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Detection of sentinel lymph nodes in patients with endometrial cancer undergoing robotic-assisted staging: A comparison of colorimetric and fluorescence imaging☆

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ABSTRACT

Objective. To retrospectively compare results from lymphatic mapping of pelvic sentinel lymph nodes (SLN) using fluorescence near-infrared (NIR) imaging of indocyanine green (ICG) and colorimetric imaging of isosulfan blue (ISB) dyes in women with endometrial cancer (EC) undergoing robotic-assisted lymphadenectomy (RAL). A secondary aim was to investigate the ability of SLN biopsies to increase the detection of metastatic disease.

Methods. Thirty-five patients underwent RAL with hysterectomy. One mL ISB was injected submucosally in four quadrants of the cervix, followed by 0.5 mL ICG [1.25 mg/mL] immediately prior to placement of a uterine manipulator. Retroperitoneal spaces were dissected for colorimetric detection of lymphatic pathways. The da Vinci® camera was switched to fluorescence imaging and results recorded. SLN were removed for permanent analysis with ultra-sectioning, H&E, and IHC staining. Hysterectomy with RAL was completed.

Results. Twenty-seven (77%) and 34 (97%) of patients had bilateral pelvic or aortic SLN detected by colorimetric and fluorescence, respectively ($p = 0.03$). Considering each hemi-pelvis separately, 15/70 (21.4%) had "weak" uptake of ISB in SLN confirmed positive with fluorescence imaging. Using both methods, bilateral detection was 100%. Ten (28.6%) patients had lymph node (LN) metastasis, and 9 of these had SLN metastasis (90% sensitivity, one false negative SLN biopsy). Seven of nine (78%) SLN metastases were ISB positive and 100% were ICG positive. Twenty-five had normal LN, all with negative SLN biopsies (100% specificity). Four (40%) with LN metastasis were detected only by IHC and ultra-sectioning of SLN.

Conclusions. Fluorescence imaging with ICG detected bilateral SLN and SLN metastasis more often than ISB, and the combination resulted in 100% bilateral detection of SLN. Ultra-sectioning/IHC of SLN increased the detection of lymph node metastasis.

Introduction

Lymphatic mapping for assessment of sentinel lymph nodes (SLN) is an accepted practice for breast, melanoma, and vulvar cancers [1–3] with the primary goal to reduce morbidity of a complete lymphadenectomy. A secondary goal is to improve detection of metastatic disease with pathology protocols that utilize ultra-sectioning of SLN and immunohistochemical (IHC) staining [4]. In 2008, a consensus panel of experts reported that sentinel node assessment in endometrial cancer was worthy of further investigation; however, there was insufficient data to comment on feasibility or benefits [5]. Since then, investigators have reported on their experiences with pelvic lymphatic mapping using colorimetric imaging of blue dyes [isosulfan blue (ISB), patent blue, and methylene blue] and/or radiocolloid mapping with Technetium-99 (Tc-99). Bilateral detection of pelvic lymph nodes is reported in 66 to 86% of cervix and endometrial cancer cases [6–9]. Furthermore, Roy et al. [9] reported a 7.8% increase in SLN detection utilizing both ISB and Tc-99 compared to ISB alone, achieving a 90.6% bilateral detection rate in patients with cervical cancer. However, radiocolloid mapping suffers from difficulties associated with coordinating injection times in the radiology suite relative to operating times when imaging is desired, variability of operators' ability to interpret the radioactive signal intraoperatively, cost, and patient concerns with injection of radioactive pharmaceuticals.

Recently, other medical dyes that fluoresce in light at the near-infrared (NIR) spectrum (700–900 nm) using laparoscopic imaging systems have been reported for use in lymphatic mapping of gastric, breast, rectal, cervical, and endometrial cancers [10–14]. Indocyanine green (ICG) is the most clinically useful agent for NIR lymphatic mapping [15], and has been used clinically for two decades with an excellent safety profile. The risk of allergic reactions with ICG has been estimated 1 per 42,000 uses [16]. The da Vinci® NIR fluorescence imaging system

