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Detection of sentinel lymph nodes in minimally invasive surgery using indocyanine green and near-infrared fluorescence imaging for uterine and cervical malignancies☆

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HIGHLIGHTS

- The use of indocyanine green is associated with a high detection of sentinel lymph nodes.
- The use of indocyanine green is associated with a high sentinel lymph node bilateral detection rate.

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ABSTRACT

Objectives. Our primary objective was to assess the detection rate of sentinel lymph nodes (SLNs) using indocyanine green (ICG) and near-infrared (NIR) fluorescence imaging for uterine and cervical malignancies.

Methods. NIR fluorescence imaging for the robotic platform was obtained at our institution in 12/2011. We identified all cases planned for SLN mapping using fluorescence imaging from 12/2011–4/2013. Intracervical ICG was the fluorophobe in all cases. Four cc (1.25 mg/mL) of ICG was injected into the cervix alone divided into the 3- and 9-o'clock positions, with 1 cc deep into the stroma and 1 cc submucosally before initiating laparoscopic entry. Blue dye was concurrently injected in some cases.

Results. Two hundred twenty-seven cases were performed. Median age was 60 years (range, 28–90 years). Median BMI was 30.2 kg/m^2 (range, 18–60 kg/m^2). The median SLN count was 3 (range, 1–23). An SLN was identified in 216 cases (95%), with bilateral pelvic mapping in 179 (79%). An aortic SLN was identified in 21 (10%) of the 216 mapped cases. When ICG alone was used to map cases, 188/197 patients mapped, for a 95% detection rate compared to 93% (28/30) in cases in which both dyes were used (P = NS). Bilateral mapping was seen in 156/197 (79%) ICG-only cases and 23/30 (77%) ICG and blue dye cases (P = NS).

Conclusions. NIR fluorescence imaging with intracervical ICG injection using the robotic platform has a high bilateral SLN detection rate and appears favorable to using blue dye alone and/or other modalities. Combined use of ICG and blue dye appears unnecessary.

Background

The importance of sentinel lymph node (SLN) mapping in the prognostication of cancer was first described over a half century ago and has since been incorporated into the routine management of various solid tumor types [1–4]. In gynecologic cancer, the SLN concept is most accepted for vulvar carcinomas, as seen with the publication of Gynecologic Oncology Group (GOG) protocol 174 and the Groningen international study on sentinel nodes in vulvar cancer (GROINSS V-1) [5–7]. Its use in cervical and uterine cancers is being increasingly investigated [8–25]. The accuracy of SLN mapping in uterine cancer remains to be determined and needs to be addressed in a prospective fashion. However, efforts to continue to improve the detection of SLNs are important.

Since 1996, blue dye, with or without technetium, has been the predominate dye used to identify SLNs [26]. More recently, SLN detection rates of approximately 80% have been reported [27–31]. However, these rates do not reflect bilateral detection. Bilateral detection rates

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of the SLN are the most clinically relevant as the lymphatic drainage in the pelvis is not unilateral [20]. “Successful” SLN mapping for cervical and uterine cancers, therefore, must reflect bilateral mapping. When specifically looking at the bilateral rates in minimally invasive surgery at our institution, bilateral mapping occurred in approximately half of the patients (61%) [14]. In robotic-assisted cases, bilateral mapping was achieved in 40% of cases using blue dyes such as isosulfan blue or methylene blue [32]. This is consistent with other published reports suggesting that bilateral mapping using blue dyes alone can only be achieved in approximately 50% of cases [14,32]. This translates into approximately half of patients requiring some form of lymphadenectomy (LND), and improvement in detection rates is needed.

Near-infrared (NIR) fluorescence imaging with indocyanine green (ICG) has been described for SLN mapping in various malignancies. ICG is the only FDA-approved fluorophobe in use for many years, but it has not yet been approved specifically for SLN mapping in the United States. NIR imaging appears to provide a beneficial technique for SLN mapping of gynecologic malignancies. NIR imaging capabilities are now available for the da Vinci Si robotic platforms (Intuitive Surgical®, Sunnyvale, CA) as well as for laparoscopic and open approaches (PINPOINT® and SPY Elite®(Novadaq Technologies, Bonita Springs, FL). Small single series have been recently published [33–35]. The primary objective of this study was to assess the detection rate of SLNs for uterine and cervical malignancies using ICG and NIR fluorescent imaging with the robotic platform at Memorial Sloan-Kettering Cancer Center.

