Surgical Principles in Endometrial Cancer

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For decades, the standard of treatment for endometrial cancer has been total abdominal hysterectomy with bilateral salpingo-oophorectomy, and the surgical assessment of lymph nodes was reported for the first time in the 1960s [1]. In 1988 the International Federation of Gynecology and Obstetrics (FIGO), following the recommendation of a seminal Gynecologic Oncology Group (GOG) study [2], replaced the clinical staging adopted in 1971 and introduced the concept of surgical staging for endometrial cancer [3]. Comprehensive surgical staging includes hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, and pelvic washing [4]. Pelvic lymphadenectomy consists of the removal of iliac nodes, including common iliac, external iliac, and internal iliac, and obturator lymph nodes. Para-aortic lymphadenectomy consists of the removal of lymph nodes above and below the inferior mesenteric artery, and up to the renal vessels [5]. The current guidelines of the American College of Obstetricians and Gynecologists [4] and the Society of Gynecological Oncology [4] recommend that "the initial management of endometrial cancer should include comprehensive surgical staging." However, after more than 25 years, the role of lymphadenectomy is still debated and the treatment of endometrial cancer varies largely across practitioners [6–9].

The potential diagnostic and therapeutic benefits of lymphadenectomy are numerous. The diagnostic role is to define the extent of disease, thus targeting adjuvant therapy and identifying patients who may not need postsurgical treatment. The potential therapeutic role is to eradicate existing disease in the nodal tissue. By

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contrast, comprehensive surgical staging is associated with an increase in morbidities and cost [10], and the gynecological oncological community has to find a balance between risks and benefits.

The overall incidence rate of pelvic and para-aortic lymph node metastasis in patients with endometrial cancer has been estimated between 9–17% and 6–12%, respectively [2, 11].

According to the 26th Annual Report of the FIGO on carcinoma of the corpus uteri, 48.7% of the patients were FIGO stage IA (tumor confined to the corpus uteri and myometrial invasion <50%), with an overall 5-year survival higher than 92% [12, 13]. However, approximately 10% of patients supposedly at stage I present with lymph node involvement at the time of diagnosis [14]. Considering the lack of standardized accurate preoperative tests to determine lymph node metastasis, surgical staging remains the gold standard to identify extrauterine dissemination.

11.1 Pre- and Intraoperative Identification of the Population at Risk of Lymph Node Involvement

Preoperative and intraoperative identification of patients at low risk for lymph node dissemination is of paramount importance, and may reduce morbidity and the cost related to unnecessary postsurgical treatment, while preserving oncologic outcome.

Stage alone, as defined by the revised FIGO staging in 2009, is not accurate at differentiating patients at low risk from patients at high risk [10].

Risk factors associated with lymph node metastasis are tumor diameter, depth of myometrial invasion, FIGO grade, lymphovascular invasion, cervical stromal invasion, adnexal involvement, positive peritoneal cytology, and subtype [2, 14, 15].

A study by Schink et al. reported that, among 142 patients with clinical stage I, only 4% of patients with tumor diameter ≤2 cm had lymph node metastasis, compared with 15% of patients with tumors >2 cm in diameter [16].

In the seminal GOG study, which drove the change of the FIGO staging from clinical staging to surgical staging in 1988, Creasman et al. demonstrated risk of lymph node metastasis in patients with stage I endometrial carcinoma is positively related with an increase in tumor grade and depth of myometrial invasion. They identified patients with absent myometrial invasion or grade 1 histology with superficial myometrial invasion (excluding clear cell and papillary serous cases) as low risk (<5%) for pelvic lymph node metastasis, and patients with grade 3 or myometrial invasion >33% as high risk (>10%). All other cases were identified as moderate risk (5–10%) for pelvic lymph node metastasis [2, 17] (Table 11.1).

