Lymphadenectomy in Endometrial Cancer: Present Status

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5.1 Introduction

The standard management of early-stage endometrial cancer includes surgical staging which comprises of total hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment. Surgical staging helps determine the FIGO stage of the disease, as well as assess the pathological data and risk factors which help guide adjuvant treatment, if any. Prognostic factors include tumor size, grade of the lesion, depth of myometrial invasion, lymphovascular space invasion (LVSI), lymph node status, and tumor involvement of the lower uterine segment. Lymph node evaluation in surgical staging consists of bilateral pelvic nodal dissection with or without para-aortic lymph node dissection. The template for pelvic lymph node dissection is common iliac bifurcation cephalad, deep circumflex iliac vein caudad, internal iliac artery medially, genitofemoral nerve laterally, and obturator nerve at the base. The template for para-aortic node dissection is renal vessels cephalad, common iliac bifurcation caudad, and bilateral ureters on each side (Fig. 5.1). Para-aortic lymph node dissection is done in addition to pelvic nodal dissection in high-risk tumors such as high-grade endometrioid histology with >50% myometrial invasion, uterine papillary serous carcinoma, clear cell carcinoma, and carcinosarcoma. However, lymph node dissection is associated with intraoperative complications like blood vessel injury, increased blood loss, and nerve injury (obturator nerve and genitofemoral nerve) and postoperative complications like ileus, lymphocyst, and lymphedema. The incidence of lymphedema is reported between 1.2 and 47%, depending on the assessment method, and increases with postoperative radiotherapy [1].

Therapeutic role of lymphadenectomy is debatable, especially in patients with negative staging. Although the data is limited by retrospective studies, proponents of lymphadenectomy emphasize that complete lymphadenectomy helps accurately stage the disease and direct adjuvant therapy, provides prognostic information and

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S. Mehta, B. Gupta (eds.), *Recent Advances in Endometrial Cancer*,
https://doi.org/10.1007/978-981-15-5317-2_5

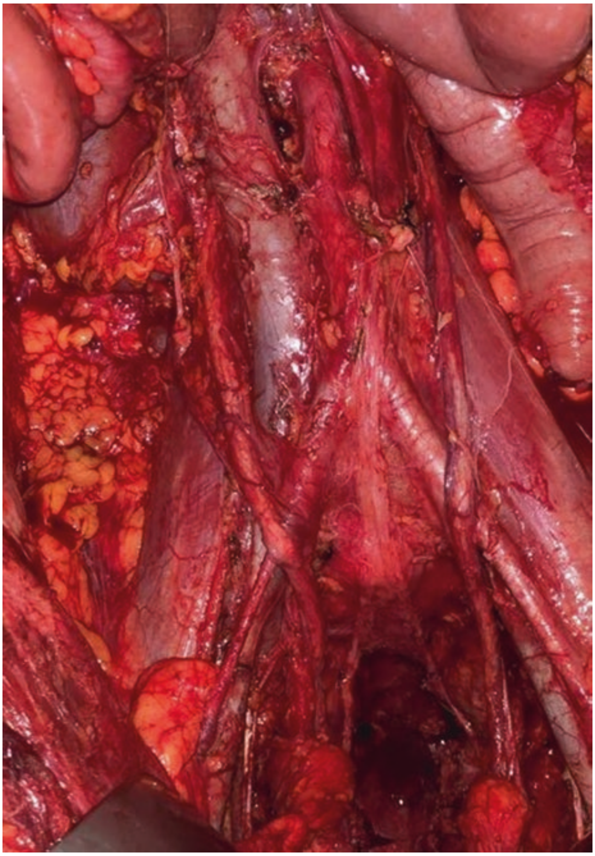

Fig. 5.1 Complete pelvic and para-aortic node dissection

also gives therapeutic benefit by removing metastatic disease in the involved nodes. Criticisms of lymphadenectomy, besides its associated morbidity, include lack of randomized trials that show a therapeutic benefit of lymphadenectomy. In fact, the published randomized trials comparing lymphadenectomy versus no lymphadenectomy in endometrial cancer have not shown any survival benefit with lymphadenectomy in low-risk patients.

Selective use of lymphadenectomy is recommended in early-stage endometrial cancer as it can reduce the morbidity associated with lymph node dissection without compromising clinical outcomes. Previously, a full lymphadenectomy, including both pelvic and para-aortic nodes was recommended for all patients irrespective of their risk factors. The recent NCCN (National Comprehensive Cancer Network) recommendations, however, favor selective lymphadenectomy including sentinel lymph node biopsy, to avoid overtreatment in low-risk patients [2]. Preoperative and intraoperative assessment of risk factors help decide whether to perform lymphadenectomy or not, and to what extent—pelvic nodes only or both pelvic and para-aortic nodes. Sentinel lymph node (SLN) mapping is an alternative to complete lymphadenectomy in the patients with disease confined to the uterus and no evidence of metastasis on preoperative imaging studies or during intraoperative exploration. Close adherence to SLN surgical algorithm recommended by the NCCN, which includes a side-specific nodal dissection in cases of failed mapping and removal of any suspicious or grossly enlarged nodes is associated with a false-negative rate of less than 5% [3, 4]. Moreover, SLN mapping with ultrastaging often increases the detection of lymph node metastasis in comparison to routine lymphadenectomy due to removal of sentinel lymph nodes which may lie outside the standard template in a few cases, and extensive sectioning and evaluation of all sentinel lymph nodes.

