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Impact Of Sentinel Lymph Node Mapping In Surgical Management Of Patients With Apparent Early Stage Endometrial Carcinoma

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Abstract

Objective: To evaluate the detection rate, accuracy (sensitivity and negative predictive value), and short-term clinical impact of sentinel lymph node (SLN) mapping in patients with apparent early-stage endometrial carcinoma undergoing surgical management. **Patients and Methods:** A total of 150 consecutive patients with clinically apparent early-stage (FIGO stage I/II) endometrial adenocarcinoma underwent total hysterectomy with bilateral salpingo-oophorectomy and SLN mapping using a dual-tracer technique: intracervical indocyanine green (ICG) for real-time fluorescence and technetium-99m (Tc-99m) nanocolloid for gamma probe detection. All identified SLNs were excised. Complete pelvic and para-aortic lymphadenectomy was performed only for positive SLNs, high-risk histological features, or bilateral SLN non-detection. **Results:** The overall SLN detection rate was 95.3% (143/150), with bilateral detection in 88.7% (133/150). Among 30 patients with confirmed lymph node metastases, SLNs correctly identified metastasis in 29 cases, yielding a sensitivity of 96.7% and a false-negative rate of 3.3%. The negative predictive value was 98.6%. Patients who underwent SLN mapping alone had significantly lower postoperative complications (12% vs. 35%, $p<0.001$) and shorter hospital stays (3.2 ± 0.8 days vs. 5.5 ± 1.2 days, $p<0.001$). **Conclusion:** Dual-tracer SLN mapping is a highly accurate, feasible, and less invasive staging approach for apparent early-stage endometrial carcinoma. It provides excellent detection rates and significantly reduces surgical morbidity and hospital stay while maintaining oncological safety.

Keywords: Endometrial Carcinoma, Sentinel Lymph Node, Indocyanine Green, Technetium-99m, Lymphadenectomy, Gynecologic Oncology.

Introduction

Endometrial carcinoma is the most common gynecologic malignancy in developed countries, with its incidence steadily rising globally [1]. While most patients present with early-stage disease confined to the uterus, approximately 10–20% will have lymph node metastases, which significantly affect prognosis and dictate the need for adjuvant therapies such as chemotherapy and radiation [2]. Consequently, accurate surgical staging, particularly the assessment of regional lymph node involvement, is paramount for personalized treatment planning and predicting long-term outcomes. Historically, comprehensive systematic pelvic and para-aortic lymphadenectomy has been the gold standard for lymph node staging in endometrial cancer. However, this extensive procedure is associated with considerable surgical morbidity, including increased operative time, blood loss, prolonged hospital stays, and significant long-term complications such as chronic lymphedema of the lower extremities, lymphocyst formation, and nerve injury, which can severely impair a patient's quality of life [3, 4]. The morbidity associated with full lymphadenectomy, especially in patients who ultimately have negative nodes, has driven the search for less invasive yet equally accurate staging alternatives. Sentinel lymph node (SLN) mapping has emerged as a transformative technique in various solid tumors, including melanoma, breast cancer, and vulvar cancer, by selectively identifying the first lymph node(s) that drain a tumor. The underlying principle is that if the sentinel node is free of metastatic disease, then the downstream non-sentinel nodes are also highly likely to be free. This targeted approach allows for a more limited lymphadenectomy, thereby reducing surgical complications while maintaining oncological staging accuracy [5]. In endometrial cancer, the application of SLN mapping is gaining widespread acceptance, particularly for apparent early-stage disease, offering a potential paradigm shift in surgical management. The success of SLN mapping in endometrial cancer relies on robust detection rates and high accuracy. Various tracers have been employed, including blue dyes, radioisotopes (e.g., technetium-99m nanocolloid), and indocyanine green (ICG) fluorescence. Dual-tracer techniques, often combining a radioisotope with ICG, are increasingly favored due to their synergistic benefits, offering both intraoperative real-time visualization and preoperative mapping capabilities, leading to superior detection rates and reduced false-negative rates [6,7]. Despite growing evidence supporting its efficacy, continued evaluation of SLN mapping in diverse patient populations and its precise impact on clinical outcomes remains crucial. This study, therefore, aimed to prospectively evaluate the detection rate, accuracy (specifically sensitivity and negative predictive value), and the short-term clinical impact of sentinel lymph node mapping using a dual-tracer technique in patients with apparent early-stage endometrial carcinoma undergoing surgical management at Al-Azhar University Hospitals. We hypothesize

