# Validation of Sentinel Lymph Node Biopsy in Robotic Endometrial Cancer Staging Surgery: Results From a High-Volume Center in India

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## ABSTRACT

**PURPOSE** Lymph node involvement is one of the most important factors influencing recurrence and survival in patients with endometrial cancer (EC). However, the therapeutic role of lymphadenectomy in early-stage disease has been called into question. Sentinel lymph node (SLN) mapping may be an acceptable alternative to omitting lymphadenectomy or performing a complete lymphadenectomy in patients with EC. To validate SLN biopsy (SLNB) using indocyanine green (ICG) dye and near-infrared imaging in the background of comprehensive lymphadenectomy in patients with EC undergoing robotic staging surgery at Tata Medical Center.

**METHODS** This was a single-center, prospective observational study involving patients with EC undergoing robotic staging. Patients received a standardized cervical injection of ICG at the 3- and 9-o'clock positions, with the dye reinjected if mapping failed. Depending on preoperative histology and radiological staging, patients had SLNB or comprehensive systematic lymphadenectomy in addition to SLNB.

**RESULTS** The study included 105 female patients, of whom 71 underwent SLN and full lymphadenectomy and 34 underwent only SLN. There was bilateral mapping in 92 (87.61%) patients, with no mapping in one patient. In 18 patients, ICG dye was reinjected. With the exception of one, the rest had successful mapping after reinjection. The sensitivity of the SLN-ICG algorithm was 92.3%, and the negative predictive value was 98.3%. Ultrastaging necessitated upstaging in 8.57% of patients.

**CONCLUSION** With a very high negative predictive value, SLN mapping with ICG dye has a high degree of diagnostic accuracy in detecting lymph node metastases in EC.



ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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## INTRODUCTION

Endometrial cancer (EC) is the most commonly diagnosed gynecological cancer in Western countries, but the incidence appears to be low in the Indian population, and the majority of women (75%-80%) have disease confined to the uterus.[1] Minimally invasive hysterectomy with or without bilateral salpingo-oophorectomy and staging lymphadenectomy is the standard treatment. One of the most contentious issues in gynecological oncology is the extent of lymph node dissection in EC. Two randomized trials (MANGO-ILIADE 2 and MRC-ASTEC) questioned the therapeutic benefit of systematic lymphadenectomy, but intraoperative and postoperative morbidity was greater in lymph node dissection patients.[2,3] As a result, many women undergo needless complete staging procedures. Because of inadequate paraaortic lymph node dissection and inappropriate criteria for postoperative adjuvant therapy, both trials have been strongly criticized. Lymph node status is still significant for high-grade histologies of EC because of the higher likelihood of nodal involvement and subsequent recurrence.[4] Since the surgical morbidity of comprehensive lymphadenectomy is high, sentinel lymph node (SLN) mapping was developed as an alternative.[5] Prospective studies, such as SENTI-ENDO[6] and FIRES,[7] confirmed the feasibility of SLN mapping, which had been previously demonstrated by numerous retrospective research. However, there is only one study showing evidence for robotic-aided surgical staging with SLN mapping from the Indian population, and all these studies are either conducted in countries other than India or involve surgery that has been performed not solely with robots.[8] Here, we present the results of a single-center, prospective research using SLN mapping with indocyanine green (ICG) dye in women with EC undergoing only robotic-assisted staging surgery.

## METHODS

This was a prospective, observational study conducted at a single center, where data were collected prospectively and

## CONTEXT

**Key Objective**
Whether sentinel lymph node (SLN) evaluation and biopsy during robotics surgery is equivalent to complete lymphadenectomy in endometrial cancer (EC) irrespective of risk types?

**Knowledge Generated**
SLN mapping is a reliable technique for accurately assessing lymph node involvement and staging in EC.
Our SLN-indocyanine green algorithm has demonstrated high sensitivity (92.3%) and negative predictive value (98.3%) consistent with other prospective studies.

**Relevance**
SLN biopsy can serve as an effective alternative to complete lymphadenectomy in EC, regardless of the risk type.

entered into the Redcap database, sourced from the Department of Gynecological Oncology at Tata Medical Center in Kolkata, West Bengal, India. All consecutive patients with EC undergoing robotic-assisted staging surgery and a SLN mapping procedure were included in this study irrespective of any risk factors. Our standard operating procedure necessitated that all patients have a computed tomography scan of the chest and upper abdomen and a magnetic resonance imaging scan of the pelvis before surgery. All participating female patients gave their written informed consent. Our hospital's institutional review board gave its approval to this study with the approval number NBE/2548/PRO (Data Supplement).

