

Review Article



Lymphadenectomy issues in endometrial cancer

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ABSTRACT

Objectives: This review aims to introduce preoperative scoring systems to predict lymph node metastasis (LNM) and ongoing clinical trials to investigate the therapeutic role of lymphadenectomy for endometrial cancer.

Methods: We summarized previous reports on the preoperative prediction models for LNM and evaluated their validity to omit lymphadenectomy in our recent cohorts. Next, we compared characteristics of two ongoing lymphadenectomy trials (JCOG1412, ECLAT) to examine the survival benefit of lymphadenectomy in endometrial cancer, and described the details of JCOG1412.

Results: Lymphadenectomy has been omitted for 64 endometrial cancer patients who met low-risk criteria to omit lymphadenectomy using our scoring system (LNM score) and no lymphatic failure has been observed. Other two models also produced comparable results. Two randomized phase III trials to evaluate survival benefit of lymphadenectomy are ongoing for endometrial cancer. JCOG1412 compares pelvic lymphadenectomy alone with pelvic and para-aortic lymphadenectomy to evaluate the therapeutic role of para-aortic lymphadenectomy for patients at risk of LNM. For quality assurance of lymphadenectomy, we defined several regulations, including lower limit of the number of resected nodes, and submission of photos of dissected area to evaluate thoroughness of lymphadenectomy in the protocol. The latest monitoring report showed that the quality of lymphadenectomy has been well-controlled in JCOG1412.

Conclusion: Our strategy seems reasonable to omit lymphadenectomy and could be generalized in clinical practice. JCOG1412 is a high-quality lymphadenectomy trial in terms of the quality of surgical procedures, which would draw the bona-fide conclusions regarding the therapeutic role of lymphadenectomy for endometrial cancer.

Keywords: Endometrial Cancer; Clinical Trial; Lymphadenectomy; Survival


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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

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INTRODUCTION

Surgical staging system has been adopted for endometrial cancer and cases with nodal involvement are classified as stage IIIC who needs adjuvant therapy to reduce the risk of recurrence and death. Thus, diagnostic value of lymphadenectomy has been established for endometrial cancer. However, it should be applied for the patients at risk of lymph node metastasis (LNM), because lymphadenectomy is associated with increased risk of adverse events such as lymphedema, lymphocele. We proposed a scoring system to preoperatively predict the risk of LNM [1,2] to avoid futile lymphadenectomy, and we have omitted lymphadenectomy for those at negligible risk of LNM in our institution [3]. We would show the validity of our scoring system to omit LNM in our recent cohort.

Regarding the survival effect of lymphadenectomy, there have been many articles in the literature. Two randomized phase III trials from Europe failed to show any survival benefit of lymphadenectomy compared with no lymphadenectomy in endometrial cancer [4,5], indicating that lymphadenectomy is not therapeutic. However, these results did not change the clinical practice, because the quality of these trials were somewhat questionable, and many retrospective studies showed survival benefit of lymphadenectomy for endometrial cancer including SEPAL study from Japan [6]. Thus, therapeutic significance of lymphadenectomy remains controversial due to lack of high-quality evidence from clinical trials. Therefore, its therapeutic role should be evaluated in well-conceived clinical trials. We would introduce 2 ongoing clinical trials to investigate the survival benefit of lymphadenectomy from Germany (ECLAT) [7] and Japan (JCOG1412) [8]. Quality assurance of the procedure is a critical issue in surgical trials. We would introduce our efforts for quality assurance of lymphadenectomy in JCOG1412 (**Supplementary Video 1**).

PREOPERATIVE SCORING SYSTEMS TO PREDICT LNM IN ENDOMETRIAL CANCER

Evaluation of nodal status greatly influences on the decision of adjuvant therapy for endometrial cancer. Because nodal disease is classified as stage IIIC and shows poor prognosis, adjuvant treatment is strongly recommended to reduce the risk of recurrent and metastatic disease. On the other hand, futile lymphadenectomy should be avoided, because lymphadenectomy is associated with longer operation time, increased blood loss and subsequent blood transfusion, and increased risk of complications related to lymphadenectomy such as lower limb lymphedema, lymph cyst. Instead of lymphadenectomy, sentinel node mapping has been widely employed for endometrial cancer in western countries. However, sentinel node mapping has been recently introduced in limited institutions, and currently could not be performed in most institutions in Japan. Thus, alternative method should be developed to predict the risk of LNM preoperatively to tailor lymphadenectomy.

