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REVIEW PAPER

Sentinel lymph node mapping in endometrial cancer to reduce surgical morbidity: always, sometimes, or never

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Abstract

Introduction: Surgical staging of nodal status is of utmost significance to determine the stage of endometrial cancer and construct a targeted treatment plan. Systematic lymphadenectomy has for years been the procedure of choice for staging purposes, enabling thorough assessment of lymph nodes. Nevertheless, it is associated with increased morbidity and severe postoperative complications. In an attempt to avoid the disadvantages of lymphadenectomy, the use of sentinel lymph node (SLN) biopsy has been examined as an alternative staging procedure.

The purpose of the present review is to summarize and provide up-to-date evidence about the role of SLN biopsy in the staging and management of endometrial cancer cases in the terms of optimal technique, efficacy, safety, and postoperative morbidity, as an alternative approach to regional lymphadenectomy.

Material and methods: A thorough literature search was conducted in MEDLINE and SCOPUS to identify recent primary research and previous review articles that explore the use of SLN mapping as a staging procedure in patients with endometrial cancer.

Results: There is increasing evidence that SLN mapping is efficient in identifying metastatic nodal disease without compromising oncological safety, achieving comparable or even superior detection rates to those of lymphadenectomy, when optimal technique and careful intraoperative nodal assessment are applied.

Conclusions: Sentinel lymph node mapping can safely replace lymphadenectomy as an acceptable alternative staging method for endometrial cancer; however, future research might further strengthen this suggestion by resolving potential areas of doubt and debate, especially for high-risk endometrial cancer cases.

Key words: endometrial cancer, staging, nodal status, sentinel lymph node biopsy, lymphadenectomy

Introduction

Endometrial cancer is the most common gynaecological malignancy and the 6th most common cancer affecting women globally [1]. The incidence of the disease continues to increase steadily, by approximately 1–2% per year [2]. In 2018, more than 382,000 new cases and 90,000 deaths were reported [3]. Endometrial cancer usually produces symptoms relatively early, with postmenopausal bleeding being the most common clinical manifestation [4]. Consequently, most women are diagnosed at an early stage and thus have a generally good prognosis and high survival rates, which otherwise tend to be low in the case of patients with advanced-stage or recurrent disease [2].

The main prognostic factors for endometrial cancer are the age of the patient, the depth of myometrial invasion, the overall stage, and the grade and histological subtype of the tumour [5]. The overall 5-year survival rate is approximately 80%; however, it varies among the different types, stages, and grades of endometrial cancer [6]. Prognosis is more favourable for early-stage cancers, with 5-year survival rates estimated at 85% for International Federation of Gynaecology and Obstetrics (FIGO) stage I and 75% for stage II carcinomas, while it is also better in cases of endometrioid carcinomas compared to clear-cell or serous subtypes. Women with early-stage, low-grade endometrial cancer have an excellent prognosis, because surgical treatment is considered curative in these cases [5].

Surgical treatment of early-stage endometrial cancer usually consists of primary tumour excision by performing hysterectomy with bilateral salpingo-oophorectomy followed by regional lymph node dissection (pelvic and para-aortic lymphadenectomy). A complete surgical staging for endometrial cancer might also include sampling of peritoneal fluid by washing, exploration of the peritoneal cavity, and selective biopsies of suspicious areas [7].

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Lymph node metastasis represents the most common form of extrauterine spread of endometrial cancer and is considered among the most important prognostic factors and the strongest predictor of recurrence. Although regional lymphadenectomy is a crucial part of the surgical staging procedure, it is associated with significant morbidity and severe intraoperative and postoperative complications [7, 8]. In this context and regarding the necessity to appropriately assess the extent of the disease without severely increasing the occurrence of complications that may result from invasive procedures, sentinel lymph node (SLN) biopsy arises as a technique with potential for adequate staging with less morbidity in patients with endometrial cancer.

