



From systematic lymphadenectomy to sentinel lymph node mapping: a review on transitions and current practices in endometrial cancer staging

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Abstract: Endometrial cancer care has undergone major changes in the past 30 years. In 1988, staging transitioned from clinical to surgical. Moreover, the surgical approach of choice is no longer open surgery, but minimally invasive surgery. An improvement in terms of nodal evaluation followed. Full systematic lymphadenectomy has been continuously replaced by sentinel lymph node mapping. Although sentinel lymph node mapping with a cervical injection of indocyanine green dye is rapidly gaining clinical acceptance, we lack consistent recommendations on a well-defined procedure that accurately and indolently assesses the lymph node status. Such recommendations are indispensable, as nodal status is the most important predictive factor of survival and is essential for tailoring adjuvant treatment to the risk of recurrence. This paper focuses on transitions in endometrial cancer care and highlights current data on sentinel lymph node mapping in endometrial cancer. We demonstrate that sentinel lymph node mapping is a safe and accurate strategy for nodal status evaluation with appropriate sensitivity, false-negative rate and negative predictive value in high- as well as low-risk settings. Furthermore, we elaborate on type and dose of tracer, site of injection, number of sentinel lymph nodes to be removed, sentinel lymph node mapping learning curve, operation mode and sentinel lymph node ultrastaging. In the future, guidelines with consistent recommendations on the above outlined features of sentinel lymph node mapping should be established to allow for a uniform and wide-spread application of the sentinel lymph node mapping procedure.

Keywords: Endometrial cancer (EC); sentinel lymph node mapping; indocyanine green; minimally invasive surgery; ultrastaging; gynecologic oncology

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Introduction: transitions in endometrial cancer staging

Endometrial cancer (EC) are a diverse group of neoplasms with a varying degree of aggressiveness, especially in early stages. An appreciable number of patients (14–22%) with stage I cancers have disease outside of the uterus (lymph node metastasis, adnexal disease, intraperitoneal spread and/

or malignant cells in peritoneal washings), thereof, 11% had pelvic (9%) and/or paraaortic (6%) nodal metastases (1).

Nodal status is the strongest predictive factor of survival and is essential for tailoring adjuvant treatment to the risk of recurrence. As nodal status and therefore true extent of disease can only be reliably assessed by surgical staging, the International Federation of Gynecology and

Obstetrics (FIGO) transitioned the EC staging from clinical to surgical in 1988 (2). The conventional surgical staging for endometrial cancer includes visual evaluation of the peritoneal cavity, total hysterectomy, bilateral salpingo-oophorectomy and a pelvic and paraaortic lymphadenectomy.

However, the performance of a pelvic and paraaortic lymphadenectomy for nodal status evaluation has been faced with controversy ever since its implementation. The procedure has been conducted reluctantly and with low compliance (35%, 66% and 90% performance in grade 1, 2 and 3 tumors, respectively) (3). However, by leaving nodal status unknown, incomplete resection of disease and prescription of inadequate adjuvant treatment is risked. As the true risk for nodal involvement is assessed by postoperative permanent pathological examination of the uterine specimen, presumed low-risk EC patients may end up having a high-intermediate- or high-risk EC with an up to 40% risk of nodal metastases. As a result, high-intermediate-risk EC patients with unknown nodal status have a worse prognosis than women with known nodal status, irrespective of whether or not the lymph nodes are metastatic. To be precise, 5-year survival rates are 85%, 71.8% and 36% when nodal status is negative, positive or unknown, respectively (4).

Several reasons contribute to the restraint of conducting a full systematic lymphadenectomy in every EC patient. First and foremost, the surgical morbidity of a full systematic lymphadenectomy is high. This is relevant, as the majority of EC patients are co-morbid and do not suffer from metastatic disease. Secondly, lymphadenectomy is technically difficult to master in obese women, representing a large proportion of type I EC patients. Thirdly, the procedure was originally adopted despite the lack of evidence demonstrating improved survival. Last but not least, the therapeutic value of lymphadenectomy is still questioned (5-7).

Over the past years, less invasive and more tailored strategies for nodal evaluation have been investigated. These include selective lymph node sampling (caveat: only 10% metastatic nodes present grossly enlarged) (1), triaging patients to lymphadenectomy based on intrauterine risk factors at frozen section of the uterus (caveat: accurate risk stratification can only be made postoperatively after permanent pathological examination of the uterine specimen) (4,8) and triaging patients to lymphadenectomy based on nodal status attained by sentinel lymph node (SLN) mapping. Best results are achieved when SLN mapping is

applied (i.e., sensitivity 97.2%, false-negative rate 2.8%, negative predictive value 99.6%) (9).