5.2 Lymphadenectomy: All, None, or Selective

The uterus drains into the pelvic (iliac and obturator chains) and the para-aortic lymph nodes. Few lymphatic channels from the uterine fundus can drain directly into the para-aortic lymph node chain via the infundibulopelvic ligament. Tumors more than 2 cm in size, high-grade histologies, deep myometrial invasion, lymphovascular space invasion, cervical stromal involvement, and lower uterine segment involvement are associated with increased risk of lymph node metastasis. The risk of lymph node metastasis in non-endometrioid cancers (papillary serous, clear cell, carcinosarcoma) is as high as 40% compared with 16% with endometrioid histology [5]. The risk of metastasis in para-aortic lymph nodes with involved pelvic lymph nodes is approximately 50% [6]. The risk of isolated para-aortic metastasis (without pelvic lymph node involvement) is small—only 2–3%, but a few series have reported higher rates (16–45%) [5, 7, 8]. There has been much debate regarding lymphadenectomy in endometrial cancer—whether it should be routinely done in all patients, or avoided in low-risk early-stage patients, and used judiciously in patients with high risk of lymph node metastasis. Controversies have also existed about the extent of lymphadenectomy—both pelvic and para-aortic or only pelvic, and also the extent of para-aortic node dissection—up to inferior mesenteric artery or renal vessels.

5.2.1 Lymphadenectomy: All

Lymphadenectomy helps assess the nodal status and determine the stage of endometrial cancer accurately. Low-risk patients may avoid radiation after complete staging with lymphadenectomy, or may only receive vaginal brachytherapy. Without lymphadenectomy, the oncologist has to rely only on uterine risk factors to decide adjuvant treatment and hence many patients without lymph node assessment receive pelvic radiation. The studies that support routine lymphadenectomy in all the patients cite the inaccuracy of preoperative imaging, intraoperative assessment, and frozen section in predicting the risk for nodal disease. Only 10% of patients with lymph node metastasis have clinically enlarged nodes and even these can be missed by intraoperative palpation through the overlying peritoneum [7]. Inaccuracies in determining grade of the lesion and depth of myometrial invasion with frozen section have been reported in up to 30% of cases [9]. Another advantage of routine lymphadenectomy is that it might provide a therapeutic benefit by removing any possible cancer in the lymph nodes and reducing the disease burden.

Retrospective studies have shown a benefit in removing bulky or involved lymph nodes during surgical staging. Havrilesky et al. noted that the 5-year disease-specific survival (DSS) was 63% in patients with lymph nodes showing microscopic disease, 50% in completely resected grossly positive nodes, and 43% in cases where bulky nodes could not be resected [10]. Bristow et al. reported that the median DSS in patients with completely debulked involved lymph nodes was 37.7 months, compared with 8.8 months in patients with gross residual lymph node disease [11]. Hence, there is definitely a survival benefit with debulking bulky involved lymph nodes and every effort must be made to completely resect all obvious lymph node metastases.

The therapeutic benefit of removing non-enlarged, negative lymph nodes has been controversial. Kilgore et al. retrospectively reviewed 649 women with stage I or II endometrial cancer—a third underwent complete lymphadenectomy, one-third had selective sampling, and the remaining third had no nodal sampling. Women who underwent multiple site pelvic nodal dissection (at least four pelvic nodal sites) and had a mean of 11 nodes removed, had improved survival compared with women who did not have any lymph nodes sampling. This advantage persisted even after stratification of cases into low and high risk, and irrespective of whether adjuvant radiation was used or not [12]. It is possible that improved outcomes in these cases were due to removal of lymph node micrometastases that could not be recognized by standard pathologic processing. Another study showing therapeutic benefit of lymphadenectomy was reported by Cragan et al., who demonstrated that removal of more than 11 pelvic lymph nodes was associated with improved overall and progression-free survival in patients with grade 3 endometrial cancers. The 5-year survival in patients with high-risk features like grade 3 lesions, >50% myometrial invasion, and serous or clear-cell histology was 82% when more than 11 nodes were removed compared to 64% when ≤11 nodes were removed. This benefit remained significant even after excluding patients who received adjuvant treatment [13].

