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Invited review

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

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Conflict of interest statement

The author declares no conflicts of interest.

Running title

25 Tailoring lymphadenectomy in endometrial cancer

26

27 **Abstract**

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

49 from lymphadenectomy are discussed.

50

51 **Reasons for tailor-made surgery**

52 Traditional medicine has been conducted on the basis of disease concept, but
53 the status of disease depends on each individual and the sensitive differences show their
54 originality. It is well known that uniform treatment for patients with the same disease is
55 not always appropriate. Although the term personalized medicine was coined in the
56 context of genetics, this notion make sense also in the context of surgical therapy. In the
57 evidence-based medicine era, results of randomized controlled trials (RCTs) tend to be
58 uncritically accepted. In a famous RCT called the Emory Angioplasty versus Surgery
59 Trial (EAST), the outcomes of percutaneous transluminal coronary angioplasty (PTCA)
60 and coronary angioplasty bypass grafting (CABG) surgery were compared [1]. Of the
61 842 eligible patients, 392 (46.6%) agreed to participate, but 450 (53.4%) were not
62 approached due to the attending or referring physician's refusal to participate (n = 353)
63 or refusal by the patient (n = 97). Two interesting results were provided by EAST: (1)
64 there was no survival difference between the PTCA group and the CABG group on the
65 basis of data for 392 patients included in the trial and (2) survival outcome for the
66 non-randomized group was significantly better than that for the randomized group on
67 the basis of data for all 842 eligible patients [2]. Two plausible explanations can be
68 provided to account for the result of the latter. One is that prognosis of patients in the
69 non-randomized group may have been better than that of patients in the randomized
70 group. The other is that physicians' judgement based on experience may be more
71 important for treatment decision-making than a random choice. CABG generally tends
72 to be performed for patients who have three-vessel disease or proximal left anterior

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

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

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

102

103 **A problem inherent in surgical studies in high-risk cancer**

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

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

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

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

147

148 **Reasons for preoperative risk assessment in surgical studies**

149 What should we do in order to maximize the therapeutic effect of surgery and minimize
150 its invasiveness? Two strategies are: (1) to remove lymph nodes most likely to harbor
151 disease and spare lymph nodes that are unlikely to be affected and (2) to allocate only
152 patients with potential benefit from lymphadenectomy to full lymphadenectomy. The
153 first strategy includes sentinel lymph node (SLN) mapping surgery [9-11] and
154 circumflex iliac nodes distal to the external iliac nodes (CINDEIN)-sparing surgery
155 [12-14]. The second strategy needs preoperative risk assessment. However, it has not
156 been clarified which patients have potential benefit from lymphadenectomy. In this
157 session, we focus on the second strategy. GOG #33 showed that there was no case with
158 nodal metastasis in the low-risk group defined as having no myometrial invasion, grade
159 1 endometrioid histology, and no intraperitoneal disease [15]. Mariani et al. confirmed a
160 low-risk group with grade 1 to 2 endometrioid histology, depth of invasion of $\leq 50\%$,
161 and tumor size of ≤ 2 cm [16]. They concluded that lymphadenectomy does not benefit
162 patients in the low-risk group (so-called Mayo criteria). Milam et al. also demonstrated
163 that these criteria led to a rate of nodal metastasis of only 0.8% in the low-risk group of
164 the Mayo criteria [17]. However, all of these criteria depend on surgicopathologic
165 findings. There have been only a few studies that aimed to establish preoperative risk
166 assessment for predicting lymph node metastasis in endometrial cancer [18-19]. The
167 results of these studies are shown in Table 1. In 2007, Todo et al. proposed a low-risk
168 group with grade 1 to 2 endometrioid histology by endometrial biopsy, volume index of

169 ≤ 36 by MRI, and low CA125 level (70 U/ml for patients aged less than 50 years and 28
170 U/ml for patients aged 50 years or over) before surgery; only 2.1% of the patients in the
171 group had lymph node metastasis at the assumed prevalence of nodal metastasis of 10%
172 [18]. In 2012, Kang et al. confirmed a low-risk group with endometrioid histology by
173 endometrial biopsy, $< 50\%$ myometrial invasion with no extension beyond the corpus
174 and no enlarged lymph nodes by MRI, and cancer antigen (CA)125 level ≤ 35 U/ml
175 before surgery; only 1.3% of the patients in the group had lymph node metastasis when
176 assuming that the prevalence of lymph node metastasis is 10% in the target patient
177 cohort [19]. Since many physicians are not familiar with measuring tumor volume of
178 endometrial cancer, volume index could not be easily used as a factor of preoperative
179 risk assessment. On the other hand, myometrial invasion assessment by MRI has a
180 problematic issue, namely, interobserver inconsistency or variability. MRI-based
181 evaluation of deep myometrial invasion in a multi-institutional cooperative study
182 showed sensitivity of 54% and specificity of 89%, indicating that results of previous
183 single institutional studies might have been biased [20]. There would be some occasions
184 where attending physicians have difficulty in judging myometrial invasion using MRI.
185 Although each set of criteria have their merits and demerits, it is possible to reconcile
186 these criteria. When it is difficult to judge myometrial invasion using MRI, volume
187 index could be used as a substitute index. When planning a prospective clinical trial on
188 the therapeutic significance of lymphadenectomy, an adequate population is needed to
189 assess the full benefit of lymphadenectomy. If a population comprises a large proportion
190 of low-risk patients, the significance of lymphadenectomy would be underestimated
191 because low-risk patients do not benefit from lymphadenectomy.

192

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260

261 Table 1. Results of preoperative risk assessment for excluding lymph node metastasis in
 262 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) : < 36cm ³ , 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