Adjuvant Therapy in Endometrial Cancer

Subjects: Oncology

Contributor: Isao Otsuka

Endometrial cancer is the most common gynecological tract malignancy in developed countries. Extrauterine disease, in particular lymph node metastasis, is an important prognostic factor. Lymphadenectomy may have a therapeutic benefit if adjuvant therapy can be omitted without decreasing oncological outcomes, as the long-term quality of life is maintained by avoiding morbidities associated with adjuvant therapy. In intermediate- and high-risk endometrioid endometrial carcinomas, adjuvant therapy may be safely omitted without decreasing long-term survival by open surgery including systematic pelvic and para-aortic lymphadenectomy when patients are node-negative.

Keywords: endometrioid endometrial carcinoma ; systematic lymphadenectomy ; pelvic and para-aortic lymphadenectomy

1. Introduction

Endometrial cancer is the most common female genital tract malignancy in developed countries. Its incidence has been increasing globally because of rising obesity rates and longer life expectancy [1][2]. The majority of endometrial cancers are confined to the uterus, and patients with such diseases have a favorable prognosis. In contrast, patients with extrauterine disease, particularly lymph node metastasis, have a poorer survival. To assess lymph node status, lymphadenectomy or sentinel lymph node biopsy is performed. Lymphadenectomy has a diagnostic benefit by providing the knowledge of pathological lymph node status that is useful for tailoring the appropriate adjuvant therapy. However, pelvic lymphadenectomy has not been thought to have a therapeutic benefit, as it did not improve survival in two randomized controlled trials [3][4]. Thus, attempts have been made to reduce surgical morbidity of lymphadenectomy with the introduction of sentinel lymph node biopsy.

In contrast, attempts to reduce the use of adjuvant therapy in the management of endometrial cancer have been limited, although its effect on overall survival, similar to that of lymphadenectomy, has not been established [5][6][7][8][9]. In node-positive patient adjuvant therapy, radiation therapy and/or chemotherapy is given to eradicate residual diseases after surgery. However, even though lymph node metastasis is not detected by lymph node assessment, adjuvant therapy is recommended for patients with uterine-confined disease considered to be at risk of recurrence under current treatment guidelines [10][11][12].

Lymphadenectomy may have a therapeutic benefit in node-negative patients if adjuvant therapy can be omitted without decreasing oncological outcomes, because morbidities that decrease long-term quality of life of survivors associated with adjuvant therapy can be avoided [13][14][15][16][17][18][19]. In this research, I discuss the characteristics of lymph node metastasis in endometrial carcinoma, the methods of lymph node assessment, and the possibility of omitting adjuvant therapy in patients with node-negative uterine-confined endometrioid carcinoma who undergo systematic lymphadenectomy.

2. Role of Adjuvant Therapy in Endometrial Cancer

There is no definitive evidence that adjuvant therapy improves the long-term survival of women with endometrial cancer apparently confined to the uterus. Randomized controlled trials have shown that external beam radiotherapy to the pelvis decreases local recurrence but does not improve overall survival [5][6][7]. Although external beam radiotherapy might improve survival in patients with high-intermediate risk disease [6], a meta-analysis indicated that in intermediate- and high-risk patients, adjuvant external beam radiotherapy did not improve overall survival [20]. In intermediate-risk disease, adjuvant vaginal brachytherapy is recommended to avoid gastrointestinal complications that are often associated with external beam radiotherapy [10][11][12][21]. In node-negative patients with deeply invasive grade 3 endometrioid tumors, no survival benefit was observed with pelvic radiation compared to vaginal brachytherapy alone [22]. However, the necessity of adjuvant vaginal brachytherapy is questioned, because most vaginal recurrences can be cured with salvage therapy [23][24][25].

Adjuvant chemotherapy in patients with high-risk stage I–II endometrioid carcinoma improved survival in one study [26], but did not in another study [27]. In high-intermediate and high-risk early-stage endometrial carcinoma, pelvic and para-aortic nodal recurrences were more common after chemotherapy and vaginal brachytherapy compared to pelvic radiation therapy [28]. Effects of chemotherapy may be limited in grade 3 tumors [29][30].

Late complications caused by adjuvant therapy may reduce the long-term quality of life of survivors. After external beam radiotherapy, gastrointestinal complications may lead to limitations in daily activities [21]. In particular, pelvic radiotherapy following surgery including lymphadenectomy significantly increased risk of serious complications compared to surgery alone [6]. Vaginal brachytherapy may cause vaginal atrophy and subsequent stenosis [17] and severe bowel complications such as rectal bleeding [16]. Chemotherapy including platinum and/or taxane often causes peripheral neuropathy that decreases quality of life [18][19].

