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Identifying safe diagnostic algorithms for sentinel lymph node mapping in high-risk endometrial cancer: The SENTIREC-endo study

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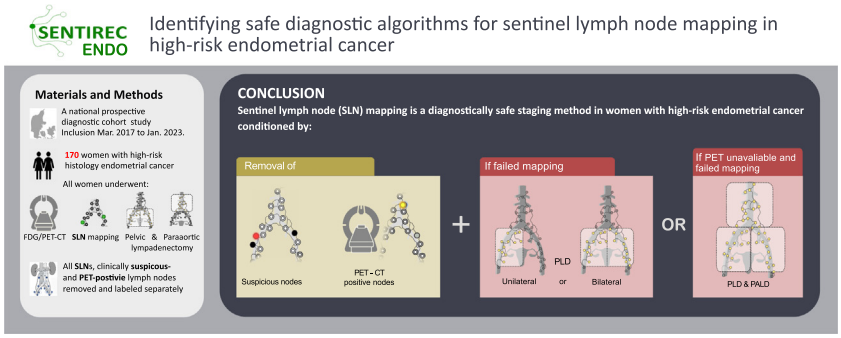
HIGHLIGHTS

- The diagnostic safety of SLN mapping for high-risk endometrial cancer is conditioned.
- A safe algorithm includes the removal of any suspicious and PET-positive lymph nodes.
- If failed SLN mapping, uni- or bilateral PLD should be performed.
- If PET/CT is unavailable, PLD and PALD are recommended in case of failed mapping.
- All accuracy analysis based on women who underwent both PLD and PALD as the reference standard.

GRAPHICAL ABSTRACT



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ABSTRACT

Introduction. It is unclear if sentinel node (SLN) mapping can replace pelvic- (PLD) and paraaortic lymphadenectomy (PALD) for high-risk endometrial cancer (EC). A diagnostically safe surgical algorithm, taking failed mapping cases into account, is not defined. We aimed to investigate the diagnostic accuracy of SLN mapping algorithms in women with exclusively high-risk EC.

Methods. We undertook a prospective national diagnostic cohort study of SLN mapping in women with high-risk EC from March 2017 to January 2023. The power calculation was based on the negative predictive value (NPV). Women underwent SLN mapping, PLD and PALD besides removal of suspicious and any FDG/PET–positive lymph nodes. Accuracy analyses were performed for five algorithms.

Results. 170/216 included women underwent SLN mapping, PLD and PALD and were included in accuracy analyses. 42/170 (24.7%) had nodal metastasis. The algorithm SLN and PLD in case of failed mapping, demonstrated a sensitivity of 86% (95% CI 74–100) and an NPV of 96% (95% CI 91–100). The sensitivity increased to

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93% (95% CI 83–100) and the NPV to 98% (95% CI 94–100) if PLD was combined with removal of any PET-positive lymph nodes. Equivalent results were obtained if PLD and PALD were performed in non-mapping cases; sensitivity 93% (95% CI 83–100) and NPV 98% (95% CI 95–100).

Conclusion. SLN-mapping is a safe staging procedure in women with high-risk EC if strictly adhering to a surgical algorithm including removal of any PET-positive lymph nodes independent of location *and* PLD *or* PLD and PALD in case of failed mapping.

1. Introduction

Lymph node metastasis is the most significant negative prognostic factor in endometrial cancer (EC) [1,2]. Surgical staging in EC serves to allocate women with lymph node metastases to adjuvant therapy with the overall purpose of improving survival [3]. Despite the lack of level 1 evidence of survival benefit [4], the standard surgical staging of early-stage, high-risk EC includes pelvic (PLD) and paraaortic (PALD) lymph node dissection. PALD is performed to identify skip metastases and to ensure macroscopic complete resection [5]. PLD is associated with morbidity, including blood loss, nerve injury, and lymphoedema [6–9]. PALD carries an even higher risk of surgical complications, including chylous ascites [10,11] and risks associated with prolonged operative time.

Sentinel lymph node (SLN) mapping is associated with decreased risk of surgical complications [12–14] and has been suggested as a safe diagnostic staging alternative for women with high-risk EC [15,16]. However, the evidence is limited as all published studies are based on mixed populations of intermediate- and high-risk EC [16–20], with diverging proportions of women who underwent PLD and PALD as the reference standard [17,19,20]. These are factors that may cause an underestimation of the false negative rate. Furthermore, the power calculations were based on sensitivity in all studies [16–18], thus neglecting the importance of evaluating the negative predictive value (NPV) of a diagnostic tool in relation to the prevalence of lymph node metastases. A consensus on the choice of a surgical algorithm in cases of failed mapping is needed, as approximately 20–48% of women with high-risk EC have failed unilateral or bilateral SLN mapping [16,17,21].

The most accurate imaging modality for detecting lymph node and peritoneal metastases in women with EC is fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) [22]. The accuracy of FDG-PET/CT is limited for small-volume disease [22,23] but may have a high sensitivity for larger metastasis >10 mm [23]. However, the role of FDG-PET/CT as an integrated part of a surgical SLN algorithm is unsettled.

