Surgical Management of Early-Stage Endometrial Cancer

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Abstract

Most endometrial cancers are diagnosed with early-stage/uterus-confined disease and are usually cured by surgery alone.

Extrafascial hysterectomy with bilateral salpingo-oophorectomy along with comprehensive surgical staging including pelvic and para-aortic lymphadenectomy (except in low-risk disease) and peritoneal wash cytology remains the mainstay of surgical treatment of endometrial carcinoma.

Ovarian preservation may be done in young patients with low-stage, low-grade endometrial cancer after thorough counselling.

Minimally invasive surgery is recommended in low- to intermediate-risk patients with early-stage endometrial carcinoma in a skilled set-up.

Tumour stage and pathological tumour grade appear to be the most important factors influencing lymph node metastasis.

Sentinel node mapping for uterine cancer is currently being widely studied.

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Introduction

Endometrial cancer is the most common malignancy of the female genital tract in developed countries and fourth most common cancer in women after breast, lung and colorectal cancers. The incidence rate in India is much lower, it being the third commonest gynaecological cancer in India after cervical and ovarian cancers.

Most cancers are diagnosed with uterus-confined disease, which are usually cured by surgery alone. The presence of extrauterine disease significantly affects recurrence rates and survival, which emphasizes the importance of sites of disease spread and provision of appropriate adjuvant post-operative therapy.

The surgical management of early endometrial cancer has evolved over the past two decades, with introduction of comprehensive surgical staging to identify patients with extrauterine disease and an emphasis on individualization of treatment based on clinicopathological risk groupings and risk of recurrence. Surgical approaches aimed at limiting morbidity and improving quality of life in these patients without affecting cure rates are now introduced at specialist centres. Several other such approaches are being investigated for their safety and efficacy before they can be considered a part of standard clinical practice. In this chapter, we review the current "state of the art" of surgical management of early stage endometrial cancer.

Assessment of Early-Stage Endometrial Cancer

Accurate assessment of tumour stage and histology is essential to plan optimum therapy for patients with early stage endometrial cancer.

Although endometrial cancer is generally diagnosed with the help of pelvic ultrasonography followed by hysteroscopic evaluation and endometrial biopsy or curettage, additional imaging may be considered in order to better define the myometrial invasion, cervical, ovarian, peritoneal, nodal involvement and distant spread. An MRI is most accurate in defining the local extent of the disease within the uterus [1], while a CT scan [2] or a PET-CT scan is necessary to define extrauterine spread of the disease [3–6]. However, since endometrial cancer is a surgically staged disease, it is not mandatory to do these pre-operative imaging studies, since these imaging studies have been rarely found to alter the management of patients with uterine cancers especially of the endometrioid variety [7].

Pre- and intraoperative assessment of histology in terms of histological subtype and the tumour grade by an experienced oncopathologist cannot be overemphasized as the management strategy, and prognosis depends on these factors [8, 9].

Surgical Management of Apparent Stage I Endometrial Cancer

Extrafascial hysterectomy with bilateral salpingo-oophorectomy along with comprehensive surgical staging including pelvic and para-aortic lymphadenectomy and peritoneal wash cytology remains the mainstay of treatment of endometrial cancer.

The need for a comprehensive staging is based on the fact that nearly 20 % of women believed pre-operatively to have early stage uterine cancer are found to have advanced (stage III–IV) disease [10]. It is no longer considered necessary to remove a vaginal cuff along with extrafascial hysterectomy at surgery.

Radical hysterectomy for stage II endometrial cancer has not been found to impart survival benefit as compared to extrafascial hysterectomy but was associated with more adverse events. However, radical hysterectomy is recommended in the presence of parametrial spread.

Ovarian preservation may be done in young patients with endometrial cancer who are more likely to have low-stage, low-grade tumours, after a thorough discussion of the benefits and risks of preserving the adnexa. This is important to avoid an early surgical menopause and the early and late consequences thereof. Before contemplating ovarian preservation, it is essential to rule out a synchronous ovarian cancer or ovarian metastases from endometrial cancer intraoperatively. Numerous studies have reported that ovarian preservation may be safe and has no adverse impact on overall survival of these young patients with early stage endometrial cancer [11]. Ovarian preservation is not recommended in patients with family history of breast/ovarian/uterine cancers, in non-endometrioid histology and in advanced stages.