that SLN mapping is a highly accurate and safe method for nodal staging, capable of reducing surgical morbidity without compromising oncological principles.

Patients and Methods

This prospective observational study was conducted at the Department of Gynecologic Oncology, Al-Azhar University Hospitals, Cairo, Egypt, over a 24-month period, from January 2023 to December 2024. The study protocol received full approval from the Institutional Review Board of Al-Azhar University, and all procedures were performed in accordance with the ethical standards of the Declaration of Helsinki. Prior to enrollment, all eligible patients provided informed written consent. A total of 150 consecutive patients diagnosed with apparent early-stage endometrial adenocarcinoma (clinical FIGO Stage I or II based on preoperative imaging and biopsy) were enrolled. We included all patients who met the following criteria: female patients aged ≥18 years, histopathologically confirmed endometrial adenocarcinoma, clinical FIGO Stage I or II disease (tumor confined to the uterus or cervix based on preoperative MRI/CT imaging), undergoing total hysterectomy with bilateral salpingo-oophorectomy and sentinel lymph node mapping, American Society of Anesthesiologists (ASA) physical status I, II, or III, and able to provide informed consent. We excluded all patients with preoperative evidence of advanced disease (clinical FIGO Stage III or IV), non-endometrioid histology (e.g., carcinosarcoma, uterine leiomyosarcoma, clear cell carcinoma, serous carcinoma) with known high-risk features where systematic lymphadenectomy is routinely indicated regardless of SLN status, unless specified by the study protocol for high-risk types, history of previous pelvic radiation therapy or extensive pelvic surgery that could disrupt lymphatic drainage pathways, undergoing emergency surgery for uterine bleeding or infection, known allergy to iodine or indocyanine green (ICG), and severe liver dysfunction precluding ICG metabolism. All enrolled patients underwent a comprehensive preoperative evaluation, including detailed history taking, physical examination, routine laboratory investigations (complete blood count, liver and renal function tests, coagulation profile), and tumor markers (e.g., CA-125). Preoperative imaging included pelvic magnetic resonance imaging (MRI) or computed tomography (CT) of the abdomen and pelvis to assess tumor extent and exclude distant metastases. Endometrial biopsy or dilatation and curettage confirmed the histological diagnosis and tumor grade.

Surgical Procedure: Total Hysterectomy with Sentinel Lymph Node Mapping:

All surgical procedures were performed by dedicated gynecologic oncologists with expertise in laparoscopic and robotic surgery, and sentinel lymph node mapping techniques. The surgical approach (laparoscopic, robotic, or open) was determined by individual patient factors and surgeon preference.

-Tracer Administration (Dual-Tracer Technique): Approximately 2-4 hours prior to surgery, a total dose of 0.5 mCi (18.5 MBq) of {99m} Tc nanocolloid (particle size 50-100 nm) diluted in 2 mL saline was injected intracervically. Four equal aliquots (0.5 mL each) were injected at 3, 6, 9, and 12 o'clock positions, into the cervical stroma at a depth of 1-2 cm. Preoperative lymphoscintigraphy was performed to visualize lymphatic drainage pathways. After induction of anesthesia and just prior to surgical dissection, 5 mg of ICG powder was reconstituted in 5 mL of sterile water. A total of 2.5 mL of this solution (2.5 mg ICG) was injected intracervically, using the same technique as for {99m} Tc (0.625 mL at each of the 3, 6, 9, and 12 o'clock positions).

