A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study

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Summary

Background Sentinel-lymph-node mapping has been advocated as an alternative staging technique for endometrial cancer. The aim of this study was to measure the sensitivity and negative predictive value of sentinel-lymph-node mapping compared with the gold standard of complete lymphadenectomy in detecting metastatic disease for endometrial cancer.

Methods In the FIRES multicentre, prospective, cohort study patients with clinical stage 1 endometrial cancer of all histologies and grades undergoing robotic staging were eligible for study inclusion. Patients received a standardised cervical injection of indocyanine green and sentinel-lymph-node mapping followed by pelvic lymphadenectomy with or without para-aortic lymphadenectomy. 18 surgeons from ten centres (tertiary academic and community non-academic) in the USA participated in the trial. Negative sentinel lymph nodes (by haematoxylin and eosin staining on sections) were ultra-staged with immunohistochemistry for cytokeratin. The primary endpoint, sensitivity of the sentinel-lymph-node-based detection of metastatic disease, was defined as the proportion of patients with node-positive disease with successful sentinel-lymph-node mapping who had metastatic disease correctly identified in the sentinel lymph node. Patients who had mapping of at least one sentinel lymph node were included in the primary analysis (per protocol). All patients who received study intervention (injection of dye), regardless of mapping result, were included as part of the assessment of mapping and in the safety analysis in an intention-to-treat manner. The trial was registered with ClinicalTrials.gov, number NCT01673022 and is completed and closed.

Findings Between Aug 1, 2012, and Oct 20, 2015, 385 patients were enrolled. Sentinel-lymph-node mapping with complete pelvic lymphadenectomy was done in 340 patients and para-aortic lymphadenectomy was done in 196 (58%) of these patients. 293 (86%) patients had successful mapping of at least one sentinel lymph node. 41 (12%) patients had positive nodes, 36 of whom had at least one mapped sentinel lymph node. Nodal metastases were identified in the sentinel lymph nodes of 35 (97%) of these 36 patients, yielding a sensitivity to detect node-positive disease of 97·2% (95% CI 85·0–100), and a negative predictive value of 99·6% (97·9–100). The most common grade 3–4 adverse events or serious adverse events were postoperative neurological disorders (4 patients) and postoperative respiratory distress or failure (4 patients). 22 patients had serious adverse events, with one related to the study intervention: a ureteral injury incurred during sentinel-lymph-node dissection.

Interpretation Sentinel lymph nodes identified with indocyanine green have a high degree of diagnostic accuracy in detecting endometrial cancer metastases and can safely replace lymphadenectomy in the staging of endometrial cancer. Sentinel lymph node biopsy will not identify metastases in 3% of patients with node-positive disease, but has the potential to expose fewer patients to the morbidity of a complete lymphadenectomy.

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Introduction

Endometrial cancer is the most commonly diagnosed gynaecological cancer in the USA, affecting approximately 54 000 women per year.[1] Most (78%) women have disease confined to the uterus.[2] Surgical staging with lymphadenectomy defines recurrence risk and helps clinicians make the decision to give adjuvant treatment to high-risk patients.[3,4] Treatment algorithms that do not include surgical staging rely upon an increased use of external beam radiation, which is associated with higher morbidity.[5] Although patients who are node positive have a survival benefit from chemotherapy compared with those who do not receive chemotherapy, this is not true for patients who are node negative, which underscores the importance of pathological assessment of lymph nodes in determining adjuvant therapies.[6] However, complete pelvic and para-aortic lymphadenectomy itself is associated with major comorbidities including lymphoedema, lymphocyst formation, and genitofemoral nerve injury,[7,8] and is technically difficult to achieve in obese populations,[9] which represent a substantial proportion of patients with endometrial cancer.

Research in context

Evidence before this study

Before the development of this study we did a comprehensive scientific literature review using PubMed with no date or language restriction on publications. Additionally, we searched ClinicalTrials.gov for ongoing or closed sentinel lymph node studies in endometrial cancer. Search terms included "sentinel lymph node" and "endometrial cancer". Sentinel-lymph-node mapping has only been described for endometrial cancer since 2006, and the scarce body of published work fails to adequately confirm the accuracy of the sentinel-lymph-node technique in detecting metastatic endometrial cancer. Several single institution retrospective and prospective studies attempted to assess this technique. These studies consistently show accuracy and feasibility of the technique; however, they are limited by small numbers of patients or surgeons and non-standardised techniques, and many lack routine systematic lymphadenectomy on all patients as a comparison. Previously, the only multi-institution prospective study in endometrial cancer sentinel lymph node biopsy, "SENTI-ENDO", was done in Europe. The study's primary objective was to measure the negative predictive value of the technique. However, a small number of patients were included in this study because it was designed to assess each hemi-pelvis of a patient. Additionally, the SENTI-ENDO study had a low frequency of comprehensive pelvic and para-aortic lymphadenectomy and low mean total node counts. The NCCN guidelines in the surgical management of endometrial cancer include sentinel lymph node biopsy as an acceptable method of staging, but with the caveat that it is only supported by level 2B evidence.