The present study aims to assess the diagnostic accuracy of five surgical algorithms to identify an SLN mapping algorithm that can safely replace routine PLD and PALD in women with high-risk EC.

2. Materials and methods

2.1. Participants and study design

The SENTIREC-endo study is a national prospective multicentre diagnostic cohort study. Women were eligible if they had EC with presumed high-risk histology (Endometrioid adenocarcinoma grade 3 or non-endometrioid histology) and FIGO (International Federation of Gynaecology and Obstetrics) stage I. Women were ineligible if they had dementia, allergy to ICG or iodine, could not understand Danish, had been in active treatment for another malignancy within the past five years, were unsuitable for robotic surgery, or if PLD was discarded or previously performed. Further, women with multiple and confluent FDG-PET/CT positive lymph nodes were not considered stage I and were ineligible. From March 2017 until January 2023, women were consecutively enrolled in the study at three gynaecological cancer centres in Denmark: Rigshospitalet, Aarhus University Hospital, and Odense University Hospital, where approximately 80% of women with high-risk EC in Denmark are managed. All hospitals undertook a surgeon proficiency study before the start of inclusion [24]. All participants provided written informed consent. The study was approved by the Danish Independent Committees on Health Research (S-20150207) and the Danish Data Protection Agency (15/52037). Study data were collected and managed using the REDCap (Research Electronic Data Capture) [25,26] tools hosted at Odense Explorative Network (OPEN). The SENTIREC-endo trial was registered at clinicaltrials.gov (NCT02820506).

2.2. Procedures

2.2.1. Imaging

FDG-PET/CT was included in the standard preoperative diagnostic work-up of women with high-risk histology EC in Denmark in 2014 to enhance the detection of women with stage IV disease and to facilitate optimal treatment planning [22]. Hence, all women underwent FDG-PET/CT in accordance with the European guidelines for FDG-PET/CT tumour imaging [27]. The CT component of the scan was performed using high-dose diagnostic quality. At each centre, a clinical report of the FDG-PET/CT was prepared by trained specialists in nuclear medicine and radiology. This was carried out following national reporting recommendations which reference international reporting guidelines [27,28]. The nuclear medicine specialists subjectively rated the imaging on a, 5-point Likert scale ranging: 0 'no sign of metastasis', 1 'probably no sign of metastasis', 2 'could be benign as well as malignant', 3 'probably sign of metastasis', 4 'obvious sign of metastasis'. All FDG-PET/CT-positive lymph nodes were dichotomized; scores 0–1 were set to 'test- negative' and scores 2–4 were set to 'test-positive. All test-positive results were registered in the REDCap database, with their exact anatomical location. This information was available to the surgeon prior to surgery.

2.2.2. Surgical procedure

All surgical procedures were performed as robotic-assisted laparoscopic surgery using the da Vinci Si or Xi Surgical System (Intuitive Surgical, Sunnyvale, CA, USA). All women underwent SLN mapping and resection of any FDG-PET/CT-positive- or clinically suspicious lymph nodes, followed by per-protocol PLD and infrarenal PALD. The PALD could be abandoned or limited to the inferior mesenteric artery (IMA) level, due to surgical complications or at the discretion of the multidisciplinary conference. A frozen section evaluation was recommended for clinically suspicious lymph nodes and if metastatic disease was identified, systematic PLD and PALD were abandoned and replaced by removal of all clinically and by imaging suspicious lymph nodes in the pelvic and paraaortic area.

Indocyanine Green (ICG) was used as tracer. Injection was performed according to a national protocol, re-injection was not allowed [24]. The near-infrared fluorescence imaging system was used to identify SLNs. All SLNs, FDG-PET/CT-positive lymph nodes, and clinically suspicious lymph nodes were removed separately marked with predefined anatomic locations, and sent for pathology. Lymph nodes could be marked with several prefixes if, for example, the same lymph node appeared suspicious and was an SLN.

2.2.3. Pathology

All endometrial samples underwent pre-operative central pathological revision to confirm the presence of high-risk histology. All SLNs were examined with ultrastaging following a national standardized ultrastaging protocol including immunohistochemistry [24]. Metastatic disease was categorized according to international standards [29], with macrometastases defined as foci >2.0 mm, micrometastases >0.2 to ≤2.0 mm, and isolated tumour cells ≤0.2 mm or as individual cells staining positive for cytokeratin AE1 or AE3. The largest metastasis in each lymph node was reported.

2.2.4. Surgical algorithms

Data were analyzed according to five algorithm categories (Fig. 1) to identify the most optimal surgical approach, taking the risk of failed mapping into account. The defined algorithm-positive metastases were compared to the total sum of metastases in women who underwent SLN mapping, PLD, and PALD.