Omentectomy is also considered a part of the standard surgical protocol for papillary serous carcinomas especially where peritoneal implants may be present. However, it is not recommended for clear cell carcinomas.

Current literature suggests that management of women by a gynaecologic oncologist in high-volume institutions results in improved disease-specific survival [12].

Surgical Approach

Surgery may be carried out by the open, laparoscopic or robotic approach.

Traditionally, surgical staging of endometrial cancer has been accomplished by laparotomy. Many prospective and retrospective studies in 1990s demonstrated feasibility of laparoscopic surgery for endometrial cancer [13, 14]. Numerous randomized controlled trials have compared the surgical- and disease-related outcomes after open versus laparoscopic surgery for endometrial cancer. The largest amongst these, the LAP-2 study, accrued 2626 patients of stage I–IIA endometrial cancer, who were randomized to open (n = 920) versus laparoscopic (n = 1696) [15]. All patients underwent hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy and peritoneal cytology. The laparoscopic arm was associated with a longer operative time but a shorter post-operative stay. The post-operative adverse events were similar in both the arms, with a lesser incidence of moderate to severe side effects in the laparoscopic arm (14 % vs. 21 %, $p < 0.0001$). Although there was a high (25.8 %) conversion rate to laparotomy in the laparoscopy arm, there was no significant difference in the overall detection of advanced-stage disease between the two arms. The high rate of conversion to laparotomy was more related to the lymphadenectomy part of the surgery and dependent on the learning curve of the operator. Long-term outcomes of the LAP-2 study published

in 2012 showed a non-inferiority (defined as no more than 40 % increase in the risk of recurrence with laparoscopy compared to laparotomy) of recurrence-free interval (HR for laparoscopy vs. laparotomy 1.14) and equivalent estimated overall survival (89.8%) [16].

Two meta-analyses have compared the outcomes between the two approaches. Zullo et al. [17] in a meta-analysis of eight trials concluded that the estimated blood loss and the post-operative complications were significantly lower in the laparoscopic arm, while the operative time was significantly longer in the laparoscopy arm. Intraoperative complications were no different in the two groups and were related to the training of the operative surgeon [17]. The updated meta-analysis published by Palomba in 2009 observed that there was no difference in the adverse events as well as in the disease-free survival, overall survival or cancer-related survival [18]. Although there is a paucity of published data from RCTs comparing robotic with open/laparoscopic approach, one expects the results of robotic approach to be equivalent to the older approaches. However, the cost [19, 20], limited availability and learning curve [21, 22], along with lack of significant measurable benefits to the patient, are limiting factors to recommend routine robotic surgery in all patients.

The findings of the randomized trials and the meta-analysis provide definitive evidence of short-term safety benefit and cost-effectiveness of laparoscopic surgery in all patients, including those with co-morbidities, obesity and advanced age, along with similar recurrence-free and overall survival [23, 24]. From the available evidence, one can conclude that minimally invasive surgery is recommended and in fact considered the preferred surgical approach in low- to intermediate-risk patients with early stage endometrial cancer, provided the surgeon is trained in advanced surgical techniques needed to perform retroperitoneal lymphadenectomy. The extrapolation of the same to high-risk patients is debatable.

In patients who are medically unfit to undergo standard open or minimally invasive surgery for endometrial cancer, vaginal hysterectomy with bilateral salpingo-oophorectomy may be considered, especially in low-risk patients who may not need systematic lymphadenectomy [25]. For some women who are old, obese or have severe medical co-morbidities, the risk associated with open or laparoscopic surgical staging may overweigh its potential benefit [12]. The vaginal approach does not allow a thorough exploration of the abdominal cavity, peritoneal washings, lymphadenectomy and omentectomy and hence is not suitable for patients at risk of extrauterine disease. Several studies have reported similar survival rates with vaginal hysterectomy versus abdominal hysterectomy for early stage endometrial cancer in patients with a high surgical risk [26–28].