The SEPAL study (Survival Effect of Para-Aortic Lymphadenectomy in endometrial cancer) from Japan evaluated the effect of para-aortic lymphadenectomy on survival in more than 600 patients. In intermediate and high-risk endometrial cancers, the recurrence-free survival and overall survival was significantly better in women who underwent combined pelvic and para-aortic lymphadenectomy than in those who had only pelvic lymphadenectomy. The survival benefit, however, did not extend to low-risk cancers [14]. The Mayo group found that when para-aortic nodes were positive, 77% of cases had positive nodes above the inferior mesenteric artery [5]. Hence, para-aortic node dissection is recommended till the level of renal vessels. Chan et al. reported the impact of complete lymphadenectomy on survival outcomes in over 12,000 women with endometrial cancer using the National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) data source. In patients with high-risk disease (IB grade 3, IC - FIGO 1988 Staging, II - IV), 5-year survival was directly proportional to the number of nodes removed, increasing from 75% to 87% when 1 versus >20 nodes were removed [15].

The concept of lymph node (LN) ratio has been defined as the number of metastatic LNs to the total number of removed LNs. This ratio shows both the burden of nodal disease as well as the extent and quality of surgical staging. Patients with LN ratios of 10%, >10–50%, and >50% have reported to have overall survival rates of 79%, 61%, and 36%, respectively ($P < 0.001$) [16].

5.2.2 Lymphadenectomy: None

There are two prospective, randomized trials that have compared survival outcomes in women undergoing hysterectomy with or without lymphadenectomy in stage I–IIA endometrial cancer—the ASTEC (A Study in the Treatment of Endometrial Cancer) trial by Kitchener et al. [17] and the Italian trial by Benedetti et al. [18]. The ASTEC trial involved 1369 patients, who were further randomized to postoperative radiation or observation following surgery. Nodal status did not direct the use of adjuvant radiation therapy, and so even node-positive patients were randomized to the observation group. Moreover, vaginal brachytherapy could be given in both observation and radiation group depending upon the institutional preference. In the Italian trial (514 patients), postoperative radiation was not prescribed according to a set protocol but left to the oncologist's discretion. Both studies found no difference in survival outcomes between the two arms, and increased morbidity in the lymphadenectomy group. The authors concluded that there was no benefit in either progression-free or overall survival with lymphadenectomy and hence it could not be recommended as a routine procedure for therapeutic purposes.

These studies, however, have been criticized and their results should be interpreted with caution. There was overrepresentation of low-risk patients, especially in the ASTEC trial which could negate the beneficial effect of lymphadenectomy, if any, due to low incidence of lymph node metastasis in stage I low-risk disease. The quality of lymph node dissection in these trials has been questioned. Both trials were designed to evaluate only pelvic lymphadenectomy. Para-aortic lymphadenectomy was performed only in the Italian study and that too in only 26% of cases. In the ASTEC trial, 8% of patients in the lymphadenectomy group had no lymph node dissection and 12% of patients had less than five lymph nodes removed. There was a lack of standardization of adjuvant therapy such that only half of the patients with pelvic node metastases in the ASTEC study received pelvic radiation, thus limiting the benefit of identification of positive nodes. In the Italian trial, postoperative radiation or chemotherapy was given by the surgeon's preference. Other concerns include the lack of central pathology review, limited statistical power to show improvement in survival rates, and the lack of quality-of-life assessment. Despite these weaknesses, these two trials provide the only level 1 evidence on the role of lymphadenectomy in endometrial cancer. They show that lymphadenectomy may provide only modest survival benefit in early-stage disease and that removing negative nodes is unlikely to have any therapeutic role or improve survival outcomes.

The Cochrane 2017 review including 1851 patients reported no differences in overall and recurrence-free survival between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy during surgical staging of endometrial cancer (pooled hazard ratio (HR) 1.07, 95% confidence interval (CI) 0.81 to 1.43 for overall survival; HR 1.23, 95% CI 0.96 to 1.58 for recurrence-free survival) [19]. There has been no evidence from any randomized trial that has shown the effect of lymphadenectomy in women with higher-stage disease and in cases at high risk of recurrence.

5.2.3 Lymphadenectomy: Selective

There are definite improved survival outcomes with debulking clinically enlarged, involved nodes or nodal macrometastasis, and possibly with resection of microscopic metastasis with pelvic and para-aortic lymphadenectomy in high-risk endometrial cancers. The therapeutic benefit of lymphadenectomy in node-negative patients is debatable.

The use of complete pelvic and para-aortic lymphadenectomy in all patients of endometrial cancer, irrespective of their risk factors, would result in overtreatment of a large fraction of low-risk patients who may not benefit from it, in addition to the surgical morbidity associated with systematic lymph node dissection. Various studies have focused on evaluating the patients' risk factors for lymph node metastasis as well as the status of lymph nodes. These factors, determined either preoperatively or intraoperatively, help decide which patients would benefit from lymphadenectomy and hence help tailor the lymph node dissection (pelvic, both pelvic and para-aortic or none) according to the risk factors in each patient.

