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Green versus blue: Randomized controlled trial comparing indocyanine green with methylene blue for sentinel lymph node detection in endometrial cancer

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HIGHLIGHTS

- The rate of successful detection of SLN in hemipelves was 90.9% if mapped with ICG, but only 64.4% if mapped with blue dye
- The number of SLN per HP with successful detection was similar using ICG or blue dye
- The duration of the SLN procedure was similar using ICG or blue dye
- Detection rates for each dye were similar whether the surgical approach was robotic or laparoscopic
- Crossover of dye to the contralateral hemipelvis was present in 3% of cases

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ABSTRACT

Objective. To ascertain the increase in detection rate of sentinel lymph node (SLN) associated with the use of indocyanine green (ICG) in comparison with methylene blue dye in women with endometrial cancer.

Methods. For this randomized controlled trial, all patients underwent SLN mapping after injection of blue dye on one side of the cervix and ICG on the other side. Randomization was for the side (right vs. left) on which ICG was used so that each patient's contralateral hemipelvis (HP) served as a control to her ipsilateral HP. We performed a two-tailed, normal-approximate McNemar test for paired-matched data. The primary endpoint was the difference in SLN detection rate for each HP according to the dye used.

Results. This trial included 132 patients, and 46 patients underwent robotic-assisted surgery while 86 had standard laparoscopic surgery. Successful detection of SLN was 90.9% using ICG and 64.4% using blue dye ($p < 0.0001$). There were no differences in the duration of the SLN procedure (median 10 min per HP) and number of SLN per HP (mean 1.2) according to the dye used. The SLN detection rates for either dye were very similar whether the surgical approach was robotic (mean BMI 45) or laparoscopic (mean BMI 29). Crossover of dye to the contralateral HP was present in 3% of cases.

Conclusion. The use of ICG instead of blue dye results in a 26.5% (95% CI 17.4%–35.6%) increase of SLN detection rates per HP in women with endometrial cancer.

1. Introduction

The role of lymphadenectomy in clinically early-stage endometrial cancer has been a topic of ongoing debate. The sentinel lymph node (SLN) procedure has been extensively studied and has been proposed as a middle ground solution to decrease the morbidity of lymphadenectomy in a low-risk population while increasing detection for metastatic disease and tailoring adjuvant treatment to individual patients. Although several gynecologic oncologists advocate the use of this procedure worldwide, not all healthcare centers are equally equipped to perform SLN procedure.

Historically, the best SLN detection rates had been achieved when the procedure was performed using a combination of technetium 99 and blue dye, resulting in an overall detection rate of around 90% and a bilateral detection rate of around 60% [1–6]. The use of technetium

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has fallen out of favor in most centers because of logistic challenges surrounding preoperative cervical injection, lymphoscintigraphy, patient inconvenience, the lack of equipment in many facilities, cost, and finally the promising initial reports on Indocyanine Green (ICG). Blue dye alone (either methylene blue, lymphazurin or patent blue) is the most commonly reported injection product used for SLN mapping in women with endometrial cancer, but results in an approximately 80% overall detection rate and a 50% bilateral SLN detection rate [7,8]. ICG with near-infrared (NIR) imaging is a more recent option for lymphatic mapping. ICG is a contrast agent which turns fluorescent when exposed to NIR light [9]. This is particularly useful in obese patients where fatty tissue is interposed between the laparoscope and target lymph nodes, as well as when tissues become tainted with blood. In published studies, the use of ICG for SLN mapping renders around 95% overall detection and 80% bilateral SLN detection [10–14].

Possible explanations for the rates of SLN detection with ICG appearing higher than with blue dye include the fact that reported studies are based on different patient populations that were led by different surgeons, and the fact that ICG with NIR is a more recent technique (the learning curve of the operator may have been achieved during the blue dye era). In the recently published FILM study [15], a randomized controlled non-inferiority trial, both ICG and blue dye were injected bilaterally in the cervix and randomization was applied to the sequence of injection (blue before green vs. green before blue). The resulting SLNs were qualified by the surgeon as being blue only, green only, or both blue and green. The per-protocol results of the FILM trial showed that when using both mapping substances together, 98% of patients (159 of 163) had at least one SLN retrieved, 81% (132/163) of patients had bilateral SLN showing green uptake (either green only or green and blue), while 32% (54/163) of patients had bilateral SLN showing blue uptake (either blue only or green and blue), suggesting a superior performance of ICG.

