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ORIGINAL ARTICLE – GYNECOLOGIC ONCOLOGY

A Comparison of Radiocolloid and Indocyanine Green Fluorescence Imaging, Sentinel Lymph Node Mapping in Patients with Cervical Cancer Undergoing Laparoscopic Surgery

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ABSTRACT

Background and Purpose. ^{99}TC combined with blue-dye mapping is considered the best sentinel lymph node (SLN) mapping technique in cervical cancer. Indocyanine green (ICG) with near infrared fluorescence imaging has been introduced as a new methodology for SLN mapping. The aim of this study was to compare these two techniques in the laparoscopic treatment of cervical cancer.

Methods. Medical records of patients undergoing laparoscopic SLN mapping for cervical cancer with either ^{99}Tc and patent blue dye (Group 1) or ICG (Group 2) from April 2008 until August 2012 were reviewed. Sensitivity, specificity, and overall and bilateral detection rates were calculated and compared.

Results. Fifty-eight patients were included in the study—36 patients in Group 1 and 22 patients in Group 2. Median tumor diameter was 25 and 29 mm, and mean SLN count was 2.1 and 3.7, for Groups 1 and 2, respectively. Mean non-SLN (NSLN) count was 39 for both groups. SLNs were ninefold more likely to be affected by metastatic disease compared with NSLNs ($p < 0.005$). Sensitivity and specificity were both 100 %. Overall detection rates were 83 and 95.5 % ($p =$ nonsignificant), and bilateral detection rates were 61 and 95.5 % ($p < 0.005$), for Groups 1 and 2, respectively. In 75 % of cases, SLNs were located along the external or internal iliac nodal basins.

Conclusions. ICG SLN mapping in cervical cancer provides high overall and bilateral detection rates that compare favorably with the current standard of care.

Early-stage cervical cancer is treated surgically with radical hysterectomy. In selected cases, a fertility-sparing approach with a trachelectomy or a wide cervical conization is indicated. In both instances, since the most important prognostic factor is lymph nodal metastases, a bilateral pelvic lymphadenectomy is mandatory. However, in the majority of cases, pelvic lymph nodes will be negative. In these patients, the routine performance of bilateral pelvic lymphadenectomy adds operative time, costs, and intraoperative and long-term postoperative complications, such as bleeding, ureteral and nerve injury, lower extremity lymphedema, lymphocysts, and sensory loss.

By identifying the first lymph node draining the tumor, lymphatic mapping with sentinel lymph node (SLN) biopsy allows to reduce surgical morbidity and to improve detection of metastatic disease. SLN biopsy has become standard of care management in various malignancies and there is increasing evidence suggesting that SLN biopsy may also safely be integrated in the management of early-stage cervical cancer.[1–7]

To date, blue dyes and ^{99}Tc have been used for SLN biopsy in cervical cancer, with an overall sensitivity and SLN detection rate of over 90 %;[8] however, these detection rates refer to the finding of any SLN, whereas bilateral SLN detection rates are significantly lower.[9] Given the importance of identifying lymph nodal metastases in cervical cancer, it is advisable to adopt a strategy in which all SLNs are excised along with every suspected lymph node, and a systematic contralateral lymphadenectomy is performed in case of unilateral SLN mapping.[10] Hence, a significant number of patients will still undergo some form of lymphadenectomy.

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Furthermore, the most diffused tracers used thus far for lymphatic mapping carry some side effects. Blue dyes cause discoloration of skin and urine, a decrease in pulse oximetry readings and, occasionally, severe allergic reactions.[11–13] Mapping with ^{99}TC is logistically complicated because of the coordination required between injection in a controlled environment, imaging acquisition and surgery, making this technique more time-consuming and expensive.

Indocyanine green (ICG), a fluorescent marker with an excellent toxicity profile, has recorded promising results in SLN mapping in several malignancies.[14–22]

No studies on laparoscopic ICG SLN detection in cervical cancer have yet been published. Furthermore, no comparisons between SLN mapping with ^{99}Tc and/or blue dye and ICG have been performed in this setting.

The aim of this study was to determine sensitivity, specificity, and overall and bilateral detection rates of SLN mapping with ICG and near infrared (NIR) fluorescence laparoscopic technology in cervical cancer, and to compare this with SLN mapping performed with ^{99}TC and blue dye.

