliatis, A. Kucukmetin, A. Patel, N. Ratnavelu, P. Cross, S. Chattopadhyay, et al., Small volume stage 1B1 cervical cancer: is radical surgery still necessary? Gynecol. Oncol. 126 (1) (2012) 73–77.

[16] E.L. Jewell, J.J. Huang, N.R. Abu-Rustum, G.J. Gardner, C.L. Brown, Y. Sonoda, et al., Detection of sentinel lymph nodes in minimally invasive surgery using indocyanine green and near-infrared fluorescence imaging for uterine and cervical malignancies, Gynecol. Oncol. 133 (2) (2014) 274–277.

[17] P.A. Clavien, J. Barkun, M.L. de Oliveira, J.N. Vauthey, D. Dindo, R.D. Schulick, et al., The Clavien-Dindo classification of surgical complications: five-year experience, Ann. Surg. 250 (2) (2009) 187–196.

[18] IBM Corp Released, IBM SPSS Statistics for Windows, Version 250 Armonk, IBM Corp, NY, 2017.

[19] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, et al., The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, Rev. Esp. Cardiol. (Engl. Ed). 74 (9) (2021) 790–799.

[20] J.T. Julian Higgins, Jacqueline Chandler, Miranda Cumpston, Tianjing Li, Matthew Page, Vivian Welch, Cochrane Handbook for Systematic Reviews of InterventionsVersion, 6, 2022 3.

[21] V. Balaya, P. Mathevet, L. Magaud, H. Bonsang-Kitzis, M. Delomenie, R. Montero Macias, et al., Predictive factors of unexpected lymphatic drainage pathways in early-stage cervical cancer, Gynecol. Oncol. 154 (1) (2019) 102–109.

[22] A.S. Bats, P. Mathevet, A. Buenerd, I. Orliaguet, E. Mery, S. Zerdoud, et al., The sentinel node technique detects unexpected drainage pathways and allows nodal ultrastaging in early cervical cancer: insights from the multicenter prospective SENTICOL study, Ann. Surg. Oncol. 20 (2) (2013) 413–422.

[23] S. Marnitz, C. Kohler, S. Bongardt, U. Braig, H. Hertel, A. Schneider, et al., Topographic distribution of sentinel lymph nodes in patients with cervical cancer, Gynecol. Oncol. 103 (1) (2006) 35–44.

[24] G.K. Lennox, A. Covens, Can sentinel lymph node biopsy replace pelvic lymphadenectomy for early cervical cancer? Gynecol. Oncol. 144 (1) (2017) 16–20.

[25] D. Cibula, J. Dusek, J. Jarkovsky, P. Dundr, D. Querleu, A. van der Zee, et al., A prospective multicenter trial on sentinel lymph node biopsy in patients with early-stage cervical cancer (SENTIX), Int. J. Gynecol. Cancer 29 (1) (2019) 212–215.

[26] F.R. Lecuru, M. McCormack, P. Hillemanns, A. Anota, M. Leitao, P. Mathevet, et al., SENTICOL III: an international validation study of sentinel node biopsy in early cervical cancer. A GINECO, ENGOT, GCIG and multicenter study, Int. J. Gynecol. Cancer 29 (4) (2019) 829–834.

[27] L. Wang, S. Liu, T. Xu, L. Yuan, X. Yang, Sentinel lymph node mapping in early-stage cervical cancer: Meta-analysis, Medicine (Baltimore) 100 (34) (2021), e27035.

[28] I.G.T. Baeten, J.P. Hoogendam, B. Jeremiasse, A. Braat, W.B. Veldhuis, G.N. Jonges, et al., Indocyanine green versus technetium-99m with blue dye for sentinel lymph node detection in early-stage cervical cancer: a systematic review and meta-analysis, Cancer Rep. (Hoboken). 5 (1) (2022), e1401.

[29] O. Luhrs, M. Bollino, L. Ekdahl, C. Lonnerfors, B. Geppert, J. Persson, Similar distribution of pelvic sentinel lymph nodes and nodal metastases in cervical and endometrial cancer. A prospective study based on lymphatic anatomy, Gynecol. Oncol. 165 (3) (2022) 466–471.

[30] P. Benedetti-Panici, F. Maneschi, G. Scambia, S. Greggi, G. Cutillo, G. D'Andrea, et al., Lymphatic spread of cervical cancer: an anatomical and pathological study based on 225 radical hysterectomies with systematic pelvic and aortic lymphadenectomy, Gynecol. Oncol. 62 (1) (1996) 19–24.

[31] A.C. Kraima, M. Derks, N.N. Smit, J.C. Van Munsteren, J. Van der Velden, G.G. Kenter, et al., Lymphatic drainage pathways from the cervix uteri: implications for radical hysterectomy? Gynecol. Oncol. 132 (1) (2014) 107–113.

[32] A. Ercoli, V. Delmas, V. Iannone, A. Fagotti, F. Fanfani, G. Corrado, et al., The lymphatic drainage of the uterine cervix in adult fresh cadavers: anatomy and surgical implications, Eur. J. Surg. Oncol. 36 (3) (2010) 298–303.

[33] R. Shayan, M.G. Achen, S.A. Stacker, Lymphatic vessels in cancer metastasis: bridging the gaps, Carcinogenesis. 27 (9) (2006) 1729–1738.
[34] V. Vargiu, A. Rosati, V.A. Capozzi, G. Sozzi, A. Gioe, R. Berretta, et al., Impact of obesity on sentinel lymph node mapping in patients with apparent early-stage endometrial Cancer: the ObeLyX study, Gynecol. Oncol. 165 (2) (2022) 215–222.
[35] L. Dostalek, M. Zikan, D. Fischerova, R. Kocian, A. Germanova, F. Fruhauf, et al., SLN biopsy in cervical cancer patients with tumors larger than 2cm and 4cm, Gynecol. Oncol. 148 (3) (2018) 456–460.
[36] K. Red-Horse, Lymphatic vessel dynamics in the uterine wall, Placenta. 29 (Suppl A) (2008) S55-9.
[37] Y. Kadan, A. Baron, Y. Brezinov, A. Ben Arie, A. Fishman, M. Beiner, Predictors of uncommon location of sentinel nodes in endometrial and cervical cancers, Gynecol. Oncol. Rep. 39 (2022), 100917.