In 1987, Creasman et al. [9] reported that frequency of nodal metastasis could be categorized into 3 groups by the combination of 3 post-operative risk factors including grade, myometrial invasion and extrauterine disease. Low-risk group (grade1, endometrium only, no intraperitoneal disease) showed no pelvic and para-aortic node metastasis. Among moderate risk group (grade2–3, inner-mid invasion, no intraperitoneal disease), those with only one factor showed 3%, 2% risk of pelvic or para-aortic node metastasis, respectively. Those with 2 factors showed 6%, 2% risk of pelvic or para-aortic node metastasis, respectively. Among high-risk group (deep myometrial

invasion, intraperitoneal disease), those with deep myometrial invasion only showed 18%, 15% risk of pelvic or para-aortic node metastasis, respectively and those with intraperitoneal disease only showed 33%, 8% risk of pelvic or para-aortic node metastasis, respectively. Those with both factors showed extremely high frequency of LNM (61% in pelvic region, 30% in para-aortic region) [9]. Todo et al. [1] proposed a preoperative scoring system, designated as LNM score, to predict the risk of LNM for endometrial cancer in 2003. They showed that among risk factors which can be assessed preoperatively, 3 factors (histologic type/grade, serum CA125 level, volume index representing tumor volume) were found to be independently related to the risk of LNM. In 2007, clinical usefulness of LNM score has been validated in other cohorts [2]. Because patients with LNM score zero showed negligible risk of para-aortic node metastasis (less than 1%), they concluded that para-aortic lymphadenectomy could be safely omitted for the patients with LNM score zero. In combination with LNM score and evaluation of myometrial invasion by magnetic resonance imaging (MRI), we omitted entire lymphadenectomy and reported the outcome and validity of our treatment strategy to omit lymphadenectomy in 2014 [3].

For this review, we re-examined the validity of our strategy to omit lymphadenectomy in our recent patients' cohort. Among 110 patients who omitted lymphadenectomy with any reasons from 2003 to 2015, 64 patients matched LNM score zero and no/minimal myometrial invasion by MRI. During median follow-up period of 60.5 months, no lymphatic failure was observed, indicating that the combination of LNM score and evaluation of myometrial invasion by MRI might serve as a good indicator to omit lymphadenectomy. Similar scoring systems, including Korean Gynecologic Oncology Group low-risk criteria which is comprised of 4 factors (endometrioid histology, myometrial invasion <1/2 by MRI, normal range of CA125 level, and no extrauterine disease) [10,11], and Kanagawa Cancer Center score from Japan which is a combination of 4 factors (histology, tumor volume and myometrial invasion by MRI, and CA125 level) [12], were also reported to be good indicators to omit lymphadenectomy, because no lymphatic failure was also observed among patients with score zero in the same cohort. **Table 1** summarized the comparison of 3 preoperative scoring systems in our recent patients' cohort.

Table 1. Comparison of 3 preoperative scoring systems in the same cohort

Variables	LNM score + MI	KGOG low-risk criteria	KCC score
Preoperative factors			
Histological type/grade	Endometrioid/G1/G2	Endometrioid/any grade	Endometrioid G1
Serum CA125 (IU/mL)			
Premenopausal	<70	<35	<70
Postmenopausal	<28	<35	<25
MRI findings			
MI	No/minimal	<1/2	<1/2
Tumor volume	<36 cm ³	Not included	<6 cm ³
Matched patients	64	91	40
Median follow-up period (mo)	60.5 (3–155)	60 (3–155)	63 (5–155)
Follow-up >3 yr	44 (69)	65 (71)	26 (65)
Post-operative findings			
Histological type/grade			
Endometrioid G1/G2	62 (97)	85 (93)	38 (95)
MI <1/2	63 (98)	90 (99)	39 (98)
LVSI (-)	63 (98)	86 (95)	39 (98)
Pathological stage I	62 (97)	88 (97)	40 (100)
Recurrence	1 (1.6)	3 (3.3)	0 (0)
Recurrent site	Lung	Lung, peritoneum, ovary	-

Values are presented as median (interquartile range) or number (%).