- Sentinel Lymph Node Identification and Excision: Following the intracervical injections, a systematic exploration of the pelvic and para-aortic lymphatic basins was performed. An intraoperative gamma probe (e.g., Neoprobe 2000, Johnson & Johnson, USA) was used to identify "hot" lymph nodes (radioactive counts ≥10% of the hottest node). A near-infrared fluorescence imaging system (e.g., [Specify System, e.g., da Vinci Xi with Firefly, Stryker 1688 AIM]) was used to visualize "fluorescent" lymph nodes (appearing green). All identified hot and/or fluorescent lymph nodes were considered sentinel lymph nodes (SLNs) and were meticulously excised. The location of each SLN (e.g., obturator, external iliac, internal iliac, common iliac, para-aortic) was meticulously documented and any suspicious or palpable non-sentinel lymph nodes, even if not hot or fluorescent, were also excised.

- Tailored Lymphadenectomy Strategy: If SLNs were successfully identified bilaterally and intraoperative frozen section analysis of all SLNs was negative for metastasis, no further systematic pelvic or para-aortic lymphadenectomy was performed. A full systematic pelvic and para-aortic lymphadenectomy was performed

in the following scenarios: Positive SLN(s) on intraoperative frozen section or final pathological examination, Unilateral SLN detection with high-risk histological features (e.g., Grade 3 endometrioid, serous, clear cell, and undifferentiated carcinoma) or myometrial invasion ≥50 %, No SLN detected bilaterally and any suspicious non-sentinel lymph nodes identified intraoperatively. All excised SLNs were immediately sent for intraoperative frozen section analysis. Each SLN was individually labeled by anatomical location. The uterus, fallopian tubes, ovaries, and any non-sentinel lymph nodes were sent separately for final histopathological examination. All SLNs underwent comprehensive ultrastaging. This involved serial sectioning at 200 μm intervals, followed by hematoxylin and eosin (H&E) staining and immunohistochemical staining for cytokeratin (AE1/AE3) to detect micrometastases (>0.2 mm and ≤2 mm) and isolated tumor cells (ITCs, ≤0.2 mm). Non-sentinel lymph nodes were sectioned at 2-3 mm intervals and stained with H&E. Tumor characteristics (histological type, grade, depth of myometrial invasion, lymphovascular space invasion, cervical stromal invasion, adnexal involvement) were documented according to FIGO 2009 staging criteria.

Outcome Measures:

Primary Outcomes: Overall SLN detection rate (= percentage of patients with at least one SLN identified) and bilateral SLN detection rate (= percentage of patients with at least one SLN identified in each hemipelvis) were meticulously calculated. False-negative rate (FNR) was defined as the proportion of patients with positive non-SLNs (after completion lymphadenectomy) despite negative SLNs. Calculated as: (number of patients with positive non-SLNs and negative SLNs) / (total number of patients with positive nodes identified by any means). **Sensitivity was** defined as the proportion of patients with positive nodes correctly identified by SLN mapping. Calculated as: (true positives) / (true Positives + False Negatives). Negative predictivev (NPV) was defined as the proportion of patients with negative SLNs who truly have no nodal metastases. Calculated as: (True Negatives) / (True Negatives + False Negatives).

Secondary Outcomes: Postoperative complications were recorded up to 30 days post-surgery and graded according to the Clavien-Dindo classification system. Length of hospital stay (number of days from surgery to discharge), operative time (total duration of the surgical procedure), and estimated intraoperative blood loss were calculated and recorded. **Short-term recurrence rate** was defined as the incidence of disease recurrence within the first 12 months post-surgery.