2.2.5. Statistical analyses

The study was based on a power calculation for the NPV. An NPV larger than 94% was considered acceptable for implementation of SLN mapping, and a confidence interval below 90% was deemed unacceptable for implementation. The power calculation was based on cases who underwent SLN mapping, followed by PLD and PALD as the reference standard. Assuming the true incidence of metastases is 20%, and the sensitivity of the SLN mapping algorithm is 96%, 150 women with PLD and PALD are needed to conclude that NPV is larger than 94% using a 95% one-sided exact Clopper–Pearson confidence interval. Consecutive recruitment continued until at least 150 patients with backup PLD + PALD were included. Descriptive statistics were used to summarise patient characteristics and SLN outcomes. Wilcoxon rank-sum test was used to compare continuous variables and the chi-squared test for categorical variables.

All statistical analyses were performed using Stata version 16.0 (STATA Inc., Texas, USA).

3. Results

Of the 250 women enrolled in the study (Fig. 2), 216 were included in the analyses of SLN detection and metastases. 170 women were included in the accuracy analyses; 165 women who underwent SLN + PLD + PALD as the reference standard, and five women with intraoperative verified metastatic disease on frozen section and removal of all clinically and by imaging suspicious pelvic *and* paraaortic lymph nodes (Table 3). No significant difference was observed between these women and those who underwent SLN + PLD only ($n = 45$) regarding age or comorbidity. BMI was significantly higher in the SLN + PLD group (Table 1).

3.1. SLN detection rate and lymph node metastases

The median number of SLNs removed was 3 (IQR 2–4) (Table 1). Most of the SLNs were identified in the obturator fossa ($n = 244$ (39.3%)) and around the external iliac vessels ($n = 222$ (35.7%)). Only 0.8% ($n = 5$) of SLNs were located in the paraaortic region, all on the right side below the IMA. Postoperative and pathological characteristics are given in Table 2. The total SLN detection rate was 93.5% (202/216), with 73.1% (158/216) bilateral and 20.4% (44/216) unilateral mapping, while 6.5% (14/216) had no SLN mapping. Lymph node metastases were identified in 23.6% (51/216) of the whole population; 24.7% (42/170) in the SLN + PLD+ PALD group; and 17.8% (8/45) in the SLN + PLD group. Paraaortic metastases were identified in 8.8% (15/170), and 2.9% (5/170) had an isolated paraaortic metastasis. Eight of 15 cases with paraaortic metastases were FDG-PET/CT-positive; all macrometastases ranging 4-40 mm. FDG-PET/CT-negative paraaortic metastases ranged 2.1–5.0 mm, three micro- and four as macrometastases, respectively. No paraaortic metastases were detected in an SLN. All five women with isolated paraaortic metastases had macrometastases, 3/5 were FDG-PET/CT-positive.

In total, four cases were converted to open surgery to ensure removal of FDG-PET/CT-positive lymph nodes in the paraaortic region. Of these, two had lymph node metastasis.

3.2. Accuracy analysis

The accuracy analyses of the five defined surgical algorithms are shown in Table 3. The *SLN algorithm PLD* obtained a sensitivity of 86% (95% CI 74–100) and a NPV of 96% (95% CI 91–100). The *SLN algorithm PLD + PET* raised the sensitivity to 93% (95% CI 83–100) and the NPV to 98% (95% CI 94–100). Expanding the surgical radicality to include PLD and PALD in cases of failed mapping did not improve the accuracy. Adding the FDG-PET/CT to this algorithm raised the sensitivity to 95% (95% CI 86–100) with no change in NPV, 98% (95% CI 95–100) (Table 3).