The present review aims to explore the role of SLN biopsy in the staging and management of endometrial cancer cases in terms of optimal technique, efficacy, safety, and postoperative morbidity, as an alternative approach to regional lymphadenectomy. It presents up-to-date evidence about the optimal technique of SLN biopsy in terms of proper administration, best performing tracers, and mapping protocols for successful intraoperative SLN detection. It further discusses in detail debatable and controversial topics regarding SLN mapping in endometrial cancer, such the number of dissected lymph nodes considered adequate for staging as well as their appropriate pathological assessment, the preferable surgical approach in node retrieval, the role of para-aortic lymph node dissection, and the application of SLN biopsy in high-risk endometrial cancer patients. Consequently, the present review includes significant information that may be implemented in clinical practice, considering continuing improvement in the management of patients with endometrial cancer, and in the field of increasing research around endometrial cancer, providing questions that still remain to be answered.

Ethical approval and consent to participate

Not applicable. The present article does not involve intervention on a population of humans and/or animals directly; it is a review of literature that gathers information from published articles.

Lymphadenectomy: advantages and disadvantages

Lymphatic vessels of the uterine fundus drain mainly into para-aortic lymph nodes; lymphatic drainage of the uterine body is via pelvic lymph nodes (external iliac and obturator chains). In endometrial cancer, lymphatic metastasis to para-aortic nodes is possible even without the involvement of pelvic lymph nodes [9, 10]. The rate of metastasis of endometrial cancer in both pelvic and para-aortic lymph nodes ranges 3–6.9%, while isolated positive para-aortic lymph nodes are found in approximately 1% of early-stage endometrial cancer cases [11].

Preoperative and intraoperative evaluation of nodal status is necessary for two main reasons: it is essential to determine the stage of the disease, and it influences the final decision of adjuvant therapy implementation to the treatment plan. Surgical staging of endometrial cancer was initially suggested in 1988 by FIGO and remains an integral part of endometrial cancer management, as per the revised FIGO staging issued in 2009 [11, 12]. According to the National Comprehensive Cancer Network (NCCN), it is recommended that surgical staging of endometrial cancer should include complete hysterectomy, bilateral salpingo-oophorectomy, evaluation of all peritoneal surfaces, pelvic and para-aortic lymphatic chains up to the level of left renal vein, and removal of suspicious lymph nodes [13].

Even though lymphadenectomy has potential advantages, including accurate surgical staging, targeted postoperative treatment, and eradication of metastatic lymphatic disease, it is a strategy that has received a lot of criticism. Removal of all pelvic and para-aortic lymph nodes at initial surgery is associated with increased morbidity and complications, such as lymphoedema, lymphocyst formation, vascular, ureteral, and visceral injuries, deep vein thrombosis, chylous ascites, and ileus, which may have an adverse impact in quality of life [7, 8, 14]. Lymphoedema of the lower extremity and the lower abdominal wall is the most common adverse effect of lymphadenectomy and is dreaded by the patients; its occurrence has been highly attributed to the removal of the most distal circumflex iliac nodes [15].

Moreover, the effect on survival and the therapeutic value of lymphadenectomy is also under dispute. The therapeutic significance of complete lymph node dissection remains controversial due to lack of high-quality evidence from randomized clinical trials [16]. Retrospective data suggesting a therapeutic benefit to lymphadenectomy is limited; in a French retrospective study of 208 patients treated with lymphadenectomy, the rate of intraoperative complications on a first lymphadenectomy was estimated at 8%, while it reached 22% for restaging, concluding that lymphadenectomy can be a source of severe morbidity (17.5%) and mortality (2.5%) [17]. Two European randomized clinical trials failed to show any survival advantages for patients who underwent pelvic lymphadenectomy [16, 18, 19]. A recent systematic review and meta-analysis conducted to examine the efficacy and safety of lymphadenectomy in endometrial cancer patients concluded that there is no sufficient evidence that lymphadenectomy decreases the risk of death or recurrence in patients with presumed stage I disease, but they are likely to experience postoperative complications [20].

At the same time, there is increasing evidence that SLN biopsy is associated with a significant decrease in the incidence of lymphoedema and other known postoperative adverse effects, compared to lymphadenectomy [21]. Sentinel lymph node biopsy has already been incorporated as a standard of care for staging purposes in the surgical management of other types of cancer, including melanoma, and breast and vulvar cancer [22]. Consequently, SLN is emerging as a potential strategy for lymph node evaluation and an acceptable alternative approach in patients with endometrial cancer in whom a futile lymphadenectomy can be avoided, being recognized as a reasonable and oncologically safe middle ground.

