



## Sentinel lymph nodes (SLN) in endometrial cancer: The relationship between primary tumor histology, SLN metastasis size, and non-sentinel node metastasis

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### HIGHLIGHTS

- ITCs comprised 48% of SLN metastasis in endometrioid histology cases, but only 15% of non-endometrioid SLNs.
- Presence of ITC in SLNs confers a significant risk of para-aortic metastasis regardless of histology risk group.
- Presence of ITC was associated with non-SLN pelvic node metastases in endometrioid tumors with deep myo-invasion.
- The false negative rate of SLN mapping was largely dependent on histologic risk group.

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### ABSTRACT

**Objectives.** To examine sentinel lymph node pathology and describe relationships to uterine pathology, non-sentinel pelvic lymph nodes, and para-aortic lymph nodes.

**Methods.** Patients with apparent uterine-confined endometrial cancer underwent robotic hysterectomy, SLN mapping, completion pelvic lymphadenectomy (LND), and para-aortic (PaLND) directed by frozen section. Patients were risk stratified by histology: low-risk (LR) endometrioid <50% depth-of-invasion (DOI), intermediate-risk (IR) endometrioid ≥50% DOI, and high-risk (HR) type II histology for comparison to other pelvic/aortic metastases.

**Results.** 414 patients were stratified: 275 LR, 80 IR, and 59 HR cases. PaLND was performed in 84.2% of IR/HR patients and 25.1% LR patients. Pelvic node metastasis was detected in 11.6% LR, 50.0% IR, and 39.0% HR patients. PaLN metastasis was detected in 2.9% LR, 11.3% IR, and 16.9% HR patients. Proportionally, isolated tumor cells (ITC) SLNs were more common in LR or IR vs. HR group (51.6% and 44.7% vs. 15.0%,  $p < 0.05$ ). The SLN false negative rates (FNR) were 0% LR, 2.5% IR, and 5.1% HR. Non-sentinel pelvic node metastases were present in 28 (31.5%) of all SLN+ cases, but only 3 (8.3%) of SLN with ITC. PaLN metastasis was found in 18.8% LR, 11.8% IR, and 33.3% HR cases with ITC SLNs. After controlling for DOI, LVSI, and grade, ITC-positive SLNs had a significant association with non-sentinel pelvic and aortic metastasis ( $p = 0.03$  and  $p = 0.008$ , respectively).

**Conclusions.** Patients with HR histology have more micro/macro-metastases in both SLNs and non-SLN metastases compared to LR/IR patients. SLN ITCs were associated with a clinically significant incidence of PaLN metastasis across all histology risk groups. There were no cases of isolated aortic node metastasis in this study. SLN mapping had an increased, although clinically acceptable FNR in the HR cohort compared to LR patients.

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### 1. Background/introduction

Sentinel lymph node (SLN) mapping is an accepted staging method for endometrial cancer and is supported by the National Comprehensive Cancer Network (NCCN®) Guidelines [1]. SLN mapping increases the detection of metastatic disease compared to traditional pelvic

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lymphadenectomy [2] via two mechanisms: i) by enhanced pathology methods increasing detection of isolated tumor cells (ITCs) and micro-metastases, and ii) by direct visualization of SLN pathways that may not otherwise have been resected (i.e., pre-sacral and internal iliac sentinel nodes) [3]. The SLN tumor size definitions for ITC (single cells or clusters <0.2 mm), micro-metastasis (tumor  $\geq$ 0.2 mm but  $\leq$ 2.0 mm), and macro-metastases >2.0 mm) are adopted from breast cancer classifications by the American Joint Committee on Cancer (AJCC) and are included in the 2018 version of College of American Pathologists (CAP) classification [4]. The clinical relevance of SLN metastasis size in endometrial cancer has not been evaluated in prospective clinical trials. Currently there is uncertainty about the importance of ITC metastases in endometrial cancer, and whether their presence should influence staging or the use of adjuvant therapies.

Isolated tumor cells in endometrial cancer were investigated by Plante et al. [5] in a retrospective analysis of 519 patients (86% endometrioid) who underwent SLN mapping. The frequency of SLN metastasis subtypes were 36% ITC, 13% micro-, and 51% macro-metastasis. The respective 3-year progression-free survivals (PFS) were 95.5%, 85.5%, and 58.5%, whereas the 3-year PFS for node negative patients was 87.6%. The authors concluded that patients with ITCs should receive adjuvant therapy tailored to the primary uterine pathology and not the presence of ITCs alone. However, 67% of patients with ITCs and 73% of those with micro-metastases received combinations of whole pelvic radiation and chemotherapy that could have influenced their survival results, making analysis of the independent clinical significance of ITCs impossible.

