Incidence of endometrial cancer and lymph node metastasis

Endometrial cancer is the eighth most common cancer and the most common cancer of the female reproductive system in developed countries. It accounts for 4.8% of all female cancer types (1). In all 320,000 women experienced endometrial cancer in 2012 and it caused 76,000 deaths, thus ranking third among the most common causes of death due to gynecological cancer (1). High-grade type 2 endometrioid and non-endometrioid carcinomas...
metastasize via the lymphatic system. In contrast, low-grade type 1 endometrioid carcinomas tend to remain confined to the uterus (2). Patients with endometrial cancer in clinical stage I are subject to the risk of pelvic or paraaortic lymph node metastasis in approximately 10% of cases (3,4). The percentage rises to 20% for poorly differentiated tumors or those with deep myometrial invasion (3,5). This underlines the importance of further research to identify the ideal strategy for lymphadenectomy.

Role of lymphadenectomy and lymph node metastasis

Lymphadenectomy may be performed for diagnostic purposes. It may be used to avoid adjuvant therapy and its harmful effects in patients with histologically negative lymph nodes. Lymphadenectomy may also be used as a therapeutic measure to eliminate lymph node metastasis. The lymph node status has remained one of the most significant prognostic factors in patients with endometrial cancer. It is estimated that patients with lymph node metastasis have a significantly lower five-year survival rate ranging from 44% to 52% (6). The therapeutic value and benefits of pelvic and para-aortic lymphadenectomy in terms of survival is still a debated issue in patients with endometrial cancer (7).

Historical development of lymphadenectomy through the identification of risk factors for lymph node metastasis

Surgical staging for endometrial cancer has made rapid but controversial advances in the last few decades. A systematic pelvic and para-aortic lymph node dissection in endometrial cancer was first performed after 1980. Some years later, staging by systematic lymphadenectomy was considered reasonable and possibly also therapeutic in all patients with endometrial cancer. This theory was confirmed in 1987 by the GOG 33 trial comprising more than 1,000 women. The large retrospective SEPAL study showed that systematic lymphadenectomy was associated with a significantly longer overall survival rate in patients with an intermediate or high risk of lymphatic metastasis (13). Until now, the need for pelvic and para-aortic lymphadenectomy in patients with high-grade endometrioid endometrial cancer or deep myometrial invasion or skin metastasis is not clearly defined. The same criteria, of lymph node metastasis is extremely low and the risk of overtreatment in terms of routine lymphadenectomy was confirmed in two randomized trials which reported no survival benefit for patients with early-stage endometrial cancer who underwent a routine lymphadenectomy (11,12). However, these two studies have been controversially discussed because they included a large number of low-risk patients without lymphatic disease and also because of the absence of a difference in radiotherapy rates between patients who underwent lymphadenectomy and those who did not. Furthermore, most of the patients only underwent a pelvic lymphadenectomy (small number of nodes) without paraaortic dissection, which might signify undertreatment in patients with lymphatic dissemination.

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In the following years, extensive efforts were made in the scientific community to identify subgroups of patients with endometrial cancer who would specifically benefit from systematic lymphadenectomy. Finally, in 2008 Mariani et al. (9) established the well-known Mayo criteria. According to the latter, patients with a tumor <2 cm, grade 1 or 2 endometrioid lesions, and myometrial invasion <50% do not benefit from systematic lymphadenectomy. The risk of lymph node metastasis is extremely low and the risk of complications rather high in this setting. The same criteria, with the exception of tumor diameter, were confirmed by the European Society of Medical Oncology a few years later (10). Overtreatment in terms of routine lymphadenectomy was confirmed in two randomized trials which reported no survival benefit for patients with early-stage endometrial cancer who underwent a routine lymphadenectomy (11,12).