SLN mapping in EC was first described in 1996 (10). With increasing acceptance in clinical practice, it is just now progressively being incorporated in international guidelines (11-13). However, there is still concern about the safety of SLN mapping in high-risk settings. In high-risk EC, the probability of nodal metastasis (and therefore occult stage IIIc disease) is high and underdiagnosis is risked if the procedure does not achieve a low false-negative (FN) rate (14). To improve the FN rate, Barlin *et al.* (2012) proposed the MSKCC (Memorial Sloan Kettering Cancer Center) SLN mapping algorithm. It goes beyond the sole removal of the mapped SLNs. Performance of ultrastaging is advised if the initial conventional histological examination of the lymph node is negative. Furthermore, removal of suspicious non-SLNs and performance of a side-specific pelvic lymphadenectomy are recommended in case of mapping failure on one hemipelvis. Paraaortic lymphadenectomy is left at the physician's discretion. Thereby, FN rate can be decreased from 15% to under 2%, a value similar to the one seen in the treatment of other malignancies (15).

In the following paragraphs, we will review current evidence on surgical staging and SLN mapping in EC, highlighting standards and research on the operation mode, type and dose of tracer, site of injection, number of SLNs to be removed, SLN mapping learning curve, and SLN ultrastaging. Moreover, clinical applicability and oncological outcome of SLN mapping in EC will be reviewed.

Surgical staging und SLN mapping in EC: non-uniformly handled features

Operation mode: minimally invasive surgery versus open surgery

In the past, EC staging has been performed through laparotomy. However, there has been a shift towards minimally invasive surgery (MIS) in the past decades. The LAP2 trial, a prospective randomized trial involving early-stage EC patients demonstrated that laparoscopic EC staging has multiple advantages over the laparotomy approach. A decrease in postoperative adverse events and duration of hospital stay were noted. Intraoperative injuries were not increased despite the longer operation duration. Detection of advanced disease was the same in both groups, which means that MIS does not compromise surgical staging (16). The LACE trial, a multinational randomized



Figure 1 SLN mapped with ICG tracer and visualized with IMAGE1 S™ RUBINA™ system.

equivalence trial involving early-stage EC patients also supported the safety of a laparoscopic approach. Disease-free and overall survival after a follow-up of 4.5 years were comparable in the laparoscopy and laparotomy group (17). As nodal spread of disease was relatively low in the two just mentioned study populations, the safety of MIS in stage IIIC patients could not be assessed. In stages with nodal involvement, complete resection of disease is prognostically highly relevant. Papadia *et al.* (2020) compared the laparoscopic approach to laparotomy in stage IIIC patients. They reported that complete resection of disease is accomplished with equal success irrespective of surgical approach. Both groups had a similar 5-year overall survival rate. At multivariate analysis, only age over 65 years was associated with impaired overall survival. Due to the complexity of the surgery, operative time was longer in the laparoscopy group (325 *vs.* 264 min). Despite the longer operative time in this setting, perioperative complications, estimated blood loss (890 *vs.* 380 mL) and need for transfusion (67% *vs.* 20%) were significantly lower in the laparoscopic group. Thus, laparoscopic surgery is a safe and feasible surgical staging strategy in stage IIIC disease (18). These results are consistent with other studies' findings (19-21). Moreover, sensitivity, FN rate and negative predictive value (NPV) are not impaired by MIS (9,22). Gehrig *et al.* (2008) investigated the optimal MIS strategy for comprehensive staging in obese and morbidly obese women, constituting the majority of EC patients. They concluded that robotic-assisted surgery leads to shorter operative time, less blood loss, and shorter hospital stay (23).

Nowadays, the German S3 guidelines support the use of

MIS in presumed early-stage disease (11). According to the US NCCN guidelines, MIS is the preferred approach when technically feasible (12). The European ESMO-ESGO-ESTRO guidelines recommend MIS for the surgical management of low- and intermediate-risk EC. It can be considered in high-risk EC as well (13).

Type of tracer

Tc-99m, blue dyes (i.e., methylene blue, isosulfan blue and patent blue) and indocyanine green (ICG) are the most commonly used tracers for SLN mapping in EC. They can be detected by radionuclide, colorimetric or near-infrared methods, respectively. The effectiveness of these tracers, either alone or in combination, is indicated by their overall and bilateral detection rates. Overall detection describes the mapping of at least one SLN in either hemipelvis, whereas bilateral detection describes the mapping of at least one SLN in each hemipelvis. Only if mapping occurs in both hemipelvises, a side-specific pelvic lymphadenectomy can safely be omitted (i.e., SLN mapping is accurate on its own).