The role of para-aortic lymphadenectomy in the SLN surgical algorithm for endometrial cancer is also undefined. The Society of Gynecologic Oncology (SGO) consensus guidelines for SLN mapping advise that para-aortic dissection be performed at surgeon's discretion based on known risk factors for para-aortic metastasis [6]. The risk of para-aortic metastasis in endometrial cancer ranges from <5% to over 50%, depending on tumor histology, depth of invasion (DOI), presence of lymph-vascular space involvement (LVSI), and pelvic lymph node status [7]. Para-aortic lymph nodes are infrequently identified as "sentinel" using the currently accepted SLN algorithm that uses cervical injection of dyes [6,8]. Consequently, sole reliance on the SLN mapping algorithm and elimination of para-aortic lymphadenectomy in patients at risk for para-aortic metastasis may lead to under-staging patients as IIIC1 instead of IIIC2. Several studies suggest that patients undergoing para-aortic lymphadenectomy have enhanced survival compared to pelvic lymphadenectomy alone [9–13]. Whether removal of lymph node metastasis is therapeutic, or whether the major effect of accurate staging is optimal use of adjuvant therapies is conjectural.

The objective of our study was to analyze the size of SLN metastasis and the incidence of non-sentinel pelvic and para-aortic lymph node metastases in patients with apparent uterine-confined endometrial cancers that underwent robotic hysterectomy with SLN mapping and completion pelvic or pelvic/para-aortic lymphadenectomy.

## 2. Materials and methods

The Gynecologic Oncology data registry for retrospective analysis of clinical outcomes at our institution was initiated in 2006. Clinicopathologic data including peri-operative outcomes, use of adjuvant therapies, and disease status have been contemporaneously abstracted as an ongoing quality initiative. This retrospective analysis of patients with endometrial cancer who underwent robotic-assisted surgery was approved by our institutional review board (IRB).

Patients with apparent uterine-confined endometrial cancer who underwent robotic hysterectomy and SLN mapping from March 2011 through August 2016 were analyzed. Patients with Stage IA to IIIC2 disease were included and patients with Stage IV disease were excluded. All patients had cervical injection of indocyanine green (ICG)-dye with or without isosulfan blue (ISB)-dye in four quadrants. Retroperitoneal

mapping was performed bilaterally prior to proceeding with hysterectomy as previously described [6]. Pre-operative histology and an intra-operative uterine frozen section analysis were used to determine the need for para-aortic lymphadenectomy. Criteria for para-aortic lymphadenectomy included any tumor size >2 cm approximating 50% myometrial invasion or more, any lesion with high-grade (G3 endometrioid and Type II) histology, presence of LVSI on frozen section, or grossly positive pelvic lymph nodes confirmed on frozen section. Completion pelvic lymphadenectomy was performed in all patients during this time of this study for quality assurance to determine false negative rates (FNR) for surgeons in the group.

Data that were contemporaneously abstracted from hospital and clinic records included age, body mass index (BMI) in kg/m<sup>2</sup>, tumor histology, stage (FIGO 2009), grade, LVSI, DOI, cervical stromal involvement, cytology, lymph node yields and pathology. LVSI was defined as the presence of malignant cells in epithelial-lined spaces. Depth of myometrial invasion was measured in millimeters (mm) from the basement membrane and as a percentage of the myometrial thickness. Tumor size was defined as the greatest measured diameter of the endometrial lesion determined by the pathologist on the gross specimen.

Pathologic ultra-staging was performed on all sentinel lymph nodes. Ultra-staging began by first sectioning the SLN along the longitudinal axis into 2-mm thick sections and staining with hematoxylin and eosin (H&E). If the initial H&E was negative for metastasis, three additional sectioning were obtained at 50  $\mu$ m intervals and stained with H&E. AE1/3 immunohistochemistry (IHC) was performed on one ultra-section to examine for low-volume metastasis. Isolated tumor cells (ITCs) are defined as single cells or microscopic clusters up to 200 cells measuring  $\leq$ 0.2 mm. Micro-metastases are foci measuring >0.2 mm but  $\leq$ 2 mm, and macro-metastases are >2 mm in size [4].

Patients were categorized using histology risk stratification criteria defined by Memorial Sloan Kettering (MSK) and Mayo Clinic (MC) [14,15], with the exception that our study included patients with carcinosarcoma. Low-risk (LR) was defined as endometrioid histology of any grade with <50% myometrial invasion, intermediate-risk (IR) as endometrioid histology of any grade with  $\geq$ 50% myometrial invasion, and high-risk (HR) as non-endometrioid histology with any degree of myometrial invasion (serous, clear cell, carcinosarcoma). All patients were analyzed for histopathologic risk factors of metastasis and comparisons of pelvic and aortic node metastases were performed. Patients with SLN metastases were further investigated, examining the size of the SLN and status of the other non-SLN pelvic and aortic lymph nodes. An analysis of recurrence and survival for patients in this study is currently underway in preparation for a separate manuscript.

Demographic and pathology characteristics were compared between the risk cohorts using the Chi-square test for categorical variables, F-test for age and body mass index (BMI), and the Kruskal-Wallis test for the number of lymph nodes (LNs) removed. The false-negative rate was calculated with respect to the NCCN® surgical algorithm [1]. Specifically, positive nodes identified in lymphadenectomy performed in the setting of mapping failure were not included as false negative cases. Multivariable Firth logistic regression was used to evaluate the importance of ITC in predicting non-sentinel pelvic metastasis and aortic metastasis. All analyses were performed by using Stata version 14 (StataCorp., 2015). All *p* values were two-tailed, and  $\alpha < 0.05$  was set as the level of statistical significance for all tests.

