TECHNOLOGY REVIEW (MINI-HTA)

LAPAROSCOPIC INDOCYANINE GREEN SENTINEL LYMPH NODE MAPPING IN ENDOMETRIAL CANCER

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
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EXECUTIVE SUMMARY

Background

Endometrial cancer is the most common gynaecologic malignancy in developed countries and ranks among the top cancers affecting Malaysian women. In 2020, Malaysia was reported among the top 10 countries with the highest incidence and mortality for this cancer.

Accurate staging is critical for treatment planning and prognostication. Traditional lymphadenectomy, while standard for high-risk patients, poses significant surgical risks and morbidity. Sentinel lymph node biopsy (SLNB) offers a less invasive alternative, identifying the first draining lymph nodes to detect metastasis. Among detection techniques, indocyanine green (ICG) combined with near-infrared imaging has shown superior sensitivity and safety.

Laparoscopic ICG SLN mapping may improve staging accuracy while minimizing complications, supporting its potential as a safer and cost-effective option for endometrial cancer management. This technology review was initiated to assess current evidence on its efficacy, safety, and economic value to inform clinical practice in Malaysia.

Objective/ aim

The objective of this systematic review and economic evaluation was to assess the effectiveness/efficacy, safety, and cost-effectiveness of laparoscopic indocyanine green sentinel lymph node mapping in endometrial cancer.

Results and conclusions:

Search results

A total of 1219 records were identified through the Ovid interface, PubMed and Embase, International HTA Database (INAHTA) and other method. Sixty-three duplicates references were found. After removal of duplicate articles, 1156 titles were screened using the inclusion and exclusion criteria. Of these, 447 potentially relevant abstracts were screened, and 85 articles were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the 85 successfully retrieved full text articles, 23 were included. Fourteen articles were excluded as those primary studies were already included in systematic review (n=14), fifteen articles irrelevant study design (n=15), eleven articles irrelevant population (n=11) and 22 articles found as irrelevant intervention (n=22). All full text articles finally selected for this review comprised of four systematic review and meta-analysis, two systematic reviews, one clinical trial, 13 observational studies, two cost-effectiveness analysis and one cost-analysis study.

Efficacy/ effectiveness

Based on the above review, there were thirteen studies consisted of three systematic reviews and meta-analysis, two systematic reviews, one non-randomised controlled trial, seven cohort studies retrieved on effectiveness of laparoscopic indocyanine green (ICG) sentinel lymph node mapping for endometrial cancer.

1. SLN Detection and Sensitivity:

- The overall SLN detection rate for ICG was high across various studies, with rates ranging from 88.4% per hemipelvis to 95.6% per patient. Bilateral detection rates varied from 64% to 80%, depending on the cohort.

- Sensitivity for SLN biopsy ranged from 84.2% to 96.4%, with high negative predictive values (NPV) of up to 98.9% in some studies, indicating ICG's strong ability to exclude lymph node metastasis.
- False-negative rates were generally low, with most studies reporting figures below 3%.
- Comparison with Systematic Lymphadenectomy (LND):
- Menezes JN et al (2024) demonstrated that while the SLN mapping group had significantly higher rates of minimally invasive surgeries (84.3% vs. 2.9%, $p<0.001$), the rate of positive lymph nodes was similar between SLN (13.1%) and LND (16.3%) groups ($p = 0.18$). Importantly, isolated para-aortic metastasis was significantly lower in the SLN group (0.5% vs. 3.3%, $p = 0.004$).
- Huang L et al (2024) found a low SLN positivity rate of 5.6% in stage IA grade 1/2 endometrioid EC, suggesting that SLN biopsy could be omitted in low-risk cases.

2. Diagnostic Accuracy:
- Several studies highlighted the high diagnostic accuracy of SLN mapping using ICG. The sensitivity for detecting metastasis ranged from 90% to 95%, with some studies achieving 100% negative predictive value for low- and intermediate-risk tumors.

3. Clinical Outcomes and Procedure Efficiency:
- SLN biopsy significantly reduced operative time (median 17 minutes compared to 40 to 70 minutes for full lymphadenectomy) and had no direct complications, as shown in Khemworapong K et al (2024).
- In Gedgaudaite M et al (2022), even in low-experience centers, SLN mapping with ICG proved feasible, with increasing detection rates over time and minimal complications.

4. Technical Comparisons:
- Restaino S et al (2022) compared two near-infrared (NIR) camera systems for SLN mapping. Th[redacted]tem showed slightly higher bilateral detection rates (85.1% vs. 75.7%), although the difference was not statistically significant.

Safety

Laparoscopic SLN ICG mapping is well-regulated across major jurisdictions, with approval from the Malaysia Medical Device Authority, the US FDA, and the European Medicines Agency. Clinical studies consistently show that ICG mapping is safe, with minimal adverse reactions. A large cohort study reported no severe allergic reactions to ICG, while another found no incidents of anaphylaxis. In patients with iodinated contrast allergies, pre-surgical dexamethasone prevented allergic reactions, and no adverse events were observed. Predictive factors for SLN mapping failure include low ICG dose, advanced cancer stage, and enlarged lymph nodes. However, body mass index (BMI) and prior surgeries were not significant factors. Studies on survival outcomes indicate that SLN mapping is not inferior to full lymphadenectomy, with no significant differences in survival or chemotherapy/radiotherapy rates, but the latter was higher in the lymphadenectomy group.

Organisational

International guidelines agree on the efficacy of laparoscopic ICG sentinel lymph node (SLN) mapping for low to intermediate-risk endometrial cancer, but variations exist for high-risk cases. Essential organisational challenges include the need for specialised training, near-infrared imaging, and pathology support. Studies on learning curves show that achieving

proficiency in SLN mapping requires a significant case volume, with surgeons needing around 30 cases to reach competence in bilateral mapping, emphasizing the importance of structured training and regular quality assessments to ensure effective adoption and practice.

Economic implication

Three economic evaluations were identified: two cost-effectiveness studies and one cost-analysis. Burg LC et al (2024) demonstrated that SLN mapping using ICG and near-infrared imaging was both more effective and less costly than routine lymphadenectomy in high-risk EC, yielding higher QALYs and lower costs due to reduced complications like lymphoedema. A prior study by the same authors (2021) found SLN mapping to be the most cost-effective strategy for low- and intermediate-risk EC, outperforming both post-operative risk factor assessment and full lymphadenectomy, with robust findings confirmed through sensitivity analyses. Dioun S et al (2021) conducted a retrospective cost analysis in the U.S., showing that SLN mapping and lymphadenectomy incurred higher hospital costs than no nodal evaluation, though SLN mapping offered a less invasive alternative with comparable short-term outcomes.

Conclusion

There were high certainty evidences on laparoscopic ICG SLN mapping which demonstrates its high efficacy in the staging of endometrial cancer. The technique has shown good sensitivity and precision in identifying SLNs, comparable or even superior detection rates compared to conventional methods.

Laparoscopic sentinel lymph node mapping with ICG has better outcomes in terms of morbidity and comparable outcomes in terms of mortality compared to conventional lymphadenectomy in endometrial cancer. No severe allergic reactions or anaphylaxis, no impact on survival or long-term complications were reported. Successful implementation of laparoscopic ICG SLN mapping requires surgeon training and access to near-infrared imaging.

Economic evaluations from high-income country showed that SLN mapping using ICG is a cost-effective alternative to full lymph node dissection in endometrial cancer. Despite higher upfront procedural costs in some settings, long-term models demonstrated lower overall costs and improved outcomes, particularly in high-risk cases, due to reduced complications such as lymphoedema.

Methods

A comprehensive search was conducted on the following databases without any restriction on publication language and publication status. The Ovid interface: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to April 18, 2025>. Searches were also run in PubMed and Embase. Google was used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 24 April 2025.

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ABBREVIATION

AEs	Adverse events or adverse effects
AEH	Endometrial hyperplasia
BMI	Body mass index
CASP	Critical Appraisal Skills Programme
CEA	Cost effectiveness analysis
CI	Cervical injection
CI	Confident interval
EEAC	Endometrial Endometrioid Adenocarcinoma
EC	Endometrial cancer
EEC	Endometrioid carcinoma
EMCA	Endometrial cancer
ESGO	European Society of Gynaecological Oncology
ESTRO	European Society for Radiotherapy and Oncology
ESP	European Society of Pathology
FIGO	International Federation of Gynecology and Obstetrics
FN	False negative
FNR	False negative rate
ICER	Incremental Cost-Effectiveness Ratio
ICG	Indocyanine Green
I^2	Inconsistency
LND	Lymphadenectomy
LS	Laparoscopic surgery
LVSI	Lymphovascular space invasion
MaHTAS	Malaysian Health Technology Assessment Section
MB	Methylene blue
MOH	Ministry of Health
NCNN	National Comprehensive Cancer Network
NIR	Near-infrared
NPV	Negative predictive value
NRCT	Non-randomised controlled trial
PLND	Pelvic lymphadenectomy
PALND	Para-aortic lymphadenectomy
POLEmut	Polymerase-mutated
QALYs	Quality-adjusted Life-Years
RCT	Randomised controlled trial
RM	Ringgit Malaysia
RoB	Cochrane Risk of Bias Tool
SGO	Society of Gynecologic Oncology
SLNB	Sentinel lymph node biopsy
SLN	Sentinel lymph node
Tc99m	Technetium-99m
US FDA	United States Food and Drug Administration
WHO	World Health Organization
AEs	Adverse events or adverse effects

1.0 BACKGROUND

Endometrial cancer (EC) is the most common gynaecologic cancer in developed nations with reported 420,368 new cases worldwide in 2022 and resulting in 97,723 deaths that year. It is the fourth most commonly diagnosed cancer in women, with an estimated 66,880 new cases and 13,240 deaths in the US in 2024. It is also one of the few cancers with expected increases in incidence and mortality, which are expected to increase by 50% and 70%, respectively, by 2045. [1,2,3,4] In 2020, the World Health Organization (WHO) reported Malaysia as one of the top 10 countries with the highest endometrial cancer incidence and mortality. In line with the WHO reports, the Malaysian National Cancer Registry report confirmed that Malaysian uterine cancer patients had an age standard incident rate (ASR) of 4.6 in 100,000 population. [5]

The endometrium is the inner uterine layer composed of gland and stroma cells, which take place in the menstrual cycle and host the embryo during pregnancy. In endometrial malignancies, cancerous cells originating from the endometrium glands in the inner uterine lining, grow uncontrollably in the female reproductive organ. This malignancy is one of the most recurrent among the uterine cancer. Endometrial cancer is a disease that occurs primarily in postmenopausal women, with 75–80% of women being postmenopausal at the time of diagnosis. The average menopausal age for the Malaysian population is around 51 years old. The Malaysian National Cancer Registry reported that the majority of women with uterine malignancy are between the ages of 55 and 64 years. The incidence of endometrial cancer in the premenopausal group is between 14% and 20%. It is relatively uncommon (5%) in a patient younger than 40 years old. [5,6]

The 2023 International Federation of Gynecology and Obstetrics (FIGO) staging system (refer Table 1) incorporates refined criteria for nodal involvement, distinguishing between macrometastases, micrometastases, and isolated tumour cells. The standard treatment for early-stage endometrial cancer (EC) typically includes total hysterectomy with bilateral salpingo-oophorectomy and pelvic or para-aortic lymphadenectomy. Currently, the patients with high-risk (not comply with any of the following: (1) well-differentiated or moderately differentiated, pathological grade G1 or G2; (2) myometrial invasion below 1/2; (3) tumour diameter < 2 cm are commonly recommended for a systematic lymphadenectomy (LND) (refer Table 3 for risk classification). However, routine lymphadenectomy is controversial due to associated risks such as vascular and nerve injuries, lymphoedema, and lymphocyst formation especially in obese patients or those with comorbidities, where extended surgery increases perioperative morbidity and recovery time. Sentinel lymph node biopsy (SLNB) has emerged as a minimally invasive alternative that detects lymph node metastases while reducing surgical morbidity. This technique identifies and removes the sentinel lymph node, the first node to receive drainage from the primary tumor and enabling accurate cancer staging. For SLNB to effectively replace traditional LND, it must achieve high bilateral detection rates and minimise false negatives. Hence, this Technology review (TR) was requested by a Consultant Gynecologic Oncologist from Sabah Women and Children Hospital, Ministry of Health (MOH) to review the best current scientific evidence on efficacy, safety and cost-effectiveness of laparoscopic indocyanine green sentinel lymph node mapping in endometrial cancer.

Table 1: 2023 FIGO staging of cancer of the endometrium. [a,b. 17]

Stage	Description	Substage
Stage I	Confined to the uterine corpus and ovary [c]	
IA	Disease limited to the endometrium or non-aggressive histological type, i.e. low-grade endometrioid, with invasion of less than half of myometrium, no or focal LVSI, or good prognosis disease.	IA1: Non-aggressive histological type limited to an endometrial polyp or confined to the endometrium. IA2: Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI. IA3: Low-grade endometrioid carcinomas limited to the uterus and ovary. [c]
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI. [d]	
IC	Aggressive histological types [e] limited to a polyp or confined to the endometrium.	
Stage II	Invasion of cervical stroma without extrauterine extension or with substantial LVSI or aggressive histological types with myometrial invasion.	
IIA	Invasion of cervical stroma of non-aggressive histological types.	
IIB	Substantial LVSI [d] of non-aggressive histological types.	
IIC	Aggressive histological types [e] with any myometrial involvement.	
Stage III	Local and/or regional spread of the tumor of any histological subtype.	
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis.	
IIIA1	Spread to ovary or fallopian tube (except when meeting Stage IA3 criteria). [c]	
IIIA2	Involvement of uterine subserosa or spread through the uterine serosa.	
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum.	IIIB1: Metastasis or direct spread to the vagina and/or the parametria. IIIB2: Metastasis to the pelvic peritoneum.
IIIC	Metastasis to pelvic or para-aortic lymph nodes or both. [f]	IIIC1: Metastasis to pelvic lymph nodes. IIIC1i: Micrometastasis. IIIC1ii: Macrometastasis. IIIC2: Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to pelvic lymph nodes.
		IIIC2i: Micrometastasis. IIIC2ii: Macrometastasis.
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distant metastasis.	
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa.	
IVB	Abdominal peritoneal metastasis beyond the pelvis.	
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone.	

Abreviation: EEC, endometrioid carcinoma

[a] Endometrial cancer is surgically staged and pathologically examined. In all stages, the grade of the lesion, the histological type and LVSI must be recorded. If available and feasible, molecular classification testing (*POLEmut*,

MMRd, NSMP, p53abn) is encouraged in all patients with endometrial cancer for prognostic risk-group stratification and as factors that might influence adjuvant and systemic treatment decisions (Table 2).

[b] In early endometrial cancer, the standard surgery is a total hysterectomy with bilateral salpingooophorectomy via a minimally invasive laparoscopic approach. Staging procedures include infracolic omentectomy in specific histological subtypes, such as serous and undifferentiated endometrial carcinoma, as well as carcinosarcoma, due to the high risk of microscopic omental metastases. Lymph node staging should be performed in patients with intermediate-high/ high-risk patients. Sentinel lymp node (SLN) biopsy is an adequate alternative to systematic lymphadenectomy for staging proposes. SLN biopsy can also be considered in low−/low-intermediate- risk patients to rule out occult lymph node metastases and to identify disease truly confined to the uterus. Thus, the ESGO-ESTRO-ESP guidelines allow an approach of SLN in all patients with endometrial carcinoma, which is endorsed by FIGO. In assumed early endometrial cancer, an SLN biopsy in an adequate alternative to systematic lymphadenectomy in high-intermediate and high-risk cases for the purpose of lymph node staging andcan also be considered in low–/ intermediate-risk disease to rule out occult lymph node metastases. An SLN biopsy should be done in association with thorough (ultrastaging) staging as it will increase the detection of low-volume disease in lymph nodes.

