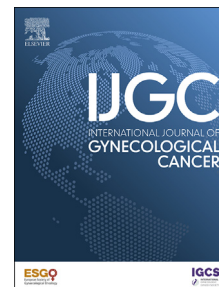


# Sentinel SENECA risk factors for unsuccessful bi-lateral sentinel lymph node mapping in endometrial cancer



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## ABSTRACT

**Objective:** Our study aims to assess the risk factors associated with bi-lateral sentinel lymph node (SLN) mapping failure in endometrial cancer.

**Methods:** The SENECA study was a retrospective multi-center international observational study that reviewed data from 2139 women with clinical stage I-to-II endometrial cancer across 64 centers in 17 countries. Between January 2021 and December 2022, patients underwent surgical treatment with SLN assessment, following the guidelines of the European Society of Gynaecological Oncology. Risk factors associated with the absence of bi-lateral mapping were analyzed using  $\chi^2$  and *t* tests. All factors that showed statistical associations were included in a multi-variate regression analysis.

**Results:** Among the 2139 patients, the bi-lateral lymph node detection rate was 82.7%, whereas the unilateral detection rate was 97.3%. In multi-variate analysis, 5 risk factors remained statistically associated with unsuccessful bi-lateral lymph node mapping: high-grade histology (OR 1.35, 95% CI 1.02 to 1.79, *p* = .03), myometrial invasion >50% (OR 1.37, 95% CI 1.07 to 1.75, *p* = .012), low-volume surgeon <20 cases/year (OR 2.11, 95% CI 1.55 to 2.89, *p* < .01), open surgical approach (OR 1.72, 95% CI 1.06 to 2.78, *p* = .03), and non-indocyanine green tracer (OR 4.59, 95% CI 2.64 to 7.99, *p* < .01). The addition of bi-lateral pelvic lymphadenectomy and/or paraaortic lymphadenectomy to SLN biopsy caused an increased rate of intra-operative complications (2% vs 8.4%, *p* < .01) and all-grade post-operative complications (4.1% vs 11.2%, *p* < .01).

**Conclusions:** Our study identifies 5 risk factors associated with unsuccessful lymph node mapping in endometrial cancer. Efforts should be made to perform this technique with indocyanine green, through minimally invasive surgery, and performed or supervised by an experienced surgeon with  $\geq 20$  endometrial cancer cases per year.

## Keywords:

Endometrial Neoplasms; Sentinel Lymph Node

## WHAT IS ALREADY KNOWN ON THIS TOPIC

High detection rates and accurate staging are achieved when sentinel lymph node biopsy is performed using a standardized protocol. Previous studies have identified risk factors for failed sentinel lymph node mapping, but the findings have varied widely owing to differences in study designs and methods.

## WHAT THIS STUDY ADDS

This study represents the largest cohort of patients published to date studying factors associated with failed bi-lateral lymph node mapping in early-stage endometrial cancer, and identifies 5 key factors: high-grade histology, myometrial invasion >50%, surgeons performing <20 cases per year, open surgical approach, and use of tracers other than indocyanine green (ICG).

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

Future studies should focus on optimizing sentinel lymph node biopsy techniques and standardizing surgical protocols to improve success rates in bi-lateral lymph node mapping. Efforts should be made to perform this technique with ICG, through minimally invasive surgery, and performed or supervised by an experienced surgeon with  $\geq 20$  endometrial cancer cases per year.