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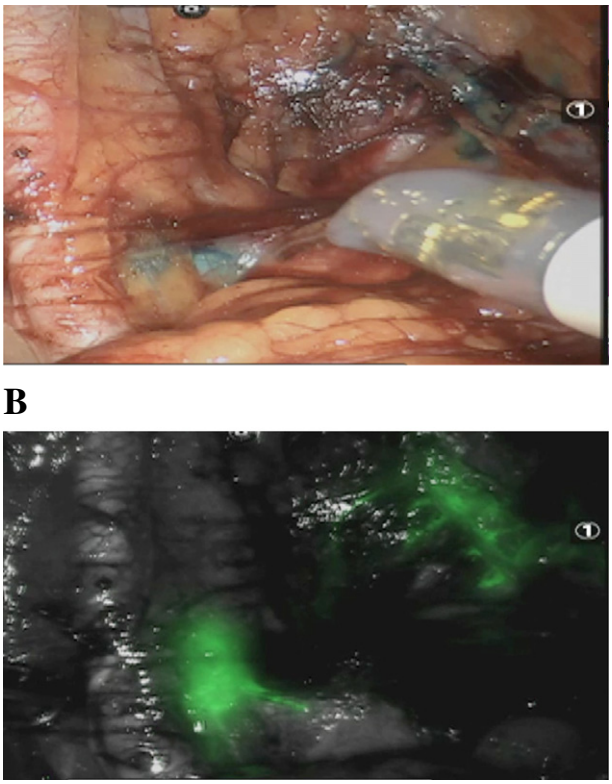

Fig. 1. (A) Colorimetric detection of isosulfan blue (ISB) in left parametrial lymphatics leading to left external iliac lymph node. (B) Near-infrared (NIR) imaging of indocyanine green (ICG) in the same patient showing parametrial lymphatics and left external iliac lymph node.

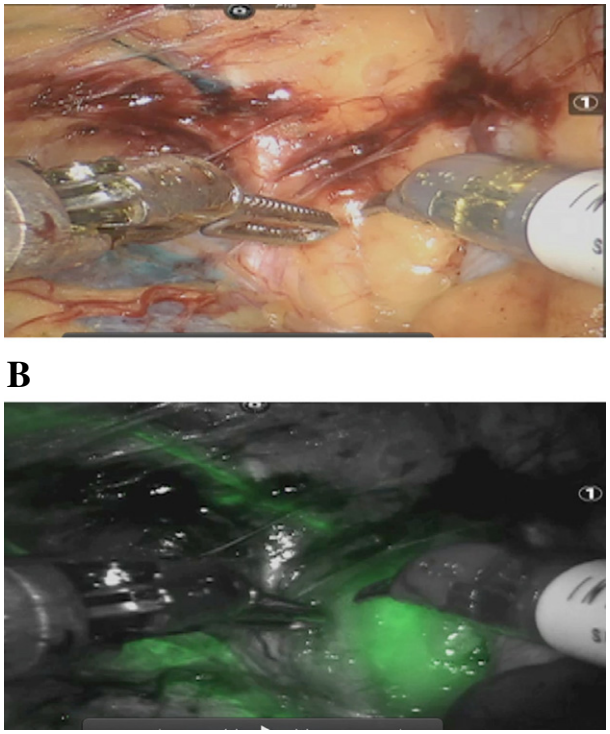

Fig. 2. (A) Colorimetric view of isosulfan blue (ISB) in right parametria leading to obturator space, but fails to identify a sentinel lymph node (SLN). (B) Near-infrared (NIR) imaging of indocyanine green (ICG) dye confirms obturator SLN.

is FDA cleared for vascular imaging and is useful for confirming patency of vascular anastamoses in cardiovascular surgery [17]. The robotic NIR system has also been used for partial nephrectomy by revealing photopenic tumor relative to the surrounding normal renal parenchyma [18]. Rossi et al. [14] recently described preliminary results with NIR fluorescence imaging used with robotic-assisted surgery in patients with cervical and endometrial cancers, recommending that a 1 mg dose of ICG was most efficacious for lymphatic mapping.

In this study, we sought to retrospectively compare the ability of fluorescence imaging of ICG and standard colorimetric analysis of ISB dyes for the detection of SLN in small cohort of women with endometrial carcinoma who underwent robotic-assisted lymphadenectomy (RAL). A secondary aim of this study was to investigate the ability of SLN mapping to increase the detection of metastatic disease by comparing SLN ultra-sectioning and IHC to traditional hematoxylin and eosin (H&E) staining results.

Materials and methods

Study subjects

The medical records from 35 patients who underwent da Vinci® (Intuitive Surgical, Inc., Sunnyvale, CA) SLN mapping during robotic-assisted hysterectomy and staging lymphadenectomy for the treatment of uterine carcinoma from May to September, 2011 were reviewed. Medical records were reviewed for patient demographics and clinicopathologic factors including the sites of SLN biopsies and method of identification. An IRB-approved clinical data analysis protocol was used for this study.

