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Review Article

Methodological considerations in the analysis of the therapeutic significance of lymphadenectomy in endometrial cancer

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Abstract

There needs to be clarification on eligibility requirements and procedure standardization with regard to the therapeutic role of lymphadenectomy. If this is not done, consensus on the role of lymphadenectomy will not be reached. Although pelvic lymphadenectomy is not necessary for patients with low-risk Stage I endometrial cancer, it has been suggested that combined pelvic and para-aortic lymphadenectomy is useful for patients with intermediate-/high-risk endometrial cancer. Therefore, the therapeutic role of lymphadenectomy should be continuously evaluated. If such a study is planned, it should not include patients with low risk of nodal metastasis, and one experimental arm of the study should assess combined pelvic and para-aortic lymphadenectomy (fundamentally including the area above the inferior mesenteric artery and the renal vein). It is necessary to establish a pre-operative risk assessment for nodal metastasis and procedural classification of lymphadenectomy. Some pre-operative risk assessments for nodal metastasis have been proposed from Asian countries. The extent of the surgical field is defined as the pelvic area alone, or combined pelvic and para-aortic area. The thoroughness of removal can be split into removal of only suspicious nodes, selective dissection, or systematic dissection. Although randomized controlled trials provide the highest level of clinical evidence, special difficulties are presented in randomized surgical trials. Nonentry of surgeons is a threat to external validity. The role of observational studies, especially prospective cohort studies should be reconsidered when assessing the therapeutic significance of lymphadenectomy.

Keywords: endometrial cancer; external validity; observational study; para-aortic lymphadenectomy; randomized controlled trial; therapeutic significance

Introduction

Endometrial cancer is one of the most common malignancies of the female genital tract, and its incidence in the industrialized world has been increasing. The number of new cases annually has increased in the United States, with 36,100 in 2000 [1] and 47,130 in 2012 [2]. The number of deaths annually has also increased, with 6500 in 2000 [1] and 8010 in 2012 [2]. Eventually, one out of six patients with endometrial cancer relapse and die of the disease. However, the FIGO annual report has demonstrated that survival rates from endometrial cancer have been increasing in recent decades [3]. This trend even applies to cases with Stage IIIc endometrial cancer. From this, physicians face two issues. Firstly, they have to treat the largest number of patients ever and consequently reduce the time required for treatment in one patient. Secondly, improvements are needed in the treatment of patients with a high-risk prognosis. They need to make interventions, including pre-operative risk assessment, surgical procedures, and follow-up programs, more efficient.

As two randomized controlled trials (RCTs) from European countries showed negative results of lymphadenectomy on prognosis [4,5], many gynecologists have since declared at conferences that standard surgery for endometrial cancer does not include lymphadenectomy. However, this conclusion is due to overgeneralization of the results of the randomized studies. Surgery has been playing the leading part in the

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treatment of endometrial cancer and there has been no paradigm shift, except for the introduction of lymphadenectomy. It is possible that many patients with endometrial cancer have benefited from lymphadenectomy. The consistent increase in survival rates may be due to it. In this article, we review the results of two RCTs and one retrospective cohort analysis and discuss the interpretation and limitations of randomized surgical trials. We also discuss whether lymphadenectomy should be recommended in the treatment of endometrial cancer. In addition, we propose a group of patients who need lymphadenectomy and a pre-operative assessment for predicting lymph node metastasis.

Therapeutic role of lymphadenectomy: Previous discussion

Before 2008, all studies regarding the role of lymphadenectomy in endometrial cancer were retrospective. Some studies supported a survival benefit of lymphadenectomy [6–13] and others did not [14–17]. Assessing nodal status is necessary for determining the stage of the endometrial cancer. However, there was no description of a procedure for this, which caused confusion on the clinical scene. The most accurate method to detect lymph node metastasis consisted of systematically removing regional lymph nodes and inspecting the specimens. Another method consisted of only palpating lymph nodes or selectively removing only enlarged nodes. The type and extent of lymph node dissection would vary greatly across the surgical field.