Sentinel lymph node biopsy: basic principles and mapping techniques

As mentioned above, primary tumours of the endometrium drain through the lymphatic pathways leading to pelvic and para-aortic lymph nodes. The sentinel lymph node is the first node to receive lymphatic drainage and metastasis from the primary tumour. Regarding this, it can be deducted that the SLN status reflects the status of the entire lymphatic basin, and therefore, if we can accurately detect the SLN, we can get adequate information regarding the extent of lymph node involvement without performing complete lymphadenectomy, thus avoiding potential surgical complications [21].

Various techniques have been suggested for SLN detection in endometrial cancer patients. The most common tracers for SLN mapping used in the majority of large studies are blue dye and technetium-99 radiocolloid (Tc-99m), which can be used either alone or in combination. However, more recent randomized controlled trials have introduced another mapping protocol, using fluorescent indocyanine green (ICG) for intraoperative identification of SLN, which is gaining increased interest and popularity among the gynaecological oncology community [22, 23].

Indocyanine green: standard of care for sentinel lymph node mapping in endometrial cancer

Indocyanine green dye was developed for near-infrared photography by Kodak Research Laboratories in 1955. It was approved by the Food and Drug Administration for clinical use in 1956, and it was initially used in clinical settings for retinal fluorescent angiography in the early 1970s. The principles of ICG for SLN mapping are easily comprehensible. Near-infrared fluorescent ICG dye is administered intravenously or directly into the tissue. Being able to bind to plasma proteins, ICG is picked up by the lymphatic system and rapidly reaches the SLN, without remaining confined to it, but rather continuing its path to nearby lymph nodes. Thus, it is important to quickly initiate the procedure of SLN detection after ICG administration to correctly identify the SLN. Excitation of IGC fluorescence is achieved with near infrared light, and the visual detection of the fluorescent signal is enabled by the use of special endoscopes [22].

The optimal way to administer ICG for SLN detection in endometrial cancer patients has been a subject of interest among gynaecological oncologists. According to published evidence, the majority of research groups seem to be in favour of intracervical administration of the tracer, usually injecting equal doses of the ICG solution at the 3 and 9 o'clock positions of the cervix. There are also the 4-quadrant options, which include the injection of tracer either at the 3, 6, 9, and 12 or 2, 4, 8, and 10 o'clock positions of the cervix. At each position, the dye is usually injected into 2 different depths in the tissue, both submucosally and deeper into the cervical stroma. The exact concentration and volume of the solution that should be used is still under discussion; many studies set the dose at 4 ml, injecting 2 ml per position, but the amount used can widely vary [24–27]. A recent 2-centre study evaluating the impact of different doses of IGC for SLN detection demonstrated that a higher concentration and volume of ICG is associated with a larger number of retrieved SLNs, but it does not increase the bilateral detection rate in endometrial cancer cases [28].

Apart from intracervical administration, other approaches have been examined. A research group from Sweden conducted a prospective study to compare fundal and cervical injection of ICG for SLN mapping in endometrial cancer patients, describing a third potential way of lymphatic drainage apart from the 2 known pelvic pathways, i.e. the infudibulo-pelvic pathway, which was prominently identified following fundal injection of ICG. The study concluded that pelvic pathways and positions of SLNs are independent of the tracer injection site, but cervical injection is preferable to fundal due to a higher technical success rate [29]. Moreover, a recent multicentre prospective randomized controlled trial attempted to compare cervical to hysteroscopic injection of ICG for SLN detection in patients with endometrial cancer. Hysteroscopic administration consisted of peritumoral subendometrial injection of the tracer. According to the results, the bilateral pelvic detection rate was statistically significant in patients that received cervical injection (85.4%) compared to hysteroscopic injection (59,4%), while no significant difference between the 2 methods was reported regarding para-aortic lymph node detection, leading to the conclusion that cervical injection of ICG allows better identification of SLNs in the pelvic area [30].