Data from GOG 33 showed the rates of pelvic and para-aortic nodal disease with different grades and depth of myometrial invasion in endometrial cancers [7]. These could help decide whether or not to perform lymphadenectomy in patients, depending upon the risk of lymph node metastasis. The risk of pelvic nodal disease in GOG 33 was none for patients with grade 1 tumors with superficial invasion, but 11% for grade 1 tumors with deep myometrial invasion. Patients with grade 3 tumors and deep myometrial invasion were found to have pelvic nodal metastases in 34% and para-aortic nodal metastases in 23% cases (Table 5.1). Patients with serous or clear cell histology have nodal involvement in about 30–50% cases and warrant systematic pelvic and para-aortic lymphadenectomy even in the absence of myometrial invasion.

Mariani et al. described the Mayo's criteria in 2000, which helped identify a low-risk group of endometrial cancer that had a very small risk of nodal disease spread [5]. The criteria described were based on intraoperative frozen section of the uterine specimen—grade 1 to 2 endometrioid histology, less than 50% myometrial invasion, and tumor size less than 2 cm. In the study population of 422 patients, 27% (n = 122) were identified as low risk using the above parameters and none of these cases had lymph node metastasis. The negative predictive value of the Mayo's criteria in identifying a low-risk subset that would not benefit from lymphadenectomy

Table 5.1 Rates of pelvic and para-aortic lymph node metastases in different grades and depths of myometrial invasion in Endometrial Cancer [7]

Depth of myometrial invasion	Grade 1		Grade 2		Grade 3	
	Pelvic LN	Para-aortic LN	Pelvic LN	Para-aortic LN	Pelvic LN	Para-aortic LN
Confined to the endometrium	0%	0%	3%	3%	0%	0%
Inner third invasion	3%	1%	5%	4%	9%	4%
Middle third invasion	0%	5%	9%	0%	4%	0%
Outer third invasion	11%	6%	19%	14%	34%	23%

was 98%. The Mayo group uses these criteria for selective use of lymphadenectomy in management of patients with endometrial cancer. Their management protocol includes an intraoperative assessment of the hysterectomy specimen with frozen section. Women defined as low risk as per the Mayo's criteria do not undergo lymphadenectomy. Patients showing more than 50% myometrial invasion or Type II histology undergo both pelvic and aortic lymphadenectomy. Tumors not showing these features but having cervical invasion, grade 3 endometrioid histology with any myometrial invasion, or size larger than 2 cm, undergo pelvic lymphadenectomy. The pelvic lymph nodes are checked for metastasis by frozen section evaluation and para-aortic lymph node dissection is carried out if pelvic nodes are positive for disease [20].

The drawback of the Mayo criteria is that since it is based on intraoperative frozen section, it may not be replicated at many institutions with similar degree of accuracy. In fact, several institutions have reported upstaging in almost 18% cases on the final histopathological reports [9]. Due to these limitations, the Mayo group has now modified the criteria, the newer criteria using the grade of preoperative endometrial biopsy and intraoperative assessment of tumor size by the surgeon to determine whether to do lymphadenectomy or not [21]. Patients with grade 1 or 2 lesions on preoperative endometrial biopsy and tumor size less than 2 cm on intraoperative assessment by the surgeon, have less than 1% risk of lymph node metastasis and do not require lymphadenectomy. The surgeon should take care to avoid distorting the anatomy when opening the uterine specimen. Studies have reported that the visual inspection of more than or less than 50% myometrial invasion corresponds to the microscopic findings in 85% cases, although this accuracy decreases in grade 3 tumors [22, 23].

The European Society for Medical Oncology (ESMO) has categorized endometrial cancer into three risk groups—Low risk (Stage IA, grade 1 or 2), Intermediate risk (Stage IA, grade 3 and Stage IB, grade 1 or 2), and High risk (Stage IB, grade 3 and Type 2 histology). Due to the low risk of lymph node metastasis, ESMO does not recommend lymphadenectomy in the low-risk group [24].

Preoperative imaging helps in assessing patients with risk factors that increase the risk of lymph node metastasis and also helps in detection of enlarged or suspicious nodes. Magnetic resonance imaging (MRI) has been found to have an accuracy of 74% in determining the depth of myometrial invasion, though the presence of large polypoidal tumors, small sized uterus, and fibroids may limit the assessment in some cases [25, 26]. The MRI also helps determine cervical invasion and nodal disease, if any. PET-CECT has moderate sensitivity (78–79%) with good specificity (98–99%) and negative predictive value (95–97%) in identifying nodal involvement but cannot identify low-volume disease [27]. The role of PET scans in early cancers is limited as they add to the cost and often do not change the management.