Added value of this study

The FIRES study was powered to determine whether sentinel lymph node biopsy is associated with a clinically acceptable negative predictive value and sensitivity compared with the gold standard lymphadenectomy. To the best of our knowledge, FIRES is the largest prospective trial in endometrial cancer sentinel-lymph-node biopsy. Patients were comprehensively staged, with a higher frequency of complete (pelvic and para-aortic) node dissections compared with previous studies. These results are generalisable because the study included surgeons who were novices to the technique at trial inception.

Implications of all the available evidence

The results of the FIRES trial are consistent with what has been shown in smaller series. The aggregate of evidence addressing the accuracy of the technique suggests that sentinel-lymph-node biopsy can detect metastatic disease for endometrial cancer with a sensitivity similar to that for breast cancer, melanoma, and vulvar cancers, all tumours for which sentinel-lymph-node biopsy is an accepted standard of care in staging and surgical management.

Sentinel-lymph-node biopsy involves selective and limited removal of tumour-specific or organ-specific lymph nodes that are identified after injection of tracer dye into, or in proximity to, the primary tumour,[10] and allows the surgeon to remove only nodal tissue that drains directly from the site of the primary tumour. The feasibility of sentinel-lymph-node mapping in endometrial cancer has been described in large, single institution, retrospective series[11] and its accuracy has been reported in smaller prospective trials.[12,13] However, these trials have not been able to provide surgeons with generalisable and definitive accuracy data because they did not have statistical power, contained incompletely staged patients, or included singular or small numbers of expert surgeons and institutions. Despite these limitations in historical studies, the National Comprehensive Cancer Network (NCCN) guidelines have endorsed sentinel-lymph-node mapping as a technique for the staging of endometrial cancer as level 2B evidence with the caveat that definitive studies to determine its accuracy and long-term outcomes are absent.[14] The Fluorescence Imaging for Robotic Endometrial Sentinel lymph node biopsy (FIRES) trial was designed with the primary objective to estimate the sensitivity and negative predictive value of sentinel-lymph-node mapping using robotic assisted fluorescence imaging of the tracer indocyanine green (ICG) in detecting lymphatic metastases in patients with endometrial cancer.

Methods

Study design and participants

The FIRES trial is a multicentre, prospective, cohort study. The protocol is available in the appendix. Consecutive patients were enrolled from the ambulatory clinics of ten participating sites in the USA (a combination of tertiary academic and community based non-academic practices; appendix p 1). Patient eligibility was centrally reviewed. Patients were eligible if they had documented endometrial cancer of any histology on pathology specimens from endometrial sampling, and if they had clinically determined stage 1 disease, defined as having no physical examination findings or radiographical suspicion of extrauterine disease. There was no age limit for eligibility. Patients were included in the study if they met the performance status and life expectancy to tolerate a surgical staging procedure. Patients who were pregnant based on urine choriogonadotropin assessments were excluded.

See Online for appendix

Patients were excluded if they had evidence of extra-uterine disease, had undergone previous hysterectomy or treatment for their endometrial cancer (such as radiotherapy, chemotherapy, or hormonal therapy), had received a previous retroperitoneal surgery or lymph-adenectomy, or had contraindications for receiving the ICG tracer, including a history of hepatic impairment or an iodine allergy. If patients were recognised to have gross extra-uterine disease at the time of surgery after tracer

injection, they were ineligible for the sentinel-lymph-node mapping. With Institutional Review Board approval at each site, written and informed consent was obtained from all eligible patients.

Procedures

The principal investigator (ECR) did a site visit before the inclusion of that site in the trial. 18 surgeons participated in the trial and all surgeons were instructed and observed in-person by ECR to confirm standardisation of the technique, including the adequacy of completion lymphadenectomy. The baseline postgraduate surgical experience (beyond fellowship training) was variable: nine surgeons had more than 10 years of postgraduate experience, three surgeons had 5–10 years of experience, and six surgeons had 1–5 years of surgical experience. The first sentinel-lymph-node mapping case of each surgeon was observed by ECR to verify standardisation of the technique and the surgeons' proficiency in doing the technique, including the adequacy of completion lymphadenectomy. These surgeons then served as site principal investigators and could verify additional surgeons at the site with case observations. Patients could only be included for analysis if their surgery was done by verified surgeons or if the surgeon was observed by a site-principal investigator.