Importantly, adjuvant therapy might not replace surgical removal as a treatment for positive nodes in some patients, as patients who underwent lymphadenectomy had an improved survival compared to those who did not undergo the procedure, even though adjuvant therapy was performed [31][32][33][34].

Theoretically, adjuvant therapy is not necessary for patients with node-negative uterine-confined disease, because residual diseases that otherwise need to be eradicated by adjuvant therapy are not left behind. Patients with clinically negative but histologically positive nodes can also become disease-free by both lymphadenectomy and/or sentinel lymph node biopsy followed by lymphadenectomy.

3. Sentinel Node-Negative Patients: Can Adjuvant Therapy Be Omitted?

Sentinel lymph node mapping has been increasingly performed instead of lymphadenectomy that may be associated with surgical morbidities and sequelae, such as vascular injury and lymphedema [35][36]. The sentinel lymph node is defined as the first node in the lymphatic basin that receives drainage from the primary tumor. If the sentinel lymph node is negative, a regional lymphadenectomy can be avoided [37]. In breast cancer and melanoma, both of which are superficial cancers with less complicated lymphatic drainage routes, the sentinel lymph node technique has been incorporated into standard practice [38][39]. In endometrial cancer, sentinel lymph node mapping has a high degree of diagnostic accuracy and detects low-volume metastasis in the sentinel nodes [40][41][42][43][44].

However, in intermediate- and high-risk endometrial cancers, the detection of the true sentinel nodes by the standard method, cervical injection of a tracer, may be difficult. Whereas low-risk diseases metastasize almost only to pelvic nodes, intermediate- and high-risk diseases metastasize to not only pelvic nodes, but also para-aortic nodes. The lymphatic network draining the uterus is complex and involves both pelvic and para-aortic nodes [45], as lymphatic channels draining from the uterine fundus course into the broad ligament and along the ovarian vessels [45][46]. The incidence of isolated para-aortic node metastasis (without pelvic node metastasis) in patients with intermediate- and high-risk diseases ranges from 2.6 to 3.1% [47][48][49], and the majority of para-aortic node metastases are observed above the inferior mesenteric artery [50]. Cervical injection is superior in detecting pelvic sentinel nodes [51] and achieves a higher sentinel node detection rate than fundal injection [52][53]. However, hysteroscopic or ultrasound-guided fundal sub-endometrial injection is necessary to detect para-aortic sentinel nodes [53][54][55][56][57][58].

Histopathological detection of metastatic lesions in the sentinel lymph nodes may be difficult during surgery. As a lymph node metastasis less than 2 mm was often missed at frozen section examination [59], ultrastaging is necessary to detect the majority of low-volume metastases in the sentinel nodes that account for 25–48% of sentinel node metastasis [40][60][61][62][63]. Many studies testing the sensitivity of sentinel lymph nodes have reported high sensitivity; however, in most studies, pathological evaluation of sentinel nodes was performed after back-up lymphadenectomy following sentinel lymph node biopsy [42][44][52][60][64][65][66][67].

Most importantly, negative sentinel nodes may lead to the omission of lymphadenectomy, but may not necessarily lead to the omission of adjuvant therapy. A false negative rate of 15% has been reported with a blue dye cervical injection [68]. Current studies on sentinel lymph node mapping were aimed at the accurate detection of metastatic lymph nodes by performing back-up lymphadenectomy; thus, lymphadenectomy was rarely omitted [42][44][52][60][64][65][66][67]. Adjuvant therapy was given even in patients with node-negative uterine-confined disease when they were considered to be at risk of recurrence based on uterine pathological factors [69][70]. In node-negative deeply invasive endometrioid carcinoma, patients who underwent sentinel lymph node mapping were more likely to receive adjuvant therapy than patients who underwent lymphadenectomy [71]. A previous study reported that of 54 sentinel node-negative patients treated with adjuvant therapy, eight (15%) developed recurrence [64]. If adjuvant therapy is given according to uterine pathological

factors irrespective of nodal status, sentinel lymph node mapping, which significantly increases the costs compared to hysterectomy alone [36], might not be necessary. To evaluate the efficacy of sentinel lymph node biopsy, prospective studies evaluating the long-term oncologic outcome are necessary [72], particularly the long-term safety of omitting both systematic lymphadenectomy and adjuvant therapy in sentinel node-negative patients. Long-term follow-up is indispensable to detect lymph node recurrence, because it often develops five years or later [73].