MATERIALS AND METHODS

An analysis of all patients with cervical cancer undergoing SLN mapping at our institution between April 2008 and August 2012 was performed. Demographic, clinical, and pathologic data were retrieved from an electronic database. Missing data were integrated using surgical reports and clinical charts. Since January 2011, the data for all patients receiving ICG SLN mapping were prospectively collected. The study was approved by the Institutional Review Board, and all patients signed informed consent.

Patients with histologically confirmed cervical carcinoma and International Federation of Gynecology and Obstetrics (FIGO) stage IA1 with positive lymph vascular space invasion–IIB underwent SLN mapping followed by laparoscopic lymph node biopsy and frozen section analysis. In case of negative response for metastatic disease in patients with early-stage cervical cancer, the planned surgical procedure was completed. If metastatic disease to the SLN was identified at frozen section, the radical procedure was aborted in favor of concurrent chemoradiotherapy. Non-SLNs (NSLNs) that appeared macroscopically suspicious were removed and sent for frozen section. At final histopathological analysis, a complete ultrastaging was performed in all cases (three slides HE 200 μm, immunohistochemistry (IHC) when there was uncertainty).

Pretreatment evaluation included medical history collection, physical examination, positron emission tomography/computed tomography (CT) scan, and examination under anesthesia. If clinical stage was unclear, a magnetic resonance imaging of the pelvis was performed to rule out parametrial invasion.

Throughout the study period, two different techniques for SLN mapping were used. From April 2008 until January 2011, SLN mapping was performed with a preoperative ^{99}Tc injection and lymphoscintigram with fusion computer tomogram (SPECT) in combination with or without intraoperative patent blue-dye injection (Group 1). From January 2011 until August 2012, SLN mapping was performed with intraoperative ICG injection in combination with or without ^{99}Tc injection (Group 2). No other significant changes in patients' management occurred throughout the study period. Three board-certified gynecologic oncologists were responsible for all the procedures. In Group 1, 120 MBq of ^{99}Tc was injected into the four quadrants of the cervix on the day before surgery. A SPECT was performed to preoperatively locate the SLN. In the operating room (OR) on the day of surgery, the patient was intracervically injected with 5 ml of patent blue dye in the four cervical quadrants. Under gamma probe (Navigator; Autosuture, Norwalk, CT, USA) guidance and patent blue-dye visual guidance, the SLN was laparoscopically located approximately 20 min after injection, and removed.

In Group 2, the patient was intracervically injected with 8–10 ml of ICG (Pulsion®) in the OR, immediately before laparoscopy. One vial of ICG (Pulsion®) had been previously suspended with 20 ml of sterile water. Under visual guidance of the fluorescent light using a laparoscopic NIR fluorescent optic device (Storz®), the SLN was located and removed (Fig. 1a, b). For these patients, data on the location of the SLN were prospectively recorded.

For both groups, after an inspection of the abdomen and pelvis was performed, the peritoneum on the pelvic side wall was opened, the retroperitoneal space developed, and the SLNs located in centripetal order; the lymphoadipose tissue in the parametrium, fossa obturatoria, along the external, internal, and common iliac vessels, was inspected. All identified SLNs were removed. Additionally, presacral and paraaortic regions were also inspected.

Demographic and clinicopathologic characteristics were evaluated using the basic descriptive statistics. Sensitivity, specificity, and overall and bilateral detection rates of SLNs in the two groups (^{99}Tc ± patent blue dye vs. ICG) were calculated and compared using Fisher's exact test.

The false positivity rate was defined as zero. The overall detection rate was calculated by the number of procedures in which at least one SLN was identified, divided by the total number of procedures performed, and the bilateral detection rate was calculated by the number of procedures in which at least one SLN was identified on each side of the pelvis, divided by the total number of procedures performed. A true positive SLN was defined as a positive SLN