5.2.4 Sentinel Lymph Node Mapping

Sentinel lymph node (SLN) mapping is based on the premise that if the sentinel node or the first draining lymph node is negative for disease, metastatic disease in the remaining non-enlarged nodes of the nodal basin can be ruled out with reasonable certainty. Hence, complete lymph node dissection can be avoided, providing the same diagnostic and prognostic information, while minimizing the morbidity. SLN mapping is validated for clinical stage I, uterine-confined endometrial cancer.

Due to the complexity of lymphatic drainage of the endometrium, there has been much debate on the best suited injection site for identifying sentinel nodes with maximum accuracy. Different techniques of dye or tracer injection have been evaluated—cervical, sub-serosal fundal, deep myometrial, and hysteroscopy guided sub-endometrial. The cervical injection technique is easy and has provided the best sentinel lymph node detection rates. Cervical injection of the dye provides excellent access to uterine lymphatics (superficial subserosal, intermediate stromal, and deep submucosal) confluencing in the parametria which lead into the pelvic and occasionally the para-aortic sentinel lymph nodes. Some lymphatics which run from the uterus into the para-aortic nodes directly via the infundibulopelvic ligaments are accessed through deep cervical injections but the accuracy of mapping para-aortic sentinel nodes by the cervical technique has not been comprehensively investigated. The dye or tracer is injected into the superficial (1-3 mm) and deep (1–2 cm) cervical tissue at 3 and 9 o'clock [2]. It should be injected slowly to increase the lymphatic uptake and minimize staining of deep pelvic tissues. The retroperitoneal spaces are then opened on both sides and the sentinel lymphatic pathways emanating from the parametria are traced. The most proximal lymph nodes in the sentinel pathway are then excised and sent for pathological assessment.

The most common site of sentinel lymph node in endometrial cancer is in the superior obturator region of pelvic nodal basin. Less commonly, the node is detected in the common iliac or presacral region [2]. FIRES trial (Fluorescence Imaging for Robotic Endometrial Sentinel lymph node biopsy), a prospective randomized study aimed to study the accuracy of sentinel lymph node mapping, found sentinel nodes in the following regions: external iliac (38%), obturator (25%), inframesenteric para-aortic (14%), internal iliac (10%), common iliac (8%), presacral (3%), infrarenal para-aortic (1%), and others (including parametrium 1%) [28]. Approximately 5% of SLNs in endometrial cancer are found in areas not routinely dissected with the standard lymphadenectomy templates, such as presacral or deep internal iliac lymph nodes [2]. In the FIRES trial, SLN mapping found positive nodes outside the traditional surgical boundaries in 20% of the patients [28].

Various tracers have been used for sentinel lymph node mapping in endometrial cancer. These include colored dyes (Isosulfan Blue 1%, Methylene Blue 1%, and Patent Blue 2.5%), radiocolloid technetium-99 m (Tc-99 m) and indocyanine green (ICG). Colorimetric lymphatic mapping employs dyes like isosulfan blue and methylene blue which are injected into the cervix and then blue-colored sentinel nodes and lymphatics are identified in the retroperitoneum within 10–20 minutes. This approach can be used in open, laparoscopic, and robotic staging. Delay from cervical injection to mapping should be avoided to prevent low detection rates due to transit of dye through the sentinel node [4]. The advantages of using colored dyes is that it does not require any costly equipment. Disadvantages include a small risk (1%) of allergic reaction especially in patients with history of asthma or multiple allergies [29], paradoxical methemoglobinemia, and interference with the measurement of oxygen saturation leading to falsely low oxygen saturation readings, and lower detection rates when used alone (as opposed to when used in combination with radioisotope).

The radiometric method of sentinel node mapping uses technetium-99 with nuclear imaging and intraoperative gamma counters to detect nodes, often in combination with blue dyes to increase the detection rate. One milliliter of 1 mCi of Tc-99 m is injected, generally 1 day prior to surgery. A gamma probe identifies areas of “hot” tracer signal intraoperatively based on audiometric signals. The areas of increased gamma signal are dissected to visually identify blue nodes and then the gamma probe is used to identify the signal strength of these nodes. Nodes which are hot and/or blue are mapped as sentinel nodes. The advantage of using both dyes and Tc-99 is that while the blue dye helps in visually localizing the representative node, the radioisotope penetrates through deep tissue and fatty nodal basins, thereby increasing the detection of sentinel lymph nodes [4]. Preoperative lymphoscintigraphy or three-dimensional single photon emission computed tomography with integrated CT (SPECT/CT) can be used along with the radiometric method in order to identify the location of sentinel lymph nodes prior to surgery.