SLN mapping procedure

Immediately prior to insertion of the uterine manipulator, 1 mL of ISB was injected sub-mucosally in four quadrants of the cervix (1 to 2 mm with no blood return prior to injection) and CO_2 intra-peritoneal insufflations initiated simultaneously during the injections. Immediately prior to docking, 0.5 mL of diluted ICG dye (25 mg of ICG in 20 mL normal saline [1.25 mg/mL]) was injected in each cervical quadrant immediately prior to the placement of a uterine manipulator. The ICG concentration used was one half that recommended for intravenous injection, as early experience revealed leakage from the lymphatics into soft tissue with standard dilution, somewhat obscuring sentinel lymphatic pathways. The pelvic dissections were initiated within approximately 10 min of the cervical injections.

The pelvis was carefully inspected, opening the pararectal and paravesical spaces with meticulous hemostasis to avoid obscuring blue lymphatic pathways during colorimetric analysis with standard "white light"(Figs. 1A and 2A). When more than one lymph node was observed on a side, the closest node to the cervix and parametrial sentinel lymphatic path was considered "sentinel". The camera was switched to NIR mode and again the findings noted. If ISB results were negative or unilateral, an additional 5 min was allotted to ensure that adequate time passed for the blue dye to reach lymph nodes while the presacral, pararectal, and lower aortic spaces were inspected for aberrant sentinel lymphatic pathways. SLN were removed separately on each side and underwent an ultra-staging and IHC protocol established for the SLN mapping in breast cancer (see below). No frozen sections were performed on SLN specimens in order to completely preserve pathology. A complete pelvic and common-iliac lymphadenectomy was performed and lymph nodes were submitted for standard (H&E) staining. Aortic lymphadenectomy was completed for higher risk lesions as determined by intra-operative frozen section analysis of the uterine tumor or suspicious pelvic lymph nodes. Findings of colorimetric and

fluorescence imaging were recorded for each side of the pelvis in the operative records.

Pathology and SLN analyses

Pathologists recorded initial H&E impressions of ultra-sectioned SLN (at least 6 serial sections 4 μm thick at 40 μm intervals) prior to IHC analysis, and then amended their reports after IHC if groups of malignant cells were subsequently identified in H&E slides with the aid of IHC. An additional 4 μm section was cut between the third and fourth levels and immuno-stained with mouse monoclonal anti-AE1/AE-3 cytokeratin (Dako, Carpentaria, CA). Standard definitions derived from breast IHC analysis were used. "Isolated cytokeratin tumor cells" were less than 0.2 mm; and micro-metastases were defined as 0.2 to 2.0 mm of tumor.

Non-sentinel lymph nodes underwent one section with routine H&E staining. Sensitivity of SLN detection, bilateral and unilateral, was analyzed for each method and compared. SLN findings for each method were compared to complete pelvic lymphadenectomy findings for an analysis of sensitivity and specificity for detecting metastatic disease.

Statistical analyses

Data are presented as percent and/or mean ± standard deviation (SD) for continuous variables, and rates in the case of discrete variables. A Student's *t*-test or Chi-squared test was used for continuous and discrete variables, respectively. A *z*-test was performed to determine the statistical significance where data were analyzed for percent difference between the groups. In all instances, a p-value of <0.05 was declared as statistically significant.

Results

The mean age of patients was 63.4 years, BMI 33.1 kg/m^2, and 26 (74.6%) of patients had "Mayo Clinic high-risk" features for lymphatic metastasis on final pathologic analysis [19]. The mean lesion size was 4.4 cm. and 63% of tumors were Grade 2 or 3. The mean myometrial depth of invasion was 41% (range 6 to 100%) and lymphovascular space invasion was detected in 37% cases (Table 1). All cases were completed with the robotic-assisted laparoscopic technique previously described [20]. Sixty-three percent of cases received comprehensive pelvic and aortic lymphadenectomy with a single central-docking procedure, and 14 (63.4%) of these had infra-renal nodes dissected. The remaining 13 patients underwent complete pelvic lymphadenectomy (Table 2). The mean pelvic lymph node yield was 22.6 ± 10.9 and the mean aortic lymph node count was 10.3 ± 6.6.

