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Original Research

Pelvic Sentinel lymph node detection in High-Risk Endometrial Cancer (SHREC-trial)—the final step towards a paradigm shift in surgical staging

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Endometrial cancer;
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Abstract ***Study aims:*** To prospectively assess the diagnostic accuracy of a pelvic sentinel lymph node (SLN) algorithm in high-risk endometrial cancer (HREC).
Patients and methods: Consecutive women with presumed FIGO stage I-II HREC underwent robotic surgery at two academic centres by five accredited surgeons. An anatomically based algorithm was adhered to, following cervical injection of indocyanine green (ICG), with reinjection of tracer in case of non-display of predefined lymphatic pathways. After removal of SLNs, a pelvic and infrarenal para-aortic lymphadenectomy was performed. Primary endpoint was sensitivity of the SLN-ICG algorithm. Secondary end-points were sensitivity of the overall SLN algorithm (including macroscopically suspect nodes as SLNs), SLN mapping rates and morbidity of the SLN procedure.
Results: Two hundred fifty-seven women were analysed; 54 had pelvic lymph node metastases (LNMs), and 52 of those were correctly identified by the SLN-ICG algorithm. In two women (one with false-negative ICG-SLNs and one non-mapped woman), the pelvic LNMs were identified by the overall SLN algorithm. The SLN-ICG algorithm had a sensitivity of 98% (95% confidence interval [CI] 89–100) and a negative predictive value of 99.5% (95% CI 97–100). The sensitivity of the overall SLN algorithm was 100% (95% CI 92–100) and the negative predictive value was 100% (95% CI 98–100). The bilateral mapping rate was 95%. Two women (1%) had isolated para-aortic metastases. No adverse events occurred during the SLN procedure.

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Conclusion: With a complete sensitivity to detect pelvic LNMs, the described pelvic SLN algorithm can, in the hands of experienced surgeons, exclude overall nodal involvement in 99% and thereby safely replace a full lymphadenectomy in HREC.
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1. Introduction

The current European guidelines recommend a pelvic lymph node dissection (PLND) and infrarenal para-aortic lymph node dissection (IRPALND) in high-risk endometrial cancer (HREC) [1]. Whether a lymphadenectomy is merely diagnostic or has a therapeutic value remains unclear [2–4]. Depending on risk criteria used, approximately 20% of patients with HREC have lymph node metastases (LNMs) [5]. The preoperative and postoperative risk assessment may differ in as much as one-fifth of women with presumed HREC [6,7]. Consequently, many women are subjected to an unnecessary full staging procedure. Comprehensive staging is often technically challenging. Perioperative and, in particular, postoperative lymphatic complications are not uncommon [8–10]. Therefore, a less invasive procedure would carry significant clinical value [11].

Sentinel lymph node (SLN) mapping in endometrial cancer (EC) has been recognised during the last decade [6,12–17]. Indocyanine green (ICG, Pulsion medical system, PICG0025SE, Feldkirchen, Germany) has emerged as the most effective tracer [18]. A major step forward for the SLN concept in EC was the insight that a peritumoural injection could be abandoned in favour of cervical injection [6,19,20]. An algorithm that includes the resection of macroscopic suspicious lymph nodes also reduces the false-negative rate [21]. Histopathological ultrastaging and immunohistochemistry (IHC) on representative lymph nodes further increase the detection rate of LNMs [22,23].

An ideal SNL biopsy concept requires a high bilateral mapping rate with a high sensitivity for locating LNMs without need for para-aortic dissection. A majority of available studies show insufficient detection rates and/or define para-aortic SLNs, the latter questionable from a lymphatic anatomy perspective [15,17]. For instance, even though a large prospective study comparing sentinel lymph node biopsy to lymphadenectomy in patients with endometrial cancer (FIRES trial) demonstrated a high sensitivity for detecting metastases, the low bilateral detection rate and the need for inclusion of para-aortic SLNs in the algorithm lead to the exposure of a not insignificant number of patients to the morbidity of at least a unilateral pelvic lymphadenectomy and/or a paraaortic dissection, thereby deviating from an ideal SLN concept [16,24]. Even though the inclusion of surgeons new to the technique in the FIRES study lead to the generalisability of results, the true potential of a sentinel node concept was not demonstrated. Hence, further studies are needed to establish the optimal prerequisites for an SLN concept in EC.

