

Sentinel Nodes Detection with Near-infrared Imaging in Gynecological Cancer Patients: Ushering in an Era of Precision Medicine

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ABSTRACT: **Background:** The sentinel lymph node (SLN) biopsy procedure is a well-known method for identifying solid tumors such as breast cancer, vulvar cancer, and melanoma. In endometrial and cervical cancer, SLN has recently gained acceptance.

Objectives: To evaluate the detection rate of SLN with an indocyanine green and near-infrared fluorescent imaging (ICG/NIR) integrated laparoscopic system in clinically uterine-confined endometrial or cervical cancer.

Methods: Patients with clinically early-stage endometrial or cervical cancer were included in this retrospective study. ICG was injected into the uterine cervix and an ICG/NIR integrated laparoscopic system was used during the surgeries. The National Comprehensive Cancer Network (NCCN) protocol was followed. SLN and/or suspicious lymph nodes were resected. Side-specific lymphadenectomy was performed when mapping was unsuccessful. Systematic lymphadenectomy was completed in patients with high-grade histology or deep myometrial invasion. Enhanced pathology using ultra-staging and immunohistochemistry were performed in all cases.

Results: We analyzed 46 eligible patients: 39 endometrial and 7 cervical cancers. Of these, 44 had at least one SLN (93.6%). In 41 patients (89%) we detected bilateral SLN, in 3 (7%) only unilateral, and in 2 (4%) none were detected. Seven patients presented with lymph node metastasis. All were detected by NCCN/SLN protocol. Of these cases, two were detected with only pathological ultra-staging.

Conclusions: SLN mapping in endometrial and cervical cancer can easily be performed with a high detection rate by integrating ICG/NIR into a conventional laparoscopic system. Precision medicine in patients evaluated by SLN biopsy changes the way patients with endometrial or cervical cancer are managed.

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The sentinel lymph node (SLN) is the first node that receives lymphatic drainage. According to the SLN hypothesis, cancer cells migrate from a primary tumor to a few lymph nodes, which are designated as SLN. The SLN identification procedure is a well-known method for determining solid tumors such as breast cancer, vulvar cancer, and melanoma. In endometrial cancer and cervical cancer, the SLN procedure has recently gained acceptance.

In the management of endometrial cancer, the status of both pelvic and para-aortic lymph nodes should be assessed intra-operatively in all patients, as advised by the International Federation of Gynecology and Obstetrics (FIGO) surgical and pathological staging system [1,2]. However, there is controversy about the role of complete lymph node dissection (LND) in the management of endometrial cancer [3-5]. Frost and colleagues [6] reported no survival advantage of lymphadenectomy in patients with presumed stage I endometrial cancer. National Comprehensive Cancer Network (NCCN) guidelines state that SLN mapping should be considered as an acceptable surgical strategy between complete LND and no nodal evaluation. This approach could prevent side effects associated with complete LND and could provide accurate nodal status [7]. In one of the largest prospective study, which included 340 women with stage I endometrial cancer, successful mapping of at least one SLN and sensitivity of SLN detecting nodal disease were reported to be 86% and 97.2% effective, respectively [8]. Although defined as a relatively new surgical approach, survival studies in patients who underwent SLN procedure have already been published. Recent studies showed no survival difference between SLN strategy and complete LND [9-11].

Lymph node status evaluation has important value in the management of patients with cervical cancer. The presence of lymph node involvement is associated with a worse prognosis [12]. In a review of 1811 women with cervical cancer who underwent sentinel lymph node mapping, the identification rate of SLN and sensitivity for metastatic disease were reported to be 95.4% and 100%, respectively, in tumors less than 2 cm [13].

NCCN guidelines recommend consideration of SLN mapping in early-stage cervical cancer and report the best detection and mapping results in tumors less than 2 cm [14].

Several techniques have been determined for detection of SLN, including blue dye, radioactive technetium-99, and indocyanine green (ICG). In a review of patients with early-stage breast cancer, a dual technique (blue dye with radioactive technetium-99) had fewer false-negative rates than single techniques [15]. However, the detection of radioactive technetium-99 in laparoscopy has logistical challenges such as staff training and the high cost of a gamma probe appropriate for minimally invasive surgery. In a study of 100 patients with endometrial cancer, How and co-authors [16] evaluated the ICG technique and reported higher detection rates than with blue dye, and similar detection rates compared to technetium-99.

We designed the current retrospective study to evaluate the detection rate of SLN with an ICG and near-infrared fluorescent imaging (ICG/NIR) integrated laparoscopic system in clinically uterine-confined endometrial and cervical cancers.