In 2008, Benedetti-Panici et al in Italy reported results from the first RCT (CONSORT trial) to assess the therapeutic effect of lymphadenectomy [4]. In 2009, results from the second RCT to assess the therapeutic role of lymphadenectomy were published by the ASTEC study group [5]. The results of both RCTs were, in particular, characterized by the unexpected finding that the survival period in the nonlymphadenectomy group was longer than in the lymphadenectomy group. In addition, they showed that lymphadenectomy increased postoperative complications. Therefore, many physicians have since declared at medical meetings that standard surgery for endometrial cancer should not include lymphadenectomy.

However, a lot of criticism of this idea has also been voiced. The problem criticized most is that implementation of para-aortic lymphadenectomy was at the discretion of the attending physicians and only a small number of patients underwent para-aortic lymphadenectomy (CONSORT trial: 26%, ASTEC trial: data not available). As a result, the median number of lymph nodes removed was less than that in the Japanese SEPAL study (CONSORT trial: 30; ASTEC trial: 14; SEPAL study: 82) [4,5,18]. Another criticism is that lymphadenectomy is used at a low frequency in European countries, probably due to skepticism about its therapeutic role and constraints based on their guidelines. According to the European Society for Medical Oncology (ESMO) guidelines, surgical treatment in Stage I endometrial cancer does not always include lymphadenectomy and surgical treatment in Stage II endometrial cancer includes pelvic lymphadenectomy but not always para-aortic lymphadenectomy [19]. It has been reported that lymphadenectomy for endometrial cancer was performed routinely in only 17–24% of centers in Europe [20,21]. However, 98% of institutions used routine pelvic lymph node dissection, and 93% of institutions used routine or selective surgical treatment of para-aortic lymph nodes in Japan [22]. It was described in that report that para-aortic dissection/biopsy was used either routinely (12%) or selectively based on tumor-related factors (81%).The fact that lymphadenectomy used in the experimental arms of the two RCTs was limited to pelvic lymph nodes means that surgery commonly performed in Europe did not include para-aortic lymphadenectomy. Therefore, many attending surgeons may be reluctant to perform lymphadenectomy, especially in the para-aortic area. Thus, it is possible that surgeries performed in the two RCTs has inadequate level of surgery to demonstrate the full benefit of lymphadenectomy.

Considering these limitations, appropriate interpretation of both trials would be that pelvic lymphadenectomy does not have therapeutic significance for low-risk clinical Stage I endometrial cancer. As clinical Stage I includes not only low-risk patients, but also intermediate- and high-risk patients, concluding that pelvic lymphadenectomy does not have therapeutic significance for clinical Stage I endometrial cancer will cause patients with intermediate- and high-risk features to miss an opportunity to undergo lymphadenectomy. If lymphadenectomy has survival benefits for intermediate and high-risk cases, they would not be able to receive optimal treatment.

In 2010, we presented results from the Survival Effect of Para-aortic Lymphadenectomy (SEPAL) study, which showed no survival benefit from combined pelvic and para-aortic lymphadenectomy over pelvic lymphadenectomy alone for low-risk patients, and significant survival benefits from implementation of para-aortic lymphadenectomy in addition to pelvic lymphadenectomy for intermediate- and high-risk patients [18]. In that study, 36 lymph nodes were harvested in the pelvic lymphadenectomy group and 82 in the combined pelvic and para-aortic lymphadenectomy group. Surgery with para-aortic lymphadenectomy was associated with decreased death in patients with a hazard ratio of 0·44 (95% CI = 0.30–0.64, $p < 0.0001$) compared with surgery without para-aortic lymphadenectomy. The combined pelvic and para-aortic lymphadenectomy showed a 10.6% increase in the 5-year overall survival compared with that from pelvic lymphadenectomy alone in intermediate-/high-risk patients (Table 1). In addition, the study demonstrated that para-aortic lymphadenectomy improved survival rates independently from the efficacy of any adjuvant treatment.