Lymphadenectomy

The indications, extent and therapeutic impact of lymphadenectomy remains one of the most controversial and contentious issues in management of endometrial cancer. Undoubtedly, it is an integral part of the comprehensive surgical staging,

endometrial cancer being a surgico-pathologically staged cancer. Currently, a systematic pelvic and para-aortic lymphadenectomy is the only way to accurately identify the presence of nodal disease in women with endometrial cancer [29, 30]. Nearly 20 % of patients with endometrial cancer are understaged in the absence of systematic lymphadenectomy [10]. It is also useful for prognostication (90 % 5-year survival in node-negative versus 54 % for node-positive patients) and for appropriate triage of patients for adjuvant therapy as the results of lymphadenectomy can identify patients at high risk of recurrence and guide the decision about appropriate adjuvant therapy (radiation therapy, chemotherapy, etc.). It thereby helps to individualize treatment and prevent unnecessary overtreatment or inappropriate undertreatment. The therapeutic value of lymphadenectomy, however, remains unclear and debated.

Risk of Lymph Node Metastases

Endometrial cancer is a surgico-pathologically staged cancer. The GOG 33 protocol, a prospective surgico-pathological study published in 1987, clearly showed the limitations of clinical staging compared with surgico-pathological assessment. Metastatic disease was identified in a significant percentage of patients, when comprehensive staging was performed in apparently stage I patients with disease confined to the uterus. Based on this, the FIGO changed over to a surgical staging system for endometrial cancer in 1988 [31].

Tumour stage and pathological tumour grade appear to be the most important factors influencing lymph node metastases. Creasman et al. [10] reported that the overall incidence of lymph node metastases in clinically uterus-confined endometrial cancer was about 3 % in grade I, 9 % in grade II and 18 % in grade III tumours and less than 5 % in <50 % myometrial invasion, 15 % of grade I–II tumours with >50 % myometrial invasion or grade III with <50 % of myometrial invasion and >40 % in grade III >50 % myometrial invasion. Boronow et al. noted that patients with outer one third of myometrial involvement had a 25 % incidence of pelvic node metastases and 17 % para-aortic lymph node metastases as compared to only 1 % incidence of nodal metastases in patients without myometrial invasion [32]. Chi et al. reporting on the incidence of lymph node metastases in patients with surgically staged endometrioid endometrial cancer confirmed that as the tumour grade increased, the risk of myometrial invasion also increased. In their series, no patient with grade I tumour on final pathology and only 2 % of patients with no myometrial invasion had lymph node metastases [33].

An intraoperative assessment of histological subtype, grade and depth of myometrial invasion in the operative specimen of hysterectomy visually and by frozen section examination is found to be fairly accurate (84–88 % accuracy) and often recommended to better define the risk of regional and distant spread and has the ability to identify patients who will benefit from systematic lymphadenectomy and adjuvant therapy [34].

Indications for Lymphadenectomy

Patients with stage I endometrial cancer are stratified into different risk groups according to their risk of extrauterine spread and relapse. This risk stratification also serves as an aid to guide optimum adjuvant therapy. Although various risk stratification models are available, the one defined by endometrial cancer consensus conference guidelines probably defines the risk groups best and is given below:

Low risk	Stage I endometrioid, grade I–II, <50 % myometrial invasion, LVSI – ve
Intermediate risk	Stage I endometrioid, grade I–II, > 50 % myometrial invasion, LVSI – ve
High-intermediate risk	Stage I endometrioid, grade III, <50 % myometrial invasion, regardless of LVSI status
	Stage I endometrioid, grade I–II, LVSI +ve, regardless of depth of invasion
High risk	Stage I endometrioid, grade III, >50 % myometrial invasion, regardless of LVSI status
	Stage II
	Stage I with non-endometrioid histology

Patients with low-risk endometrial cancer have a low risk of lymph node involvement and do not benefit with systematic lymphadenectomy, and hence it is not routinely recommended in them [25, 35, 36].

Patients with intermediate-, high-intermediate- and high-risk endometrial cancer have a higher probability of having extrauterine disease and also have demonstrated survival benefit with systematic lymphadenectomy. Hence, a comprehensive pelvic and para-aortic lymphadenectomy is recommended in them for staging and therapeutic planning purposes [25].

