Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis

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Summary

Background In response to findings that pelvic lymphadenectomy does not have any therapeutic benefit for endometrial cancer, we aimed to establish whether complete, systematic lymphadenectomy, including the para-aortic lymph nodes, should be part of surgical therapy for patients at intermediate and high risk of recurrence.

Methods We selected 671 patients with endometrial carcinoma who had been treated with complete, systematic pelvic lymphadenectomy (n=325 patients) or combined pelvic and para-aortic lymphadenectomy (n=346) at two tertiary centres in Japan (January, 1986–June, 2004). Patients at intermediate or high risk of recurrence were offered adjuvant radiotherapy or chemotherapy. The primary outcome measure was overall survival.

Findings Overall survival was significantly longer in the pelvic and para-aortic lymphadenectomy group than in the pelvic lymphadenectomy group (HR 0·53, 95% CI 0·38–0·76; p=0·0005). This association was also recorded in 407 patients at intermediate or high risk (p=0·0009), but overall survival was not related to lymphadenectomy type in low-risk patients. Multivariate analysis of prognostic factors showed that in patients with intermediate or high risk of recurrence, pelvic and para-aortic lymphadenectomy reduced the risk of death compared with pelvic lymphadenectomy (0·44, 0·30–0·64; p<0·0001). Analysis of 328 patients with intermediate or high risk who were treated with adjuvant radiotherapy or chemotherapy showed that patient survival improved with pelvic and para-aortic lymphadenectomy (0·48, 0·29–0·83; p=0·0049) and with adjuvant chemotherapy (0·59, 0·37–1·00; p=0·0465) independently of one another.

Interpretation Combined pelvic and para-aortic lymphadenectomy is recommended as treatment for patients with endometrial carcinoma of intermediate or high risk of recurrence. If a prospective randomised or comparative cohort study is planned to validate the therapeutic effect of lymphadenectomy, it should include both pelvic and para-aortic lymphadenectomy in patients of intermediate or high risk of recurrence.

Funding Japanese Foundation for Multidisciplinary Treatment of Cancer, and the Japan Society for the Promotion of Science.

Lancet 2010; 375: 1165–72

Published Online February 25, 2010 DOI:10.1016/S0140-6736(09)62002-X

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Introduction

Systematic lymphadenectomy is often part of surgical staging of endometrial carcinoma. However, this procedure is not done universally. Findings from a US study showed that compared with gynaecologists, gynaecological oncologists do lymph node dissection with increased frequency (26% *vs* 83%) and intensity (average of 7·7 *vs* 19·5 lymph nodes).[1] In a Japanese survey, 97·8% of member institutions of the Japanese Gynecologic Oncology Group routinely did pelvic lymphadenectomy, and 73·3% did para-aortic lymphadenectomy either routinely (8·6%) or selectively (64·7%) based on tumour-related factors.[2] In the UK, however, lymphadenectomy is not a common procedure.[3]

The therapeutic effects of lymphadenectomy are an issue of great debate. Findings from two large prospective randomised trials of pelvic lymphadenectomy failed to show any therapeutic benefits.[4,5] However, these studies were limited by the short duration of follow-up, use of small-scale and selective lymphadenectomy, and the absence of para-aortic lymphadenectomy, all of which hinder drawing of definite conclusions about the therapeutic role of lymphadenectomy.

In view of these limitations, we compared two cohorts of patients receiving either pelvic lymphadenectomy or combined pelvic and para-aortic lymphadenectomy for endometrial cancer in the Survival Effect of Para-Aortic Lymphadenectomy (SEPAL) study.