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## INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in high-income countries, with an estimated number of 420,242 new cases and 97,704 deaths worldwide in 2022.<sup>1</sup> Lymph node involvement is a crucial prognostic indicator in patients with endometrial carcinoma, influencing both the selection of therapeutic strategies and patient outcomes. In recent years, the technique of sentinel lymph node biopsy has gained increasing popularity as a minimally invasive alternative to systematic lymphadenectomy, aiming to provide precise information about lymphatic spread while reducing surgical morbidity. Prospective clinical trials have confirmed the high sensitivity to detect lymph node metastasis and the high negative predictive value using a standardized sentinel lymph node (SLN) algorithm even in high-risk endometrial cancer.<sup>2-4</sup>

Although SLN biopsy holds promise, it is not infallible and can occasionally fail to identify the SLN accurately. Understanding the predictive factors associated with failed SLN mapping in patients with endometrial carcinoma is imperative for refining the application and efficacy of this technique. Several studies have examined these factors, but much heterogeneity and disparity can be observed among the results published in the literature.<sup>5-10</sup>

In 2023, to assess the rate of SLN involvement according to the different molecular subtypes in patients with stage I-to-II endometrial cancer, the SENECA study<sup>11</sup> was established. With 2139 patients treated with hysterectomy and SLN biopsy and >200 variables related to surgery and lymph nodes assessment, it represents the largest database available to study factors associated with SLN mapping nowadays.

The main objective of this study was to assess the risk factors associated with the failure of lymph node mapping in a large cohort of patients with early-stage endometrial cancer. The secondary objective was to evaluate the impact of avoiding bi-lateral pelvic and/or paraaortic lymphadenectomy.

## METHODS

The retrospective multi-centric international observational study reviewed data of patients diagnosed with early-stage (International Federation of Gynecology and Obstetrics [FIGO] stage I-II) endometrial cancer who underwent surgery with lymph node evaluation between January 2021 and December 2022, both included. All factors previously described as possible risk factors for non-sentinel mapping and factors related to SLN technique were included in the SENECA database and were analyzed and retrieved. High volume per surgeon was defined as >20 cases per year following the European Society of Gynaecological Oncology (ESGO) recommendations for quality indicators in endometrial cancer.<sup>12</sup> The study protocol was reviewed by the institutional review board (IRB) of Clinica Universidad de Navarra (CUN 2022.195). Each institution was responsible for obtaining its own IRB/European Commission approval.

Patients were deemed eligible if all the following criteria were met: aged  $\geq 18$  years; histologic confirmation of endometrial cancer with endometrioid histology or high-risk histology (serous, clear cell, carcinosarcoma, and mixed histologies); pre-operative FIGO stage I or II by magnetic resonance imaging (MRI) or ultrasound; and pre-operative computed tomography (CT) scan or

positron emission tomography-CT without evidence of local or distant disease (could be omitted in low-risk and intermediate-risk endometrial carcinoma with low-grade histology according to ESGO guidelines). In addition, a detailed SLN study protocol had to be accredited, either by ultra-staging or one-step nucleic acid amplification. Molecular analysis had to be performed on the pre-operative biopsy or hysterectomy specimen (polymerase epsilon mutation analysis could be omitted in low-risk and intermediate-risk endometrial carcinoma with low-grade histology according to ESGO guidelines).

Patients were excluded if they were pregnant; if they underwent previous hysterectomy and/or previous pelvic/paraortic lymphadenectomy; and in cases of presence of extra-uterine disease (peritoneal, visceral, or suspicious lymph node metastasis) or medical history of any invasive tumor, previous abdominal, or pelvic radiotherapy of any type (including brachytherapy), and history of pre-operative neoadjuvant chemotherapy.

Risk factors associated with the absence of bi-lateral mapping (unilateral detection or no detection) were analyzed using  $\chi^2$  and *t* tests, as appropriate. A receiver-operating characteristic (ROC) curve was obtained with body mass index (BMI) to try to predict the best cut-off point for failed bi-lateral mapping. All factors that showed statistical associations were included in a multi-variate regression analysis. A  $p < .05$  was considered to indicate statistical significance. Statistical analysis was performed using SPSS 27.0 (IBM SPSS Statistics).