ICG tracer was injected into the cervix after anaesthesia induction. A standardised dose of 0·5 mg/mL was created by diluting 1 mL of the stock solution (2·5 mg/mL) into 4 mL of sterile water.[15] A spinal needle was used to inject 1 mL (0·5 mg) of the ICG solution into the uterine cervix at 3 o'clock and 9 o'clock of the ectocervix to a 1 cm depth, achieving a total dose of 1 mg.

The da Vinci Si or Xi surgical robots (Intuitive Surgery, Sunnyvale, CA, USA) were used in all patients. After obtaining peritoneal entry, fluorescence imaging was used to visualise the ICG tracer in the lymphatics. A successful mapping was defined by observing a channel leading from the cervix directly to at least one candidate lymph node in at least one hemi-pelvis. Identified sentinel lymph nodes were then retrieved and labelled for location. Completion bilateral lymphadenectomy (removal of all remaining non-sentinel lymph node tissue within the relevant nodal basins) was then done on all patients according to the Gynecologic Oncology Group surgical handbook.[16] Pelvic lymphadenectomy was required in all patients, but surgeons were permitted to omit para-aortic lymphadenectomy if it was technically unfeasible or clinically irrelevant because of low risk factors for para-aortic nodal involvement.[17]

Surgeons also provided graphical data on sentinel lymph node location (external iliac, internal iliac, obturator, presacral, inframesenteric and supra-mesenteric para-aortic, and other) and whether the sentinel lymph node was located outside of the standard basins of lymph-adenectomy. The data maps completed by surgeons included graphical and descriptive numerical labelling of the sentinel lymph nodes according to the order in which they were located on the lymphatic channel (eg, first in chain or second in chain) and whether the node occurred on the same or on a different channel on each individual side (because several channels can originate from the uterine cervix on each side). If it was unclear to the surgeon whether the node was a primary first-in-chain sentinel lymph node, the surgeons were instructed to remove this node as a true sentinel lymph node.

Sentinel lymph node specimens were handled by pathologists according to a standardised ultra-staging protocol. Sentinel lymph nodes were cut at 3 mm intervals, in a bread-loaf fashion, or bivalved if less than 1·5 cm in any dimension. Two paraffin-embedded slides were created from each section, 50 µm apart. One slide was stained for haematoxylin and eosin (H&E) and the other was reserved for immunohistochemistry staining. If no metastatic disease was identified on the first haematoxylin and eosin slide, the reserved slide was stained for pancytokeratin AE1 and AE3. Non-sentinel lymph nodes were handled according to institutional standard-of-care practices, and therefore negative haematoxylin and eosin slides from non-sentinel lymph nodes were not subjected to immunohistochemistry staining. Pathologists were not blinded to the results of the H&E staining of the sentinel lymph node or non-sentinel lymph node when assessing the specimens.

Metastatic disease was categorised and reported in a standardised fashion according to the American Joint Committee on Cancer definitions[18] with macro-metastases defined as foci of metastasis greater than 2 mm, micro-metastases defined as disease volume 0·2–2 mm, and isolated tumour cells defined as foci of disease measuring less than 2 mm in greatest dimension or individual pathological cells staining positive for pancytokeratin AE1 or AE3.

The lead pathologist at each site received instruction on the standardised processing and reporting of specimens required by the protocol before enrolment of patients. Pathology reports from each site were audited on a quarterly basis by the principal investigator to ensure compliance with processing and reporting according to protocol specifications.

Adverse events were monitored and recorded by the site investigator 24 h after the procedure.

Outcomes

The primary endpoints were the sensitivity of the sentinel lymph node specimen in detecting metastatic disease and the negative predictive value of the technique. Sensitivity was defined as the proportion of patients with node-positive disease who had successful sentinel-lymph-node mapping (either unilateral or bilateral) and had metastatic disease correctly identified in the sentinel lymph node. Negative predictive value was defined as the proportion of negative sentinel lymph node specimens that were associated with negative non-sentinel lymph node specimens.

Statistical analysis

Patients who had mapping of at least one sentinel lymph node were included in the sensitivity and negative predictive value analysis (per protocol). All patients who received study intervention (injection of dye), regardless of mapping result, including those deemed ineligible for sentinel-lymph-node mapping, were included as part of the assessment of mapping and the safety analysis in an intention-to-treat manner (29 patients who voluntarily withdrew before study intervention or who did not receive study intervention [dye injection] were not included as part of the assessment of mapping and the safety analysis). Each patient served as their own control, with sentinel lymph node results compared with non-sentinel lymph node results within the same patient.