Considering previous results from retrospective and prospective studies, standard primary surgery in low-risk endometrial cancer includes hysterectomy and bilateral salpingo-oophorectomy, but does not include lymphadenectomy. However, a therapeutic role for lymphadenectomy should be continuously assessed in intermediate-/high-risk endometrial cancer, as combined pelvic and para-aortic lymphadenectomy might have survival benefits. However, such a

Table 1
Clinical studies regarding the therapeutic significance of lymphadenectomy in endometrial cancer.

	CONSORT trial	ASTEC trial	SEPAL study
Jornal	J Natl Cancer Inst (2008)	Lancet (2009)	Lancet (2010)
Study design	prospective randomized controlled study	prospective randomized controlled study	retrospective comparative cohort study
Participating hospital (*n*)	31	85	2
Eligibility	Clinical stage I	Clinical stage I	Clinical stage I-III/operable stage IV
Cases (*n*)	514	1408	671
FIGO (1988) stage	Stage I: 75%	Stage I: 79%	Stage I: 65%
	Stage II: 8%	Stage II: 13%	Stage II: 10%
	Stage III-IV: 15%	Stage III-IV: 7%	Stage III-IV: 25%
	Unknown: 2%	Unknown: 1%	Unknown: 0%
Intervention	LNX-: n = 250	LNX-: n = 704	PLX: n = 325
	LNX+: n = 264	LNX+: n = 704	PLX+PALX: n = 346
Adjuvant treatment	LNX-: RT 25%, CT 10%	LNX-: RT 33%, CT 4%	PLX: RT 23%, CT 27%
	LNX+: RT 17%, CT 14%	LNX+: RT 33%, CT 4%	PLX+PALX: RT 1%, CT 47%
The number of LN removed (median)	LNX-: 0	LNX-: 0	PLX: 34
	LNX+: 30	LNX+: 14	PLX+PALX: 8
5-year overall survival	LNX-: 90%	LNX-: 81%	PLX: L 94%, I/H 73%*
	LNX+: 86%	LNX+: 80%	PLX+PALX: L 96%, I/H 83% *
5-year disease free survival	LNX-: 82%	LNX-: 79%	PLX: L 93%, I/H 65%**
	LNX+: 81%	LNX+: 73%	PLX+PALX: L 95%, I/H 81%**
Follow-up period	49 months	37 months	92 months

LN = lymph node; LNX = lymphadenectomy; PLX = pelvic lymphadenectomy; PALX = para-aortic lymphadenectomy; RT = radiation therapy; CT = chemotherapy; L = nbsp;low-risk (less than half myoinvasion, Grade 1/2, no lymphovascular space invasion); I = intermediate-risk (other than low-risk and high-risk); H = high-risk (extrauterine disease). * $p = 0.0009$, ** $p < 0.0001$.

risk is based on pathological findings. It is a postoperative risk assessment. Although postoperative risk assessment is useful for deciding whether adjuvant therapy should be conducted, it is not useful when deciding what kind of surgery should be performed. Pre-operative risk assessment is needed to decide the type of surgery. This issue will be discussed in the following section.