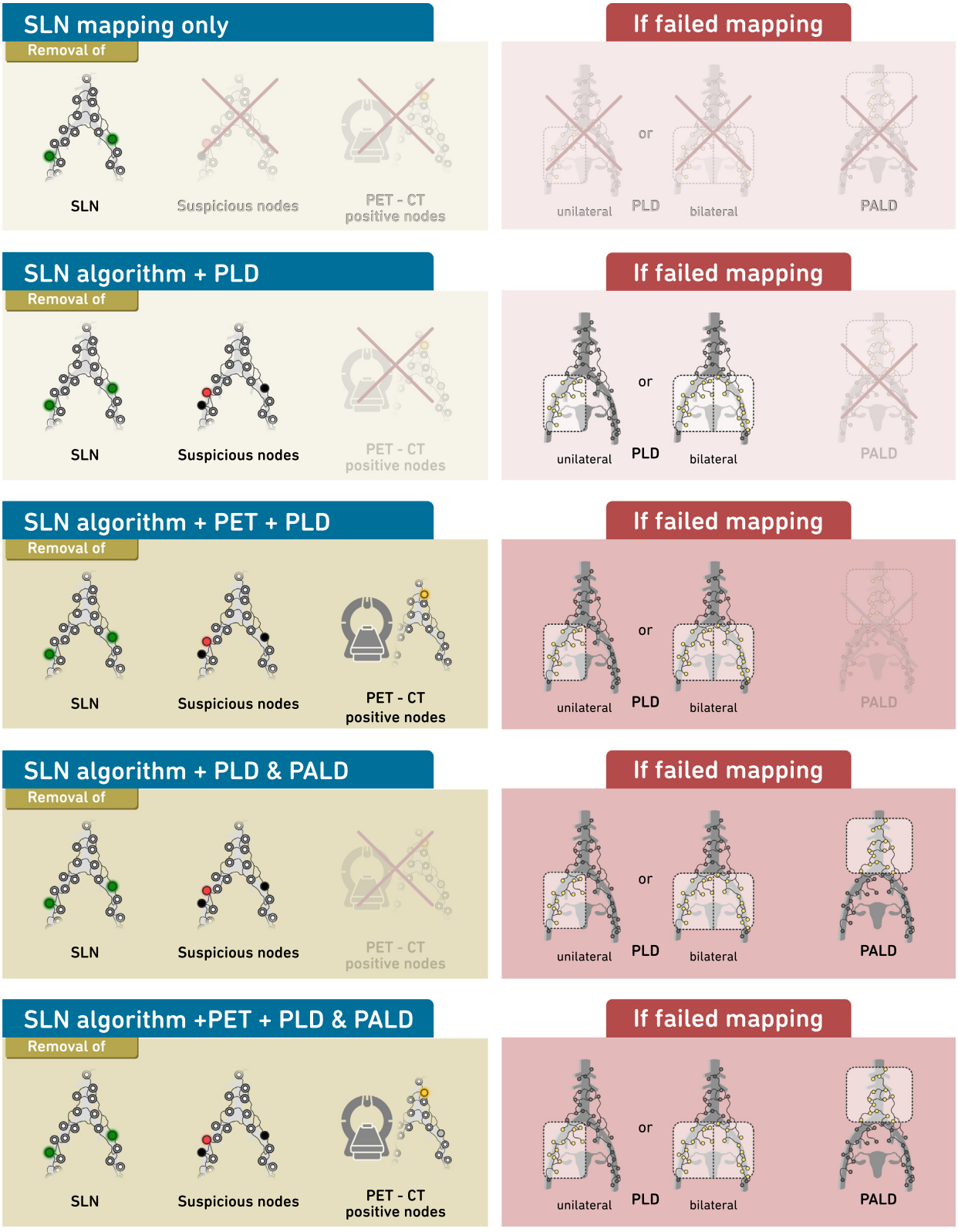
Six women were diagnostically misclassified by at least one of the five algorithms. Two women were deemed to have a false-negative result by all five algorithms. These women had bilateral SLN mapping with non-metastatic SLNs, no FDG-PET/CT-positive lymph nodes, and metastases in non-SLNs, one in the pelvic and one in the paraaortic lymph nodes. A third woman with bilateral SLN mapping with non-metastatic SLNs had several paraaortic FDG-PET/CT-positive metastases. A fourth woman had bilateral failed mapping and an FDG-PET/CT-negative paraaortic metastasis and was thus deemed false negative by the two algorithms with PLD only in the case of non-mapping. The last two women had unilateral mapping, both with FDG-PET/CT-positive paraaortic metastases and were thus deemed false negative by the *SLN algorithm PLD* but identified as true positive by the algorithms including FDG-PET/CT and the algorithm including PLD *and* PALD.

4. Discussion

To the best of our knowledge, this is the first study to evaluate the diagnostic accuracy of SLN mapping algorithms in women with exclusively high-risk histology EC that is sufficiently powered to determine the NPV, and with accuracy analysis based only on women who underwent PLD and PALD as the reference. We recommend SLN mapping *and* systematic removal of any clinically suspicious lymph nodes *and* any FDG-PET/CT-positive lymph nodes regardless of location and mapping. In cases of failed mapping, PLD should be performed in the non-mapped hemipelvises. With this approach, 98% of those with a negative algorithm have node-negative disease. For centers lacking confidence with FDG-PET/CT in this population, PLD and PALD are required in cases of failed mapping to obtain the same low rate of false negative findings. The diagnostic accuracy observed by the above two algorithms is similar to those observed for low- and intermediate-risk EC [16,17] and breast cancer [30], where the SLN mapping is implemented as the surgical staging standard.

A recent meta-analysis has suggested that SLN mapping can replace lymphadenectomy for high-risk EC [15]. However, the meta-analysis had several limitations, e.g., inclusion of studies with varying proportions and small numbers of women with high-risk histology, and several studies used PLD as the reference standard [15]. Moreover, as women with bilateral failed mapping were excluded from the accuracy analysis, no conclusions could be drawn on SLN algorithms. At least one-fourth of the patients undergoing SLN mapping for high-risk EC have uni- or bilateral failed mapping [16,17,21]. Therefore, evidence-based consensus on a surgical algorithm for non-mapping cases is required before the SLN technique can be implemented [5]. The present data represent evidence valuable for institutional adaptation of the SLN mapping technique in the high-risk EC population.

