Gynecology and Obstetrics Clinical Medicine 3 (2023) 1–6

Contents lists available at ScienceDirect

Gynecology and Obstetrics Clinical Medicine

journal homepage: www.keaipublishing.com/en/journals/gynecology-and-obstetrics-clinical-medicine

Review Article

Update of sentinel lymph node mapping assessment in endometrial cancer

Se Ik Kim, Jae-Weon Kim *

Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, 03080, Republic of Korea

ARTICLE INFO

Keywords:
Endometrial cancer
Sentinel lymph node
Lymph node metastasis
Accuracy
Prognosis
Survival

ABSTRACT

Endometrial cancer is the most common gynecologic malignancy in developed countries. Pathologic confirmation of lymph node metastasis is important for risk stratification and the administration of adjuvant treatments. Therefore, comprehensive, systematic lymphadenectomy has been routinely performed but has been associated with various morbidities. Meanwhile, the concept of sentinel lymph node (SLN) mapping and biopsy has emerged and is now accepted as an alternative to conventional systematic lymphadenectomy in early-stage endometrial cancer. For better management of endometrial cancer, we conducted a literature review to summarize the role and diagnostic accuracy of the SLN mapping strategy in endometrial cancer. Evidence from the monumental and recent literature and ongoing clinical trials will be introduced.

1. Introduction

Endometrial cancer is a worldwide problem, with an estimated 417,000 new cases each year.[1] In the United States, endometrial cancer is expected to be the fourth most commonly diagnosed female cancer and the sixth most common cause of female cancer deaths in 2023, and both the incidence and mortality rates of endometrial cancer are rising.[2,3] Incidence rates of endometrial cancer in Asian countries and regions increased rapidly, partly reflecting increases in the prevalence of risk factors such as excess body weight and physical inactivity.[4] In Korea, endometrial cancer now accounts for the most common gynecologic malignancy.[5,6] Lymph node metastasis (LNM) is one of the most important prognostic factors in endometrial cancer.

Pathologic confirmation of LNM helps with precise risk stratification, followed by appropriate administration of adjuvant treatments in endometrial cancer. Therefore, comprehensive systematic lymphadenectomy has been routinely performed to ascertain lymph node (LN) status. However, such systematic lymphadenectomy causes prolonged operative times and various morbidities, such as lymphatic leakage, lymphocele, lymphedema, nerve or vessel injury, and wound infection. These morbidities definitely deteriorate patients' quality of life significantly.[7] For example, lower limb lymphedema (LLL), which is common after pelvic lymphadenectomy as a result of damage to the lymphatic system,[8,9] is chronic, often irreversible, so that LLL could limit mobility and daily activity, and have a negative effect on the psychological and social wellbeing.[7] The incidence of LLL in patients treated with hysterectomy plus lymphadenectomy was reported at up to 52.3%.[10] In planning gynecologic cancer survivorship, management of LLL after pelvic lymphadenectomy is one of the important issues.[11]

Because of this, the concept of sentinel lymph node (SLN) mapping and biopsy has emerged and is now introduced as an alternative to conventional systematic lymphadenectomy in the National Comprehensive Cancer Network (NCCN)[12] and European Society of Medical Oncology (ESMO)[13] clinical practice guidelines for early-stage endometrial cancer. Sentinel refers to a person employed to guard something. The SLN is the first LN or group of LNs in a lymphatic chain where cancer spreads from its organ of origin. Therefore, SLN has the highest risk of metastasis, and if disease is present in the first LN, it suggests that the rest of the chain may also have possibilities of metastasis.[14] SLN mapping has the potential to expose fewer patients to the morbidity of systematic lymphadenectomy.

Endometrial cancer may be managed better with the SLN mapping

* Corresponding author. Department of Obstetrics and Gynecology, Seoul National University College of Medicine, 101 Daehak-Ro, Jongno-Gu, Seoul, 03080, Republic of Korea.
E-mail address: kjwksh@snu.ac.kr (J.-W. Kim).

Publishing services by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.gocm.2023.01.005
Received 28 January 2023; Accepted 30 January 2023
Available online 3 February 2023

strategy in selected patients. Thus, we conducted a literature review to summarize the role and diagnostic accuracy of the SLN mapping strategy in patients with early-stage endometrial cancer. We prioritized phase III randomized controlled trials (RCTs). We also searched prospective and retrospective observational studies, as well as ongoing clinical trials.

2. Importance of lymph node assessment

The current International Federation of Gynecology and Obstetrics (FIGO) staging system assigns endometrial cancer patients with positive pelvic LNs and those with positive para-aortic LNs with or without positive pelvic LNs to stages IIIC1 and IIIC2, respectively, if the patients have no invasion of bladder or bowel mucosa and no distant metastases.[15] Even in patients with apparent uterine-confined or clinical stage I endometrial cancer, a considerable number of patients have pelvic and/or para-aortic LNM.[16] Therefore, surgical assessment of pelvic and para-aortic LNs is essential for precise staging without missing potential LNM.[17]

According to the historical GOG 33 study[16] that evaluated the pathologic features of 621 patients with clinical stage I endometrial cancer who underwent surgical staging, 70 (11.3%) had pelvic and/or para-aortic LNM; notably, 12 (1.9%) had metastases to the para-aortic LNs only. Using grade of tumor, depth of myometrial invasion, and intraperitoneal metastasis, low- (n = 44), moderate- (n = 426), and high-risk (n = 151) groups were generated. Then, pelvic LNM was identified in 0%, 3–6%, and 18–61% of patients in the low-, moderate-, and high-risk groups, respectively. This study suggests that certain patients are at increased risk of LNM.

Two previous RCTs have investigated the impact of systematic lymphadenectomy during staging surgery on survival outcomes in endometrial cancer.[18,19]

An Italian RCT enrolled 514 patients with clinical stage I endometrial cancer and randomly assigned them to systematic pelvic lymphadenectomy arm (n = 264) or no lymphadenectomy arm (n = 250).[18] Although systematic pelvic lymphadenectomy improved surgical staging, it did not improve both overall survival (OS; hazard ratio [HR], 1.20; 95% confidence interval [CI], 0.70–2.07; $P = 0.50$) and disease-free survival (DFS; HR, 1.10; 95% CI, 0.70–1.71; $P = 0.68$).