PATIENTS AND METHODS

This retrospective study was conducted between August 2016 and November 2017. We performed an SLN biopsy on all patients. In addition, LND was performed on endometrial cancer cases with high-risk factors for nodal metastasis (deep myometrial invasion, high-grade histology, tumor size larger than 2 cm). After November 2017, we performed only SLN biopsies. Between August 2016 and January 2018, a total of 46 consecutive patients with early-stage endometrial or cervical cancer were enrolled in the study (39 endometrial cancers, 7 cervical cancers). All patients underwent SLN mapping. In endometrial cancer patients with high-grade histology or intra-operatively observed deep myometrial invasion sentinel lymph node biopsy (SLNB), SLN was followed by LND. All procedures were performed laparoscopically.

SLN PROCEDURE AND LYMPH NODE MAPPING

Four milliliters of diluted dry ICG powder (25 mg ICG in 20 ml sterile water) was prepared. Four doses (superficial and deep) of 1 ml were injected into the uterine cervix, as described by Abu-Rustum [7]. For the identification of SLN, an ICG/NIR integrated laparoscopic system (Spies Full HD D-Light P ICG Technology, Karl Storz, Germany) was used during the surgeries. In all cases, SLN mapping was performed before hysterectomy. The SLN was documented with the visualization of blue colored lymph nodes/lymphatic traces [Figure 1]. The locations of SLNs were recorded intra-operatively. The lymph node mapping and dissections were performed according to NCCN guidelines [7,14]. All suspicious lymph nodes were removed regardless of mapping, and if there was no mapping on a hemipelvis, a site-specific lymph node dissection was performed.

The histologic evaluation of SLNs was performed according to the pathology department protocol. All nodes were bivalved and stained with hematoxylin and eosin (H&E) as part of metastasis detection. Nodes with no metastasis according to initial H&E stain underwent ultrastaging, cutting 5 µm sections. Sections at each level were then stained with H&E and with immunohistochemistry using anti-cytokeratin AE1: AE3.

Metastatic nodes that were identified with ultrastaging were defined as macrometastasis (focal tumor larger than 2 mm), micrometastasis (focal tumor 0.2-2 mm), or isolated cell (focal tumor less than 0.2 mm).

RESULTS

The clinicopathological data is presented in Table 1. The detection of at least one SLN was achieved in 44 patients (96%). All nodes were detected in iliac, obturator, or para-aortic areas. We identified seven patients with metastatic disease (6 endometrial, 1 cervical). Twenty-seven patients underwent LND. In all patients with nodal metastasis, SLN was also involved. Of seven cases with nodal metastasis, five macrometastases and two micrometastases were observed.

Figure 1. Sentinel node identified with fluorescent imaging



Table 1. Clinicopathological characteristics

Age, years	61 ± 14.7
Weight, kg	83 ± 13
Endometrial cancer histology, preoperative	
Endometrioid grade 1	11 (28%)
Endometrioid grade 2,3	14 (36%)
Papillary serous carcinoma	11 (28%)
Other	3 (8%)
Cervical cancer histology	
Squamous cell carcinoma	5 (71%)
Adenocarcinoma	2 (29%)
Sentinel lymph node detection	
Bilateral detection	41 (89%)
Unilateral detection	3 (7%)
No detection	2 (4%)

In five cases of patients with metastatic endometrial cancer, preoperative histology was endometrioid carcinoma grade 2 (n=3) and serous papillary carcinoma (n=2). In one case with the preoperative and postoperative diagnosis of endometrioid carcinoma grade 1 and superficial myometrial invasion, we found micrometastasis. The patient was identified as stage IIIC1G1 and referred for adjuvant therapy.

In one case with stage Ia2 cervical cancer, frozen section of SLN detected a micrometastasis, subsequently confirmed in permanent sections and by immunohistochemistry [Figure 2]. The surgery was aborted.

DISCUSSION

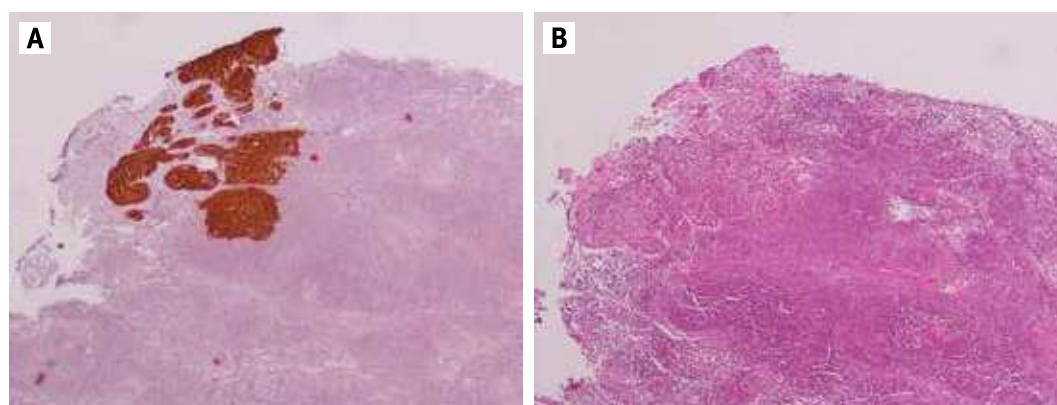
In the current study, ICG/NIR techniques had a detection rate of 96% for at least one SLN, which compares favorably with previously reported results [8,16]. The prognosis of endometrial cancer primarily depends on stage and tumor grade. Lymph node metastases have an important prognostic value in patients with endometrial cancer. Therefore, accurate nodal evaluation remains as the standard staging procedure for these patients [17]. The SLN procedure provides an accurate venue for detect-

