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Sentinel lymph node mapping in endometrial cancer: new insights into an essential tool

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ABSTRACT

Objective. This narrative review summarizes current evidence on sentinel lymph-node (SLN) mapping in endometrial cancer (EC), focusing on tracer performance, injection techniques, detection rates (DR), surgical approaches, and ultrastaging. A comprehensive search of PubMed, Embase, and the Cochrane Library was performed (inception – 15 April 2025) using the terms “sentinel lymph node” AND “endometrial cancer”, without year limits. Studies, guidelines, and technical reports addressing SLN mapping in EC were screened, and data were extracted narratively according to SANRA recommendations.

Results. Three tracer classes are routinely used: indocyanine green (ICG), technetium-99m colloid, and methylene blue. Cervical ICG injection, performed superficially and deeply at 3 and 9 o'clock or in four quadrants, provides the highest bilateral detection rate (DR; approximately 93-98%), with intraoperative re-injection increasing DR by about 5%. Hysteroscopic and trans-myometrial routes improve para-aortic mapping but are technically more demanding and achieve lower pelvic DRs. Combining ICG with technetium or methylene blue offers no consistent benefit over ICG alone. Minimally invasive surgery maintains high DRs (91-95%) while reducing postoperative morbidity compared with laparotomy. Serial-section ultrastaging with cytokeratin immunohistochemistry detects an additional 3-4% of micro-metastases or isolated tumour cells compared with routine haematoxylin-eosin assessment.

Conclusions. SLN biopsy provides an accurate nodal assessment while sparing patients the morbidity associated with systematic lymphadenectomy. Cervical ICG injection, coupled with minimally invasive surgery and meticulous ultrastaging, currently represents the most effective and reproducible strategy for SLN mapping in EC.

INTRODUCTION

Endometrial cancer (EC) is the most common gynaecologic malignancy in high-income countries, and its incidence continues to rise worldwide [1]. Most women present early with abnormal uterine bleeding; a small proportion remain asymptomatic, and some rare gynaecologic tumours that mimic EC may instead present late with non-specific signs and an elevated thrombo-embolic risk [2-5]. If neglected, it may lead to severe anaemia requiring blood transfusion or iron supplementation [6].

Beyond classical risk factors, dysbiosis of the gut microbiome is emerging as a potentially modifiable contributor to EC pathogenesis [7].

The primary treatment for EC involves surgical intervention, typically comprising a total hysterectomy and bilateral salpingo-oophorectomy, accompanied by minimal lymphadenectomy [8].

Minimally invasive surgery, including conventional laparoscopy, single-site access, and robotics, achieves oncologic equivalence with less morbidity in early-stage disease [9-11], allowing for successful lymph node sampling [12, 13].

In advanced EC, multivisceral cytoreduction may require bowel resection [14] or ureteral reimplantation [15], similar to the surgical approach used in other advanced multiorgan involvement gynaecological diseases, such as endometriosis [16-21]. Because nodal metastasis is detected in only ~4% of apparent stage-I cases, current guidelines permit omission of systematic lymphadenectomy in low-risk disease [22, 23].

Nonetheless, nodal status remains critical for adjuvant-therapy decisions, and sentinel lymph-node (SLN) mapping has replaced complete lymphadenectomy in many centres, lowering rates of lower-limb lymphoedema [24, 25]. The most widely used SLN mapping algorithm is the Memorial Sloan Ketterin algorithm [26].

Attention is now shifting to survivorship: fatigue, insomnia, and overall quality-of-life decrements are common after EC surgery [27, 28]. In other gynaecological cancers, such as advanced cervical carcinoma, neoadjuvant chemotherapy after surgery has been applied, although with poor results [29]. In EC, the gold standard, when possible, is radical surgery followed by adjuvant therapy, which can be chemotherapy, radiotherapy, or a combination of these [22].