In ASTEC, a large European RCT, 1048 patients with clinical stage I endometrial cancer were enrolled and randomly assigned to systematic pelvic lymphadenectomy arm (n = 704) or no lymphadenectomy arm (n = 704).[19] There was no benefit with pelvic lymphadenectomy in terms of OS (adjusted HR, 1.04; 95% CI, 0.74–1.45; $P = 0.83$) or DFS (adjusted HR, 1.25; 95% CI, 0.93–1.45; $P = 0.83$), but a substantial increase in the incidence of LLL. Accordingly, the researchers recommended against routine pelvic lymphadenectomy in presumed early-stage endometrial cancer.

Although these two RCTs showed no survival benefit from systematic pelvic lymphadenectomy, controversy still exists. Besides the selection bias issue, the ASTEC trial suffers from criticism that patients with intermediate- or high-risk early-stage endometrial cancer were secondarily randomized to external-beam radiotherapy or observation with no external-beam radiotherapy, whether pelvic lymphadenectomy was conducted or not. Additionally, the benefit of para-aortic lymphadenectomy was not addressed.[20,21]

Currently ongoing AGO-OP.6/ECLAT (NCT03438474) aims to evaluate the effect of comprehensive or systematic pelvic plus para-aortic lymphadenectomy on survival outcomes in patients with clinical stage I-II endometrial cancer having one or more high-risk factors, including myometrial invasion ≥50%, cervical stromal invasion, grade 3 type I (endometrioid, endometrioid with squamous differentiation, or mucinous), or any grade type 2 (serous, clear cell, or carcinosarcoma) tumors.[22] Patients are randomly assigned to pelvic plus para-aortic lymphadenectomy arm or no lymphadenectomy arm with a 1:1 ratio. In total, 640 patients will be enrolled. The primary endpoint is OS, and the secondary endpoints include DFS, perioperative complications, and health-related quality of life. If pelvic and para-aortic lymphadenectomy significantly improves OS in patients with stage I-II high-risk endometrial cancer and the morbidity of the intervention is acceptable, recommending systematic lymphadenectomy to this population is justified. Otherwise, systematic lymphadenectomy should be abandoned, as it offers no benefit but only harm.[22]

Meanwhile, SEPAL study retrospectively reviewed 671 patients with endometrial cancer who had been treated with systematic pelvic plus para-aortic lymphadenectomy (n = 346) or systematic pelvic lymphadenectomy only (n = 325) at two tertiary centers in Japan.[23] In intermediate- or high-risk patients (n = 407), the pelvic plus para-aortic lymphadenectomy group showed significantly better OS than the pelvic lymphadenectomy group, but similar OS was observed between the two groups in low-risk patients. In multivariate analysis, pelvic and para-aortic lymphadenectomy reduced the risk of death compared with pelvic lymphadenectomy in intermediate- or high-risk patients. These findings suggest that additional para-aortic lymphadenectomy might have survival benefits for patients at intermediate or high risk of recurrence.

Based on the SEPAL study, JCOG1412/SEPAL-P3, a Japanese phase III RCT, is currently ongoing to confirm the superiority of pelvic plus para-aortic lymphadenectomy to pelvic lymphadenectomy alone in patients with clinical stage IB-IIIC1 endometrial cancer.[24] Only those who have no evidence of para-aortic LNM and multiple pelvic LNM during surgery are included and randomly assigned to pelvic plus para-aortic lymphadenectomy arm or pelvic lymphadenectomy alone arm with a 1:1 ratio. Adjuvant chemotherapy is administered to patients with intermediate or high risk of recurrence. A total of 760 patients will be enrolled. The primary endpoint is OS, and the secondary endpoints include DFS, short-term surgical outcomes, and recurrence patterns. The JCOG1412/SEPAL-P3 will clarify the clinical utility of para-aortic lymphadenectomy in endometrial cancer.

3. Sentinel lymph node mapping and biopsy as alternative to systematic lymphadenectomy

Since systematic lymphadenectomy has little therapeutic benefit for patients with endometrial cancer, especially those with low risk of LNM, SLN mapping strategy has emerged as it enables evaluation of nodal status and staging. The feasibility and safety of SLN mapping and biopsy in endometrial cancer was demonstrated in previous retrospective[25–28] and prospective[29] studies.

The diagnostic efficacy of SLN mapping and biopsy in identifying LNM for endometrial cancer is assessed in comparison to complete lymphadenectomy (the gold standard). Herein, the following measurements are used[30]: the SLN detection rate is defined as the proportion of cases in which at least one SLN was identified among patients who underwent SLN mapping. Researchers regard sensitivity as the most clinically relevant index to decide whether to administer adjuvant therapy. Failed mapping refers to cases in which an SLN was not detected. A true-negative means a negative SLN in a patient with no LNM. A false-negative means a negative SLN in a patient with LNM. A true-positive means a positive SLN in a patient with LNM, whereas a false-positive is impossible to define. Sensitivity is calculated as the number of true positives divided by all patients with LNM. The false-negative rate is the number of false-negatives divided by the number of patients with LNM. The negative predictive value is determined by dividing the number of true negatives by the number of patients with a negative SLN.