Bilateral and/or overall detection rates are highest for near-infrared ICG SLN mapping. SLN mapping with blue dye alone or in combination with Tc-99m is less accurate. To be concrete, overall detection rates range from 87–100% for ICG, 95–97% for a combination of blue dye with Tc-99m and 57–81% for blue dye alone. Bilateral detection rates range from 65–88% for ICG, 50–74% for blue dye in combination with Tc-99m and 32–54% for blue dye alone (24-31). These findings have been confirmed in a recent randomized phase 3 trial (32).

Gasparri *et al.* suggest that the high detection rates achieved by using ICG result from the long retention of the tracer in the SLNs. This might contribute to a less time-pressured SLN sampling, resulting in higher detection rates. However, special attention has to be drawn not to mistake echelon lymph nodes for SLNs, as sampling of those would increase surgical morbidity without increasing FN rate (33). Further benefits of ICG include its excellent toxicity profile (severe allergic reactions <0.05%), low cost and quick transcutaneous real-time visualization. Moreover, it attenuates the detrimental effect of body mass index (BMI) on detection rates (34). Based on this evidence, ICG is currently the preferred tracer for SLN mapping in EC. For illustration see *Figure 1*: SLN mapped with ICG tracer and visualized with IMAGE1 S™ RUBINA™ system (Karl Storz).

Dose of tracer

As ICG is only FDA-approved for intravenous injections, its dose for interstitial injections has been set empirically. A meta-analysis on detection rate and diagnostic performance of ICG suggests that ICG achieves best performance when applied in large volumes and low concentrations (0.5 to 1.25 mg/mL) (35). Most centers follow the dosage used by Frumovitz *et al.* (2018) at the FILM-trial: 1 mL of a 1.25 mg/mL ICG solution per superficial and deep injection (32).

Papadia *et al.* (2018) investigated the impact of different doses of ICG on detection rate. Although they were not able to show any correlation of dose to detection rate, they pointed out that the number of SLNs removed correlates with volume and concentration of ICG. It is however unclear whether the additionally sampled lymph nodes were true SLNs of independent lymphatic pathways or echelon lymph nodes (36).

Site of injection

As the uterus is a midline structure, its lymphatic drainage is complex. Four different uterine lymphatic draining systems are described in literature. Most metastatic spread happens along the lymph nodes of the upper paracervical pathway (37). As a theoretical difference between the lymphatic drainage of the cervix and the uterine corpus must be expected, there is no consensus on the optimal site of tracer injection. Three different sites of injection exist: cervical injection, hysteroscopic myometrial/peritumoral injection and transabdominal subserosal/myometrial injection at the uterine fundus.

The cervical injection route is the most practical and shows the highest technical success rate. Specifically, the ICG solution is injected superficially into the submucosa (2–3 mm) and deeply into the stroma (1–2 cm) of the four cervical quadrants (38). Overall and bilateral detection rates are 62–100% and 57–98%, respectively (37,39,40). A hysteroscopic injection of tracer does not only result in lower detection rates (e.g., due to intraabdominal leakage of ICG and a longer learning curve) but is also more challenging to perform. However, it increases the detection of paraaortic SLNs, which is especially relevant in settings where isolated paraaortic lymph nodes are common (e.g., deep myometrial invasion or poor differentiation) (41). A systematic review by Cormier *et al.* (2015) demonstrated that paraaortic lymph nodes are mapped in 39%, 2% and 17% after corporal (i.e., fundal and peritumoral), usual

cervical and deeper (3–4 cm) cervical injection of dye (39). Considering the low risk of isolated paraaortic metastasis (<5%) in the majority of EC patients, cervical injection of tracer is safe and accurate. Moreover, the ease of use allows for a more wide-spread implementation of the technique.

Failure to map

Mapping success depends on tumor-, patient- and surgeon-specific factors. The identification of such factors may prevent mapping failure and thereby reduce the morbidity resulting from the performance of a side-specific pelvic lymphadenectomy. Moreover, mapping of the SLN is of great importance as it is the only positive node in 46–65% of all stage IIIc cases (42,43). A meta-analysis by Kang *et al.* (2011) demonstrated that the overall detection rate of different SLN mapping strategies (in terms of type and dose of tracer, site of injection, operation mode) is about 78%. However, about 39% (range 19–80%) fail to map bilaterally (44). Successful mapping is associated with type and site of injection of the tracer, presence of clinically enlarged lymph nodes, lymphovascular space invasion, obesity (BMI >30 kg/m²), history of radiation, and surgical experience of the physician. Overall, type of tracer is the most pivotal factor affecting detection rate.