Total of 110 consecutive patients who omit lymphadenectomy in our institution were analyzed retrospectively. KCC, Kanagawa Cancer Center; KGOG, Korean Gynecologic Oncology Group; LNM, lymph node metastasis; LVSI, lymphovascular space invasion; MI, myometrial invasion.

SURVIVAL BENEFIT OF LYMPHADENECTOMY IN ENDOMETRIAL CANCER

Therapeutic role of lymphadenectomy in endometrial cancer has been one of the major topics of debate in gynecologic oncology area. Two randomized clinical trials from Europe (ASTEC trial, Italian study) were conducted to compare pelvic lymphadenectomy and no lymphadenectomy [4,5]. Both of them failed to show any survival benefit of pelvic lymphadenectomy. However, several criticisms have been made for those trials. First, around 40% of the recruited patients were found to be post-operative low-risk for recurrence, who also showed low-risk of LNM. Second, median number of resected nodes was small in ASTEC trial (median; 12), and modest in Italian study (median=26), which may lead to inadequate impact of lymphadenectomy on patients' survival. Third, para-aortic node dissection was not performed in both studies, even though para-aortic nodes are defined as regional lymph nodes in endometrial cancer in UICC-TNM classification 5th edition [13]. In contrast, a retrospective study in Korea supports the association between an increase of the number of resected nodes and improved survival regardless of node positivity in endometrial cancer. In the intermediate/high-risk patients (stage IB, grade 3; stage IC and II–IV, all grades), a more extensive lymph node resection (1, 2–5, 6–10, 11–20, and >20) was associated with improved 5-year disease-specific survivals across all 5 groups at 75.3%, 81.5%, 84.1%, 85.3%, and 86.8%, respectively ($p < 0.001$). [14]. Recently from the US, among stage I endometrioid endometrial cancer in the national cancer database, comparison of overall survival between pelvic lymphadenectomy cohort ($n=7,487$) and no lymphadenectomy cohort ($n=7,487$), or pelvic lymphadenectomy alone cohort ($n=7,060$) and pelvic and para-aortic lymphadenectomy cohort ($n=7,060$) were analyzed using propensity score matching. They showed that pelvic lymphadenectomy significantly improved overall survival compared with no lymphadenectomy (5-year survival, 91.4% vs. 87.3%; $p < 0.001$), pelvic and para-aortic lymphadenectomy significantly improved overall survival compared with pelvic lymphadenectomy alone (5-year survival, 91.0% vs. 89.8%; $p < 0.003$) [15]. They also analyzed association of lymph node count and overall survival in node-negative endometrial cancers ($n=15,402$ from stage IA to IIIB). They showed that increased number of resected nodes tended to improve overall survival in each stage [15]. SEPAL study from Japan, a retrospective cohort study, showed that addition of para-aortic lymphadenectomy to hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy significantly reduced the risk of death from endometrial cancer compared with pelvic lymphadenectomy alone in 407 cases of intermediate/high relapse risk group (5-year survival, 83.2% vs. 72.6%) [6]. We assume that the positive result of SEPAL study was at least in part, due to larger number of resected nodes (34 in pelvic lymphadenectomy alone cohort and 59 in pelvic and para-aortic lymphadenectomy cohort) in pelvic region than those in 2 European randomized trials (12 in ASTEC trial, 26 in Italian study). However, adjuvant therapy was not uniformly given in SEPAL study. Indeed, 163 of 165 patients (98.8%) received adjuvant chemotherapy in pelvic and para-aortic lymphadenectomy cohort, whereas 75 of 163 patients (46.6%) received adjuvant whole pelvic radiotherapy in pelvic lymphadenectomy alone cohort [6], which might affect the result of SEPAL study, because it was reported that chemotherapy significantly improved overall survival compared with radiotherapy for patients with recurrent/advanced disease in GOG122 [16]. Although the incidence of nodal metastasis in SEPAL study was only 16% (108/671), post-operative complications with or without para-aortic lymphadenectomy in SEPAL cohort was acceptable. There was no fatal accident associated with surgery. Comparing pelvic and para-aortic lymphadenectomy cohort and pelvic lymphadenectomy alone cohort, there are no significant differences in the rate of cases of lymphedema (23.2% vs. 28.3%), lymphocyst (9.2% vs. 9.4%), thrombosis (4.9% vs. 2.2%) and severe ileus (1.4% vs. 0.7%) [17]. We, therefore,