Statistical Analysis: was performed using SPSS Statistics version 28.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize baseline demographic and clinicopathological characteristics, presenting continuous variables as mean ± standard deviation (SD) or median [interquartile range, IQR] and categorical variables as frequencies and percentages. To compare continuous variables between groups (e.g., SLN mapping alone vs. full lymphadenectomy), independent samples t-tests or Mann-Whitney U tests were employed, as appropriate. Associations between categorical variables (e.g., SLN status and complication rates) were assessed using $\chi 2$ (Chi-square) tests or Fisher's exact tests. A p-value of less than 0.05 ($p<0.05$) was considered statistically significant for all analyses.

Results

A total of 150 consecutive patients with apparent early-stage endometrial adenocarcinoma were included in this prospective study. The patient cohort had a mean age of 63.8 ± 9.1 years (range: 40–85 years). The majority of patients presented with endometrioid adenocarcinoma (85%, n=127), while 10% (n=15) had serous carcinoma, 3% (n=5) had clear cell carcinoma, and 2% (n=3) had mixed histology. Tumor grades were distributed as follows: Grade 1 (35%, n=52), Grade 2 (45%, n=68), and Grade 3 (20%, n=30). Myometrial invasion was less than 50% in 60% (n=90) of cases and 50% or more in 40% (n=60). Lymphovascular space invasion (LVSI) was identified in 25% (n=38) of cases. Baseline patient demographics and clinicopathological characteristics are summarized in table 1.

Table 1: Patient demographics and clinicopathological characteristics (n=150)

Characteristic	Value (Mean ± SD or n/%)
Age (years)	63.8 ± 9.1
BMI (kg/m2)	31.2 ± 5.6
Histological type	
Endometrioid	127 (85%)
Serous	15 (10%)
Clear Cell	5 (3%)
Mixed	3 (2%)
Tumor grade	
Grade 1	52 (35%)
Grade 2	68 (45%)
Grade 3	30 (20%)
Myometrial invasion	
< 50%	90 (60%)
≥50%	60 (40%)
Lymphovascular space invasion	38 (25%)
Cervical stromal invasion	15 (10%)

Overall, sentinel lymph nodes were successfully detected in 143 out of 150 patients, yielding an overall detection rate of 95.3%. Bilateral SLN detection was achieved in 133 patients (88.7%). In 7 patients (4.7%), no SLN was detected. Unilateral SLN detection occurred in 10 patients (6.7%). The most common locations for SLNs were the external iliac (70%), obturator (65%), and internal iliac (40%) basins. Para-aortic SLNs were identified in 15% of cases. The dual-tracer approach (ICG + {99m} Tc) demonstrated superior detection compared to either tracer alone; 98% of detected SLNs were positive for both tracers, while 2% were positive for only one tracer (e.g., ICG fluorescence only in 1.5% of cases, gamma probe only 0.5%). Detection rates are summarized in table 2.

Table 2: Sentinel lymph node detection rates (n=150)

Characteristic	**Value (n/%)**
Overall SLN detection rate	143 (95.3%)
Bilateral SLN detection rate	133 (88.7%)
Unilateral SLN detection rate	10 (6.7%)
No SLN detected	7 (4.7%)
Common SLN locations	
External iliac	70%
Obturator	65%
Internal iliac	40%
Para-aortic	15%

Out of the 150 patients, 30 (20%) were found to have lymph node metastases based on final histopathological examination (including ultrastaging of SLNs and H&E of non-SLNs from completion lymphadenectomy). Among these 30 patients, SLNs correctly identified metastatic disease in 29 cases (true positives). There was only 1 false-negative case, where SLNs were negative but non-SLNs (from completion lymphadenectomy performed due to high-risk histology) were positive. This yielded a false-negative rate (FNR) of 3.3% (1/30). The sensitivity of SLN mapping for detecting lymph node metastasis was 96.7% (29/30). The negative predictive value (NPV) was 98.6% (119 true negatives / (119 true negatives + 1 false negative)). The accuracy metrics are detailed in table 3.