[c] Low-grade EECs involving both the endometrium and the ovary are considered to have a good prognosis, and no adjuvant treatment is recommended if all the below criteria are met. Disease limited to low-grade endometrioid carcinomas involving the endometrium and ovaries (Stage
IA3) must be distinguished from extensive spread of the endometrial carcinoma to the ovary (Stage IIIA1), by the following criteria: (1) no more than superficial myometrial invasion is present (<50%); (2) absence of extensive/substantial LVSI; (3) absence of additional metastases; and (4) the ovarian tumor is unilateral, limited to the ovary, without capsule invasion/rupture (equivalent to pT1a).

[d] LVSI as defined in WHO 2021: extensive/substantial, ≥5 vessels involved.

[e] Grade and histological type.

• Serous adenocarcinomas, clear cell adenocarcinomas, mesonephric-like carcinomas, gastrointestinal-type mucinous endometrial carcinoma, undifferentiated carcinomas, and carcinosarcomas are considered high-grade by definition. For EECs, grade is based on the proportion of solid areas: low grade = grade 1 (≤5%) and grade 2 (6% 50%); and high grade = grade 3 (>50%). Nuclear atypia excessive for the grade raises the grade of a grade 1 or 2 tumor by one. The presence of unusual nuclear atypia in an architecturally low-grade tumor should prompt the evaluation of p53 and consideration of serous carcinoma. Adenocarcinomas with squamous differentiation are graded according to the microscopic features of the glandular component.

• Non-aggressive histological types are composed of low-grade (grade 1 and 2) EECs. Aggressive histological types are composed of high-grade EECs (grade 3), serous, clear cell, undifferentiated, mixed, mesonephric-like, gastrointestinal mucinous type carcinomas, and carcinosarcomas.

• It should be noted that high-grade EECs (grade 3) are a prognostically, clinically, and molecularly heterogenous disease, and the tumor type that benefits most from applying molecular classification for improved prognostication and for treatment decision-making. Without molecular classification, high-grade EECs cannot appropriately be allocated to a risk group and thus molecular profiling is particularly recommended in these patients. For practical purposes and to avoid undertreatment of patients, if the molecular classification is unknown, high-grade EECs were grouped together with the aggressive histological types in the actual FIGO classification.

[f] Micrometastases are considered to be metastatic involvement (pN1 (mi)). The prognostic significance of isolated tumor cells (ITCs) is unclear. The presence of ITCs should be documented and is regarded as pN0(i+). According to TNM8, macrometastases are >2 mm in size, micrometastases are 0.2‑2 mm and/or >200 cells, and isolated tumor cells are ≥0.2 mm and ≤200 cells.33Based on staging established by FIGO and the American Joint Committee on Cancer (AJCC). *AJCC Cancer Staging Manual*. 8th ed. New York: Springer, 2017.

Table 2: FIGO endometrial cancer stage with molecular classification. [a. 17]

Stage Designation	**Molecular Findings in Patients with Early Endometrial Cancer (Stages I and II after Surgical Staging)**
Stage IAm $_{POLEmut}$	**POLEmut** endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type.
Stage IICm $_{p53abn}$	**p53abn** endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type.

[a] When feasible, the addition of molecular subtype to the staging criteria allows a better prediction of prognosis in a staging/prognosis scheme. The performance of complete molecular classification (*POLEmut*, MMRd, NSMP, p53abn) is encouraged in all cases of endometrial cancer for prognostic risk-group stratification and as potential influencing factors of adjuvant or systemic treatment decisions. Molecular subtype assignment can be done on a biopsy, in which case it need not be repeated on the hysterectomy specimen. When performed, these molecular classifications should be recorded in all stages.

• Good prognosis: pathogenic *POLE* mutation (*POLEmut*)

• Intermediate prognosis: mismatch repair deficiency (MMRd)/microsatellite instability and no specific molecular profile (NSMP)

• Poor prognosis: p53 abnormal (p53abn)When the molecular classification is known:

• FIGO Stages I and II are based on surgical/anatomical and histological findings. In case the molecular classification reveals *POLEmut* or p53abn status, the FIGO stage is modified in the early stage of the disease. This

is depicted in the FIGO stage by the addition of “m” for molecular classification, and a subscript is added to denote *POLEmut* or p53abn status, as shown below. MMRd or NSMP status do not modify early FIGO stages; however, these molecular classifications should be recorded for the purpose of data collection. When molecular classification reveals MMRd or NSMP, it should be recorded as Stage ImMMRd or Stage ImNSMP and Stage IImMMRd or Stage IImNSMP.

• FIGO Stages III and IV are based on surgical/anatomical findings. The stage category is not modified by molecular classification; however, the molecular classification should be recorded if known. When the molecular classification is known, it should be recorded as Stage IIIm or Stage IVm with the appropriate subscript for the purpose of data collection.

Table 3: Risk classification based on ESGO/ESTRO/ESP guidelines. [18]

Risk Group	Molecular Classification Unknown	Molecular Classification Known*†
Low	► Stage IA endometrioid + low-grade‡ + LVSI negative or focal	► Stage I–II **POLEmut** endometrioid carcinoma, no residual disease ► Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal
Intermediate	► Stage IB endometrioid + low-grade‡ + LVSI negative or focal ► Stage IA endometrioid + high-grade‡ + LVSI negative or focal ► Stage IA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion	► Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal ► Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade‡ + LVSI negative or focal ► Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High–Intermediate	► Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ► Stage IB endometrioid high-grade‡ regardless of LVSI status ► Stage II	► Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion ► Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade‡ regardless of LVSI status ► Stage II **MMRd/NSMP** endometrioid carcinoma
High	► Stage III–IVA with no residual disease ► Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	► Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ► Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease ► Stage I–IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced Metastatic	► Stage III–IVA with residual disease ► Stage IVB	► Stage III–IVA with residual disease of any molecular type ► Stage IVB of any molecular type

Abbreviations**:** LVSI, lymphovascular space invasion; MMRd, mismatch repair deficient; NSMP, non-specific molecular profile; p53abn, p53 abnormal; POLEmut, polymerase-mutated.

* For stage III–IVA **POLEmut** endometrioid carcinoma and stage I–IVA **MMRd** or **NSMP** clear cell carcinoma with myometrial invasion, insufficient data are available to allocate these patients to a prognostic risk group in the molecular classification. Prospective registries are recommended. † See text on how to assign double classifiers (e.g., patients with both **POLEmut** and **p53abn** should be managed as **POLEmut**). ‡ According to the binary FIGO grading, grade 1 and grade 2 carcinomas are considered as low-grade and grade 3 carcinomas are considered as high-grade.

2.0 OBJECTIVE / AIM

The objective of this systematic review was to assess the effectiveness/efficacy, safety, and cost-effectiveness of laparoscopic indocyanine green sentinel lymph node mapping in endometrial cancer.

3.0 TECHNICAL FEATURE

Surgical approach

Lymph node assessment is a key component of the surgical management of endometrial cancer (EC), which also includes total hysterectomy (TH) and bilateral salpingo-oophorectomy (BSO). Surgery is vital for staging, prognosis, and guiding adjuvant therapy. There are two main surgical approaches: [10]

- Laparotomy (open surgery)
- Minimally invasive surgery (MIS), including laparoscopic (LS) and robot-assisted surgery (RS)

Indocyanine green SLN mapping is performed as part of a surgical procedure utilising minimally invasive approaches, specifically laparoscopic surgery (LS) and robot-assisted surgery (RS). This technique is integrated as the lymph node assessment component within these MIS procedure. [10]

Sentinel Lymph Nodes

Sentinel lymph nodes refer to the first group of lymph nodes that drain the primary tumour lymph, which is the first area involved when the tumour metastasis occurs, reflecting the state of lymph node involvement in the entire region.

Sentinel lymph node (SLN) mapping is a surgical technique used to identify the first lymph node(s) that receives lymphatic drainage from a primary tumour. By injecting a tracer near the tumour, surgeons can trace the lymphatic pathway to locate and remove the SLN for pathological examination. If the SLN is free of cancer, it is highly likely that the remaining lymph nodes are also negative, due to the high negative predictive value of this method. The effectiveness of SLN mapping is assessed by its detection rate, sensitivity, and false negative rate—since false negatives can lead to underdiagnosis and missed opportunities for necessary adjuvant therapy. [13]

SLN mapping plays a key role in evaluating whether the tumour has spread to the lymphatic system. A negative SLN indicates no lymphatic metastasis, while a positive SLN confirms nodal involvement. The pathological findings from the SLN provide crucial prognostic information and help guide decisions about the need for additional postoperative treatment.[11,13]

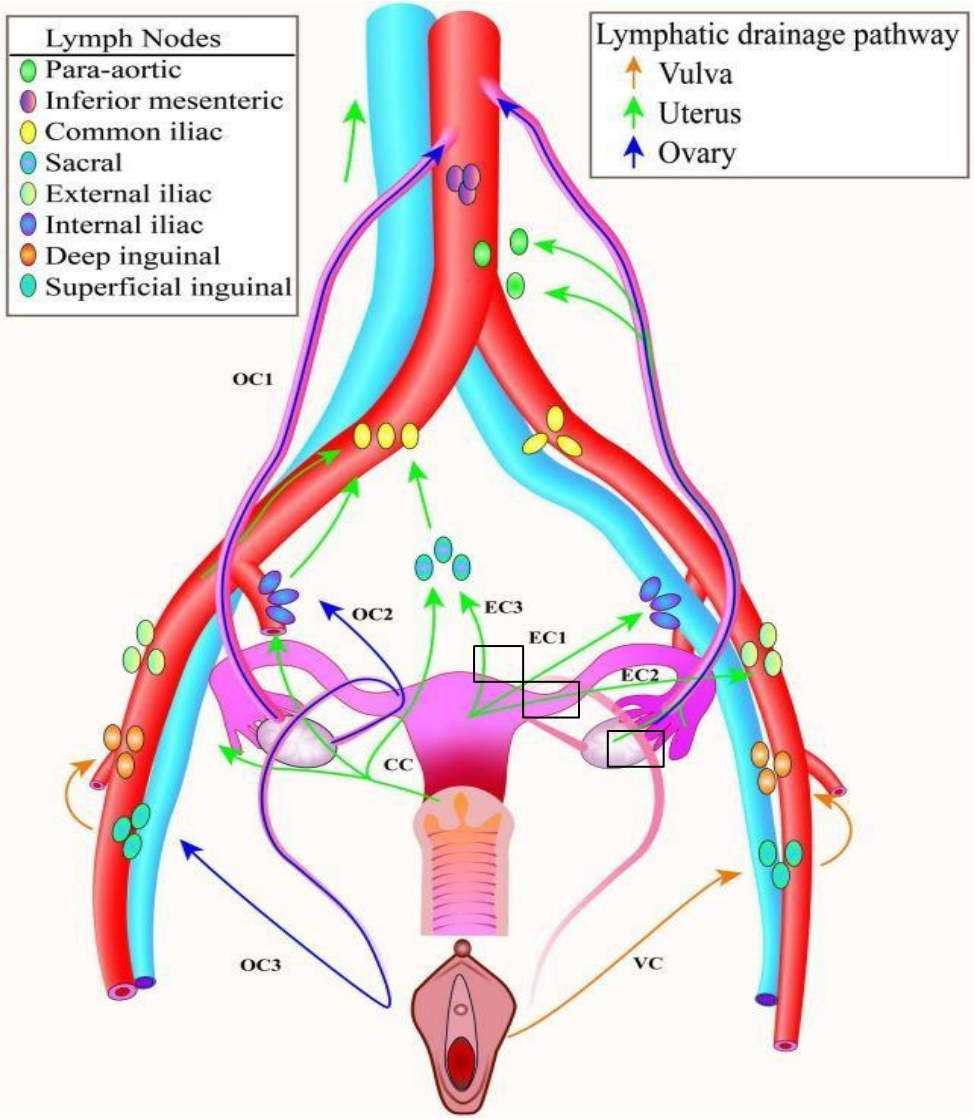

Figure 1: Pelvic lymphatic drainage. The common lymphatic drainage pathways of the ovary, the uterus, the cervix, the vagina and the vulva. To facilitate display, only one side lymphatic drainage route was drawn for each tumor. CC, cervical cancer; EC, endometrial cancer; OC, ovarian cancer; VC, vulva cancer. [11]

Sentinel Lymph Node Mapping Technique

Detection rate is influenced by tracer type, injection site, surgeon's experience, and patient factors. For site of injection, cervical injection (CI) is the most favoured technique, typically at the 3 and 9 o'clock positions. Hysteroscopic injection (HI) near the tumour or subserosal injection at the uterine fundus may offer higher para-aortic detection rates.

Choice of Dye: Indocyanine green (ICG) is claimed as currently preferred over blue dyes and technetium-99 m (Tc-99 m) due to its higher detection rate, low toxicity, and low cost, particularly in obese women and during minimally invasive surgery

Failed Mapping: Mapping failure can occur due to operator experience, enlarged nodes, obesity, extrauterine disease, or tracer issues. Strategies include side-specific complete pelvic LND (following the Memorial Sloan Kettering algorithm), tracer

reinjection, or intraoperative frozen section analysis. Operator experience is claimed to significantly improves detection rates. [10]

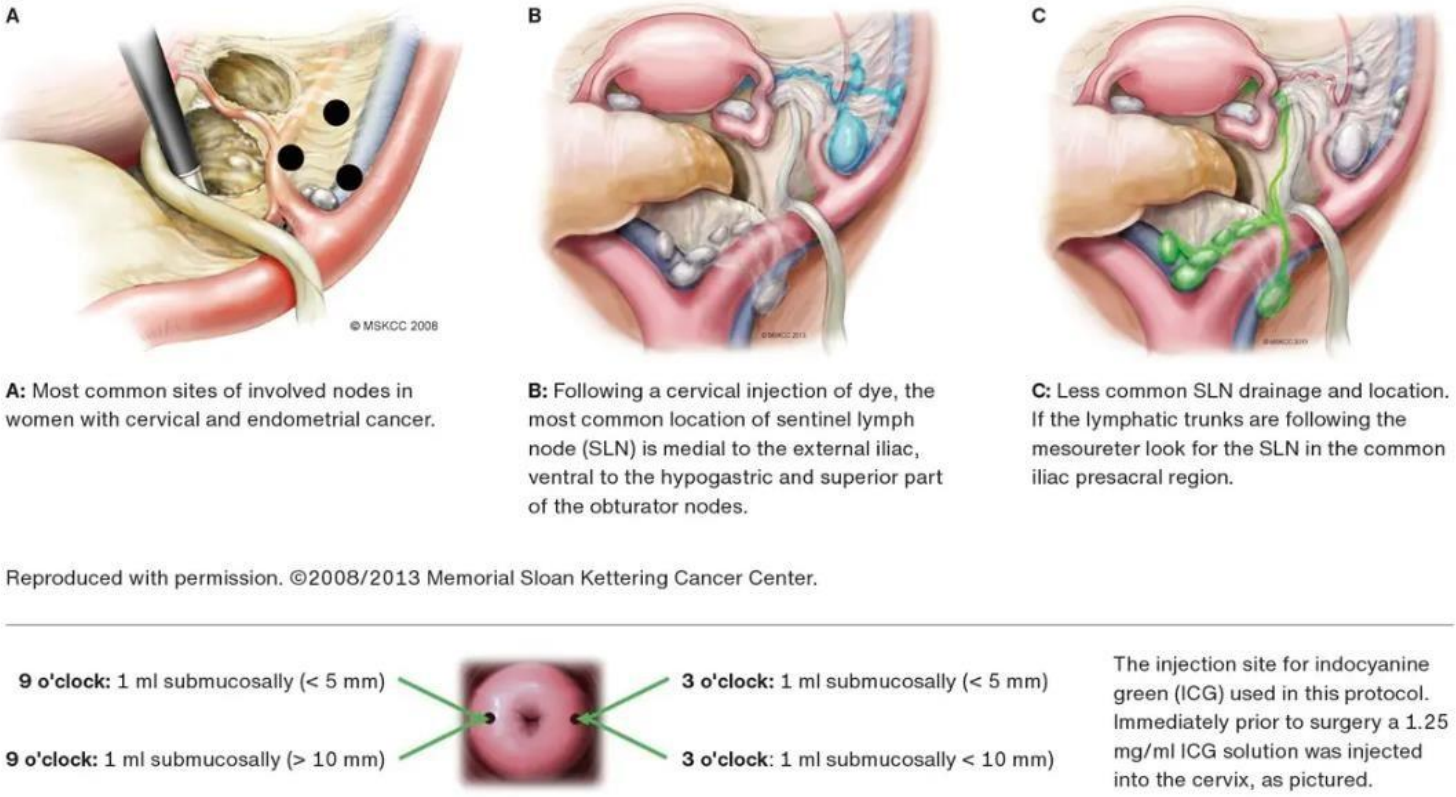

Figure 2: Example of sentinel lymph node mapping. [12]