The first prerequisite for clinical trials to assess the therapeutic role of lymphadenectomy: Preoperative risk assessment for nodal metastasis

When the therapeutic effect of lymphadenectomy in endometrial cancer is assessed, patients with low risk of lymph node metastasis should not be included. However, there has been no consensus for identifying the low-risk group for nodal metastasis. Gynecologic Oncology Group study number 33 (GOG #33) showed that there was no case with nodal metastasis in the low-risk group, defined as having no myometrial invasion, Grade I endometrioid histology, and no intraperitoneal disease [23]. Mariani et al confirmed a low-risk group with Grade I to II endometrioid histology, a depth of invasion of $\leq$50%, and tumor size of $\leq$2cm; only 5% of the group had lymph node metastasis [24].They concluded that lymphadenectomy does not benefit patients in the low-risk group (the so-called Mayo criteria). Milam et al also demonstrated that these criteria led to a rate of nodal metastasis of only 0.8% in the low-risk group of the Mayo criteria [25]. However, all of these criteria depend on surgicopathologic findings. We need prior informed consent procedures regarding implementation of lymphadenectomy before surgery, but these criteria are not available in the pre-operative settings of clinical practice. We proposed a low-risk group with Grade I to II endometrioid histology by endometrial biopsy, volume index of $\leq$36 by MRI, and low CA125 level (70 U/mL for patients aged $<$50 years and 28 U/mL for patients aged $\geq$50 years) before surgery; only 2.1% of the group had lymph node metastasis at the assumed prevalence of nodal metastasis of 10% [26]. Kang et al confirmed a low-risk group with endometrioid histology by endometrial biopsy, less than half myometrial invasion and no extension beyond corpus and no enlarged lymph nodes by MRI, and CA125 level of $\leq$35 before surgery; only 1.3% of the group had lymph node metastasis at the assumed prevalence of nodal metastasis of 10% [27]. These criteria not only give patients information required for treatment decision-making but also present suitable eligibility in a clinical study to assess the therapeutic effect of lymphadenectomy. In the future, surgical treatment of endometrial cancer will be followed by an individualized (tailor-made) progression through scrutiny of clinical trials. Appropriate application of surgical procedures requires appropriate pre-operative risk assessment. A worldwide consensus regarding preoperative risk assessment should be established as soon as possible.

The second prerequisite for clinical trials to assess the therapeutic role of lymphadenectomy: Procedural classification of lymphadenectomy

In the TNM classification of malignant tumors developed by the Union for International Cancer Control (UICC), regional lymph nodes of endometrial cancer must be pelvic

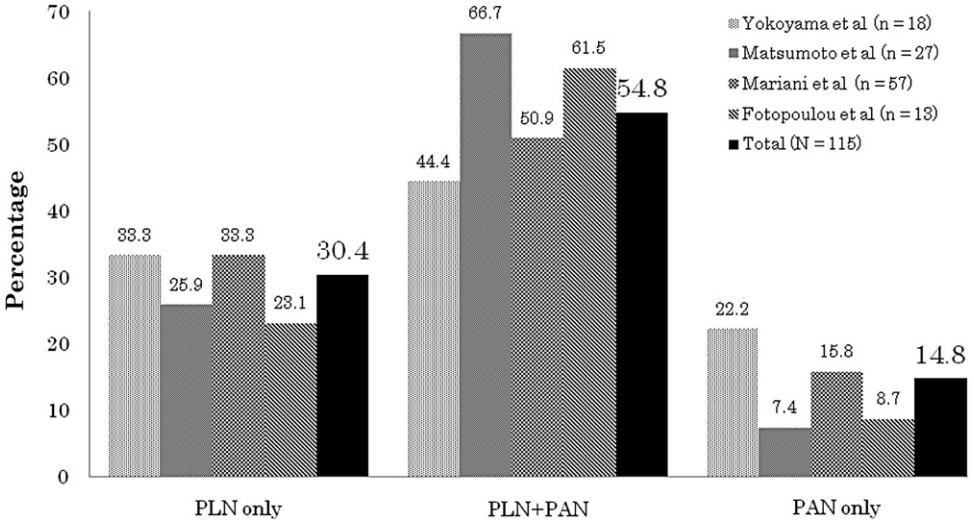

Fig. 1. Distribution of affected nodes in Stage IIIC endometrial cancer. PAN = para-aortic node; PLN = pelvic node.

lymph nodes and para-aortic lymph nodes [28]. According to reports about autopsy series, 61% of the patients had para-aortic node metastasis; para-aortic nodes and interiliac nodes were the most frequent sites susceptible to metastasis [29]. GOG #33 showed that 18% and 15% of patients with deep myometrial invasion had pelvic node metastasis and para-aortic node metastasis, respectively [23]. Previous reports revealed that 57–73% of patients with pelvic node metastasis had para-aortic node metastasis [30–33].