Similarly, the accurate identification of hysteroscopic criteria underscores the importance of precise diagnostic techniques in managing gynaecological

pathologies [30]. This precision in the diagnostic approach mirrors sentinel lymph node mapping for endometrial carcinoma, where correctly identifying lymph nodes is crucial. Such meticulous nodal mapping can significantly influence therapeutic decisions and surgical staging strategies, demonstrating the vital role of accuracy in improving patient outcomes across gynaecological oncology.

Recently, TCGA-based molecular subgroups (POLE-mutated, MMR-deficient, p53-abnormal, NSMP) are likely to individualize the need for nodal assessment in EC. This is because these subgroups have distinct clinical and prognostic implications that can guide treatment decisions, including the necessity for lymph node dissection [31].

This narrative review critically appraises contemporary evidence on SLN mapping in EC, with emphasis on tracer choice, injection technique, detection rate (DR), surgical performance, and ultrastaging.

MATERIALS AND METHODS

This article is a narrative review of the existing literature on the types of tracers used for SLN biopsy in EC. It specifically examines the effectiveness of different tracers, analysing their impact on DR, including the method of injection, surgical techniques, and subsequent outcomes when employing ultra-staging protocols.

An extensive literature search was conducted on PubMed, Embase, and the Cochrane Library from inception to April 15, 2025. Articles were searched using the keywords “sentinel lymph node and endometrial cancer”. No filter on the year of publication was applied.

For this review, we considered any human investigation that examined SLN mapping in EC. To be eligible, a study had to focus on one or more elements of the SLN pathway, such as the tracer employed, the site or technique of injection, the diagnostic or bilateral detection rate, the histopathological ultrastaging protocol, or subsequent surgical and oncological outcomes (recurrence-free or overall survival). We accepted a wide range of study designs, including randomised or non-randomised clinical trials, prospective or retrospective cohort studies, case-control series, larger case series, systematic reviews or meta-analyses, and guidelines or consensus papers from relevant societies.

Conversely, we excluded articles that dealt exclusively with systematic lymphadenectomy and offe-

red no SLN component, or that combined EC with other tumour sites without providing separable results, were also omitted. The selected articles were thoroughly reviewed and evaluated to identify studies that aligned with the goals of this review. The narrative review was assessed according to SANRA guidelines [32].

TRACERS AND INJECTION TECHNIQUE: METHOD OF INJECTION FOR A SINGLE TRACER

In EC, tracers used for SLN biopsy can be categorized into three types: colorimetric, radio-nuclear, and near-infrared dyes. Indocyanine green (ICG) is used as a near-infrared tracer; Technetium colloid 99 (99mTc) serves as the radio-nuclear tracer; and methylene blue (MB) is employed as the colorimetric tracer [33] that enables the visualization of the lymphatic vessel path [34].

Types of tracers and method of injection for SNL biopsy: advantages and disadvantages

- ICG is a tricarbo-cyanine dye that emits a fluorescent signal within the near-infrared (NIR) light range. It is FDA-approved for vascular and hepatobiliary imaging, although it is commonly used off-label for lymphatic mapping [35]. The pharmacokinetics of ICG show a consistent volume of distribution closely matching that of plasma, with minimal tissue binding and a negligible fraction of unbound molecules in the blood [36]. However, ICG binds significantly to plasma proteins, particularly alpha-lipoproteins, which restricts its extravascular distribution but does not impede its clearance. The elimination of ICG involves active hepatic uptake and subsequent biliary excretion, leading to its appearance in the feces, which turn green. The dye's half-life ranges from 2.2 to 3 minutes in healthy adults [37]. The primary advantages of ICG include its capacity for real-time lymphatic mapping, non-radioactivity, reduced risk of allergic reactions, and the feasibility of completing the procedure in a single surgical stage. The main limitation is the necessity for specialized NIR imaging equipment [38]. Despite its low risk of anaphylaxis (1/42,000), ICG should be avoided in patients with severe iodine allergies or liver failure [37]. Several ICG tracer studies for SNL biopsy in EC describe the cervical injection route [12]. The