We used a Fleming-type two-stage design to stop early based on sensitivity. The null hypothesis that sensitivity is 80% was tested against a one-sided alternative. Based on anticipated node positive rates (15%), an estimated 240 patients would be required to achieve the goal of 36 node positive patients with sentinel lymph nodes mapped. This number assumed 100% rates of lymphadenectomy and successful mapping of a sentinel node which did not occur. The study would be stopped for futility if there were 29 or fewer patients identified by sentinel-lymph-node mapping as having metastases. If there were 35 or 36 patients correctly identified by sentinel-lymph-node mapping as having metastases, the study would be stopped and the null hypothesis rejected. Otherwise, 45 additional patients with node-positive disease would be accrued to a total of 81 patients. The null hypothesis would be rejected if 71 or more patients were identified with metastatic disease by sentinel-lymph-node mapping among 81 patients. This design yielded a type I error of 0·05 and power of 0·8 when the true sensitivity is 90%. This design minimises $(N + EN_0 + EN_1)/3$, where N is the total maximum sample size, EN_0 is the expected sample size under the null, and EN_1 is the expected sample size under the alternative. Sensitivity, negative predictive value, and false-negative rate were estimated by proportions. We reported exact 95% CIs. Specificity and positive predictive value were not reported in this study because if a sentinel lymph node is positive, lymph node metastasis is certain. It is possible for sentinel lymph nodes to be the only location for metastatic disease (positive sentinel lymph node, negative non-sentinel lymph node).

The two techniques were compared using the McNemar test. The proportions of sentinel lymph nodes and non-sentinel lymph nodes containing metastatic disease were compared using the Fisher's exact test as a post-hoc analysis. All analyses were done in R (version R.3.3.0).[19] This study is registered with ClinicalTrials.gov, number NCT01673022, and is closed to accrual and completed.

Role of funding source

The sponsors had no role in the study design, data collection, analysis, interpretation, or writing of the report. Access to raw data was limited to the authors ECR, MA, and AI. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

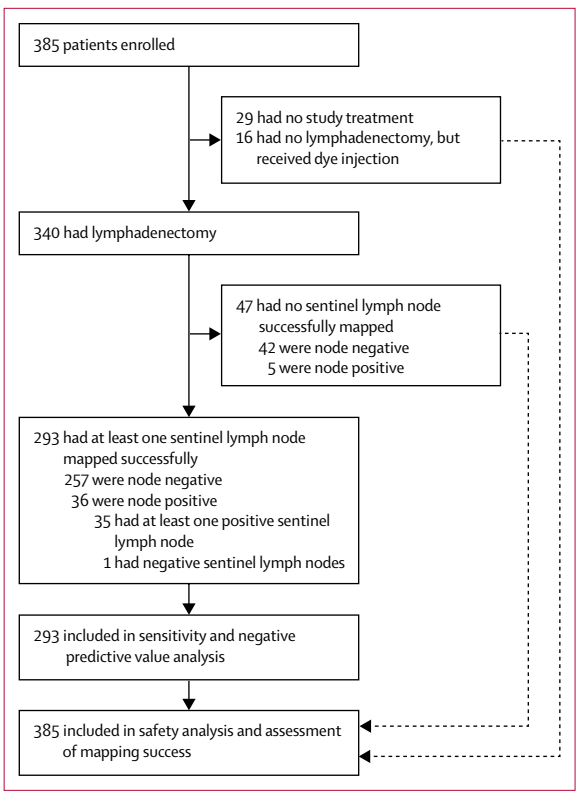

Figure 1: **Trial profile**
Assessment of mapping=a surgeon assessing the proportion of patients who mapped at least one sentinal lymph node, and whether the sentinal lymph nodes were found bilaterally.

Results

Between Aug 1, 2012, and Oct 20, 2015, 385 patients were enrolled. Figure 1 shows the interventions for all patients. The median age of patients was 63 years (range 29–83). The mean body-mass index of patients was 33·4 kg/m² (SD 7·9; range 17·8–60·5).