The use of ICG has been appointed a standard of care for SLN mapping in endometrial cancer because there is strong evidence supporting its superiority to blue dyes, Tc-99m, or a combination of them, as well as its efficacy and safety. According to a systematic review and

meta-analysis that studied the diagnostic performance of ICG as a tracer for SLN detection in gynaecological and non-gynaecological cancers, ICG is considered both safe and promising for detecting lymph node metastases in different clinical settings [31]. One of the largest existing series on laparoscopic ICG SLN mapping performed on 75 endometrial cancer patients reported excellent overall and bilateral SLN detection rates (96% and 88%, respectively), combined with high sensitivity (91.7%) and low false negative rate (8.3%) [32]. A multicentre study enrolling 342 patients with endometrial cancer from 5 different European centres that attempted to compare Tc-99m combined with blue dye vs. ICG dye in terms of SLN detection rates showed a statistically significant higher rate of bilateral SLN mapping in the group of patients receiving ICG as a tracer (84.1%), compared to patients injected with the combination of Tc-99m and blue dye (73.5%) [26]. Enhanced performance of ICG at SLN detection was also demonstrated in a recent non-inferiority trial examining whether ICG is non inferior to isosulfan blue dye in detecting the SLN in 180 patients with cervical or uterine cancer who underwent curative surgery. Enrolled patients were randomized into 2 groups; one receiving lymphatic mapping with isosulfan blue dye followed by ICG and one being injected with ICG followed by isosulfan blue dye. The study concluded that ICG is superior to blue dye because it identified at least one SLN or bilateral SLNs at a higher rate and further supported that the combination of ICG and blue dye is not more efficient than ICG alone in detecting lymph nodes [33]. Finally, another recent randomized trial with 132 enrolled endometrial cancer patients, aiming to compare SLN detection rates of ICG vs. methylene blue, reached a similar conclusion. Using a different methodological approach (as methylene blue was injected in one side and ICG in the other side of the cervix in each patient), this study reported that the overall SLN detection rate was significantly higher with ICG (90.9%) than with methylene blue (64.4%). Although it was not possible to assess bilateral performance of the tracers, given the fact that the randomization was applied to the side that ICG was injected in each patient, the study underlined that the use of ICG is associated with a 26.5% increase in SLN detection rates compared to methylene blue [34]. Taking all the above into consideration and especially the evidence from the last 2 important studies, it can be deducted beyond any doubt that the use of ICG should be considered the standard of care for SLN mapping in endometrial cancer.

Sentinel lymph node detection and excision: important topics and areas of debate

Apart from careful administration and use of the most appropriate tracer, successful intraoperative SLN detection also requires deep knowledge of the anatomy of the pelvic lymphatic drainage pathways. The common and less common pathways (anterior and posterior pathways or ventral and dorsal paracervical pathways) have been described in detail in the literature. In most cases, the lymphatic trunks cross over the obliterated umbilical ligament, and the most common locations of sentinel lymph nodes after a cervical injection, detected across the anterior paracervical pathway, are medial to the external iliac, ventral to the hypogastric, or in the superior part of the obturator space. The less common locations of sentinel lymph nodes, across the posterior paracervical pathway, are usually seen when lymphatic trunks do not cross over the umbilical ligament but follow the mesoureter cephalad to the common iliac and presacral sentinel lymph nodes [27].

Adequate knowledge of the anatomy of pelvic lymphatic drainage is only one of the factors affecting the success of SLN mapping. There are also other principles, regarding the mapping technique, that should be followed to enhance the successful identification of SLNs, starting with the correct injection technique. Sentinel lymph node detection should be always performed ahead of other procedures during surgery to keep surgical field as clean as possible, which will facilitate the recognition of coloured nodes. Surgical manoeuvres during the search for SLNs should include division of the round ligament, identification of obliterated umbilical artery, and development of paravesical and pararectal spaces. After finding and following the lymphatic trunks crossing the umbilical ligament, it is also important to check less common lymphatic pathways for coloured nodes [35]. Additionally, it is significant to point out that the surgeon should not only focus on identified coloured nodes, but also enlarged ones, taking into consideration that macroscopically involved lymph nodes can be uncoloured, despite the low false negative rate of ICG in SLN identification. This phenomenon is not as frequent with ICG as it is with blue dye, which can be attributed to a blockage, formed by cancerous cells, of the lymphatic vessels leading to the actual SLN, which can be an enlarged but not coloured lymph node. In this case, the ICG migration pathway is altered and the dye is directed to a normal-appearing node, which can be falsely recognized as the SLN. Consequently, it is important to dissect any suspicious enlarged lymph nodes during SLN mapping, even in the absence of colouration, because the alteration of size is indicative of metastasis [35].