Highest detection rates are achieved with a cervical injection of ICG tracer. Only paraaortic SLN detection is higher with corporal injection (37,39,45).

Bilateral mapping success is lower when lymph nodes are clinically enlarged (33%) compared to when they are not (66%). The probability of nodal metastasis in presence of clinically enlarged lymph nodes is 25%, whereas it is 4% in clinically unremarkable lymph nodes (45). Consequently, mapping failure (possibly caused by inhibited tracer flow due to lymphatic obstruction by the tumor) might correlate with the presence of metastatic disease. This has two implications. First, it is important to remove any suspicious nodes regardless of mapping (although 90% of patients with metastatic disease do not present with grossly enlarged lymph nodes). Second, the performance of a side-specific pelvic lymphadenectomy in case of bilateral mapping failure is crucial (1,15).

Another reason for failed mapping is obesity. Mapping failure in obese women (BMI >30 kg/m²) is believed to result from an increase in adipose tissue surrounding the SLNs. This, in turn, impairs visualization of the stained SLNs. The detrimental effect of obesity on detection rate can be reduced by using ICG as a tracer (45,46).

Furthermore, mapping success is lower with a history

of radiation. Papadia *et al.* (2016) speculate that radiation induces fibrosis, which might alter lymphatic flow and thereby interfere with SLN mapping (28).

Last but not least, surgical experience is associated with mapping success. According to Khoury-Collado *et al.* (2009), there is an increase in SLN detection rate from 77% to 94% following a 30-case experience (47).

Number of SLNs to be removed and learning curve

According to Papadia *et al.* (2016), the number of SLNs removed only depends on surgical experience. They suspect that with greater experience in ICG SLN mapping, the surgeon can more confidently detect and differentiate between true SLNs and more downstream echelon lymph nodes. Consequently, solely true SLNs are removed, even if more lymph nodes are stained. In fact, removing more than three SLNs per patient does not increase the accuracy of SLN mapping. This phenomenon might partly be explained due to the temporally long persistence of ICG dye and therefore staining of echelon lymph nodes, whose removal and analysis would not result in a reduction in FN rate, but adds to surgical morbidity. It follows that inexperienced surgeons cannot compensate for an inability to identify SLNs by removing additional nearby non-SLNs. As the performance of over 20 laparoscopic ICG SLN mappings resulted in retrieval of a smaller number of SLNs without increasing the FN rate of the procedure, Papadia *et al.* (2016) suggest that at least 20 SLN mapping procedures with completion lymphadenectomy should be performed before applying the SLN mapping procedure on its own. This number should be even higher in low-risk settings, as nodal metastases occur with lower frequency in these patients (48). These findings support other studies' results (45,47).

Pathological analysis of the SLNs and low-volume metastases

Whenever the SLN is negative by haematoxylin-eosin stain examination, it should be further examined by ultrastaging. Ultrastaging is a more thorough pathological analysis with deeper serial sections and immunohistochemical stain for cytokeratin. Thereby, low-volume metastatic spread to SLNs can be detected. A systematic review and meta-analysis by Bodurtha *et al.* (2017) revealed that positive SLNs are macrometastases in 29%, micrometastases in 39% and isolated tumor cells in 32% of the cases (49).

Several studies examined the effect of ultrastaging on

upstaging in EC. Kim *et al.* (2013) conducted the largest study on ultrastaging results. They found that around 40% of all patients with metastatic SLNs are detected by ultrastaging. In their cohort 12.6% of patients had metastatic disease. This translates to an upstaging of 5% of EC patients. These stage IIIC patients' low-volume metastases would have been missed by conventional pathologic processing (50). Similar numbers are described by Touhami *et al.* (2015). In their cohort, 44% of all patients with metastatic SLNs were detected by ultrastaging, which leads to an upstaging of 7% of patients (43). These findings are in accordance with a systematic review on the topic (39).

Due to the paucity of literature, the clinical significance and management of low-volume, ultrastage-detected metastases is not yet clear and requires long-term follow-up. The risk of accompanying positive non-SLNs in presence of a positive SLN depends on the size of the SLN metastasis. Overall, it is about 35–54%. In presence of macrometastases it can reach up to 60.8%, whereas it drops to <5% if the SLN metastasis is <2 mm (42,43).