The aim of this study was to evaluate the diagnostic accuracy of a surgically and anatomically defined SLN-ICG algorithm and overall SLN algorithm for the detection of pelvic LNMs in women with HREC when performed by select high-volume robotic surgeons. Furthermore, the unilateral and bilateral mapping rates and morbidity of the procedure were investigated.

2. Material and methods

The pelvic SLN detection in high-risk endometrial cancer (SHREC) study is a prospective non-randomised trial. Consecutive women, with presumed International Federation of Obstetrics and Gynecology stage I-II HREC, were assessed for eligibility (Table 1). The extent of myometrial and/or cervical invasion as well as presence of locally advanced disease was evaluated by expert vaginal ultrasonography or MRI. All patients underwent a preoperative computed tomography scan of the thorax and abdomen. Preoperative histological diagnosis and grade was decided on specimen obtained from endometrial biopsy, hysteroscopy or curettage. Written informed consent was obtained from all enrolled women. The study was approved by the respective institutional review boards (Skåne University Hospital, Dnr 2013/163, Karolinska University Hospital Dnr Ö 7-2017) and registered at Clinical Trials.gov (NCTO02690259).

The SHREC study was conducted at two Swedish tertiary referral centres (Skåne University Hospital, Lund [June 2014–May 2018] and Karolinska University Hospital, Stockholm [May 2017–May 2018]) with 8-year prior experience in robotic surgery and an annual caseload of 180–250 EC procedures. Participating surgeons ($n = 5$) were required to have performed at least 100 robotic procedures prior to partaking in a case observation and a local audit performed by the principal investigator (J.P.) to ensure adherence to protocol. Enrolled women were scheduled for robotic hysterectomy, bilateral salpingo-oophorectomy, pelvic SLN biopsy and PLND and IRPALND, the latter omitted in a minority of women due to relative comorbidity. If applicable, an infracolic omentectomy was

Table 1
Eligibility criteria for women with high-risk endometrial cancer planned for a pelvic sentinel lymph node biopsy followed by a pelvic and para-aortic lymphadenectomy.

Inclusion criteria (all fulfilled)	- Age 18 years and older at the time of informed consent. - A pathologically proven endometrial carcinoma of any histologic subtype, clinically stage I-II planned for primary surgery. - At least one of the following preoperative high-risk criteria (endometrioid cancer FIGO grade III, a non-endometrioid histology, ≥50% myometrial tumour invasion, cervical stromal invasion or, until February 14th 2017, a non-diploid cytometry). - Ability to understand and sign an informed consent in Swedish language.
Exclusion criteria (none fulfilled)	- Non-consenting patients. - Pregnancy - Inability to understand written and/or oral study information. - WHO performance status III or more excluding BMI>40 kg/m^2. - Age > 85 years and WHO performance status II or more. - Surgical contraindication to a laparoscopic approach or lymphadenectomy at surgeon's discretion. - Anaesthesiologic contraindication to a laparoscopic approach at the anaesthetist's discretion. - Preexisting lower limb lymphoedema grade II or more. - Locally advanced disease or intra-abdominal/distant metastases at preoperative CT, MRI or ultrasonography. - Allergy to iodine. - A known liver disease. - A bleeding disorder or mandatory antithrombotic treatment.

CT, computed tomography; MRI, Magnetic resonance imaging; BMI, body mass index.

performed. A da Vinci® Si or Xi Surgical System was used (Intuitive Surgical, Sunnyvale, CA, USA).