SENTI-ENDO[31] was a multicenter prospective cohort study that aimed to assess the detection rate and diagnostic accuracy of SLN mapping and biopsy in predicting the pathologic pelvic LN status in patients with early-stage endometrial cancer. A total of 125 patients with clinical stage I-II endometrial cancer underwent cervical dual injection (technetium-99m and patent blue) and pelvic SLN mapping and biopsy, followed by complete pelvic lymphadenectomy. The results of the SENTI-ENDO

were published in 2011. The detection rate was 88.8% (111/125). When the hemipelvis was considered as the unit of analysis, sensitivity and negative predictive value were 100% and 100%, respectively. When the patient was considered as the unit of analysis, three patients had false-negative results, yielding a sensitivity of 84% and a negative-predictive value of 97%. In terms of safety, there were no complications after the injection of technetium-99m colloid, and there were no anaphylactic reactions after the injection of patent blue. Furthermore, no surgical complications were reported during SLN mapping and biopsy, including procedures that involved conversion to open surgery. This European study successfully showed the feasibility and safety of SLN mapping strategy; however, it has several limitations, such as the small number of patients and low frequency of para-aortic lymphadenectomy (12%).[31]

After SENTI-ENDO, there were two pivotal, large multicenter prospective cohort studies that investigated the diagnostic accuracy and safety of SLN mapping strategy in endometrial cancer.[32,33]

FIRES trial[32] enrolled 385 patients with clinical stage I endometrial cancer of all histologic types and grades undergoing robotic staging. Of them, 340 patients received a standardized cervical injection of indocyanine green (ICG) and SLN mapping and biopsy using near-infrared (NIR) fluorescence imaging, followed by systematic pelvic lymphadenectomy. Para-aortic lymphadenectomy was conducted in 196 (57.6%) patients. SLN specimens were examined according to a standardized ultra-staging protocol. The results of the FIRES trial were published in 2017; noteworthy, it was the largest prospective study on SLN mapping strategy in endometrial cancer. Successful mapping of at least one SLN was achieved in 293 (86.2%) patients, and sensitivity and negative predictive value were measured at 97.2% and 99.6%, respectively. In this pivotal trial, the researchers concluded that SLN biopsy has a high degree of diagnostic accuracy in detecting LNM and can safely replace lymphadenectomy in the staging of endometrial cancer. At the same time, they pointed out that SLN biopsy will not identify 2.8% of patients with LNM (false negative rate).[32]

SHREC,[33] a Swedish prospective cohort study, also aimed to assess the diagnostic accuracy of a pelvic SLN mapping and biopsy in clinical stage I-II endometrial cancer. However, unlike the FIRES trial, SHREC targeted patients having at least one of the following preoperative high-risk criteria: endometrioid grade 3, non-endometrioid histology, myometrial invasion ≥50%, or cervical stromal invasion, or, until February 14th, 2017, a non-diploid cytometry. Patients underwent robotic staging surgery with an anatomically based surgical SLN-ICG algorithm, in which reinjection of ICG in case of failed mapping is one of the key elements.[34] After SLN mapping and biopsy, pelvic lymphadenectomy was performed in all patients, while para-aortic lymphadenectomy was omitted in some patients. The results of the SHREC were published in 2019. In total, 257 patients were included in this analysis, and 81% of patients received infra-renal para-aortic lymphadenectomy. The SLN-ICG algorithm had a sensitivity of 98% and a negative predictive value of 99.5%. Two women (1%) had isolated para-aortic metastases. There were no adverse events related to the injection of ICG or the SLN procedure. These findings suggest that implementation of SLN mapping strategy is also feasible in high-risk endometrial cancer.[33]

Although SLN mapping strategy has gained acceptance in low-grade endometrial cancer, its role in high-grade endometrial cancer remained unclear. Only 13%, 28%, and 49% of patients in SENTI-ENDO,[31] FIRES,[32] and SHREC[33] trials, respectively, had high-grade endometrial cancer. Meanwhile, SENTOR, a Canadian multicenter prospective cohort study, included patients with intermediate- and high-grade endometrial cancer.[35] In total, 156 patients with clinical stage I endometrial cancer whose histologic subtypes were grade 2 endometrioid (n = 30) or high-grade tumors (n = 126) were included in the analysis. All patients underwent cervical injection of ICG and SLN mapping and biopsy, followed by pelvic lymphadenectomy. Patients with high-grade tumors also underwent para-aortic lymphadenectomy. The SENTOR study's findings were published in 2021. SLN mapping and biopsy had a sensitivity of 96.3% and a negative predictive value of 99.2% for the detection of LNM. The false negative rate was 3.7% (1/27). Based on these results, the researchers concluded that, compared with lymphadenectomy, SLN mapping strategy had acceptable diagnostic accuracy for patients with high-grade endometrial cancer at increased risk of LNM.[35]

These prospective cohort studies demonstrated that SLN mapping strategy is a viable alternative to systematic lymphadenectomy, with acceptable diagnostic accuracy in both low- and high-risk patients with clinical stage I endometrial cancer.

4. Current clinical practice guidelines on SLN mapping strategy

The current NCCN guidelines clarify that SLN mapping strategy can be considered for the surgical staging of apparent uterine-confined malignancy when there is no metastasis demonstrated by imaging studies or no obvious extrauterine disease at exploration.[12] SLN mapping and biopsy with ultrastaging may increase the detection of LNM and additional low-volume metastases.[36] Recent evidence indicates that SLN mapping strategy may be used in both low- and high-risk groups.

The current ESMO guidelines clarify that SLN mapping and biopsy can be considered as a strategy for nodal assessment in low- or intermediate-risk endometrial cancer, and SLN mapping and biopsy is also an acceptable alternative to systematic lymphadenectomy in high-intermediate or high-risk stage I-II endometrial cancer.[13]

In related to methodology, the current NCCN guidelines introduce superficial (1–3 mm) and deep (1–2 cm) cervical injection with dye is a useful and validated technique for SLN mapping.[12,17] The radiolabeled colloid most commonly injected into the cervix is technetium-99m; colored dyes are available in a variety of forms (isosulfan blue 1%, methylene blue 1%, and patent blue 2.5% sodium). ICG recently emerged as a useful imaging dye that requires a near-infrared (NIR) camera for localization, provides a very high SLN detection rate, and is commonly used in many practices at the present time. ICG is diluted to 0.5–1.25 mg/ml concentration using sterile water and 2–4 ml are then injected into the cervix.[17] For cases of failed SLN mapping, reinjection of the cervix may be considered. The NCCN guidelines emphasize that the key point to a successful SLN mapping is the adherence to the SLN algorithm, which requires the performance of a side-specific lymphadenectomy in cases of failed mapping and removal of any suspicious or grossly enlarged nodes regardless of mapping.[12]