4. Benefit of Systematic Lymphadenectomy in Node-Negative Patients: Omission of Adjuvant Therapy

For an accurate evaluation of the therapeutic effects of lymphadenectomy, appropriate patients need to undergo appropriate surgery, as selection of appropriate patients is necessary to detect survival difference between patients who undergo lymphadenectomy and those who do not. First, patients at low-risk for lymph node metastasis need to be excluded [74][75][76]. In these patients, the incidence of lymph node metastasis is at most 5.9%, when considering low-volume metastasis [61]; thus, survival difference cannot be detected without a sufficient power. It is plausible that effects of lymphadenectomy on survival cannot be detected in randomized trials, considering the rate of low-risk disease in endometrioid endometrial carcinoma [3][4][77][78]. Second, patients with high-risk histological subtypes, i.e., serous carcinoma and carcinosarcoma, also need to be excluded, as they often develop peritoneal and hematogenous spread independent of lymph node metastasis [79][80][81].

In intermediate- or high-risk endometrioid carcinomas, systematic lymphadenectomy, particularly pelvic with para-aortic lymphadenectomy, appears to improve survival [33][82][83][84][85][86][87]. Incidences of lymph node metastasis in intermediate- and high-risk endometrioid carcinomas were 17% and 25%, respectively, in the previous study [47]. These incidences may be underestimated, and when ultrastaging was performed, the incidence of lymph node metastasis in high-intermediate risk endometrioid endometrial carcinoma was 24–43% [88][89].

Additionally, for lymphadenectomy to have a therapeutic benefit, no positive lymph nodes are left behind at the completion of surgery. Namely, it is necessary to remove lymph nodes bearing not only macroscopic but also low-volume metastases. Moreover, lymph nodes in the para-aortic region as well as those in the pelvic region need to be removed in intermediate- and high-risk endometrial carcinoma when deep myometrial invasion is observed [90].

However, the procedures performed during lymphadenectomy range from a mere sampling of enlarged or suspicious lymph nodes for staging purposes to systematic removal of all accessible lymphatic tissue with a therapeutic intent [75]. Systematic complete lymphadenectomy is performed to remove enlarged nodes and to skeletonize the vessels of node-bearing tissue [75][91]. The number of nodes removed varies among studies: the median numbers of nodes removed in the pelvic and para-aortic region were in the ranges of 11–54 and 5–23, respectively [47][48][82][84][85][90][92]. The quality of surgical resection may be measured by a nodal count that is indicative of the extent of nodal dissection, although the number of nodes reported by the pathologist depends on surgical expertise, the comprehensiveness of pathological analysis, and anatomical variations in patients [75]. The removal of 10 or more regional lymph nodes was associated with improved survival in intermediate- and high-risk endometrioid carcinomas [31][32][93]. The number of nodal stations sampled may be a more accurate predictor of lymph node metastasis than lymph node count [94][95].

The number of nodes removed is associated with improved survival also in patients with other cancers, i.e., breast, lung, and cervical cancers, even when all regional lymph nodes are interpreted as pathologically negative [96][97][98][99]. In particular, with the removal of larger numbers of nodes, regional relapse was significantly decreased for breast cancer patients not receiving systemic therapy [97].

Node-negative patients consist of true node-negative and false node-negative patients. False node-negative patients have occult lymph node metastasis that cannot be detected by standard pathological evaluation or that cannot be removed by non-systematic lymphadenectomy.

Systematic lymphadenectomy can remove all lymph nodes bearing macroscopic and low-volume metastases, as patients with endometrioid carcinoma who undergo systematic lymphadenectomy rarely develop lymph node recurrence, even without adjuvant therapy [47][91][100][101][102]. Similarly, nodal recurrences were rare in patients who underwent systematic lymphadenectomy with subsequent vaginal brachytherapy alone [92][103][104][105].

More importantly, in intermediate- and high-risk endometrioid endometrial carcinomas, adjuvant therapy may be omitted without decreasing survival by open surgery with systematic pelvic and para-aortic lymphadenectomy when patients are node-negative (**Table 1**) [47][100][101][102]. In the prospective cohort study of 77 node-negative patients with intermediate- and high-risk endometrioid carcinoma, only two understaged high-risk patients died of disease [47]. Although

hematogenous spread (pulmonary metastasis is most commonly observed) may develop in endometrioid carcinoma, its risk is low in patients without extrauterine diseases [106][107]. Thus node-negative patients undergoing systematic lymphadenectomy that can remove all lymph nodes including positive nodes containing undetectable low-volume metastasis may be considered to be true node-negative. In contrast, sentinel node-negative patients without back-up lymphadenectomy might have a higher possibility of having undetected residual lymph node metastasis at the completion of surgery. Of note, in patients with positive peritoneal cytology, adjuvant therapy may not be omitted, as positive peritoneal cytology in low-stage disease was associated with decreased survival [108].