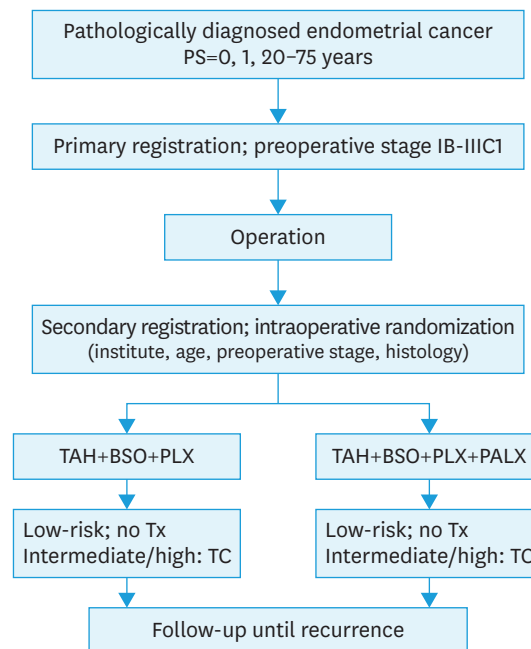


Fig. 1. JCOG1412 trial scheme.

BSO, salpingo-oophorectomy; PALX, para-aortic lymphadenectomy; PLX, pelvic lymphadenectomy; PS, performance status; TAH, total abdominal hysterectomy; TC, paclitaxel + carboplatin; Tx, treatment.

decided to conduct a new randomized phase III trial (JCOG1412) [8] for the patients at risk of LNM (preoperative stage IB, II, IIIA, IIIB, and IIIC1), because we concluded that therapeutic significance of lymphadenectomy remained controversial in endometrial cancer surgery. We exclude whole preoperative stage IA patients to decrease the registration of stage IA patients with non-high-risk pathology that are thought as the low-risk of LNM, because differentiating G1/2 and G3 or special type is sometimes difficult in preoperative histologic diagnosis. JCOG1412 aimed to compare the overall survival between pelvic lymphadenectomy alone arm and pelvic and para-aortic lymphadenectomy arm. We uniformly apply 6 cycles of adjuvant chemotherapy (paclitaxel/carboplatin) for patients at post-operative intermediate-/high-risk for recurrence (**Fig. 1**). Target accrual is 760 randomized patients [8].

Lymphadenectomy has been strongly recommended for the patients with high-risk histology. Venigalla et al. [18] demonstrated that pelvic lymphadenectomy significantly improved overall survival compared with no lymphadenectomy, pelvic and para-aortic lymphadenectomy also significantly improved overall survival compared with pelvic lymphadenectomy alone in patients with high-risk histology (serous, clear cell, carcinosarcoma). Papatthemelis et al. [19,20] reported the survival benefit of systematic pelvic and para-aortic lymphadenectomy compared with elective lymphadenectomy or no lymphadenectomy in patients with high-grade endometrial cancer, but not those in stage IB with endometrioid G1–2 tumors. Based on these backgrounds described above, the German Arbeitsgemeinschaft für Gynäkologische Onkologie has started a randomized phase III trial (ECLAT) to investigate therapeutic role of pelvic and para-aortic lymphadenectomy compared with no lymphadenectomy for patients with preoperative stage IA, endometrioid G3/high-risk histology (serous, clear cell, carcinosarcoma), IB, II disease with any histology/grade [7]. Chemotherapy with carboplatin and paclitaxel plus vaginal brachytherapy is recommended as adjuvant therapy for all patients. Target accrual is 640 patients. Another randomized

Table 2. JCOG1412 vs. ECLAT

Characteristics	JCOG1412	ECLAT
Phase, design	III, superior	III, superior
Primary endpoint	OS	OS
Treatment arm	PLX vs. PLX + PALX	No LNX vs. PLX + PALX
Preoperative stage	IB, II, IIIA, IIIB, IIIC1*	IA (high-risk histology), IB, II
Adjuvant therapy	Chemotherapy†	Vaginal brachytherapy + chemotherapy†
Target accrual	760	640