Extent of Lymphadenectomy

In published literature, the extent of lymphadenectomy for endometrial cancer has been extremely variable, ranging from no lymphadenectomy to pelvic and/or para-aortic lymph node sampling to a comprehensive pelvic and para-aortic lymphadenectomy. Although there is no standard definition of "optimum lymphadenectomy" for endometrial cancer, it is clear that lymph node sampling has a low sensitivity for detecting lymph node metastases, since para-aortic lymph nodes may be involved in the absence of positive pelvic nodes [10].

The question of the optimal extent of lymphadenectomy was answered in a retrospective study of 281 patients with endometrial cancer who underwent comprehensive pelvic and para-aortic lymphadenectomy. Twenty-two percent of patients with high-risk endometrial cancer had lymph node metastases – 51 % of these had metastases in both pelvic and para-aortic nodes, 33 % had positive pelvic nodes only, while 16 % had isolated positive para-aortic nodes in the absence of metastatic

pelvic nodes, with majority of patients with para-aortic metastatic nodes (77 %) having positive nodes above the level of inferior mesenteric artery [37]. On the other hand, they also found that patients with low-risk disease had no lymph node metastases and did not benefit from a systematic lymphadenectomy. Similar findings have been reported by other authors [38]. This suggests that para-aortic nodes should be removed whenever lymphadenectomy is indicated and that it is essential to extend the upper limit of lymphadenectomy to the level of renal vessels.

There are two ways to judge the adequacy of lymphadenectomy. The more accurate way is to perform a complete pelvic and para-aortic lymphadenectomy as per the anatomic templates. The other is to measure the lymph node count in the surgical specimen, which is a surrogate marker for adequacy of lymph node dissection (it has been shown that patients with more than 10–12 nodes removed during lymphadenectomy have an improved survival). In the collated data of 16,995 patients of endometrial cancer from two randomized controlled trials and seven observational studies, Kim et al. demonstrated an improved overall survival with systematic lymphadenectomy (i.e. removal of more than 10–11 nodes) in patients with intermediate- and high-risk endometrial cancer but limited survival benefit in low-risk patients [39–41]. Based on this, lymph node counts have become a surrogate for adequacy of lymphadenectomy with the recommendation that more than ten nodes should be removed in an adequate lymphadenectomy [42, 43].

Does Lymphadenectomy Improve Survival?

Two randomized studies [44, 45] comparing systematic pelvic lymphadenectomy to no lymphadenectomy in the surgical management of patients with endometrial cancer demonstrated that lymphadenectomy improved surgical staging but had no impact on overall survival.

However, despite the randomized trials showing no survival benefit with comprehensive surgical staging, controversy still exists regarding the role of lymphadenectomy, mainly due to the criticisms of the ASTEC trial [46]. This trial was criticized for a faulty trial design, a high rate of crossover to radiation therapy and selection bias. Neither trial included para-aortic lymphadenectomy, and the ASTEC trial also had low lymph nodal counts. This omission of para-aortic lymphadenectomy may have negated the therapeutic effect of lymphadenectomy since more than half of the patients with positive pelvic nodes have para-aortic nodal metastases, and about 10 % of lymph node metastases occur exclusively in the para-aortic region without pelvic lymph nodal involvement as shown by the sentinel node studies [47]. Removal of para-aortic lymph nodes could probably explain the significant effect of para-aortic lymphadenectomy as shown by Todo et al. [48]. They analyzed their study of intermediate and high-risk patients who underwent surgery with pelvic lymphadenectomy with or without para-aortic lymphadenectomy. Those who had para-aortic lymphadenectomy had a survival benefit as compared to those who did not [48]. The findings of this SEPAL study, similar to the ASTEC trial, suggested that the survival effect of

lymphadenectomy is rather limited in low-risk patients but is quite substantial in the intermediate- or high-risk patients, with reduction in the risk of death (HR 0.44, $p < 0.0001$). In the ASTEC trial, patients were secondarily randomized to radiation therapy based on uterine pathology only without considering the nodal status, leaving some patients with metastatic nodes with no adjuvant therapy. The clinical benefit of triage to adjuvant therapy was obscured as 50 % of patients with lymph node metastases were randomized to no adjuvant therapy. Besides, the lymphadenectomy versus no lymphadenectomy arms were unbalanced in terms of high-risk criteria, with the lymphadenectomy arm having a greater percentage of patients with high-risk histology, high-grade tumours, presence of lymphovascular invasion and deep myometrial invasion. Lastly, this trial did not address the issue of benefit from para-aortic lymphadenectomy as patients underwent para-aortic node palpation with selective sampling rather than systematic lymphadenectomy.