Near-infrared (NIR) method came into use after the colorimetric and radiometric procedures. It uses indocyanine green (ICG), a tricarbocyanine dye which shows florescence when seen through a near-infrared light (range, 700–900 nm). Near-infrared imagers are required to receive the 830 nm wavelength emitted by ICG and visualize its drainage into the lymphatic vessels and these are available at present for laparotomy, laparoscopic, and robotic procedures (Fig. 5.2). A concentration of 0.5–1.25 mg/mL is generally used. The advantage of indocyanine green is that not only does it allow real-time visualization during sentinel node mapping, the signal also penetrates deep tissue, hence combining the positives of colorimetric and radiometric techniques. ICG is superior to blue dyes in obese patients and has higher overall and bilateral detection rates in comparison to even combined (blue dye plus Tc-99) methods. It also has a better safety profile than blue dyes (anaphylaxis, skin necrosis) and Tc-99 m (radioactivity) and the risk of adverse events is extremely

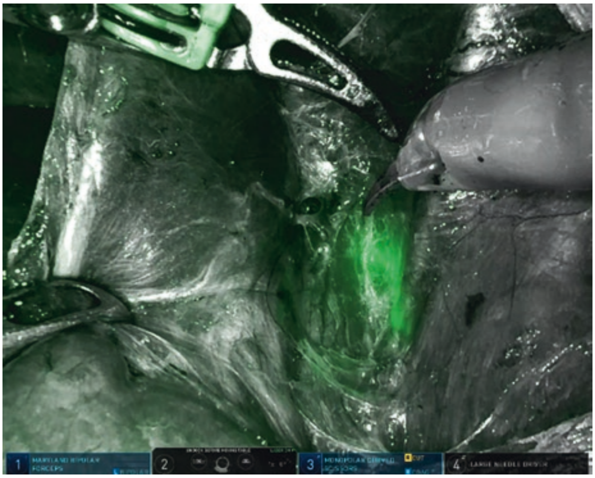

Fig. 5.2 Sentinel lymph node mapping using indocyanine green

low (1/42,000 for anaphylaxis) [4]. Even so, it should be avoided in patients with severe iodine allergy and in liver failure, as it is excreted completely by the liver. The disadvantage of ICG is that expensive NIR imaging equipment is required with this method. Due to the high SLN detection rate, ICG is commonly used in many centers at present.

In order to maximize the rates of successful SLN mapping, it is imperative to follow the NCCN SLN algorithm, which recommends side-specific nodal dissection in cases of failed mapping and removal of any suspicious or grossly enlarged nodes regardless of mapping (Fig. 5.3). Close adherence to this algorithm has been found to have less than 5% false-negative rate in detecting nodal metastasis. The Society of Gynecologic Oncology (SGO) recommends that surgeons should perform at least 20 SLN procedures with concomitant completion lymphadenectomy prior to adopting SLN algorithm for routine management of early endometrial cancers [4]. Abu Rustum et al. reported a learning curve with an increase in SLN detection from 77% to 94% ($p = 0.03$) over 30 cases [30, 31].

Sentinel lymph node biopsy is combined with ultrastaging to increase the detection of nodal metastasis, especially low volume disease not detected on routine histology. Ultrastaging involves serial sectioning and combined hematoxylin and eosin (H&E) staining with immunohistochemistry which improves the accuracy of detecting micrometastases. Though there are no formal guidelines for pathologic assessment of sentinel nodes in endometrial cancer, the Memorial Sloan Kettering Cancer Center (MSKCC) group proposes initial evaluation by routine H&E, and if negative, cut two adjacent 5-μm sections (one H&E and one cytokeratin AE1/AE3) from each paraffin block 50 μm apart [32]. By increasing the detection of metastatic disease, ultrastaging can lead to upstaging in 5–15% of patients. A retrospective study of 780 patients undergoing SLN mapping with lymphadenectomy compared with lymphadenectomy alone showed that SLN mapping detected more metastasis (30.3% vs 14.7%; $P < 0.001$) and was associated with greater use of adjuvant therapy [33].

Fig. 5.3 The SLN algorithm for surgical staging of endometrial cancer [2] (Courtesy of Dr. Nadeem R. Abu-Rustum at Memorial Sloan Kettering Cancer Center)

Low-volume metastases accounts for approximately half of the lymph node metastases detected through sentinel node ultrastaging in endometrial cancer [33]. Although most patients with micrometastases or isolated tumor cells (ITCs) detected on SLN ultrastaging receive adjuvant treatment, it is uncertain what impact this treatment has on the survival outcomes, and the prognosis and appropriate management of these cases is not yet clear. In a retrospective analysis of 844 patients with endometrial cancer undergoing SLN mapping, 3 year recurrence-free survival was almost similar for patients with negative SLNs, ITCs, and micrometastasis—90% for those with negative SLNs, 86% for ITCs, and 86% for micrometastasis but significantly lower—71% ($p < 0.001$) for those with SLN macrometastasis [34].