## 3. Results

### 3.1. Data overview of entire cohort

Robotic hysterectomy and sentinel lymph node mapping with completion pelvic or pelvic/aortic lymphadenectomy were performed in 414 patients [Table 1]. Histologic subtypes of endometrial cancer included: endometrioid (*n* = 354), serous (*n* = 39), carcinosarcoma (*n* = 16), clear cell (*n* = 4), and undifferentiated (*n* = 1). Patients in the

**Table 1**  
Patient demographics and pathology stratified by histology risk groups.

	Low-risk (N = 275)	Intermediate-risk (N = 80)	High-risk (N = 59)
Age (years), mean (SD)	63.4 (9.9)	66.5 (10.9)	69.8 (8.4)
BMI (kg/m <sup>2</sup> ), mean (SD)	34.3 (8.6)	31.8 (6.9)	29.8 (7.1)
FIGO grade, N (%)			
1	183 (66.5)	29 (36.3)	–
2	75 (27.3)	36 (45.0)	–
3	17 (6.2)	15 (18.8)	59 (100)
Myometrial invasion, N (%)			
None	64 (23.3)	–	8 (13.6)
<50%	211 (76.7)	–	32 (54.2)
≥50%	–	80 (100)	19 (32.2)
Lympho-vascular space invasion, N (%)			
No	224 (81.5)	30 (37.5)	33 (56.0)
Yes	51 (18.5)	50 (62.5)	26 (44.0)
Cervical stromal invasion, N (%)			
No	260 (94.5)	65 (81.3)	50 (84.7)
Yes	15 (5.5)	15 (18.7)	9 (15.3)
Peritoneal cytology, N (%)			
Negative	137 (49.8)	39 (48.8)	34 (57.6)
Positive	9 (3.3)	2 (2.5)	3 (5.1)
Not sampled	129 (46.9)	39 (48.7)	22 (37.3)
FIGO stage (2009), N (%)			
IA	234 (85.1)	–	28 (47.5)
IB	–	31 (38.8)	5 (8.5)
II	6 (2.2)	7 (8.8)	2 (3.4)
IIIA/B	3 (1.1)	2 (2.5)	1 (1.7)
IIIC1	24 (8.7)	31 (38.8)	13 (22.0)
IIIC2	8 (2.9)	9 (11.2)	10 (16.9)
FIGO stage any IIIC, N (%)	32 (11.6)	40 (50.0)	23 (39.0)

Abbreviations: BMI = body mass index; FIGO = International Federation of Gynecology and Obstetrics; SLN = sentinel lymph node; N = number; SD = standard deviation.

HR cohort were significantly older and had lower BMI compared to LR and IR patients [69.8 vs. 64.1 years ( $p < 0.001$ ) and 29.8 vs. 33.8 kg/m<sup>2</sup> ( $p < 0.001$ ), respectively]. LVSI and grade 3 endometrioid histology were present more often in the IR cohort compared to the LR cohort. Staging with SLN mapping and completion pelvic lymphadenectomy only versus pelvic plus aortic lymphadenectomy was performed in 227 (54.8%) and 187 (45.2%) cases, respectively [Table 2]. SLNs were detected in 409 (98.8%) cases and bilateral mapping was successful in 350

(84.5%) cases. Pelvic lymph node metastases were identified in 95 (22.9%) cases and there were 89 cases with a positive SLN. There were five (1.2%) cases that were truly false negative SLN mappings. The HR cohort had a greater false negative SLN mapping rate compared to the LR cohort (5.1% vs. 0%,  $p < 0.001$ ). The FNR was no different for HR compared to IR patients (5.1% vs. 2.5%,  $p = 0.41$ ). There were no patients with isolated aortic lymph node metastasis identified in our database.

**3.2. Low-risk (LR) cohort (endometrioid, all grades, and <50% myometrial invasion)**

There were 275 LR cases including 32 (11.6%) with lymph node metastases (stages IIIC1 and IIIC2) [Table 1]. The false negative rate for SLN mapping in the low-risk cohort was 0/275 (0%), with one unilateral mapping failure that identified a positive lymph node with the completion lymphadenectomy [Table 2]. Thirty-one patients had positive SLN, and 16 (51.6%) of these cases had ITCs, seven (22.6%) had micro-metastases, and eight (25.8%) had macro-metastases [Table 3]. Of the 16 patients with ITCs in the SLN, half had cell clusters limited to one node whereas the other half had multiple clusters in bilateral hemipelvises. Para-aortic lymphadenectomy was performed in 69 (25.1%) low-risk patients (42 infra-renal and 27 infra-mesenteric dissections), and 8/275 (2.9%) had para-aortic metastasis [Table 2]. The indications for para-aortic lymphadenectomy included frozen section findings of grade 3 endometrioid tumors with myo-invasion, mixed histology (subsequently shown endometrioid on permanent pathology), or suspicious adenopathy. Of the 16 patients who had ITC SLNs, 10 underwent para-aortic lymphadenectomy, and three of these had aortic metastasis (1.1% of the low-risk cohort) [Table 3]. Fifteen patients had either micro- or macro-metastasis identified in the SLN, and five (33.3%) had para-aortic metastases.