Indocyanine Green (ICG)

Currently, three primary methods are used for SLN detection: (1) radioisotopic tracers like technetium-99m (Tc99m), (2) dyes such as Patent Blue, and (3) fluorescent optical tracers like indocyanine green (ICG). Among dyes, indocyanine green (ICG) is widely favored due to its high sensitivity and near-infrared fluorescence. However, potential allergic reactions and lymphatic oedema must be considered in its use.[7,8,9] Sentinel lymph node (SLN) mapping may also improves staging accuracy, helping guide adjuvant therapy and enhance patient outcomes. Indocyanine green (ICG) is a water-soluble dye that emits fluorescence in the near-infrared (NIR) light range. Although commonly used in vascular and hepatobiliary imaging, its application in lymphatic mapping remains off-label. To detect the ICG signal, NIR imaging equipment is required, which is widely available across laparotomic, laparoscopic, and robotic surgical platforms. ICG offers advantages such as rapid penetration of both superficial and deep tissues and real-time visualisation following injection. However, it is excreted entirely through the liver and should not be used in patients with liver failure or iodine allergy. [10]

According to Society of Gynecologic Oncology (SGO) guideline, indocyanine green (ICG) is prepared by diluting it to a concentration of 0.5 to1.25 mg/mL in sterile water, followed by an injection of 2 to 4 mL. [14]

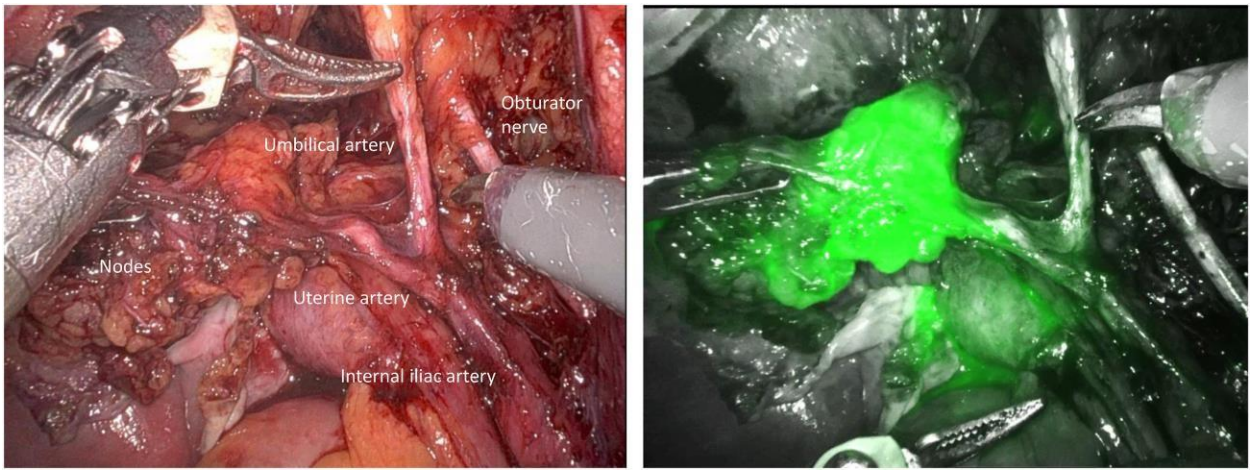

Figure 3: Example of uterus with right mesometrium along the uterine artery and medial external lymph node region with normal light on the left and following ICG labeling of the lymphatic system following corporal injection (infrared light) on the right. [15]

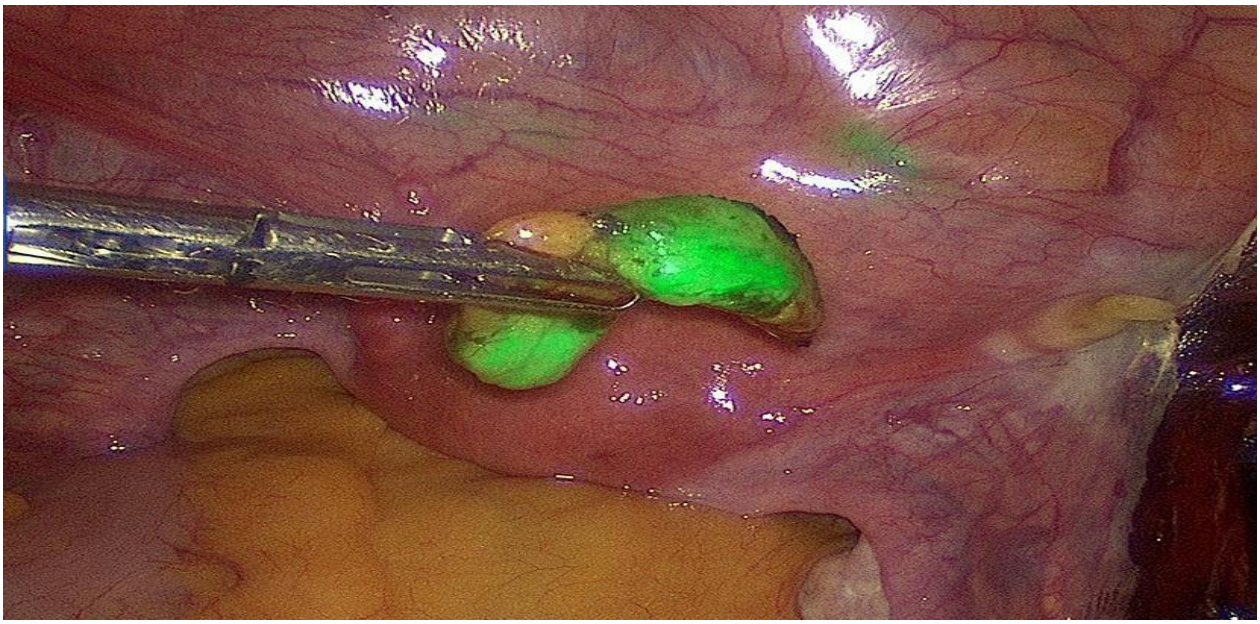

Figure 4: SLN mapped with ICG tracer and visualized with 4K, 3D and fluorescence imaging technologies (NIR/ICG) IMAGE1 S™ RUBINA™ system. [16]

4.0 METHODS

A systematic review was conducted. Search strategy was developed by the main author and an *Information Specialist*.

4.1 SEARCHING

The following electronic databases were searched through the Ovid interface:

- MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to April 18, 2025> HTA Full-Text Journals

Other databases: PubMed, Embase, INAHTA
Other website: USFDA, MDA

General databases such as Google were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles. **Appendix 1** showed the detailed search strategies. The last search was conducted on 24th April 2025.

4.2 SELECTION

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria. Relevant articles were then critically appraised depending on the type of the study design. Studies were graded according to *US/ Canadian Preventive Services Task Force* (**Appendix 2**). All data were extracted and summarised in evidence table as in **Appendix 3**.

The inclusion and exclusion criteria were:
Inclusion criteria:

a.	**Population**	Patients with endometrial cancer
b.	**Intervention**	Laparoscopic indocyanine green (ICG) sentinel lymph node mapping
c.	**Comparator**	Standard lymphadenectomy, conventional or systematic lymphadenectomy
d.	**Outcomes**	Detection rate, accuracy, and clinical effectiveness in identifying metastatic disease Safety: Adverse events (AEs) related to treatment, false negative, false positive detection rate Organisational issues: procedural time, training or learning curve, surgeon experience Economic implications: Cost, cost-effectiveness, cost-utility analysis
e.	**Study design**	HTA reports, systematic review with/out meta-analysis, randomised controlled trial (RCT), cohort, diagnostic, case-control, cross-sectional and economic evaluation studies
f.	Full text articles published in English	
g.	2020 to 2025	

Exclusion criteria:

a.	**Study design**	Case report, case series, animal study, laboratory study, narrative review
b.	Non-English full text articles	

5.0 RESULTS

Search results

An overview of the search is illustrated in Figure 5. A total of 1219 records were identified through the Ovid interface, PubMed and Embase, International HTA Database (INAHTA) and other method. Sixty-three duplicate references were found. After removal of duplicate articles, 1156 titles were screened using the inclusion and exclusion criteria. Of these, 447 potentially relevant abstracts were screened, and 85 articles were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the 85 successfully retrieved full text articles, 23 were included. Fourteen articles were excluded as those primary studies were already included in systematic review (n=14), fifteen articles irrelevant study design (n=15), eleven articles irrelevant population (n=11) and 22 articles found as irrelevant intervention (n=22). All full text articles finally selected for this review comprised of four systematic review and meta-analysis, two systematic reviews, one randomised controlled trial,13 observational cohort studies, two cost-effectiveness analysis and one cost-analysis study.

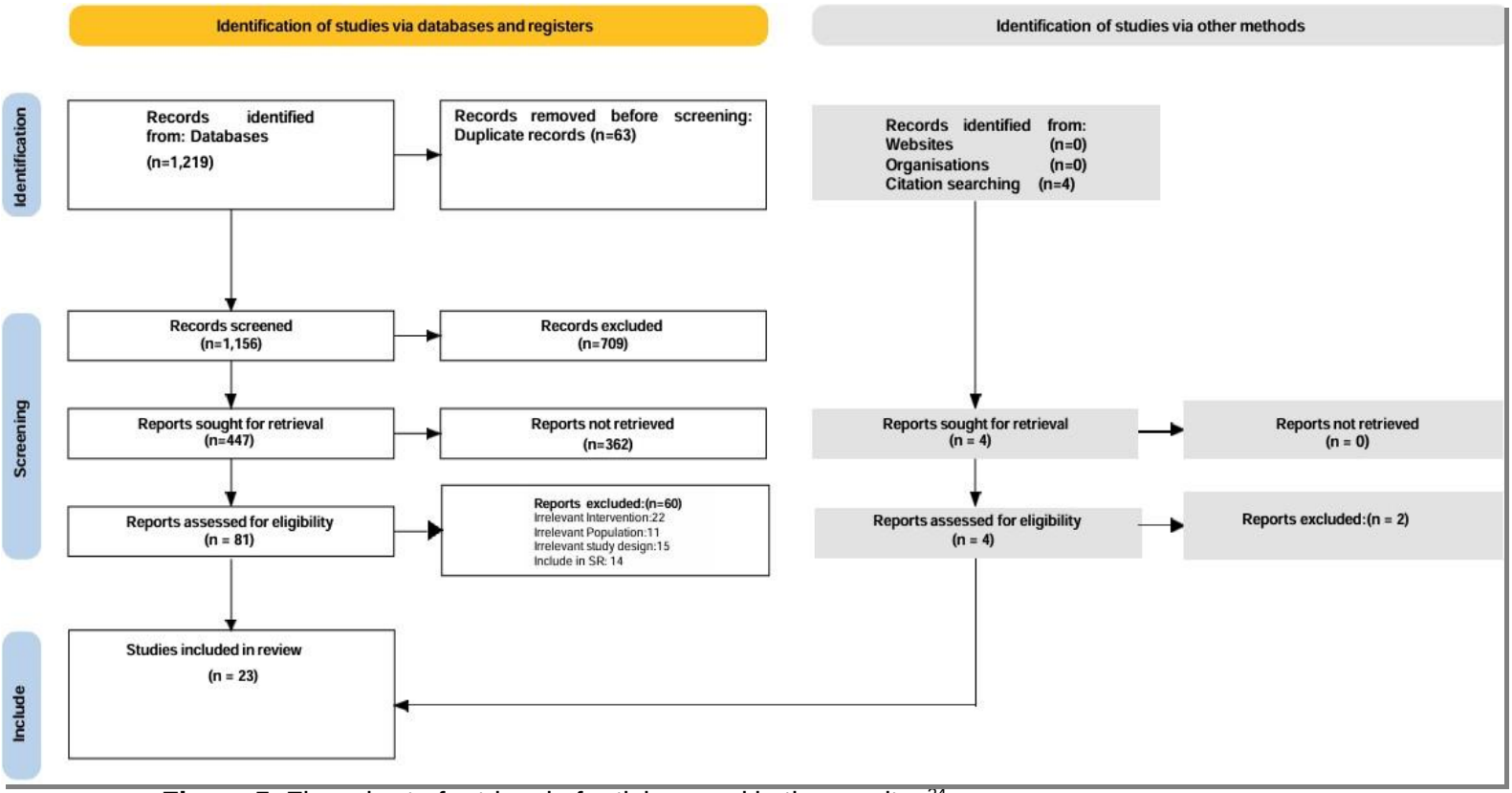

Figure 5: Flow chart of retrieval of articles used in the results. [24]

Quality assessment of the studies

The risk of bias or quality assessment (methodology quality) of all retrieved literatures was assessed depending on the type of the study design. These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias: using the relevant checklist of National

Collaborating Centre for Methods and Tools (ROBIS) for systematic review and meta-analysis [25], The Risk Of Bias In Non-randomized Studies – of Interventions, Version 2 (ROBINS-I V2) for non-randomised interventional study [26], version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) [27] and Critical Appraisal Skill Programme (CASP) checklist for observational cohort study [28]. All full text articles were graded based on guidelines from the *U.S. / Canadian Preventive Services Task Force*.[29]

Risk of bias assessment for included systematic review and meta-analysis

Six systematic reviews were included in this assessment and were judged to have an overall low risk of bias following uncertainty in the data collection or risk of bias assessment process. All the studies had pre-specified their clinical questions and inclusion criteria for study eligibility. The method used to identify and select the studies was clearly described. All studies provided the search terms, and the full search strategy used. The inclusion assessment, appraisal and data collection process were reported to have been conducted independently by at least two reviewers in most of the studies. The quantitative synthesis (meta-analysis) undertaken was considered appropriate. Statistical heterogeneity was addressed accordingly. Sensitivity analyses were used to assess the robustness the findings (Figure 6.1)

Authors	**Risk of bias domains**				
	1-STUDY ELIGIBILITY CRITERIA	**2-IDENTIFICATION AND SELECTION OF STUDIES**	**3-DATA COLLECTION AND STUDY APPRAISAL**	**4-SYNTHESIS AND FINDINGS**	**OVERALL RISK OF BIAS IN THE REVIEW**
Raffone A et al. 2022. [30], level II-2	☺	☺	☺	☺	☺
Burg LC et al. 2022 [31],level I	☺	☺	☺	☺	☺
Nagar H et al. 2021 [33], level I	☺	☺	☺	☺	☺
Marchocki Z et al. 2021 [34], level II-2	☺	☺	☺	☺	☺
Yao H et al. 2023 [32], level II-3	☺	☺	☺	☺	☺
Raffone A et al. 2023 [48], level II-2	☺	☺	☺	☺	☺

☺ low risk; ☹ high risk ? unclear risk

Figure 6.1: Risk of bias assessment for systematic review and meta-analysis using ROBIS

Risk of bias assessment for included non-RCT using ROB

One study was included in this assessment and summarised in Figure 6.2. The overall judgement for this study is serious risk of bias due to non-random allocation of patients based on pre-operative risk, protocol deviations where planned lymphadenectomy was abandoned for some patients who were re-assigned in analysis, and the absence of ultra-staging for lymph node evaluation, which undermines the accuracy of sensitivity and NPV calculations. These issues raise significant concerns about confounding, protocol adherence, and outcome measurement, compromising the reliability of the findings. [37 level II-1]

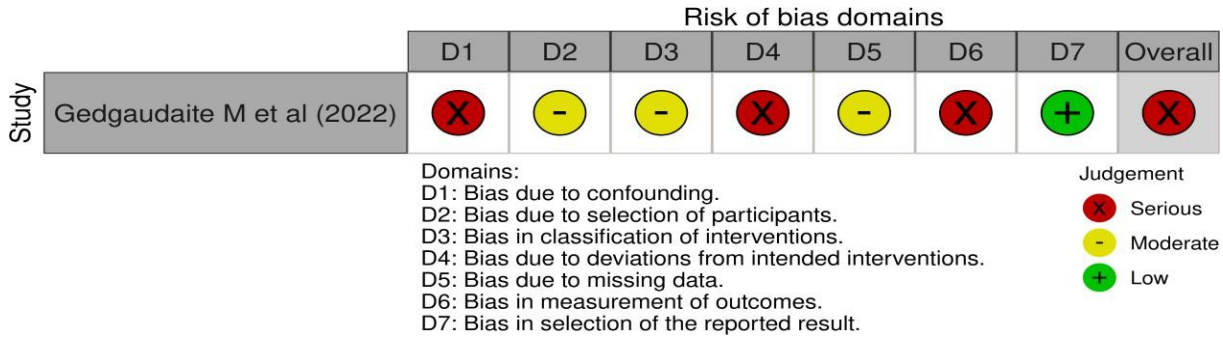

Figure 6.2: Risk of bias assessment for non-randomised study using ROBINS-I V2.