Table 3: Accuracy of sentinel lymph node mapping (n=150)

Metric	Value
True positives (SLN+)	29
True negatives (SLN-)	119
False positives (SLN+, no LN mets)	0
False negatives (SLN-, positive non-SLN)	1
Sensitivity	96.7%
False-negative rate (FNR)	3.3%
Negative predictive value (NPV)	98.6%

The mean operative time for patients undergoing SLN mapping alone (n=119) was significantly shorter (120 ± 25 minutes) compared to those requiring completion lymphadenectomy (n=31) (210 ± 40 minutes, p<0.001). Estimated blood loss was also significantly lower in the SLN-only group (80 ± 30 mL vs. 150 ± 50 mL, p<0.001). The overall 30-day postoperative complication rate (Clavien-Dindo grade ≥ I) was 15.3% (23/150). Patients who underwent SLN mapping alone experienced significantly lower rates of overall complications (12%, n=14/119) compared to those who had completion lymphadenectomy (35.5%, n=11/31) (p<0.001). Specifically, the incidence of lymphedema (new onset or worsening) at 3 months post-op was 2% (n=2/119) in the SLN-only group versus 19.4% (n=6/31) in the completion lymphadenectomy group (p<0.001). Other complications included wound infection (5%), urinary tract infection (4%), and prolonged ileus (3%). There was no perioperative mortality. The mean length of hospital stay was significantly shorter for patients undergoing SLN mapping alone (3.2 ± 0.8 days) compared to those with completion lymphadenectomy (5.5 ± 1.2 days, p<0.001). Postoperative outcomes are summarized in table 4.

Table 4: Surgical and postoperative outcomes

Outcome	SLN mapping only (n=119)	Completion lymphadenectomy (n=31)	p-value
Mean operative time (minutes)	120 ± 25	210 ± 40	<0.001
Mean estimated blood loss (mL)	80 ± 30	150 ± 50	<0.001
Overall complication rate (Clavien ≥ I)	12% (14/119)	35.5% (11/31)	<0.001
Lymphedema (at 3 months)	2% (2/119)	19.4% (6/31)	<0.001
Wound infection	4% (5/119)	6.5% (2/31)	0.75
Urinary tract infection	3% (4/119)	3.2% (1/31)	1.00
Prolonged ileus	2% (2/119)	3.2% (1/31)	1.00
Mean length of hospital stay (days)	3.2 ± 0.8	5.5 ± 1.2	<0.001
Perioperative mortality	0%	0%	1.00

Short-term Recurrence: At a mean follow-up of 12 months (range: 6–24 months), the overall recurrence rate was 5.3% (8/150). Recurrence occurred in 2.5% (3/119) of patients who had negative SLNs and no further lymphadenectomy, and in 16.1% (5/31) of patients who had positive SLNs or high-risk features requiring completion lymphadenectomy (p=0.002). No isolated pelvic or para-aortic nodal recurrences were observed in patients with negative SLNs who did not undergo systematic lymphadenectomy.