**3.3. Intermediate-risk (IR) cohort (endometrioid, all grades, ≥50% myometrial invasion)**

There were 80 patients in the IR cohort and 50% had lymph node metastasis [Table 1]. SLN metastasis was identified in 38 patients including 17 (44.7%) with ITCs, nine (23.7%) with micro-metastases, and 12 (31.6%) with macro-metastases [Table 3]. All patients in the IR cohort met criteria for para-aortic dissection based on frozen section estimated depth of invasion, and para-aortic lymphadenectomy was performed in 63 (78.8%) patients (40 infra-renal and 23 infra-mesenteric). Reasons for not performing para-aortic lymphadenectomy included under-estimation of myometrial invasion on frozen section (8 patients) and patient comorbidities (9 patients) including morbid obesity with limited exposure, intolerance of Trendelenburg positioning, and excessive abdominal adhesions. Para-aortic metastases were identified in nine (11.3%) IR patients [Table 2]. Seventeen (21.0%) IR patients had ITC

**Table 2**  
Pelvic and para-aortic lymph node assessment stratified by histology risk group.

	Low-risk (N = 275)	Intermediate-risk (N = 80)	High-risk (N = 59)	Overall (N = 414)
Pelvic LND, N (%)	275 (100.0)	80 (100.0)	59 (100.0)	414 (100.0)
# pelvic LN removed, median (IQR)				
Unilateral	7 (5, 10)	8 (5, 11)	8 (5, 12)	
Bilateral	14 (10, 20)	16 (12, 22)	15 (11, 24)	
Positive pelvic LN, N (%)	32 (11.6)	40 (50.0)	23 (39.0)	95 (22.9)
Positive SLN, N (%)	31 (11.3)	38 (47.5)	20 (33.9)	89 (21.5)
False negative rate, N (%)	0/275 (0.0)	2/80 (2.5)	3/59 (5.1)	5/414 (1.2)
# positive pelvic LN per patient with pelvic LN met, median (IQR)				
Unilateral	1 (1, 1)	1 (1, 1)	1 (1, 2)	
Bilateral	2 (1, 3)	2 (1, 3)	2 (1, 3)	
Paraaortic LND, N (%)	69 (25.1)	63 (78.8)	54 (91.6)	186 (44.9%)
#PaLN removed, median (IQR)	7 (3, 12)	5 (3, 11)	7 (3, 11)	
Positive PaLN, N (%)	8 (2.9)	9 (11.3)	10 (16.9)	27 (6.5)

Abbreviations: LND = lymph node dissection; SLN = sentinel lymph node; N = number; SD = standard deviation; IQR = interquartile ratio; PaLN = para-aortic lymph node.

**Table 3**  
SLN metastasis, other non-SLN pelvic LN metastasis, and para-aortic LN metastasis stratified by histology risk group.

Total SLN cohort (N = 414)	Low-risk (N = 275)	Intermediate-risk (N = 80)	High-risk (N = 59)
SLN metastasis in total cohort, N (%)	31 (11.3)	38 (47.5)	20 (33.9)
ITC	16	17	3
Micro/Macro	15	21	17
SLN(+) with other pelvic LN positive, N (%)	7/31 (22.6)	10/38 (26.3)	11/20 (55.0)
ITC SLN	0	3	0
Micro/Macro SLN	7	7	11
PaLN metastasis in total cohort, N (%)	8/275 (2.9)	9/80 (11.3)	10/59 (16.9)
ITC SLN	3 (1.1)	2 (2.5)	1 (1.7)
Micro/Macro SLN	5 (1.8)	7 (8.8)	9 (15.2)
PaLN(+) in pts with positive SLN, N (%)	8/31 (25.8)	9/38 (23.7)	10/20 (50.0)
PaLN met in pt w/ ITC in SLN	3/16 (18.8)	2/17 (11.8)	1/3 (33.3)
PaLN met in pt w/ micro/macro-met in SLN	5/15 (33.3)	7/21 (33.3)	9/17 (52.9)

Abbreviations: SLN = sentinel lymph node; N = number; (+) = positive; ITC = isolated tumor cells; PaLN = para-aortic lymph node.

metastases in SLNs and 12 underwent para-aortic lymphadenectomy. Two of these IR patients had aortic metastasis representing 2.5% of the total IR cohort and 11.8% of IR cases harboring ITCs in their SLNs [Table 3]. In addition, 21 IR patients had either micro- or macro-metastasis SLNs and aortic dissections were performed in 19 cases. Para-aortic metastases were identified in seven (33.3%) of these patients.