Complications of lymphadenectomy

Since the benefits of lymphadenectomy are controversially discussed, the complications of the procedure deserve attention (19). The most common complications are intraoperative bleeding, injury to neighboring organs, lower-limb lymphedema and postoperative lymph cysts (20), which are usually a random finding on routine follow-up imaging examinations (21). It has been reported that 37.4% of patients who underwent lymphadenectomy for endometri
cancer developed a lower-limb lymphedema (22). This study revealed that the use of adjuvant radiotherapy, the resection of more than 31 lymph nodes, and the removal of circumflex iliac nodes and distal external iliac nodes are independent risk factors (22). Furthermore, a prospective study comprising 385 patients with low-risk endometrial cancer, of whom some underwent lymphadenectomy and some did not, revealed a significantly higher 30-day complication rate in the lymphadenectomy group (37.4%). It is concluded that lymphadenectomy increases morbidity rates and the costs of medical care very significantly (23). The absence of benefits from lymphadenectomy in patients with low-risk endometrial cancer justifies concerns about its complications, which result in a significantly higher morbidity rate and impair quality of life to a considerable extent.

Can lymph node metastasis be diagnosed preoperatively?

In view of the high complications rates of lymphadenectomy, it would appear reasonable to consider alternative diagnostic procedures. The sensitivity and specificity of magnetic resonance imaging (MRI) in identifying lymph node metastasis is reported to be low (46–56% and 88–95%, respectively) (24). Recently the Korean GOG reported that patients with an endometrioid lesion with no evidence of deep myometrial invasion on MRI or enlarged lymph nodes, and no suspicion of metastasis, with serum cancer antigen 125 (CA 125) levels below 35U/mL had a negative predictive value of 97.1% for lymph node metastasis (24). However, currently we lack established alternatives to surgical staging that would identify patients who need adjuvant therapy and reduce the possibility of under- or overtreatment (25-28). More research is needed to establish the ideal preoperative diagnostic procedure in patients with lymph node metastasis.

SLN in gynecology and minimally invasive surgery for endometrial cancer

The need for preoperative detection of pathological lymph nodes led to the development of intraoperative techniques, such as SLN biopsy, and thus reduce morbidity in patients who undergo an unnecessary lymphadenectomy (29). SLN biopsy was first described by Cabanas in 1977. The technique gained widespread acceptance for the treatment of melanoma, vulvar and breast cancer, and is currently the gold standard for these indications (30). Detection and false-negative rates of 97% and 9.8%, respectively, have been reported for breast cancer; and 91% and 1.6%, respectively, for vulvar cancer (30-32). Could SLN reduce the radical nature of treatment for endometrial cancer as well? We investigate this hypothesis in the following. Sentinel node mapping of cervical cancer was first reported in 1995 (33). Several studies have yielded strong evidence of its accuracy and feasibility. The rapid development of minimally invasive surgery for endometrial staging enhanced the popularity of sentinel node mapping. The establishment of laparoscopic and robot-assisted systems that contain software for the detection of sentinel nodes is one of the major advances in this field (29,30). Furthermore, the oncologic safety of laparoscopy has been well established. The large randomized phase-3 trial GOG-LAP2 reported the same 5-year survival rate (89.8%) and 3-year recurrence

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>GOG 33 (3)</td>
<td>Surgical staging</td>
</tr>
<tr>
<td>1988</td>
<td>FIGO (8)</td>
<td>Surgical staging</td>
</tr>
<tr>
<td>2009</td>
<td>ASTEC (12)</td>
<td>No LND</td>
</tr>
<tr>
<td>2009</td>
<td>Revised FIGO (14)</td>
<td>Surgical staging in selected cases</td>
</tr>
<tr>
<td>2010</td>
<td>SENTI ENDO (15)</td>
<td>SLN biopsy</td>
</tr>
<tr>
<td>2015</td>
<td>ESMO ESGO ESTRO guidelines (16)</td>
<td>No SLN biopsy, radical LND in selected cases</td>
</tr>
<tr>
<td>2017</td>
<td>FIRES (17)</td>
<td>SLN biopsy</td>
</tr>
<tr>
<td>2018</td>
<td>FILM (18)</td>
<td>ICG</td>
</tr>
</tbody>
</table>

LND, lymphadenectomy; SLN, sentinel lymph node; ICG, indocyanine green.