SLNs should undergo ultrastaging for the detection of low-volume metastasis.[12] Ultrastaging commonly necessitates serial sectioning of the gross SLN and review of multiple hematoxylin and eosin (H&E)-stained sections with or without cytokeratin immunohistochemical (IHC) staining. Although isolated tumor cells (ITCs) should be clearly reported in the pathology review, the presence of ITCs should not upstage patients.[12] However, ITCs should be considered in the discussion of adjuvant treatment. According to a prospective study of 519 endometrial cancer patients, patients with ITCs showed significantly better 3-year PFS than those with macrometastasis but similar survival outcomes compared to those with negative LNs.[37] However, there is still debate on the appropriate management of ITCs.

5. Unanswered questions surrounding sentinel lymph node and ongoing clinical trials

There are several unanswered questions surrounding SLN mapping and biopsy in endometrial cancer.

First, SLN mapping and biopsy may not remove all the metastatic LNs. According to the FIRES trial, among 35 SLN-positive patients, only 60% had disease limited to the SLN; 40% had additional positive LNs after lymphadenectomy. Up to date, whether positive or negative pelvic SLNs necessitate further pelvic and/or para-aortic lymphadenectomy is not yet defined. However, a Brazilian multi-center, non-inferiority RCT, ALICE (NCT03366051),[38] is currently ongoing.

The ALICE trial[38] hypothesized that there is no survival benefit in

adding systematic lymphadenectomy to SLN mapping and biopsy in high-intermediate and high-risk endometrial cancer. This trial includes endometrial cancer patients with high-grade histologies or endometrioid grades 1–2 with myometrial invasion ≥50% and/or cervical invasion. Patients with extrauterine disease are excluded. Staging surgery by minimally invasive approach is preferred. All patients receive SLN mapping and biopsy using blue dye or ICG and cervical injection methods. The SLNs will not undergo frozen section, except for those grossly suspicious of LNM. If LNM is identified intraoperatively, the patient will be excluded from the study. Meanwhile, the uterus will be sent to frozen section to evaluate myometrial invasion and cervical invasion. After confirmation of the inclusion criteria, are randomized into no further lymphadenectomy arm or systematic pelvic and para-aortic lymphadenectomy arm with a 1:1 ratio. A total of 148 patients will be enrolled. The primary endpoint is 3-year DFS, and the secondary endpoints are 5-year OS, morbidity, LLL, and quality of life.[38]

Second, SLN mapping strategy may miss isolated para-aortic LNs, which also results in a poor outcome.[39] Especially, some researchers may raise concerns about cervical injection for para-aortic SLN mapping. To overcome this issue, Eoh et al. suggested a two-step SLN mapping method.[40] For the first step, ICG is injected into the bilateral uterine corneal areas, and the para-aortic SLNs are harvested first. Next, for the second step, ICG is injected at the cervix, and the pelvic SLNs are harvested. This two-step method seems reasonable, feasible, and effective.[40] Furthermore, the same research team retrospectively compared the two-step method (n = 76) with the conventional cervical injection (n = 123), and reported the two-step method improved the para-aortic SLN detection rate.[41] However, this method has not yet been widely accepted as a standard. Further large prospective validation studies are warranted.

Third, since The Cancer Genome Atlas (TCGA) reported four molecular classifications of endometrial cancer,[42] research groups have developed more practical molecular classification tools for clinical use,[43,44] and molecular classification is now included in the current clinical practice guidelines.[12,13] Both in the ESMO guidelines[13] and ESGO/ESTRO/ESP guidelines,[45] molecular classification is incorporated in risk stratification and considered in determining adjuvant treatments. Survival outcomes and clinicopathologic factors significantly differ among the four molecular classification groups; polymerase epsilon-ultramutated (*POLE*mut), mismatch repair deficiency (MMRd), p53 abnormal (p53abn), and no specific molecular profile (NSMP).[43–47] Therefore, the impact of SLN mapping and biopsy or systematic lymphadenectomy may be different for each molecular classification group. Also, since MMRd is known as an independent risk factor for LNM in endometrioid endometrial cancer,[48] MMR status could be added to the SLN mapping strategy to predict LNM more accurately before surgery.

Lastly, the survival outcomes of SLN mapping strategy, compared with systematic lymphadenectomy, have not yet been established via a prospective study. Only data that support the SLN mapping strategy in terms of prognosis have been obtained from retrospective studies.[49,50] Currently, there are two ongoing RCTs to confirm the survival outcomes associated with SLN mapping strategy are non-inferior to those associated with systematic lymphadenectomy for early-stage endometrial cancer.[51,52] SNEC (NCT04276532),[51] a Chinese multi-center, non-inferiority RCT, enrolls endometrial cancer patients whose diseases are confined to the uterus and having one or more intermediate-high risk factors, including endometrioid grade 3, non-endometrioid histology, myometrial invasion ≥50%, tumor size >2 cm, and cervical involvement. Patients are randomly assigned to SLN arm or pelvic lymphadenectomy arm with a 1:1 ratio. In the SLN arm, a cervical injection with ICG is preferred, but different colored dyes are also allowed for SLN mapping. In the pelvic lymphadenectomy arm, patients also receive para-aortic lymphadenectomy or LN sampling. The principles of surgical procedures and postoperative adjuvant treatments follow the NCCN clinical practice guidelines. A total of 780 patients will be enrolled from 6 hospitals in China. Accrual time will be 3 years, and follow-up time will be 5 years. The primary endpoint is 2-year progression-free survival (PFS), and the secondary endpoints are 5-year PFS, 5-year OS, surgery-related adverse events, and quality of life.[51]

