

Sentinel Lymph Nodes in Endometrial Cancer Update 2018

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Abstract

There are no established data about lymphadenectomy during treatment of endometrial cancers (ECs) and to what extent lymphadenectomy should be performed. In addition, retroperitoneal lymphadenectomy increases the intraoperative and postoperative complications. Sentinel lymph node (SLN) mapping has the lowest costs and highest quality-adjusted survival. SLN is the most cost-effective strategy in the management of low-risk ECs. Women staged with SLN mapping were more likely to receive adjuvant treatment compared with women staged with systemic lymphadenectomy. This review article designed to evaluate the diagnostic accuracy and the methods of SLN detection in ECs.

Keywords: Cancer, endometrial, nodes, sentinel, update

INTRODUCTION

Endometrial cancer (EC) is the most common gynecological cancer in Europe.^[1] Lymph node evaluation is the key point in EC staging and prognosis.^[2]

The International Federation of Gynecology and Obstetrics (FIGO) staging of ECs revised in 2009 to include the pelvic and para-aortic lymphadenectomy (PPLND) as one of the most important prognostic factors in ECs.^[3]

There are no established data about lymphadenectomy during treatment of ECs and to what extent lymphadenectomy should be performed.^[4] The authors argue that the retroperitoneal lymphadenectomy increases the intraoperative and postoperative complications.^[5]

Zikan *et al.* found that the frequency of lymphoceles was significantly high in patients who underwent combined PPLND compared to those who had pelvic lymphadenectomy only.^[6]

Ma *et al.* found that infected lymphocysts were more frequently in patients with combined PPLND and higher number of resected pelvic lymph nodes.^[7]

Systemic lymphadenectomy is not necessary in women at low risk of lymph node involvement (Stage 1a-1c ECs).^[8] Selective lymphadenectomy has been widely employed for staging evaluations of ECs because it is simple and provides reliable data regarding the lymph node status.^[9]

In addition, Selman *et al.* concluded that the noninvasive or the minimal invasive assessment of the lymph node status to target specific lymph nodes for sampling is more beneficial than complete or systemic lymphadenectomy in primary ECs.^[9]

Sentinel lymph node (SLN) is the first node receiving lymphatic drainage from the primary tumor, and the

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pathological status of SLN reflects the overall status of entire lymphatic basin.^[10]

Women with negative SLN for metastasis may be managed by SLN biopsy instead of systemic lymphadenectomy.^[10]

The Medical Research Council of ASTEC trial concluded that there was no benefit of systemic lymphadenectomy for early-stage EC on patients' survival and/or prevention of recurrence.^[11]

This review article designed to evaluate the diagnostic value and the methods of SLN detection in ECs.

METHODS OF THE REVIEW

Using the words; sentinel lymph node (SLN), endometrial cancer (EC) and year 2018 a PubMed search done and twenty-five articles retrieved; 20 studies and one systematic review [Table 1], 2 literature review, one case report and one article about the SLN mapping in cervical cancers.

DIAGNOSTIC VALUE OF SENTINEL LYMPH NODES IN ENDOMETRIAL CANCERS

Systemic lymphadenectomy is not necessary in ECs (Stage 1a-1c ECs) with low risk of lymph node involvement.^[8] In addition, the noninvasive selective lymphadenectomy provides reliable data regarding the lymph node status and more beneficial than systemic lymphadenectomy in primary ECs.^[9]

Schlappe *et al.* compared the outcome in the staging of deeply invasive endometrioid endometrial carcinoma using SLN algorithm versus PPLND (94 – PPLND and 82 – SLN).^[12] They found that SLN patients had more lymphovascular space infiltration ($P < 0.001$). About 9.8% in the SLN and 29.8% in the PPLND cohorts, respectively, received no adjuvant therapy ($P < 0.001$).^[12] Schlappe *et al.* concluded that the use of an SLN dissection in invasive EC does not impair the oncologic outcome.^[12]

A retrospective study done by Buda *et al.* included 66 patients in the SLN mapping-algorithm (SLN-A) and 105 in the selective lymphadenectomy (SLND) to compare the impact of SLN-A to SLND on the staging of the high-risk EC.^[13] Buda *et al.* found that the SLND strategy did not compromise the prognosis of patients with high risk of recurrence.^[13]