injection is made in the cervix indifferently at 3 o'clock and 9 o'clock deep and superficial or in the four quadrants of the uterine cervix [37, 39]. Different dilutions of ICG with sterile injectable solutions are proposed. Usually, 25 mg of ICG is diluted in 20 mL of sterile injectable solution or 25 mg of ICG in 10 mL [37]. A substantial portion of the literature describes the use of ICG via the hysteroscopic injection route, targeting both the subendometrial area around the tumour and the four quadrants of the uterus, tailored according to the lesion's extent [40]. Moreover, while cervical ICG injection yields a higher SLN DR than hysteroscopic endometrial injection in EC patients [41], reinjecting ICG during the surgical procedure can significantly enhance the DR. This strategy aims to improve SLN mapping accuracy and outcomes during surgery [42].

- Technetium colloid 99 (99mTc) is a metastable nuclear isomer used in SLN detection via nuclear imaging and intraoperative gamma counters. Its property to emit gamma rays with suitable photon energy and a short biological half-life minimizes radiation exposure while allowing timely scanning [43]. These properties make the isotope appropriate only for diagnostic applications, not for therapeutic interventions. A gamma-detecting probe identifies areas with "hot" tracer signals during surgery. Once the general region of elevated uptake is localized, the surgeon employs dissection techniques to visually locate the blue (or green) dyes within the area showing increased gamma signal activity [44]. The gamma-detecting probe is then used to quantify the signal strength of the resected SLN. It is one of the original techniques of SLN mapping utilized in managing other cancers, such as breast and vulvar cancer. The advantage of radiolabeled isotopes is their ability to penetrate deeply into tissue, which can benefit patients with EC, where lymphatic drainage can be unpredictable and nodal basins may contain fat [45]. Disadvantages include the need for a separate injection procedure in nuclear medicine, which means the intervention must be performed with a different medical team and at a different time [46]. Radiocolloid injections for EC SLN biopsy are administered hysteroscopically or via the cervical route [47]. Typically, the hysteroscopic method is performed a day before the surgical intervention, targeting the subendometrial layer both around the tumour and across the four quadrants of

the uterus. Conversely, cervical injections occur at the classical landmarks of 3 and 9 o'clock or throughout the four quadrants of the uterine cervix [43]. While literature extensively documents hysteroscopy and cervical injections of technetium-99m (Tc99m), only a few studies discuss the use of TUMIR, applying Tc99m via ultrasound to inject both the anterior and posterior parts of the myometrium for EC SLN biopsy [48].

- Methylene blue (MB), an aromatic heterocyclic organic compound, is a cost-effective alternative for SNL biopsy. Though not FDA-approved, it is often used off-label, showing equivalence to isosulfan blue in other cancers [33]. MB reaches lymph nodes within five minutes post-injection and stains them within twenty-one minutes. While economical and straightforward to administer, MB carries risks of paradoxical methemoglobinemia and serotonin syndrome, especially in patients on serotonergic medications, and is contraindicated in individuals with favism [49,50]. The MB colorimetric dye injections use various routes, including cervical, hysteroscopic, and uterine subserosal and combinations of trans-cervical and trans-uterine methods [49]. Typically, MB cervical injections are administered into the four quadrants of the cervix [51]. Hysteroscopically, MB is injected into the four walls of the uterus and/or around any isolated tumours or skip lesions [34]. While MB injections via hysteroscopy and the cervical route are generally performed pre-operatively, uterine subserosal MB injections are conducted intraoperatively. Specifically, MB is injected into eight subserosal sites during abdominal surgery: the most superior parts of the anterior and posterior midlines of the fundus, the anterior and posterior midparts of the uterus, the anterior and posterior lower parts of the uterus, and at both cornual ends. Additionally, injections are made into the cervicosubserosal myometrium at the 12, 3, 6, and 9 o'clock positions, often combining subserosal and cervico-subserosal approaches [52].

The diverse applications and combinations of these tracers, ICG, 99mTc, and MB, illustrate their varied utility in clinical studies, offering distinct benefits and challenges in sentinel lymph node mapping for EC.