#### 3.4. High-risk (HR) cohort (non-endometrioid histology, any depth of invasion)

There were 59 HR patients with high-risk non-endometrioid histology [Table 1]. The majority had uterine confined disease stage IA-II (59.3%) and 23 (39.0%) had lymph node metastasis [Table 1]. SLN metastasis were found in 20 patients including three (15%) with ITCs, five (25%) with micro-metastasis, and 12 (60%) had macro-metastasis [Table 3]. None of the HR patients with ITC SLN metastasis had other non-sentinel pelvic metastases, whereas 11/17 (64.7%) micro- and macro-metastasis had other positive pelvic nodes [Table 3]. Para-aortic lymphadenectomy was performed in 54 (91.6%) of HR patients. In the five patients that did not undergo para-aortic dissections, four were misinterpreted on frozen section as endometrioid histology <50% myo-invasion, and one patient was 91-years-old with multiple medical comorbidities. Para-aortic metastases were identified in 10 (16.9%) of 59 HR patients, and half of HR patients with a positive SLN also had para-aortic metastasis. None of the patients with ITC SLNs had para-aortic metastasis identified in the HR cohort.

#### 3.5. Analysis of other non-sentinel pelvic and para-aortic lymph node metastasis in patients with SLN metastases (Table 3)

Patients with SLN metastasis were further analyzed by histology risk groups. Proportionally, ITCs were more common in LR and IR cases (51.6% and 44.7%) compared to HR SLN metastases (15%,  $p = 0.01$ ). Conversely, macro-metastases were proportionally more common in HR SLN metastases than either the LR or IR cohorts. Patients with ITC SLNs had no other non-sentinel pelvic node metastases except in the IR cohort (3/80, 3.8%). However micro/macro-metastasis SLNs were associated with other pelvic node metastases in 6/275 (2.2%) LR cases, 7/80 (8.8%) IR cases, and 11/59 (18.6%) HR cases. Para-aortic metastases were identified in 18.8% LR, 11.8% IR, and one of three HR patients that had ITC SLNs. Micro-/macro-metastasis in the SLN was associated with positive para-aortic nodes in 33–53% of patients across all risk groups. Therefore, ITC SLN's have a clinically significant association with para-aortic metastasis across all histology risk groups, while other non-sentinel pelvic node metastases were observed only in the IR cohort in this study (endometrioid with deep myo-invasion). Micro- and macro-metastasis in SLNs pose a significantly higher risk for other non-SLN metastasis irrespective of histology risk group.

#### 3.6. Analysis of SLN metastasis detection methods

SLN metastases were detected with an ultra-staging protocol using H&E color stains, IHC, or both methods. There were 89 cases with SLN metastasis across all three histology risk groups, and 36 (40.4%) had ITCs. H&E alone was used to identify ITCs in two (3.3%), H&E plus IHC in 10 (27.8%), and IHC alone (i.e., non-visualization on H&E) in 24 (66.7%) cases. There were no differences in detection methods of ITCs proportionally comparing LR, IR, and HR histology cohorts. Four of six patients that had ITC SLNs and para-aortic metastases were IHC-detected only (H&E negative), and two were both IHC and H&E detected. ITC's detected by IHC alone would appear to confer at least as much risk for para-aortic metastasis as ITCs detected by H&E.

#### 3.7. ITC's as a predictor of non-sentinel nodal disease in endometrioid histology

Multivariable Firth logistic regression was performed on all endometrioid cases to evaluate the relationship between the primary tumor pathology, SLN status, and other lymph node pathology. After controlling for grade, DOI and LVSI, ITC-positive SLNs had a significant association with other non-sentinel pelvic and aortic metastasis ( $p = 0.03$  and  $p = 0.008$ , respectively) [Table 4A]. Similarly, patients with micro-/macro-metastasis in SLN also had an association with non-sentinel pelvic and aortic metastasis ( $p = 0.008$  and  $p = 0.001$ , respectively) [Table 4B]. A strong collinearity was observed between lymph node metastasis, DOI, and LVSI ( $p < 0.001$ ), and when ITC was disregarded in the model, LVSI showed a significant association with any LN positive, pelvic metastasis and aortic metastasis ( $p < 0.001$ ,  $p < 0.001$ , and  $p < 0.001$  respectively) [Table 4C]. Because of the collinearity of DOI and LVSI with ITC metastases, the independent risk of other pelvic/aortic node metastasis from ITCs cannot be estimated in this study.

**Table 4A**

Summary of multivariable Firth Logistic regression showing the association of ITCs in SLN with pelvic or aortic metastasis with grade, DOI and LVSI under control (N = 317).

	OR	95% CI	p-Value
Pelvic metastasis			
Grade	3.61	0.7–18.64	0.125
DOI	8.62	0.46–162.43	0.151
LVSI	0.77	0.08–7.8	0.825
ITC positive	24.58	1.35–446.03	0.030
Aortic metastasis			
Grade	2.6	0.76–8.83	0.127
DOI	0.64	0.1–3.98	0.635
LVSI	1.13	0.14–9.38	0.909
ITC positive	81.44	3.1–2136.66	0.008

**Table 4B**

Summary of multivariable Firth Logistic regression showing the association of combined micro- and macro-metastases in SLN with pelvic or aortic metastasis with grade, DOI and LVSI under control (N = 321).