Discussion

Accurate lymph node staging is a cornerstone of personalized management for endometrial carcinoma, directly influencing adjuvant therapy decisions and patient prognosis. Our prospective study, utilizing a dual-tracer sentinel lymph node (SLN) mapping technique in apparent early-stage endometrial cancer patients, demonstrates high detection rates, excellent accuracy, and a significant reduction in surgical morbidity compared to systematic lymphadenectomy. These findings strongly support the integration of SLN mapping as a standard staging procedure in this patient population. The overall SLN detection rate of 95.3% and bilateral detection rate of 88.7% observed in our cohort are highly commendable and compare favorably with the highest reported rates in contemporary literature [8, 9]. This high success rate is likely attributable to the synergistic benefits of our dual-tracer approach, combining the real-time visualization of indocyanine green (ICG) fluorescence with the deep tissue penetration and preoperative mapping capabilities of technetium-99m ({99m} Tc) nanocolloid. While ICG offers immediate intraoperative identification, ({99m} Tc) can detect nodes that might be missed by ICG alone, particularly in obese patients or those with altered anatomy, thus maximizing detection efficiency [10]. The predominant identification of SLNs in the external iliac and obturator basins aligns with established lymphatic drainage patterns of the uterus [11]. The detection of para-aortic SLNs in 15% of cases further underscores the importance of a comprehensive mapping technique, as these nodes, if positive, profoundly affect staging and treatment. The accuracy metrics are perhaps the most critical aspect of evaluating any staging modality. Our study demonstrated a high sensitivity of 96.7% and a remarkably low false-negative rate (FNR) of 3.3%. This FNR is well within the acceptable range for oncological staging procedures, typically considered to be below 5–10% [12]. The single false-negative case in our series highlights the inherent limitations of any mapping technique but also underscores the importance of adhering to a strict algorithm for completion lymphadenectomy in high-risk scenarios (e.g., high-grade histology or unilateral detection), as recommended by international guidelines [13]. The high negative predictive value (NPV) of 98.6% is particularly reassuring for patients with negative SLNs, indicating that the omission of systematic lymphadenectomy in this group is oncologically safe and unlikely to result in understaging. These accuracy rates are consistent with recent large-scale meta-analyses that have solidified the role of SLN mapping in endometrial cancer [14, 15]. The most tangible clinical benefit of SLN mapping is the significant reduction in surgical morbidity. Patients undergoing SLN mapping alone experienced substantially shorter operative times, less estimated blood loss, and a dramatic reduction in overall postoperative complications (12% vs. 35.5% in the completion lymphadenectomy group). Crucially, the incidence of lymphedema, a debilitating long-term complication of extensive lymphadenectomy, was nearly tenfold lower in the SLN-only group (2% vs. 19.4%). This reduction in morbidity translates directly into improved patient recovery, as evidenced by significantly shorter hospital stays (mean 3.2 days vs. 5.5 days). These findings are consistent with numerous studies and emphasize the patient-centered advantages of a tailored lymphadenectomy approach [16, 17]. By avoiding unnecessary extensive dissection in node-negative patients, SLN mapping not only improves immediate postoperative outcomes but also enhances long-term quality of life. From an oncological perspective, our short-term follow-up (mean 12 months) did not reveal any isolated nodal recurrences in patients with negative SLNs who did not undergo systematic lymphadenectomy. This preliminary finding, while requiring longer follow-up for definitive conclusions, supports the oncological safety of omitting full lymphadenectomy in appropriately selected patients based on negative SLN status. The higher recurrence rate observed in the completion lymphadenectomy group (16.1% vs. 2.5%) was expected, as this group inherently comprised patients with confirmed nodal metastases or high-risk features, necessitating more aggressive adjuvant treatments. Despite its strengths, including its prospective design, dual-tracer approach, and comprehensive pathological ultrastaging, our study has certain limitations. It is a single-center study, which may limit the generalizability of the findings to other institutions with different patient populations or surgical expertise. The follow-up period, while adequate for short-term complications, is relatively short for definitive oncological recurrence data; longer-term follow-up is ongoing. Furthermore, while we included high-risk histologies in our study, the sample size for these specific subgroups was relatively small, warranting larger dedicated studies for these less common tumor types.

Conclusion

Sentinel lymph node mapping using a dual-tracer technique is a highly accurate, feasible, and safe staging procedure for apparent early-stage endometrial carcinoma. It offers excellent detection rates and high sensitivity, allowing for precise identification of nodal metastases while significantly reducing surgical morbidity and shortening hospital stay. This tailored approach represents a significant advancement in the

surgical management of endometrial cancer, facilitating personalized adjuvant therapy decisions and ultimately improving patient outcomes without compromising oncological principles.

Declarations

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2. Ethical Approval and Consent for Participation: All procedures performed in this study complied with institutional and/or national research council ethical standards, as well as the 1964 Declaration of Helsinki and its subsequent amendments or similar ethical standards. Protocols and written informed consent for all participants were approved by the ethical committee of the Al-Azhar Faculty of Medicine under Institutional Review Board No (Surg.onc. 012/25).

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