Tracer injection site in EC

Injection sites for sentinel lymph node (SLN) biopsy in EC are typically cervical or uterine [27]. The

tracer is directly inoculated into the cervix using a needle [28]. Options for uterine injections include hysteroscopic-guided administration, transvaginal ultrasound-guided myometrial injection of the radiotracer (TUMIR), or through trans-subserosal abdominal surgery [5, 48, 52-57]. Obesity, a well-established risk factor for EC, has been shown to disrupt lymphatic architecture, thereby potentially affecting lymphatic drainage and the accuracy of sentinel lymph node mapping [58]. Moreover, conditions such as polycystic ovary syndrome (PCOS), which are characterized by hormonal imbalances and metabolic dysregulation, may further compound these alterations in lymphatic function [59]. These metabolic and endocrine factors not only increase the incidence of EC but might also influence the pattern of lymphatic spread, underscoring the need for early, tailored diagnostic and staging strategies [60] in affected patients [61-63] (**Table 1**).

Tracer injection methods: pros and cons

Cervical injection has become the most favoured technique, as it is simple and yields the highest rates of SLN detection. It is good practice to inject the tracer slowly into the submucosa or superficial cervical stroma to maximize lymphatic absorption and minimize staining of deep pelvic tissues [56]. Mounting evidence suggests that cervical injection preserves the accuracy of detection of pelvic metastatic disease that may result from the confluence of lymphatic pathways from different regions of the uterus exiting the cervix through the lateral parameters [57]. The uterus has three lymphatic drainage pathways: the upper paracervical pathway, which is the classical pelvic pathway; the lower paracervical pathway; and the pelvic-infundibulum pathway. Some para-aortic lymph nodes are likely reached only through lymphatics with deep injections via this latter route. However, the accuracy of para-aortic mapping has not been thoroughly studied or documented [55].

Differently, the hysteroscopy method of injection for SNL biopsy in EC has been investigated in several studies [64]; particularly, the subserosal uterine fundus [65], myometrium [66], and subendometrial layer have been explored with injection both around the tumour if the lesion is localized and in the four walls of the uterus. Hysteroscopic injection offers superior lymphatic mapping at the lumbar aortic level, although the technique can be challenging, particularly in EC patients where normal anatomy may be altered [55]. Numerous retro-

Table 1. Summary overview of tracer and injection site.

Tracer	Injection Site	Method of Injection	Advantages	Disadvantages
ICG	Cervix	Slow injection into the submucosa or superficial cervical stroma in the four quadrants of the cervix or at 3 and 9 o'clock.	Easy procedure; accurate detection of pelvic lymph nodes; possibility of re-injection during surgery.	Less detection of lymphatic drainage from the uterine parameters.
ICG	Uterus (hysteroscopy-guided)	Subendometrial injection around the tumour and in the four quadrants of the uterus.	Enhanced lymphatic mapping at the lumbar aortic level.	Technique complexity, especially in patients with altered anatomy due to endometrial cancer.
99mTc	Cervix	Injection at classic landmarks at 3 and 9 o'clock or in the four quadrants of the uterine cervix.	High detection rate of SNL biopsy as a single tracer without reinjection.	Procedure must be performed a day before the surgical intervention.
99mTc	Uterus (hysteroscopy-guided)	Injection around the tumour and the four quadrants of the uterus.	Improved lymphatic mapping at the lumbar aortic level.	Procedure must be performed a day before the surgical intervention.
99mTc	TUMIR	Ultrasound-guided injection into the anterior and posterior parts of the myometrium.	Enhances the ability to perform para-aortic SNL biopsy.	Multidisciplinary approach required; anaesthesia necessary; potential for complications such as transabdominal lesions.
MB	Cervix	Injection into the four quadrants of the uterine cervix.	Inexpensive and readily available.	Risks of paradoxical methemoglobinemia and serotonin syndrome, particularly in patients on serotonergic psychiatric medications; contraindicated in patients with G6PD deficiency.
MB	Uterus (hysteroscopy-guided)	Injection around the tumour and the four quadrants of the uterus before surgery.	Higher detection rate than cervical injection.	Injection performed pre-operatively.
MB	Uterine subserosal	Injection at eight uterine subserosal sites or at the cervicosubserosal myometrium at four sites (12, 3, 6, and 9 o'clock positions).	Injection performed during surgery.	Lacks a specific injection site; technique variability.