KGOG2029/SELYE (NCT04845828)[52] is a Korean multi-center RCT that enrolls clinical stage I-II endometrial cancer patients with all histologic subtypes (except neuroendocrine carcinoma) and grades whose pelvic and para-aortic LNs are less than 15 mm in preoperative magnetic resonance imaging (MRI) or computed tomography scans and who are scheduled to undergo minimally invasive staging surgery. Patients are randomly assigned to SLN arm or lymphadenectomy arm with a 1:1 ratio, considering stage (stage I vs. II), histological subtype (endometrioid vs. non-endometrioid), risk of LNM (low/intermediate-risk group vs. high-risk group), surgical method (laparoscopic surgery vs. robotic surgery), and participating institutes as the stratification factors. In this trial, the high-risk group is defined when patients have one or more of the following risk factors: high-grade histology, myometrial invasion ≥50%, and cervical involvement. In the SLN arm, ICG and fluorescence imaging are used. While patients in the low/intermediate-risk receive cervical injections, those in the high-risk group undergo the aforementioned two-step SLN mapping.[40] If SLN mapping fails despite two injections at the same site, ipsilateral pelvic or para-aortic lymphadenectomy will be conducted. In addition to SLNs, if there are LNs larger than 1 cm in short diameter or suspicious of metastasis, they must be removed. An ultrastaging protocol is used to examine all SLNs. In the conventional lymphadenectomy arm, only pelvic lymphadenectomy is performed for the low/intermediate-risk group, while pelvic plus para-aortic lymphadenectomy is performed for the high-risk group. Adjuvant treatments are administered as per the Korean Society of Gynecological Oncology (KSGO) guidelines, considering the pathologic risk factors after surgery.[53] A total of 810 patients will be enrolled from KGOG member institutions. The primary endpoint is 3-year DFS. The secondary endpoints include 3-year OS, 5-year DFS and OS, recurrence patterns, complications, and quality of life. Both accrual and follow-up times will be 3 years.[52]

Interestingly, ANZGOG's phase III RCT, ENDO-3 (NCT04073706),[54] aims to ascertain whether SLN biopsy is as effective as no lymphadenectomy in early-stage endometrial cancer, or whether clinical management can be performed without the information from SLN biopsy. This trial enrolls patients with clinical stage I endometrial cancer, and randomly assigns them to SLN mapping and biopsy arm or no lymphadenectomy arm with a 1:1 ratio. All patients receive laparoscopic or robotic staging surgery. In the SLN biopsy arm, ICG is injected into the cervix, and resected SLNs undergo ultrastaging. After surgery, adjuvant treatments are administered to patients who are at high risk of relapse or who have LNM. In stage 1, 444 patients will be enrolled to demonstrate feasibility and quality of life. If this is demonstrated, another 316 patients will be enrolled in stage 2, where the primary endpoint is 4.5-year DFS.[54]

Upcoming survival and quality of life outcomes of these RCTs will broaden our insights into SLN mapping strategy and be helpful to physicians' and patients' decision-making.

6. Future perspective on sentinel lymph node mapping strategy

Before SLN mapping strategy became common and popular, researchers put effort into developing preoperative or intraoperative models for predicting LNM. For example, KGOG developed a logistic regression-based preoperative model to discriminate a low-risk group for LNM among patients with endometrial cancer. The low-risk group was defined as patients who had none of the following four parameters: serum CA-125 levels (>35 IU/ml) and three MRI parameters (deep myometrial invasion, LN enlargement, and extension beyond the uterine corpus). In the validation of the developed model, a notably low false negative rate of 1.4% was observed.[55] The KGOG model was also validated in the external cohorts.[56,57]

Similarly, researchers suggested various preoperative models for predicting a low-risk group for LNM; histologic grade, tumor volume measured by MRI, myometrial invasion by transvaginal ultrasound, IHC markers, such as hormone receptors or Ki67 were used as variables.[58–62]

More recently, researchers extracted radiomics features from MRI and constructed a radiomics signature associated with myometrial invasion[63] or LNM.[64] Such a radiomics signature might be combined with clinical variables to develop models or nomograms for predicting LNM preoperatively. Considering rapid advances in digital imaging processing and machine learning techniques, the development of more individualized, accurate preoperative models for predicting LNM can be expected. Such models could compete with the current SLN mapping strategy, or by combining models with the current SLN mapping strategy, a novel clinical algorithm might be generated.

By using dual or hybrid tracers (e.g., ICG and technetium-99m), each other's strengths are put together and might improve the diagnostic accuracy of the SLN mapping strategy. Recently, Sánchez-Izquierdo et al. investigated the feasibility of a hybrid tracer, ICG-technetium-99m-albumin nanocolloid, in the detection of SLNs.[65] In total, 52 patients with intermediate- and high-risk endometrial cancer underwent preoperative and intraoperative detection of SLNs using lymphoscintigraphic study and NIR optical camera with gamma probe, respectively. Interestingly, there was an inconsistency in detection of SLN between the radioactive and fluorescent components (97.1% vs. 80%), suggesting the use of the hybrid tracer allows a potential increase in SLN detection.[65]

Modifying the current ICG or synthesizing new tracers might be another solution to improving the diagnostic accuracy of the current SLN mapping strategy. For example, adsorption of ICG to human serum albumin increased the fluorescence intensity and hydrodynamic diameter, improving detection of SLNs.[66]

Through the diverse methods mentioned above, the SLN mapping strategy is expected to be further advanced than it is now. Such an advanced SLN mapping strategy will guide physicians' and patients' decisions towards accurate prediction of LNM, admission of or omission of systematic lymphadenectomy, and minimization of complications, such as LLL, and ultimately facilitate more individualized, precision cancer surgery.

7. Conclusion

In this article, we reviewed the importance of LN assessment, the current role of SLN mapping strategy, and unanswered questions surrounding this strategy with the introduction of ongoing clinical trials. We also suggested a future perspective on the SLN mapping strategy.

Management of endometrial cancer is rapidly evolving, and the SLN mapping strategy represents a concentration of physicians' efforts to implement precision cancer surgery. A vast body of evidence supports SLN mapping and biopsy with ultrastaging as a safe and accurate method to detect LNM, enabling the omission of futile systematic lymphadenectomy and improving patients' quality of life.

