IntRoductIon

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

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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.

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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.[9] 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.[23]

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 et al.[32]     | Multicenter study of 176 patients (94 - PPLND and 82 - SLN).                                    | Use of an SLN algorithm in invasive EEC does not impair oncologic outcomes                            |
| Buda et al.[33]         | 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 et al.[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 et al.[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 et al.[34]      | 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 et al.[26]      | Retrospective analysis of 168 patients with two different injection protocols                    | ICG dose was the only factor associated with number of removed SLNs                                   |
| Body et al.[37]         | 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                                                     |
| Papadia et al.[28]      | Retrospective analysis of 42 patients with EC undergoing a laparoscopic NIR-ICG SLN mapping followed by a systematic lymphadenectomy | Advanced FIGO stage correlated with failed bilateral detection                                        |
| Mendivil et al.[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 laparoscopic NIR-ICG SLN mapping in high-risk EC patients has acceptable sensitivity, false-negative rate, and negative predictive value |
| Ruiz et al.[30]         | Prospective study of 111 patients who underwent laparoscopic surgery for EC. SLN biopsy performed with dual cervical and fundal ICG injection | The minimally invasive SLN staging using ICG is potentially effective procedure at detecting metastases |
| Geppert et al.[32]      | Prospective study of 188 patients with EC planned for robotic surgery ICG used to identify the SLNs | The SLN biopsy with both cervical and fundal ICG injections offers good overall detection rates and improved mapping of the aortic area |
| How et al.[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                           |
| Zuo et al.[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) | ICG results in the highest SLN detection rates                                                       |
| Tanaka et al.[35]       | Prospective study of 121 patients with EC who underwent FDG PET/CT before hysterectomy and received SNB followed by PLND | 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 |
| Fanfani et al.[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 combined diagnosis of FDG PET/CT and SNB improves the sensitivity                               |
| El-Agwany and Meleiu[30] | Prospective study of 120 patients with early-stage EC and low risk for nodal metastasis who underwent surgical staging | 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 |
| Tanaka et al.[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 | 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 |
| Euscher et al.[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 | 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 |
| Suidan et al.[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 | A more comprehensive ultra-staging protocol had no significant advantages over a single wide interval and immunohistochemistry |

Contd...
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. 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).

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. Papadia et al. found the NPV and the sensitivity of the NIR-ICG SLN mapping in high-risk EC patients were acceptable.

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.

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.

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.

A prospective study was conducted by Geppert et al., evaluating the lymphatic complications in women with EC undergoing SLN biopsy versus full lymphadenectomy. 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.

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.

**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. 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.

Tanaka et al. concluded that the combined diagnosis of fluorodeoxyglucose-positron emission tomography/computed tomography (FDG PET/CT) and SLN 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.

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.

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

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. In addition, they found the blue methylene dye good for SLN detection in low-resource countries.

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 SNL biopsy.

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.

**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.\cite{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.\cite{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.\cite{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.\cite{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 ($P < 0.001$).\cite{43}

Bogani et al. concluded that the SLN mapping represents an attractive mid-way between the omission of lymph node dissection and full lymphadenectomy.\cite{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.\cite{44}

The SLN mapping algorithm for the surgical staging of EC has gained a significant acceptance and is now commonly applied in many practices.\cite{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.\cite{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).\cite{47}

Cea García et al. used cervical injection of 99mTc-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.\cite{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.\cite{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.\cite{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.\cite{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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