The clinical-pathological features for the 356 patients who received any study intervention and the postoperative staging results for the 340 patients who received complete study intervention (injection of dye, attempted sentinel-lymph-node mapping, and lymphadenectomy) are shown in table 1 (340 patients had staging with a lymph node dissection and 16 patients did not have lymph node assessment). Of those 16 patients, four were staged by having sampling of disease outside of the uterus (eg, they had positive disease in their omentum or peritoneum that was biopsied and confirmed their advanced stage), therefore we included staging information on these patients in table 1 to better reflect the patients who were surgically staged beyond hysterectomy alone. 102 (29%) of

	Patients
Final pathology (postoperative grade) (n=356)*	
Endometrioid grade	292 (82%)
Grade 1	152 (43%)
Grade 2	102 (29%)
Grade 3	38 (11%)
Serous	41 (12%)
Carcinosarcoma	13 (4%)
Clear cell	6 (2%)
Other	4 (1%)
Postoperative stage (n=344)†	
IA	228 (66%)
IB	47 (14%)
II	15 (4%)
IIIA	10 (3%)
IIIB	0
IIIC	41 (12%)
IV	3 (1%)

Data are n (%). *Patients who received complete study intervention (injection of dye, attempted sentinel-lymph-node mapping, and complete surgical staging) †Patients who received complete study intervention (injection of dye, attempted sentinel lymph node mapping, and lymphadenectomy).

***Table 1*: Clinical-pathological features**

	Patients (n=340)
Pelvic lymphadenectomy	340 (100%)
Pelvic and para-aortic lymphadenectomy	196 (58%)
Successful mapping of sentinel lymph nodes	293 (86%)
Bilateral mapping	177 (52%)
Para-aortic sentinel lymph node detected	81 (23%)
Isolated para-aortic sentinel lymph node detected	3 (<1%)
Median number of sentinel lymph nodes removed	2 (0–20)
Mean number of total nodes removed	19 (10·3; 1–61)

Data are n (%), median (range), or mean (SD; range).

***Table 2*: Surgical results in patients who had pelvic lymphadenectomy**

356 patients had high-grade endometrial pathology (grade 3 endometrioid or high-grade non-endometrioid cell types) on final pathology (table 1). 41 (12%) of 340 patients had metastatic disease identified in their sentinel lymph nodes or lymphadenectomy specimens.

33 (9%) of 356 patients had an adverse event and 22 of these patients had a serious adverse event (appendix p 2). The most common grade 3 or 4 adverse events or serious adverse events were postoperative neurological changes, such as peripheral nerve injuries, or central nervous symptoms, such as syncope or vertigo (4 patients); postoperative respiratory distress or failure (4 patients); postoperative nausea and vomiting (3 patients); and bowel injury (3 patients). One study-attributable serious adverse event was noted: a ureteral injury incurred during sentinel lymph node dissection. The surgeon reported difficulty visualising the ureter in the retroperitoneum during activation of the near infrared imaging modality when bleeding was encountered. The ureter received a thermal injury that was immediately recognised. The ureter was stented and the patient did not sustain long-term adverse sequelae.

The surgical staging outcomes and sentinel-lymph-node mapping outcomes for the 340 assessable patients are shown in table 2. Pelvic lymphadenectomy was done in all patients. Para-aortic dissection was done in 74 (74%) of 100 patients with high-grade tumours. Removal of ten or more lymph nodes (adequate lymphadenectomy) was done in 285 (84%) of 340 patients. Mapping identified at least one sentinel lymph node in 293 (86%) of 340 patients (table 2). Two of three patients with a mapped isolated para-aortic sentinel lymph node had metastatic disease identified in this lymph node but were otherwise pelvic node negative.

888 sentinel lymph nodes were mapped: 415 sentinel lymph node specimens were removed from the left side and 472 from the right side. 1098 sentinel lymph nodes were identified within these 888 specimens by pathology. Sentinel nodes were identified by surgeons in the following locations by frequency: external iliac (335 [38%] of 888, obturator (218 [25%]), inframesenteric para-aortic (128 [14%]), common iliac (68 [8%]), internal iliac (92 [10%]), presacral (26 [3%]), infrarenal para-aortic (11 [1%]), and other (including parametrium (10 [1%]; figure 2). 41 of the 340 patients who had lymphadenectomy had positive nodes, and 36 of the 293 patients who had at least one sentinel lymph node had positive nodes. 35 (97%) of these patients had their disease correctly identified in their sentinel lymph nodes, at which time the study was stopped and did not move on to the second stage because the null hypothesis could be rejected according to predetermined endpoints. 59 positive sentinel lymph nodes were identified in 35 patients; most commonly in the obturator (22 sentinel lymph nodes in 16 patients) and external iliac locations (20 in 13 patients; figure 2). Six (17%) patients had positive sentinel lymph nodes found exclusively in regions the surgeon identified as lying outside of routine lymphadenectomy (such as pre-sacral or internal iliac regions), with corresponding negative non-sentinel lymph nodes in conventional spaces. One patient with node-positive disease had a negative sentinel lymph node and a positive (ipsilateral) non-sentinel lymph node representing a false-negative sentinel lymph node. This patient had undergone a previous retroperitoneal surgery (lumbar spine fusion via an anterior approach) and should have been deemed ineligible for the study. However, because they received study intervention, they were included in the analysis.