Table 11.1 Frequency of Pelvic and Para-aortic Nodal disease by histologic grade and depth of invasion (adapted from Creasman et al. [2])

	Grade		
Depth of Invasion	Grade I (n = 180)	Grade II (n = 288)	Grade III (n = 153)
Endometrial only (n = 86)	0%/0%	3%/3%	0%/0%
Inner one-third (n = 281)	3%/1%	5%/4%	9%/4%
Middle one-third (n = 115)	0%/5%	9%/0%	4%/0%
Outer one-third (n = 139)	11%/6%	19%/14%	34%/23%

In 2000, Mariani et al. proposed a stratification system (later defined as the "Mayo criteria") able to identify patients at low risk who can be adequately treated with hysterectomy and bilateral oophorectomy alone, while preserving oncologic outcomes. This algorithm, which relies entirely on intraoperative frozen section, considers patients with the following characteristics to have low-risk disease: (1) type 1, (2) grade 1 or 2, (3) myometrial invasion <50%, and (4) primary tumor diameter ≤ 2 cm. Results showed that no patients with primary tumor diameter ≤ 2 cm had positive lymph nodes or died of disease. By contrast, node involvement was detected in 7% of patients with primary tumor diameter ≥ 2 cm [18]. Subsequently, these findings have been prospectively validated by the same group [10] and other groups [19, 20]. In the validation cohort of 1393 patients with endometrial cancer surgically managed at Mayo Clinic, the low-risk group accounted for 27.6% of the entire cohort and 34.1% of the endometrioid type, with a prevalence of lymph node metastasis of 1/385 (0.3%) [10]. Based on this very low prevalence of lymph node involvement, and a cause-specific survival of 98.6%, the lymphadenectomy in this low-risk population is not justifiable. Therefore, using the Mayo criteria, approximately 76% of patients with endometrial cancer require complete surgical staging [10].

Selective lymphadenectomy based on Mayo criteria has been criticized due to lack of accurate intraoperative frozen section in the majority of hospitals worldwide [21, 22]. In fact, although high accuracy rates of intraoperative frozen section (agreement between frozen section findings and final pathology reports) in the assessment of histologic grade and myometrial invasion has been reported by different groups [23–25], several reports showed a poor correlation of intraoperative frozen section with permanent section analysis [21, 22, 26]. Unfortunately, the lack of homogeneous quality of frozen sections remains an obstacle to individualized lymphadenectomy on a wider scale. Therefore, Al Hilli et al. recently demonstrated that, when an accurate frozen section is not available, patients with endometrial cancer can be effectively stratified into risk categories (low, intermediate, high) on the basis of (1) preoperative biopsy (which is usually available), (2) intraoperative tumor diameter (easily measured on fresh tissue), and (3) presence/absence of macroscopic extrauterine disease. They observed that patients at low risk (type 1 endometrial cancer with grade 1 and 2, primary tumor diameter <2 cm, and no gross extrauterine disease) have <1% risk of lymph node metastasis or lymph node recurrence. By contrast, patients at intermediate risk (type 1 endometrial cancer with grade 1 and 2, primary tumor diameter >2 cm, no gross extrauterine disease) and high-risk (type 1 endometrial cancer with grade 3 or type 2 endometrial cancer, or presence of gross metastatic disease) have a higher risk of lymph node involvement (11% and 27%, respectively), and may benefit from lymphadenectomy [27].

Imaging modalities, such as magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET)/CT, and ultrasound, have been proposed in the preoperative identification of lymph node metastasis [28–31]. A prospective study comparing MRI, PET/CT, and transvaginal two-dimensional ultrasound (2D-US) showed that PET/CT was the most reliable of the three techniques in predicting lymph node dissemination [29]. Unfortunately, due to their low-moderate sensitivity, imaging modalities alone cannot replace surgical staging

and can be useful only in patients who are poor candidates for lymphadenectomy. However, higher sensitivity in the identification of lymph node dissemination is achieved when imaging modalities are associated with other preoperative variables. Several groups have proposed different risk prediction models to identify patients at low risk for lymph node dissemination using preoperative imaging [32, 33]. The Korean Gynecologic Oncology Group (KGOG), using serum CA-125 levels and MRI to assess myometrial invasion, lymph node enlargement, and extension of disease beyond the uterus, developed and externally validated a model able to identify 43% of patients at low risk for lymph node metastasis, with a false negative rate of 1.4% [32]. Subsequently, the ability of KGOG criteria in identifying patients at low risk has been confirmed in two Japanese cohorts [34]. Further, Todo et al. showed that serum CA-125 levels, histology, grade, and MRI (to assess myometrial invasion and volume index) can predict retroperitoneal lymph node dissemination in the preoperative setting [33]. However, both the high cost associated with MRI and the lack of demonstrated clinical benefit for the use of these preoperative risk prediction models do not allow us to support their systematic use in clinical practice.