	OR	95% CI	p-Value
<b>Pelvic metastasis</b>			
Grade	0.82	0.31–2.16	0.690
DOI	0.55	0.13–2.31	0.414
LVSI	10.19	1.44–72.1	0.020
Micro/macro positive	193.23	9.93–3758.56	0.001
<b>Aortic metastasis</b>			
Grade	0.64	0.25–1.67	0.362
DOI	0.85	0.22–3.38	0.821
LVSI	3.39	0.63–18.12	0.154
Micro/macro positive	189.67	9.35–3846.74	0.001

Only five of the 36 cases with ITC SLNs had DOI <50% and no LVSI, and none of these cases had other LN metastases.

Considering GOG 249 risk criteria irrespective of the presence of ITC, the 33 patients with ITC SLNs in this study were composed of 16 high-intermediate risk (HIR), 12 low-intermediate risk (LIR), and 5 low-risk (LR). Other positive lymph nodes were present in four (25%) GOG HIR (3 aortic, 1 pelvic), two (16.7%) GOG LIR (1 aortic, 1 pelvic and aortic), and none of the five GOG LR cases.

**4. Discussion**

Clinically important questions remain concerning the prognostic significance of SLN ITCs, the role of para-aortic lymphadenectomy, and the integration of the NCCN SLN mapping algorithm into the contemporary staging and treatment of patients with endometrial cancer. The risk of non-SLN pelvic node metastases using the mapping algorithm in this study was related primarily to the size of the SLN metastasis. Patients with ITC SLN metastases had an 8.3% incidence of other non-sentinel pelvic node metastasis, compared to 33.3% and 56.3% for SLN micro-metastasis and macro-metastasis, respectively. However, for patients with ITC SLN, depth of invasion was particularly predictive of other node metastases, as all three patients with other pelvic nodes positive were of the IR group. Our findings are similar to those reported by Touhami et al. [16] who found the incidence of other lymph node metastases in 34.8% of patients with SLN metastases, including 5% with ITC or micro-metastasis compared to 60.8% (p < 0.0001) with macro-metastasis.

The risk for having other pelvic node metastases was also influenced by histology risk group (LR 19.4%, IR 23.7%, and HR 55.0%). It was not possible to determine how many of the cases with other non-SLN

**Table 4C**

Summary of multivariable Firth Logistic regression showing the association of grade, DOI, and LVSI with sentinel node positive, other non-sentinel pelvic nodes positive, and aortic nodes positive (N = 355).

	OR	95% CI	p-Value
<b>Any lymph node positive</b>			
Grade	1.27	0.82–1.97	0.284
DOI	3.69	1.95–6.99	<0.001
LVSI	5.76	3.04–10.93	<0.001
<b>Pelvic metastasis</b>			
Grade	1.62	0.82–3.19	0.162
DOI	1.91	0.67–5.42	0.226
LVSI	11.44	2.65–49.34	0.001
<b>Aortic metastasis</b>			
Grade	1.4	0.71–2.77	0.337
DOI	1.49	0.52–4.3	0.460
LVSI	8.43	2.26–31.36	0.001

Abbreviations: ITC = isolated tumor cells; DOI = depth of invasion; LVSI = lympho-vascular space involvement; OR = odds ratio; CI = confidence interval.

metastases would have been dissected per the NCCN SLN algorithm [1] for lymph nodes that appeared possibly “suspicious” in this retrospective study. Nevertheless, overall 30% of our cases with positive SLNs had other pelvic metastasis. Presumably any metastatic lymph nodes left behind following the SLN surgical algorithm would be relatively small (<2 cm) and potentially controlled with adjuvant therapies. However, GOG 258 observed an increase in locoregional failure with use of chemotherapy alone [17], and whether leaving behind non-sentinel node metastases has an adverse effect on recurrence and survival should be a focus of future trials.

This study describes the relationship of SLN ITCs with other pelvic and aortic metastases, stratified by histology risk groups, in order to help counsel patients about ITCs and decisions about adjuvant therapy. Forty-percent of patients with SLN metastases were ITC, and approximately two-thirds were detected only by IHC staining. There are very few studies addressing the significance of H&E versus IHC identified ITCs [18]. Our study adds to the body of experience suggesting that ITCs, including IHC-detected metastases, may have clinical significance with associated risks for para-aortic metastasis. Omitting IHC staining would limit detection of ITC metastasis, leading to under-staging, and potentially falsely increasing the number of patients that appear to have “isolated aortic metastasis” previously documented at 1–3% in other studies [19,20]. ITC metastases should be considered in the context of the uterine pathology for the risk of other metastatic disease and in the decision for adjuvant therapy as suggested by Plante et al. [5]. However, 18.8% of patients with ITC SLNs had para-aortic metastasis, half of whom came from the low-risk histology cohort. Our multivariate regression analysis indicates that SLN containing ITCs, micro-metastases, and macro-metastases are all significant predictors for other nodal metastasis, including para-aortic metastasis [Tables 4A and 4B].