According to Fig. 1, >80% and nearly 70% of lymph node metastases in endometrial cancer are found in the pelvic area and the para-aortic area, respectively. From the viewpoint of the diagnostic role of lymphadenectomy, pelvic lymphadenectomy can detect >80% of all the affected nodes. From the viewpoint of the therapeutic role of lymphadenectomy, however, pelvic lymphadenectomy would leave >60% of all the affected nodes behind and end in incomplete surgery.

Para-aortic nodes are divided into two sections: (1) an area between the inferior mesenteric artery and the renal vein (high para-aortic nodes); and (2), another area between the bifurcation of aorta and the inferior mesenteric artery (low para-aortic nodes). Some sentinel node mapping studies in endometrial cancer showed that more than half of para-aortic nodes identified as sentinel were located above the inferior mesenteric artery [34,35]. In 1997, Hirahatake et al showed that 64% of patients with para-aortic lymph node metastasis harbor disease at the high para-aortic nodes [36]. Other researchers showed that 54–77% of patients with para-aortic node metastasis harbor disease at the high para-aortic nodes (Fig. 2).

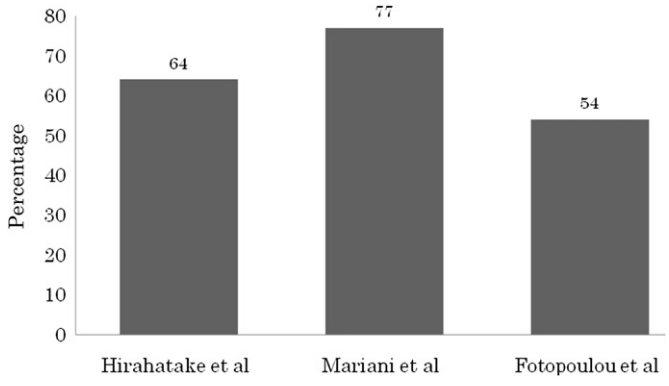

Fig. 2. Metastatic rate of para-aortic nodes above the inferior mesenteric artery in Stage IIIC2 endometrial cancer.

The eligibility requirements for lymphadenectomy, extent of lymphadenectomy, and procedure standardization should be clarified on the discussion about a therapeutic role of lymphadenectomy. We are proposing a classification of procedure by extent of lymphadenectomy and degree of thoroughness in removal (Table 2). The extent of the surgical field would be defined as pelvic area alone or combined pelvic and para-aortic area. Degree of thoroughness in removal would be defined as removal of only suspicious nodes, selective dissection, or systematic dissection. Although a certain level of variation is unavoidable on the clinical practice, a minimal standardization of procedure is desired in order to assess the therapeutic role of lymphadenectomy in a prospective comparative trial. The number of lymph nodes harvested

Table 2
Level of retroperitoneal lymph node dissection in gynecological cancer.

Level	Extent and procedure
0	No surgical exploration of lymph nodes
1	Removal of only suspicious nodes in the pelvic area (1A) or pelvic and para-aortic area (1B)
2	Sampling (2A) or systematic dissection (2B) of pelvic nodes
3	Sampling (2A) or systematic dissection (2B) of pelvic and para-aortic nodes
3-Low	Upper limit of para-aortic node dissection is inferior mesenteric artery (low para-aortic lymphadenectomy)
3-High	Upper limit of para-aortic node dissection is left renal vein and base of right ovarian vein/right renal vein (high para-aortic lymphadenectomy)

would be an index of degree of thoroughness in removal. Considering previous literature, the number of lymph nodes harvested that promotes improvement of survival in endometrial cancer would be not less than 10. The median [interquartile range (IQR)] number of pelvic lymph nodes harvested in the SEPAL study were 34 (21−42) in the pelvic lymphadenectomy alone group and 59 (46−73) in the pelvic and para-aortic lymphadenectomy group. The median (IQR) number of para-aortic lymph nodes harvested in the SEPAL study was 23 (16−30) in the pelvic and para-aortic lymphadenectomy group [18].