Other authors have proposed risk scoring systems that can be used to predict lymph node metastasis and identify patients who can benefit from secondary surgical staging after incomplete surgical staging, due to either incidental diagnosis of endometrial cancer or to discrepancy between pre- or intraoperative and final histology [14, 35]. Interestingly, Al Hilli developed and internally validated a nomogram, using a set of five variables; lymphovascular space invasion, myometrial invasion, tumor diameter, cervical stromal invasion, and FIGO grade, which provide an accurate estimate of the risk of lymphatic dissemination and can facilitate postsurgical counseling [14]. Recently, Bendifallah et al. externally validated the nomogram developed by Al Hilli et al. [36].

Alternatively, investigators have proposed the use of molecular and serum biomarkers to identify patients at high risk of lymph node metastasis [37]. Serum levels of human epididymis protein 4 (HE4) have shown to be elevated in a high proportion of endometrial cancer patients, when compared with matched controls without a history of cancer [38]. Furthermore, HE4 showed higher sensitivity than CA-125, and a high correlation with tumor diameter and myometrial invasion [38]. Future studies are needed to confirm HE4's role in risk stratification and screening for patients with endometrial cancer. DNA ploidy in curettage specimens has been recently demonstrated as an independent predictor of lymph node metastasis among patients without distant metastasis at diagnosis [39]. Stathmin overexpression, detected both in curettage and hysterectomy specimens, has been linked to aggressive endometrial cancer and identifies endometrial cancer with lymph node metastasis and poor survival [40]. These findings had been already suggested in the study by Mariani et al., which determined the utility of histologic and molecular analysis on pretreatment curettage specimens in the prediction of lymph node status [41]. Furthermore, a multicenter prospective trial has recently recognized double negative hormone receptor status (ER/PR loss) in preoperative endometrial carcinoma biopsies as an independent predictor of lymph node dissemination and poor survival [42]. However, further prospective multicenter studies are needed to validate and

integrate these promising biomarkers in standard clinical practice. This process will allow us to better identify patients at risk of lymph node metastasis, thus tailoring individualized surgical and adjuvant treatment.

11.2 Pattern of Lymph Node Metastasis

The lymphatic circulation draining the uterus is complex and involves both pelvic and para-aortic nodes [43]. In fact, in contrast to cervical cancer, which tends to have a more orderly dissemination, the pattern of dissemination of endometrial cancer is less predictable with more routes of spread available [44]. Understanding the patterns of lymphatic dissemination of endometrial cancer is imperative and provides essential information on the extent of lymphadenectomy required.

An investigation to determine the lymphatic dissemination of endometrial cancer included 188 randomly selected cases of endometrial cancer ranging from stage I to IV at necropsy. Pelvic and para-aortic lymph nodes were reported positive in 62% and 18%, respectively [44].