According to previous records, as per our hospital electronic database, approximately 40 patients with EC undergo staging surgery per annum by robotics. Sample size (N = 106 patients) was estimated by assuming a 20% prevalence of node metastasis, a 90% SLN detection rate, a sensitivity per patient of 87.5%, and 95% CI of 63 to 97 for sensitivity and 90 to 99 for negative predictive value.

### Inclusion Criteria

1. Patients with pathologically confirmed EC
2. Surgical procedure—robotic-assisted surgery with SLN mapping

### Exclusion Criteria

1. History of hysterectomy or radiotherapy or chemotherapy
2. History of retroperitoneal lymphadenectomy
3. Contraindication to ICG

### SLN Mapping and Surgery

Two 2-mL syringes were filled with the diluted ICG dye (0.5 mg/mL). The cervix was exposed using two Sims speculum while the patient was in the lithotomy position after sterile draping and bladder catheterization. These dye injections were made at the 3- and 9-o'clock positions when the cervix was in a tensed state. Approximately 1 mL was injected into the cervical stroma on both sides, superficially (about 1-2 mm depth) and deeply (about 2 cm depth). Thereby, a total of 4 mL (2 mg) was injected in each patient.[9]

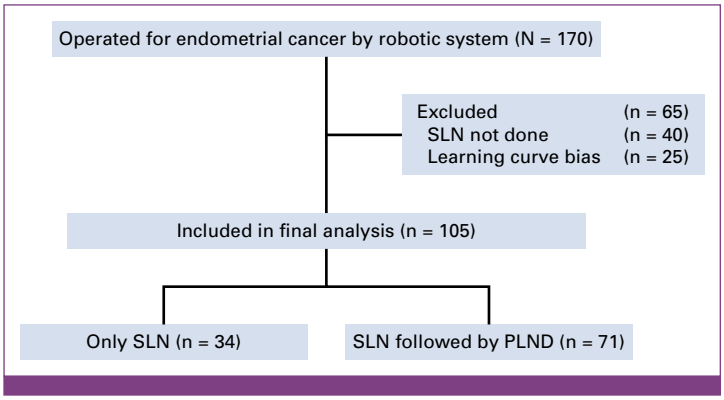


**FIG 1.** STROBE checklist for our patients with endometrial cancer undergoing robotic staging surgery with SLN algorithm. PLND, pelvic lymphadenectomy; SLN, sentinel lymph node; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

 

**TABLE 1.** Demographic Data

| Characteristic | No. (N = 105) |
|---|---|
| Age, years, median (IQR) [range] | 62 (57-67) [31-87] |
| BMI, years, median (IQR) [range] | 29.9 (25.3-33.0) [16.2-47.7] |
| ECOG, No. (%) | |
| 0 | 65 (61.9) |
| 1 | 39 (37.1) |
| 2 | 1 (1.0) |
| SLN + LND | 71 (67.60) |
| SLN only | 34 (32.30) |
| Pelvic lymphadenectomy, No. (%) | 71 (67.60) |
| Pelvic and para-aortic lymphadenectomy, No. (%) | 34 (32.30) |
| Final histologic subtype, No. (%) | |
| Grade 1 endometrioid | 38 (36.2) |
| Grade 2 endometrioid | 28 (26.6) |
| Grade 3 endometrioid | 14 (13.3) |
| Serous | 15 (14.3) |
| Carcinosarcoma | 7 (6.7) |
| High-grade NOS | 2 (2.0) |
| Low-grade ESS | 1 (0.9) |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, endometrial stromal sarcoma; LND, lymphadenectomy; NOS, not otherwise specified; SLN, sentinel lymph node.

**TABLE 2.** Postoperative Histopathological Details

| Pathological Details | No. (%) |
|---|---|
| Lymph node metastases | 15 (14.2) |
| Lymphovascular space invasion | 38 (36.1) |
| Myometrial invasion | |
| No invasion | 11 (10.5) |
| <50% | 42 (40.0) |
| ≥50% | 52 (49.5) |
| FIGO stage | |
| IA | 48 (45.7) |
| IB | 34 (32.4) |
| II | 3 (2.9) |
| IIIA | 2 (1.9) |
| IIIB | 4 (3.8) |
| IIIC1 | 9 (8.6) |
| IIIC2 | 4 (3.8) |
| IV | 1 (0.9) |
| Postoperative risk category | |
| Low | 31 (29.5) |
| Intermediate | 19 (18.0) |
| High intermediate | 15 (14.3) |
| High | 40 (38.1) |