The SLN procedure was performed according to a defined anatomically based surgical algorithm [25]. A 2.5 mg/ml sterile water solution of ICG was prepared. A 23G x 1 $^1/_2$″ needle was used to slowly inject 0.25 ml into the cervix at 2, 4, 8 and 10 o'clock, respectively. Half the volume was injected submucosally, the remaining half injected three centimetres into the cervical stroma. A compression-free fornix presenter without an intracervical device was used. The FireFly® mode was utilised for identification of the upper paracervical pathway (UPP) and lower paracervical pathways (LPP) [6]. If a pathway was not visualised through the peritoneum, the avascular presacral, paravesical and pararectal planes were opened, keeping the lymphatic vessels intact. In case of non-display in any pathway after 10 min, an ipsilateral reinjection at 3 or 9 o'clock of 0.25 ml of the ICG solution was performed. SLN type 1 was defined as the juxtauterine ICG-positive node with an afferent ICG-positive lymph vessel in the UPP and LPP, respectively, with possible parallel lymphatics in the UPP to the external, common iliac and obturator areas. In case of an ICG-positive pathway with no ICG-positive nodes, the node draining the ICG-positive lymphatic channel was defined as SLN type 2. Nodes macroscopically suspect of metastatic disease were defined as SLN-macro, regardless of ICG uptake. The upper paracervical parametria were removed separately and treated as SLN tissue. The positions and types of SLNs were drawn on an anatomical chart. After removal of SLNs, a PLND and IRPALND were performed. A standardised chart of defined dissected lymph node stations was used with corresponding anatomical positions and numbers on premade labelled jars (Appendix D).

All SLN tissues were embedded and bisected if the minimum thickness exceeded 3 mm. Ultrastaging using haematoxylin and eosin staining (H&E) was performed in five sections at three different levels, 200 μm apart, if the maximum diameter of the sentinel node tissue exceeded 1 mm. IHC with staining for pan-cytokeratin and cytokeratin MNF 116 was performed.

Non-SLNs with a thickness less than 3 mm were embedded entirely, and for nodes exceeding 3 mm, at least half the node was embedded. Non-SLNs were stained with H&E but were not subjected to IHC. Metastatic disease was classified according to a modification of the American Joint Committee on Cancer staging definitions for axillary nodes in breast cancer (macrometastases = tumour greater than 2.0 mm in diameter, micrometastases = tumour cell aggregates between 0.2 and 2.0 mm in diameter, isolated tumour cells = individual tumour cells or aggregates that are less than 0.2 mm in diameter and less than 200 cells) [26]. The pathologists were not blinded to the results of SLNs and non-SLNs when performing their assessment.

Adverse events that caused death or were considered life threatening, unexpected and/or related to study intervention were to be reported within 24 h to the study coordinator and to the Safety Monitoring Committee for clinical studies at the respective centres for an independent evaluation.

All adverse events occurring after injection of ICG were registered, and their relation to the different steps of the surgical procedure was noted. Complications up