Risk of bias assessment for included RCT using Cochrane Risk of Bias (RoB 2.0)

One study was rated to have an overall low risk of bias as shown in Figure 6.3. The method of randomisation was stated while random sequence generation was performed adequately. Outcomes were analysed using intention to treat analysis while selective reporting was considered to have a low risk of bias as all pre-specified outcomes were reported and analysed.

Review	**Risk of bias domains**					
	D1	**D2**	**D3**	**D4**	**D5**	**Overall**
	Bias arising from the randomisation process	**Bias due to deviations from intended intervention**	**Bias due to missing outcome data**	**Bias in measurement of the outcome**	**Bias in selection of the reported result**	
Andreika L et al. 2024 [49, level I]	☺	☺	☺	☺	☺	☺

☺ low risk; ☹ high risk ? unclear risk

Figure 6.3: Summary of risk of bias assessment for RCT using RoB 2.

Risk of bias assessment for included cohort using CASP

Based on the CASP checklist, all of the included studies had low risk of bias (Figure 6.4).

Review	Risk of bias domains					
	D1	D2	D3	D4	D5	Overall
	Selection of cohort	Exposure accurately measures	Outcome accurately measures	Confounding factors	Follow-up and timing	
Dampali R et al. 2025. [50], level II-2	☺	☺	☺	☺	?	☺
Menezes JN et al. 2024. [40], level II-2	☺	☺	☺	☺	☺	☺
Huang L et al. 2024. [41], level II-2	☺	☺	☺	☺	☺	☺
Khemworapong K et al. 2024. [36], level II-2	☺	☺	☺	☺	☺	☺
Kulhan M et al. 2023. [42], level II-2	☺	☺	☺	☺	?	☺
Restaino S et al. 2022. [39], level II-2	☺	☺	☺	☺	☺	☺
Altin D et al. 2022. [38], level II-3	☺	☺	☺	☺	?	☺
Cianci S et al. 2021. [35], level II-2	☺	☺	☺	☺	☺	☺

☺ low risk; ☹ high risk ? unclear risk

Figure 6.4: Risk of bias assessment for cohort study using CASP

Risk of bias assessment for included cost-effectiveness and cost-analysis study using CHEC-extended list.

Table 4 showed the CHEC-extended list which used to critically appraised the cost-effectiveness analysis study. Several key methodological aspects are lacking in cost analysis study (Dioun S et al. 2021) including complete cost measurement, incremental cost comparison, discounting, and sensitivity analysis. In addition, conflict-of-interest disclosure and ethical considerations are not reported, limiting transparency.

Table 4: Quality assessment of cost-effectiveness analysis studies by using CHEC-extended.

Question	Checklist	Decision		
		Burg LC et al. 2023. [53]	**Burg LC et al. 2021. [54]**	**Dioun S et al. 2021. [55]**
1	Is the study population clearly described?	Y	Y	Y
2	Are competing alternatives clearly described?	Y	Y	Y
3	Is a well-defined research question posed in answerable form?	Y	Y	Y
4	Is the economic study design appropriate to the stated objective?	Y	Y	Y
5	Are the structural assumptions and the validation methods of the model properly reported?	Y	Y	Y
6	Is the chosen time horizon appropriate in order to include relevant costs and consequences?	Y	Y	Y
7	Is the actual perspective chosen appropriate?	Y	Y	Y
8	Are all important and relevant costs for each alternative identified?	Y	Y	Y
9	Are all costs measured appropriately in physical units?	Y	Y	N
10	Are costs valued appropriately?	Y	Y	Y
11	Are all important and relevant outcomes for each alternative identified?	Y	Y	Y
12	Are all outcomes measured appropriately?	Y	Y	NA
13	Are outcomes valued appropriately?	Y	Y	NA
14	Is an appropriate incremental analysis of costs and outcomes of alternatives performed?	Y	Y	N
15	Are all future costs and outcomes discounted appropriately?	Y	Y	N
16	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Y	Y	N
17	Do the conclusions follow from the data reported?	Y	Y	Y
18	Does the study discuss the generalisability of the results to other settings and patient/client groups?	Y	Y	Y
19	Does the article/report indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Y	Y	N
20	Are ethical and distributional issues discussed appropriately?	Y	Y	N
Total Yes		20	20	12
Total No		0	0	6
Total Unclear		0	0	0
Total Percentage of Yes		**100%**	**100%**	**67%**

5.1 EFFICACY/EFFECTIVENESS

There were 13 studies on the effectiveness of laparoscopic indocyanine green sentinel lymph node mapping for endometrial cancer included in this review.

Raffone A et al. (2022) conducted a systematic review and meta-analysis to evaluate the role of SLN biopsy using ICG cervical injection in high-risk early-stage endometrial carcinoma patients. The study included peer-reviewed studies that compared the detection rate and accuracy of SLN biopsy through cervical ICG injection against systematic lymphadenectomy. The data was extracted based on the PICO framework, and sensitivity, false negative (FN) rate, and detection rates per hemipelvis (DRh), per patient (DRp), and bilateral detection (DRb) were calculated. Studies were evaluated for bias using QUADAS-2 criteria, and statistical heterogeneity was assessed using the Higgins' inconsistency index (I^2). The analysis showed pooled estimates with 95% confidence intervals, employing random effect models for data synthesis. A total of five observational cohort studies, involving 684 EC patients (84.5% with high-risk EC), were

included in the analysis. The pooled sensitivity for detecting EC metastasis was 90% (95% CI: 0.03 to 0.95; I^2: 76.6%), with a FN rate of 2.8% (95% CI: 0.6 to 11.6%; I2: 79.8%). Detection rates per hemipelvis (DRh), per patient (DRp), and bilateral detection (DRb) were 88.4% (95% CI: 86 to 90.5%), 96.6% (95% CI: 94.7 to 97.8%), and 80% (95% CI: 75.4 to 83.9%), respectively. For heterogeneity greater than 50%, the authors adopted the random effect model of DerSimonian and Laird for all analyses. This approach was used independently from the statistical heterogeneity, as recommended by the Synthesizing Evidence from Diagnostic Accuracy Tests (SEDATE) guidelines for meta-analysis of diagnostic accuracy. [30 level II-2]

A systematic review and meta-analysis by Burg LC et al. (2022) evaluated the detection rate of SLN mapping using cervical ICG in early-stage, low- and intermediate-risk EC patients and to compare its diagnostic value against systematic pelvic lymph node dissection. Random-effects meta-analysis was used to estimate the overall detection rates, bilateral and unilateral detection rates, incidence of SLN metastases, and the negative predictive value of SLN mapping. The detection rate and negative predictive value were estimated using various statistical methods, with forest plots displaying the results. The analysis included studies with all histological grades (1, 2, and 3) of EC, assuming tumour grade did not affect SLN identification. This study included 14 studies, with 13 studies were observational cohort studies and one randomised controlled trial (n=2,620 patients). The total number of 2,117 patients underwent SLN mapping with ICG via cervical injection and were analysed for SLN detection rate. A smaller subset of 1,464 patients who also had full lymph node dissection was used to assess the negative predictive value. The overall SLN detection rate was 95.6% (95% CI: 92.4% to 97.9%), with a bilateral detection rate of 76.5% (95% CI: 68.1% to 84.0%) and a unilateral detection rate of 18.2% (95% CI: 12.2% to 25.1%). The pooled incidence of SLN metastases was 9.6% (95% CI: 5.1% to 15.2%) for grade 1 and 2 tumors, and 11.8% (95% CI: 8.1% to 16.1%) for grade 1 to 3 tumors. The negative predictive value (NPV) was 100% (95% CI=98.8% to 100%) for grade 1 and 2 tumors and 99.2% (95% CI=97.9% to 99.9%) for grade 1 to 3 tumors. [31 level I]

Yao H et al. (2023) conducted a meta-analysis to evaluate the impact of SLN assessment versus full LND on the prognosis of patients with advanced endometrial cancer (FIGO stage III to IV). The study systematically searched four major databases (PubMed, Embase, Web of Science, and the Cochrane Library) up to 19th March 2022, and included high-quality, controlled studies published in English or Chinese that reported survival outcomes, lymphatic invasion, and adjuvant therapy rates. Heterogeneity was assessed with I^2 statistics, and appropriate models (fixed- or random-effects) were applied accordingly. In this meta-analysis, four retrospective cohort studies involving 7,181 patients (SLN: 492; LND: 6,689) assessed the effect of SLN assessment on overall survival in advanced EC. The findings revealed no statistically significant difference in overall survival between the SLN and LND groups (OR = 1.14, 95% CI: 0.92 to 1.41; I^2 = 0%; p = 0.39), and subgroup analysis for three year and five-year survival rates also showed comparable results. Additionally, regarding lymphovascular invasion, two studies involving 1,536 patients (SLN: 165; LND: 1,371) reported no significant difference between the groups (OR = 1.26, 95% CI: 0.85 to 1.86; p = 0 .25; I^2 = 0%). For chemotherapy rates, three studies (n = 7,099; SLN: 452; LND: 6,647) showed no significant difference (p = 0.42), though high heterogeneity (I^2 = 81%) warranted descriptive analysis. For radiotherapy, three studies (same sample) initially showed high heterogeneity (I^2 = 82%, p = 0.004), but after

removing one outlier study, pooled data from two homogeneous studies (I^2 = 0%, p = 0.76) reported significantly higher radiotherapy rates in the LND group (OR = 2.15, 95% CI: 1.47to 3.14; p = 0.0001). [32 level II-3]

A Cochrane systematic review conducted by Nagar H et al in 2021 to assess the diagnostic accuracy of SLNB, including the detection rate, for identifying pelvic lymph node involvement in women with presumed early-stage endometrial cancer prior to surgery. The secondary objectives were to compare the accuracy and detection rate based on different detection methods (like Technetium-99m, blue dye, and ICG) and different injection sites (subserosal, cervical, or combined), as well as comparing the accuracy of detection between pelvic and para-aortic lymph node basins. Studies included women who underwent SLNB with ultrastaging, followed by systematic pelvic or para-aortic lymphadenectomy, serving as the reference standard. Both prospective and retrospective diagnostic accuracy studies with ≥10 participants were eligible. Studies without full lymphadenectomy or SLN ultrastaging were excluded. A comprehensive search of MEDLINE and Embase (to July 2019) was conducted without language restrictions. The index test involved injection of tracers (blue dye, Tc-99m, ICG) into the cervix or uterus, followed by surgical SLN removal and ultrastaging. The reference standard was systematic lymphadenectomy with routine histopathology. Study quality was assessed using QUADAS-2. Pooled sensitivity was calculated using a random-effects logistic regression model. Detection rates were summarised as means. Meta-regression explored heterogeneity by FIGO stage, tracer type, injection site, and lymph node basin. Sensitivity analyses addressed verification bias and missing data. Certainty of evidence was evaluated using GRADE. This review included 33 diagnostic accuracy studies, with a total of 2237 women. The studies were conducted in inpatient hospital settings in 15 countries (Brazil, Canada, China, Czech Republic, France, Germany, Iran, Italy, Japan, Serbia, Spain, Sweden, Switzerland, Turkey, USA). Index tests varied across studies, 11 used blue dye alone, 4 used technetium-99m alone, 12 used a combination of blue dye and technetium-99m, 9 used ICG alone, 2 used ICG with blue dye, and 1 used ICG with technetium-99m. Tracer injection was cervical in 19 studies, subserosal uterine in 10, and combined in 4. Reporting of adverse events and perioperative complications was limited. In the 33 studies, ICG was used as a tracer in nine studies. The pooled sensitivity for SLNB using ICG alone was 92.5% (95% CI: 81.8% to 97.1%), with detection rates varying by tracer. Studies using ICG and technetium-99m combined had a 100% sensitivity (very low-certainty evidence). Meta-regression analyses showed no significant difference in sensitivity between ICG alone, blue dye, or technetium-99m, with p-values of 0.81 for a six-level model and 0.90 for a three-level model, indicating that tracer choice (including ICG) did not significantly affect diagnostic performance. Sensitivity rates were similar regardless of the injection site, and studies with mixed injection sites had a sensitivity of 100%, but were excluded from further analysis due to limited variance. [33 level I]

A systematic review was conducted by Marchocki Z et al (2021) to evaluate the diagnostic performance of SLNB using ICG injection in patients with clinical stage I, high-grade EC, using complete pelvic lymphadenectomy (PLND), with or without para-aortic lymphadenectomy (PALND), as the reference standard. The primary outcome was SLNB sensitivity, while secondary outcomes included patient-specific and bilateral detection rates, node positivity rate, NPV, and FNR. The study included prospective cohort studies published from 1st January 2000 to 26th January 2021, identified through systematic searches of MEDLINE, Embase, Cochrane databases, and

ClinicalTrials.gov, supplemented by manual reference checks. Eligible studies enrolled patients with high-grade EC undergoing surgical staging with SLNB and complete PLND and studies were excluded if they were retrospective, used non-cervical or non-ICG injection, lacked PLND, included only low-grade histology, or were non-English or non-original data. Study quality and applicability were assessed using the QUADAS-2 tool. Data from studies were pooled using a generalised linear mixed-effects model with a logit transformation, and heterogeneity was assessed using the I^2 statistic. Nine prospective cohort studies were included in this review with the total number of patients with high-grade EC specifically was 429. The pooled SLN detection rate was 91% per patient (95% CI: 85 to 95%; I^2 = 59%) and 64% bilaterally (95% CI: 53 to 73%; I^2 = 69%). The overall node-positivity rate was 26% per patient (95% CI: 19 to 34%; I^2 = 44%) and 20% per hemipelvis (95% CI: 16 to 26%; I^2 = 46%). The SLNB sensitivity was 92% per patient (95% CI: 84 to 96%; I^2 = 0%) and 90% per hemipelvis (95% CI: 83 to 94%; I^2 = 0%). The negative predictive value (NPV) was 97% per patient (95% CI: 95 to 99%; I^2 = 0%) and 98% per hemipelvis (95% CI: 96 to 99%; I^2 = 8%). The false negative rate was 8% per patient (95% CI: 4 to 16%; I^2 = 0%) and 10% per hemipelvis (95% CI: 6 to 17%; I^2 = 0%). [34 level II-2]