In accordance with the journal's guidelines, we will provide our data for independent analysis by a team selected by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

## RESULTS

A total of 2139 patients were included in the study. The rate of bi-lateral lymph node detection was 82.7%, whereas the rate of unilateral detection was 97.3%. Mean age was 64.5 years (standard deviation [SD] 10.80). Mean BMI was 30.2 kg/m<sup>2</sup> (SD 6.65). Clinical characteristics are listed in [Table 1](#). The median surgical time was 144 minutes (SD 68). The injection of the tracer for SLN biopsy was most frequently performed by a senior surgeon, using indocyanine green (ICG) as the tracer with a concentration of 1.25 mg/mL, in a volume of 4 mL, and injected both deeply and superficially at the 3 o'clock and 9 o'clock positions. All the details regarding the SLN biopsy technique are listed in [Table 2](#).

A total of 319 patients (14.9%) underwent bi-lateral pelvic lymphadenectomy and/or paraaortic lymphadenectomy in addition to the SLN biopsy. When any of these procedures were added to SLN biopsy, intra-operative complications and all-grade post-operative complications increased from 2% to 8.4% ( $p < .01$ ) and from 4.1% to 11.2% ( $p < .01$ ). Length of stay and duration of surgery also increased from 2.6 to 3.8 days ( $p > .01$ ) and from 133 to 207 minutes ( $p < .01$ ).

All factors associated with failed bi-lateral detection in univariate analysis are listed in [Table 3](#). Data on BMI were available in 600 patients (28.1%). BMI was not associated as a continuous variable to bi-lateral detection. A ROC curve was designed to determine the best cut-off point for predicting bi-lateral detection. The area under

**Table 1** Baseline Characteristics of Study Participants

Baseline characteristics	N = 2139
Age (y) (mean/SD)	64.55 (10.80)
Body mass index (kg/m <sup>2</sup> ) (mean/SD)	30.24 (6.65)
Surgery duration (min) (mean/SD)	144 (69.7)
Surgical approach n (%)	
Laparoscopic	1432 (66.9)
Robotic	594 (27.8)
Open	113 (5.3)
Previous pelvic surgery n (%)	
Yes	301 (14.1)
No	1482 (69.3)
Not reported	356 (16.6)
Uterine manipulator n (%)	
Yes	1147 (53.6)
No	957 (44.7)
Not reported	35 (1.6)
Histology n (%)	
Endometrioid	1866 (87.2)
Serous	129 (6.0)
Mixed histology	63 (2.9)
Carcinosarcoma	42 (2.0)
Clear cell	30 (1.4)
Not reported	9 (0.4)
Grade n (%)	
Low grade	1655 (77.4)
High grade	432 (20.2)
Not reported	52 (2.4)
Myometrial invasion n (%)	
No	1649 (77.1)
Yes	479 (22.4)
Not reported	11 (0.5)
Cervical invasion n (%)	
Yes	181 (8.5)
No	1951 (91.2)
Not reported	7 (0.3)
FIGO stage n (%)	
IA	1278 (59.7)
IB	523 (24.5)
II	152 (7.1)
IIIA	41 (1.9)
IIIB	8 (0.4)
IIIC1	126 (5.9)
IIIC2	4 (0.2)
IV	7 (0.3)
Molecular profile n (%)	
POLE-mut	95 (4.4)
MMR-d	581 (27.2)
NSMP	1191 (55.7)
p53-abn	272 (12.7)

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; MMR-d, mismatch repair deficiency; NSMP, no specific molecular profile; POLE, polymerase epsilon; POLE-mut, polymerase epsilon-mutated; SD, standard deviation.

the curve was 0.46, and the most predictive cut-off point was 30 kg/m<sup>2</sup>. BMI >30 kg/m<sup>2</sup> was not associated with failed bi-lateral detection either.

