Invited review

Tailoring lymphadenectomy according to the risk of lymph node metastasis in endometrial cancer

Yukiharu Todo[a], MD, PhD, Hidemichi Watari[b], MD, PhD, Sokbom Kang[c], MD, PhD, Noriaki Sakuragi[b], MD, PhD

[a]Division of Gynecologic Oncology, National Hospital Organization, Hokkaido Cancer Center, 4-2 Kikusui, Shiroishi-ku, Sapporo 003-0804, Japan

[b]Department of Obstetrics and Gynecology, Hokkaido University School of Medicine, Sapporo, Japan

[c] Center for Uterine Cancer, National Cancer Center, Goyang, Republic Korea

Correspondence to:

Yukiharu Todo

Division of Gynecologic Oncology, National Hospital Organization,

Hokkaido Cancer Center, 4-2 Kikusui, Shiroishi-ku, Sapporo 003-0804, Japan

Telephone: +81-11-811-9111; Fax: +81-11-811-9180

E-mail: yukiharu@sap-cc.go.jp

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Running title

Tailoring lymphadenectomy in endometrial cancer

Abstract

It has been strongly suggested that patients with endometrial cancer with low risk of lymph node metastasis do not benefit from lymphadenectomy and intermediate-risk/high-risk endometrial cancer patients benefit from complete pelvic and para-aortic lymphadenectomy. This hypothesis needs to be validated by prospective studies. For randomized controlled trials (RCTs), heterogeneity of intervention compromises internal validity and non-participation of experienced doctors compromises external validity. As these situations easily occur in randomized surgical trials (RSTs) intended for high-risk patients, the effects of complicated surgery, such as full lymphadenectomy, might be underestimated in RSTs. In a famous RST, data for all eligible patients implied that survival outcome for the non-randomized group was significantly better than for the randomized group. One of plausible explanations is that physicians' judgement and experience produce better treatment decisions than do random choices. Although two RCTs from European countries showed negative results of lymphadenectomy on prognosis, valuing the care of individual patients may be more important than uncritically adopting the results of RCTs. In endometrial cancer, lymphadenectomy must be tailored to maximize the therapeutic effect of surgery and minimize its invasiveness and adverse effects. Two strategies are: (1) to remove lymph nodes most likely to harbor disease while sparing lymph nodes that are unlikely to be affected; and (2) to perform full lymphadenectomies only on patients who can potentially benefit from them. Here, we focus on the second strategy. Preoperative risk assessments used in Japan and Korea to select low-risk patients who would not benefit

from lymphadenectomy are discussed.

Reasons for tailor-made surgery

Traditional medicine has been conducted on the basis of disease concept, but the status of disease depends on each individual and the sensitive differences show their originality. It is well known that uniform treatment for patients with the same disease is not always appropriate. Although the term personalized medicine was coined in the context of genetics, this notion make sense also in the context of surgical therapy. In the evidence-based medicine era, results of randomized controlled trials (RCTs) tend to be uncritically accepted. In a famous RCT called the Emory Angioplasty versus Surgery Trial (EAST), the outcomes of percutaneous transluminal coronary angioplasty (PTCA) and coronary angioplasty bypass grafting (CABG) surgery were compared [1]. Of the 842 eligible patients, 392 (46.6%) agreed to participate, but 450 (53.4%) were not approached due to the attending or referring physician's refusal to participate (n = 353) or refusal by the patient (n = 97). Two interesting results were provided by EAST: (1) there was no survival difference between the PTCA group and the CABG group on the basis of data for 392 patients included in the trial and (2) survival outcome for the non-randomized group was significantly better than that for the randomized group on the basis of data for all 842 eligible patients [2]. Two plausible explanations can be provided to account for the result of the latter. One is that prognosis of patients in the non-randomized group may have been better than that of patients in the randomized group. The other is that physicians' judgement based on experience may be more important for treatment decision-making than a random choice. CABG generally tends to be performed for patients who have three-vessel disease or proximal left anterior

descending artery stenosis. Therefore, the right treatment may have been conducted in the right disease status on the basis of physicians' appropriate experience. Valuing the care of individual patients may be more important than uncritically adopting the results of RCTs.