Methods

Patients

We searched for patients with endometrial carcinoma who were treated between January, 1986, and June, 2004, from the gynaecological tumour registries in two tertiary centres in Japan: Hokkaido University Hospital (Department of Gynaecology) and Hokkaido Cancer Centre (Division of Gynaecologic Oncology). Patients were excluded if they had uterine sarcoma, carcinosarcoma, or concurrent primary ovarian cancer; or had not undergone lymphadenectomy or surgery. This study was approved by the institutional review boards at each treatment centre, and the report was prepared in accordance with the STROBE statement.[6]

	Tumour type	Lymph-vascular space invasion
Low risk		
FIGO stage IA	Grade 1–2 endometrioid adenocarcinoma	Negative
FIGO stage IB	Grade 1–2 endometrioid adenocarcinoma	Negative
Intermediate risk		
FIGO stage IA	Grade 3 endometrioid adenocarcinoma; any grade of non-endometrioid carcinoma (serous adenocarcinoma, clear cell adenocarcinoma, or other type of carcinoma)	Any
FIGO stage IB	Grade 1–2 endometrioid adenocarcinoma	Positive
FIGO stage IB	Grade 3 endometrioid adenocarcinoma; any grade of non-endometrioid carcinoma (serous adenocarcinoma, clear cell adenocarcinoma, or other type of carcinoma)	Any
FIGO stage IC	Any	Any
FIGO stage II	Any	Any
High risk		
FIGO stage III	Any	Any
FIGO stage IV	Any	Any

FIGO=International Federation of Gynecology and Obstetrics.

Table 1: **Categorisation of risk of recurrence in endometrial cancer**

Written informed consent was obtained from all patients before treatment.

Procedures

In this report, type of lymphadenectomy refers to the target area (pelvic alone *vs* combined pelvic and para-aortic), and whether the technique was used routinely for all patients or selectively for some. Intensity of lymphadenectomy indicates the thoroughness of removal of target lymph nodes and the extent of dissection: systematic dissection of all regional lymph nodes versus selective dissection of parts of regional lymph nodes; and complete dissection versus sampling dissection. In Hokkaido University Hospital, complete, systematic pelvic and para-aortic lymphadenectomy was done routinely. In Hokkaido Cancer Centre, complete, systematic pelvic lymphadenectomy alone was done routinely. Systematic pelvic lymphadenectomy included resection of the internal iliac nodes, external iliac nodes, medial deep inguinal nodes, lateral deep inguinal nodes, obturator nodes, sacral nodes, and common iliac nodes. Para-aortic lymphadenectomy included systematic resection of all nodes from the precaval, laterocaval, interaortocaval, preaortic, and lateroaortic areas up to the renal veins.

Recurrent risk is related to depth of myometrial invasion, tumour grade, histological subtype, and lymph-vascular space invasion in clinically proven early stage endometrial cancer.[7–10] In this study, categorisation of risk grouping was based on International Federation of Gynecology and Obstetrics (FIGO) stage, tumour grade, histological subtype, and lymph-vascular space invasion. Patients with disease of FIGO stages III and IV were classified as high risk, those with FIGO stages IA and IB with grade 1–2 endometrioid adenocarcinoma and no lymph-vascular space invasion