The results from the 293 patients who had at least one sentinel lymph node successfully mapped were used to calculate the sensitivity and negative predictive value of the sentinel lymph node technique. The study protocol recommended omission of each surgeon's first three

patients in the sensitivity analysis to minimise the effect of their learning curve on observed technique accuracy. However, no false-negative sentinel lymph node cases were observed during any surgeon's first three patients, and therefore the results from all patients were included in the reported sensitivity analysis.

Sensitivity and specificity data are shown in table 3. The sensitivity of the sentinel lymph node technique to identify nodal metastatic disease was 97·2% (95% CI 85·0–100; McNemar's p=1). Among the 258 patients with negative sentinel lymph node results, 257 had truly negative non-sentinel lymph nodes, resulting in a negative predictive value of 99·6% (95% CI 97·9–100). In a post-hoc analysis, pathologically identified sentinel lymph node specimens were significantly more likely to contain metastatic disease than non-sentinel lymph node specimens (58 [5%] of 1098 *vs* 63 [1%] of 5416, p=0·0001).

Patients with risk factors for lymphatic metastasis are shown in table 4. All patients with node-positive disease, including those with micrometastatic disease, had at least one known risk factor for lymph-node metastases (table 4). 21 (60%) of 35 patients with positive sentinel lymph nodes had disease limited to the sentinel lymph nodes, and 14 (40%) of 35 patients had additional positive nodes in their non-sentinel lymph node specimens. The sentinel lymph nodes represented the largest volume of tumour metastasis in 30 (83%) of the 36 patients with node-positive disease. 19 (54%) patients with positive sentinel lymph nodes had low-volume disease identified only with ultra-staging (negative routine H&E analysis but micro-metastases or isolated tumour cells identified on immunohistochemistry). Of these 19 patients, nine (47%) had micro-metastases, and ten (53%) had isolated tumour cells. Notably, of the remaining 16 patients with sentinel-lymph-node-positive disease who had high-volume disease with H&E-identified metastases, two had micro-metastatic or isolated tumour cell foci that were identified on this type of pathological analysis. Six (29%) of the 21 patients with low-volume metastatic sentinel lymph node disease found on ultra-staging had accompanying positive non-sentinel lymph nodes (macro-metastatic), compared with nine (64%) of 14 patients with high-volume sentinel lymph-node metastases (p=0·08).

The sentinel lymph nodes represented the most distal level of metastatic disease (pelvic *vs* para-aortic) in 28 (80%) of 35 patients. In other words, the sentinel lymph nodes did not reflect the extent of affected nodal basins in 20% of cases of stage IIIC disease. Three patients had positive sentinel lymph nodes in the para-aortic region, with two of these patients having isolated para-aortic metastases found in para-aortic sentinel lymph nodes. One additional patient had isolated para-aortic nodal metastases identified on routine para-aortic lymphadenectomy after they failed to map any sentinel lymph nodes.