The overall incidence rate of pelvic and para-aortic lymph node metastasis in patients with early-stage endometrial cancer has been estimated between 5–9% and 3–6%, respectively [2, 45]. However, among patients with positive pelvic lymph nodes, the incidence of positive para-aortic lymph nodes increases to approximately 50% [11]. Moreover, when pelvic lymph nodes are positive bilaterally, para-aortic nodes are positive in approximately 60% of patients, compared to 24% when pelvic lymph nodes are positive unilaterally [46]. In addition to positive pelvic lymph nodes, other risk factors for para-aortic involvement include lymphovascular space invasion, advanced stage, FIGO grade, myometrial invasion >50%, and cervical involvement [47, 48]. Recently, Todo et al. reported that ultrastaging (defined as assessment of the presence of isolated tumor cells and micrometastasis with immunohistochemistry (IHC) using anti-cytokeratin AE1:AE3) of para-aortic lymph nodes in patients with stage IIIC can frequently identify occult para-aortic lymph node metastasis (11/15 patients = 73%) [49]. Although some studies on breast cancer report a poor prognostic value of micrometastasis [50], the impact on survival of isolated tumor cells (≤0.2 mm) and micrometastasis (>0.2 mm but ≤2 mm) in endometrial cancer has not yet been adequately studied. In fact, only limited series have been reported in the literature [49, 51, 52]. This suggests a possible role of micrometastases as a poor prognosticator in patients with high-risk endometrial cancer and "negative" lymph nodes, when analyzed with traditional pathology techniques.

Performed at Mayo Clinic, a study evaluating the different patterns of lymphatic spread among 112 patients with pelvic and para-aortic lymph node metastasis showed that the external iliac lymph nodes were the most frequently involved site of metastasis. They were also determined as the most common site harboring an isolated metastasis [53].

Recently, Odagiri et al. retrospectively evaluated the precise mapping of lymph node metastasis among 266 patients with endometrial cancer treated with systematic pelvic and para-aortic lymphadenectomy. After analyzing the anatomical

location of positive lymph nodes among 42 (15.8%) patients with lymph node metastasis, the most prevalent site of positive lymph nodes was found to be the para-aortic area (9.8%, 26/266), followed by obturator nodes (9.4%, 25/266), and internal iliac nodes (7.1%, 19/266). Interestingly, the involvement of the deep inguinal nodes [namely, circumflex iliac nodes distal to the external iliac nodes (CINDEIN) and circumflex iliac nodes distal to obturator nodes] was extremely rare (1/266, 0.38%) [54]. Moreover, Abu-Rustum et al. [55] and Hareyama et al. [56] previously reported that the removal of CINDEIN increased the incidence of lower limb lymphedema in patients treated for endometrial cancer. Taken together, these findings suggest that CINDEIN could be preserved.

11.3 Extent of Lymphadenectomy

The extent of lymphadenectomy varies among practitioners, reflecting the current controversies on surgical staging. Among SGO members who were asked about their surgical management of endometrial cancer, respectively 66% and 90% of respondents perform both pelvic and para-aortic lymph node dissection in grade 2 and grade 3 endometrial cancer. Furthermore, when performing para-aortic lymphadenectomy, 50% of gynecologic oncologists carry the dissection to the level of the inferior mesenteric artery (IMA), whereas only 11% extend the lymphadenectomy up to the renal vessels [57].

A prospective assessment of lymphatic dissemination in 422 patients with endometrial cancer was performed at Mayo Clinic. Among 310 (73%) patients with endometrial cancer deemed at high risk of lymph node dissemination based on Mayo Criteria, 281 underwent systematic pelvic and para-aortic lymphadenectomy, resulting in 63 (22%) patients with lymphatic dissemination. After stratifying the prevalence by histologic type, lymph node dissemination among endometrioid type and non-endometrioid type was documented in 34 (16%) and 29 (40%) patients, respectively. Evaluation of the pattern of spread in the 63 patients with lymph node involvement showed that 53 cases (84%) had positive pelvic nodes and 39 cases (62%) had positive para-aortic nodes. In particular, 24 cases (38%) had only positive pelvic nodes, 10 cases (16%) had only positive para-aortic nodes, and 29 (46%) had both pelvic and para-aortic node involvement [5]. Moreover, Kumar et al. demonstrated that the majority of the patients with involvement of the para-aortic nodes have metastasis above the IMA. Thirty-five percent of these patients were declared free of metastatic disease in the ipsilateral nodes below the IMA [11]. However, considering this group accounts for only 4% of patients at risk for lymph node metastasis, extending the lymphadenectomy up to the IMA in all patients at risk for lymph node metastasis is controversial. Table 11.2 shows the prevalence of para-aortic lymph node metastasis and their location.