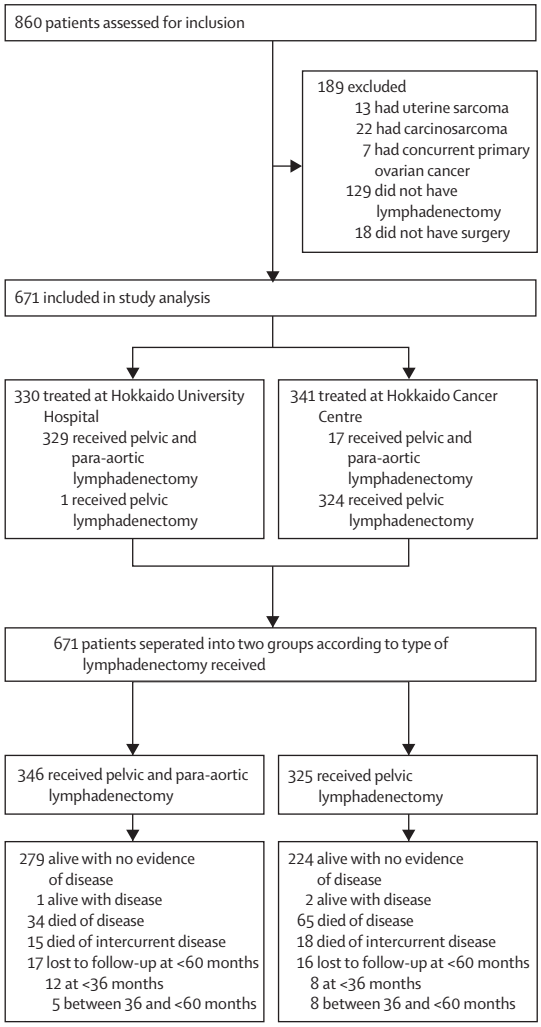

Figure 1: **Study design**

were classified as low risk, and all other tumours were classified as intermediate risk (table 1). Patients of intermediate or high risk were offered adjuvant radiotherapy or chemotherapy. Radiotherapy was done with whole pelvic external beam radiation (50 Gy in 25 fractions), and chemotherapy consisted of a cisplatin-based regimen for four to six cycles. In Hokkaido University Hospital, adjuvant therapy was limited to chemotherapy, whereas in Hokkaido Cancer Centre, patients could have radiotherapy or chemotherapy, dependent on patient preference and physician discretion.

The primary outcome measure was overall survival, defined as the time from surgery to death from any cause. Secondary endpoints were disease-specific and recurrence-free survival. Disease-specific survival was defined as the time from surgery to death from endometrial carcinoma or death due to treatment; patients known to be alive or lost to follow-up at the time of analysis were censored at

their last follow-up. Recurrence-free survival was defined as the time from surgery to first evidence of recurrent disease or death from any cause; patients known to be alive without recurrent disease or lost to follow-up at the time of analysis were censored at the time of their last follow-up.

Statistical analysis

Correlation of variables was assessed with Fisher's exact test, χ^2 test, and Mann-Whitney *U* test. Survival rates were estimated by Kaplan-Meier analysis. The log-rank test was used to compare survival curves. Cox regression analysis was used to select the risk factors for prognosis with hazard ratios (HRs). We regarded p values of less than 0·05 to be significant. For several comparisons of survival curves between subgroups of patients, we applied Bonferroni's correction. Statistical analyses were done with StatView J (version 5.0).

Role of the funding source

The study sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. NS had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the number of patients assessed at every stage in the study. 860 patients with malignant tumours of the uterine corpus had been treated at one of two tertiary centres, of whom 671 were eligible for analysis in the study. Table 2 shows the clinical and pathological characteristics of eligible patients. Median age of the group was 56 years (IQR 51–62), and mean age was 56·2 years (SD 9·2). No significant differences were recorded in the distribution of the variables, except for the number of lymph nodes removed and the use of radiotherapy versus chemotherapy. A significant difference was recorded between the two treatment groups of patients who died of disease (p=0·0002), but not for patients who died of intercurrent disease (p=0·47) or were lost to follow-up before 60 months (p=0·99).

Cox regression analysis for all patients included in the study showed that overall survival in the pelvic and para-aortic lymphadenectomy group was significantly longer than in the pelvic lymphadenectomy group (figure 2). The survival effect of type of lymphadenectomy in relation to recurrent risk is a common concern among gynaecological oncologists. Overall, 264 (39%) patients were at low risk of recurrence and 407 (61%) were at intermediate or high risk (table 2). Table 3 shows the clinical and pathological characteristics of patients with intermediate or high risk of recurrence. The distribution of important prognostic factors did not differ significantly between the pelvic and para-aortic lymphadenectomy group and the pelvic lymphadenectomy group.