Clinical trials are currently underway to elucidate the impact of the SLN mapping strategy on survival outcomes. Until more robust evidence is accumulated, efforts to optimize the SLN mapping techniques and improve the diagnostic accuracy of the SLN mapping strategy are needed.

Author contributions

JWK: conceptualization, methodology, original draft writing, review & editing, and supervision; SIK: original draft writing, and review & editing.

Declaration of competing interest

No conflicts of interest, relevant to this article, exist.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA A Cancer J Clin.* 2021;71(3):209–249. https://doi.org/10.3322/caac.21660.
2. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. *CA A Cancer J Clin.* 2023;73(1):17–48. https://doi.org/10.3322/caac.21763.
3. Henley SJ, Ward EM, Scott S, et al. Annual report to the nation on the status of cancer, part I: National cancer statistics. *Cancer.* 2020;126(10):2225–2249. https://doi.org/10.1002/cncr.32802.
4. Lortet-Tieulent J, Ferlay J, Bray F, et al. International patterns and trends in endometrial cancer incidence, 1978-2013. *J Natl Cancer Inst.* 2018;110(4):354–361. https://doi.org/10.1093/jnci/djx214.
5. Jung K-W, Won Y-J, Hong S, et al. Prediction of cancer incidence and mortality in korea, 2021. *Cancer Res Treat.* 2021;53(2):316–322. https://doi.org/10.4143/crt.2021.290.
6. Lim MC, Won Y-J, Ko MJ, et al. Incidence of cervical, endometrial, and ovarian cancer in Korea during 1999–2015. *J Gynecol Oncol.* 2019;30(1):e38. https://doi.org/10.3802/jgo.2019.30.e38.
7. Kim SI, Lim MC, Lee JS, et al. Impact of lower limb lymphedema on quality of life in gynecologic cancer survivors after pelvic lymph node dissection. *Eur J Obstet Gynecol Reprod Biol.* 2015;192:31–36. https://doi.org/10.1016/j.ejogrb.2015.06.011.
8. Beesley V, Janda M, Eakin E, et al. Lymphedema after gynecological cancer treatment : prevalence, correlates, and supportive care needs. *Cancer.* 2007;109(12):2607–2614. https://doi.org/10.1002/cncr.22684.
9. Abu-Rustum NR, Alektiar K, Iasonos A, et al. The incidence of symptomatic lower-extremity lymphedema following treatment of uterine corpus malignancies: a 12-year experience at Memorial Sloan-Kettering Cancer Center. *Gynecol Oncol.* 2006;103(2):714–718. https://doi.org/10.1016/j.ygyno.2006.03.055.
10. Yost KJ, Cheville AL, Al-Hilli MM, et al. Lymphedema after surgery for endometrial cancer: prevalence, risk factors, and quality of life. *Obstet Gynecol.* 2014;124(2 Pt 1):307–315. https://doi.org/10.1097/AOG.0000000000000372.
11. Salani R. Survivorship planning in gynecologic cancer patients. *Gynecol Oncol.* 2013;130(2):389–397. https://doi.org/10.1016/j.ygyno.2013.05.022.
12. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Uterine neoplasms. Version 1.2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed December 24, 2022.
13. Oaknin A, Bosse TJ, Creutzberg CL, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol.* 2022;33(9):860–877. https://doi.org/10.1016/j.annonc.2022.05.009.
14. Hari AY, Tewari KS. Sentinel lymphatic mapping for gynecologic malignancies. *Curr Opin Obstet Gynecol.* 2023;35(1):43–53. https://doi.org/10.1097/GCO.0000000000000841.
15. Koskas M, Amant F, Mirza MR, et al. Cancer of the corpus uteri: 2021 update. *Int J Gynaecol Obstet.* 2021;155(Suppl 1):45–60. https://doi.org/10.1002/ijgo.13866. Suppl 1.
16. Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. *Cancer.* 1987;60(8 Suppl):2035–2041. https://doi.org/10.1002/1097-0142(19901015)60:8+<2035::aid-cncr2820601515>3.0.co;2-8.
17. Abu-Rustum NR. Sentinel lymph node mapping for endometrial cancer: a modern approach to surgical staging. *J Natl Compr Cancer Netw.* 2014;12(2):288–297. https://doi.org/10.6004/jnccn.2014.0026.
18. Benedetti Panici P, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. *J Natl Cancer Inst.* 2008;100(23):1707–1716. https://doi.org/10.1093/jnci/djn397.
19. Kitchener H, Swart AM, Qian Q, et al. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet.* 2009;373(9658):125–136. https://doi.org/10.1016/S0140-6736(08)61766-3.
20. Creasman WT, Mutch DE, Herzog TJ. ASTEC lymphadenectomy and radiation therapy studies: are conclusions valid? *Gynecol Oncol.* 2010;116(3):293–294. https://doi.org/10.1016/j.ygyno.2009.10.065.
21. Rungruang B, Olawaiye AB. Comprehensive surgical staging for endometrial cancer. *Rev Obstet Gynecol.* 2012;5(1):28–34.
22. Emons G, Kim JW, Weide K, et al. Endometrial Cancer Lymphadenectomy Trial (ECLAT) (pelvic and para-aortic lymphadenectomy in patients with stage I or II endometrial cancer with high risk of recurrence; AGO-OP.6). *Int J Gynecol Cancer.* 2021;31(7):1075–1079. https://doi.org/10.1136/ijgc-2021-002703.
23. Todo Y, Kato H, Kaneuchi M, et al. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. *Lancet.* 2010;375(9721):1165–1172. https://doi.org/10.1016/S0140-6736(09)62002-X.
24. Watari H, Katayama H, Shibata T, et al. Phase III trial to confirm the superiority of pelvic and para-aortic lymphadenectomy to pelvic lymphadenectomy alone for endometrial cancer: Japan Clinical Oncology Group Study 1412 (SEPAL-P3). *Jpn J Clin Oncol.* 2017;47(10):986–990. https://doi.org/10.1093/jjco/hyx108.
25. Frumovitz M, Bodurka DC, Broaddus RR, et al. Lymphatic mapping and sentinel node biopsy in women with high-risk endometrial cancer. *Gynecol Oncol.* 2007;104(1):100–103. https://doi.org/10.1016/j.ygyno.2006.07.033.
26. Altgassen C, Pagenstecher J, Hornung D, et al. A new approach to label sentinel nodes in endometrial cancer. *Gynecol Oncol.* 2007;105(2):457–461. https://doi.org/10.1016/j.ygyno.2007.01.021.
27. Ballester M, Dubernard G, Rouzier R, et al. Use of the sentinel node procedure to stage endometrial cancer. *Ann Surg Oncol.* 2008;15(5):1523–1529. https://doi.org/10.1245/s10434-008-9841-1.
28. Bats AS, Clément D, Larousserie F, et al. Does sentinel node biopsy improve the management of endometrial cancer? Data from 43 patients. *J Surg Oncol.* 2008;97(2):141–145. https://doi.org/10.1002/jso.20857.
29. Geppert B, Lönnerfors C, Bollino M, et al. Sentinel lymph node biopsy in endometrial cancer-Feasibility, safety and lymphatic complications. *Gynecol Oncol.* 2018;148(3):491–498. https://doi.org/10.1016/j.ygyno.2017.12.017.