**Table 2** SLN Procedure Characteristics

SLNB characteristics	N = 2139
Center caseload >20 cases/surg/y n (%)	
<20	461 (21.6)
>20	1544 (72.2)
Not reported	134 (6.3)
Nodes Approach n (%)	
SLNB	1686 (78.8)
SLNB + PLND (only 1 pelvic side)	131 (6.1)
SLNB + PLND (both pelvic sides)	188 (8.8)
SLNB + PLND (1 side) + PALND	7 (0.3)
SLNB + PLND (both sides) + PALND	115 (5.4)
SLNB + PALND	12 (0.6)
Tracer n (%)	
ICG	1865 (87.2)
Radiocolloid and ICG	189 (8.8)
Blue dye	74 (3.5)
Blue dye and ICG	5 (0.2)
Radiocolloid and blue dye	2 (0.1)
Not reported	4 (0.2)
Tracer volume n (%)	
4 cm <sup>3</sup>	1544 (72.2)
2 cm <sup>3</sup>	371 (17.3)
1 cm <sup>3</sup>	90 (4.2)
Not reported	134 (6.3)
ICG dilution n (%)	
0.5 mg/mL	386 (18)
1.25 mg/mL	878 (41)
2.5 mg/mL	622 (29.1)
Not reported	253 (4.3)
Injection technique n (%)	
Superficial 3-9	159 (7.4)
Superficial and deep 3-9	1720 (80.4)
Superficial 3-6-9-12	25 (1.2)
Superficial and deep 3-6-9-12	185 (8.6)
Not reported	50 (2.3)
Re-injection of ICG if failed n (%)	
Yes	1489 (69.6)
No	650 (30.4)
Dissection of pre-sacral space if failed n (%)	
Yes	1042 (48.7)
No	1097 (51.3)
Injector n (%)	
Attending	1208 (56.5)
Fellow	527 (24.6)
Resident	311 (14.5)
Not reported	93 (4.3)
SLN total number (median)	2.8
SLN distribution n (%)	
Both pelvic sides	1729 (80.8)
Right pelvic side	152 (7.1)
Left pelvic side	150 (7.0)
Both pelvic sides + aortic area	41 (1.9)
Left pelvic side + aortic area	8 (0.4)
Right pelvic side + aortic area	1 (0.05)
Aortic area	1 (0.05)
Not any SLN identified	57 (2.7)
SLN involvement n (%)	205 (9.6)
Isolated tumor cells	51 (24.9)

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**Table 2** (continued)

SLNB characteristics	N = 2139
Micro-metastases	58 (28.3)
Macro-metastases	56 (27.3)
Not reported	40 (24.9)

Abbreviations: ICG, indocyanine green; PALND, paraaortic lymph node dissection; PLND, pelvic lymph node dissection; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; surg, surgeries.

All factors associated with failed bi-lateral detection in univariate analysis were included in a multi-variate analysis (Table 4). Only 5 risk factors remained statistically associated with unsuccessful bi-lateral lymph node mapping in the multi-variate analysis: high-grade histology (OR 1.35, 95% CI 1.02 to 1.79,  $p=.039$ ), myometrial invasion >50% (OR 1.37, 95% CI 1.07 to 1.75,  $p=.012$ ), low-volume surgeon <20 cases per year (OR 2.11, 95% CI 1.55 to 2.89;  $p<.01$ ), open surgical approach (OR 1.72, 95% CI 1.06 to

2.78,  $p=.03$ ), and non-ICG tracer (OR 4.59, 95% CI 2.64 to 7.99,  $p<.01$ ).

## DISCUSSION

### Summary

Our study found that the factors associated with failed lymph node mapping included high-grade histology, myometrial invasion >50%, surgeons performing <20 cases per year, an open surgical approach, and the use of a non-ICG tracer. SLN biopsy should be performed using ICG, through minimally invasive surgery, and conducted or supervised by a surgeon who manages  $\geq 20$  procedures annually.