We did further Kaplan-Meier analysis of survival with patients in the two treatment groups separated into two subgroups of low risk and intermediate or high risk of recurrence (figure 3). For patients with intermediate or high risk, 77% (165/213) in the pelvic and para-aortic lymphadenectomy group and 84% (163/194) in the pelvic lymphadenectomy group received adjuvant therapy (p=0·10). No significant differences were recorded between the treatment groups for overall, disease-specific, and recurrence-free survival for patients at low risk of recurrence. However, for patients at intermediate or high risk of recurrence, overall, disease-specific, and recurrence-free survival was significantly longer in the pelvic and para-aortic lymphadenectomy group than in the pelvic lymphadenectomy group (overall survival

	Pelvic lymphadenectomy (n=325)	Pelvic and para-aortic lymhadenectomy (n=346)	p value
Age (years)	57 (56–62); 56·3 (9·2)	56 (51–62); 56·0 (9·2)	..
FIGO surgical stage*			0·22
IA	54 (17%)	37 (11%)	..
IB	114 (35%)	126 (36%)	..
IC	51 (16%)	57 (16%)	..
IIA	15 (5%)	11 (3%)	..
IIB	21 (6%)	18 (5%)	..
IIIA	20 (6%)	32 (9%)	..
IIIC	39 (12%)	54 (16%)	..
IV	11 (3%)	11 (3%)	..
Tumour type			0·12†
Grade 1 endometrioid adenocarcinoma	188 (58%)	160 (46%)	..
Grade 2 endometrioid adenocarcinoma	69 (21%)	96 (28%)	..
Grade 3 endometrioid adenocarcinoma	41 (13%)	62 (18%)	..
Serous adenocarcinoma	17 (5%)	18 (5%)	..
Clear cell adenocarcinoma	4 (1%)	7 (2%)	..
Other carcinoma	6 (2%)	3 (1%)	..
Lymph node metastasis			0·19
Negative	279 (86%)	284 (82%)	..
Positive	46 (14%)	62 (18%)	..
Risk of recurrence			0·14
Low	131 (40%)	133 (38%)	..
Intermediate	124 (38%)	116 (34%)	..
High	70 (22%)	97 (28%)	..
Adjuvant therapy			0·52‡; <0·0001§
None	162 (50%)	181 (52%)	..
Radiotherapy	75 (23%)	2 (1%)	..
Chemotherapy	88 (27%)	163 (47%)	..
Lymph nodes removed			<0·0001
Pelvic nodes	34 (21–42)	59 (46–73)	..
Para-aortic nodes	0 (0–0)	23 (16–30)	..
Follow-up period	94 (66–131)	91 (60–129)	0·66

Data are median (IQR), mean (SD), or number (%). FIGO=International Federation of Gynecology and Obstetrics. ..=data not calculated. *No patients had stage IIIB tumour. †For grade 1–2 endometrioid adenocarcinoma versus grade 3 endometrioid adenocarcinoma and non-endometrioid carcinoma (serous adenocarcinoma, clear cell adenocarcinoma, and other types of carcinoma). ‡For adjuvant therapy done versus not done. §For adjuvant radiotherapy versus chemotherapy.

Table 2: **Clinical and pathological characteristics of patients with endometrial carcinoma**

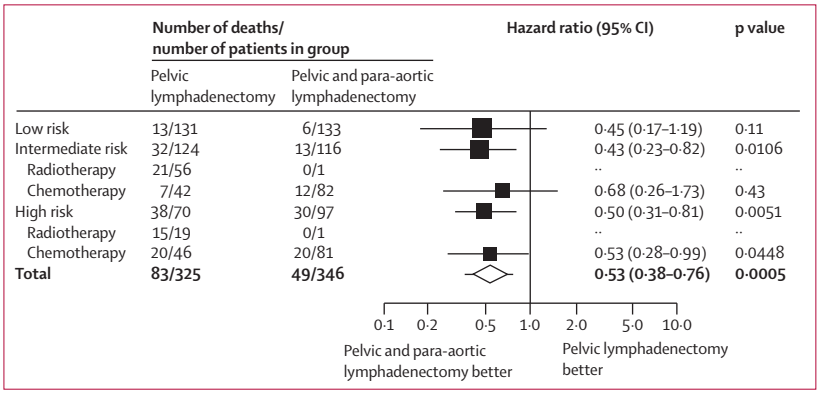

Figure 2: **Cox regression analysis of overall survival with pelvic and para-aortic lymphadenectomy compared with pelvic lymphadenectomy alone according to risk of recurrence**
··=data not available.