Table 1. Long-term outcomes of patients with intermediate- and high-risk endometrial carcinoma treated with open surgery alone, including pelvic and para-aortic lymphadenectomy.

Author (Year)	No. of Patients	Stage, Grade; Histology	Lymphadenectomy (LA)	No. of Nodes Removed	5-Year Survival Rate	Median Follow-Up
Chen (1989) [101]	18	IAG3, IB	Selective biopsy of pelvic and para-aortic lymph nodes	Not available	100% (DFS)	5–13 years
Ayhan (2002) [102]	25	IAG3, IB; endometrioid	Pelvic and para-aortic LA	27, median	92% (OS)	96 months
Straughn (2003) [103]	121	IB; serous and clear cell were excluded	Pelvic and para-aortic LA	20, mean	92% (OS)	41 months
Otsuka (2022) [47]	77	IAG3, IB, II; endometrioid	Pelvic LA in all patients and para-aortic LA in selected patients	19 (pelvic) 8 (para-aortic), median	97% (DSS)	75 months

DFS, disease-free survival; OS, overall survival; DSS, disease-specific survival.

Node-positive patients, in particular patients with low-volume metastasis, can be cured with surgery alone including systematic lymphadenectomy. A previous study has reported that five-year overall survival was 40% for node-positive patients treated with surgery alone [109]. Researchers have experienced the long-term survival of a case with grade 3 endometrioid endometrial carcinoma with para-aortic node metastasis treated with surgery alone [110]. She had a pelvic node, a para-aortic node, and an adnexal metastasis, but all metastatic diseases were micrometastasis (<2 mm). Similarly, isolated tumor cells detected in removed sentinel nodes may not decrease survival, even without adjuvant therapy [111][112][113][114].

The patient age, which has been incorporated into the existing risk classification systems [5][6], may influence the effect of lymphadenectomy in endometrioid endometrial carcinoma (**Table 2**). In elderly women, lymphadenectomy may be less effective than in younger women, which might be indicated in German population-based studies where median age of the patients was 69 years or older [115][116]. This may be explained by the association of older age with adverse pathologic features [117][118], hematogenous dissemination [106], and immunosenescence [119]. Otherwise, the route of surgical approach, which was not described in some recent studies, might affect the results.

Table 2. Effects of pelvic and para-aortic lymphadenectomy by age.

Author (Year)	No. of Patients	Lymphadenectomy	Number of Nodes Removed	Age	Tumor Type
Positive effects of PLA/PALA on survival					
Huang (2013) [86]	961	PLA, PALA	18 (pelvic) 5 (para-aortic)	53 y, median	Endometrioid
Todo (2010) [85]	671	PLA, PALA	59 (pelvic) 23 (para-aortic)	56 y, median	Other than low-risk (pT1A, G1-2)
Abu-Rustum (2008) [94]	1035	PLA, PALS (up to IMA)	16	61 y, median	Endometrioid
Mariani (2000) [82]	137	PLA, PALA	16 (pelvic) 6 (para-aortic)	67 y, mean	Patients at high risk for para-aortic lymph node involvement *

Author (Year)	No. of Patients	Lymphadenectomy	Number of Nodes Removed	Age	Tumor Type
Eggemann (2016) [87]	1502	PLA, PALA	19	66 y (PLA and PALA) 68 y (PLA) 72 y (no LA), mean	Other than low-risk (pT1A, G1-2)
No effects of PLA/PALA on survival					
Papathemelis (2018) [117]	299	PLA, (PALA)	26	69 y, median	pT1B G1-2, type I
Ignatov (2020) [116]	2392	PLA, PALA	29	69 y (LA) 74 y (no LA), median	Endometrioid, intermediate-risk (pT1A G3, pT1B G1-2) high-risk (pT1B G3, pT2 Gany)

PLA, pelvic lymphadenectomy; PALA, para-aortic lymphadenectomy; PALS, para-aortic lymph node sampling; IMA, inferior mesenteric artery; NA, not available. * Myometrial invasion >50%, macroscopically positive pelvic nodes or positive adnexae, excluding stage IV disease.

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