RCTs in surgery: Limitations and counter-proposal

Limitations of the SEPAL study derive from the retrospective design. Thus, a therapeutic effect of para-aortic lymphadenectomy should be prospectively validated. However, is it possible to conduct a prospective RCT to validate that issue? RCTs must be internally valid, but the results of each study are relevant to just a definable group of patients in a particular setting. Namely, RCTs must be externally less valid [37,38]. Special difficulties are presented in RCTs for surgical procedures. The recruitment issue is closely related to success or failure of a randomized surgical trial. It is a threat to external validity, which is almost a synonym of generalizability. Many studies have been conducted by dividing the issues into patients' reasons and physicians' reasons [39−49]. Typical patients' reasons for declining to participate in RCTs are preference for one form of treatment [40,41], disagreement with the idea of randomization [41−43], desire to be involved in decision making [43,44], and insurance coverage [39]. On the other hand, typical physicians' reasons for nonentry of eligible patients into RCTs are preference for one form of treatment [41], negative impact on the doctor−patient relationship [40,45,46], time constraints [40,41], lack of staff and training [40], difficulty with informed consent [46], feelings of personal responsibility [46], risk of recurrence [47], priorities of individual care [48], and incentives [49]. Some factors are related to each other and are not independent. Time constraints and lack of staff may be almost synonymous with additional workload. Feelings of personal responsibility, risk of recurrence, and priorities of individual care may be batched together as an ethical issue. Abraham et al demonstrated that a preference for one form of surgery by the patient or the surgeon was the most common reason for nonentry of eligible patients [41].

Non-participation of experienced surgeons is a major problem. When there is a RCT in which pelvic lymphadenectomy versus combined pelvic and para-aortic lymphadenectomy is compared for patients with high-risk endometrial cancer, some physicians would not participate in this trial because they would think highly of the effectiveness of para-aortic lymphadenectomy and would feel uneasy about performing pelvic lymphadenectomy alone. Experienced surgeons tend to be familiar with para-aortic lymphadenectomy and its benefits and may decline participation in such a RCTs due to an ethical dilemma. Conversely, surgeons with limited experience may be assigned the task of performing para-aortic lymphadenectomy, and the desired outcome may not be achieved due to inadequate experience of the doctor. Both scenarios give rise to a situation in which quality control of treatment might be reduced in the para-aortic lymphadenectomy group. A prospective randomized design in surgical treatment for high-risk cancer patients would inevitably be involved in a selection bias if surgeons can predict which procedure should be more effective. From that viewpoint, a high-risk group in malignant disease is not suitable for a randomized surgical trial.

A prospective cohort study may be the most reasonable method for assessing the therapeutic significance of lymphadenectomy for high-risk patients. When a small number of institutions are selected for two different cohorts characterized by respective surgical intervention, a prescribed surgery is coherently performed in each cohort, and a common adjuvant treatment is used in both cohorts, such an observational study would have an advantage over a prospective randomized study in that it would promote homogenization of intervention which eliminates bias. This is because surgeons can perform a surgery without being influenced by random order and then nonparticipation of surgeons, especially experienced surgeons, would decrease. Some high-level journals have demonstrated that results of well-designed observational studies can be reliable and bear comparison with those of RCTs [50,51]. This may be the time to reconsider the significance of cohort studies.

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