The accuracy of SLN mapping in endometrial cancer has improved progressively over the years. A recent meta-analysis of 48 studies, including 5348 patients, reported that the pooled SLN detection rates were 87% (95% CI: 84–89%, 44 studies) for overall detection and 61% (95% CI: 56–66%, 36 studies) for bilateral detection. Indocyanine green use was associated with improved overall (94%, 95% CI: 92–96%, 19 studies) SLN detection rates compared to blue tracer (86%, 95% CI: 83–89%, 31 studies) or technetium-99 (86%, 95% CI: 83–89%, 25 studies). There was no difference in para-aortic SLN detection rate between each tracer. The pooled estimates from 34 studies showed a 94% sensitivity and 100% negative predictive value (NPV). Diagnostic accuracy of SLN mapping was not negatively affected in patients with high-grade endometrial histology [35]. A comparative analysis between complete lymphadenectomy at the Mayo Clinic and the SLN algorithm at MSKCC showed pelvic node metastases in 2.6% and 5.1% of patients, respectively ($p = 0.03$), and para-aortic node metastases in 1.0% and 0.8%, respectively ($p = 0.75$). Though there were some differences in the patient characteristics and adjuvant therapy in both groups, the 3-year disease-free survival rates were similar—96.8% [95% CI, 95.2–98.5] and 94.9% [95% CI, 92.4–97.5], respectively [36].

The FIRES trial, a multicenter, prospective, cohort study published in 2017 was designed to evaluate the sensitivity and negative predictive value of SLN mapping and compare it with the gold standard of complete lymphadenectomy in detecting metastatic disease for endometrial cancer. Patients with clinical stage 1 endometrial cancer of all grades and histologies undergoing robotic staging received an intracervical injection of ICG dye with sentinel-lymph-node mapping followed by pelvic lymphadenectomy with or without para-aortic lymphadenectomy. Of the 385 patients enrolled in the trial, 340 underwent SLN mapping with complete lymphadenectomy with 58% of these having para-aortic lymphadenectomy. Eighty-six percent of patients had successful mapping of at least one sentinel lymph node. The sensitivity to detect node-positive disease using SLN mapping was 97.2% (95% CI, 85–100), and a negative predictive value of 99.6% (95% CI, 97.9–100). The authors concluded that SLN biopsy has a high degree of accuracy in detecting endometrial cancer metastases and even though it may not identify metastases in 3% of patients with node-positive disease, it can safely replace complete lymphadenectomy in staging of endometrial cancer [28].

SLN mapping has been controversial in patients with high-risk histology (serous carcinoma, clear cell carcinoma, carcinosarcoma) but promising results have been reported recently [2, 4]. The FIRES trial study group included 28% patients with high-grade histologies, but the role of SLN biopsy in this subset has not been addressed definitively. The one false-negative result in the study was in a patient with a high-grade (serous) cancer [28].

One important issue with SLN detection using cervical injection of dyes is the lower rates of para-aortic SLN detection compared to fundal or intra-tumoral injection techniques. Failure to identify metastasis in para-aortic nodes would result in failure to prescribe the necessary adjuvant treatment, thereby affecting the outcomes of the disease. In the FIRES trial, there were no cases of missed isolated para-aortic nodal metastases among patients who mapped at least one SLN and underwent para-aortic lymphadenectomy. In order to avoid missing metastatic disease in the para-aortic region, preoperative imaging must be done for patients with high-grade tumors who are at a high risk for lymph node metastases, in order to detect any suspicious para-aortic lymph nodes. These nodes should be removed during surgery regardless of SLN mapping. In addition, frozen section should be employed intra-operatively to detect high-risk factors in the uterine specimen (high-grade histology, deep myometrial invasion), if any, and pelvic nodal metastasis to identify patients at high risk for para-aortic disease. During the surgery, the surgeon should carefully inspect the para-aortic region for identification of SLNs, especially in cases where no pelvic SLN could be mapped on one or both sides. Furthermore, patients with high-grade histologies, more than 50% myometrial invasion and positive pelvic nodes should undergo para-aortic lymphadenectomy, and the SLN algorithm should be used only for pelvic nodal evaluation [4].

Routine frozen section of SLNs is not advocated because of the low sensitivity of frozen for detection of metastasis in normal appearing lymph nodes. Also, frozen section may distort the nodal tissue precluding the ultrastaging to detect low volume disease. In cases where SLNs are found positive on final histology and ultrastaging, completion lymphadenectomy has little role as it does not change further management, nor is it therapeutic in clinically normal nodes. Postoperative imaging is advised in these cases to ensure there are no gross bulky residual nodes that were missed during initial staging and these are the only cases that may benefit from surgical cytoreduction. Imaging also helps guide adjuvant treatment including radiotherapy and deciding the dosing and fields of radiation with extended radiation to the para-aortic region for patients with proximal iliac SLN metastases, positive para-aortic findings on imaging, or high-grade cancers.