The algorithm with the removal of SLNs, any clinically suspicious lymph nodes, and ipsilateral PLD in a non-mapped hemipelvis



Abbreviations: PLD, pelvic lymph node dissection; SLN, sentinel lymph node; PALD, Paraaortic lymph node dissection

Fig. 1. Surgical algorithms.

demonstrated a sensitivity of 86% (95% CI 74–100) and an NPV of 96% (95% CI 91–100). This algorithm leaves the paraaortic region unexposed in cases of failed mapping. For high-risk EC, one significant concern of implementing SLN mapping is the risk of leaving paraaortic lymph node metastases due to the worse prognosis in women with paraaortic dissemination [32]. Thus, the ESGO/ESTRO/ESP guidelines currently

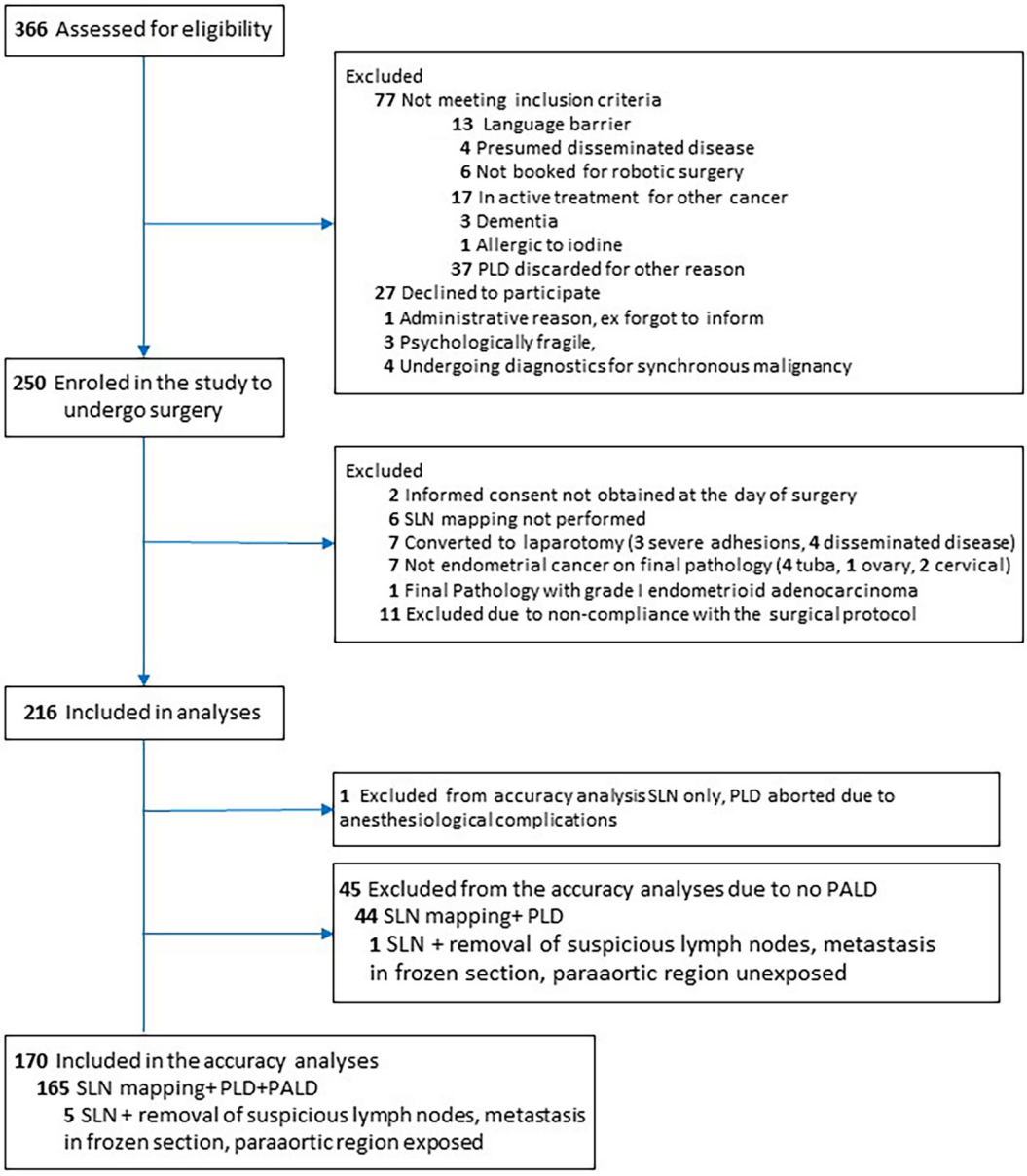


Fig. 2. Flowchart of inclusion.