Cianci S et al (2021) conducted a multicenter retrospective cohort study across four referral cancer centers in Italy, retrieving data from May 2015 to March 2021. The study population comprised 844 patients with apparently early-stage endometrial cancer who underwent minimally invasive complete surgical staging including SLN biopsy using intracervical stromal injection of ICG. Patients were categorised into two groups based on age: under 65 years (group 1) and 65 years or older (group 2). The primary objective was to assess the overall, bilateral, and unsuccessful SLN mapping rates in these two age groups, with secondary objectives focusing on SLN anatomical distribution and identifying predictors of mapping failure. Statistical analysis involved comparing clinical, surgical, and histopathological factors between groups and using univariate and multivariate analysis as well as binomial logistic regression to determine predictors of mapping failure. Of 844 patients, 449 were in group 1 and 395 patients were in group 2. The study found that, regarding the primary endpoint, patients aged 65 and older (group 2) had significantly lower overall detection rates (87.6% vs. 93.8%, p = 0.002) and successful bilateral mapping rates (66.8% vs. 77.1%, p = 0.001), along with a significantly higher mapping failure rate (33.2% vs. 22.9%, p = 0.001) compared to the younger group (Group 1). Multivariate analysis identified age 65 years and older (OR: 1.5, p = 0.01), higher BMI (OR: 1.02, p = 0.05), non-endometrioid histotype (OR: 1.6, p = 0.02), and LVSI (OR: 1.407, p = 0.04) as independent predictors of unsuccessful mapping. There was also a reduction in "unexpected" SLN mapping sites in older women, significantly so in the left hemipelvis. While overall intraoperative complications were similar between groups, vascular lesions were more frequent and estimated blood loss was higher in the older group. The postoperative complications were significantly higher in the younger group. The study also reported a significantly higher rate of surgical under-staging and a trend toward adjuvant undertreatment in older patients, particularly in the high-risk category. [35 level II-2]

Khemworapong K et al (2024) conducted a prospective cohort study at a single centre institution, Department of Obstetrics-Gynecology, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand. This study aimed to evaluate the detection rate, sensitivity, and false-negative rate of SLN biopsy versus full lymphadenectomy in endometrial cancer patients between November 2019 and June 2023. The total number of 142 eligible

patients underwent laparoscopic or open surgery with ICG-guided SLN mapping followed by pelvic/para-aortic lymphadenectomy. The SLNs were identified using near-infrared fluorescence after cervical ICG injection and analysed through ultrastaging. Data on SLN detection, pathology, complications, and operative metrics were statistically evaluated to determine the diagnostic performance of SLN biopsy. The study reported that out of 142 enrolled patients, 136 were included in the final analysis. The study achieved a detection rate of the SLN biopsies of 91.2%. When compared to systematic pelvic and para-aortic lymphadenectomies performed in the same patients, the study found the sensitivity for finding metastatic SLNs was 84.2%, with a negative predictive value of 97.2% overall. The accuracy of the SLN biopsies was reported as 97.6%. Notably, the median operative time for SLN biopsies (17 minutes) was significantly shorter than for full pelvic lymphadenectomies (40 minutes) or pelvic and para-aortic lymphadenectomies combined (70 minutes). No immediate or late complications associated with the ICG injections or SLN biopsies themselves were reported, although one inferior vena cava injury occurred during a para-aortic lymph node dissection. The study identified false-negative cases where the SLN was negative, but the subsequent full lymphadenectomy found positive nodes, often in cases with high-risk features or specific histologies. The authors concluded that SLN biopsy has a high detection rate and accuracy and can potentially replace systemic lymphadenectomies. [36 level II-2]

Gedgaudaite M et al (2022) conducted a prospective interventional study from March 2018 to December 2021 to evaluate the feasibility of ICG-mapped SLN biopsy in low, intermediate, and high-risk EC patients in a center with no previous experience of this procedure. Patients with histologically confirmed primary EC undergoing surgical treatment were included. Patients were assigned to either the low-risk group receiving SLNB only or the intermediate/high-risk group receiving SLN followed by systematic pelvic lymphadenectomy (LND), based on pre-operative risk assessment using ESGO/ESTRO/ESP guidelines. The SLN mapping technique involved injecting ICG dye into four quadrants of the uterine cervix, followed by laparoscopic visualisation of mapped SLN using a near-infrared light camera after opening retroperitoneal spaces. Mapped SLN were removed separately, as were any macroscopically suspected pathological nodes not mapped. For the intermediate and high-risk groups, LND was performed subsequent to SLN removal. The surgeries were carried out by eight different surgeons with no previous experience in this laparoscopic SLNB procedure, and data on patient characteristics, surgical outcomes, SLN locations, and histological results were collected and analysed to determine SLNB sensitivity, FNR, and NPV using results from patients who underwent both SLNB and LND. The study included 170 patients with primary endometrial carcinoma, predominantly endometrioid-type (95.9%), categorised pre-operatively into low (37.1%), intermediate (58.8%), and high (4.1%) risk groups. Surgical outcomes included median surgery times of 180 and 150 minutes for SLNB plus LND and SLNB only groups respectively, with a median blood loss of 50 mL in both groups. Seven patients (4.1%) experienced post-operative complications: infections (n=3), vaginal lymphorrhea (n=1), and bowel injuries leading to peritonitis and sepsis requiring re-laparotomy (n=2). One SLNB-only patient had an intraoperative bowel injury, which was promptly repaired without further issues. Sentinel lymph-node mapping demonstrated an overall detection rate of 88.8%, with bilateral mapping in 68.2%. Detection rates by risk group were 93.7% (low), 85.0% (intermediate), and 100% (high), showing no statistical difference ($p = 0.23$), and improved overall and bilateral rates were observed over the study period. Mapped SLs

were most commonly located in the external iliac (45.8% right, 46.6% left) and obturator regions (20.9% right, 25.6% left). Full lymph node dissection (LND) was performed in 90 patients (52.9%), all from intermediate or high-risk groups, with a median of 7.5 nodes removed. Positive lymph nodes were found in 8 patients (4.7%). Among 77 evaluated patients, the SLNB showed a sensitivity of 75.0% and a NPV of 97.2%. [37] level II-1

Altın D et al (2022) in a retrospective cohort study evaluated the sensitivity, NPV and FNR of the SLN mapping algorithm for lymph node metastasis detection in a large patient cohort with non-endometrioid, high grade and/or deep myoinvasive endometrial cancer. This study involved a retrospective, multicentric analysis of 244 patients with high-risk endometrial cancer treated between February 2016 and April 2021 at 11 institutions. Patients included had either high-grade histologies (grade 3 endometrioid, serous, clear cell, carcinosarcoma, mixed, undifferentiated or dedifferentiated) or grade 1–2 endometrioid carcinoma with deep myometrial invasion. Those with distant/gross extra-uterine disease, bulky lymph nodes, dye allergy, or preoperative radiotherapy/chemotherapy were excluded. The surgical procedure for all included patients comprised total hysterectomy and SLN biopsy, followed by at least bilateral pelvic lymph node dissection (BPLND); 152 patients also underwent paraaortic lymphadenectomy (BPPALND). Surgeries were performed via laparotomy, laparoscopy, or robotic assisted laparoscopy. Indocyanine green (ICG) and methylene blue (MB) were used as tracers, injected into the cervix at 3 and 9 o'clock positions. The SLN mapping algorithm included removing identified SLNs, removal of any suspicious or enlarged non-SLN, and performing side-specific lymphadenectomy in case of mapping failure. Pathological evaluation of SLNs involved serial sectioning with H&E staining and ultrastaging (pankeratin immunoperoxidase stain) if no metastasis was found on H&E, classifying metastases as macrometastasis, micrometastasis, or isolated tumour cells (ITCs). The study found that the SLN algorithm has high diagnostic accuracy. The overall SLN detection rate was 91%. Lymphatic metastasis was present in 22.5% of patients. While SLN biopsy alone had a sensitivity of 81.8% and NPV of 95%, applying the full SLN algorithm improved sensitivity to 96.4% (95% CI: 87.5–99.6) and NPV to 98.9% (95% CI: 96–99.7), with a FNR of 3.6%. This improvement was due to detecting additional metastases via side-specific lymphadenectomy in cases of mapping failure. The true isolated paraaortic metastasis rate was low at 1.9% after accounting for those detected by ultrastaging of pelvic SLNs. Of the metastatic SLNs, 62.2% were macrometastases, 13.3% were micrometastases, and 24.4% were is ITCs. Indocyanine green demonstrated a significantly better overall detection rate (95% vs 87.1%, p = 0.026) compared to MB. [38] level II-3

A prospective observational study by Restaino S et al (2022) evaluated the bilateral detection rate compared between the two near-infrared (NIR) camera systems for ICG-mapped SLN in determining the number of sentinel lymph nodes detected in the same patient and to assess the SLN metastasis identified with the two systems. This study was conducted from September 2020 and May 2021. After laparoscopic access was established and ICG dye was injected into four cervical quadrants (0.5 mL superficial and deep at 3 and 9 o’clock, following a specific algorithm), retroperitoneal spaces were accessed. [redacted]nd the [redacted] were used alternatively in the same patient to visualise and identify fluorescent SLNs. Mapped SLNs were retrieved, along with any suspicious

unmapped nodes. Seventy-four patients with presumed uterine-confined endometrial cancer undergoing surgical staging were enrolled in this study. Patients excluded were those with allergy to ICG/iodine, ineligible for surgery, BMI more than 35, or prior pelvic surgery potentially altering lymphatic drainage. All removed pelvic lymph nodes, including SLNs, were sent for ultrastaging. The study found that 74 consecutive patients undergoing surgical staging for presumed uterine-confined endometrial cancer, with most having endometrioid histology (83.8%) and FIGO stage IA (64.9%). Median operative time was 119 minutes with 50 mL blood loss, and no post-operative complications were observed within 30 days. Comparing the two near-infrared camera systems, th[redacted] showed a bilateral SLN detection rate of 85.1%, while the [redacted]ad a rate of 75.7%, though this difference was not statistically significant ($p = 0.21$). The median number of SLNs detected was two for both systems ($p = 0.37$), and there was no significant difference in the site of SLN detection ($p = 0.99$). Sentinel lymph node metastases were found in 12 patients (16.2%), and in all these cases, the metastatic SLNs were detected by both the Olympus and Medtronic cameras. Inter-rater reliability (Cohen's Kappa) indicated substantial to almost perfect agreement between the two systems for mapping detection (0.72), SLN location on both sides (right 0.98, left 0.89), and SLN number on both sides (right 0.83, left 0.65). [39] level II-2

Menezes JN et al (2024) conducted a retrospective study at a single institution (A.C.Camargo Cancer Center) comparing two groups of patients who underwent surgical staging for endometrial cancer between 2007 and 2021. This study evaluated the impact of SLN mapping for isolated para-aortic lymph node metastasis compared with systematic lymph node dissection. The SLN group included 426 patients who underwent SLN mapping using cervical injection of patent blue dye or ICG, followed by hysterectomy and bilateral salpingo-oophorectomy. Backup systematic lymphadenectomy was performed in some SLN cases based on specific criteria or trial inclusion. The LND group was a historical series of 209 patients who underwent systematic pelvic and para-aortic lymphadenectomy based on Mayo Clinic criteria for high-risk tumours. Sentinel lymph nodes were examined by haematoxylin and eosin and immunohistochemistry, with positive nodes classified by size. Isolated para-aortic recurrences during follow-up were included in the SLN group analysis for that specific outcome. The study found that the SLN group had significantly higher rates of minimally invasive surgeries (84.3%) compared to the LND group (2.9%, $p<0.001$). They also had higher rates of LVSI (24.2% vs. 13.4%, $p<0.001$) but fewer other uterine risk factors, such as high-grade tumours (26.1% vs 47.4%, $p<0.001$) and deep myometrial invasion (20.7% vs. 44%, $p<0.001$). Despite these differences in risk factors, the overall rate of positive lymph nodes was similar between the SLN group (13.1%) and the LND group (16.3%, $p=0.18$), although the LND group had significantly higher rates of para-aortic lymph node metastasis overall (8.6% vs. 2.6%, $p=0.001$). The overall SLN detection rate was high at 90.4%, and SLNs were successfully mapped outside the pelvis in some cases, including the pre-sacral (2.8%), common iliac (11.5%), and para-aortic regions (1.6%). Importantly, 5.7% of positive SLNs were found outside the pelvis. The study's primary finding was that the incidence of isolated positive para-aortic lymph node metastasis (without pelvic involvement) was significantly lower in the SLN group, occurring in only two cases (0.5%, including one para-aortic recurrence) compared to seven cases (3.3%) in the LND group ($p=0.004$). When backup lymphadenectomy was performed in a subset of the SLN group, the SLN mapping showed a sensitivity of 91.8%, a NPV of 97.8%, and a false-negative

predictive value of 2.2%. These findings revealed that SLN protocol accurately predicts lymph node status and may decrease the risk of failed identification of isolated para-aortic lymph node metastasis compared with systematic lymphadenectomy. [40 level II-2]

A retrospective cohort study was conducted by Huang L et al (2024) at a single institution in China, analysing data from 182 EC patients who received surgical treatment between January 2018 and April 2022. Patients were divided into four groups based on stage/grade and lymph node staging: Group A (stage IA grade 1/2 endometrioid EC with SLNB, Group B (stage IA grade 1/2 endometrioid EC with no LND), Group C (higher-grade EC with systematic LND based on SLNB results), and Group D (higher-grade EC with direct systematic LND). Surgical management included radical hysterectomy and bilateral salpingo-oophorectomy. Sentinel lymph node biopsy was performed using fluorescence-guided imaging with ICG injected into the cervix, with backup systematic pelvic and para-aortic lymphadenectomy (PPALN) performed in fluorescent-guided cases based on positive frozen section, suspicious non-SLNs, or unsuccessful mapping. Systematic LND was the primary lymph node staging method for higher-grade patients without SLNB (Group D) or guided the extent of dissection in Group C. Perioperative, pathological, and postoperative follow-up data, including complications, recurrence, metastasis, and mortality, were collected for all patients. Statistical analysis employed Analysis of Variance for continuous data and chi-squared or Fisher's exact tests for categorical data, with statistical significance set at $p < 0.05$. The study found that for stage IA grade 1 and 2 endometrioid EC, the SLNB group (n=36) had a low SLN positivity rate of 5.6% compared to patients without lymphadenectomy (n=31). There were no significant differences in most perioperative outcomes, pathological characteristics (neither group had lymph node metastasis detected), or postoperative follow-up, although Group A saw significantly earlier time of flatus (p=0.001) and significantly more radiotherapy use (p=0.017). This low incidence of lymph node positivity suggests omitting SLNB might be feasible in this low-risk subpopulation. For higher-grade EC, patients in the SLNB group (n=52) had a SLN positivity rate of 38.4%. When compared to patients undergoing direct systematic LND (n=67), there were no significant differences in most perioperative outcomes, pathological characteristics including similar lymph node metastasis rates (23% in Group C vs 22% in Group D), or postoperative follow-up metrics such as recurrence/metastasis and mortality, despite baseline differences and significantly higher chemotherapy use in the LND group (p=0.003). The overall SLNB procedure using ICG in the 88 patients across all groups achieved detection of at least one SLN in 89% and bilateral detection in 80%. [41 level II-2]

Kulhan M et al (2023) in a retrospective cohort study compared patients who underwent SLNB with ICG and those who underwent laparoscopic complete surgical staging in terms of survival. This study reviewed the records of 182 patients who underwent laparoscopic surgical staging for endometrial cancer at a single university hospital between March 2010 and December 2021. Patients were divided into two groups based on the type of lymph node sampling performed: a SLN mapping cohort (92 patients) who underwent SLN using indocyanine green (ICG) injection into the cervix and biopsy of detected fluorescent lymph nodes, and a systematic complete lymphadenectomy (SCL) cohort (90 patients) who underwent extensive pelvic and paraaortic lymphadenectomy. The decision regarding which lymph node sampling method was used was at the surgeon's discretion. All patients underwent laparoscopic total hysterectomy and adnexa removal, performed by the same surgical team. The

primary objective was to compare these two groups in terms of oncological outcomes, specifically Disease-Free Survival (DFS) and Overall Survival (OS), by retrospectively analysing patient characteristics, pathological data, treatments, complications, recurrences, DFS, and OS. This study found that the SCL cohort had significantly more lymph nodes removed and detected a higher rate of positive lymph nodes, including para-aortic metastases, compared to the SLN group. While the SLN cohort was overall associated with reduced DFS and OS compared to the SCL cohort (p=0.001 for both), and this difference persisted in node-negative patients, the authors suggest this may be due to the significantly longer follow-up time in the SCL group (mean 5.2 years vs 3.6 years). The study concluded that SLN dissection has no negative effect on survival in lymph node positive patients, finding no difference in survival between the two groups when lymph nodes were positive. [42] level II-2

Summary of studies related to the efficacy/ effectiveness of laparoscopic ICG SLN mapping for endometrial cancer are shown in **Table 5**.