In the present “Green vs. Blue” trial, both ICG and methylene blue were assessed individually in the same patient. This trial design allowed comparison of both injection products in a perfectly balanced “matched” randomized cohort, while also controlling for surgeon experience. We aimed to ascertain if there is an increased detection rate of SLN associated with the use of ICG in comparison with blue dye in women with endometrial cancer, and if so, to what extent.

2. Methods

2.1. Study design

This is a parallel, randomized controlled superiority trial. Fig. 1 presents a flow diagram of the study design. All patients had intracervical injection with both dyes (ICG and methylene blue); one dye was injected on the left side of the cervix (3 o'clock) and the other dye was injected on the right side (9 o'clock). The unit of randomization was the side that received each dye. Block randomization with computer generated random block size was used. The allocation sequence was concealed from the surgeons in sequentially numbered opaque and sealed envelopes that were opened at the time of surgery in the operating room. This trial received institutional ethics board approval and was registered with ClinicalTrials.gov, number NCT02564276.

2.2. Participants

Patients were recruited at the Centre Hospitalier de l'Université de Montréal (CHUM). All patients with endometrial carcinoma diagnosed by endometrial biopsy or curettage and with preoperative FIGO (International Federation of Gynecology and Obstetrics) stage I who were intended for staging via laparoscopic or robotic surgery were eligible. Exclusion criteria included the following: age < 18 years, previous pelvic or paraaortic lymphadenectomy/radiotherapy/surgery that could change uterine lymphatic drainage, iodine allergy, and pregnancy. Patients were also excluded when SLN procedure was not completed per protocol due to reasons unrelated to the dye such as inadvertent injection of dye on wrong side of the cervix, intraoperative finding of suspicious lymph nodes or advanced disease, or surgical complications interrupting SLN procedure.

2.3. Intervention

Surgery was performed by one of three surgeons (BC, VS, TW) who all had previously performed at least 200 cases with SLN procedure for endometrial cancer. Included women were intended for bilateral SLN mapping, but completion lymphadenectomy was at the surgeon's discretion based on patient risk factors. A sealed envelope indicating randomization allocation was opened at the beginning of surgery. Tracers used were methylene blue (2 ml of a 10 mg/ml solution manufactured

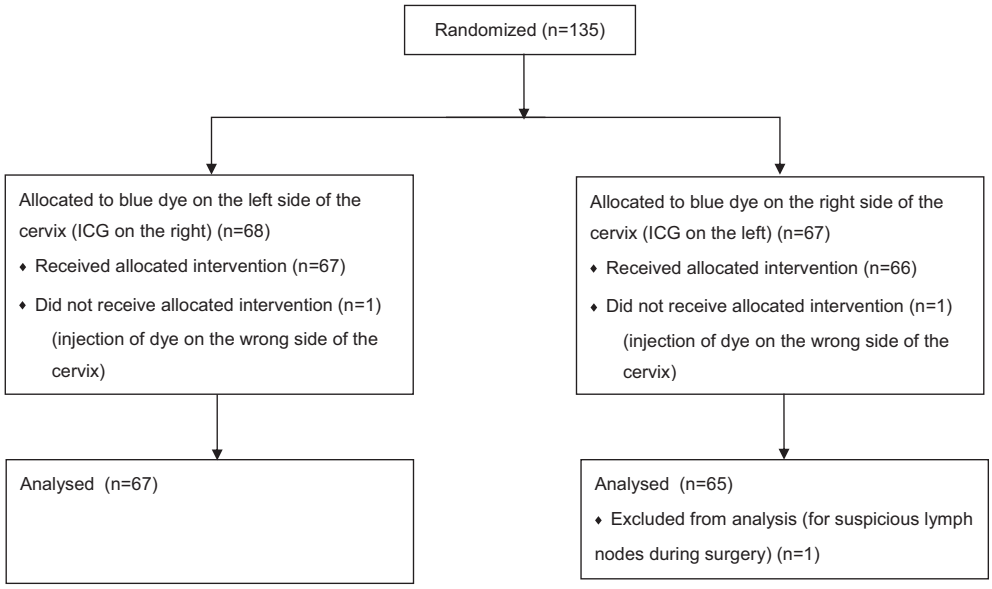

Fig. 1. Flow diagram of study design.

by Omega®, Montreal, Canada) and ICG (2 ml of a 1.25 mg/ml solution manufactured by Akorn®, Lake Forest, Illinois, USA). The ICG 1.25 mg/ml is a commonly used concentration [12,15]; also, in our experience before the trial, this concentration offered less second- and higher echelon mapping.