Bilateral SLN were detected in all but one patient (97%) using the robotic NIR imaging system, and 27 (77%) patients by colorimetric analysis(Figs. 1 and 2). Considering each hemi-pelvis separately, 15/70 (21.4%) hemi-pelvises had weak or indeterminate uptake of ISB in SLN, subsequently confirmed positive with fluorescence imaging. All patients had at least unilateral SLN identified by each method, and by combining methods bilateral detection was 100%. Two cases had sentinel nodes identified in the pre-sacral and lower aortic areas by fluorescent imaging that were not identified by ISB. Three cases had common iliac SLN, and all remaining SLN were identified in the true pelvis (obturator or external iliac chains). Only one patient had a pelvic SLN identified by a weak blue colorimetric signal that was also fluorescence negative.

Ten (28.6%) patients were identified with nodal metastasis (Table 3). Five patients had positive pelvic nodes, and five had both positive pelvic and aortic nodes, three of whom also had infra-renal metastasis. All positive SLN biopsies were pelvic nodes, correctly identifying nine cases (90% sensitivity). The one false negative SLN biopsy failed to detect the metastasis in an immediately adjacent external iliac lymph node. Twenty-five patients had normal lymph nodes on final assessment, and SLN biopsies correctly predicted all cases (100% specificity). Metastasis was solely identified by ultra-sectioning and IHC staining lymph nodes in four of the 10 patients with node metastasis, which represents a 67% increase in identification of node metastasis compared to routine H&E staining. Two of these SLN with IHC-identified metastases were subsequently recognized to have H&E staining cancer cells (micrometastasis), and the remaining two cases were IHC cytokeritin-positive for isolated tumor cells with negative H&E findings. Seven of nine SLN with metastasis were detected using standard light and two additional SLN (a total of nine) were detected with NIR imaging.

Table 1
Demographics and primary tumor characteristics.

Age (years)	63.4 ± 10.4 (range 35–88)
Body mass index (kg/m^2)	33.1 ± 9.3 (range 18–56)
Tumor grade	
1	13 (37.1%)
2	14 (40%)
3	8 (22.9%)
Lesion size (cm)	4.4 ± 2.3 (range 0.2–10.0)
Myometrial invasion	41% (range 6–100)
Lymphovascular space invasion	13 (37%)
Positive nodes[a]	10 (28.8%)
Mayo Clinic criteria	
"Low-risk"	9 (25.7%)
"High-risk"	26 (74.3%)

[a] All 10 positive node cases were "Mayo Clinic criteria" [19] high-risk cases.

Table 2
Clinico-pathological data.

Operative time (min)	169 ± 37 (range 103–236)
Estimated blood loss (mL)	118 ± 47 (range 50–250)
Hospital length-of-stay (days)	1.3 ± 0.9 (range 1–5)
Transfusion rate (%)	0
Comprehensive pelvic-and-aortic lymph node dissection	22 (63%)
Pelvic nodes	22.6 ± 10.9 (range 13–59)
Aortic nodes	10.3 ± 6.6 (range 1–28)
Patients with positive nodes	10 (28.6%)
Pelvic	5 (14.3%)
Pelvic ± aortic	5 (14.3%)
Conversion to laparotomy	0

Discussion

The role of complete pelvic and aortic lymphadenectomy for patients with EC continues to be debated. Retrospective studies from both individual institutions and large national databases suggest that lymphadenectomy may be therapeutic or improve outcomes [21,22]. However, two randomized clinical trials have called into question routine pelvic and aortic lymphadenectomy because survival outcomes were not improved for patients randomized to the lymphadenectomy arms [23,24]. These two studies have been thoroughly criticized for several design and methodological flaws [25,26], and many experts

Table 3
Data on lymph node metastasis.

Total sentinel lymph node cases	35
Cases with lymph node metastasis	10 (28.6%)
Cases with sentinel lymph node metastasis	9 (90% sensitivity)
Cases with normal lymph node	25
Cases with negative sentinel lymph node	26 (100% specificity)
Positive predictive value (PPV)	100%
Negative predictive value (NPV)	96%
Cases with sentinel lymph node metastasis by IHC	4 (40%)

continue to recommend that complete lymphadenectomy is preferable for staging, treatment planning, and prognosis [27,28].