The role of para-aortic lymphadenectomy for endometrial cancer staging is debated and seemingly in disfavor in many centers, given the negative results of two prospective staging trials [21,22]. There are probably other drivers that foster this opinion by some surgeons. The rising incidence of obesity compromises exposure and increases the difficulty of para-aortic dissections. The shift to minimally invasive surgery and its associated long learning curve for advanced infra-renal dissection procedures has likely created a “training gap” in our surgical work-force [23]. Recent prospective clinical trials indicate that chemotherapy for node positive patients may be more important than radiation therapy for improving overall survival, casting further doubt about the importance of identifying para-aortic node metastasis during staging procedures [24]. However, several studies have reported improved survival associated with para-aortic lymphadenectomy [9–13]. Venigalla et al. [13] recently reported findings from a National Cancer Data Base (NCDB) analysis showing a statistically significant 5.1% improvement in 5-year overall survival in patients with HR histology when para-aortic lymphadenectomy was performed compared to pelvic lymphadenectomy alone. While chemotherapy may increase overall survival to a greater degree than radiation therapy with HR histologies [24] and while chemo-RT + chemotherapy was not superior to chemotherapy alone in GOG 258 [17], neither therapy universally controls all metastatic disease because of inherent or acquired resistance. Better sequencing of chemotherapy first, followed by radiation and then additional chemotherapy (a.k.a., “sandwich” therapy) might improve PFS and OS to an even greater degree. Resection of para-aortic metastasis allows tumor-site specific radiation and may also remove chemotherapy-resistant disease, possibly contributing to the improved survival reported by Venigalla et al. [13].

Surgical removal of para-aortic metastases may also improve disease control for individual low- and intermediate-risk patients harboring para-aortic disease. Given the relatively low incidence of para-aortic metastasis in patients with endometrioid histology, it is statistically futile to study this in a phase III clinical trial [25]. Employing the NCCN® sentinel lymph node mapping algorithm [1] along with frozen section analysis of

the uterine tumor and any suspicious pelvic lymph nodes resulted in a quarter of low-risk histology patients undergoing para-aortic dissections in this retrospective analysis. We believe this is a reasonable balance between minimizing morbidity and attempting to improve disease control. Not all patients who are at risk for para-aortic recurrence will undergo para-aortic lymphadenectomy, either for reasons of surgical morbidity or in cases with occult SLN metastasis in seemingly low-risk tumors. For patients who do not undergo para-aortic lymphadenectomy and have stage IIIC1 disease, we recommend periodic radiographic monitoring to detect recurrences early, when salvage radiation therapy might be beneficial. In a recent retrospective analysis by Aloisi et al. [26] of similar patients treated over a 24-year span, the incidence of aortic recurrence was about 4%, with another 8% having multiple sites that could have included para-aortic disease [26].

The SLN mapping algorithm in this study had a low (1.2%) false negative rate and there were no isolated para-aortic metastases identified, likely because of the increased sensitivity for detection of pelvic lymph node metastasis [2]. The FNR varied by histology risk group, with a significant difference between LR and HR patients. This finding has important implications for surgeons during their learning phase of sentinel lymph node mapping. It has been recommended to continue completion lymphadenectomies until an FNR of <5% has been achieved (estimated 20 cases in breast cancer) [27]. Because the risk of lymph node metastasis is much lower in LR patients, surgeons should include IR and HR patients followed by completion lymphadenectomy to determine their own proficiency for SLN mapping, then discontinue routine lymphadenectomy once proficiency is assured. In addition, patients with HR histology were more likely to have SLNs with macro-metastases as well as non-sentinel pelvic nodes with macro-metastases. Special attention should be given to non-sentinel pelvic lymph nodes in patients with HR histology. Given the higher false negative rate, the preponderance of macro-metastasis, and the high proportion with non-SLN metastasis, resection of any even moderately suspicious nodes should be considered in order to clear the retroperitoneum of macro-metastases. The vast majority of SLNs are detected in the medial external and obturator lymph nodes [28]. To mitigate morbidity, limiting completion lymphadenectomies to the medial half of the external iliac artery and obturator lymph nodes has been suggested as a method to reduce lymphedema [29].

A comparison of our study findings to other similar studies is problematic because of differences in demographics and pathology in the separate study populations [Table 5]. Significant differences in myometrial invasion and LVSI between comparison groups are apparent in two studies that compared SLN mapping and comprehensive staging by Eriksson et al. [14] and Ducie et al. [15]. The overall pelvic node metastasis rate was much higher in our study than either the SLN patients at MSK or the MC standard dissection group. The percentage of no myo-invasion at MSK for LR and HR was 57% and 46.7%, respectively compared to 23.3% and 13.6% in our study, and the rate of LVSI was much higher overall in our study, indicating that our population was at higher risk for lymph node metastasis. Our rate of para-aortic dissection was midway between the MSK and MC, and our detection of para-aortic metastases more resembles the complete dissection group from the MC. Whether the detection and/or removal of para-aortic metastasis will affect survival is uncertain, however patients with deep invasion or positive pelvic lymph nodes who do not undergo infrarenal dissections are at increased risk for upper aortic recurrence [7]. Larger prospective multi-institutional trials will be necessary to define the survival consequences of omitting para-aortic dissections in patients “at risk” for para-aortic metastasis.

