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Prospective clinical trial of robotic sentinel lymph node assessment with isosulfane blue (ISB) and indocyanine green (ICG) in endometrial cancer and the impact of ultrastaging (NCT01818739)

Floor J. Backes [a,*], David Cohen [b], Ritu Salani [a], David E. Cohn [a], David M. O'Malley [a], Emily Fanning [a], Adrian A. Suarez [b], Jeffrey M. Fowler [a]

[a] Division of Gynecologic Oncology, The Ohio State University Wexner Medical Center, James Cancer Hospital, Columbus, OH, USA
[b] Division of Pathology, The Ohio State University Wexner Medical Center, James Cancer Hospital, Columbus, OH, USA

HIGHLIGHTS

- SLN assessment in endometrial cancer is feasible and safe with high NPV (99%)
- Increasing BMI decreased the chance of successful SLN mapping
- Indocyanine green dye had higher SLN detection rates than isosulfane blue dye
- There were no recurrences in patients with isolated tumor cells only
- Treatment based on routine sectioning of SLNs (without ultrastaging) did not impair outcomes

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ABSTRACT

Objectives. To assess the performance sentinel lymph node (SLN) biopsy and effect of ultrastaging in clinically early stage endometrial cancer.

Methods. Patients with endometrial cancer prospectively enrolled after informed consent was obtained. The cervix was injected superficially with 1 mL of ISB and 1 mL of ICG (diluted 1:25) at 3 and 9 o'clock each. SLN biopsy was followed by complete pelvic lymphadenectomy (aortic lymphadenectomy at the discretion of the surgeon). Lymph nodes (LNs) were analyzed by standard sectioning with H&E; ultrastaging of SLN was done retrospectively and blinded to treating physicians.

Results. 204 patients received dye injections. In 184 (90.2%) patients at least one SLN was identified. Of all patients, 138 (68%) had bilateral mapping. In the patients with successful mapping of a hemipelvis, ICG detected SLNs in 83% and ISB in 64% of cases ($p < 0.0001$). Median BMI (kg/m^2) for patients with successful mapping was 35.7 compared to 40.1 for those who did not map ($p = 0.01$). Twenty-three (11.3%) patients had positive LNs. Applying the SLN algorithm, positive nodes were detected in 21/23 (91.3%). The negative predictive value (NPV) was 98.9% (95% CI: 96.01% to 99.71%). Eleven patients had positive SLN with isolated tumor cells (ITCs) or micrometastases detected on ultrastaging. Including these patients, 34 (17%) had positive LNs, increasing the NPV to 99% and sensitivity to 94%. There were no recurrences in patients with ITCs only.

Conclusions. SLN assessment in endometrial cancer is feasible and safe with high NPV (99%). ICG was more effective in detecting SLN compared to ISB. Although ultrastaging detected additional positive LNs, treatment based on standard sectioning appears reasonable but further research is needed.

1. Introduction

In 2018, an estimated 63,230 women were affected by endometrial cancer [1]. As a result of the obesity epidemic, the incidence of endometrial cancer continues to increase by 1–2.5% per year [1]. The cornerstone of endometrial cancer treatment is hysterectomy, bilateral salpingo-oophorectomy, with surgical staging. Although surgical

* Corresponding author at: Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, The Ohio State University College of Medicine, The James Cancer Hospital and Solove Research Institute, M-210 Starling-Loving, 320 West 10th Avenue, Columbus, OH 43210-3078, USA.
E-mail address: Floor.backes@osumc.edu (F.J. Backes).

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staging with lymphadenectomy provides valuable information regarding prognosis and helps tailor adjuvant therapy, prospective studies have not been able to demonstrate a survival benefit associated with lymphadenectomy [2,3]. In an attempt to reduce the risks associated with lymphadenectomy, such as lymphedema and lymphocele formation, investigators have explored sentinel lymph node assessment in endometrial cancer [4,5]. A variety of techniques have been described, including cervical, hysteroscopic and fundal injections; as well as the use of different dyes such as isosulfane or methylene blue, indocyanine green, and radiotracers (Technetium 99) [6–12].