Table 5: Efficacy/ effectiveness of laparoscopic indocyanine green sentinel lymph node mapping for endometrial cancer reported by the included studies

Study	Patient characteristic/ disease	Follow-up duration	Intervention Treatment	Comparison	Findings
Raffone A et al (2022)	**Studies Included**: 5 observational cohort studies **Total Patients**: 684 EC patients **High-Risk Patients**: 578 (84.5%) **Age Range**: Mean age 53–71 years BMI Range: 24.8–27.5 kg/m²	not specify	SLN ICG	Systematic lymphadenectomy	Pooled Sensitivity: 90% (95% CI: 3%–95%) – SLNB correctly identified lymph node metastasis in 90% of cases with nodal disease. False Negative Rate (FNR): 2.8% (95% CI: 0.6%–11.6%) – Very low rate of missed metastases, supporting SLNB reliability. Detection Rate per Hemipelvis (DRh): 88.4% (95% CI: 86%–90.5%) – SLN identified on each pelvic side in ~88% of cases. Detection Rate per Patient (DRp): 96.6% (95% CI: 94.7%–97.8%) – SLN identified in nearly all patients. Bilateral Detection Rate (DRb): 80% (95% CI: 75.4%–83.9%) – SLNs identified on both pelvic sides in 80% of patients.
Burg LC et al (2022)	13 observational cohort studies (4 were prospective and 9 were retrospective) 1 study was a randomised controlled trial (n= 21 patients) Patients with presumed early	Not specify	SLN ICG	Systematic (pelvic) lymph node dissection	**Overall SLN detection rate:** 95.6% (95% CI=92.4%–97.9%). This means that in nearly all patients, at least one SLN could be identified. **Bilateral SLN detection rate:** 76.5% (95% CI=68.1%–84.0%). This indicates that SLNs were successfully identified on both sides of the pelvis in about three-quarters of patients. **Incidence of SLN metastases:** 9.6% (95% CI=5.1%–15.2%) in studies

	stage, low- and intermediate-risk endometrial cancer				including grade 1 and 2 endometrial cancer patients. 11.8% (95% CI=8.1%–16.1%) in studies including grade 1, 2, and 3 patients. This indicates that despite being low- or intermediate-risk based on standard criteria, a notable percentage of these patients still harboured lymph node metastases. **Negative predictive value (NPV) of SLN mapping**: 100% (95% CI=98.8%–100%) in studies including only grade 1 and 2 patients. This means that when SLN mapping was negative in this specific group, the systematic lymphadenectomy almost always confirmed the absence of metastasis elsewhere. 99.2% (95% CI=97.9%–99.9%) in studies including grade 1, 2, and 3 patients
Nagar H et al (2021)	33 studies 15 to 340 participants The mean/ median body mass index (BMI) of patients ranged from 24.8 to 35.3 mean or median age of the women ranged from 54 to 69.5 years	Not specify	SLNB	SLNB was systematic pelvic, plus or minus para-aortic lymphadenectomy	**Overall SLN Detection Rate:** Mean detection rate: 86.9% (95% CI: 82.9%–90.8%). **Bilateral SLN Detection Rate:** Mean detection rate: 65.4% (95% CI: 57.8%–73.0%) in studies that reported it. **Variation by Tracer Used:** Blue dye alone: 77.8% detection rate. ICG + Technetium-99m: 100% detection rate (based on a single study). **Sensitivity for Detecting Lymph Node Involvement:** Technetium-99m + Blue Dye (12 studies, 548 women): Pooled sensitivity = 91.9% (95% CI: 74.4%–97.8%), with low certainty evidence. ICG alone (9 studies, 408 women): Pooled sensitivity = 89.7% (95% CI: 67.4%–96.9%), with low certainty evidence.
Marchocki Z et al (2021)	9 prospective cohort studies (n=429) The study focused on patients with EC with high-grade histology median age of	Not specify	SLNB ICG	Systematic lymphadenectomy	Based on the meta-analysis of data from 429 patients with high-grade EC: **SLN Detection Rates**: Overall SLN detection rate: 91% (95% CI: 85%–95%). Bilateral SLN detection rate: 64% (95% CI: 53%–73%). **Node Positivity:** Overall node positivity rate: 26%.

	these patients was 66 years median BMI was 28.6 kg/m2				**SLNB Performance:** Sensitivity (correctly identifying metastasis): 92% (95% CI: 84%–96%). Negative Predictive Value (NPV) (likelihood that a negative SLNB indicates no metastasis): 97% (95% CI: 95%–99%). False Negative Rate (FNR) (missed metastasis on negative SLNB): 8% (95% CI: 4%–16%).
Cianci S et al (2021)	Retrospective cohort N=844 Patients had apparently early-stage endometrial cancer based on radiological assessment Patients were divided into two groups based on age: Group 1 (<65 years old, n=449) and Group 2 (≥65 years old, n=395). The median age of the whole population was 64 years. The mean age at diagnosis of endometrial cancer is approximately 63 years	Not specify	SLN dissection/ mapping with ICG	The study compared the outcomes of SLN mapping between two age groups: patients aged <65 years (Group 1) and patients aged ≥65 years (Group 2)	**SLN Detection Rates:** Overall SLN detection rate: 90.9%. Successful bilateral mapping: 72.3%. Mapping failure rate: 27.7%. **Age Comparison:** Older patients (Group 2, ≥65 years) had lower SLN detection rates (87.6% vs. 93.8%, p = 0.002) and lower successful bilateral mapping rates (66.8% vs. 77.1%, p = 0.001). Mapping failure rate was significantly higher in older patients (33.2% vs. 22.9%, p = 0.001). **Multivariate Analysis:** Age ≥65 years was an independent predictor of unsuccessful mapping (OR: 1.495, 95% CI: 1.095–2.042, p = 0.011). Other predictors included higher BMI, non-endometrioid histotype, and presence of lymphovascular space invasion (LVSI). Each 10-year increase in age led to a 1.280-fold increase in mapping failure risk (OR: 1.280, 95% CI: 1.108–1.479, p = 0.001). **SLN Anatomical Distribution:** Older women had fewer "unexpected" SLN mapping sites, especially in the left hemipelvis. "Expected" sites (external iliac and obturator) were the most frequent in both age groups. **Surgical Outcomes:** Older patients: -higher rate of surgical under-staging (3.3% vs. 0.9%, p = 0.012), likely due to less side-specific lymphadenectomy in case of mapping failure. -higher rates of adjuvant undertreatment, particularly for high-risk tumors (p = 0.018). I**ntraoperative Findings:** Estimated blood loss was significantly higher in older women (p ≤ 0.001). Vascular lesions were more common in

					older patients, although the overall intraoperative complication rate was similar between the two groups. **Postoperative Complications**: Surprisingly, younger patients had higher postoperative complication rates, possibly due to the small number of specific complications like vaginal cuff dehiscence.
Khemworapong K et al (2024)	Prospective cohort (n= 142 patients) Diagnosis: Endometrial cancer patients scheduled for surgical staging. Median Age: 59 years. Median BMI: 28 kg/m². Stage Distribution: Stage IA: 44.1% Stage IB: 27.9% Stage II: 8.1% Stage IIIA: 5.1% Stage IIIC1: 10.3% Stage IIIC2: 4.4%	Not specify	Primary Intervention: SLN mapping using NIR camera. Tracer: Indocyanine Green (ICG) - 1 mL (1.25 mg/mL concentration) injected at four sites (2, 4, 8, 10 o'clock) around the cervix, with both superficial (1 mm) and deep (10 mm) injections.	systematic pelvic and para-aortic lymphadenectomies	**SLN Detection Rates:** Overall SLN detection rate: 91.2% (124/136). Bilateral detection rate: 75.7% (103/136). SLN Accuracy: 97.6%. **Person-Based Analysis:** Sensitivity for detecting metastatic SLNs: 84.2% (16/19). Negative Predictive Value (NPV): 97.2% (105/108). Specificity: 100% (no false positives). **Risk Group Comparison:** Low-risk histology (Endometrioid G1/G2) showed higher sensitivity (92.3%) and NPV (98.8%) compared to high-risk histology. **Lymph Node Metastases:** 19 cases of lymph node metastasis. 1 isolated para-aortic LN metastasis. 3 false-negative SLN cases, where pelvic lymphadenectomy revealed positive nodes (associated with high-risk features like carcinosarcoma, serous carcinoma, or deep myometrial invasion). **Safety**: No immediate or late complications from ICG injections or SLN biopsies. One intraoperative complication: inferior vena cava injury during para-aortic lymphadenectomy. Full lymphadenectomies may have higher long-term complications, but this was not evaluated. **Operative Times:** SLN biopsy: median 17 minutes. Full pelvic lymphadenectomy: 40 minutes. Combined pelvic and para-aortic lymphadenectomies: 70 minutes. **Risk Factor for Metastasis:** Lymphovascular space invasion (LVSI)

					was the only statistically significant risk factor for lymph node metastasis. However, the study was not powered to detect all possible risk factors.
Gedgaudaite M et al (2022)	Clinical trial (non-randomised) Sample Size: 170 patients with primary endometrial carcinoma (EC) undergoing surgical treatment. Demographics: Median age: 63.5 years (range 43–88) Median BMI: 30.05 kg/m² (range 19.23–48.05)	Not specify	SLNB ICG	systematic lymphadenectomy (LND)	**Feasibility**: ICG-based SLN biopsy (SLNB) was feasible despite the center's lack of prior experience. **Overall SLN detection rate**: 88.8%. **Bilateral mapping rate**: 68.2%. **Detection rates by risk group**: Low-risk 93.7%, intermediate-risk 85.0%, high-risk 100% (p = 0.232); trend toward improvement over time indicated a learning curve. **SLN anatomical locations**: Most commonly found in external iliac and obturator regions; para-aortic SLNs found in 1.8% of cases. **Node positivity**: 4.7% (8/170 patients). **Diagnostic accuracy (in LND subset):** Sensitivity: 75.0%. Negative predictive value (NPV): 97.2%. False negatives: 2 cases (metastases missed by SLB, found by LND). **Safety**: Overall post-operative complication rate: 4.1%. Lymphatic complication (vaginal lymphorrhea): 0.6% (SLB+LND group); none in SLB-only group. **Upstaging**: Some low-risk patients were upstaged post-operatively, including one with SLN metastasis.
Altın D et al (2022)	Retrospective cohort Total patients: 244 with endometrial carcinoma. Demographics: Mean age: 62.9 years. Median BMI: 30 kg/m².	Not specify	Surgical procedure: All patients underwent total hysterectomy, with or without adnexectomy followed by Sentinel Lymph Node (SLN) biopsy. SLN mapping: Performed using Indocyanine Green (ICG) or methylene blue (MB)	Comprehensive lymphadenectomy results were used as the reference standard to determine the true lymph node status	**SLN Detection Rates:** At least one SLN was detected in 91% of patients. Bilateral SLN detection occurred in 65.6%. Lymph Node Metastasis: 55 patients (22.5%) had lymphatic metastases. 45 of these 55 had at least one metastatic SLN detected. **Diagnostic Accuracy:** SLN Biopsy Alone: Sensitivity: 81.8% (95% CI: 69.1–90.9) Negative Predictive Value (NPV): 95% (95% CI: 91.5–97.1) False Negative Rate (FNR): 18.2%

			injected into the cervix.		**SLN Algorithm** (including side-specific dissection and suspicious node removal): Sensitivity: 96.4% (95% CI: 87.5–99.6) NPV: 98.9% (95% CI: 96–99.7) FNR: 3.6% All pelvic lymphatic metastases were detected by the SLN algorithm. **False Negatives:** 2 cases were missed even by the SLN algorithm—both had isolated para-aortic metastases. True Isolated Para-Aortic Metastasis Rate: 1.9% Subgroup Performance: Grade 3 Tumors: Sensitivity: 97.1%, NPV: 98.9%, FNR: 2.9% Grade 1–2 Endometrioid with Deep Myometrial Invasion: Sensitivity: 95%, NPV: 98.9%, FNR: 5% **Metastasis Types in SLNs**: Macrometastasis: 62.2% Micrometastasis: 13.3% Isolated Tumor Cells (ITCs): 24.4% Among those with positive SLNs, 48.9% also had non-SLN metastases, underlining the importance of complete assessment in SLN-positive cases.
Restaino S et al (2022)	Prospective cohort Number of patients enrolled: 74 consecutive patients Median age: 60 years (range 29–75). Mean BMI: 24.1 kg/m² (range 18.3–34.9)	mentions evaluating post-operative complications during the first 30 days after surgery, but no long-term follow-up period for survival or recurrence is reported.	SLN ICG using [redacted] a new laser near-infrared (LNIR) fluorescence laparoscope	SLN ICG using [redacted] considered the standard (SNIR).	**Overall SLN detection rate:** At least one SLN detected in 72/74 patients (97.3%) **Bilateral SLN detection rate:** [redacted]): 56/74 (75.7%) [redacted]: 63/74 (85.1%) Trend favoring LNIR, but not statistically significant (p = 0.214) **Total SLNs identified (left/right):** SNIR: 65 (left), 74 (right) LNIR: 70 (left), 76 (right) No statistically significant difference (p = 0.370) **Median SLNs per patient**: 2 for both systems **SLN anatomical distribution:** No significant difference between systems (p = 0.994) **Most common sites:** obturator and external iliac nodes **Diagnostic Accuracy** Patients with SLN metastasis: 12/74 (16.2%) In all 12 metastatic cases, SLNs were detected by both NIR systems.