The SGO has laid forth the following recommendations for SLN mapping in endometrial cancer [4]:

1. Cervical injection of tracers detects pelvic lymph node metastasis accurately and has a low (<5%) false-negative rate when the NCCN SLN algorithm is strictly adhered to. Completion lymphadenectomy should be done by the surgeon before adopting the algorithm into clinical practice until he or she can elicit similar rates of SLN detection as documented in current literature and with a <5% false-negative rate.
2. Cervical injection of ICG dye with infrared imaging is preferable for SLN mapping whenever available, because of the technical ease and high rates of successful SLN detection. Radiocolloid Tc-99 combined with blue dye is also an acceptable approach when ICG is not available.
3. SLN mapping using the NCCN SLN algorithm can be performed in place of systematic pelvic lymphadenectomy for women with uterine confined grade1 and 2 endometrioid cancers.
4. SLN mapping along with ultrastaging increases the detection of nodal metastasis compared to routine lymphadenectomy. Patients should be counseled regarding the small (<5%) risk for missing metastatic disease with SLN biopsy.
5. SLN mapping is accurate in detecting pelvic nodal metastasis and also detects some para-aortic SLNs. The decision about performing para-aortic nodal dissection is at the surgeon's discretion and based on high-risk factors like high-grade histology, deep uterine invasion, and positive pelvic nodes.

6. Pathologic processing of each SLN should be done by serial sectioning at 2-mm intervals along the longitudinal plane of the node, and microscopic examination of all slices with at least one representative H&E level. Ultrastaging increases the detection of ITCs and micrometastasis, but the clinical significance of ITCs is currently uncertain.
7. The NCCN SLN algorithm can be incorporated into the staging of high-grade endometrial cancer (grade 3 endometrioid, serous, clear cell, or carcinosarcoma) and is currently being used by various institutions, with encouraging early results. But until more data regarding the accuracy and safety of SLN biopsy in this group of patients becomes available, completion lymphadenectomy with para-aortic assessment is advisable in these cases.

5.3 Conclusions

Therapeutic role of lymphadenectomy in patients with negative nodes is debatable but there is definite clinical benefit in debulking enlarged nodes. Selective use of lymphadenectomy has been advocated in early-stage endometrial cancer to avoid overtreatment in low-risk cases and reduce the morbidity associated with systematic lymph node dissection without compromising survival outcomes. This can be done by appropriate patient selection—doing lymphadenectomy in cases at high risk for nodal metastasis but avoiding it in low-risk cases. Sentinel lymph node assessment is feasible in uterine confined disease and may eliminate the need for complete lymphadenectomy in low-risk patients. The question of whether lymphadenectomy has a therapeutic benefit in high-risk endometrial cancer could be answered by a prospective randomized trial comparing sentinel lymph node assessment to complete pelvic and para-aortic lymphadenectomy in this group.

Key Points

- The standard management of early-stage endometrial cancer includes surgical staging which comprises total hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment. Complete lymphadenectomy includes both pelvic and para-aortic lymph node assessment.
- Lymphadenectomy has a definite therapeutic benefit and is associated with improved survival outcomes with debulking clinically enlarged nodes or nodal macrometastasis, and possibly with resection of microscopic metastasis. The therapeutic role of lymphadenectomy in node-negative patients is debatable.
- Previous guidelines including older NCCN recommendations recommended complete pelvic and para-aortic lymph node assessment in all patients of endometrial cancer, irrespective of risk factors. The current guidelines recommend selective use of lymphadenectomy in early-stage endometrial cancer as it can reduce the morbidity associated with lymph node dissection without compromising clinical outcomes, and avoid overtreatment in low-risk cases (Stage IA, grade 1 or 2).

- In patients with grade 1 to 2 endometrioid tumors, less than 50% myometrial invasion, and tumor size less than 2 cm, the risk of lymph node metastasis is very low (Mayo's criteria). Lymphadenectomy can be avoided in this low-risk group.
- Patients with grade 3 endometrioid tumors and more than 50% myometrial invasion, and those with high-risk histologies (serous carcinoma, clear cell carcinoma, carcinosarcoma) should undergo both pelvic and para-aortic lymph node assessment.
- Sentinel lymph node (SLN) mapping is validated for uterine confined grade1 and 2 endometrioid cancers. The preferred technique is cervical injection at 3 and 9 o'clock using indocyanine green dye. The SLN algorithm proposed by the NCCN has shown high rates of successful SLN mapping with very low (<5%) false-negative rates. Side-specific nodal dissection should be done in cases of failed mapping and any suspicious or grossly enlarged nodes should be removed regardless of mapping.

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