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

**TABLE 3.** Lymph Node Details

| Characteristic | Enrolled Patients (N = 105) |
|---|---|
| Sentinel lymph node detection, No. (%) | |
| Any (unilateral/bilateral) | 104 (99.0) |
| Bilateral | 92 (87.60) |
| Lymph nodes removed, median (IQR) | |
| Sentinel node | 1 (1-2) |
| Bilateral pelvic nodes | 13 (11-16) |
| Para-aortic nodes | 7 (1-13) |

The da Vinci surgical system (Intuitive Surgery, CA) was used in all patients for staging. The ICG tracer in the lymphatic system and the SLN were visualized with near infrared (NIR) imaging. A SLN mapping was considered successful if at least one node was seen to have lymphatic pathways draining from the cervix. Next, the SLNs were extracted and sent off for ultrastaging, which included five sections cut at 200 m intervals, and immunohistochemistry (IHC) for pancytokeratin. Macrometastasis (clusters of tumors larger than 2 mm), micrometastasis (clusters of tumors between 0.2 and 2.0 mm), or isolated tumor cells (ITCs; tumor cells or clusters <0.2 mm) are all indicators of positive SLNs.[10]

Concerning the SLN algorithms, we analyzed the sensitivity and negative predictive value on an individual patient basis. In terms of pelvic nodal status, each woman was her own control. In the primary outcome analysis, we included all women who had the intended procedure performed in accordance with established guidelines.

## RESULTS

In the time span between August 2018 and August 2021, 170 patients had undergone robotic surgery for EC. In 40 patients, the SLN technique was not conducted, and because of the learning curve effect, the first 25 patients of our SLN

**TABLE 4.** Final Histopathological Analysis

| Histopathology Detail | Patients with Positive SLN (n = 15) |
|---|---|
| Final histologic subtype, No. (%) | |
| Grade 1 endometrioid | 6 (40) |
| Grade 2 endometrioid | 5 (33.3) |
| Serous | 4 (26.7) |
| Lymphovascular space invasion, No. (%) | |
| Present | 8 (53.3) |
| Absent | 7 (46.7) |
| Myometrial invasion, No. (%) | |
| <50% | 5 (33.3) |
| ≥50% | 10 (66.7) |

Abbreviation: SLN, sentinel lymph node.

**TABLE 5.** Primary Outcome (validation of SLNB)

| Result | LND Positive, No. | LND Negative, No. | Total, No. |
|---|---|---|---|
| SLNB positive | 12 | 0 | 12 |
| SLNB negative | 1 | 58 | 59 |
| Total | 13 | 58 | 71 |

NOTE. Sensitivity = 12/13 × 100 = 92.3%. Specificity = 58/58 × 100 = 100%. Negative predictive value = 58/59 × 100 = 98.3%.
Abbreviations: LND, lymphadenectomy; SLNB, sentinel lymph node biopsy.

mapping were excluded from the study analysis. In this study, 105 patients were included, with 71 receiving SLN mapping followed by full pelvic/pelvic and para-aortic lymph node dissection and 34 receiving only SLN mapping.