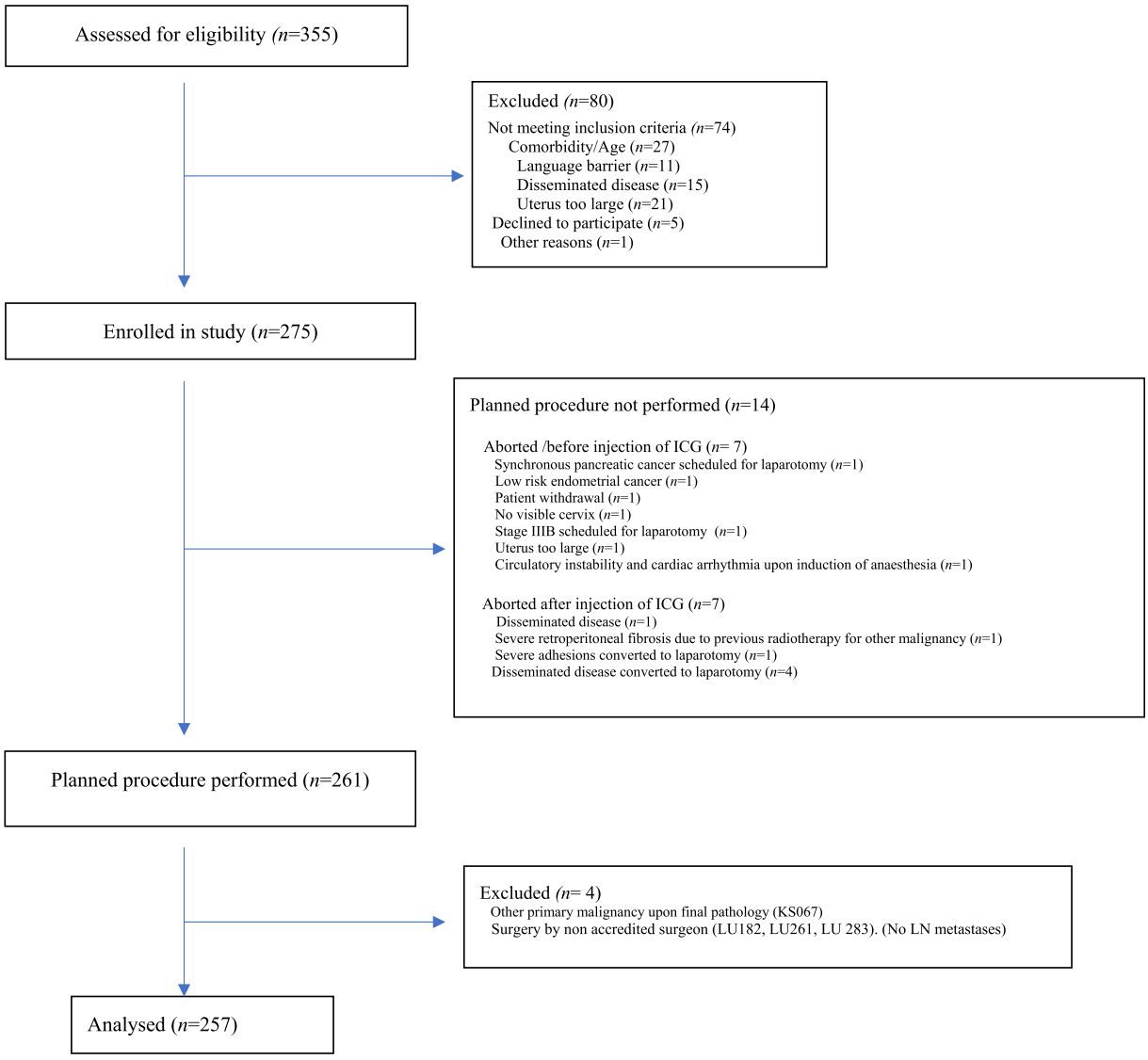

Fig. 1. Strobe flowchart for consecutive women with presumed high-risk endometrial cancer assessed for eligibility for a prospective study evaluating a pelvic sentinel node concept using a cervical injection of indocyanine green as tracer during robot-assisted surgery. Women were planned for a completory pelvic and para-aortic lymphadenectomy after the detection of sentinel lymph nodes.

to 30 days postoperatively were classified according to the Clavien-Dindo classification [27].

2.1. Statistical plan and analysis

The analysis of sensitivity and negative predictive value was evaluated per patient with regard to the SLN-ICG- and the overall SLN algorithms. As at least a full PLND was performed after the removal of SLNs, each woman served as her own control in terms of pelvic nodal status. All women who underwent the planned procedure according to protocol were included in the analyses of the primary outcome. All women injected with ICG were included in the safety assessment.