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**Table 1** Landmark studies in the development of surgical staging for endometrial cancer
rate for laparoscopy or laparotomy group (11.4% and 10.2%, respectively) in patients who underwent staging for endometrial cancer (34). These data concur with two systematic reviews (35,36) of 17 randomized controlled trials, which reported the same overall and recurrence free survival rates at 4.5 years for laparoscopy and laparotomy group. These studies also confirmed the well-known advantages of minimally invasive surgery, such as reduced hospital stays and operative morbidity. The minimally invasive approach is currently the gold standard for surgical staging of endometrial cancer.

**SLN in endometrial cancer**

The performance of SLN biopsy in patients with endometrial cancer was first reported in 1996 (37). In 15 women who underwent abdominal surgery for endometrial cancer, 1.0 mL of blue dye was injected in three different sites of the subserosal myometrium; deposition of the dye was observed in 10 cases (67%). This was followed by a small number of studies in the next ten years. In contrast, the subject has been extensively researched in the last ten years; more than 300 studies have been published. A landmark study for the development of SLN in endometrial cancer was published by the Memorial Sloan Kettering Cancer Center group in 2012 (38). It was a large prospective study comprising 498 patients who received a blue dye cervical injection for SLN mapping; at least one SLN was identified in 81% and the false negative rate was 2%. This was followed by the publication of several studies. The recognition of the SLN algorithm as an acceptable alternative standard procedure for the treatment of endometrial cancer by the National Comprehensive Cancer Network (NCCN) guidelines in 2018 facilitated its use in clinical practice (39). We present our strategy for sentinel mapping of endometrial cancer in Figure 1.

**Tracers used for sentinel node mapping and their accuracy**

The most common tracers for sentinel node mapping in endometrial cancer are technetium-99 radiocolloid (Tc-99m), blue dyes (methylene or patent blues) and indocyanine green (ICG). The characteristics of these tracers are summarized in Table 2. ICG appears to be superior in terms of its excellent toxicity profile. Detection rates and bilateral mapping with the use of these tracers have been examined in many studies. Papadia et al. (41) reported higher detection rates (95.5%) and bilateral mapping rates (95.5%) for ICG compared to the simultaneous use of Tc-99m and patent blue (93% and 61%, respectively). Large multicenter studies have confirmed these results (40). Subsequently, many studies were specifically focused on the accuracy of ICG and reported similar results (Table 3). The landmark FIRES trial (17), a prospective study comprising 385 patients with endometrial cancer in clinical FIGO stage I who underwent SLN mapping with ICG, confirmed the excellent sensitivity (97.2%) and negative predictive value (99.6%) of the technique. Furthermore, Eriksson et al. (47) presented a stratified by body mass index (BMI) analysis of 472 patients undergoing SLN mapping for endometrial cancer, and showed that successful mapping decreases significantly as BMI increases. However, much better results were achieved with the use of ICG. In Figure 2 we present our intraoperative experience with ICG sentinel mapping. When technically possible, ICG should be given preference because it is the most cost-effective tracer for SLN mapping in patients with endometrial cancer.

**Morbidity of SLN biopsy vs. systematic lymphadenectomy**

In a prospective study comprising 188 patients with endometrial cancer, Geppert et al. (45) analyzed complication rates in patients who underwent SLN biopsy with ICG versus pelvic and para-aortic lymphadenectomy using robotic surgery. The incidence of leg lymphedema was significantly higher after lymphadenectomy compared with sentinel node mapping (18.1% vs. 1.3%; P<0.001). Moreover, the additional average time taken for a lymphadenectomy was 91 minutes as opposed to 33 minutes for the removal of SLNs. In a similar study of 250 patients treated with minimally invasive or open surgery, Accorsi et al. (48) registered a higher 30-day complication rate in the lymphadenectomy group while the operating time was approximately 20 minutes shorter in the SLN mapping group. The high accuracy of SLN biopsy in combination with reduced operating times and lymphatic complications are arguments in favor of its use. Further randomized studies are needed to prove the role of SLN biopsy in reducing morbidity.

**Detection of lymph node metastasis and oncologic outcome with the use of SLN mapping**

SLN mapping for endometrial cancer revealed metastases in unexpected areas. Two consistent lymphatic pathways with
Figure 1 Flowchart diagram of sentinel mapping with ICG for endometrial cancer at the University Hospital of Schleswig Holstein (UKSH). MIS, minimally invasive surgery; SLNB, sentinel lymph node biopsy; LND, lymphadenectomy; ICG, indocyanine green.