Brugger *et al.* found that the detection rate (DR) of the SLN was 61% on both sides and 86% on at least one side, and they spared 26 PPLND using SLN dissection.^[14] Brugger *et al.* concluded that the SLN reduced the radical lymphadenectomy by 50% in patients with “higher than low risk” EC.^[14]

Touhami *et al.* concluded that the risk of lymph node involvement in patients with a preoperative diagnosis of “atypical hyperplasia-only” is null, and lymph node assessment in such patients could be omitted, while the risk is high in patients with preoperative diagnosis of “atypical hyperplasia-cannot rule out cancer;” the SLN mapping in such patients could be valuable.^[15]

Suri and Arora found that only a few studies assessed the place of SLN biopsy in the management of ECs.^[16]

The Society of Gynecologic Oncology recommended SLN mapping into the surgical staging of ECs to reduce the morbidities associated with systemic lymphadenectomy.^[17]

Tschernichovsky *et al.* concluded that SLN biopsy was more accurate alternative to comprehensive lymphadenectomy for determining the nodal spread in early-stage ECs.^[18]

Naoura *et al.* found that the SLN mapping and the lymphovascular infiltration (LVSI) status can select which high-risk patients with ECs would benefit from comprehensive systemic staging.^[19]

The lymph node status is one of the most important features to determine the EC adjuvant treatment, and the SLN biopsy has emerged as an alternative to retroperitoneal lymphadenectomy in EC with the same diagnostic ability while minimizing morbidity.^[20,21]

METHODS OF SENTINEL LYMPH NODE DETECTION IN ENDOMETRIAL CANCERS

Sentinel lymph node detection in endometrial cancers using indocyanine green tracer

Rajanbabu and Agarwal's prospective study carried out with intracervical indocyanine green (ICG) injection for SLN detection in women with early-stage EC who underwent staging.^[22] Rajanbabu and Agarwal found that it is essential that the steps mentioned in the SLN mapping algorithm are followed when doing SLN mapping and biopsy during EC staging as SLN mapping alone seems to have limitation in detecting positive nodes, especially in high-risk subtypes of EC.^[22]

The SLN mapping may be considered an alternative standard of care in the staging ECs, and the ICG cervical injection has the highest SLN DRs.^[23,24]

Shimada *et al.* found that the SLN mapping with the use of cervical tracer injection is highly feasible in Japanese women with early-stage EC.^[25]

Papadia *et al.* concluded that large dose of ICG associated with high number of retrieved SLNs but not with an increased bilateral DR.^[26]

Table 1: Type, population, and the conclusion of the PubMed retrieved studies and systematic review