Clinical applicability and oncological outcome of SLN mapping in high- and low-risk settings

A survey by Casarin *et al.* (2019) revealed that 50.3% of the surveyed gynecological oncologists apply SLN mapping as part of EC staging. Thereof, 93.1% do a cervical injection of tracer and 62.6% use ICG as a tracer. The SLN algorithm is followed by 65.0% of respondents. However, 66.7% still perform a backup lymphadenectomy in high-risk patients. Ultrastaging is part of the staging protocol in 78.9% of respondents (51). This considerable heterogeneity in terms of strategies for nodal evaluation in EC may partly be attributed to the lack of consensus on this topic in international guidelines. While some guidelines accept SLN mapping as a valid strategy for nodal assessment even in high-risk EC patients (12), others restrict its use to study settings only (11,13). As a result, surgeons use a large variety of nodal evaluation strategies ranging from full bilateral pelvic and/or paraaortic lymphadenectomy, selected lymphadenectomy based on frozen section results or SLN mapping, random node sampling or no-node dissection.

There has been established evidence that SLN mapping is a safe and effective strategy for nodal evaluation in high- and low-risk EC patients with appropriate sensitivity of 97.2%, FN rate of 2.8% and NPV of 99.6% (9). With these numbers in mind, the risk of underdiagnosing patients due to undetected nodal metastases (i.e., FN rate of SLN

mapping) does not exceed the risk of overtreatment and increased morbidity when performing a full systematic lymphadenectomy in every patient (i.e., risk of major complications). As EC patients have greatly different prevalences of nodal metastases, the safety of SLN mapping has been assessed for each risk category separately. Unlike high-risk EC patients, low-risk EC patients present with a low incidence of lymph node metastases. One could therefore assume that the low FN rates and the high NPVs observed in the low-risk setting could easily result from the high proportion of true negatives in this group. As a result, there was concern that the good FN rates and NPVs of SLN mapping in low-risk settings cannot be easily translated into high-risk scenarios, involving an increased number of patients with metastatic lymph nodes. The SENTI-ENDO trial (2011) contributed to this concern, as all their patients with FN results had high-risk disease (14). As a reaction, multiple institutions, including ours, evaluated the accuracy of SLN mapping in high-risk settings. We retrospectively assessed the safety of SLN mapping in a high-risk population. The sensitivity, FN rate and NPV were 90%, 10% and 97%, respectively. The values could be lowered to 0% and raised to 100% by applying the MSKCC algorithm (i.e., removing clinically suspicious lymph nodes as well) (52). Several retro- and prospective series on SLN mapping in high-risk settings attained similar sensitivity, FN rates and NPVs, reaching from 91.2–95.8%, 4.2–8.8% and 96–98.6%, respectively (22,53–55). In the retrospective series by Ehrisman *et al.* 2016, FN rate could be lowered to 0% and NPV elevated to 100% after the MSKCC algorithm was applied. This once again illustrates that, especially in high-risk settings, close adherence to the mapping algorithm is crucial. Moreover, profound knowledge of the uterine lymphatic drainage contributes to a higher accuracy of SLN mapping.

Irrespective of risk setting, the application of SLN mapping in EC staging is associated with improved oncological outcomes. A retrospective study showed that overall survival (90% *vs.* 81%), progression-free survival (85% *vs.* 75%) as well as recurrence-free survival (95% *vs.* 90%) are significantly better when SLN mapping is performed compared to full systematic lymphadenectomy alone (56). These ameliorated oncological outcomes are in accordance with other studies' findings (57–59). However, none of these studies were randomized, making them more susceptible for selection or information bias and heightening their potential for imbalance regarding prognostic factors.

Conclusions

In this review, the benefits, safety and effectiveness of SLN mapping in EC were highlighted. Not only does SLN mapping result in a reduction of surgical morbidity associated with full systematic lymphadenectomy, but it also increases the detection of metastatic disease through mapping of lymph nodes in locations not routinely removed during lymphadenectomy as well as a more thorough pathological evaluation of the SLNs. Low-risk patients benefit most from an indolent increase in detection of metastatic disease, making adjuvant treatment more tailored and increasing survival. High-risk patients benefit most from a reduction in surgical morbidity as the use of adjuvant therapy is anyway high in this setting. Moreover, the application of SLN mapping in EC staging is associated with improved oncological outcomes in terms of overall survival, progression-free survival and recurrence-free survival as compared to full systematic lymphadenectomy alone. Provided that the SLN mapping algorithm is closely adhered to, SLN mapping constitutes a safe and effective strategy for nodal evaluation in high- as well as low-risk EC, limiting both over- and undertreatment and allowing for an appropriate triage of patients to adjuvant therapy. The accuracy of SLN mapping is highest when performed through minimally invasive surgery and with a cervical injection of ICG tracer.

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