ICG: Indocyanine Green; MB: Methylene Blue; 99mTc: Technetium-99m; DR: Detection Rate.

spective studies and reviews have also established hysteroscopy as the gold standard for examining the endometrium [67]. This surgical approach has a wide range of applications. It is especially effective for treating benign conditions like intrauterine adhesions [47], submucosal uterine fibroids [53], or genitourinary syndrome [68], which can significantly impact a patient's quality of life and sexual function. The importance of addressing these conditions extends beyond immediate symptom relief, as they often affect intimate aspects of life, underscoring the need for innovative treatments that consider overall well-being, fertility, and sexual health [69, 70]. Hysteroscopy also serves as a valuable surveillance tool for patient groups such as breast cancer survivors, offering a potentially helpful predictive model based on hysteroscopic findings [5].

Additionally, another method for uterine injection is the TUMIR [48]. This procedure is conducted by a gynaecologist ultrasound specialist in collaboration with a nuclear medicine physician and involves the transabdominal injection of the radiotracer into the anterior myometrium [48]. Leading scien-

tific societies recognize TUMIR injection for intermediate/high-risk EC due to its enhanced ability for SNL biopsy in para-aortic dissection [71]. While TUMIR injection offers significant advantages, it also presents drawbacks, such as the need for anaesthesia, the involvement of multiple specialists, and potential complications like transabdominal lesions during the injection process [48].

Moreover, in preventive care for EC, particularly among postmenopausal women, hysteroscopic sampling is often the preferred method for endometrial biopsy [54] even in the presence of severe adhesiolysis that hardens the endoscopic procedures [72, 73]. This offers new insights into interventions on social media platforms, which reflect contemporary practices and patient engagement trends addressing the importance of increasing prevention [74, 75]. Ultimately, office hysteroscopy enables prompt diagnosis and, in selected cases, treatment of intrauterine pathology before further surgical procedures, generally without the need for anaesthesia. Its feasibility relies on standardized minimally invasive techniques, although procedural pain remains an important determinant of

patient tolerance and successful completion, and the optimal pain-management strategy has yet to be established [76-79].

DR OF SNL BIOPSY

The SNL biopsy targets the uterine lymphatic drainage system's initial lymph node or nodes [80]. The DR evaluates the success of the SNL biopsy, measuring the procedure's ability to unilaterally or bilaterally identify lymph nodes positive for metastases [51]. Current research on SLN mapping in EC is highly encouraging [47]. If the SLN is not detected, the surgeon must perform a systematic lymphadenectomy. Additionally, even if the SLN is identified, any visibly enlarged lymph nodes must be excised [26]. On one hand, the DR is influenced by the surgeon's expertise and meticulous attention to technical details. On the other hand, the DR of an SLN biopsy can be affected by various factors, including the type of tracer used, the injection site, surgical techniques, and the anatomopathological analysis protocol [26] (Table 2).

DR related to the type of tracers and the method of injection

In many studies of SNL biopsy in EC, MB is used either as a single dye or in combination with radiocolloid [47]. Studies comparing hysteroscopic to cervical injection of MB alone have shown a higher unilateral DR for hysteroscopic MB injections

[49]. Conversely, when MB is combined with radiocolloids, cervical injections are more prevalent than hysteroscopic injections [55]. While several studies report no significant difference in DR sensitivity between radiocolloid MB99m cervical injections and hysteroscopic or TUMIR injections [40, 48], it is crucial to note that TUMIR injections have shown high DRs in patients with high-risk EC but significantly lower DRs in early-risk EC patients [48]. Furthermore, ICG, whether used alone or in combination and injected into the cervix, has demonstrated the most effective pelvic SNL biopsy success [81]. Re-injection of ICG during surgery has been shown to increase DR, achieving a peak of 98% significantly [82]. The simplicity of performing cervical ICG injections, their reproducibility, low cost, minimal adverse reactions, and the feasibility of re-injection during surgery have led to a consensus in the literature that cervical injection of ICG is the most successful method for detecting SNL in EC [83].