recommend that if SLN mapping is implemented for high-risk EC, an algorithm should include PLD and PALD in cases of failed mapping [5]. Moreover, if pelvic lymph node metastases are identified, further para-aortic staging by either imaging or surgery should be performed [5]. The algorithm presented in this study with routine PLD and PALD in cases of failed mapping achieved a sensitivity of 93% (95% CI 83–100) and an NPV of 98% (95% CI 94–100), thus supporting the ESGO/ESTRO/ESP guidelines. However, in clinical practice, with a bilateral mapping rate of 73–75% [16], an adaptation of this algorithm would translate into a comparatively high proportion of women who should be prepared preoperatively for full PLD and PALD. In our study, the average operative time was 95 min longer for women undergoing PALD compared to PLD only, and although not significant, most postoperative complications were observed in women undergoing PALD (data not shown). Paraaortic staging with postoperative imaging may be unreliable and render a high false-positive rate and concomitant overtreatment. Therefore, it is reassuring that the surgical algorithm and targeted removal of any preoperatively detected FDG-PET/CT-positive lymph nodes, and PLD in cases of failed mapping, obtained the same sensitivity and NPV as the surgical algorithm including radical PALD. Translated into clinical practice, only women with FDG-PET/CT-positive lymph nodes in the paraaortic region would need targeted paraaortic lymph node dissection. Implementing this algorithm would thus optimize treatment planning and significantly reduce surgical time and the potentially related risk of complications without compromising the diagnostic accuracy of detecting and removing lymph node metastases.

Despite the intention to perform PALD in all women, we had to exclude 20% of the women from the accuracy analyses. These women only underwent PLD due to intraoperative difficulties or decisions

Table 1
Baseline and surgical characteristics.

	All women[1] ($n = 216$)	**SLN+ PLD+ PALD[2]** ($n = 170$)	**SLN+ PLD[3]** ($n = 45$)	**P–value**
	median (IQR)	**median (IQR)**	**median (IQR)**	
Age	71 (64–76)	70 (64–75)	74 (68–79)	0.20
BMI	27 (24–32)	26 (23−31)	30 (25–37)	0.009
Charlson Comorbidity Index (CCI)	**No. (%)**	**No. (%)**	**No. (%)**	
CCI = 0	140 (64·8)	116 (68·2)	24 (53·3)	0.24
CCI = 1	52 (24·1)	38 (22·4)	13 (28·9)	
CCI ≥ 2	24 (11·1)	16 (9·4)	8 (17·8)	
Surgical lymph node assessment				
PLD and PALD to infrarenal level	130 (60·5)	130 (76·5)	0 (0·0)	
PLD and PALD to IMA	35 (16·3)	35 (20·6)	0 (0·0)	
PLD	44 (20·5)	0 (0·0)	44 (97·8)	
No PLD, only clinically suspicious nodes	6 (2·8)	5 (2·9)	1 (2·2)	
Omentectomy				
Omentectomy infracolic	121 (56·0)	101 (59·4)	19 (42·2)	
Infra- and supracolic	2 (0·9)	2 (1·2)	0 (0·0)	
Omental biopsy	5 (2·3)	2 (1·2)	3 (6·7)	
Number of lymph nodes removed	**median (IQR)**	**median (IQR)**	**median (IQR)**	
SLNs[4]	3 (2–4)	3 (2–4)	2 (2–4)	
Pelvic non-SLN[5]	15 (12−20)	15 (12–20)	15 (12–17)	
Paraaortic non-SLN[6]	10 (6–15)	10 (6–15)	0 (0–0)	
Clinically suspicious or PET-positive	3 (1–5)	3 (1–5)	3 (1–5)	

Abbreviations: SLN, sentinel lymph node mapping; PLD, pelvic lymph node dissection; PALD, paraaortic lymph node dissection; IQR, interquartile range; BMI, body mass index. IMA: inferior mesenteric artery. [1]Including one woman without PLD and PALD and thus only visible in the column with all women. [2] Five women included after removal of only suspicious paraaortic nodes with metastasis in frozen section [3]. One woman included after removal of only suspicious pelvic nodes. [4] Includes all women, also women with failed mapping. [5] Excluding one woman without PLD. [6] Excluding five women who did not undergo PLD and PALD. [7] Only includes women with removal of suspicious or PET-positive lymph nodes.

taken in collaboration with the patient. This proportion is likely to represent the clinical reality as it equals the proportion of those not undergoing PALD in recently published series [16,18]. In our study, we found paraaortic metastases in 8.8% (15/170) of the women who all had exposure to the paraaortic region and 2.9% (5/170) had isolated paraaortic metastases. These findings are in agreement with previous

Table 2
Postoperative and histopathological characteristics.