As it has the highest probability of early termination under the efficacy hypothesis, we used the Fleming two-stage design for determination of the sample size, interim analysis and decision to stop accrual based on sensitivity [28]. The null hypothesis that sensitivity was 85% was tested against a one-sided alternative with a desired sensitivity of at least 92.5%. The interim analysis was planned after 50 ICG-mapped women with pelvic LNMs were identified. Enrolment was paused, and interim analyses were performed accordingly. Enrolled women awaiting final histology at this point were included.

If the number of patients with pelvic LNM correctly identified by at least one ICG-mapped SLN was equal to or lower than 43, the study would be stopped for futility. If the number of patients identified was equal to or higher than 48, the hypothesis of inefficacy could be rejected with no further enrolment. If the total number

of success was between the lower and the upper cut-off points, the trial would continue by including an additional 69 patients with pelvic LNMs. The hypothesis of inefficacy would be rejected if 107 or more patients with pelvic LNMs were correctly identified by an ICG-mapped SLN. This design yielded a type 1 error of 0.05 and a power of 0.8 when the true sensitivity is 92.5%.

Exact 95% confidence intervals (CIs) and sensitivity and negative predictive values are reported and estimated by proportions. Descriptive data are presented with numbers and percentage or median and range.

3. Results

A total of 355 women were assessed for eligibility, 275 women were enrolled and 257 women were included in the final analysis (Fig. 1). Demographic and clinical data are presented in Table 2.

The ICG-SLN algorithm had a sensitivity of 98% (95% CI 89–100) and a negative predictive value of 99.5% (95% CI 97–100). The corresponding values for the overall SLN algorithm were 100% (95% CI 92–100) and 100% (95% CI 98–100).

Prior to and after reinjection, the bilateral mapping rate was 82% and 95%, respectively. An incomplete lymphatic mapping was more common in women with LNMs (8/54 vs. 6/203, $p < 0.001$) (Appendix A).

All 257 women underwent pelvic SLN mapping and a PLND. An IRPALND was performed in 208 (81%) women. The median number of pelvic and para-aortic nodes was 29 (range 8–75) and 12 (range 2–51), respectively. The median number of type 1–2 SLNs was 4 (range 1–7) when evaluated intraoperatively and 6 (1–22) after final histology. The location of SLNs is shown in Fig. 2. Fifty-four women had pelvic LNMs, and 52 of those were correctly identified by the SLN-ICG algorithm. In two women (one had false-negative ICG-SLNs and one woman was not mapped), the pelvic LNMs were identified as SLN-macro, i.e by the overall SLN algorithm.

Nineteen of the 52 women (37%) with ICG-mapped metastatic SLNs had only micrometastases or isolated tumour cell aggregates in their SLN's; three of these women (16%) had para-aortic LNM constituting 13% of women with para-aortic LNM (Table 3).

Eleven of the 56 (20%) women with LNMs had presacral LNMs, and 27% of these did not map along the LPP. One woman had an isolated presacral LNM. Presacral SLN-LNMs were more common in women with a non-endometrioid histology ($p = 0.03$). One hundred eight patients (42%) had lymph nodes in the resected parametria, and eight (3%) had metastatic parametrial nodes (Table 3, and Appendix B).

According to the final histology, erroneous risk group allocation occurred in 37 women, mainly due to preoperative overestimation of myometrial depth invasion in women with endometrioid histology. Three (8%) of the incorrectly staged true low risk endometrial cancer (LREC) had LNM compared with 26% of the true HREC ($n = 220$).

Table 2
Characteristics of 257 patients with preoperatively presumed high-risk endometrial cancer operated with robotic hysterectomy, a pelvic sentinel lymph node (SLN) biopsy and a completory pelvic and para-aortic lymphadenectomy.