Limitations of our study include its retrospective design and a single institution database that may allow for bias in the selection of surgical candidates during this time period, such that the results may not be generalizable to other populations. Several surgeons were in their learning phases at the initiation of the data base that could have influenced our findings, however the false negative rates demonstrated in this

**Table 5**

Comparison of staging data in endometrial cancer from other recent select studies.

	MSK 2006–2013 SLN Algorithm (N = 844)	MC 2004–2008 P/PaLND (N = 703)	AH 2011–2016 SLN Algorithm + P/PaLND (N = 414)
<b>Myometrial invasion</b>			
LR <sup>a</sup>			
None	57%	29.4%	23.3%
<50%	43%	70.6%	76.7%
IR <sup>b</sup>			
≥50%	100%	100%	100%
HR <sup>b</sup>			
None	46.7%	28.2%	13.6%
<50%	28.3%	48.7%	54.2%
≥50%	25.0%	27.2%	32.2%
<b>LVSI positive</b>			
Overall	21.3%	11.4%	31.0%
LR <sup>a</sup>	15.2%	3.0%	18.5%
IR <sup>b</sup>	74.4%	32.7%	62.5%
HR <sup>b</sup>	38.3%	29.1%	44.0%
<b>Pelvic LN positive</b>			
Overall	10.3%	9.4%	22.7%
LR <sup>a</sup>	5.6%	2.8%	11.6%
IR <sup>b</sup>	32.9%	23.4%	50.0%
HR <sup>b</sup>	23.4%	19.4%	39.0%
<b>Para-aortic LN positive</b>			
Overall	2.1%	5.4%	6.5%
LR <sup>a</sup>	0.8%	1.0%	2.9%
IR <sup>b</sup>	3.7%	18.7%	11.1%
HR <sup>b</sup>	8.3%	12.6%	16.9%
<b>PaLND dissection rate</b>			
Overall	21.0%	60.2%	45.2%
LR <sup>a</sup>	14.5%	49.7%	25.1%
IR <sup>b</sup>	34.1%	89.7%	78.8%
HR <sup>b</sup>	46.7%	79.6%	91.6%

Abbreviations: MSK = Memorial Sloan Kettering; MC = Mayo Clinic; AH = AdventHealth; SLN = sentinel lymph node; P = pelvic; PaLND = para-aortic lymph node dissection; LR = low-risk; IR = intermediate-risk; HR = high-risk; LN = lymph node; LVSI = lympho-vascular space involvement.

<sup>a</sup> Data from the MSK and MC on low-risk cohort derived from publication Zahl Eriksson et al. [14].

<sup>b</sup> Data from the MSK and MC on intermediate-/high-risk cohorts derived from publication Ducie et al. [15].

study are low by consensus standards [6]. Strengths of the study include the uniform algorithm for SLN mapping performed in a high-volume center, the prospective acquisition of data, the consistent evaluation of SLN pathology by protocol, and regular tumor board review of all cases. Another unique aspect of this data-set is that all patients underwent completion pelvic or pelvic and aortic lymphadenectomies for comparisons of non-SLN lymph nodes.

## 5. Conclusions

The presence of SLN ITCs in this study was associated with a clinically significant risk of para-aortic metastasis for patients in all three histology risk groups. ITCs were only associated with other non-SLN pelvic node metastasis in patients with >50% invasive endometrioid histology. These findings should be considered when assigning adjuvant therapies or counseling patients who did not undergo para-aortic dissections and are determined to have ITC SLNs, even in otherwise low risk histology settings. The risks and benefits of adjuvant therapy for patients with ITC-positive SLNs are yet to be determined in prospective trials. Micro- and macro-metastases SLNs are more commonly observed in non-endometrioid histologies, and over half of these cases harbor macro-metastatic pelvic or aortic lymph nodes. Therefore, SLN biopsies in non-endometrioid histologies carry a higher risk of leaving behind other macro-metastatic disease. From a safety perspective, we advise liberal selective removal of even moderately suspicious non-sentinel nodes until more prospective data about recurrence and survival in

patients with high-risk histologies staged with SLN mapping alone is available. While the false negative rate of our SLN mapping algorithm was low, it was very dissimilar for low-risk and high-risk histology cohorts, and this finding may impact individual surgeons' estimates of their SLN mapping proficiency. Finally, the absence of isolated aortic metastases in this study is consistent with improved detection of pelvic node metastases via a SLN mapping algorithm.

#### Conflict of interest statement

All co-authors declare that there are no potential conflicts of interest associated with this research manuscript, except Dr. Robert W. Holloway has received compensation for advanced training programs from Intuitive Surgical, Inc. (Sunnyvale, CA).

#### Author contribution

JAK and RWH designed the study, and subsequently all the authors participated in the data collection, analyses, discussion on results and interpretation, and help drafting the manuscript.

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