Two reports in The Lancet [3,4] strongly suggest that pelvic lymphadenectomy (PLX) has no survival benefit for patients with endometrial cancer with low risk of lymph node metastasis and that combined pelvic and para-aortic lymphadenectomy (PLX+PALX) improves survival of patients with intermediate-risk/high-risk endometrial cancer. The former report was based on a randomized controlled trial by A Study in the Treatment of Endometrial Cancer (ASTEC), while the latter report was based on a retrospective cohort study. Some gynecologists seem to have been skeptical about the efficacy of lymphadenectomy in endometrial cancer based on the results of the ASTEC trial. Some physicians have believed that standard surgery for endometrial cancer does not include lymphadenectomy despite many previous reports suggested the efficacy of lymphadenectomy. Such an idea is an overgeneralization of the results of the ASTEC trial because the study population included only a small number of patients with high-risk endometrial cancer. If lymphadenectomy has a survival benefit for high-risk patients and lymphadenectomy is excluded from standard surgery in endometrial cancer, high-risk patients would not be able to receive optimal treatment. On the other hand, full lymphadenectomy was shown to have a survival benefit for patients with intermediate-risk/high-risk endometrial cancer in the Survival Effect of Para-aortic Lymphadenectomy (SEPAL) study [4]. Although omission of lymphadenectomy can be applied to patients with clinical stage I endometrial cancer according to the results of the ASTEC trial, clinical stage I includes not only low-risk

patients but also intermediate-risk and high-risk patients. The range of application for omission of lymphadenectomy should probably be limited to patients with low-risk endometrial cancer. Although the results of these two studies in The Lancet are referred to as contradictory statements, they can be compatible. We need to deepen discussions regarding tailoring of lymphadenectomy in endometrial cancer.

A problem inherent in surgical studies in high-risk cancer

The SEPAL study was based on a retrospective observational study [4]. Another observational study from the Mayo Clinic also showed the effectiveness of full lymphadenectomy for patients with high-risk endometrial cancer [5]. Some physicians have underestimated these results due to the study design inherent in a retrospective cohort study. However, the authors believe that study design is not grounds for underestimating the value of the SEPAL study. Well-designed cohort studies may in fact be more appropriate formats than RCTs for assessing optimal surgery in high-risk cases. Special difficulties are encountered in randomized surgical trials intended for high-risk patients. Some physicians would decline participation in a randomized controlled trial in which pelvic lymphadenectomy versus combined pelvic and para-aortic lymphadenectomy is compared for patients with high-risk endometrial cancer because they might be familiar with para-aortic lymphadenectomy and its benefits and would be reluctant to perform pelvic lymphadenectomy alone. Conversely, doctors with limited experience may be assigned the task of performing complicated surgery. However, they might not achieve the optimal desired outcome due to inadequate experience. Both scenarios create a situation where quality control of treatment might be reduced in the para-aortic lymphadenectomy group. The situation

easily occurs in randomized surgical trials intended for high-risk patients. It is generally accepted that RCTs are internally valid. However, non-participation of experienced doctors is a threat to external validity. Heterogeneity of intervention is also a threat to internal validity. Should we stick to randomized surgical trials intended for high-risk patients? A high risk group is not suitable for a randomized surgical trial. In my humble opinion, a prospective cohort study is an option for assessing the role of lymphadenectomy in high-risk EM cancer because it would promote homogeneity of surgical intervention.

There are two interesting reports published in the New England Journal of Medicine in which results of RCTs and those of well-designed observational studies on the same topics were compared [6-7]. Benson et al. reviewed 136 reports about 19 diverse treatments, such as calcium channel-blocker therapy for coronary artery disease, and hormone-replacement therapy for osteoporosis, and showed that well-designed observational studies and RCTs overall produce similar results [6]. Concato et al. reviewed 99 reports published in five major journals (Annals of Internal Medicine, the British Medical Journal, the Journal of Amerian Medical Association, the Lancet, and the New England Journal of Medicine) about five clinical topics and showed that results of RCTs are inconsistent in some series. In contrast, results of well-designed observational studies are mostly consistent [7]. In view of the reproducibility of study results, observational studies were superior. How can we account for these results? McKee et al. pointed out that RCTs have been conducted using very small groups and that subjects excluded from an RCT tend to have a poorer prognosis than that of subjects included in the trial [8]. RCTs definitely rank at the top of all types of clinical studies because they are internally valid. However, the results of RCTs are relevant to

just a definable group of patients in a particular setting. Therefore, results of RCTs cannot be easily overgeneralized.