Variable n (%) or median (range) as appropriate	
Age (years)	71 (44–90)
Body mass index (kg/m^2)	26.7 (17.3–47.3)
ECOG performance status	
0	234 (91%)
1	23 (9%)
ASA-class	
I	66 (25.7%)
II[a]	191 (64.9%)
Previous malignancy	70 (26.9%)
Postoperative histology	
Endometrioid adenocarcinoma FIGO grade I-II	132 (51.4%)
Endometrioid adenocarcinoma FIGO grade III	34 (13.3%)
Serous adenocarcinoma	59 (23%)
Clear cell adenocarcinoma	13 (5%)
Carcinosarcoma	13 (5%)
Other	6 (2.3%)
Stage (FIGO 2009)	
I	180 (70%)
II	13 (5.1%)
IIIA-B	3 (1.1%)
IIIC1	33 (12.8%)
IIIC2[b]	23 (10.6%)
IVA-B	5 (1.9%)
Uterine stage (irrespective of the overall surgical stage)	
Ia	140 (54.5%)
Ib	90 (35%)
II	27 (10.5%)
High risk (preoperatively assessed)	257 (100%)
High risk (postoperatively assessed)	220 (85.6%)
Operative time (skin to skin, minutes)	224 (115–440)
Estimated blood loss (mL)	50 (0–1400)
Conversion to laparotomy[c]	9 (3.5%)
Surgical lymph node assessment	
SLN + pelvic + infrarenal para-aortic LND	208 (80.9%)
SLN + pelvic + inframesenteric para-aortic LND	9 (3.5%)
SLN + pelvic LND	40 (15.6%)
Pelvic lymph node count	29 (8–75)
Para-aortic lymph node count[b]	12 (2–51)
Patients with LNM	56 (21.8%)
Patients with isolated para-aortic metastases[b]	2 (1%)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; ASA, American Society of Anesthesiologists; FIGO, International Federation of Obstetrics and Gynecology; LND, lymph node dissection; LNM, lymph node metastases.

[a] Including ASA class III due to body mass index ≥40.

[b] Among patients with a para-aortic lymphadenectomy.

[c] Including conversions due to disseminated disease.

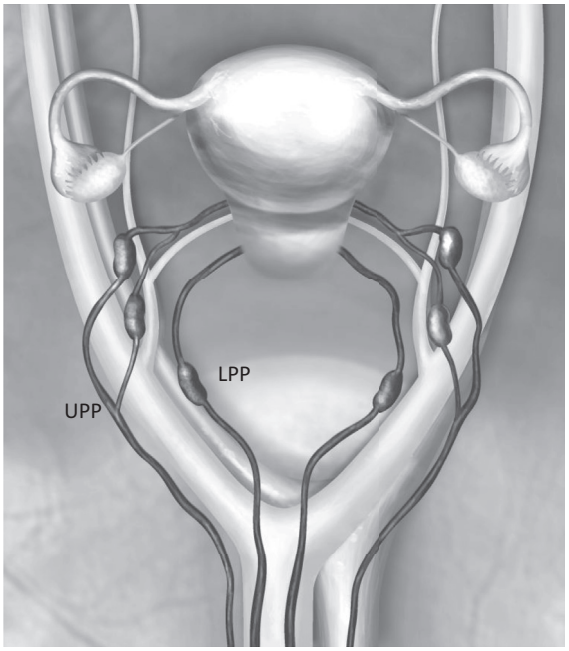

Fig. 2. Distribution and typical localisations of pelvic sentinel nodes defined by indocyanine green (ICG) and proportion of metastatic sentinel nodes per pelvic lymphatic compartment/uterine lymphatic pathway in high-risk endometrial cancer. [1]Percentages refer to the total number of patients/[2]percentages refer to the total number of node-positive patients; more than one indocyanine green−positive or metastatic sentinel lymph node was possible per patient. UPP, upper paracervical pathway; LPP, lower paracervical pathway. Left parametrium: lymph nodes in 18 of 56 patients, of which four were metastatic. Right parametrium: lymph nodes in 22 of 56 patients, of which five were metastatic.