DR related to surgical technique

Among the key factors in SLN mapping is the execution technique. SLN biopsy in EC can utilize invasive methods like laparotomy and minimally invasive techniques such as laparoscopy, robotic surgery, single-port, or multi-site approaches [84, 85]. The benefits of minimally invasive techniques over laparotomy include reduced postoperative pain, better cosmetic outcomes, quicker recovery, and decreased risk of surgical dehiscence [9]. Ad-

Table 2. Overview of DR related to SLN biopsy technique.

Tracer	Injection Method	Detection Rate (DR)	Advantages	Disadvantages
MB	Cervical	High	Cost-effective, simple to administer.	Risk of methemoglobinemia, serotonin syndrome in some cases.
MB	Hysteroscopic	Lower than cervical	Allows targeted injection close to tumour.	Higher complexity, risk of methemoglobinemia.
MB+99mTc	Cervical	Unspecified	Enhanced tissue penetration due to radiocolloid combination.	Requires nuclear medicine facilities, potential radiation exposure.
ICG	Cervical	Up to 98%	High detection rate, real-time mapping, minimal side effects.	Requires specialized NIR imaging equipment.
ICG	Hysteroscopic	Lower than cervical	Detailed mapping close to tumour.	Requires specialized equipment, more complex procedure.
99mTc	Hysteroscopic	High DR	Deep tissue penetration, precise localization.	Requires separate nuclear medicine procedure, radiation exposure.
99mTc	Cervical	Unspecified	Allows for timely scanning and localization.	Requires nuclear medicine capabilities, radiation exposure.
99mTc	TUMIR	Lower in early-risk EC	Enhanced ability for para-aortic dissection in high-risk EC.	Involves anaesthesia, higher complexity, requires multiple specialists.

ICG: Indocyanine Green; MB: Methylene Blue; 99mTc: Technetium-99m; TUMIR: Transvaginal Ultrasound-guided Myometrial Injection of Radiotracer.

ditionally, these techniques mitigate complications associated with auxiliary ports and shorten surgical times, particularly in single-site laparoscopy, which is considered the gold standard for adnexal pathologies and requires further evaluation for its feasibility in lymphadenectomy or SLN biopsy [83, 86-88]. However, non-invasive surgical techniques are related to a greater surgical complexity and learning curve [89] except for the hysterectomy via vaginal natural orifice transluminal endoscopic surgery (vNOTES) which has shown to have a less learning curve [87, 90]. Laparotomy remains a method for SLN biopsy in EC, especially when using ^{99m}Tc for myometrium and/or subserosal injections, with DR ranging from 61% to 93% [91]. Adding MB dye to laparotomy does not significantly alter the DR, which remains between 63% and 89% [55, 92]. Literature indicates that non-invasive surgical techniques are widely employed for SLN biopsy in early-stage EC, whether using single tracers, dyes, or radiocolloids. These techniques are preferred because laparoscopic and robotic optics incorporate infrared systems tailored for ICG, providing significant advantages with a simple switch [93]. The DR for SLN biopsy using ICG and ^{99m}Tc through non-invasive methods like laparoscopy or robotic surgery has been investigated both with the infrared tracer alone and in combination with ^{99m}Tc , showing no significant differences in DR, which typically remains between 91% and 95% [94]. Non-invasive techniques using ICG alone achieve a nearly unilateral DR ranging from 91% to 98%, whether in laparoscopy or robotic surgeries [95]. It is crucial to emphasize that higher DRs are obtained through non-invasive surgical performance and ICG reinjection during the surgical procedure [96].