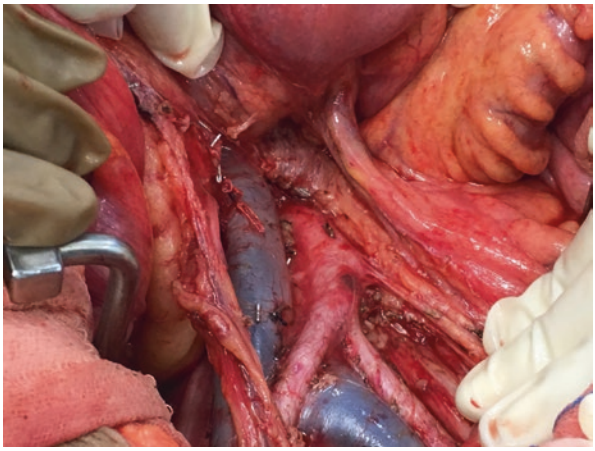
Retrospective data suggests that patients undergoing systematic lymphadenectomy had improved survival over those who had limited or no lymphadenectomy [43]. An analysis of 42,184 patients from the SEER database revealed that systematic lymphadenectomy was associated with overall and cancer-specific survival benefit (HR 0.81 and 0.78, respectively), and removal of more than 11 nodes was associated with HRs of 0.74 and 0.69, respectively [49]. Although statistically significant, the retrospective nature of the data was subject to selection bias and stage migration. Trimble et al., using a large national database, reported benefit with lymphadenectomy in grade III tumours only [50].

Sentinel Node Mapping

The lymphatic drainage of uterus is complex, with several anatomical areas at risk for metastases. The sentinel node is defined as the first node in the lymphatic basin that receives the lymphatic flow. If the SLN is negative for metastatic disease, other nodes in the template are expected to be free of disease involvement. The advantage of SLN biopsy is the potential for improved diagnostic accuracy with use of ultrastaging while lowering morbidity [51, 52]. Sentinel node biopsy in particular has the advantage of limiting the risk of lymphedema, which is seen in 6–38 % of patients following pelvic lymphadenectomy [53, 54].

Sentinel node mapping for uterine cancer was first described by Burke et al. [55]. They reported on 15 patients who had SLN mapping followed by complete pelvic and para-aortic lymphadenectomy. They reported an overall SLN detection rate of 67 %. Four patients had positive lymph nodes – two of these were detected by SLN mapping with blue dye, one had a positive non-sentinel node and one had bulky nodes without dye uptake. Khoury-Collado et al. (2011) could successfully identity the sentinel node in 84 % of the cases in their study of 266 cases of endometrial cancer, with 12 % incidence of metastatic nodes and 3 % metastatic nodes being confirmed by immunohistochemistry [56]. Ballester et al. [51] in their multicentre SENTI-ENDO trial showed that 10 % of low-risk and 15 % of intermediate-risk patients were upstaged using the sentinel node technique [51].

The greatest challenge in using the SLN technique in endometrial cancer is to identify the optimum injection site that properly represents the drainage of the tumour. Most large series till date have used cervix as the injection site. In recent times, endometrial site of injection using the hysteroscopic, ultrasound-guided, laparoscopic and open approaches has been investigated. Hysteroscopy allows injection of the tracer in the mucosal space just around the tumour and at least conceptually should be the best way to delineate the drainage of the tumour. Hysteroscopic injection also allows a complete detection of the drainage of the uterine corpus directed to both pelvic and para-aortic nodes, thereby decreasing the false-negative rates. The first report of hysteroscopy-guided SLN technique by Nilkur et al. [47] showed a detection rate of 82 % with no false negatives. Subsequently, Maccauro et al. [57] and Raspagliesi et al. [58] reported a detection rate of 100 % with no false negatives [57, 58]. Presently, however, there is no definite evidence that these technically more demanding injection approaches have a definite benefit over cervix as the injection site [59].



Para Aortic Lymphadenectomy

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