30. Barlin JN, Khoury-Collado F, Kim CH, et al. The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: beyond removal of blue nodes. *Gynecol Oncol*. 2012;125(3):531–535. https://doi.org/10.1016/j.ygyno.2012.02.021.
31. Ballester M, Dubernard G, Lécuru F, et al. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). *Lancet Oncol*. 2011;12(5):469–476. https://doi.org/10.1016/S1470-2045(11)70070-5.
32. Rossi EC, Kowalski LD, Scalici J, et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. *Lancet Oncol*. 2017;18(3):384–392. https://doi.org/10.1016/S1470-2045(17)30068-2.
33. Persson J, Salehi S, Bollino M, et al. Pelvic Sentinel lymph node detection in High-Risk Endometrial Cancer (SHREC-trial)-the final step towards a paradigm shift in surgical staging. *Eur J Cancer*. 2019;116:77–85. https://doi.org/10.1016/j.ejca.2019.04.025.
34. Persson J, Geppert B, Lönnerfors C, et al. Description of a reproducible anatomically based surgical algorithm for detection of pelvic sentinel lymph nodes in endometrial cancer. *Gynecol Oncol*. 2017;147(1):120–125. https://doi.org/10.1016/j.ygyno.2017.07.131.
35. Cusimano MC, Vicus D, Pulman K, et al. Assessment of sentinel lymph node biopsy vs lymphadenectomy for intermediate- and high-grade endometrial cancer staging. *JAMA Surg*. 2021;156(2):157–164. https://doi.org/10.1001/jamasurg.2020.5060.
36. Kim CH, Soslow RA, Park KJ, et al. Pathologic ultrastaging improves micrometastasis detection in sentinel lymph nodes during endometrial cancer staging. *Int J Gynecol Cancer*. 2013;23(5):964–970. https://doi.org/10.1097/IGC.0b013e3182954da8.
37. Plante M, Stanleigh J, Renaud MC, et al. Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: does adjuvant treatment matter? *Gynecol Oncol*. 2017;146(2):240–246. https://doi.org/10.1016/j.ygyno.2017.05.024.
38. Baiocchi G, Andrade C, Ribeiro R, et al. Sentinel lymph node mapping versus sentinel lymph node mapping with systematic lymphadenectomy in endometrial cancer: an open-label, non-inferiority, randomized trial (ALICE trial). *Int J Gynecol Cancer*. 2022;32(5):676–679. https://doi.org/10.1136/ijgc-2022-003378.
39. Touboul C, Bentivegna E, Uzan C, et al. Sentinel lymph node in endometrial cancer: a review. *Curr Oncol Rep*. 2013;15(6):559–565. https://doi.org/10.1007/s11912-013-0345-1.
40. Eoh KJ, Lee YJ, Kim HS, et al. Two-step sentinel lymph node mapping strategy in endometrial cancer staging using fluorescent imaging: a novel sentinel lymph node tracer injection procedure. *Surg Oncol*. 2018;27(3):514–519. https://doi.org/10.1016/j.suronc.2018.07.001.
41. Kim YN, Eoh KJ, Lee JY, et al. Comparison of outcomes between the one-step and two-step sentinel lymph node mapping techniques in endometrial cancer. *Int J Gynecol Cancer*. 2020;30(3):318–324. https://doi.org/10.1136/ijgc-2019-000962.
42. Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. *Nature*. 2013;497(7447):67–73. https://doi.org/10.1038/nature12113.
43. Stelloo E, Nout RA, Osse EM, et al. Improved risk assessment by integrating molecular and clinicopathological factors in early-stage endometrial cancer-combined analysis of the PORTEC cohorts. *Clin Cancer Res*. 2016;22(16):4215–4224. https://doi.org/10.1158/1078-0432.CCR-15-2878.
44. Talhouk A, McConechy MK, Leung S, et al. A clinically applicable molecular-based classification for endometrial cancers. *Br J Cancer*. 2015;113(2):299–310. https://doi.org/10.1038/bjc.2015.190.
45. Concin N, Matias-Guiu X, Vergote I, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. *Int J Gynecol Cancer*. 2021;31(1):12–39. https://doi.org/10.1136/ijgc-2020-002230.
46. Talhouk A, McConechy MK, Leung S, et al. Confirmation of ProMisE: a simple, genomics-based clinical classifier for endometrial cancer. *Cancer*. 2017;123(5):802–813. https://doi.org/10.1002/cncr.30496.
47. Kommoss S, McConechy MK, Kommoss F, et al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. *Ann Oncol*. 2018;29(5):1180–1188. https://doi.org/10.1093/annonc/mdy058.
48. Diniz TP, Menezes JN, Goncalves BT, et al. Can mismatch repair status be added to sentinel lymph node mapping algorithm in endometrioid endometrial cancer? *Gynecol Oncol*. 2022;169:131–136. https://doi.org/10.1016/j.ygyno.2022.12.010.
49. Schiavone MB, Scelzo C, Straight C, et al. Survival of patients with serous uterine carcinoma undergoing sentinel lymph node mapping. *Ann Surg Oncol*. 2017;24(7):1965–1971. https://doi.org/10.1245/s10434-017-5816-4.