The para-aortic nodes were dissected in accordance with the standard operating procedure for other potential high risk factors. Dissection of the para-aortic nodes was performed on 34 patients. The final clinicopathological characteristics are outlined in Table 1 and Table 2. The median age of all patients was 62 years (range, 31-87), and the mean BMI of patients was 29.9 kg/m$^2$ (range, 16.2-47.7), and most (99%) were having good performance status. Pelvic lymphadenectomy was undertaken in 71 patients. In 34 patients (30.47%) with high-grade tumors, both pelvic and para-aortic dissection was performed, systematic dissection in 32 patients, and sampling in two patients. Ninety-two patients (87.61%) had bilateral mapping, 12 patients (11.42%) had unilateral mapping, and one patient had no mapping at all (Table 3). None of the patients had isolated para-aortic SLN mapping. Of those 92 patients with bilateral mapping, in 80 patients, lymph nodes were successfully extracted from the SLN sample on the right side and on the left side in 82 patients. In bilateral lymph node mapping, the yield was 140/80 (right) and 135/82 (left). Similarly, in unilateral mapping with 12 patients, with the exception of one patient, lymph nodes were extracted from the SLN sample. On the right side of the pelvis, 10 patients had positive SLNs. Similarly, left SLNs were positive in 10 patients. In five patients, SLN was detected on both sides of the hemi pelvis. SLNs were predominantly located in the external iliac and obturator regions. Outside of the expected locations, no SLNs were seen. After ultrastaging, 10 of 15 patients with positive SLN status had macrometastasis, two had micrometastasis, and three had ITCs. After ultrastaging, nine of the 12 patients (08.57%) with a positive SLNB for macrometastasis or micrometastasis were upstaged because their pelvic lymph nodes were negative for malignancy or because pelvic lymph node biopsy was not performed for low-risk disease. ITC did not upstage the disease which was found in three patients. Table 4 lists the risk variables of 15 SLN-positive patients. Four patients (26.66%) exhibited serous histology, eight (53.33%) had lymphovascular space invasion (LVSI), and 10 (66.66%) had myoinvasion >50%. Table 5 contains specificity and sensitivity results. The sensitivity of the SLN method per patient for detecting nodal metastatic disease was 92.3% (95% CI, 63.9 to 99.8). Among the 59 patients with negative SLN results, 58 had negative non-SLNs, yielding a negative predictive value of 98.3% (95% CI, 90.9 to 99.9). One patient with false-negative results had endometrioid grade 3 histology, as well as other high-risk characteristics, such as >50% myometrial invasion and positive LVSI. Molecular analysis revealed that she had a mismatch repair defect. We were unable to determine the cause of this failure.

## DISCUSSION

The results of this prospective single-center study from India suggest that SLN mapping by ICG dye with NIR imaging can be considered equivalent to lymphadenectomy in the staging of EC. Although our rate of bilateral mapping was lower than the SHREC trial[11] (95%), it was significantly higher than the 62% seen in SENTI-ENDO and the 52% seen in the FIRES study. Again, our study's detection rate of SLNs (99%) is higher than that of the aforementioned two major multicenter prospective trials. In the SENTI-ENDO trial, the longtime interval between radio colloid injection and the SLN technique was the primary factor behind the low detection rate (median, 22 hours). In the FIRES trial, the bilateral detection rate was poor because most surgeons had a long learning curve. Once again, using the right SLN algorithm is critical in multicenter investigations. This explains why our detection rate was higher than other studies conducted at many locations. We found that a high rate of bilateral mapping is indicative of a successful SLN mapping. Although we performed para-aortic lymphadenectomy up to the left renal vein because the risk of nodal involvement beyond the inferior mesenteric artery is fairly significant in high-risk EC, we did not find any isolated para-aortic SLN mapping.[12,13] Possible explanations for this include the small number of patients who fell into the high-risk category and the rarity of isolated para-aortic metastases in EC. Two of the three patients with para-aortic metastases in the FIRES trial had isolated para-aortic metastases. Although three and one false-negative cases were discovered in the SENTI-ENDO and FIRES trials, respectively, just one patient in our study had a false-negative SLN mapping. One crucial part of the SLN mapping process is ultrastaging, which involves the use of serial sectioning and IHC to determine the stage of lymph nodes.[14] Ultrastaging resulted in upstaging in 8.57% patients in our study. High accuracy of SLN mapping in EC was seen in our investigation, correlating with previous meta-analyses by Smith et al[15] and How et al[16] in terms of sensitivity (92.3%) and negative predictive value (98.1%), respectively. Because of the relatively small number of cases with high-risk histologies, our analysis cannot corroborate the results of the SHREC trial or the trial by Soliman et al,[17] which applied SLN mapping to high-risk EC. The fact that our study was conducted at a single center with high volume of patients, our surgeons had previous experience with robotic surgery which makes it difficult to generalize the results, and the oncological safety of the SLN procedure was not investigated are some of the limitations of our research.

In conclusion, our study demonstrates that SLN mapping with ICG dye using the robotic platform is an acceptable option and has a reasonable diagnostic accuracy compared with complete lymphadenectomy in the surgical management of EC regardless of risk types. Nevertheless, it is crucial to note that appropriate algorithms should be used after a certain learning curve to optimize outcomes. Moreover, validating the SLNB procedure in low- and middle-income countries (LMICs) can contribute to the development of more inclusive and equitable clinical practices in gynecological oncology. Therefore, future research should focus on examining the reliability, accuracy, and reproducibility of SLNB in LMICs to expand its accessibility and impact on patient outcomes.

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## DATA SHARING STATEMENT

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**Data analysis and interpretation:** Arunava Roy, Subhashree Rout, Jaydip Bhaumik
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors
**Accountable for all aspects of the work:** All authors

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

No potential conflicts of interest were reported.

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