					Types of metastases identified in SLNs: Isolated tumor cells (ITCs), Micrometastasis, Macrometastasis All detected with both SNIR and LNIR cameras
Menezes JN et al (2024)	Retrospective cohort The study compared a group of **426 patients who underwent SLN mapping** with a historical series of **209 cases who underwent systematic pelvic and para-aortic lymphadenectomy** N=681 SLN group: 426 patients LND group: 209 patients	SLN group: Median follow-up was 50.7 months. LND group: data collected June 2007–April 2015 Recurrence:42 months post-surgery.	**SLN group**: SLN biopsy using patent blue dye or ICG (n=197) via cervical injection.	Systematic pelvic and para-aortic lymphadenectomy (data was collected between June 2007 and April 2015)	**Isolated para-aortic metastasis:** SLN group: 2 cases (0.5%) LND group: 7 cases (3.3%) Statistically significant (p = 0.004) **Overall lymph node positivity:** SLN: 13.1% LND: 16.3% Not significant (p = 0.18) **Overall para-aortic metastasis (with or without pelvic involvement):** SLN: 2.6% LND: 8.6% Statistically significant (p = 0.001) **SLN Detection & Mapping** **Detection rate**: 90.4% (overall), 78% (bilateral) **SLN mapped outside the pelvis**: Pre-sacral: 2.8% Common iliac: 11.5% Para-aortic: 1.6% **Positive SLNs outside pelvis**: 3 cases (5.7% of positive SLNs) **SLN Diagnostic Accuracy (in those with backup lymphadenectomy)** Sensitivity: 91.8% Negative Predictive Value: 97.8% False-negative rate: 2.2%
Huang L et al (2024)	Retrospective cohort N: 182 Patient Groups **Group A** (N=36) **Group B** (N=31) **Group C** (N=52) **Group D** (N=67)	Not explicitly mentioned but follow-up for any individual patient would fall within January 1, 2018, to April 1, 2022 , relative to their surgery date.	SLNB, fluorescence-guided imaging was used with ICG tracer injected into the cervix. A standard dose of 0.83 mg/mL of ICG was used	**1. Low-Risk Patients (Stage IA, Grade 1–2 Endometrioid EC)** Group A (SLNB): Underwent Sentinel Lymph Node Biopsy Group B (No Lymphadenectomy): Underwent hysterectomy/BSO only, without lymph node assessment **2. Higher-Risk Patients (Higher-Grade EC)** Group C (SLNB-Directed LND): Started with SLNB Proceeded to systematic LND only if SLNs were positive or not mapped Group D (Direct Systematic LND): Underwent routine systematic pelvic ± para-aortic lymphadenectomy directly, without SLNB	**Group Comparisons** **Low-Risk EC (Stage IA, Grade 1–2)** **Group A (SLNB) vs. Group B (No LND)** SLN positivity rate (Group A): 5.6% No significant differences in: Pathological stage Lymph node metastasis (0% in both) Complications: Recurrence/metastasis,mortality Significant differences: Surgical approach (favoring minimally invasive surgery in SLNB group) Time to flatus More Group A patients received radiotherapy **Higher-Grade EC** **Group C (SLNB-directed LND) vs. Group D (Direct LND)** SLN positivity rate (Group C): 38.4% No significant differences in:Complications, recurrence/metastasis and Mortality Significant differences in:Age, surgical approach,hysterectomy type More Group D patients received chemotherapy

Yao H et al (2023)	Systematic Review and Meta-Analysis (4 retrospective study) N=7181 SLN group: 492 patients LND group: 6,689 patients	Not applicable	SLN assessement	Lymphadenectomy (LND)	A meta-analysis of advanced endometrial cancer found no significant difference in overall survival between SLN and LND groups (OR = 1.14, P = 0.39), with consistent results across studies. Chemotherapy rates were similar, though high heterogeneity was noted. Radiotherapy rates were higher in the SLN group (OR = 2.15, P < .0001) after sensitivity analysis, potentially impacting prognosis. No significant difference was observed in lymphovascular invasion rates, with low heterogeneity.
Kulhan M et al (2023)	Retrospective cohort study design N: 182 SLNM cohort: 92 patients (sentinel lymph node mapping with ICG + biopsy) SCL cohort: 90 patients (systematic pelvic + paraaortic lymphadenectomy) (SCL generally had more advanced disease)	SLNM (3.6 years) vs SCL (5.2 years).	SLN ICG	Laparoscopic complete surgical staging	**Survival** (Node-Negative Cases): SLNM group had significantly worse DFS and OS than SCL (DFS: 36.5 ± 13.3 vs. 51.2 ± 25.0 months, p = 0.001; OS: 36.7 ± 13.4 vs. 52.2 ± 24.3 months, p = 0.001). Kaplan–Meier analysis confirmed significance (log-rank p = 0.019). **Survival** (Node-Positive Cases): No significant difference between groups. **Death & Recurrence**: Across all patients, death rates were higher in SCL (p = 0.035), and in node-negative patients (p = 0.039); no difference in recurrence rates. Lymph Node Yield: SLNM removed fewer pelvic nodes (17.3 vs. 21.8, p = 0.005) and far fewer paraaortic nodes (0.6 vs. 7.4, p < 0.001). Positive pelvic nodes were less frequent in SLNM (4.3% vs. 17.7%, p = 0.004); no paraaortic metastases in SLNM vs. 10% in SCL. Adjuvant Therapy: Used less in SLNM (32.6% vs. 63.3%, p = 0.001).

5.2 SAFETY

Regulatory approval

The regulatory status of laparoscopic ICG SLN mapping is well established across major jurisdictions. Under the Malaysia Medical Device Authority (MDA), several near-infrared (NIR) imaging systems compatible with ICG are registered, including the [redacted] as well as the [redacted] categorised under general non-active, general active, and electromechanical medical devices. [43] In the United States, ICG is regulated as a pharmaceutical product by the United States Food Drug Administration (US FDA), with [redacted] was previously approved but later discontinued for commercial reasons unrelated to safety or efficacy. [44] While in Europe, the European Medicines Agency (EMA) has authorised the use of ICG under the trade nam [redacted] (authorisation number 34009 360 841 7 9) as a powder and solvent for injectable solution. [45]

Clinical studies

Capasso I et al (2023) conducted a retrospective cohort study at the Mayo Clinic in Rochester, Minnesota. This study aimed to evaluate the rate and severity of adverse reactions to ICG occurring intraoperatively or within seven days after surgery. The researchers reviewed the electronic medical records of 923 consecutive patients with EC who underwent primary surgery, including SLN assessment using intracervical stromal injection of ICG for mapping, between June 2014 and December 2018. The standard ICG protocol involved injecting 4 mL (5 mg ICG) at the 3 and 9 o'clock positions, with 1 mL superficially and 1 mL deeply, although some surgeons transitioned to only superficial injection during the study period. Any potential allergic and other adverse reactions within the first seven days post-surgery were identified, and a specialist in allergic diseases retrospectively reviewed the records to determine the likelihood that the reaction was triggered by ICG. Anaphylaxis and reaction severity were defined according to established criteria. This study found no cases of immediate anaphylaxis or severe allergic reactions following ICG injection in a large patient cohort. Although 1.1% (10 patients) experienced transient skin reactions within a week post-surgery, these were deemed unlikely to be caused by ICG upon retrospective review by an allergy specialist. Likely causes included skin disinfectants, surgical tape, or new medications. Importantly, patients with a history of allergies, including to contrast media or asthma, also tolerated ICG well. The study refutes the misconception that iodine causes contrast or shellfish allergies, explaining that contrast reactions are due to histamine release and shellfish allergies stem from tropomyosin, not iodine. [46 level II-2]

Balogun Z et al (2024) conducted a retrospective cohort between 1st January 2017 and 31st December 2020. The researchers identified all patients diagnosed with clinically early-stage EC who underwent minimally invasive surgical staging involving SLN mapping using ICG dye during this period. The specific objective was to examine the use of ICG in patients with a documented history of iodinated contrast allergies prior to surgery. Data regarding documented allergic reactions or other adverse events

following ICG administration were collected through electronic medical record review, with consideration also given to perioperative administration of medications like intravenous dexamethasone used in the institution's enhanced recovery after surgery (ERAS) protocol. A total of 820 patients underwent minimally invasive surgical staging with SLN mapping using ICG dye with 25 patients were identified who had a documented history of iodinated contrast allergy prior to surgery. The documented prior reactions to iodinated contrast in these 25 patients included rash/hives (40%), anaphylaxis (24%), shortness of breath (20%), diarrhea (4%), and not specified (12%). The mean age of these patients was 64.5 years, and the mean BMI was 35.8 kg/m². A significant majority of these patients (96%, 24 out of 25) received 4 mg intravenous dexamethasone during induction of general anaesthesia as part of the institutional ERAS protocol. The study reported no patients in this cohort experienced an allergic reaction or any other adverse event after the intracervical injection of ICG. No additional medications considered prophylaxis against allergic reactions were administered. [47] level II-2

Predictive factors of sentinel lymph node (SLN) mapping failure:

Raffone A et al. (2023) conducted a systematic review and meta-analysis to evaluate predictive factors of SLN mapping failure in early-stage endometrial cancer patients undergoing SLN biopsy through cervical ICG injection. The study followed the PRISMA guidelines and included a comprehensive search of databases such as MEDLINE, Scopus, and Embase until October 2021. Peer-reviewed studies were selected based on specific inclusion criteria, and risk of bias was assessed using the Methodological Index for Non-Randomized Studies (MINORS). This review included six observational cohort studies with a total of 1345 patients. The study found that the rate of SLN failed mapping was 21.7%. Specifically, the study determined that ICG dose below 3 mL, International FIGO stage III- IV, enlarged lymph nodes, and lymph node involvement are predictive factors of SLN failed mapping. In contrast, the analysis concluded that BMI more than 30 kg/m², menopausal status, adenomyosis, prior pelvic or cervical surgery or Cesarean sections, lysis of adhesions at the beginning of surgery, deep myometrial invasion, FIGO grade 3, non- endometrioid histotype, and lymph- vascular space invasion were not significantly associated with SLN mapping detection outcome. [48] level II-2

A randomised controlled trial study by Andreika L et al (2024), conducted at Vilnius University Hospital Santaros Clinics between April 2020 and June 2024, investigated predictive factors associated with unsuccessful SLN mapping in 120 early-stage EC patients (18 years of age and older) undergoing laparoscopic hysterectomy with SLN biopsy via cervical ICG, MB, or their combination. Patients were stratified into tracer groups (MB, ICG, or a combination) with 40 patients in each group using block randomisation, and all underwent laparoscopic staging surgery with SLN mapping. SLN tracers were injected intracervically under general anesthesia. Pathologic evaluation used Hematoxylin and Eosin staining (H&E) staining without routine ultrastaging. Successful SLN mapping was defined as bilateral or aortic node detection; failure included unilateral or no detection. If mapping failed, low- and intermediate-risk patients had lymphadenectomy only if nodes were suspicious. High-intermediate- and high-risk patients underwent pelvic/aortic lymphadenectomy, unless comorbidities limited the procedure. Statistical analyses included univariate logistic regression to identify predictors of mapping failure, followed by multiple linear regression using significant variables. Fluorescent detection with ICG was performed using the Olympus Visera Elite II OTV-S300 video system, the CH-S200-XZ-EB camera, ESG-400 and USG-400 generators, and a CLV-S200-IR light source. The overall SLN detection rate was 73.4%, with bilateral detection at 49.2% and unilateral detection at 24.2%. Bilateral mapping success rates varied significantly by tracer: MB

had a 27.5% success rate, ICG had 52.8%, and the ICG–MB combination had 67.5% ($p = 0.006$). Univariate analysis associated older age ($p < 0.001$), menopause ($p = 0.001$), the use of MB as the sole tracer ($p = 0.006$), a shorter tumor-to-serosa distance ($p = 0.048$), and bulky lymph nodes ($p = 0.018$) with unsuccessful mapping. Multiple linear regression analysis identified age ($p = 0.007$), tracer type ($p = 0.013$), and enlarged lymph nodes ($p = 0.013$) as independent predictors of SLN mapping failure. Factors like BMI, previous pelvic operations, uterine volume, tumor grade, histological type, molecular type, tumor size, tumor distance to the resection edge, LVSI, lymph node involvement, myomatosis, or adenomyosis did not show significant associations with unsuccessful mapping. A total of 212 SLNs were removed from 144 sites, with the majority in the external iliac region (56.9% of sites, 51.9% of nodes). Of the analysed SLNs, 92.9% were negative for metastases, 4.7% were positive, and 2.4% were empty node. [49 level I]

Dampali R et al (2025) conducted a retrospective cohort study at a single tertiary care centre, United Kingdom. The study included 112 patients diagnosed with EC between 2020 and 2022. Patients were divided into two groups based on BMI: non-obesity (below 30 kg/m²) and obesity (30 kg/m² and above). The primary objective was to evaluate the relationship between BMI and the technical success of SLN mapping in these patients. All participants underwent laparoscopic hysterectomy with SLN mapping using intracervical injection of ICG dye (total 2 ml administered at 3 and 9 o'clock positions, with 0.5 ml injected deep into the stroma and 0.5 ml submucosally at each site) and near-infrared fluorescence imaging. Mapping success was defined by the detection of bilateral or unilateral SLNs, while failure meant no SLNs were found. Statistical analysis involved comparing characteristics between the BMI groups and using univariable and multivariable logistic regression to identify predictors of SLN biopsy results. The study found an overall SLN detection rate of 77.7%, with bilateral mapping achieved in 54.5% of patients overall. Mapping success appeared higher in the non-obesity group (59.7% bilateral mapping) compared to the obesity group (49.1% bilateral mapping), although this difference was not statistically significant ($p = 0.099$). Correspondingly, mapping failure rates were higher in obese patients (30.9%) than in non-obese patients (14.0%) but not significant ($p = 0.099$). The median number of SLNs identified was 2, with no significant difference between BMI groups. Positive SLN biopsy results were found in 14.3% of patients overall, with similar rates between BMI groups ($p = 0.316$). Multivariable logistic regression analysis identified advanced cancer stage (stage II/III) as a significant predictor of SLN positivity (adjusted odds ratio (aOR) = 30.2, $p = 0.002$), but BMI was not a statistically significant predictor of SLN biopsy outcome in this analysis ($p = 0.463$). Operative time was longer in the obesity group, but estimated blood loss was comparable between groups. [50 level II-2]

Goncalves BT et al (2024) in a prospective cohort study included women with early--stage EC who underwent lymph node staging, grouped as follows: SLN group (SLN only) and SLN+LND group (SLN biopsy with addition of systematic lymphadenectomy). This study evaluated the prevalence of post-operative complications and QoL related to SLN biopsy compared to systematic lymphadenectomy in endometrial cancer. The total of 152 patients included in this study with presumed early-stage EC undergoing SLN mapping, with 113 in the SLN-only group and 39 in the SLN+LND group. Indocyanine green was used in 84 (55.3%) cases and blue dye in 68 (44.7%). There were no significant differences in age ($p=0.15$) or BMI ($p=0.62$) between the groups, but the SLN+LND group had significantly longer surgical time (mean 274±65 min vs. 160±104 min; $p<0.001$) and higher intensive care unit use (23.1% vs 3.5%; $p<0.001$). Early surgical complications

occurred in 29 (19.1%) cases overall, with the SLN+LND group experiencing significantly higher overall rates than the SLN group (33.3% vs 14.2%; OR = 3.03, 95% CI 1.29 to 7.09; p = 0.01), and the addition of lymphadenectomy remained an independent risk factor after adjustment (OR = 3.45, 95% CI 1.40 to 8.47; p = 0.01). Lymphocele developed in 8 patients (5.3%), occurring only in the SLN+LND group (p < 0.001). Clinically assessed lymphedema at 12 months was seen in 21.2% of the SLN group and 33.3% of the SLN+LND group (p = 0.14), and while clinical criteria and perimetry did not correlate well, there was an association between clinical assessment and lymphedema reported via the QoL questionnaire (p < 0.001). Lymphedema symptom scores were significantly higher for the SLN+LND group compared to the SLN group at 12 months (means 23.5 vs 12.4; p = 0.022). Regarding patient-reported outcomes, social functioning scores were significantly more preserved in the SLN group at 1 month (83.4 vs 71.7; p = 0.012) and 6 months (86.8 vs 74.01; p = 0.011), and physical function scores were more preserved in the SLN group at 1 month (78.3 vs 71.7; p = 0.03); however, no statistically significant difference was found between the groups for overall global health status score, and no difference was found for overall QoL when comparing SLN biopsy with back-up lymphadenectomy. [51] level II-2