50. Schiavone MB, Zivanovic O, Zhou Q, et al. Survival of patients with uterine carcinosarcoma undergoing sentinel lymph node mapping. *Ann Surg Oncol*. 2016;23(1):196–202. https://doi.org/10.1245/s10434-015-4612-2.
51. Guan J, Xue Y, Zang RY, et al. Sentinel lymph Node mapping versus systematic pelvic lymphadenectomy on the prognosis for patients with intermediate-high-risk Endometrial Cancer confined to the uterus before surgery: trial protocol for a non-inferiority randomized controlled trial (SNEC trial). *J Gynecol Oncol*. 2021;32(4),e60. https://doi.org/10.3802/jgo.2021.32.e60.
52. Park JY, Kim JH, Baek MH, et al. Randomized comparison between sentinel lymph node mapping using indocyanine green plus a fluorescent camera versus lymph node dissection in clinical stage I-II endometrial cancer: a Korean Gynecologic Oncology Group trial (KGOG2029/SELYE). *J Gynecol Oncol*. 2022;33(6):e73. https://doi.org/10.3802/jgo.2022.33.e73.
53. Korean Society of Gynecologic Oncology. Practice guideline for uterine corpus cancer version 4.0, 2020. Avaialbie at: https://cdn.medsoft.co.kr/201/date/guid_04_03.pdf. Accessed December 30, 2022.
54. Obermair A, Nicklin J, Gebski V, et al. A phase III randomized clinical trial comparing sentinel node biopsy with no retroperitoneal node dissection in apparent early-stage endometrial cancer - ENDO-3: ANZGOG trial 1911/2020. *Int J Gynecol Cancer*. 2021;31(12):1595–1601. https://doi.org/10.1136/ijgc-2021-003029.
55. Kang S, Kang WD, Chung HH, et al. Preoperative identification of a low-risk group for lymph node metastasis in endometrial cancer: a Korean gynecologic oncology group study. *J Clin Oncol*. 2012;30(12):1329–1334. https://doi.org/10.1200/JCO.2011.38.2416.
56. Kang S, Todo Y, Odagiri T, et al. A low-risk group for lymph node metastasis is accurately identified by Korean gynecologic oncology group criteria in two Japanese cohorts with endometrial cancer. *Gynecol Oncol*. 2013;129(1):33–37. https://doi.org/10.1016/j.ygyno.2013.01.005.
57. Koskas M, Fournier M, Vanderstraeten A, et al. Evaluation of models to predict lymph node metastasis in endometrial cancer: a multicentre study. *Eur J Cancer*. 2016;61:52–60. https://doi.org/10.1016/j.ejca.2016.03.079.
58. Lee JY, Jung DC, Park SH, et al. Preoperative prediction model of lymph node metastasis in endometrial cancer. *Int J Gynecol Cancer*. 2010;20(8):1350–1355. https://doi.org/10.1111/IGC.0b013e3181f44f5a.
59. Mitamura T, Watari H, Todo Y, et al. Lymphadenectomy can be omitted for low-risk endometrial cancer based on preoperative assessments. *J Gynecol Oncol*. 2014;25(4):301–305. https://doi.org/10.3802/jgo.2014.25.4.301.
60. Lee J, Kong TW, Paek J, et al. Predicting model of lymph node metastasis using preoperative tumor grade, transvaginal ultrasound, and serum CA-125 level in patients with endometrial cancer. *Int J Gynecol Cancer*. 2016;26(9):1630–1635. https://doi.org/10.1097/IGC.0000000000000820.
61. Ballester M, Canlorbe G, Cortez A, et al. Histological and immunohistochemical profiles predict lymph node status in women with low-intermediate risk endometrial cancer. *Gynecol Oncol*. 2013;130(3):457–462. https://doi.org/10.1016/j.ygyno.2013.06.001.
62. Yang B, Shan B, Xue X, et al. Predicting lymph node metastasis in endometrial cancer using serum CA125 combined with immunohistochemical markers PR and Ki67, and a comparison with other prediction models. *PLoS One*. 2016;11(5), e0155145. https://doi.org/10.1371/journal.pone.0155145.
63. Wang Y, Bi Q, Deng Y, et al. Development and validation of an MRI-based radiomics nomogram for assessing deep myometrial invasion in early stage endometrial adenocarcinoma. *Acad Radiol*. 2022;S1076–6332(22). https://doi.org/10.1016/j.acra.2022.05.017, 00320-00328.
64. Liu XF, Yan BC, Li Y, Ma FH, et al. Radiomics nomogram in assisting lymphadenectomy decisions by predicting lymph node metastasis in early-stage endometrial cancer. *Front Oncol*. 2022;12, 894918. https://doi.org/10.3389/fonc.2022.894918.
65. Sánchez-Izquierdo N, Vidal-Sicart S, Campos F, et al. Detection of the sentinel lymph node with hybrid tracer (ICG-[(99m)Tc]Tc-albumin nanocolloid) in intermediate- and high-risk endometrial cancer: a feasibility study. *EJNMMI Res*. 2021;11(1):123. https://doi.org/10.1186/s13550-021-00863-x.
66. Ohnishi S, Lomnes SJ, Laurence RG, et al. Organic alternatives to quantum dots for intraoperative near-infrared fluorescent sentinel lymph node mapping. *Mol Imag*. 2005;4(3):172–181. https://doi.org/10.1162/15353500200505127.