p=0·0009, disease-specific survival p=0·0004, recurrence-free survival p<0·0001; figure 3 and table 4). For overall, disease-specific, and recurrence-free survival, the difference was significant even after Bonferroni's correction, which meant that p values of less than 0·0083 were judged to be significant. In intermediate-risk and high risk patients, pelvic and para-aortic lymphadenectomy added a 10·6% increase in 5-year overall survival compared with pelvic lymphadenectomy (figure 3 and table 4).

Cox regression analysis showed that the survival effect of para-aortic lymphadenectomy was significantly related to risk of recurrence; the strongest improvement was recorded in high-risk patients (figure 2). Subgroup analysis of survival according to type of adjuvant therapy, in patients at intermediate or high risk, was not possible in patients receiving radiotherapy because few patients were included from the pelvic and para-aortic lymphadenectomy group (figure 2). However, in the chemotherapy group, survival of high-risk patients was significantly improved by pelvic and para-aortic lymphadenectomy compared with pelvic lymphadenectomy alone, but this effect was not shown in intermediate-risk patients (figure 2).

In patients at intermediate or high risk, multivariate analysis confirmed that age, tumour type, lymph node metastasis, and type of lymphadenectomy were independently related to survival (table 5). Pelvic and para-aortic lymphadenectomy was associated with significantly lower mortality than was pelvic lymphadenectomy alone.

Type of adjuvant treatment differed substantially across treatment groups, with use of radiotherapy especially low in the pelvic and para-aortic lymphadenectomy group (table 6). However, to avoid any bias caused by exclusion of patients treated with radiotherapy, we did multivariate Cox regression analysis on all patients of intermediate or high risk who received adjuvant therapy (table 7). Pelvic and para-aortic lymphadenectomy and adjuvant chemotherapy were independently and significantly associated with improved survival (table 7).

	Pelvic lymph-adenectomy (n=194)	Pelvic and para-aortic lymhadenectomy (n=213)	p value
Age (years)	57 (52–62); 56·5 (9·8)	57 (52–64); 57·1 (9·3)	..
FIGO surgical stage*			0·45
IA	9 (5%)	5 (2%)	..
IB	28 (14%)	25 (12%)	..
IC	51 (26%)	57 (27%)	..
IIA	15 (8%)	11 (5%)	..
IIB	21 (11%)	18 (8%)	..
IIIA	20 (10%)	32 (15%)	..
IIIC	39 (20%)	54 (25%)	..
IV	11 (6%)	11 (5%)	..
Tumour type			0·14†
Grade 1 endometrioid adenocarcinoma	79 (41%)	67 (31%)	..
Grade 2 endometrioid adenocarcinoma	47 (24%)	56 (26%)	..
Grade 3 endometrioid adenocarcinoma	41 (21%)	62 (29%)	..
Serous adenocarcinoma	17 (9%)	18 (8%)	..
Clear cell adenocarcinoma	4 (2%)	7 (3%)	..
Other carcinoma	6 (3%)	3 (1%)	..
Myometrial invasion			0·56
<1–2	83 (43%)	85 (40%)	..
≥1–2	111 (57%)	128 (60%)	..
Cervical involvement			0·77
Negative	134 (69%)	150 (70%)	..
Positive	60 (31%)	63 (30%)	..
Adnexal metastasis			0·08
Negative	172 (89%)	176 (83%)	..
Positive	22 (11%)	37 (17%)	..
Lymph node metastasis			0·22
Negative	148 (76%)	151 (71%)	..
Positive	46 (24%)	62 (29%)	..
Adjuvant therapy			0·10‡; <0·0001§
None	31 (16%)	48 (23%)	..
Radiotherapy	75 (39%)	2 (1%)	..
Chemotherapy	88 (45%)	163 (77%)	..