Another issue that is still debated, regarding SLN mapping, is the number of dissected lymph nodes considered adequate for accurate surgical staging. The count of lymph nodes removed during surgical staging has always been a topic of great interest for surgeons, because it was considered among the most important ways to assess the success of the staging

process. However, as the shift from quantity to quality is being gradually applied in surgical culture, and it is becoming more acceptable that we should focus more on the accuracy of the techniques rather than on numbers. One positive metastatic lymph node is sufficient to change the stage of endometrial cancer, so more attention should be paid to proper identification, retrieval, and thorough pathological evaluation of lymph nodes, rather than to their actual count.

Careful pathological assessment of retrieved lymph nodes plays an important role in achieving accurate staging via SLN mapping. Intraoperative frozen section biopsy is widely used for quick evaluation of excised nodes, but it can unfortunately be unreliable due to low sensitivity [36]. In this context, ultrastaging of SLNs can provide more accurate and detailed information that may greatly affect staging on some occasions, upstaging approximately 4–19% of patients. Micrometastases (0.2–2 mm) and isolated tumour cells (< 0.2 mm) can be detected more efficiently by ultrastaging, and although their treatment remains controversial, their presence affects the prognosis and survival rate [37, 38]. Micrometastatic disease represents an independent prognostic factor, so patients with micrometastatic deposits in pelvic lymph nodes might be candidates for adjuvant treatment [39].

But what should be done when no lymph nodes are mapped during SLN detection? This question has already been answered by the SLN algorithm for surgical staging of endometrial cancer issued by the NCCN [13]. The sentinel lymph node algorithm dates back to 2014, but it remains valid till today, being applied for all types and grades of endometrial carcinoma, as long as the disease appears to be limited to the uterus. However, an important change in clinical practice that should be taken into consideration when applying the algorithm is the current predominance of ICG as the tracer of choice for SLN mapping, because the algorithm was issued when blue dye and Tc-99m were mainly used, and it recommended the excision of all coloured SLNs. However, as described above, not everything that is green is necessarily a SLN when using ICG as a tracer, so it is important to emphasize on the correct technique and precise assessment of the mapping by following the anatomy of pelvic lymphatic drainage and additional excision of all suspicious lymph nodes indicative of extrauterine spread of the disease [40]. In the case that there is no mapping in a hemi-pelvis after tracer injection, a side-specific pelvic lymphadenectomy should be performed, while the decision to perform an additional para-aortic lymphadenectomy is left to the discretion of the attending doctor.

The role of para-aortic lymph node dissection in endometrial cancer remains controversial, considering that anatomic landmarks and dissection boundaries remain less defined, compared to other types of cancer [41]. There are certain parameters that may indicate the need for aortic node sampling, such as suspicious aortic or common iliac nodes, grossly positive adnexa, grossly positive pelvic nodes, high-risk histological subtypes of endometrial carcinomas, and high-grade tumours showing full thickness myometrial invasion [42]. Current data support that isolated para-aortic metastasis is observed in less than 5% of cases with negative pelvic lymph nodes. This rate further decreases to less than 1% for patients with endometrioid endometrial cancer (0.9%), while for serous, clear cell carcinomas and carcinosarcomas it is estimated at 2.5% [41]. In a recent study by Multinu *et al*. involving 394 endometrial cancer patients with both pelvic and para-aortic lymphadenectomy, the rate of isolated para-aortic metastasis was 2.5% (10 patients). Ultrastaging and pathological re-review of pelvic lymph nodes initially labelled as negative revealed occult pelvic dissemination in 3 out of 10 patients, 2 of which had micrometastases and one had isolated tumour cells. These results are indicative that ultrastaging can reduce the prevalence of true isolated para-aortic metastasis [43]. Nevertheless, further research is required to reach definitive conclusions regarding the necessity of para-aortic lymphadenectomy in patients with endometrial cancer.

Sentinel lymph node mapping in endometrial cancer can be performed both by laparoscopy and laparotomy. There is increasing evidence that the laparoscopic approach is superior because it is associated with a significantly decreased risk of postoperative complications, less postoperative pain, shorter hospital stays, and faster recoveries [44–46], without compromising oncological safety or adversely affecting survival [44, 47, 48]. It is considered a safe option even for patients with high-risk endometrial cancer [49], and additionally it presents higher detection sensitivity and bilateral detection rates compared to laparotomy [50]. However, the surgical approach should be tailored to the needs and characteristics of each patient, as well as the experience and skills of the attending gynaecological oncologist.