Methods

Institutional review board approval was obtained for this retrospective study. All consecutive cases planned for SLN mapping using fluorescence imaging from 12/2011 to 4/2013 were identified and prospectively entered into our database, which is maintained for quality assurance purposes for all our robotic cases. Intracervical ICG was the fluorophobe used in all cases. The concentration used was 1.25 mg/mL. For each patient, a 25 mg vial with ICG powder was diluted in 20 cc of aqueous sterile water. Four cc of this ICG solution was injected into the cervix alone divided into the 3- and 9-o'clock positions, with 1 cc deep into the stroma and 1 cc submucosally on the right and the left of the cervix, usually prior to initiating laparoscopic entry. Isosulfan blue was concurrently injected in some cases using the same method as described for ICG. Isosulfan blue was our preferred blue dye at the time these cases were performed. The cervix was injected after the patient was prepped and draped but prior to the insertion of any uterine manipulator or the docking of the robot. Once the cervix was injected, the robotic platform was docked as per surgeon preference. Our previously published SLN algorithm (Fig. 1) [36], which included pelvic washings for endometrial cancers, the evaluation of the retroperitoneum, and the removal of SLNs and any grossly enlarged nodes regardless of mapping, was followed by all surgeons.

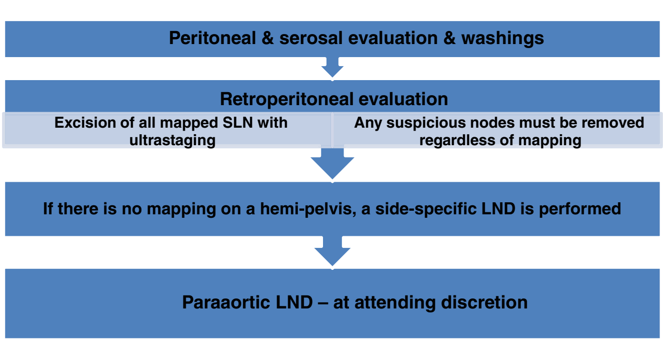

Fig. 1. Sentinel lymph node mapping algorithm.

Table 1
Clinicopathologic demographics of the entire cohort.

	Median (range)
Age (years)	60 (28–90)
Body mass index (kg/m^2)	30.2 (18–60)
Estimated blood loss (mL)	50 (5–1000)
OR time (min)	240 (146–440)
	Frequency (%)
Postoperative diagnosis	$n = 227$
Complex hyperplasia with atypia	11 (5%)
Endometrioid adenocarcinoma of the uterus	168 (74%)
Serous carcinoma of the uterus	15 (7%)
Carcinosarcoma of the uterus	13 (6%)
Clear cell of the uterus	1 (0.04%
Leiomyosarcoma of the uterus	1 (0.04%)
Cervical cancer	18 (8%)
Grade	$n = 168$
1	100 (60%)[a]
2	38 (23%)[a]
3	30 (18%)[a]

[a] Grade assessment in 168 cases of endometrioid adenocarcinoma.

Demographics and surgical data were collected. Final pathology results were examined. The median age, body mass index (BMI), estimated blood loss (EBL), time to find the SLN, number of SLNs identified, and anatomic location of the SLN were recorded. The time to perform the SLN mapping was defined as the time from the initial development of the retroperitoneal space until the surgeon felt that SLNs were or were not identified. Overall detection rates and bilateral detection rates to find the SLN were calculated. Chi-square and Fisher's exact tests were used, as appropriate, to compare SLN detection rates and the dye used. The Mann–Whitney *U* test and Kruskal–Wallis test were performed to assess the impact of BMI on SLN detection. SPSS version 21.0 statistical software was used to perform all statistical tests.

Results

Two hundred twenty-seven patients with endometrial or cervical cancer were identified. The median age of the patients was 60 years (range, 28–90 years), median BMI was 30.2 kg/m^2 (range, 18–60 kg/m^2), and median EBL was 50 cc (range, 5–1000 cc). The majority of patients (138/227, 61%) were diagnosed with grade 1 or 2 endometrioid adenocarcinoma of the uterus. The median surgical time to complete the SLN mapping was 30 min with some cases being mapped within 3 min (range, 3–84 min). The median number of SLNs removed was 3 (range, 1–23) (Table 1). ICG dye alone was used in 87% of cases ($n = 197$), and ICG and blue dye were used in 13% of cases ($n = 30$) (Table 2).

The overall detection rate of the SLN (uni- or bilateral) for this cohort of patients was 95% (216/227). An SLN was not identified in 11 cases. In cases in which ICG only was used, 95% (188/197) mapped either unilaterally or bilaterally compared to 93% (28/30) of cases in which both the ICG and blue dyes were used ($P =$ NS) (Table 2). The bilateral detection

Table 2
Sentinel lymph node detection rates in the entire cohort ($n = 227$).

Variable	Patients, frequency (%)
SLN mapping time (min), median (range)	30 (3–84)
SLN identified per patient, median (range)	3 (1–23)
Dye used	
ICG alone	197 (87%)
ICG and blue	30 (13%)
Overall detection rate	216 (95%)
Mapping by pelvis	
None	11/227 (5%)
Unilateral	37/227 (16%)
Bilateral	179/227 (79%)

SLN, sentinel lymph node; ICG, indocyanine green.