5.3 ORGANISATIONAL ISSUES

Guidelines

Dick A et al (2023) conducted a descriptive comparative study of the National Comprehensive Cancer Network (NCCN), the Society of Gynecologic Oncology (SGO), the European Society of Gynecological Oncology (ESGO), the British Gynecological Cancer Society (BGCS), and the Japan Society of Gynecologic Oncology (JSGO) guidelines regarding the topic of SLN in EC. The study found broad consensus that SLN mapping is an appropriate alternative to pelvic lymphadenectomy for uterine-confined endometrioid EC, particularly for low–intermediate risk patients or those unable to tolerate full lymphadenectomy. There is also agreement that ICG mapping is superior to other methods and results in higher detection rates, the cervix is the preferred injection site, pathology ultrastaging of SLNs is advocated by most guidelines for detecting low volume metastases and increasing detection of ITCs and micrometastasis. A full or side-specific lymphadenectomy should be performed in case of failed SLN mapping, especially for higher-risk patients where nodal staging is indicated. However, significant variations exist regarding the role of SLN mapping as the sole method for lymph node evaluation in high-risk patients such as those with high-grade histology or non-endometrioid carcinomas, with some guidelines accepting it as an alternative while others advocate for completion lymphadenectomy. There is also no consensus on the management of para-aortic lymph nodes in patients with positive pelvic SLNs, no uniform ultrastaging protocol is advised, and routine frozen section of SLNs is generally not recommended by some guidelines due to low sensitivity. Overall, while surgical technique and management of failed mapping show comparability, variations persist, particularly concerning high-risk cases and positive pelvic nodes. [52]

The organisational issue for the implementation of laparoscopic SLN ICG mapping by the international guidelines available are as in the table 6. Based on the recommendations, the main organisational issue highlighted include the need for dedicated surgeon and team training, availability of near-infrared imaging equipment, and adequate pathology infrastructure for ultrastaging and micrometastasis detection. The guidelines also emphasize the importance of standardized institutional protocols,

strong multidisciplinary collaboration among surgical, pathological, and oncological teams, and the implementation of quality assurance measures and regular audits to ensure consistency and accuracy in practice. [18,19,20,21,22,23]

Table 6 : International guidelines (NCCN, SGO, ESGO, BGCS, and JSGO) recommendations and Issues for Implementing SLN Mapping with ICG in Endometrial Cancer. [17,18,20,21,22,23]

Organisation	Recommendations / Issues
NCCN (USA)	Recommends SLN mapping with ICG as a valid alternative to full lymphadenectomy in apparent early-stage endometrial cancer. Emphasizes the need for institutional experience, proper surgeon training, and standardised protocols for SLN detection and pathological ultrastaging.
SGO (USA)	Endorses SLN mapping as part of a structured algorithm, advocating for training programs, quality assurance, and multidisciplinary coordination. It emphasises centralised expertise for interpretation of ultrastaging results.
ESGO (Europe)	Supports ICG-based SLN mapping in early-stage endometrial cancer, but highlights the importance of high surgical expertise, resource availability, and pathology infrastructure for ultrastaging. Recommends SLN mapping in high-volume centers with established protocols.
BGCS (UK)	Recommends implementation in centers with appropriate laparoscopic experience, access to near-infrared imaging systems, and pathology support for SLN ultrastaging. Emphasizes the need for national training and audit mechanisms.
JSGO (Japan)	Acknowledges SLN mapping as promising but calls for further validation in Japanese populations. Highlights the need for infrastructure, surgeon education, and institutional standardization before widespread adoption.

Learning curves

Gedgaudaite M et al (2023) conducted a prospective observational study at Lithuanian University of Health Sciences Hospital. During the period March 2018 to June 2022, 190 patients with histologically confirmed EC scheduled for minimally invasive surgery were included in the study. Eight gynecologic oncologists without prior experience in laparoscopic SLN biopsy with ICG tracer participated in this study. Cumulative sum (CUSUM) analysis was used to create learning curves for the performance of eight surgeons, based on a specific result over a time period. Two different cumulative sum plots were made for each surgeon: successful bilateral SLN mapping and removal of SLN specimens containing actual lymphatic tissue. This study focusing on two outcomes, achieving successful bilateral SLN mapping and the removal of SLN specimens containing actual lymphatic tissue. Findings indicate that attaining an acceptable level of competence, defined as a bilateral detection rate of at least 75%, required surgeons to perform at least 30 procedures. While the overall bilateral detection rate for the centre significantly improved over the study period, only one surgeon statistically demonstrated reaching this competence threshold after 30 surgeries. For the outcome of removing specimens containing lymphatic tissue, competence was achieved more rapidly, with most surgeons crossing the statistical limit after at least six consecutive successful removals. These results highlight that organisation adopting this procedure must account for the substantial case volume needed per surgeon, particularly for mastering bilateral mapping, and suggest the importance of implementing structured training pathways and potentially using methods like CUSUM analysis to monitor individual surgeon progress and overall service quality during implementation. [37]

CUSUM analysis is a statistical process control technique that allows for the quantitative assessment and graphical representation of performance trends over consecutive procedures

5.4 ECONOMIC IMPLICATION

There were two cost-effectiveness studies, and one cost-analysis study retrieved.

Burg LC et al (2024) conducted a cost-effectiveness analysis of SLN mapping in high-risk EC. This study employed a decision–analytic model from a healthcare perspective to compare the cost-effectiveness of SLN mapping against routine pelvic lymphadenectomy for assessing lymph nodes in patients with high-risk EC in Dutch Healthcare System, Netherlands. The model used a decision tree and a Markov model over a 20-year time horizon to simulate outcomes. For the SLN strategy, the technique involved a cervical injection of ICG detected with a NIR camera which compatible with commonly used laparoscopic and robotic devices including robotic (Da Vinci) and conventional laparoscopic systems (Storz, Olympus). If SLN mapping failed, a side-specific lymphadenectomy was performed. Model inputs were derived from literature and expert consensus, measuring outcomes in costs (in Euros) and QALYs. The primary goal was to determine if SLN mapping is a more cost-effective strategy (i.e., provides more QALYs for an acceptable or lower cost) compared to lymphadenectomy, with uncertainty assessed through sensitivity analyses. The analysis demonstrated that SLN mapping using ICG and a NIR was consistently both more effective and less costly than lymphadenectomy across various adjuvant therapy scenarios, making it the dominant strategy. Specifically, SLN mapping resulted in higher QALYs (up to 11.76 QALYs vs. 11.49 to 11.69 QALYs for lymphadenectomy strategies) and lower costs (approximately EUR 3500 to 3600 (RM 16,957.43 to RM 17,441.93 less per patient). This advantage was primarily attributed to a significant reduction in lymph node assessment-related side effects, such as lymphoedema. Sensitivity analyses confirmed these robust findings, with probabilistic analysis showing SLN mapping was cost-effective in 100% of iterations at the EUR 20,000 / RM 96,899 per QALY threshold. The authors concluded that SLN mapping is the most cost-effective strategy to determine the need for adjuvant therapy in patients with high-risk endometrioid and non-endometrioid endometrial cancer. [53]

Another study by Burg LC et al (2021) evaluated the cost-effectiveness of SLN mapping compared to risk factor assessment and routine full lymph node dissection for the assessment of lymph nodes in patients with low- and intermediate-risk endometrioid EC. The study setting was in Dutch Healthcare System, Netherlands. It employed a methodology centred on a decision–analytic model constructed from a healthcare perspective. Three primary strategies were compared: SLN mapping, using a decision rule for managing failed mapping; post-operative risk factor assessment; and routine full LND. The model's structure combined a decision tree to map the initial clinical pathways and a Markov model to simulate long-term outcomes over a 20-year time horizon, incorporating factors like survival, health-related quality of life (HRQOL), and healthcare costs. Input data for the model, including probabilities, costs (measured in Euros), and utility values (used to calculate QALYs), were derived from systematic literature searches and expert opinion. The study determined cost-effectiveness by calculating the incremental ICER for comparing strategies based on their costs and QALYs, against a willingness-to-pay threshold of € 20,000 / RM 96,954.60 per QALY. The robustness of the model's findings was evaluated through one-way deterministic sensitivity analysis and probabilistic sensitivity analysis involving 1000 iterations, with model validity additionally checked through expert consultations and cross-validation. The study found that for patients with low- and intermediate-risk endometrioid EC, SLN mapping emerged as the most cost-effective strategy for lymph node assessment. The analysis, conducted using a decision-

analytic model over a 20-year horizon, showed that SLN mapping (specifically the SLN 1 strategy where failed mapping led to risk factor assessment) was more effective than post-operative risk factor assessment, and although more costly, its incremental cost-effectiveness ratio (€ 5588 (RM 26972.16) / QALY) remained well below the € 20,000 / RM 96536 per QALY willingness-to-pay threshold. Crucially, SLN mapping was dominant compared to routine full LND, meaning it was both more effective and less costly. This superiority of SLN mapping over LND was largely attributed to a significantly lower rate of side effects, particularly lymphoedema, associated with the less extensive procedure. Sensitivity analyses confirmed these results were robust across varying input values, strongly supporting SLN mapping as the preferred approach. [54]

Dioun S et al (2021) conducted a retrospective analysis using data from the Premier Perspective Healthcare Database, United States for women who had a hysterectomy for complex atypical endometrial hyperplasia between 2012 and 2018. The core of the method was to compare three distinct approaches to lymph node assessment SLN mapping, LND, and no nodal evaluation which identified using diagnosis, procedure, and charge codes. The analysis focused on examining the utilisation patterns, short-term perioperative morbidity and mortality, and hospital costs associated with each of these strategies. The cost analysis in the study found that the median hospital costs for women who underwent SLN mapping (£9,673 / RM 55,154.07) and lymph node dissection (£9,754 / RM 55,615.92) were higher than for those who did not undergo nodal assessment (£8,435 / RM 48095.17) ($p < 0.001$). [55]

5.5 LIMITATIONS

It is acknowledged that there were limitations in this review and these should be considered when interpreting the results. The selection of the studies and appraisal was done by one reviewer. Although there was no restriction in language during the search, only English full-text articles were included in the report, which may have excluded some relevant articles and further limited our study numbers. Most were observational in design, with few randomised controlled trials, limiting causal inference. Methodological heterogeneity was common, including variations in tracer types (ICG, blue dye, technetium-99m), injection sites, imaging technologies, and ultrastaging protocols, which complicate comparisons across studies. Economic evaluations were based on data from high-income countries, lacking local cost inputs and long-term outcome considerations, which may not reflect the Malaysian healthcare context.

6.0 CONCLUSION

There were high certainty evidences on laparoscopic ICG SLN mapping which demonstrates its high efficacy in the staging of endometrial cancer. The technique has shown good sensitivity and precision in identifying SLNs, comparable or even superior detection rates compared to conventional methods.

Laparoscopic sentinel lymph node mapping with ICG has better outcomes in terms of morbidity and comparable outcomes in terms of mortality compared to conventional lymphadenectomy in endometrial cancer. No severe allergic reactions or anaphylaxis, no impact on survival or long-term complications were reported. Successful

implementation of laparoscopic ICG SLN mapping requires surgeon training and access to near-infrared imaging.

Economic evaluations from high-income country showed that SLN mapping using ICG is a cost-effective alternative to full lymph node dissection in endometrial cancer. Despite higher upfront procedural costs in some settings, long-term models demonstrated lower overall costs and improved outcomes, particularly in high-risk cases, due to reduced complications such as lymphoedema.

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8.0 APPENDIX

APPENDIX 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to April 18, 2025>

Search Strategy:
1 ENDOMETRIAL NEOPLASMS/ (26360)
2 (endometrial adj1 neoplasm*).tw. (180)
3 (endometrial adj1 carcinoma*).tw. (11971)
4 (endometrium adj1 cancer*).tw. (221)
5 cancer of the endometrium.tw. (440)
6 cancer of endometrium.tw. (73)
7 (endometrium adj1 carcinoma*).tw. (162)
8 carcinoma of endometrium.tw. (119)
9 (endometrial adj1 cancer*).tw. (25216)
10 adenocarcinoma*.tw. (195776)
11 (malignant adj1 adenoma*).tw. (216)
12 (basal cell adj2 adenocarcinoma*).tw. (245)
13 (granular cell adj2 carcinoma*).tw. (77)
14 (granular cell adj2 adenocarcinoma*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] (5)
15 (tubular adj1 adenocarcinoma*).tw. (1136)
16 (tubular adj1 carcinoma*).tw. (606)
17 NEOPLASM RECURRENCE, LOCAL/ (153839)
18 (local neoplasm adj2 recurrence*).tw. (4)
19 (locoregional neoplasm adj2 recurrence*).tw. (0)
20 CARCINOMA, ENDOMETRIOID/ (4304)
21 (endometrioid adj1 carcinoma*).tw. (2310)
22 (endometrioid adj1 adenocarcinoma*).tw. (1978)
23 UTERINE NEOPLASMS/ (44333)
24 (uterus adj1 neoplasm*).tw. (7)
25 (uterine adj1 neoplasm*).tw. (396)
26 (uterus adj1 cancer*).tw. (191)
27 (uterine adj1 cancer*).tw. (4024)
28 SENTINEL LYMPH NODE/ (2542)
29 (sentinel adj2 lymph node*).tw. (14816)
30 (sentinal adj1 node*).tw. (19)
31 SENTINEL LYMPH NODE BIOPSY/ (14215)
32 (sentinel adj2 lymph node biopsy).tw. (7224)
33 INDOCYANINE GREEN/ (11022)
34 (indocyanine adj1 green).tw. (16209)
35 (cardio adj green).tw. (37)
36 LAPAROSCOPY/ (110444)
37 laparoscopy*.tw. (41196)
38 surgery, laparoscopic.tw. (1025)
39 (laparoscopic assisted adj2 surgery*).tw. (295)
40 (laparoscopic surgical adj2 procedure*).tw. (313)
41 (laparoscopic adj1 surgery*).tw. (24177)
42 LYMPH NODES/ (96904)
43 (lymph adj1 node*).tw. (260558)
44 (tissue adj1 stain*).tw. (3254)
45 OPTICAL IMAGING/ (17517)

46 (optical adj1 imaging).tw. (12298)
47 (fluorescence adj1 imaging).tw. (18671)
48 (autofluorescence adj1 imaging).tw. (1311)
49 (fundus autofluorescence adj2 imaging*).tw. (677)
50 FLUORESCENT DYES/ (89756)
51 (fluorescent adj1 dye*).tw. (17810)
52 (fluorescent* adj1 agent*).tw. (522)
53 fluorochrome*.tw. (6029)
54 (fluorescent adj1 probe*).tw. (26525)
55 SPECTROSCOPY, NEAR-INFRARED/ (17748)
56 (near-infrared adj2 spectroscopy*).tw. (18710)
57 (near-infrared adj2 spectrometry*).tw. (225)
58 (nir adj1 spectroscopy*).tw. (3452)
59 1 or 2 or 3 or 7 or 8 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (76699)
60 33 or 34 (18309)
61 28 or 29 or 30 or 31 or 32 or 42 or 43 or 44 (298941)
62 60 and 61 (1872)
63 59 and 62 (225)
64 limit 63 to humans (212)
65 limit 64 to english (205)

Other Databases	
PubMed	Similar MeSH, keywords, limits used as per MEDLINE search
Embase	
INAHTA	
US FDA	

APPENDIX 2: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS

DESIGNATION OF LEVELS OF EVIDENCE

I	Evidence obtained from at least one properly designed randomized controlled trial.
II-I	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 3: EVIDENCE TABLE

Only available upon request.

TECHNOLOGY REVIEW (MINI HTA) LAPAROSCOPIC INDOCYANINE GREEN SENTINEL LYMPH NODE MAPPING IN ENDOMETRIAL CANCER

e ISBN 978-629-7842-01-1

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