DR related to ultrastaging

Ultra-staging enhances the detection of malignant cells in lymph nodes removed during surgeries for EC. This process involves advanced techniques such as deeper serial sectioning and immunohistochemical (IHC) staining to uncover tumour cells that are not visible with routine Hematoxylin and Eosin (H&E) staining [97]. The protocol for the pathological processing of SLNs varies among institutions, including the number of sections examined, the depth of sectioning within the tissue block, the distance in μm between sections, and the incorporation of IHC. Typically, a non-sentinel lymph node examination involves

a single H&E section along the node's long axis, with deeper levels or IHC applied at the pathologist's discretion [98]. A typical histological examination of a non-sentinel lymph node involves a single H&E section along the long axis of the lymph node (intact or bisected), with deeper levels or IHC performed at the pathologist's discretion [98]. The ultrasound examination for SLNs typically entails slicing along the long axis at 2 mm intervals, inspecting all slices under a microscope, and conducting at least one representative H&E level; additional H&E levels or IHC studies may be incorporated [88].

No universal guideline for the SLN ultra-staging protocol in EC exists, but several methods were proposed between 2011 and 2016:

- The Memorial Sloan Kettering (MSK) group suggests an initial routine H&E evaluation, followed by two adjacent 5 μm sections (one H&E and one AE1/AE3 cytokeratin) cut from each paraffin block at intervals of 50 μm [51, 88].
- The Touhami *et al.* group employs six serial sections cut at 40 μm intervals examined by H&E, with an additional section stained with IHC (AE1/AE3 cytokeratin) between the third and fourth levels [99].
- Desai *et al.* analysed SLNs by sectioning the block at 50 μm intervals, staining levels 1, 3, and 5 with H&E and levels 2 and 4 with AE1/AE3 [100].
- Raimond *et al.* prepared a cytological smear, sectioned it at 3 mm intervals, and further sectioned it at 200 μm intervals, with H&E-negative nodes undergoing AE1/AE3 staining [101].

The key benefit of immunohistochemical ultra-staging is its ability to detect an additional 3-4% of SLN micrometastases and isolated tumour cells (ITCs), the latter being less than 0.2 mm in diameter, which would be missed by routine H&E staining. The clinical relevance of ITCs is debated, but their identification highlights ultra-staging sensitivity [102].

Consequently, the DR is significantly improved in studies utilizing ultra-staging protocols, regardless of the tracer type or surgical technique employed [103].

DISCUSSION

There is now broad agreement that cervical ICG injection provides the most reliable and reprodu-

cible SLN mapping in apparent stage-I EC. Bilateral DR consistently exceed 90%, false-negative rates are < 5%, and the procedure virtually eliminates lower-limb lymphoedema when compared with systematic lymphadenectomy. Minimally invasive approaches, including laparoscopy, robotics, and single-site surgery, do not compromise oncologic safety, provided that the SLN algorithm and ultrastaging are applied rigorously [104].

Survival evidence: what do the data really show?

Early prospective cohorts were underpowered for survival end-points, but recent multicentre series provide substantive long-term data.

The most extensive propensity-matched analysis to date utilized the Surveillance, Epidemiology, and End Results database (6019 SLN *vs* 6019 lymph node dissection group). Nahshon *et al.* found higher 1-year overall survival in the SLN group, an advantage limited to grade 1-2 endometrioid cancers, while survival was equivalent in high-grade tumours, indicating that SLN sampling does not compromise early survival across disease grades [105].

In a contemporary, multicentre Italian cohort restricted to high-intermediate/high-risk histotypes (n = 242; 60-month follow-up), sentinel mapping alone yielded disease-free and overall survival curves that were superimposable to those of complete nodal dissection, while halving the rates of lower-limb lymphoedema [106].

Taken together, these studies strongly suggest that, when performed correctly, SLN mapping does not compromise oncologic outcomes, even in patients with intermediate- and high-risk EC.

Persisting controversies

Regarding paraortic mapping, hysteroscopic or TUMIR technetium injections improve lumbar-aortic detection, but they add logistical complexity and radiation exposure. Whether knowledge of para-aortic status alters adjuvant-therapy decisions or survival remains unproven [46, 48].

Retroperitoneal staging in EC has evolved from systematic para-aortic dissection to selective techniques such as TUMIR tracer injection, yet emphasises that robust survival data are still lacking [107].