Para-aortic lymph node dissemination is uncommon, occurring in 6% of patients with clinical stage I endometrial cancer [2]. In addition, a systematic infrarenal lymphadenectomy is associated with significant morbidity [10]. With the aim of defining a subgroup of patients at negligible risk of para-aortic metastasis, who may

Table 11.2 Summary of the probability of lymph node metastasis in the para-aortic area and their location in different subgroups of patients (adapted from Kumar et al. [11])

Subgroup	% with PA LNM	% with high PA LNM	% with high PA LNM with negative low PA nodes
Total "at-risk" population	12%	9%	4%
Patients with negative pelvic nodes	3%	3%	2%
Patients with positive pelvic nodes	51%	46%	12%
Patients with positive para-aortic nodes	100%	88%	35%

LNM Lymph Node Metastases, *PA* Para-aortic

potentially forego para-aortic lymphadenectomy, Kumar et al. assessed the risk of para-aortic dissemination in a cohort of 946 patients treated at Mayo Clinic. Para-aortic metastasis (among patients who underwent para-aortic lymphadenectomy) or para-aortic recurrence within 2 years (among patients without para-aortic lymphadenectomy, or with negative para-aortic lymph nodes when an inadequate [<5 nodes] para-aortic lymphadenectomy was performed) were observed in 4% (36/946) of patients. Also, they found that involvement of para-aortic dissemination is strongly related with (1) positive pelvic lymph nodes, (2) lymphovascular space invasion, and (3) deep myometrial invasion (>50%). Using these criteria, they predicted that when all three factors are absent (77% of cases in their cohort) the PA lymphadenectomy may be omitted with a probability of PA metastasis or PA recurrence of 0.6%, obtaining a reduction in surgical morbidity and cost in the majority of patients [48].

11.4 Therapeutic Role of Lymphadenectomy

The therapeutic role of lymphadenectomy is one of the most debated issues in the management of patients with endometrial cancer. The main criticisms are based on the results of two randomized controlled trials that assessed the role of lymphadenectomy in early-stage endometrial cancer [58, 59]. Both trials showed pelvic lymphadenectomy to have no benefit on overall or recurrence-free survival. However, these studies have been criticized due to several limitations in the study design [60–64]. In particular, the ASTEC study has been criticized for the following reasons. First, the number of lymph nodes harvested was inadequate in many patients. Although patients who had more than 11 pelvic lymph nodes removed had better overall and progression-free survival [45], only 65% of patients had ten or more nodes removed (median 12). Second, one of the potential benefits of comprehensive surgical staging is the utility of nodal status in modulating adjuvant therapy. The study design does not consent to evaluate this hypothesis. Third, since para-aortic metastases are detected in 67% of endometrial cancer patients with positive nodes [5], in order to remove metastatic nodal disease the lymphadenectomy must be extended bilaterally up to the renal vessels. However, the study did not include systematic para-aortic

lymphadenectomy, and para-aortic node sampling was performed at the discretion of the surgeon. Fourth, the high rate of patients at low risk included in the study (44.7% of all cases had stage IA-IB, with grade 1 or 2 disease) decreased the possibility of identifying a therapeutic effect of lymphadenectomy in the high-risk group.

The most relevant data on the therapeutic role of para-aortic lymphadenectomy comes from the SEPAL (survival effect of para-aortic lymphadenectomy in endometrial cancer) study [65]. In response to two randomized trials that failed to demonstrate therapeutic value from pelvic lymphadenectomy, Todo et al. conducted a retrospective study to establish the role of comprehensive surgical staging in patients at intermediate and high risk of recurrence. They demonstrated that, among a subgroup of patients at intermediate or high risk of recurrence, overall, disease-specific, and recurrence-free survival were significantly higher in the group of patients who underwent pelvic and para-aortic lymphadenectomy when compared with the group of patients who underwent only pelvic lymphadenectomy. The authors concluded that both pelvic and para-aortic lymphadenectomy are recommended for patients with endometrial carcinoma at intermediate or high risk of recurrence. Furthermore, no significant benefits were recorded between the treatment groups for overall, disease-specific, and recurrence-free survival for patients at low risk of recurrence (stage IA-IB with grade 1–2 endometrioid subtype and no lymphovascular space invasion) [65]. The SEPAL study has, however, been criticized because the use of adjuvant therapy was different between the two groups. In fact, patients in the systematic pelvic and para-aortic group received chemotherapy or radiotherapy in 77% and 1% respectively, compared with 45% and 39% received by the patients who underwent only pelvic lymphadenectomy. Furthermore, only 8% of patients enrolled had type 2 endometrial cancer which prevents generalization of the results to patients with type 2 endometrial cancer [65].