Bilateral detection of sentinel lymph nodes has been reported in 52–86% of cases [6–11]. Existing algorithms recommend removal of all enlarged or suspicious lymph nodes, and to perform full site-specific lymphadenectomy if mapping is unsuccessful [13]. We hypothesized that detection of sentinel lymph nodes using colorimetric (blue) dye and immunofluorescent (indocyanine green) dye in endometrial cancer is accurate and safe with a low false negative rate, and safely can replace full lymphadenectomy. The primary objective of the current study was to determine the detection rate and negative predictive value (NPV) of sentinel lymph node (SLN) assessment in clinically early stage endometrial cancer. Secondary objectives included evaluation of sentinel lymph nodes by ultrastaging and endometrial cancer outcomes in relation to ultrastaging findings.

2. Methods

This was an Institutional Review Board approved single institution surgical intervention trial, registered on Clinicaltrials.gov under NCT01818739. The study was subject to periodic Data Safety Monitoring Committee review. Patients with clinically early stage endometrial cancer (all histologic subtypes) scheduled to undergo robotic hysterectomy and lymph node dissection were eligible. Patients were excluded if they had a contra-indication to any of the dye (elevated bilirubin or iodine allergy), or had previous retroperitoneal surgery. Patients were prospectively enrolled after informed consent was obtained.

2.1. Sentinel lymph node injection

Immediately prior to insertion of the uterine manipulator, 1 mL of ISB was injected superficially (1 to 5 mm with no blood return prior to injection) at the 3 and 9 o'clock positions on the cervix with a spinal needle, while CO_2 intra-peritoneal insufflation was initiated, followed by 1.0 mL of diluted ICG dye (25 mL normal saline to one 25 mg ampule of ICG) also at the 3 and 9 o'clock positions. Xi or Si da Vinci® surgical robots (Intuitive Surgical, Sunnyvale CA) equipped with the Firefly immunofluorescence detection system were used. The retroperitoneal spaces were carefully opened and SLN were identified and separately sent, labeled for location and positive for green/blue, and whether they were suspiciously enlarged. Sentinel lymph node dissection was followed by complete pelvic lymphadenectomy according to the Gynecologic Oncology Group surgical handbook Gynecologic Oncology Group: Surgical Procedures Manual (Revised July 2005 www.gogmember.gog.org). Aortic lymphadenectomy could be omitted if it was deemed not feasible or safe, and was at the discretion of the attending surgeon.

2.2. Pathology and SLN analysis

SLN were sent to pathology for permanent analysis clearly labeled with the additional word “sentinel”. Frozen section was not allowed. All lymph nodes (regular and sentinel) were assessed similarly and analyzed by standard sectioning with hematoxylin and eosin (H&E). H&E diagnosis was based on the standard of care “top” 4 μm section of each paraffin embedded block. The pathology report provided results based on standard sectioning and H&E only (no ultrastaging).

2.3. Ultrastaging

Ultrastaging of SLN was completed remote from surgery and treatment (at least 4 months and up to a year from the surgical procedure), and results were not available to the treating physician and patient. Therefore, treatment was determined at the discretion of the attending gynecologic oncologist and based solely on the standard sectioning with H&E lymph node evaluation and pathology report available under the standard clinical circumstances and equal to patients not on this study. If the sentinel lymph node was positive by standard sectioning and H&E, no further assessment was done. If the SLN was negative our protocol entailed 6 serial H&*E*-stained sections 4 μm thick at 40 μm intervals with an additional 4 μm section cut between the third and fourth levels for possible immunohistochemistry with mouse monoclonal anti-AE1/AE-3 cytokeratin (Dako, Carpentaria, CA). The research pathologist (AS and DC) examined the H&E-stained “endometrial SLN protocol” sections. The research pathologist proceeded with AE1/AE3 immunohistochemistry only if carcinoma was not detected in those sections. The research pathologist recorded results using standard definitions derived from breast IHC protocols. Isolated tumor cells (ITCs) were defined as <0.2 mm, and micro-metastases were defined as 0.2 to 2.0 mm of tumor, macrometastases were defined as >2 mm.