	All women[1] (n = 216)	**SLN + PLD + PALD[2]** (n = 170)	**SLN + PLD[3]** (n = 45)	***P*-value**
SLN detection	**No. (%)**	**No. (%)**	**No. (%)**	
Total detection rate	202 (93.5)	157 (92·4)	44 (97·8)	
Bilateral SLN detection	158 (73·1)	127 (74·7)	30 (66·7)	
Unilateral SLN detection	44 (20·4)	30 (17·6)	14 (31·1)	
No SLN detection	14 (6·5)	13 (7·6)	1 (2·2)	
Lymphovascular space invasion	43 (20·0)	32 (18·9)	10 (22·2)	
Lymph node metastasis	51 (23·6)	42 (24·7)	8 (17·8)	0·33
Paraaortic metastasis	15 (6·9)	15 (8·8)	–	
Isolated paraaortic metastasis	5 (2·3)	5 (2·9)	–	
Size category of metastases				
Macrometastasis (> 2·0 mm)	34 (66·7)	31 (73·8)	3 (37·5)	0·06
Micrometastasis (> 0·2 to ≤2·0 mm)	11 (21·6)	6 (14·3)	4 (50·0)	
Isolated tumour cells (≤ 0·2 mm)	6 (11·8)	5 (11·9)	1 (12·5)	
Final FIGO stage				
FIGO IA	119 (55·1)	88 (51·8)	31 (68·9)	
FIGO IB	20 (9·3)	16 (9·4)	4 (8·9)	
FIGO II	18 (8·3)	16 (9·4)	2 (4·4)	
FIGO IIIA	4 (1·9)	4 (2·4)	0 (0·0)	
FIGO IIIB	4 (1·9)	4 (2·4)	0 (0·0)	
FIGO IIIC1	34 (15·7)	26 (15·3)	7 (15·6)	
FIGO IIIC2	11 (5·1)	11 (6·5)	0 (0·0)	
FIGO IVA	0 (0·0)	0 (0·0)	0 (0·0)	
FIGO IVB	6 (2·8)	5 (2·9)	1 (2·2)	
Final Histology				
Endometrioid adenocarcinoma grade III	37 (17·1)	29 (17·1)	8 (17·8)	
Serous adenocarcinoma	100 (46·3)	84 (49·4)	15 (33·3)	
Clear cell adenocarcinoma	36 (16·7)	25 (14·7)	11 (24·4)	
Un- or de-differentiated carcinoma	3 (1·4)	3 (1·8)	0 (0·0)	
Carcinosarcoma	34 (15·7)	24 (14·1)	10 (22·2)	
Mixed type II Histology	5 (2·3)	4 (2·4)	1 (2·2)	
Mesonephric-Like Adenocarcinoma	1 (0·5)	1 (0·6)	0 (0·0)	
Adjuvant treatment	72 (33·8)	61 (36·5)	10 (22·2)	

Abbreviations: SLN, sentinel lymph node mapping; PLD, pelvic lymph node dissection; PALD, paraaortic lymph node dissection; BMI, body mass index; FIGO, The International Federation of Gynaecology and Obstetrics. [1]Including one woman without PLD and PALD and thus only visible in the column with all women. [2] Five women included after removal of only suspicious paraaortic nodes with metastasis in frozen section [3]. One woman included after removal of only suspicious pelvic nodes.

Table 3
Accuracy analysis based on different surgical algorithms for women with high-risk endometrial cancer.

Surgical algorithm	True positive No.	True negative No.	Sensitivity (CI)	NPV (CI)
SLN only			71 (58–100)	91 (86–100)
Positive SLN	30	0		
Negative SLN or failed mapping	12	128		
SLN algorithm PLD			86 (74–100)	96 (91–100)
Positive algorithm PLD	36	0		
Negative algorithm PLD	6	128		
SLN algorithm PLD + PET			93 (83–100)	98 (94–100)
Positive algorithm PLD + PET	39	0		
Negative algorithm PLD + PET	3	128		
SLN algorithm PLD PALD			93 (83–100)	98 (94–100)
Positive algorithm PLD PALD	39	0		
Negative algorithm PLD PALD	3	128		
SLN algorithm PLD PALD +PET			95 (86–100)	98 (95–100)
Positive algorithm PLD PALD +PET	40	0		
Negative algorithm PLD PALD +PET [2]	2	128		

Abbreviations: SLN, sentinel lymph node mapping; PLD, pelvic lymph node dissection; PALD, paraaortic lymph node dissection; PET; fluorodeoxyglucose positron emission tomography.
Positive algorithm; algorithm finds metastases. Negative algorithm; algorithm finds no metastases.
True Positive: Metastasis in any lymph nodes. True negative: No metastasis in any lymph nodes.

studies [33–36], albeit somewhat higher than the 1% isolated paraaortic metastasis reported in the SHREC study [18]. This proportion is, however, likely underestimated due to the inclusion of patients with intermediate-risk histology EC and 20% who had the paraaortic region left unexposed [18].