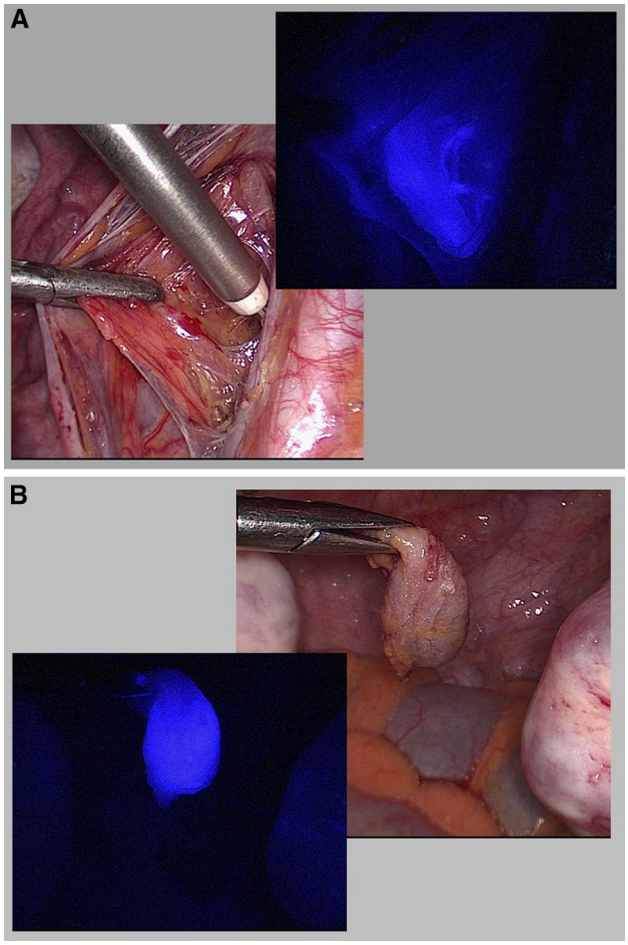

FIG. 1 **a** Right pelvic ICG-positive SLN as seen with laparoscopic NIR technology. **b** ICG-positive SLN as seen with laparoscopic NIR technology. *ICG* indocyanine green, *NIR* near infrared, *SLN* sentinel lymph node

identified with histopathological techniques (hematoxylin and eosin staining, serial sectioning, IHC), independent of regional lymph node status. A false negative SLN was defined as a negative SLN in combination with metastatic NSLN. Statistical analyses were performed using the R software (version 3.1.0). All p values were two sided, and p values <0.05 were considered statistically significant.

RESULTS

During the study period, 58 patients with cervical cancer underwent SLN mapping, which was performed with ^{99}TC in 36 patients (Group 1). In 86 % of cases, SLN mapping was performed with ^{99}TC and patent blue dye combined, with ICG in 22 patients (Group 2), and with ICG and ^{99}TC combined in 32 % of cases. The combined SLN mapping technique with ICG and ^{99}TC was performed in the first seven patients after having transitioned to the ICG technique. In these cases, the SLN was initially identified with ICG and NIR technology. After its retrieval, the correct identification of the SLN was controlled with the gamma probe.

The two groups did not differ with regard to mean age, FIGO stage, tumor diameter, and histology. The mean number of removed SLNs was 2.1 for Group 1 and 3.7 for Group 2, and the mean number of lymph nodes removed with the systematic pelvic lymphadenectomy was 39 for both groups. Patient characteristics are presented in Table 1.

Overall SLN detection rates were 83 and 95.5 %, and bilateral SLN detection rates were 61 and 95.5 %, for Groups 1 and Group 2, respectively. Detection rates are presented in Fig. 2. In 22 % of cases, SLN detection was unilateral in Group 1; however, in one of these cases, secondary to the diagnosis of lymph node metastases at frozen section, the procedure was aborted and the other side of the pelvis was not assessed. The overall SLN detection rate did not differ between the two groups. A significantly higher bilateral detection rate was observed in Group 2 ($p = 0.0201$).

Tumor diameter was $\leq$2 cm in 13 and 6 patients, and $>$2 cm in 23 and 16 patients, in Groups 1 and 2, respectively. When comparing bilateral detection rates based on tumor diameter $\leq$2 versus $>$2 cm, the difference among the two groups lost statistical significance. A trend toward a higher bilateral detection rate in patients with tumor diameter $>$2 cm was recorded in Group 2 ($p = 0.091$).

SLNs were located between the internal and external iliac vessels, along the internal iliac vessels, the external iliac vessels, the common iliac vessels, and in the presacral area in 53, 10, 11, 19, and 6 % of cases, respectively (Fig. 3).