Authors	Type and population of the study	Conclusion
Schlappe <i>et al.</i> ^[12]	Multicenter study of 176 patients (94 - PPLND and 82 - SLN).	Use of an SLN algorithm in invasive EEC does not impair oncologic outcomes
Buda <i>et al.</i> ^[13]	Retrospective analysis of database of 171 women; 66 in SLN-A and 105 in SLND group	The SLN-A strategy did not seem to compromise the prognosis of patients' HR of recurrence
Brugger <i>et al.</i> ^[14]	Retrospective study of SLN dissection in 109 patients of 154 consecutive patients according to NCCN guidelines	SLN dissection reduced the radical lymphadenectomy by 50% in patients with "higher than low risk" EC
Touhami <i>et al.</i> ^[15]	Retrospective study of 120 women with preoperative diagnosis of AH who underwent primary surgery with SLN mapping followed by pelvic lymphadenectomy	The risk of EC is high in patients with the diagnosis of "AH-cannot rule out cancer"
Rajanbabu and Agarwal ^[22]	Retrospective study of 60 patients with intracervical injection of ICG, for SLN identification and biopsy for women with early-stage EC	SLN mapping alone seems to have a limitation in detecting positive nodes, especially in HR EC
Shimada <i>et al.</i> ^[25]	Retrospective study of 57 patients with EC. Technetium colloid and/or ICG injected into the uterine cervix and a gamma-detecting probe used to locate hotspots during surgical staging	SLN mapping with the use of cervical tracer injection is highly feasible in Japanese women with early-stage EC.
Papadia <i>et al.</i> ^[26]	Retrospective analysis of 168 patients with two different injection protocols	ICG dose was the only factor associated with number of removed SLNs
Body <i>et al.</i> ^[27]	Retrospective analysis of 119 patients, detection rate, sensitivity, and negative predictive value calculated to evaluate factors associated with failed bilateral detection of SLNs	ICG is an excellent tracer for SLN mapping in EC Advanced FIGO stage correlated with failed bilateral detection
Papadia <i>et al.</i> ^[28]	Retrospective analysis of 42 patients with EC undergoing a laparoscopic NIR-ICG SLN mapping followed by a systematic lymphadenectomy	The laparoscopic NIR-ICG SLN mapping in high-risk EC patients has acceptable sensitivity, false-negative rate, and negative predictive value
Mendivil <i>et al.</i> ^[29]	Retrospective study of 87 women with clinical stage I-EC who underwent robotic-assisted surgery that incorporated mapping with ICG and SLN dissection	The minimally invasive SLN staging using ICG is potentially effective procedure at detecting metastases
Ruiz <i>et al.</i> ^[30]	Prospective study of 111 patients who underwent laparoscopic surgery for EC. SLN biopsy performed with dual cervical and fundal ICG injection	The SLN biopsy with both cervical and fundal ICG injections offers good overall detection rates and improved mapping of the aortic area
Geppert <i>et al.</i> ^[32]	Prospective study of 188 patients with EC planned for robotic surgery ICG used to identify the SLNs	The high feasibility, the absence of intraoperative complications, and the low risk of lymphatic complications support SLN biopsy in low-risk EC
How <i>et al.</i> ^[33]	Systematic search for all studies published until October 31, 2017. Studies included for review if they contained at least 30 EC patients undergoing SLN mapping and reported detection rates	SLN mapping is feasible and accurate alternative to stage patients with EC ICG results in the highest SLN detection rates
Zuo <i>et al.</i> ^[34]	Prospective study of 50 patients received fundal subserosal injections at 4 sites (fundal group), while 65 patients received cervical submucosal injections at 2 sites (cervical group)	SLN mapping by CNPs in laparoscopic surgery for EC is safe and effective alternative with a higher detection rate and better accuracy in cervical injection than fundal injection
Tanaka <i>et al.</i> ^[35]	Prospective study of 121 patients with EC who underwent FDG PET/CT before hysterectomy and received SNB followed by PLND	The combined diagnosis of FDG PET/CT and SNB improves the sensitivity
Fanfani <i>et al.</i> ^[36]	Retrospective study of 40 consecutive FIGO Stage I-EC patients and SLN mapping performed in all patients SLN was examined by OSNA and by frozen section analysis	The combination of OSNA procedure with the SLN mapping could represent an efficient intraoperative tool for the selection of early-stage EC patients to be submitted to systematic lymphadenectomy
El-Agwany and Meleis ^[38]	Prospective study of 120 patients with early-stage EC and low risk for nodal metastasis who underwent surgical staging	Hysteroscopic-guided blue dye injection was the best technique for SLN detection, and the SLN can be used in patients with low risk for lymph node metastasis
Tanaka <i>et al.</i> ^[39]	Prospective study of 211 patients with EC who underwent SLN biopsy at hysterectomy using three kinds of tracers including 99m-technetium (99mTc), indigo carmine, and ICG	Patients who underwent laparoscopy with <50% myometrial invasion and low-grade ECs not only have higher detection rates but also have lower false-negative rates
Euscher <i>et al.</i> ^[41]	Prospective study of the following histologic subtype; endometrioid, serous, carcinosarcoma, clear cell, and undifferentiated carcinomas. In all, 172 patients had ultra-staging: M1=65; M2=58	A more comprehensive ultra-staging protocol had no significant advantages over a single wide interval and immunohistochemistry
Suidan <i>et al.</i> ^[42]	Prospective study comparing the three lymphadenectomy strategies: 1. Routine lymphadenectomy, 2. Selective lymphadenectomy, and 3. SLN mapping, to evaluate the cost-utility of three lymphadenectomy strategies in the management of low-risk EC	Selective lymphadenectomy was both less costly and more effective than routine lymphadenectomy. SLN mapping has the lowest cost and highest quality-adjusted survival, making it the most cost-effective strategy in the management of low-risk EC

Contd...

Table 1: Contd...