Because ICG is expensive, 25 mg vials were dissolved in 20 ml of H_2O, aliquoted in 10 syringes (2 ml each) and stored frozen at −20 °C. ICG was thawed at room temperature 30 min before surgery. Each tracer was injected on one side of the cervix (1 ml submucosally and 1 ml 1–2 cm deep) at either the 3 o'clock or the 9 o'clock position based on the side assigned by randomization. This commonly used cervical injection is more convenient than a corporeal injection, while resulting in similar or superior SLN detection rate [3]. The same sequence of injection and mapping was used in all patients: left-side cervical injection preceded the right side, and search for the left hemipelvis (HP) SLN preceded the search on the right. Surgery was done by laparoscopy or robotically at surgeon's discretion. We used the Pinpoint endoscopic fluorescence imaging system for ICG mapping, as the main camera during laparoscopy, and used the imaging system through the assistant port during robotic surgery. After the SLN procedure, a total hysterectomy with bilateral salpingoophorectomy was performed; ovarian conservation was also acceptable in rare select cases, at the surgeon's discretion. Ultrastaging of the SLN was performed, with serial sectioning and immunohistochemistry.

2.4. Outcomes

The primary outcome was the difference in SLN detection rates per HP according to the dye used. Secondary outcomes included the number of SLNs and the proportion of sides with cross-mapping (defined as a blue SLN on the side mapped with ICG, or a NIR fluorescent SLN on the side mapped with blue dye).

2.5. Statistical analysis

To compare the SLN detection rate for each dye in the same patient, we performed a two-tailed McNemar test using normal approximation for paired-matched data. We used the Wald asymptotic formula to calculate the corresponding 95% confidence interval (CI). Descriptive statistics were used to characterize women according to the dye used on left or right side of the pelvis. This included mean, median, standard deviation and interquartile range (IQR) for quantitative variables, and frequency distribution for categorical variables. Sample size calculation was based on the two-tailed normal-approximate McNemar test.

Based on data from the largest study of SLN in endometrial cancer using blue dye [7], we calculated that the correlation between left and right HP detection was approximately 0.35. Since our study compares the detection rate achieved by different dyes, we chose a lower correlation of 0.2. A sample size of 115 women would achieve a power of 80% to detect a 15% difference in the proportion of hemipelves with successful detection, with a significance level of 5%. We expected some cases would be excluded from the planned "per-protocol" analysis due to reasons unrelated to the dye such as inadvertent injection of dye on wrong side; intraoperative finding of suspicious lymph nodes, intraoperative stage >1; or surgical complications interrupting SLN procedure. Therefore, we conservatively adjusted our sample size to 135 patients. All computations were performed using the SAS software version 9.3 (SAS Institute Inc., Cary, NC).

3. Results

Between March 2016 and April 2017, 135 patients were randomized in our study (Fig. 1). Three patients were excluded after randomization (two for injection on the wrong side, one for clinically suspicious lymph nodes). Therefore, 132 patients were available for analysis: 67 patients who were randomized to blue dye on the left (ICG on the right), and 65 patients who were randomized to blue dye on the right (ICG on the left). Patient characteristics are presented in Table 1.

All surgeries were minimally invasive: 46 patients underwent robotic-assisted surgery while 86 had standard laparoscopic surgery (no conversions to laparotomy). Mean body mass index (BMI) was 35 overall and was higher in the patients with robotic surgery (mean BMI 45) compared with laparoscopic surgery (mean BMI 29). Most patients in this study had low grade (98/132, or 74% were grade 1), and early stage disease (82/132, or 62% of patients were stage IA).

Detection of at least one SLN on the side injected with blue dye was achieved in 85 of 132 patients (64.4%) compared with 120 of 132 patients (90.9%) on the side injected with ICG ($p < 0.0001$) (Table 2).

Median time spent on SLN dissection was 10 min for the blue side (range 2–32) and 10 min for the green side (range 3–31); this included the time spent on complete pelvic lymph node dissection if an HP was associated with failure of SLN detection. Median surgical time was 138 min (range 80–243).

The proportion of HP with successful SLN detection was similar whether surgery was performed robotically or laparoscopically: for blue dye, 65.2% with the robot vs. 63.9% with laparoscopy; and for ICG, 89.1% with the robot vs. 91.9% with laparoscopy (Table 2).

Excluding all HP with failure of SLN detection, median SLN count was 1 for blue dye (range 1–3) and 1 for ICG (range 1–4), and the mean number of SLN per HP was 1.2 for both blue dye and ICG.