2.4. Statistics

The sample size was calculated to require 200 patients, assuming a negative predictive value (NPV) of 98% in this population and that the 2-sided 95% confidence interval for the NPV 94.4%–99.3%, using the methods of Mercaldo et al. The bilateral detection rate was calculated as the number of patients with bilaterally detected pelvis SLN divided by a total number of patients who underwent SLN mapping. The unilateral detection rate was calculated as the number of patients with unilaterally detected pelvic SLN divided by a total number of patients who underwent SLN mapping. Diagnostic performance was calculated for hemi-pelvises with at least one SLN harvested. Sensitivity was calculated as the proportion of true positives (patients with positive SLN) among the patients with lymph node metastases. Negative predictive value (NPV) was calculated by dividing the number of true negatives (patients with negative SLN) by the number of all patients without lymph node metastases. Patients were considered to have a false negative SLN if the node would have been missed applying the algorithm previously described by Barlin et al. [13] and as recommended in the National Comprehensive Cancer Network (NCCN) guidelines. For example, patients who did not have successful mapping (unilateral or bilateral), but positive lymph nodes on the side of unsuccessful mapping, were not considered as false negatives, as those would have a side-specific complete lymphadenectomy. Patients with suspiciously enlarged pelvic nodes that were confirmed positive in the setting of ipsilateral negative sentinel lymph nodes were also not considered false-negative as any enlarged lymph nodes would have to be removed per the algorithm.

3. Results

Between March 2013 and November 2016 a total of 204 patients received dye injections. Table 1 shows patient and tumor characteristics of the study population. The median age was 60 (range 30–81) and most patients were considered morbidly obese (BMI > 35 kg/m^2) with a median BMI of 36.5 (range 18.2–65.6). The majority (80%) had endometrioid adenocarcinoma while the remainder had high risk histologies with either pure or mixed serous or clear cell carcinoma or carcinosarcoma. At least one SLN was identified in 184 (90.2%) of cases, and of those 75% had bilateral mapping. Of all 204 patients 138 (68%) had bilateral mapping, 11% right and 11% left mapping only. Of the patients with successful mapping of a hemipelvis, ICG detected SLNs in 83% and ISB in 64% of cases ($p < 0.0001$). Median BMI (kg/m^2) was lower

Table 1
Patient and tumor characteristics represented as n (%) except for age and BMI. BMI body mass index, SLN sentinel lymph node.

	All (N = 204)	Mapping N = 184	No mapping N = 20	P-value
SLN mapping		184 (90.2%)	20 (9.8%)	
Age, median (range)	60 (30–81)	60 (30–81)	62 (49–76)	0.33
BMI (kg/m^2) (range)	36.5 (18–66)	35.7 (18.2–65.6)	40.1 (23.4–53.6)	0.014
Histology				
Endometrioid	164 (80.4%)	146 (79.4%)	18 (90%)	
Serous/endometrioid	9 (8.3%)	9 (4.9%)	0	
Mixed clear cell	3 (1.5%)	3 (1.6%)	0	
Serous	17 (8.3%)	15 (8.2%)	2 (10%)	
Clear cell	1 (0.5%)	1 (0.5%)	0	
Undifferentiated	1 (0.5%)	1 (0.5%)	0	
Carcinosarcoma	9 (4.4%)	9 (4.9%)	0	
Myometrial invasion				0.44
<50%	144 (80.6%)	128 (69.6%)	16 (80%)	
>50%	60 (29.4%)	56 (30.4%)	4 (20%)	
Grade				0.52
1	127 (62.3%)	113 (61.4%)	14 (70%)	
2	26 (12.7%)	23 (12.5%)	3 (15%)	
3	51 (25%)	48 (26.1%)	3 (15%)	
Stage				
IA	136 (66.7%)	122 (66.3%)	14 (70%)	
IB	33 (16.2%)	31 (16.9%)	2 (10%)	
II	6 (2.9%)	5 (2.7%)	1 (5%)	
IIIA	4 (2%)	3 (1.6%)	1 (5%)	
IIIB	1 (0.5%)	1 (0.5%)	0	
IIIC1	19 (9.3%)	18 (9.8%)	1 (5%)	
IIIC2	2 (1%)	2 (1.1%)	0	
IV	3 (1.5%)	2 (1.1%)	1 (5%)	

for patients with successful mapping (35.7 kg/m^2) compared to 40.1 kg/m^2 for those who did not map ($p = 0.014$). Twenty-three (11.3%) patients had positive LNs by standard sectioning. Applying the SLN algorithm, positive nodes were detected in 21/23 (sensitivity 91.3%, 95%CI: 72%–98.9%). One patient had a negative SLN and two out of 23 positive ipsilateral pelvic lymph nodes (true false negative SLN). One patient had no true nodal tissue in the SLN specimen (empty node) and had one out of fifteen positive ipsilateral pelvic lymph nodes. The negative predictive value was 98.8% (95% CI: 95.5% to 99.7%) and accuracy 99.02% (95%CI: 96.5–99.88%). There were an additional 11 patients who had positive SLN found on ultrastaging. While standard sectioning detected macrometastases, ultrastaging detected small volume metastases (micrometastases and ITCs). When we included patients with positive SLN detected by ultrastaging, 34 (17%) of patients had positive LNs, increasing the NPV to 99% (95%CI: 95.1%–99.7%) and sensitivity to 94% (95%CI: 80.3%–99.3%). (See Table 2.)