### Results in the Context

SLN biopsy is now deemed the standard of care in the treatment of endometrial cancer. It has been associated with less morbidity (as shown in our study) and even higher detection rates of nodal metastases than in traditional lymphadenectomy.<sup>2-4,13</sup> One of the

**Table 3** Univariate Analysis of Factors Associated With Failed Bi-Lateral Detection

Variable	Bi-lateral detection rate				p-value
	Yes	No			
FIGO stage III-IV	83.3%	82.7%			.82
Nodal positivity	85.9%	82.4%			.21
SLN frozen	80.5%	83.2%			.34
Uterine manipulator	84%	81.7%			.08
Previous pelvic surgery	81.1%	83%			.4
Injection performed by resident	80.4%	83%			.26
Endometrioid histology	79.9%	83.5%			.17
BMI >30	82.5%	79.7%			.37
Volume tracer >3 mL	84.1%	81.3%			.17
High grade	79.2%	83.5%			<b>.03</b>
Cervical invasion	77.3%	83.2%			<b>.04</b>
Myometrial invasion	79.7%	84.2%			<b>.01</b>
ICG as tracer	83.9%	53%			<b>&lt;.01</b>
MIS approach	83.5%	69%			<b>&lt;.01</b>
>20 cases/surg/year	85.5%	81.2%			<b>&lt;.01</b>
Re-injection if failed	84.9%	78%			<b>&lt;.01</b>
Pre-sacral dissection if failed	85.3%	80.4%			<b>&lt;.01</b>
Injection technique	<b>SD 3-9</b>	<b>SD 3-9</b>	<b>SD 3-6-9-12</b>	<b>SD 3-6-9-12</b>	<b>.03</b>
	83.4%	84.9%	75.5%	72%	
Molecular profile	<b>POLE</b>	<b>p53</b>	<b>NSMP</b>	<b>MMR-d</b>	.75
	87.3%	80.5%	82.7%	83.4%	
Dilution of ICG	<b>0.5 mg/mL</b>	<b>1.25 mg/mL</b>	<b>2.5 mg/mL</b>		.08
	85%	83%	82.6%		
Age (mean, y)	58.8	62.1			.65
BMI (mean, kg/m <sup>2</sup> )	31.1	32.1			.55

Abbreviations: BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; ICG, indocyanine green; MIS, minimally invasive surgery; MMR-d, mismatch repair deficiency; NSMP, no specific molecular profile; POLE, polymerase epsilon; SD, standard deviation; SLN, sentinel lymph node; surg, surgeries. Boldface and italic if statistically significant.

**Table 4** Multi-Variate Analysis of Factors Associated With Failed Bi-Lateral Detection

Multi-variate analysis			
Variable	OR (no detection)	95% CI	p-value
<b>Myometrial invasion &gt; 50%</b>	<b>1.37</b>	<b>1.07 to 1.75</b>	<b>.01</b>
<b>High grade</b>	<b>1.35</b>	<b>1.02 to 1.79</b>	<b>.04</b>
<b>Non-ICG tracer</b>	<b>4.59</b>	<b>2.64 to 7.99</b>	<b>&lt; .01</b>
<b>Open surgery</b>	<b>1.72</b>	<b>1.06 to 2.78</b>	<b>.03</b>
<b>Low volume surgeon (&lt; 20/y)</b>	<b>2.11</b>	<b>1.56 to 2.89</b>	<b>&lt; .01</b>
Injection technique	1.1	0.91 to 1.33	.32
Pre-sacral dissection	0.88	0.68 to 1.13	.31
Re-injection if failure	0.86	0.66 to 1.12	.27
Cervical invasion	1.45	0.9 to 2.15	.06

Abbreviation: ICG, indocyanine green.  
 Boldface if statistically significant (p < 0.05).

main challenges with SLN biopsy is the heterogeneity in techniques. In our study, we observed significant variation in the techniques used, although none of these differences seemed to affect detection rates. In 2021, to address these disparities, Moloney and colleagues<sup>14</sup> published an assessment tool that we highly recommend to the reader.