Lymph node metastases were found in 9/132 patients (7%), and eight of these patients had at least one positive SLN on each affected HP. The only patient with lymph node metastasis that was not diagnosed through SLN had failed mapping (no green or blue nodes detected on either side) but had bilateral positive pelvic lymph nodes on lymphadenectomy. One patient had a pre-sacral SLN with easy to follow lymphatic channels traveling through the mesoureter. In this case, there was no other SLN on the left-HP, but the left pre-sacral SLN was metastatic. Two patients had common iliac SLN with drainage visualized through the mesoureter pathway. Six patients had paraaortic lymph nodes removed: five due to high-risk histology and one because SLN mapped directly to a right paraaortic lymph node. Of note, two of these six patients had metastasis found in paraaortic nodes, but they

Table 1
Descriptive statistics by group of randomization.

	Blue side	
	Left (N = 67)	Right (N = 65)
Age		
Median (min, max)	64.0 (44.0, 83.0)	64.0 (35.0, 90.0)
Mean ± SD	64.1 ± 8.5	63.7 ± 10.7
IQR	57.0–71.0	58.0–69.0
BMI		
Median (min, max)	33.3 (19.2, 56.9)	32.9 (21.4, 55.7)
Mean ± SD	34.8 ± 8.8	34.7 ± 9.8
IQR	29.3–39.3	27.3–42.1
Surgical approach		
Robot (%)	26 (38.8)	20 (30.8)
Laparoscopy (%)	41 (61.2)	45 (69.2)
Final pathology		
Endometrioid		
- Grade 1	50	48
- Grade 2	5	5
- Grade 3	6	5
Serous	3	5
Carcinosarcoma	3	2
Postoperative stage		
IA	41	41
IB	20	17
II	0	2
IIIA	2	1
IIIB	0	0
IIIC	4	4
IV	0	0

SD: standard deviation; IQR: interquartile range; BMI: Body Mass Index.

Table 2
Detection rate (per hemipelvis) and duration of sentinel lymph node procedure according to each dye.

	Blue side	Green side	
Detection rates[a]			
Robot	65.2% (30/46)	89.1% (41/46)	
Laparoscopy	63.9% (55/86)	91.9% (79/86)	
Overall	64.4% (85/132)	90.9% (120/132)	$p < 0.0001$
Duration of SLN procedure (median in minutes (range))	10 (2−32)	10 (3−31)	

SLN = sentinel lymph node.
[a] Detection rate defined as at least one SLN in the determined hemipelvis.

also had positive pelvic lymph nodes. There were no cases of isolated paraaortic lymph node metastasis.

Crossover of the dye to the opposite HP was noted in four patients (3%). In each case, the green dye had crossed over (no cases of blue dye crossover). In one of these patients, the blue SLN was also green; in another, the only SLN detected was a green SLN on the side that had been injected with blue dye; and in the other two patients, no blue SLNs were detected but one green SLN was detected on each side.

4. Discussion

Several retrospective or prospective non-randomized studies have reported the performance of ICG and/or blue dye in SLN mapping. Two randomized controlled trials have compared performance of blue dye and ICG but in those studies patients were injected with both dyes bilaterally, in different sequences, but always with potential bias of the first dye leading to easier mapping with the second dye [14,15]. The design of this current trial is original in that the mapping performance of ICG and blue dye was compared within the same patient by injecting a different dye on either side of her cervix. In this manner, there was no imbalance in patient demographic characteristics and in surgeon characteristics between the two groups. The randomization (which side would receive blue dye vs. ICG) was added to control for any potential confounder of left-side vs. right-side lymph node mapping that could have led to SLN mapping favoring one dye over the other. Also, systematically localizing the SLN first on the side mapped with the surgeon's preferred tracer may have hinted to the SLN localization in the contralateral HP. For this reason, the sequence of injection and mapping was standardized for all cases: left first followed by right, irrespective of which dye was injected on the left.

By controlling for these surgical variables, we could evaluate the mapping rates of two different tracers in conditions that are as close to being perfectly matched as possible.

We chose to perform a per-protocol analysis because the conditions in this study do not represent everyday practice: injection of the wrong dye on a specific side of the cervix would not occur outside of such a study. Moreover, the presence of clinically suspicious lymph nodes, which should lead to the interruption of the SLN procedure in favor of a complete lymph node dissection [16], is not associated with the type of dye used. Bilateral mapping rate is an important result to report in studies of SLN detection in endometrial cancer. In this study, the overall detection rate was 95.5% (126/132) and this reflects the high mapping rate with ICG, while the bilateral detection rate was 59.8% (79/132), which reflects the low mapping rate with blue dye. However because no single dye was injected bilaterally in the same patient, overall and bilateral detection rates are in this case less relevant. Instead, we primarily report results in terms of HP with successful detection, which likewise evaluates the performance of the SLN procedure. We found that a SLN was detected 90.9% of times on the side injected with ICG and detected only 64.4% of times on the side injected with blue dye. This is a statistically significant difference of 26.5% (95% CI 17.4%–35.6%). These results are very similar to the proportions of HP with successful detection that we calculated based on previous reports: around 65% with blue dye [7,8] and around 90% with ICG [11–13].