Table 3 shows the eleven patients who had a positive SLN by IHC (9 with isolated tumor cells (ITC) and 2 with micrometastases) in 1–3 SLNs (no positive non-SLNs). Nine had stage I or II endometrioid adenocarcinoma, one with stage IA mixed serous/endometrioid adenocarcinoma, and one had IIIB carcinosarcoma. Of the 10 early stage patients 5 received no adjuvant therapy, 2 vaginal brachytherapy, 2 whole pelvic radiation therapy (WPRT), and one chemotherapy (based on uterine factors only). None of the ten early stage patients with ITCs/micrometastases (excluding the patient with IIIB carcinosarcoma) have recurred with a median follow up time of 31 months (20–63 months).

Table 2
Distribution of patients with positive lymph nodes (LN). SLN sentinel lymph node.

Positive lymph nodes	N = 34	Positive non-SLN
Macrometastases	23 (11%)	
SLN mapping	21	7 (33%)
LN debulking	2	
Micrometastases	2 (1%)	0
Isolated tumor cells	9 (4%)	0

None of the patients with ITCs or micrometastases had positive non-SLNs. One patient with unilateral mapping had ITCs in the SLN and had a positive macrometastasis on the contralateral side (with unsuccessful mapping). Seven (22%) patients with successful SLN mapping had non-SLN metastases.

All patients with macrometastases had LVSI, compared to 45% of patients with ITCs or micrometastases only.

There were no serious adverse events directly related to study dye. One patient presented to the emergency department on postoperative day six with facial swelling around the cheek and upper lip. The rash started on her back and developed to her neck and skull on postoperative day 7 and continued her entire body. It slowly resolved with oral steroids and antihistamines. Although the late development of the rash does not suggest a temporal relationship to ISB or ICG, as well as the many other medications she received during her perioperative stay, it was deemed possibly related.

4. Discussion

Our study shows that sentinel lymph node assessment can be safely performed in patients with endometrial cancer with a high detection rate (90%) and reassuring negative predictive value of 99%. This is in line with other sentinel lymph node trials in endometrial cancer [6,14–17] and further supports sentinel lymph node assessment as part of standard of care for endometrial cancer.

As we incorporate sentinel lymph node assessment into our daily practice, this study reinforces the importance of adherence to the previously published sentinel lymph node algorithm by Barlin and Abu-Rustum [13]. For example, twelve of the thirty-four patients with positive lymph nodes in our cohort had suspiciously enlarged lymph nodes at the time of surgery. Four of those patients had one or more positive non-sentinel lymph nodes that were removed per the algorithm. This stresses the importance of removing all suspiciously enlarged lymph nodes and completion lymphadenectomy for the side that does not map. Preoperative imaging was not mandatory for our study thus it is not possible to know if these would have been visualized with preoperative imaging.

Our study is unique compared to other studies due to the fact that treatment was based on regular pathologic assessment of the sentinel lymph nodes (similar to non-sentinel lymph nodes). Ultrastaging was completed remote from the surgery and the results remained blinded to the treating physicians and patients. All patients received standard of care treatment as directed by the treating physician after discussion at a multi-disciplinary tumor board. Since patients underwent standard of care comprehensive surgical staging with complete lymphadenectomy and received treatment based on those results, there was no breach from standard of care treatment. Our rationale for performing ultrastaging "remotely" allowed us to obtain preliminary data on the impact of ultrastaging on NPV and to evaluate if detection (and treatment) of ITCs is truly necessary. Interestingly, only 1 patient with ITCs received chemotherapy (1A mixed serous/endometrioid adenocarcinoma), and none of the patients with ITCs only recurred. These findings are in line with very favorable outcomes for patients with low volume metastasis with and without treatment [18,19]. Certainly, definitive treatment recommendations cannot be made without larger case series, longer follow up, and preferably randomized clinical trials. However, we believe this preliminary dataset in combination with studies mentioned above suggests that further study is needed to determine whether chemotherapy is warranted for anyone with positive ITCs in the setting of early stage disease.