Authors	Type and population of the study	Conclusion
Gómez-Hidalgo <i>et al.</i> ^[43]	Retrospective study of 54,039 women with EC in the National Cancer Database from 2013 to 2014	There was no association between use of SLN biopsy and use of radiation

CNPs: Carbon nanoparticles, EC: Endometrial Cancer, EEC: Endometrioid endometrial carcinoma, FDG PET/CT: Fluorodeoxyglucose-positron emission tomography/computed tomography, FIGO: International Federation of Gynecology and Obstetrics, ICG: Indocyanine green, NCCN: National comprehensive cancer network, NIR-ICG: NIR: Near infrared-indocyanine green, OSNA: One-step nucleic acid amplification, PLND: Pelvic lymphadenectomy, PPLND: Pelvic and para-aortic lymphadenectomy, SLN: Selective lymphadenectomy, SLN-A: Sentinel lymph node mapping-algorithm. SLND: Selective lymphadenectomy, SNB: Sentinel lymph node biopsy, HR: High risk, AH: Atypical hyperplasia

A retrospective analysis of patients who underwent primary surgery for EC with SLN mapping using ICG, followed by pelvic lymphadenectomy, was conducted by Body *et al.*, to determine the validity of SLN mapping with ICG in EC.^[27] Body *et al.* found that ICG is an excellent tracer for SLN mapping in EC, while advanced FIGO stage associated with failed bilateral detection ($P = 0.01$).^[27]

Another retrospective analysis by Papadia *et al.* conducted to evaluate the accuracy of the near infrared-ICG (NIR-ICG) SLN mapping in patients with poorly differentiated EC who have undergone a full lymphadenectomy.^[28] Papadia *et al.* found the NPV and the sensitivity of the NIR-ICG SLN mapping in high-risk EC patients were acceptable.^[28]

Mendivil *et al.* found that the minimally invasive SLN staging using ICG is an effective procedure for detection of metastases with decreased risk of surgical morbidity.^[29]

Ruiz *et al.* found that the SLN biopsy with both cervical and fundal ICG injections offers good overall DRs and improved mapping of the aortic lymph nodes.^[30]

In addition, Mangeshikar *et al.* concluded that with the advent of ICG, the morbidity and radicality associated with treating gynecological malignancy will be greatly reduced.^[31]

A prospective study was conducted by Geppert *et al.*, evaluating the lymphatic complications in women with EC undergoing SLN biopsy versus full lymphadenectomy.^[32] Geppert *et al.* concluded that the absence of intraoperative complications and the low risk of lymphatic complications support implementing detection of SLN biopsy in low-risk EC patients.^[32]

A systematic search utilizing Medline, Web of Science, and EMBASE databases was conducted by How *et al.* and concluded that the SLN mapping is a feasible and accurate alternative to stage patients with EC.^[33]

Sentinel lymph node detection in endometrial cancers using tracers other than indocyanine green

Zuo *et al.* conducted a prospective consecutive study (Canadian Task Force classification II) to evaluate the DR and accuracy of SLN mapping using cervical and fundal injection of carbon nanoparticles (CNPs) during laparoscopic

surgery for endometrioid EC.^[34] Zuo *et al.* found that the SLN mapping by CNPs in laparoscopic surgery for EC is a safe and effective alternative with higher DR and better accuracy in cervical injection than fundal injection.^[34]

Tanaka *et al.* concluded that the combined diagnosis of fluorodeoxyglucose-positron emission tomography/computed tomography (FDG PET/CT) and SNL biopsy improves the sensitivity; PET-positive nodes should be dissected regardless of SNL biopsy status, and hemipelvises in which SNL biopsy was not detected should be dissected systematically regardless of FDG PET/CT status.^[35]

Fanfani *et al.* found that the combination of one-step nucleic acid amplification (OSNA) procedure with the SLN mapping could represent an efficient intraoperative tool for the selection of early-stage EC patients to be submitted to systematic lymphadenectomy.^[36]

Nagai *et al.* found that the OSNA assay using cytokeratin-19 mRNA was applicable for detecting lymph node metastasis in ECs.^[37]

El-Agwany and Meleis concluded that the hysteroscopic-guided blue dye injection was the best technique for SLN detection, and the SLN can be used in patients with low risk for lymph node metastasis.^[38] In addition, they found the blue methylene dye good for SLN detection in low-resource countries.^[38]

Tanaka *et al.* concluded that patients who underwent laparoscopic staging with <50% myometrial invasion and low-grade ECs have high DRs and can avoid systemic lymphadenectomy according to the status of the SLN biopsy.^[39]