LNX, lymphadenectomy; OS, overall survival; PALX, para-aortic lymphadenectomy; PLX, pelvic lymphadenectomy. *Single node enlargement in pelvic nodes; †Paclitaxel + carboplatin.

controlled trial from Europe was designed to address the use of systematic lymphadenectomy to appropriately apply adjuvant therapy (other than vaginal brachytherapy) to node-positive patients. Selective Targeting of Adjuvant Therapy for Endometrial Cancer started in 2015 and terminated due to poor recruitment in 2019 [21]. We summarized JCOG1412 and ECLAT for comparison in **Table 2**. Our study has a limitation that endoscopic (laparoscopic or robot-assisted) surgery is not allowed in this trial, because endoscopic surgery has been covered by medical insurance recently to treat early stage endometrial cancer (stages IA) and the effectiveness and safety of endoscopic surgery has not been fully evaluated for endometrial cancer in stages IB–IIIC1 that are the subjects of this trial in Japan. But we think that our conclusion from JCOG1412 may apply for endoscopic surgery if endoscopic approach for lymphadenectomy will show the same quality as that of laparotomic approach in the future.

Quality assurance of procedures is one of the most critical issues in the surgical trial to investigate its therapeutic role, because low quality of the procedures might draw incorrect conclusions even from prospective studies. In ECLAT, all participating surgeons must show their qualification and to document the correct extent of systematic lymphadenectomy for the purpose of quality assurance of lymphadenectomy [22]. To assure the quality of lymphadenectomy in our JCOG1412, we defined 3 regulations [8]. First, board-certified surgeons should be responsible for all procedures. Second, we defined the lower limit of the number of resected nodes (25 in pelvic region, 15 in para-aortic region). Third, we asked investigators to take photos of the entire dissected area after completing lymphadenectomy to evaluate its thoroughness. For central review of the submitted photos, we determined the criteria to evaluate the quality of lymphadenectomy as shown in **Table 3**. The submitted photos were evaluated at the same time and place by 5 board-certified gynecologic surgeons. We carried out central review of the photos approximately every 60 cases. We sent the result of the central reviews back to each participating institution to improve thoroughness of their lymphadenectomy.

We obtained the data on the number of resected nodes from 257 patients (128 in pelvic lymphadenectomy alone arm and 129 in pelvic and para-aortic lymphadenectomy arm) according to the latest regular monitoring report issued from the JCOG data center in March, 2020. In the pelvic lymphadenectomy alone arm, median number of resected pelvic nodes

Table 3. Criteria to review the quality of lymphadenectomy in JCOG1412

Criterion
Pelvic region
1) No residual tissues around iliac vessels and obturator nerve
2) Easy identification of the surface of sacrum
Para-aortic region
1) Easy identification of the margin of renal vein
2) Easy identification of the stump of ovarian vessels
3) No residual tissues around inferior mesenteric artery
4) Removal of inter-aortic nodes

Table 4. Summary on the number of resected nodes in JCOG1412

Region	Pelvic lymphadenectomy arm (n=128)	Pelvic and para-aortic lymphadenectomy arm (n=129)
Pelvic region	45 (35–56)	43 (34–55)
Para-aortic region	0 (0–0)	26 (20–35)

Data are median (interquartile range).

was 45 (interquartile range [IQR]=35–56). In the pelvic and para-aortic lymphadenectomy arm, median number of resected nodes was 43 (IQR=34–55) in pelvic region, 26 (IQR=20–35) in para-aortic region (**Table 4**). The central review of the photos demonstrated that 50 of the recent 60 cases (83.3%) took full marks, suggesting that feedback of the results of central review to investigators might lead to better procedures afterwards.

We confirmed that the quality of lymphadenectomy has been well controlled in our ongoing JCOG1412 at this moment. We are pretty confident that we would draw the bona-fide conclusions regarding the therapeutic role of lymphadenectomy for endometrial cancer from JCOG1412.

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SUPPLEMENTARY MATERIAL

Supplementary Video 1

Seoul National University Hospital Gynecologic Oncology Webinar #6, August 21, 2020.
Video can be found with this article online at <https://vimeo.com/494349896/62fae61f57>.

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