Other groups evaluated the therapeutic role of lymphadenectomy [66–69]. Chan et al., using the Surveillance, Epidemiology, and End Results (SEER) database, demonstrated that patients with intermediate or high-risk endometrioid uterine cancer have survival benefit from an extensive lymphadenectomy. This result was not confirmed in patients with low-risk endometrioid uterine cancer [67]. In addition, when the survival of patients who underwent lymphadenotomy with patients was compared with those who did not undergo lymphadenectomy, results showed that lymphadenectomy is associated with better survival in patients with stage I grade 3 and more advanced stage disease [69]. However, several limitations may affect the interpretations of these results [67, 69].

11.5 Morbidity and Costs of Lymphadenectomy

Given the lack of standardized surgical treatment in patients with endometrial cancer, the assessment of lymphadenectomy-related complications has important relevance in guiding the surgical decision. Further, the increased morbidity

and costs associated with lymphadenectomy are probably among the main reasons for which the debate on the role of lymphadenectomy is still open. The evaluation of the morbidity directly attributable to lymphadenectomy is challenging. Many confounders such as the presence of comorbidities (e.g. diabetes, obesity, etc.) and the administration of adjuvant therapy should be taken into account in the assessment of lymphadenectomy-related complications. Due to these limitations, studies addressing the complications associated with lymphadenectomy have varied and contradictory results have been reported [10, 70–72].

In particular, the clinical trial evaluating the role of pelvic lymphadenectomy conducted by Benedetti Panici et al. showed a statistically significant increase in both early and late postoperative complications among the lymphadenectomy arm when compared with the no-lymphadenectomy arm. The difference was largely attributable to lymphocysts and lymphedema [59]. Moreover, the ASTEC trial reported that, despite the low risk of major complications in both arms, the lymphadenectomy group experienced longer median operative time and a higher number of specific complications such as ileus, deep vein thrombosis, lymphocyst, and major wound dehiscence [58].

By contrast, two studies published in the early 1990s reported that lymphadenectomy does not significantly increase the morbidity from hysterectomy [71, 72].

At Mayo Clinic, we analyzed 30-day complications and cost associated with pelvic and para-aortic lymphadenectomy in 1369 patients treated for endometrial cancer at our institution. Results showed that patients who underwent pelvic and para-aortic lymphadenectomy experienced more than double the risk (OR = 2.3) of grade 2 or higher complications (categorized according to the Expanded Accordion Classification [73]). Further to this, compared with patients who underwent hysterectomy alone, patients who underwent pelvic lymphadenectomy and pelvic plus para-aortic lymphadenectomy incurred a 25% and 56% higher 30-day cost, respectively ($P < 0.01$) [70]. When the analysis focused only on patients with low-risk endometrial cancer (as defined by the Mayo criteria), lymphadenectomy significantly impacted operating time, length of hospital stay, blood loss, and 30-day morbidity, without survival advantages [10].

Lymphedema has been reported as the most frequent and disabling complication by several studies [74–76]. A study performed at Mayo Clinic estimated the prevalence of lower-extremity lymphedema among patients surgically treated for endometrial cancer using a validated 13-item questionnaire. Interestingly, nearly half of the 591 responders were affected by lower extremity lymphedema. Lymphadenectomy was also independently associated with lymphedema with an attributable risk of 23% [76, 77]. Whether the introduction of sentinel lymph node (SLN) mapping will reduce the rate of lymphedema among women with endometrial cancer remains to be determined. Studies addressing the overall complication rate related to SLN mapping are needed and will be the subject of future investigation.

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