Table 3
Frequency and localisation of metastatic lymph nodes in 257 patients with preoperatively assessed high-risk endometrial cancer operated with a pelvic sentinel lymph node biopsy followed by a pelvic and para-aortic lymphadenectomy.

Localisation of metastatic lymph nodes	Endometrioid histology (n = 166)		Non-endometrioid histology (n = 91)	
Metastatic lymph nodes (all positions)	31 (18.7%)		25 (27.5%)	
Upper paracervical pathway	31 (18.7%[a]/100%[b])		22 (24.2%[a]/88%[b])	
Lower paracervical pathway	3 (1.8%[a]/9.7%[b])		8[c] (8.8%[a]/32%[b])	
Para-aortic	10 (7.4%[d]/40%[e])		13 (15.9%[d]/54.2%[e])	
Isolated para-aortic	0 (0%[d]/0%[e])		2 (2.4%[d]/8.3%[e])	
In sentinel lymph nodes only	18 (10.8% [a]/58.1%[b])		11 (12.1% [a]/44%[b])	
Parametria	5 (3.1% [a]/16.1%[b])		3 (3.3% [a]/12%[b])	
Identified by SLNs with micrometastases or isolated tumour cells only	11 (6.6% [a]/35.5%[b])		8 (8.8% [a]/32%[b])	
Micrometastases in 1 SLN	2 (6.4%[b])		3 (12%[b])	
Micrometastases in >1 SLN	3 (9.7%[b])		1 (4%[b])	
Isolated tumour cells in 1 SLN	4 (12.9%[b])		2 (8%[b])	
Isolated tumour cells in >1 SLN	2 (6.4%[b])		2 (8%[b])	
	Para-aortic metastases	Pelvic metastases in Non-SLN	Para-aortic metastases	Pelvic metastases in Non-SLN
Micrometastases in 1 SLN	0/2	0/2	1/3	0/3
Micrometastases in >1 SLN	1/3	1/3	0/1	0/1
Isolated tumour cells in 1 SLN	0/2[d]	0/4	0/2	0/2
Isolated tumour cells in >1 SLN	0/2	0/2	1/2	0/2

[a] All women with that histology.
[b] All node-positive women with that histology.
[c] One isolated.
[d] All node-positive women with a para-aortic lymphadenectomy with that histology.
[e] All women with a para-aortic lymphadenectomy with that histology.

An intention-to-treat analysis was performed with regard to adverse events, i.e., all women in whom ICG was injected ($n = 268$). In nine women, a conversion to laparotomy was necessary (Fig. 1) and eight (3%) experienced an intraoperative complication. No adverse events occurred during injection of ICG or during the SLN procedure *per se*.

Eighty-five (32%) women had a postoperative complication within 30 days after surgery. According to the Clavien-Dindo classification, 64 (24%) had grade I-II, 19 (7%) had grade III and two (1%) had grade IV complication. Nine women (3%) experienced a serious adverse event, three during surgery and six after surgery. The readmission and reoperation rate within 30 days postoperatively was 3% and 7%, respectively (Appendix C).

4. Discussion

The overall pelvic SLN algorithm applied in the SHREC trial demonstrates a sensitivity to identify pelvic LNMs of 100% mainly due to a 95% bilateral mapping rate and a 98% sensitivity of the SLN-ICG algorithm.

Importantly, the SHREC algorithm exclusively considered pelvic disease, thereby keeping with a minimalistic surgical approach. Neither did this impact the sensitivity of detection of LNMs nor did it increase the rate of isolated para-aortic LNMs. The uterine lymphatic drainage continues via the UPP and LPP to the inframesenteric and subsequently to the infrarenal para-aortic area [6]. Consequently, an inframesenteric SLN would require the absence of nodes along the pelvic pathways which was not seen in the SHREC trial. Neither were ICG-positive supramesenteric nodes, originating from a mapped infundibulopelvic pathway observed. Logically, inframesenteric ICG-positive nodes should be considered as secondary echelon nodes and supramesenteric SLNs are rarely definable. Inadequately defined SLNs, in our opinion, account for para-aortic SLNs reported by other authors [16,24].