Table 2 Characteristics of tracers for sentinel mapping in patients with endometrial cancer (40,41)

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Preparation/injection</th>
<th>Number of allergic reactions</th>
<th>Duration of the signal</th>
<th>Other toxicity</th>
<th>Costs</th>
<th>Ease of application</th>
<th>Need for additional equipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tc-99m</td>
<td>Preoperative lymphoscintigraphy/ SPECT necessary</td>
<td>1–6/100,000</td>
<td>24 hours</td>
<td>Radioactive drug</td>
<td>High</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Blue dyes</td>
<td>Intraoperative</td>
<td>2%</td>
<td>30 minutes</td>
<td>Discoloration of skin and urine, skin necrosis</td>
<td>Low</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ICG</td>
<td>Intraoperative</td>
<td>0.05%</td>
<td>Persistent but after 20–30 minutes not only for sentinel</td>
<td>none</td>
<td>Low</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ICG, indocyanine green.
Table 3  Accuracy of sentinel mapping with ICG in patients with endometrial cancer

<table>
<thead>
<tr>
<th>Studies</th>
<th>Type of study</th>
<th>Number of patients</th>
<th>Overall detection %</th>
<th>Bilateral detection %</th>
<th>Sensitivity %</th>
<th>NPV %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body et al. (42)</td>
<td>Retrospective</td>
<td>119</td>
<td>93</td>
<td>74</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Papadia et al. (43)</td>
<td>Retrospective</td>
<td>42 (only G3)</td>
<td>100</td>
<td>90.5</td>
<td>90</td>
<td>97.1</td>
</tr>
<tr>
<td>Togami et al. (44)</td>
<td>Prospective</td>
<td>133</td>
<td>96</td>
<td>80</td>
<td>91</td>
<td>99</td>
</tr>
<tr>
<td>Geppert et al. (45)</td>
<td>Prospective</td>
<td>188</td>
<td>na</td>
<td>96</td>
<td>Na</td>
<td>Na</td>
</tr>
<tr>
<td>Rozenholc et al. (46)</td>
<td>Randomized trial</td>
<td>132</td>
<td>90.9</td>
<td>na</td>
<td>Na</td>
<td>Na</td>
</tr>
</tbody>
</table>

NPV, negative predictive value; ICG, indocyanine green; na, not available.

Figure 2  Intraoperative images demonstrating the sentinel lymph node operative procedure with the robotic da Vinci Xi surgical system after mapping with ICG. Department of Obstetrics and Gynecology, University Hospital of Schleswig Holstein. (A) Use of Firefly technology (fluorescence imaging system) to identify the direction of lymphatic flow to the sentinel lymph node, which was deep in the obturator foramen. (B) Preserving the sentinel lymph node near the obturator nerve. (C) Excision of the sentinel lymph node. (D) Confirmation of the sentinel lymph node specimen with Firefly technology. ICG, indocyanine green.
pelvic SLNs exist: a lower paracervical pathway that drains the internal iliac and/or presacral nodes, and an upper paracervical pathway that drains the medial external iliac and/or obturator lymph nodes (49). How et al. (50) reported metastatic SLNs in the presacral area or medial portion of the hypogastric vein area. Thus, lymph node metastases appear to be detected more frequently by the use of SLN biopsy. In a study comprising 425 patients with low-risk endometrioid carcinoma (grade 1-2, myometrial invasion <50%), Kim et al. (51) reported lymph node metastasis in 5.9%, which was significantly in excess of the expected detection rate. A further study (52) reported more frequent identification (16.7%) of patients with stage IIIICI tumor by the use of SLN mapping compared with lymphadenectomy (7.3%). A really important issue arises from these data. What does one need in terms of optimum oncological treatment? The excision of a large number of lymph nodes from easily accessible areas or the targeted excision of less easily accessible SLNs? We presume that an algorithm based on lymphatic anatomy should be used. Not only the upper paracervical pathway but all pelvic pathways should be included. The detection of lymph node metastases might influence the decision to use adjuvant therapy and thus determine the outcome of cancer.