Ultrastaging detects an additional 3-4% of micrometastases and isolated tumour cells; however, the prognostic significance of these findings and the need for intensified adjuvant therapy remain a topic of debate. Although both modern series included such patients, randomised evidence is lacking; ongoing trials

should clarify whether SLN mapping alone suffices in serous, clear-cell, and carcinosarcoma subtypes (non-endometrioid, grade 3) [102, 103].

Quality of life and enhanced recovery

Patient-reported outcomes consistently favour SLN mapping owing to shorter hospital stay, quicker mobilisation and dramatically lower rates of chronic lymphoedema. Integration of Enhanced Recovery After Surgery (ERAS) programmes has further reduced fatigue and sleep disturbance during survivorship. These gains underscore the importance of balancing oncologic efficacy with functional outcomes [108].

Italian data on minimally invasive surgery in gynaecologic oncology confirm that laparoscopy combined with ERAS shortens median length of stay from 4 to 2 days in early-stage EC, without increasing readmissions [109].

Future directions

Emerging genomic data, exemplified by the four TCGA classes reviewed by Besharat *et al.* [110], are set to reshape nodal surgery in EC. POLE-ultramutated tumours, which carry an excellent prognosis, may safely forgo any nodal assessment, whereas p53-abnormal (copy-number-high) cancers could still justify systematic para-aortic dissection and intensified adjuvant therapy. Machine-learning models that combine radiomic features with these molecular fingerprints are being explored to pre-operatively assign patients to either sentinel-node mapping or complete lymphadenectomy. Definitive proof will come from the prospective randomised trials now comparing cervical ICG-guided SLN biopsy with conventional lymphadenectomy in high-risk cohorts. These trials are crucial for validating a genomically tailored surgical strategy.

CONCLUSIONS

Recent revisions of the FIGO system illustrate how EC staging has shifted from a purely anatomical, uterus-confined framework [111] to an integrated model that now weighs extra-uterine spread, molecular subtype, host immunocompetence, and nodal status (FIGO 2023). This broader perspective has re-framed surgical staging: rather than removing every pelvic and para-aortic node, the current goal is to obtain the correct nodal information with the least morbidity [112].

Evidence remains mixed. Some series still report a survival benefit for systematic lymphadenectomy in biologically aggressive tumours. In contrast, others demonstrate that, in low-risk disease, where nodal positivity is as low as 0-4% and seldom exceeds 10% even in intermediate-risk cases, the additional risks of comprehensive dissection outweigh any oncologic gain [113]. Against this backdrop, sentinel-node biopsy offers a logical compromise: it targets the first echelon nodes that truly determine stage, maintains the false-negative rate within accepted limits, and simultaneously curtails lymphoedema, operative time, hospital stay, and antibiotic use [114]. Technical refinements have made the approach increasingly robust. Superficial and deep cervical injections of ICG remain the most reproducible route, achieving near-universal pelvic mapping [37]. When combined with robotic or laparoscopic optics capable of near-infrared imaging, and, when required, a second intra-operative ICG injection, detection rates routinely exceed 95s% [115].

Finally, meticulous ultra-staging with serial sectioning and immunohistochemistry uncovers a further 3-4% of micrometastases or isolated tumour cells, safeguarding diagnostic accuracy without resorting to blanket lymphadenectomy [51].

In summary, contemporary data support a paradigm in which sentinel-node mapping, performed with cervical ICG and comprehensive ultra-staging, should be the default strategy for nodal evaluation across most risk groups. Systematic lymphadenectomy is increasingly reserved for selected p53-abnormal or grossly node-positive cases, a shift that aligns surgical ambition with molecular risk and patient-centred outcomes.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

F.S.: Conceptualization, project administration, writing – original draft. S.D.M.: Writing – review & editing, supervision. S.D.S, G.T.: Visualization. G.S.: Investigation, methodology. S.T.: Conceptualization. B.P.: Data curation. B.C., G.S.: Supervision.

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The authors declare that they have no conflict of interests.

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N/A.

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