It is important to note that none of the patients with ITCs only, had positive non-SLNs. However, one patients with ITCs had a positive non-sentinel lymph node (macrometastasis on the contralateral site dissected after no successful mapping) further emphasizing the need

Table 3
Characteristics of patients with low volume metastases. Gr grade; LVSI lymphovascular space invasion; SLN sentinel lymph node; ITC isolated tumor cells; Micro micrometastasis; VBT vaginal brachytherapy; WPRT whole pelvic radiation therapy; Chemo chemotherapy.

Case ID	Stage/grade	Histology	LVSI	SLN	PVLN	PALN	Adjuvant therapy	Recurrence
3	IA gr 2	Endometrioid	No	ITC (1/3 SLN)	0/18	0/7	VBT	No
18	IB gr 1	Endometrioid	No	ITC (1/4 SLN)	0/22	–	None	No
47	IA gr 3	Endometrioid	Yes	ITC (1/4 SLN)	0/20	0/2	None	No
161	IA gr 1	Endometrioid	No	ITC (1/5 SLN)	0/18	–	None	No
170	IA gr 1	Endometrioid	No	ITC (2/4)	0/35	–	None	No
190	IB gr 3	Endometrioid	Yes	ITC (3/5 SLN)	0/21	0/21	WPRT	No
225	IA gr 1	Endometrioid	No	ITC (1/13 SLN)	0/22	0/12	None	No
237	IA gr 3 (mixed)	Serous/Endometrioid	Yes	ITC (2/3 SLN)	0/23	0/8	Chemo	No
239	IB gr 1	Endometrioid	Yes	ITC (1/7 SLN)	0/30	0/15	VBT	No
79	II gr 1	Endometrioid	No	Micro (1/1 SLN)	0/17	–	WPRT	No
195	IIIB gr 3	Carcinosarcoma	Yes	Micro (1/4 SLN)	0/20	0/9	Chemo + WPRT	Yes

for complete lymphadenectomy on the side of no mapping. Several authors have reported that the SLN node was the only positive node in approximately 40% of cases [14,15]. Holloway noted that the risk of non-SLN metastasis decreased depending on the size of the SLN metastasis, with 29% of patients having a positive non-SLN metastasis in the setting of SLN ITCs compared to 50% of those with macrometastases [9]. Other studies have reported slightly lower rates in the setting of SLN ITCs only. Rossi et al. reported that 29% of patients with low volume metastases (ITCs and/or micrometastases) had positive non-SLNs. However, of the 10 patients with ITCs, there was 1 patient (10%) with ITCs who had a positive non-SLN (personal communication), compared to 64% if macrometastases were present [10]. In the study by Plante et al., none of the patients with low volume metastases had other positive non-SLN [18]. Similarly, Touhami et al. reported a 5% risk of positive non-SLN if ITC/MM were present compared to 61% if macrometastases were present [20]. It is unclear whether pathologic evaluation is the cause for lower rate of positive non-SLN especially in the setting of low volume metastasis.

In conclusion, sentinel lymph node mapping is feasible and a safe alternative for complete lymph node dissection. Although ultrastaging identified additional positive SLNs (with low volume metastases), treatment based on standard sectioning did not impair outcomes and the risk of positive non-SLN is low for patients with ITCs only. No recurrences have been detected in patients with ITCs only, despite a paucity of systemic chemotherapy use. From this unique data set, we believe further study is needed to determine whether treatment of patients with ITCs in the absence of micro-or macrometastases is warranted. Furthermore, while our data does not yet allow definite conclusions regarding the necessity of ultrastaging, omitting ultrastaging could potentially save cost and pathologist time without compromising patient outcomes.

Conflict of interest statement

Dr. Backes, Dr. Cohn, Dr. O'Malley, and Dr. Salani have disclosed a conflict of interest outside of the scope of this manuscript. Dr. Fowler, Dr. Fanning, Dr. Cohen and Dr. Suarez have no conflict of interest to disclose.

Author contribution section

All authors contributed to the design and safe conduction of this clinical trial. Doctors Backes, Salani, Cohn, O'Malley, Fowler enrolled patients on the study and performed the procedures. Doctors Cohen and Suarez developed the ultrastaging protocol and performed the pathologic evaluation and ultrastaging. Dr. Fanning assisted with data collection, analysis and review. All authors critically reviewed the manuscript, edited it, and approved the final version.

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