Although the inability to detect extrapelvic disease limits the diagnostic accuracy, the used pelvic SNL algorithm is supported by a lower rate of isolated para-aortic metastases than previously reported [5,9,29]. The high mapping rate and ultrastaging of SLNs account for this finding, where the latter identified micrometastases or isolated tumour cell aggregates only in the sentinel nodes of 13% of patients with para-aortic LNMs, decreasing the rate of true isolated para-aortic LNMs from 2.4% to 1%.

A recent review reported a pooled bilateral SLN mapping rate of 61% and a sensitivity of 94% [30]. This is lower than the present trial, even though several of the included studies identified both pelvic and para-aortic SLNs [30]. In the SHREC trial, the anatomically based algorithm, reinjection of tracer and surgical proficiency were, in our opinion, crucial for achieving the high bilateral mapping rate essential for the general acceptance of an SLN concept, in particular, in women with LREC. If widely adopted, the proposed SLN-ICG algorithm would have necessitated a unilateral and bilateral site-specific lymphadenectomy in as few as 4% and 1%, respectively, and even fewer with the overall SNL algorithm. The lower ICG mapping rate in women with LNMs further emphasises the importance of surgical experience to correctly identify SLN-macro when present. The SHREC trial included a systematic evaluation of the previously underinvestigated presacral area. Even though isolated presacral LNMs were rare, presacral LNMs were associated with a non-endometrioid histology, which suggests modifying the algorithm regarding dissection along the LPP depending on histology.

There were no adverse events related to injection of ICG or the SLN procedure. A previous study from our institution found a 14-fold decreased risk of lower extremity lymphoedema following SLN removal when compared to full lymphadenectomy, which emphasises the potential for reducing morbidity with an SNL concept [11].

The strength of our trial includes the prospective design, with consecutive recruitment of women within a publicly available healthcare system. Moreover, only women with HREC were included and 81% were subjected to a comprehensive staging procedure including IRPALND. The definition of the surgical procedure was exact and performed by five accredited surgeons, resulting in a high internal validity. The generalisability of the results can be questioned, and surgery according to the proposed algorithm should, in our opinion, be performed at high-volume centres by high-volume surgeons. This is supported by the FIRES trial where the authors suggested that a limited experience with SLN mapping in most of the included surgeons contributed to a bilateral mapping rate of only 52% [16].

The SHREC trial is the largest prospective trial investigating an SNL algorithm in HREC and the first to systematically investigate a pelvic SLN algorithm, an important and final step towards the implementation of an SLN concept in EC. With a high bilateral mapping rate and a complete sensitivity to detect pelvic LNMs, the pelvic SNL algorithm has the potential, in the hands of experienced surgeons, to safely replace lymphadenectomy in HREC without the need for para-aortic dissection.

Author contributions

The study was designed by Jan Persson and Barbara Geppert. All authors contributed to data acquisition, analysis and interpretation as well as writing and revising of the draft and the final approval of the

manuscript. The corresponding author confirms he had full access to all data in the study and has the final responsibility for the decision to submit the manuscript. All authors have given their written permission to publish the manuscript in the present form.

Conflict of interest statements

Jan Persson and Celine Lönnerfors have received honoraria from Intuitive Surgical for proctoring and lecturing on robot-assisted surgery, and Henrik Falconer has received honoraria from Intuitive Surgical and Medtronics for similar services. Jan Persson, Celine Lönnerfors and Henrik Falconer have no other relevant financial interests, activities, relationships or affiliations. No disclaimers for any of the other coauthors or relatives of any of the authors.

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Role of the funding source

The funding sources solely contributed with means for carrying out of the study but were otherwise not involved.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.04.025.

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