Kataoka *et al.* concluded that the SLN mapping for ECs using hysteroscopic subendometrial injection of 99m-technetium labeled phytate (Radio-isotope; RI method) and subserosal ICG injection in ECs revealed high DR with high sensitivity and negative predictive value.^[40]

Sentinel lymph node detection in endometrial cancers using ultra-staging and immunohistochemistry stain

Euscher *et al.* compared two ultra-staging protocols for negative SLN by routine processing in EC, and they concluded that a more comprehensive ultra-staging protocol

had no significant advantages over a single wide interval and immunohistochemistry.^[41]

COST-EFFECTIVENESS OF SENTINEL LYMPH NODE STRATEGY IN ENDOMETRIAL CANCERS

Suidan *et al.* compared three lymphadenectomy strategies in women undergoing minimally invasive surgery for low-risk EC, and they found that the selective lymphadenectomy was less costly and more effective than routine lymphadenectomy.^[42] In addition, they concluded that the SLN mapping has the highest quality-adjusted survival and lowest cost making it the most cost-effective strategy in the management of low-risk EC.^[42]

ACCEPTANCE OF THE SENTINEL LYMPH NODE STRATEGY

Selective lymphadenectomy has been widely employed for staging of ECs because it provides reliable data regarding the lymph node status.^[9]

Gómez-Hidalgo *et al.* analyzed 54,039 women with EC in the National Cancer Database (from 2013 to 2014) including 38,453 (71.2%) who underwent lymphadenectomy and 1929 (3.6%) who underwent SLN mapping. SLN mapping increased from 2.8% to 4.3% in 2013 and 2014, respectively ($P < 0.001$).^[43]

Bogani *et al.* concluded that the SLN mapping represents an attractive mid-way between the omission of lymph node dissection and full lymphadenectomy.^[44]

In addition, they concluded that the SLN mapping can identify more cases of lymphatic disease than conventional lymphadenectomy and improve the adjuvant treatments in high-risk patients.^[44]

The SLN mapping algorithm for the surgical staging of EC has gained a significant acceptance and is now commonly applied in many practices.^[45]

A case report of a positive precaval SLN with negative pelvic SLN in a 45-year-old woman with Grade 2 endometrioid EC reported by Montero Macias *et al.*, and they concluded that in this woman, the SLN biopsy improved risk-assessment and adjuvant treatment.^[46]

SENTINEL LYMPH NODE STRATEGY IN GYNECOLOGIC CANCERS

SLNs mapping strategy has gained a significant acceptance in all gynecologic cancers not only the ECs.

Kim *et al.* concluded that SLN mapping with ICG in cervical cancer is feasible and has high DR with 100% sensitivity in early-stage tumors (<2 cm).^[47]

Cea García *et al.* used cervical injection of ^{99m}Tc-nanocolloid of albumin and methylene blue followed by imaging and SLN biopsy to assess the diagnostic value of SLN biopsy in initial cancer cervix stages.^[48] Cea García *et al.* concluded that their technique has a high detection, but the sensitivity is still. The intraoperative ultra-staging could increase the sensitivity of their technique and reduce the false negatives.^[48]

In addition, the National Comprehensive Cancer Network guidelines recommended SLN mapping strategy for lymphatic assessment not only for endometrial but also for cervical and vulvar cancers.^[49]

Recently, Tantitamit and Lee found that the SLN mapping in the natural orifice transluminal endoscopic surgery (NOTES) technique had overall DR, and bilateral DR was 100% (4/4). Tantitamit and Lee concluded that the SLN mapping in NOTES surgery appears to be feasible and can be considered as an alternative to radical lymphadenectomy.^[50]

CONCLUSION

This review article concluded that the SLNs mapping is an accurate alternative to systemic lymphadenectomy for determining the nodal spread in early-stage ECs and its cost-effective strategy in the management of low-risk EC. SLN mapping allows upstaging in low- or intermediate-risk ECs in whom adjuvant therapy could be omitted. Women with ECs staged with SLNs were more likely to receive adjuvant treatment compared with women staged with systemic lymphadenectomy. Decreased lymphatic complications and operative time strongly motivate the SLN biopsy concept in high-risk ECs. Although ICG cervical injection offers the highest SLN DRs, others concluded that this technique is controversial because the distribution of SLNs in ECs is different from distribution of SLNs in cervical cancers.

Ethical committee approval was not required because this review does not contain any research on human or animal subjects.

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Conflicts of interest

There are no conflicts of interest.

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