ing metastatic tumors. In a recent large study, How et al. [18] found SLNs in unusual locations including para-aortic lymph nodes above the inferior mesenteric artery, the internal iliac vein, parametrium, and presacral lymph nodes. In How's study, the rate of SLNs in unusual areas was 13.1%. Metastatic lymph nodes could be missed in these areas because these locations are not routinely explored in standard lymph node dissection in endometrial cancer. However, in the current series, we did not locate SLN in unusual locations.

The decision whether to perform lymph node dissection (LND) in endometrial cancer can be based on preoperative and intra-operative findings. The widely used criteria for the low-risk nodal disease include: no or superficial myometrial invasion, tumor less than 2 cm, and preoperatively well-differentiated histology [19,20]. In low-risk patients, lymph node dissection is omitted. Nevertheless, these criteria do not fully exclude nodal disease. In our series, we had one case with grade 1 endometrial cancer and superficial myometrial invasion that was also confirmed by postoperative histology. In this case, we detected a micro-metastatic node by SLN mapping. The patient was staged as IIIC1G1 and referred to adjuvant therapy. As she had no risk for nodal disease, under standard practice lymph node sampling would have been omitted. Without SLN mapping this case could be missed and incompletely treated. Similarly, in the study by How and colleagues [21], which included 100 women with endometrial cancer who underwent SLN mapping, they found metastatic SLNs in four cases with preoperatively diagnosed grade 1 endometrioid endometrial cancer [21].

In early cervical cancer, patients routinely undergo radical hysterectomy, which entails parametrial resection that is often associated with significant postoperative morbidity. In an Israeli multicenter study, Gerner et al. [22] found that conducting a clinicopathologic evaluation, including tumor size and lymphovascular invasion (LVSI), and lymph node evaluation, was important before deciding to perform parametrectomy in early-stage cervical cancer. In that study, in patients with a tumor ≤ 2 cm, no LVSI, and no nodal metastasis, the parametrial involve-

Figure 2. Preserved lymph node architecture with barely perceptible metastasis with keratin stain [A] and hematoxylin and eosin stain [B]



ment rate was 0%. Application of these criteria using the SLN procedure allows tailoring of the surgical procedure; thereby, eliminating the need for parametrectomy in patients with early cervical cancer. SLN biopsy/frozen section could be a useful surgical approach. In the current series, we evaluated a patient with stage Ia2 cervical cancer with no LVSI. Standard treatment in such a case includes modified radical hysterectomy and pelvic lymphadenectomy. At the beginning the surgery, the SLN procedure detected a micrometastasis, subsequently confirmed in permanent sections and by immunohistochemistry. In this patient, we aborted the surgery to avoid both radical hysterectomy and adjuvant radiation, and she was referred for chemoradiation therapy. Conversely, if the node would have been negative, we would have performed a simple hysterectomy, which would have sufficed. In the management of cervical cancer, it is essential to avoid treating patients with both radical hysterectomy and adjuvant chemoradiation. This case exemplifies the benefits of precision medicine, in which treatment, surgery in this case, is tailored to the patient.

CONCLUSIONS

Sentinel lymph node mapping in endometrial and cervical cancers can easily be performed with high detection rates by using an ICG/NIR integrated conventional laparoscopic system. SLN procedures reduce the complications associated with LND. At the same time, the yield and accuracy are increased as the selected nodes undergo pathological ultra-staging allow detection of metastatic disease that otherwise would have gone undetected. This tailored treatment allows individualization of surgical and postoperative treatment, or precision medicine.

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“Men often hate each other because they fear each other; they fear each other because they don't know each other; they don't know each other because they can not communicate; they can not communicate because they are separated”

Martin Luther King, Jr. (1929–1968) African-American civil rights leader best known for advancing civil rights through nonviolence and civil disobedience