Two recent retrospective studies on FDG-PET/CT found a 100% sensitivity to detect para-aortic metastases in high-risk EC, whereas the sensitivity for pelvic metastasis was lower 58–60% [23,37]. Both studies suggest that FDG-PET/CT may strengthen the credibility of the SLN algorithm by improving the diagnostics of metastatic lymph nodes in the paraaortic region [23,37]. As FDG-PET/CT has a high sensitivity to larger metastases (> 10 mm) [22,23,37], adding FDG-PET/CT may optimize the diagnostics in the paraaortic region and ensure macroscopic complete resection [5,38]. A randomized study found that 80% of paraaortic metastases were located above the IMA and concluded that PALD to the level of the IMA may be insufficient to reveal the full extent of lymph node metastases in high-risk EC [35]. However, performing routine PALD above the IMA may carry a higher risk of complications, significantly increase the surgical time, and challenge even the highly skilled surgeon. In our study, 20% (35/170) of the women underwent PALD to the IMA only despite the intention to fully expose the infrarenal level. Adding the removal of any FDG-PET/CT-positive lymph nodes to the algorithm with PLD in cases of failed mapping identified another three women with FDG-PET/CT-positive paraaortic macrometastases. Further conversion to open surgery in four cases to ensure the removal of FDG-PET/CT-positive lymph nodes in the paraaortic region revealed another two cases with metastatic lymph nodes. Hence, adding FDG-PET/CT imaging to the clinical staging and complete resection efforts in high-risk EC seems to reduce the risk of overlooking paraaortic metastatic disease. Incorporating FDG-PET/CT into the preoperative staging process could have implications on healthcare costs. The cost-effectiveness of integrating FDG-PET/CT into the diagnostic work-up should be evaluated in the light of savings regarding optimized treatment planning and from less radical surgery in patients with potential lymph node metastases.

In 2023 the FIGO classification was changed to include molecular classification [39]. Our study did not include molecular profiling and we are therefore not able to identify women who could be candidates for adjuvant treatment based on this information. We aimed to provide evidence for clinicians to potentially offer less radical surgery to the majority of patients with high-risk EC, without compromising the identification of lymph node metastases, as these women are likely to have a survival benefit of adjuvant treatment [40]. Future studies should uncover the contribution of molecular profiling, surgical staging, and imaging, in the risk stratification, allocation to adjuvant treatment, and survival in women with high-risk EC.

4.1. Strengths and limitations

The major strength of this study is its multicentre prospective design and the inclusion of consecutive patients in a national setting. The population was homogenous in terms of histology, surgery, ICG injection, and ultrastaging protocol. In the optimal setting, a study evaluating the different histologies separately would have been preferable. Due to the rarity of the different high-risk histologies (serous-, clear cell-, and endometrioid adenocarcinoma grade 3, carcinosarcoma etc), obtaining sufficient power in such study is not realistically accomplished. However, in contrast to prior studies in the field [16–19], we only included women with histologically verified high-risk histology. The power calculation was based on the NPV, as predictive values are recommended in a clinical diagnostic setting [41]. The surgery was performed in a real-life clinical setting including gynaecological-oncological specialist apprenticeship, making the study generalizable to other countries with similar centralization of gynaecological cancer surgery. That 20% of the women only underwent PALD to the IMA may have caused an underestimation of metastatic lymph nodes and hence, the sensitivity and the NPV. However, adding systematic FDG-PET/CT and removal of any image-positive lymph nodes likely reduced the risk of missing macroscopic disease. The FDG-PET/CT interpretations were conducted using a subjective Likert scale. This could compromise the reproducibility of these assessments.

5. Conclusion

Sentinel node mapping can replace routine systematic PLD and PALD in women with high-risk histology EC. However, a diagnostically safe clinical adaptation demands removal of any FDG-PET/CT-positive lymph nodes independent of location and mapping *and* full adherence to an algorithm including PLD in cases of failed mapping. For centres lacking confidence in the interpretation of FDG-PET/CT in this population, PLD and PALD are required in cases of failed mapping.

Authorship contribution statement

PTJ, OM, SMB, SES and MGH contributed to study conceptualisation. PTJ, OM, SMB and SES contributed to funding acquisition and project

administration. PTJ, OM, MGH, KB and SMB contributed to writing – original draft and methodology. PTJ, SMB and EP contributed to visualization. SMB and EP contributed to formal analysis. PTJ, OM, KB, EP and MGH contributed to supervision. PTJ and SMB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the data curation, investigation, validation, writing- review & editing and shared the final responsibility for the decision to submit for publication.

CRediT authorship contribution statement

Sarah Marie Bjørnholt: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Ole Mogensen:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **Kirsten Bouchelouche:** Data curation, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing. **Sara Elizabeth Sponholtz:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Validation, Writing – review & editing. **Erik Thorlund Parner:** Data curation, Formal analysis, Investigation, Supervision, Validation, Visualization, Writing – review & editing. **Malene Grubbe Hildebrandt:** Conceptualization, Data curation, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing. **Annika Loft:** Data curation, Investigation, Validation, Writing – review & editing. **Gudrun Neumann:** Data curation, Investigation, Validation, Writing – review & editing. **Signe Frahm Bjørn:** Data curation, Investigation, Validation, Writing – review & editing. **Katja Dahl:** Data curation, Investigation, Validation, Writing – review & editing. **Algirdas Markauskas:** Data curation, Investigation, Validation, Writing – review & editing. **Ligita Paskeviciute Frøding:** Data curation, Investigation, Validation, Writing – review & editing. **Pernille Tine Jensen:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

There are no conflicts of interest to disclose.

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