Out of the nine patients with lymph node metastasis, only one was not identified through a positive SLN. No SLNs were retrieved from this patient because of failed mapping. We considered this case to be a technical failure of the mapping procedure rather than an actual false-negative. When failed mapping to an HP is encountered in cervix or in endometrial cancer, it has been proposed to proceed to ipsilateral lymphadenectomy in order to minimize the possibility of missed metastatic disease [7,17]. In this study, we did not encounter a HP with successful SLN detection in which the only positive lymph node was a non-SLN. When we applied the NCCN algorithm [16], all metastatic patients were correctly diagnosed.

The lymph node metastasis rate in this study is low (7%). Final pathology showed an important proportion of grade 1 endometrioid cancer (74%), which is higher than in many recent SLN studies (grade 1 in 43% of patients [10,14], in 46% of patients [11], in 60% of patients [12]) and could explain our relatively low metastatic rate.

Patients who underwent robotic surgery had higher BMIs, which is consistent with our policy for the use of hospital resources. In the literature, a higher BMI is linked to decreased detection of the SLN [18–20]. Nevertheless, we did not observe any difference in the proportions of HP with successful detection between surgeries that were robotic (mean BMI 44.6) or laparoscopic (mean BMI 29.4).

One of the problems with ICG is sometimes exaggerated uptake/mapping (all of the pelvic lymph nodes appear green, sometimes even continuing up to the common and paraaortic nodes). This can make it difficult to determine the first echelon of lymphatic drainage without removing multiple lymph nodes and negating the advantage of SLN procedure. In this study, with appropriate dilution of ICG dye and experienced surgeons, we did not find that ICG detects more second- and higher echelon lymph nodes that were considered SLN.

The unique design of this study showed that lymphatic crossover can occur, which to the best of our knowledge, had not previously been demonstrated in vivo. We observed crossover of ICG to the contralateral pelvis in four cases; however, this may not be of significance when ICG is injected on both sides of the cervix. As the crossover we observed is uncommon, a proper injection technique on both sides of the cervix is important to achieve high rates of successful bilateral mapping.

5. Conclusion

The use of ICG instead of methylene blue dye results in a 26.5% increase of the proportion of hemipelves with successful SLN detection in women with endometrial cancer undergoing minimally invasive surgery. In addition to previous reports, this study confirms that the use of blue dye results in a successful detection of SLN in 2 out of 3 hemipelves, whereas the use of ICG results in a successful detection of SLN in 9 out of 10 hemipelves in this patient population. If surgical algorithms are applied and women who do not map on one HP undergo ipsilateral lymphadenectomy, then using ICG as a tracer rather than blue dye could lead to a potential important decrease in the number of control pelvic lymphadenectomies and the cost of managing the associated morbidity. Moreover, successful mapping is known to be associated with an increase in the detection of metastatic lymph nodes as compared to lymphadenectomy, so the cost of missing metastatic disease with failed mapping must also be taken into account.

Whether the results reported in the present Green vs Blue trial are sufficiently important to justify the added cost of acquiring and maintaining NIR-fluorescent technology in all specialized centers is a complex question that could be addressed in further cost-effectiveness studies.

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Author contributions

Dr. Rozenholc generated the concept for the study, was involved in writing and revision, and approved the final manuscript.

Dr. Samouelian generated the concept for the study, provided data, was involved in writing and revision, and approved the final manuscript.

Dr. Gauthier provided data, was involved in writing and revision, and approved the final manuscript.

Dr. Warkus provided data, was involved in writing and revision, and approved the final manuscript.

Dr. Sauthier provided data, was involved in writing and revision, and approved the final manuscript.

Dr. Provencher provided data, was involved in writing and revision, and approved the final manuscript.

France Gauthier set up the computerized database.

Dr. Drakopoulos was involved in writing, revision and approved the final manuscript.

Dr. Cormier generated the concept for the study, provided data, was involved in writing and revision, and approved the final manuscript.

Conflict of interest statement

The authors declare that they have no competing interests.

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