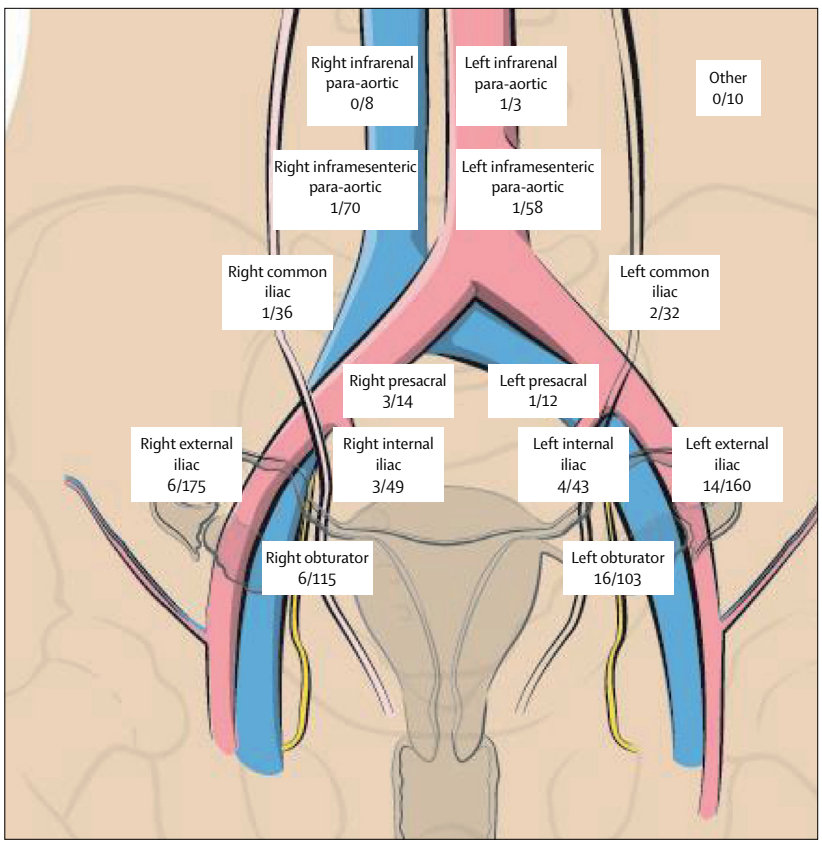

Figure 2: **Anatomic location of sentinel lymph nodes.**
Numbers are positive sentinel lymph nodes/successfully mapped sentinel lymph nodes.

	True positive nodes	True negative nodes
Positive sentinel lymph node	35	0
Negative sentinel lymph node	1	257

Table 3: **Sensitivity and specificity data**

Discussion

The FIRES study was powered to determine the sensitivity and negative predictive value of sentinel lymph node biopsy for endometrial cancer using near-infrared imaging of ICG. These results show that sentinel lymph node biopsy is equivalent to lymphadenectomy in the staging of endometrial cancer. Patients with sentinel lymph nodes negative for metastatic disease can be reassured that this result is accurate in more than 99% of cases, and only approximately 3% of patients with nodal metastases will have their disease unrecognised by sentinel lymph node biopsy (false-negative rate).

Although systematic staging for endometrial cancer offers diagnostic information that can guide clinical decisions about adjuvant radiation and chemotherapy, randomised controlled trials show no survival advantage.[20,21] Furthermore, lymphadenectomy is

	Node negative (n=269)	Node positive (n=40)
Tumour size		
<2 cm	86 (32%)	3 (8%)
≥2 cm	183 (68%)	37 (92%)
Grade		
1 or 2	199 (74%)	20 (50%)
3	30 (11%)	6 (15%)
Non-endometrioid	40 (15%)	14 (35%)
Lymphovascular space invasion		
Absent	225 (84%)	15 (38%)
Present	44 (16%)	35 (62%)
Myometrial invasion		
None	96 (36%)	1 (3%)
<50%	120 (44%)	16 (40%)
≥50%	53 (20%)	23 (57%)
Lower uterine segment involvement		
Absent	181 (67%)	19 (48%)
Present	88 (33%)	21 (52%)
Age (years)		
<50	25 (9%)	3 (8%)
50–69	183 (68%)	25 (63%)
≥70	61 (23%)	12 (29%)

Data are n (%). Includes 309 patients who had lymphadenectomies and in whom complete pathological risk-factor data were available.

Table 4: **Risk factors for lymphatic metastasis**

associated with morbidity.[7] Systematic surgical staging does, however, significantly reduce use of external beam radiation, which is associated with more frequent and severe comorbidities than lymphadenectomy.[5] Given that patients with node-positive disease have improved survival with chemotherapy, correctly identifying this population would improve survival.[22] Algorithms that can limit the extent of lymphadenectomy while still providing staging information would theoretically reduce morbidity for patients with endometrial cancer and more accurately guide adjuvant therapy.

To minimise lymphadenectomy, some surgeons have proposed algorithms that select patients for comprehensive staging based on high-risk features for lymph node metastases (high-grade, large, and deeply invasive primary tumours).[17] Selective removal of sentinel lymph nodes has emerged as an alternative to obtain staging information while minimising morbidity. The results from this trial have provided evidence of a clinically acceptable sensitivity and negative predictive value in determining metastatic endometrial cancer. These results and those of other studies[11] are contingent upon the algorithm of a surgeon well trained in the technique, removal of all suspicious nodes, side-specific comprehensive staging in a hemi-pelvis that fails to map, and exclusion of patients according to the guidelines outlined in the methods section.

Results from the FIRES trial also suggest that the sentinel lymph node algorithm might be better than traditional complete lymphadenectomy because sentinel lymph nodes are more likely to contain metastatic disease; pathologists are required to ultra-stage a smaller number of more relevant nodes; and sentinel-lymph-node mapping identifies positive nodes that lie outside of traditional surgical boundaries. This occurred in 20% of FIRES patients.

ICG was chosen as the tracer for mapping in this trial. ICG can be used with technetium; however, the addition of technetium to sentinel-lymph-node mapping is less commonly used in the USA because ICG alone can achieve some of the benefits of technetium (penetration of signal through tissue) without the challenges of incorporating nuclear medicine techniques. Although the robotic surgical platform was used for mapping in this particular study, ICG and near-infrared imaging is available for laparoscopic and open surgeries, which means that the results of this study can be generalised to other surgical approaches using the ICG tracer.