Nine and five patients had positive pelvic lymph nodes in Groups 1 and 2, respectively. There were no false negative SLNs, accounting for a sensitivity and specificity of 100 % and a negative predictive value of 100 %. In other words, if an SLN was identified and was negative for metastases at final pathological analysis, all other lymph nodes were also negative. Only one SLN was positive at IHC analysis only. SLNs were, statistically, more frequently affected by metastatic disease compared with NSLNs. Overall, 11/130 (8.5 %) SLNs were positive compared with 16/1709 (0.9 %) NSLNs ($p = 0.00001$).

DISCUSSION

In our study, we found that lymph nodal metastases were ninefold more likely to be identified in SLNs than in NSLNs, confirming data from the literature that the SLN is the most representative lymph node to assess for

TABLE 1 Patient characteristics

	Group 1 ($N = 36$)	Group 2 ($N = 22$)	p value
Age at diagnosis, years (mean)	47	43.4	NS
FIGO stage [n (%)]			NS
I	27 (75)	19 (86.4)	
II	9 (25)	3 (13.6)	
IA1	1 (2.8)	1 (4.5)	
IA2	2 (5.6)	1 (4.5)	
IB1	20 (55.5)	12 (54.6)	
IB2	4 (11.1)	5 (22.8)	
IIA1	4 (11.1)	1 (4.5)	
IIA2	3 (8.3)	2 (9.1)	
IIB	2 (5.6)	0 (0)	
Median tumor diameter (mm)	25	29	NS
Histology [n (%)]			NS
Squamous cell cancer	27 (75)	15 (68.2)	
Adenocarcinoma	7 (19.4)	4 (18.2)	
Other	2 (5.6)	3 (13.6)	
Mean number SLNs	2.1	3.7	NS
Mean number NSLNs	39	39	NS

Group 1: patients undergoing SLN mapping with ^{99}TC combined with patent blue dye

Group 2: patients undergoing SLN mapping with ICG and NIR technology

FIGO International Federation of Gynecology and Obstetrics, *ICG* indocyanine green, *NIR* near infrared, *NSLN* nonsentinel lymph node, *NS* nonsignificant, *SLN* sentinel lymph node

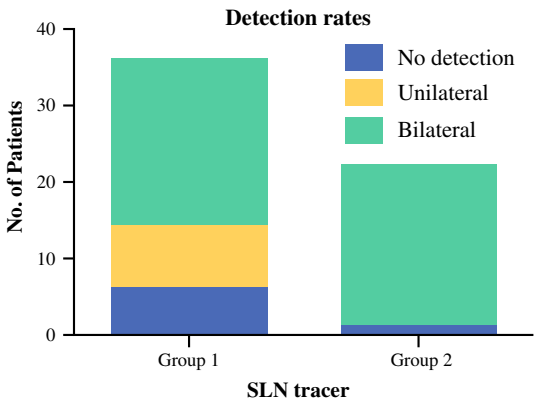

FIG. 2 Overall SLN detection rates were 83 and 95.5 % for Groups 1 and 2, respectively (p = NS). Bilateral SLN detection rates were 61 and 95.5 % for Groups 1 and 2, respectively ($p = 0.0201$). *SLN* sentinel lymph node

extrauterine spread.[24] We were able to identify at least one SLN in 83 and 95.5 % of patients in whom the mapping was performed with ^{99}TC combined with patent blue dye and ICG, respectively. In the literature, reported detection

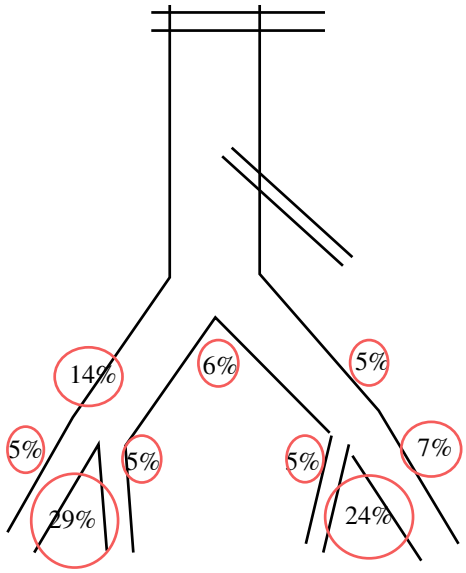

FIG. 3 SLNs were located in the interiliac region in 53 % of cases, along the external iliac vessels in 12 % of cases, along the internal iliac vessels in 10 % of cases, along the common iliac vessels in 19 % of cases, and in the presacral area in 5 % of cases