The routine performance of pelvic and aortic lymphadenectomy for patients with EC adds operative time, cost, and complications including lower extremity lymphedema, lymphocysts, and transient neuralgias [29]. Attempts have been made to define a low-risk group of patients with EC that would not benefit from lymphadenectomy in order to reduce overall morbidity. Most gynecologic oncologists agree that small endometrioid Grade 1, 2 tumors with early myometrial invasion identified on frozen section have low-risk for lymphatic metastasis [30]. Unfortunately, the inherent limitations of intra-operative frozen section analysis may lead to errant omission of lymphadenectomy for some cases subsequently identified as "Mayo Clinic high-risk" on permanent pathology. SLN mapping has been widely adopted for routine management of breast cancer, melanoma, and vulvar cancers [2,5,31], reducing the need for complete lymphadenectomy.

A recent multi-center French study (SENTINO-ENDO) of sentinel node biopsy in 125 patients with EC using dual Tc-99 and Patent blue dye cervical injections identified bilateral SLN in 69% of patients [7]. There were three false negative SLN cases, yielding sensitivity for detection of metastatic disease of 84% and negative predictive value (NPV) 97%. Five percent of patients had aortic SLN. Perhaps equally important, SLN detection was more sensitive for detection of metastatic disease because ultra-sectioning and IHC more than doubled the number of metastasis identified by routine H&E stains. Our results in this study are similar using NIR imaging of ICG and colorimetric imaging of ISB. Bilateral SLN were identified in nearly all patients (97%) using NIR and 77% using ISB. Each method likely compliments the other, as ISB pathways are usually seen quickly upon opening spaces in white light, and NIR imaging of ICG frequently confirms or rejects uncertain colorimetric findings. As reported in the SENTINO-ENDO trial [7], IHC and ultra-staging SLN resulted in improved detection of metastatic disease in our study (67% increase). However, unlike the French study, 63% of our patients underwent aortic lymphadenectomy, and 50% of cases with metastasis had aortic involvement including infra-renal lymph nodes. Curiously, none of the positive node cases in this study were isolated to the aortic lymph nodes as reported by others [19], although not all cases received infra-renal aortic LN biopsies in this study. Perhaps pelvic SLN detection with more sensitive ultra-sectioning and IHC reduces the reported incidence of isolated infra-renal metastasis. Clearly, a larger cohort will be necessary to study the issue of isolated infra-renal metastasis when SLN biopsies are performed.

Uterine fundal subserosal injections of blue dyes and Tc-99 have been described by several authors with SLN detected in 45 to 90% cases [32], indicating considerable variability in SLN detection among investigators. Hysteroscopic injection of tumors has also been reported with variable results. Hysteroscopy adds significant cost, inconvenience, and is therefore may not be feasible for routine clinical use [32]. Cervical injection is clearly the easiest and most reproducible technique for pelvic SLN mapping. There are several routes of lymphatic drainage from the uterus. Through the lower uterine segment and cervix, lymph primarily drains laterally through the parametria to the pelvic side wall, but may also course into the para-rectal and pre-sacral spaces [9]. Uterine fundal drainage is relatively consistent through the ovarian veins to the infra-renal para-aortic lymph nodes. Hence, it is our recommendation that pelvic lymphatic mapping be performed by cervical injection with visualization of the parametrial lymphatic channels to the pelvic side wall. If SLN are not identified, we recommend inspecting the para-rectal space for SLN, and the pre-sacral space which may lead to identification of common iliac or infra-mesenteric aortic SLN. In our opinion, the decision to dissect aortic lymph nodes, including the infra-renal lymph nodes, should be determined by intra-operative analysis of the primary uterine tumor and pelvic nodal status.

In this exploratory analysis, we found that use of the NIR imaging system and ICG dye with robotic-assisted surgery was quite easy to master and complimented traditional colorimetric analysis of ISB. It is possible that ICG alone could be as efficacious, but our initial impression is that colorimetric assessment also assisted in retroperitoneal dissection, avoiding frequent switching back and forth from NIR to white light. Of note, we used 2.5 mg of ICG per patient, considerably more than reported by Rossi et al. [14], possibly accounting for our improved detection of SLN. A future prospective trial with larger numbers of patients will be necessary to confirm the sensitivity, specificity, and especially negative predictive value for this technique. Perhaps if our findings are confirmed in a larger multi-institutional trial, gynecologic oncologists will be confident omitting lymphadenectomy for Mayo Clinic low-risk cases by performing less-morbid SLN biopsies (searching for the 1 to 2% with metastasis), and conversely improve the precision of staging for high-risk cases through the rational use of ultra-staging and IHC.

Conflict of interest statement

Dr. Robert Holloway is a training consultant for Intuitive Surgical, Inc. All other co-authors declare that there are no conflicts of interest associated with this manuscript.

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