In this study population, sentinel lymph nodes were identified bilaterally in approximately half of the patients, meaning that the number of extensive node dissections was reduced, but not eliminated. Bilateral mapping was lower in this study than in some previously reported studies.[13,23–25] One explanation for this observation is a learning curve with the technique. Studies reporting higher frequencies of bilateral mapping (65–88%) represent single institution series with experienced surgeons. Two of the 18 FIRES surgeons had previous experience with sentinel-lymph-node mapping, though for the others, this was a novel technique. Therefore, the detection frequency reported in this trial is probably underestimated, but represents what surgeons should anticipate in their learning curve.

Sentinel lymph node algorithms have the highest accuracy if each hemi-pelvis is viewed as a distinct diagnostic unit and side-specific lymphadenectomy is done on unmapped sides, because an unmapped hemi-pelvis might harbour unrecognised metastatic disease.[11,12] In the FIRES population, this approach would result in approximately 40% of patients requiring a unilateral lymphadenectomy, and 10% requiring a bilateral lymphadenectomy.

Surgeons have questioned the use of cervical injection versus uterine injection for sentinel-lymph-node mapping because of concern that isolated para-aortic metastases might be unmapped and therefore missed after cervical injection. The results of this trial do not support this concern. Cervical injection achieves a higher overall detection frequency for sentinel lymph nodes, with a similar anatomic distribution when compared with endometrial injection.[26] In the FIRES trial, there was a high frequency of para-aortic non-sentinel lymph node sampling, when clinically indicated, particularly in patients with high-grade cancers in whom isolated

para-aortic metastases are the most prevalent, with no cases of missed isolated para-aortic metastases in patients who mapped at least one sentinel lymph node.

A major strength of this study is its prospective design with predetermined statistical endpoints. Furthermore, the results of this trial are similar to those that have been reported in breast cancer and vulvar cancer,[27,28] two disease sites in which sentinel lymph node biopsy has replaced complete lymphadenectomy as the standard of care. Our results are also consistent with smaller and retrospective series in endometrial cancer.[13,23] An additional strength of this study is its inclusion of multiple sites and surgeons, including surgeons from academic and non-academic practices, which predicts the generalisability of the technique.

This study is limited in its ability to generalise the accuracy of other sentinel lymph nodes techniques or highly experienced surgeons. Furthermore, the study is unable to address questions of morbidity or oncological outcomes with the sentinel lymph nodes technique. Although 28% of the FIRES study population had high-grade histologies, which are at highest risk for metastases and isolated para-aortic metastases, the role of sentinel lymph node biopsy in these highest risk patients is not definitively addressed in this study population. It can be noted that the one false-negative result in the study occurred in a patient with a high-grade (serous) cancer.

The scope of the FIRES trial was to determine the diagnostic accuracy of the technique, and these results are unable to guide surgeons in the management of positive sentinel lymph nodes, including on the differential handling of low-volume metastases. It is the authors' practice to not do frozen sections of sentinel lymph nodes because the diagnostic accuracy of frozen sections is poor, with many false negatives;[29] frozen sections distort the nodal tissue in such a way that prevents ultra-staging of the lymph node to detect micrometastatic disease; and decisions about systemic adjuvant therapy are not contingent upon the specific number or anatomical distribution of positive nodes. Lymphadenectomy is, in itself, not therapeutic,[20,21] and therefore we do not do completion lymphadenectomies in patients who are determined to have positive nodal metastases on permanent sectioning. We do advocate postoperative imaging in cases of positive sentinel lymph nodes to ensure there are no gross bulky residual nodal metastases that would benefit from either surgical cytoreduction or, if appropriate, alterations in the dosing and fields of radiation.

In response to the results of the FIRES trial, surgeons should be reassured that sentinel lymph node biopsy can accurately stage endometrial cancer, but should still be applied with algorithms that address failures in mapping.[14] Further work should be done to define the clinical significance and optimum treatment of micro-metastasic disease and the procedure's morbidity.

Contributors

ECR, MA, AI, and JFB contributed to the conceptualisation and study design. ECR, LDK, JS, LC, KS, RKH, MM, and JFB contributed to participant enrolment. ECR, LDK, JS, LC, KS, RKH, MM, MA, and JFB contributed to data collection. Data analysis and interpretation was done by ECR, MA, AI, and JFB. Figure and table creation was done by ECR, RHK, MA, AI, and JFB. All authors were involved in the writing or review of the manuscript and approved the final manuscript.

Declaration of interests

We declare no competing interests.

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