Reasons for preoperative risk assessment in surgical studies

What should we do in order to maximize the therapeutic effect of surgery and minimize its invasiveness? Two strategies are: (1) to remove lymph nodes most likely to harbor disease and spare lymph nodes that are unlikely to be affected and (2) to allocate only patients with potential benefit from lymphadenectomy to full lymphadenectomy. The first strategy includes sentinel lymph node (SLN) mapping surgery [9-11] and circumflex iliac nodes distal to the external iliac nodes (CINDEIN)-sparing surgery [12-14]. The second strategy needs preoperative risk assessment. However, it has not been clarified which patients have potential benefit from lymphadenectomy. In this session, we focus on the second strategy. GOG #33 showed that there was no case with nodal metastasis in the low-risk group defined as having no myometrial invasion, grade 1 endometrioid histology, and no intraperitoneal disease [15]. Mariani et al. confirmed a low-risk group with grade 1 to 2 endometrioid histology, depth of invasion of $\leq$50%, and tumor size of $\leq$2 cm [16]. They concluded that lymphadenectomy does not benefit patients in the low-risk group (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 [17]. However, all of these criteria depend on surgicopathologic findings. There have been only a few studies that aimed to establish preoperative risk assessment for predicting lymph node metastasis in endometrial cancer [18-19]. The results of these studies are shown in Table 1. In 2007, Todo et al. proposed a low-risk group with grade 1 to 2 endometrioid histology by endometrial biopsy, volume index of

≤36 by MRI, and low CA125 level (70 U/ml for patients aged less than 50 years and 28 U/ml for patients aged 50 years or over) before surgery; only 2.1% of the patients in the group had lymph node metastasis at the assumed prevalence of nodal metastasis of 10% [18]. In 2012, Kang et al. confirmed a low-risk group with endometrioid histology by endometrial biopsy, <50% myometrial invasion with no extension beyond the corpus and no enlarged lymph nodes by MRI, and cancer antigen (CA)125 level ≤35 U/ml before surgery; only 1.3% of the patients in the group had lymph node metastasis when assuming that the prevalence of lymph node metastasis is 10% in the target patient cohort [19]. Since many physicians are not familiar with measuring tumor volume of endometrial cancer, volume index could not be easily used as a factor of preoperative risk assessment. On the other hand, myometrial invasion assessment by MRI has a problematic issue, namely, interobserver inconsistency or variability. MRI-based evaluation of deep myometrial invasion in a multi-institutional cooperative study showed sensitivity of 54% and specificity of 89%, indicating that results of previous single institutional studies might have been biased [20]. There would be some occasions where attending physicians have difficulty in judging myometrial invasion using MRI. Although each set of criteria have their merits and demerits, it is possible to reconcile these criteria. When it is difficult to judge myometrial invasion using MRI, volume index could be used as a substitute index. When planning a prospective clinical trial on the therapeutic significance of lymphadenectomy, an adequate population is needed to assess the full benefit of lymphadenectomy. If a population comprises a large proportion of low-risk patients, the significance of lymphadenectomy would be underestimated because low-risk patients do not benefit from lymphadenectomy.

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Table 1. Results of preoperative risk assessment for excluding lymph node metastasis in endometrial cancer

Author	Todo et al.		Kang et al.	
Journal	Gynecol Oncol (2007)		J Clin Oncol (2012)	
Study design	retrospective cohort study		retrospective cohort study	
Study aim	Model Derivation	Validation	Model Derivation	Validation
Cases (number)	214	211	360	180
Median age (range)	56 (23-80)	57 (24-77)	53 (29-76)	54 (31-82)
FIGO stage (1988)	I:68% II:5% III/IV:27% unknown:0%	I:64% II:8% III/IV:28% unknown:0%	I:71% II:7% III/IV:20% unknown:2%	I:76% II:5% III/IV:19% unknown:0%
Histological subtype	Endometrioid:97% Non-endometrioid:3%	Endometrioid:94% Non-endometrioid:6%	Endometrioid:94% Non-endometrioid:6%	Endometrioid:94% Non-endometrioid:6%
LNM (rate)	14.5%	17.1%	12.5%	12.8%
PANM (rate)	8.9%	12.3%	n/a	n/a
Number of lymph nodes harvested (median)	70	77	27	22
Para-aortic node dissection (rate)	99%	100%	61%	51%
Low risk criteria for LNM	Histologic subtype/grade (endometrial biopsy): endometrioid G1 or G2, Tumor volume (MRI): < 36㎤, CA125: < 70U/ml (less than 50 years),< 28U/ml (50years or over)		Histologic subtype (endometrial biopsy): Endometrioid, Myometrial invasion (MRI): < 1/2, Extension beyond uterine corpus (MRI): none, Lymph node size (MRI): < 1cm in short axis, CA125: < 35U/ml	
Proportion of patients in the low-risk group	54%	45%	53%	43%
LNM (false-negative) rate in the low-risk group	3.6%	3.2%	1.7%	1.4%
Bayesian-adjusted LNM (false-negative) rate in the low-risk group #	2.5%	1.9%	1.4%	1.1%

LNM: lymph node metastasis, PANM: para-aortic node metastasis, , #: adjusted rate at the prevalence of nodal metastasis of 10%.

Figure 1. Results of preoperative risk assessment for excluding lymph node metastasis in endometrial cancer