rates vary widely between 70 and 100 %.[23] In the largest multi-institutional, prospective study on SLN in early-stage cervical cancer, the SENTICOL study, a 97.8 % detection rate was reported in patients mapped with ^{99}TC combined with blue dye.[25] Our reported SLN detection rate in Group 1 is somewhat smaller than that reported in the SENTICOL study. This may be related to the inclusion of patients with more advanced stages and larger tumor diameter. The SENTICOL study included only patients with up to stage IB1 cervical cancer and in whom the reported mean tumor diameter was very small (13 mm).[25] There is some evidence that detection rates are higher when SLN mapping is performed in smaller tumors, and decreases in larger tumors.[6,8,26] A higher possibility of lymph vascular invasion, lymph nodal involvement, and complete node replacement with tumor cells may hamper lymphatic flow, thus reducing detection rates and increasing false negative rates in larger tumors. On the contrary, sensitivity was not impaired in larger tumors or in higher stages in a study including patients with cervical cancer stages IA1–IIB with bilateral SLN detection.[27] Interestingly, in our study, Groups 1 and 2 did not differ with regard to tumor stage and tumor diameter, suggesting that the recorded difference in performance might be related to the different SLN mapping technique. When statistical analysis was performed after stratifying for tumor diameter, the difference in bilateral detection rate lost its significance. We speculate that this may be related to the size of the sample. In fact, a trend towards higher bilateral detection rates in Group 2 was maintained for patients with a tumor diameter >2 cm.

If future studies confirm our data, the use of SLN mapping might be extended to all cervical cancer patients who are candidates for radical surgery, regardless of tumor diameter.

Reported detection rates refer to the finding of any SLN in a patient. When only bilateral SLN identifications are considered, detection rates drop to 60–75 %.[9] However, with the uterine cervix being a midline structure, its lymphatic flow involves the bilateral pelvic lymph nodes. In our study, we recorded a statistically significant improvement in bilateral detection rates in the group of patients in whom SLN mapping was performed with ICG. This finding is clinically relevant since it may ultimately lead to a reduction in lymphadenectomies. Similar results have been reported by Jewell et al. who recorded an improvement in bilateral SLN detection rate in a large series of uterine and cervical cancer patients undergoing robotic surgery and SLN mapping with ICG.[18] In their cohort of 227 patients, SLNs mapped bilaterally in 79 % of cases, suggesting that ICG and NIR technology may be more effective than older techniques in obtaining a complete mapping. Recently, Andikyan et al. reported on ten patients with small, early-stage cervical cancer who were treated with a conization and SLN biopsy only.[28] In this small series, after a median follow-up of 17 months, no recurrences were recorded. Although these women represent a group of patients with an excellent prognosis and a small risk of lymph node metastases, this study represents the first step towards a wider application of the 'real' concept of SLN biopsy in cervical cancer. If SLN mapping substitutes systematic pelvic lymphadenectomy, a higher bilateral detection rate will lead to a reduced number of patients needing unilateral pelvic lymphadenectomy.

In line with the data reported in the literature, in our study the SLNs were preferentially localized along the external or internal iliac nodal basins.[23] SLNs are typically located dorsal of the external iliac vessels, ventral of the obturator nerve, and medial of the superior vesical artery. In a smaller percentage of cases (yet still relevant), SLNs are located in other areas such as along the common iliac basins or in the presacral region. Another important advantage of SLN mapping is the identification of these lymph nodes that might otherwise remain nonsampled.

This is the first study comparing ICG SLN mapping with more traditional mapping techniques. Probably the most important strength of the study is the comparison between a new SLN mapping technique with what is currently considered the gold standard. To date, the combined mapping with ^{99}Tc and patent blue dye has been proven to be the most solid mapping technique in cervical cancer. Furthermore, the routine use of SPECT has been shown to further increase detection rates.[29] However, in our study the ICG mapping technique proved to be better.

CONCLUSIONS

ICG SLN mapping with NIR technology is a simple technique that seems to yield higher bilateral detection rates compared with mapping with ^{99}Tc and patent blue dye in the laparoscopic treatment of cervical cancer. When indicated, SLN mapping in cervical cancer should be performed with ICG.

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