Several studies have indicated the superior performance of ICG to that of blue dye or radiocolloid.<sup>2,5,10,15-18</sup> In our study, the use of any other tracer was associated with nearly a 5-fold higher likelihood of failure to detect the SLN bi-laterally. The rate of bi-lateral detection improves when the surgery is performed or supervised by a surgeon with >20 cases per year. This threshold was established by ESGO in their quality indicators. Although this benchmark might seem arbitrary, it highlights the importance of surgical volume in endometrial cancer, as shown in the existing literature. In a study published by Gedgudaite and colleagues,<sup>19</sup> 190 patients were prospectively evaluated to assess the learning curve for SLN biopsy in endometrial cancer. The authors found that  $\geq 30$  procedures using ICG-traced laparoscopic SLN biopsy were required to achieve an acceptable level of competence, with a bi-lateral SLN detection rate of  $\geq 75\%$ . This finding aligns with the only prospective study analyzing risk factors in the literature. Ianieri and colleagues<sup>20</sup> prospectively analyzed 110 patients and found that the only factor significantly associated with successful bi-lateral lymph node mapping was the surgeon.

All previous studies analyzing these factors were primarily conducted using minimally invasive surgery. In endometrial cancer surgery, SLN biopsy is typically performed through minimally invasive surgery. In our study, 5% of the patients underwent open surgery. However, on the basis of our findings, it is crucial to consider that when choosing to operate through an open approach, the rates of bi-lateral lymph node detection are likely to decrease. The association between open surgery and lower SLN detection rates may be due to increased tissue manipulation, anatomical

distortion, or differences in tracer dispersion. Similarly, aggressive histologic subtypes and myometrial invasion might have altered lymphatic architecture, reducing tracer migration. This finding aligns with previous studies.<sup>21</sup>

Pre-operative molecular profiling and advanced imaging (MRI or specialized ultrasound) could help identify patients at higher risk for failed mapping, guiding decisions on comprehensive lymphadenectomy. Furthermore, our results emphasize the importance of adhering to the Memorial Sloan Kettering SLN algorithm for surgical staging in patients with endometrial cancer, particularly in high-risk cases.<sup>22</sup>

Enlarged lymph nodes on pre-operative imaging, BMI, and the use of a tracer volume <3 mL have previously been described as factors associated with failed lymph node mapping. Regarding enlarged lymph nodes, we must note that our study included only patients with pre-operative stage I-to-II endometrial cancer, so these cases were excluded. BMI was not found to be associated with failed mapping, either as a continuous variable or with a BMI >30 kg/m<sup>2</sup>. The literature on this topic is inconsistent, with some studies suggesting that higher BMI is associated with failed detection<sup>21,23,24</sup> whereas others suggest the opposite.<sup>6,8,9</sup> In our data, it is important to acknowledge that BMI information was available for 600 patients (28% of the cohort), which may have biased our results.

A recent meta-analysis reported that using >3 mL of tracer is associated with higher rates of bi-lateral lymph node mapping. However, although the meta-analysis<sup>6</sup> included 1345 cases, the volume of tracer was analyzed in only 325 patients. In our study, with data on tracer volume for 2005 patients, we did not observe any differences in bi-lateral detection rates. This is consistent with a more recent study by Mauro and colleagues,<sup>5</sup> which specifically analyzed tracer volume in 352 patients and found no differences in detection rates between 2 mL and 4 mL.

### Strengths and Weaknesses

To the best of our knowledge, this is the largest cohort study in endometrial cancer analyzing factors associated with failed lymph node mapping. With up to 22 variables potentially influencing bi-lateral lymph node mapping, we consider our multi-variate analysis to be robust and reliable. Our cohort also shows a high rate of bi-lateral lymph node mapping, minimizing potential surgical biases related to suboptimal SLN biopsy technique.

The primary limitation of our study is its retrospective nature. It is also important to note that BMI data were available for only 28% of cases, which may have influenced our findings regarding this variable. Although ICG is well-established for its superior detection performance, only 76 cases (3.6%) did not receive ICG, which could represent a potential bias to the study.

### CONCLUSION

Our study identifies 5 risk factors associated with unsuccessful lymph node mapping. SLN biopsy is a safe technique that improves surgical morbidity with high rates of bi-lateral detection. Efforts must be made to perform this technique with ICG, by minimally invasive surgery, and conducted or supervised by an experienced surgeon with  $\geq 20$  endometrial cancer cases per year.

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**Declaration of Competing Interests** None declared.

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