However, recent data suggested that the use of SLN mapping in patients with endometrial cancer does not affect the oncologic outcome compared with lymphadenectomy. Two large studies with 1,100 (53) and 802 (52) patients evaluated recurrence and death rates three years after SLN mapping or lymphadenectomy, and reported no difference between these groups. These data support the use of SNL mapping in selected patients with endometrial cancer. We found no study reporting contrary data. However, the above mentioned studies are limited by their short follow-up periods and retrospective nature. Prospective studies will be needed to determine the oncologic outcome of using SNL mapping for endometrial cancer.

**Is there any need for lymphadenectomy in patients with isolated lymph node metastasis?**

A recent analysis conducted at the Mayo Clinic and by the MSKCC research team (54) reported very interesting results concerning SLN mapping in endometrial cancer and the need of adjuvant therapy. The authors analyzed 104/1,625 patients with isolated lymph node metastasis using a multivariate analysis (48 in the lymphadenectomy group and 56 in the SLN group), and reported no significant difference in disease-specific survival rates, but significantly better survival in patients who received combined chemotherapy and radiotherapy compared to chemotherapy or radiotherapy alone. Importantly, the authors concluded that patients with endometrial cancer in FIGO stage IIIC, without bulky nodes, who receive combined chemotherapy and radiotherapy, need not undergo systematic lymphadenectomy and would experience no adverse effect on the oncologic outcome. This could lead to less radical surgery in patients with endometrial cancer and isolated lymph node metastasis. However, the retrospective nature of the analysis limits is value in regard of adjuvant treatment. Further limitations of the study include the low incidence of lymph node metastasis (6.7%), and significant differences in clinical parameters (the lymphadenectomy group was heavier, had low rates of lymphovascular space invasion, and was treated more frequently with laparotomy) and adjuvant treatment (the SLN group received more chemotherapy with or without brachytherapy) between the two groups. Prospective studies will be needed to evaluate this novel hypothesis.

**Estimated costs and cost effectiveness**

Median hospital costs for patients with endometrial cancer without lymph node metastasis undergoing a minimally invasive operation with a simple hysterectomy or SLN biopsy or lymphadenectomy are reported to be $8,877, $9,550, and $10,256, respectively (55). However, these costs may vary depending on the country and the type of SLN biopsy used. ICG may be the most cost-effective tracer. ICG powder is very economical. The main element of its use is the hardware needed to find the fluorescent signal. The study performed by Suidan et al. (56) in low-risk patients with endometrial cancer concurs with the above mentioned data and showed that SNL biopsy is less costly than routine lymphadenectomy.

**Conclusions**

SLN mapping, especially with an ICG tracer, is widely accepted as a cost-effective strategy for early stages of endometrial cancer. Several studies have confirmed its positive effects, such as upstaging in low- or intermediate-risk tumors. SLN mapping permits more accurate detection of nodal metastases and the identification of those patients who could dispense with adjuvant therapy. Oncologic outcomes could thus be improved. However, the existing
data suggest that SLN mapping is associated with similar oncologic outcomes as systematic lymphadenectomy. The oncologic outcome and the omission of systematic lymphadenectomy in patients with isolated lymph node metastasis receiving radio-chemotherapy must be investigated further in large prospective studies. Furthermore, the reduced complication rates and operating times achieved by SLN mapping favor its use in high-risk endometrial cancer. The NCCN accepted SLN mapping as an alternative to lymphadenectomy in selected cases of endometrial cancer in 2014, and recommended its use in high-grade tumors as well after four years (39). In 2015 ESMO-ESGO-ESTRO guidelines (16) recommended the use of SLN only in controlled trials. We believe that the current scientific evidence in this field could lead us away from the notion of “everything or nothing at all” to the acceptance of “not much, but good”, as it nowadays applies to breast surgery. Like any new development, the procedure will probably traverse a period of trial before it is established as a standard. Further development of nanotechnology such as multimodal nanoprobes, and robotic surgery such as intraoperative high-quality navigation and imaging systems, could open fascinating new avenues for more appropriate non-invasive SLN imaging.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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