Approximately 90% of patients with endometrial cancer are diagnosed with early-stage disease, which can be managed without systematic lymphadenectomy. However, 10–15% of these cases are complicated with metastatic nodal disease; at the same time, more that 15% of the patients who preoperatively were deemed to have G1 (grade 1) tumours will be proven to have higher-grade disease based on the final pathological review after initial surgery. A study evaluating the oncological safety of SLN biopsy in low-risk endometrial cancer patients showed that the recurrence-free survival (RFS) and overall survival (OS) were improved when these patients received SLN mapping compared to complete omission of lymph node status evaluation [51]. It is evident that these early-stage patients can significantly profit from SLN mapping.

Currently, it is advised that complete lymphadenectomy is reserved for cases with high-risk features, but it is worth considering how SLN detection would perform in intermediate- and high-risk patients. According to a retrospective study by Touhami *et al*. that assessed the performance of SLN mapping with cervical ICG administration in 128 patients with high-risk endometrial carcinomas, at least one SLN was identified in 89.8% of the patients (115/128) and bilateral SLN mapping was successful in 63.2% of the patients (81/128), while only one false negative case occurred. The study demonstrated that SLN detection has increased sensitivity and high negative predictive value even in high-risk endometrial cancer cases [52]. Another prospective multicentre cohort study, enrolling 156 patients diagnosed with stage I G2 (grade 2) endometrioid or high-grade endometrial carcinomas, performed both SLN mapping and pelvic lymphadenectomy, and para-aortic lymphadenectomy was additionally performed in 101 high-grade patients. Again, SLN detection rates were impressively high (97.4% per patient and 77.6% bilaterally), as was the sensitivity (96%) and the negative predictive value of the method (99%), with the false negative rate being as low as 4% [53]. A recent retrospective multicentre study by Schlappe *et al*. attempted to investigate the oncological safety of SLN mapping in high-risk endometrial cancer patients by comparing survival outcomes between patients with uterine-confined serous or clear cell endometrial carcinoma who underwent comprehensive pelvic and para-aortic lymphadenectomy (LND) (n = 96) and patients with the same diagnosis who received SLN biopsy as a method of surgical assessment of nodal status (n = 118). The inverse-probability of treatment weighting (IPTW)-adjusted hazard ratio (HR) for the association of nodal assessment method (SLN vs. LND) with death due to any cause was 0.44 (95% CI: 0.19, 1.02, p = 0.06), with IPTW-adjusted 3-year OS rates of 88% for the SLN cohort and 77% for the LND cohort. The association between surgical approach (SLN vs. LND) and recurrence of the disease was also not statistically significant, with an IPTW-adjusted HR of 1.46 (95% CI: 0.70, 3.04, p = 0.32) and IPTW-adjusted 3-year RFS rates of 69% and 80%, respectively. However, in the case that only patients with negative lymph nodes were taken into consideration, the IPTW-adjusted HR for the association of surgical approach (SLN vs. LND) with progression of the disease was 3.12 (95% CI: 1.02, 9.57, p = 0.05), which is marginally statistically significant, while no significant difference was detected in the association of nodal assessment method with death by any cause (IPTW-adjusted HR = 0.69, 95% CI: 0.24, 1.95, p = 0.48) [54]. The results of all the aforementioned studies challenge current clinical practice regarding the management of high-risk endometrial cancer patients, but there is a need for more research to draw safer conclusions about the use of SLN mapping in these cases.

Conclusions

Sentinel lymph node mapping with use of indocyanine green as a tracer is gradually being established as the most suitable procedure for lymph node status evaluation in patients with endometrial cancer. It is characterized by a high degree of diagnostic accuracy in detecting metastatic nodal disease, with the additional advantage of decreased perioperative morbidity, without compromising oncological safety. Current evidence support that it can safely replace lymphadenectomy in the staging of endometrial cancer. Future research should aim to resolve any controversial topics regarding the use of SLN mapping in endometrial cancer, to further expand its role in the management and treatment of endometrial cancer patients.

Disclosure

The authors report no conflict of interest.

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