Data are median (IQR), mean (SD), or number (%). FIGO=International Federation of Gynecology and Obstetrics. *No patients had stage IIIB tumour. †For grade 1–2 endometrioid adenocarcinoma versus grade 3 endometrioid adenocarcinoma and non-endometrioid carcinoma (serous adenocarcinoma, clear cell adenocarcinoma, and other types of carcinoma). ‡For adjuvant therapy done versus not done. §For adjuvant radiotherapy versus chemotherapy.

Table 3: **Clinical and pathological characteristics of patients with endometrial carcinoma of intermediate or high risk of recurrence**

We investigated the pattern of recurrence in 657 patients who had no residual tumour at the end of surgery. The intrapelvic recurrence rate did not differ significantly between the pelvic and para-aortic lymphadenectomy group (10/341, 3%) and the pelvic lymphadenectomy group (15/316, 5%; p=0·23). By

contrast, the extrapelvic recurrence rate in the pelvic and para-aortic lymphadenectomy group (21/341, 6%) was significantly lower than in the pelvic lymphadenectomy group (51/316, 16%; p<0·0001). Recurrence in the para-aortic node region was also significantly lower in the pelvic and para-aortic lymphadenectomy group (2/341, 1%) than in the pelvic lymphadenectomy group (16/316, 5%; p=0·0004).

Discussion

Findings from the SEPAL study have shown that para-aortic lymphadenectomy has survival benefits for patients at intermediate or high risk of recurrence, and that pelvic lymphadenectomy alone might be an insufficient surgical procedure for endometrial cancer in patients at risk of lymph node metastasis. The results also suggest that adjuvant chemotherapy could further improve survival of patients at high risk of lymph node metastasis.

The therapeutic significance of combined pelvic and para-aortic lymphadenectomy for patients with endometrial cancer is a matter of great debate.[11,12] However, few studies have investigated the therapeutic role of para-aortic lymphadenectomy.[13–15] Our study aimed to address the limitations of two large trials of pelvic lymphadenectomy: the ASTEC trial[4] and Benedetti-Panici and colleagues' study[5] in Italy. First, in the ASTEC trial, the follow-up period was short (median of 37 months, with 35·7% of surviving patients followed up for less than 3 years), and lymphadenectomy was selective rather than systematic. Nine or fewer lymph nodes were removed in 35% of patients in the lymphadenectomy group, despite the fact that removal of at least ten pelvic nodes has been shown to be needed for an improved effect on survival.[13,16,17] Second, neither study included para-aortic lymphadenectomy, which would have negated the therapeutic effect of lymphadenectomy because more than half of patients with pelvic lymph node metastasis have para-aortic node metastasis.[18,19] Last, Benedetti-Panici and colleagues' study did not consider risk of recurrence in the analysis. Similar to the ASTEC trial, our results have suggested that the survival effect of lymphadenectomy is restricted in low-risk patients; however, in patients of intermediate or high risk, complete, systematic lymphadenectomy in both the pelvic and para-aortic regions has substantial therapeutic effects.

In restriction of the institutes participating in our study to two tertiary hospitals treating gynaecological cancers, we were able to standardise surgical method to provide a good comparison of surgical effect on survival. Patients were treated concurrently according to an almost identical protocol, except for type of lymphadenectomy. We recorded no difference in distribution of disease stage, tumour type, risk of recurrence, or use of adjuvant therapy between the two cohorts. Therefore, analysis bias was kept to a minimum even though the study was not a randomised controlled trial. We used complete, systematic lymphadenectomy, not selective, sampling

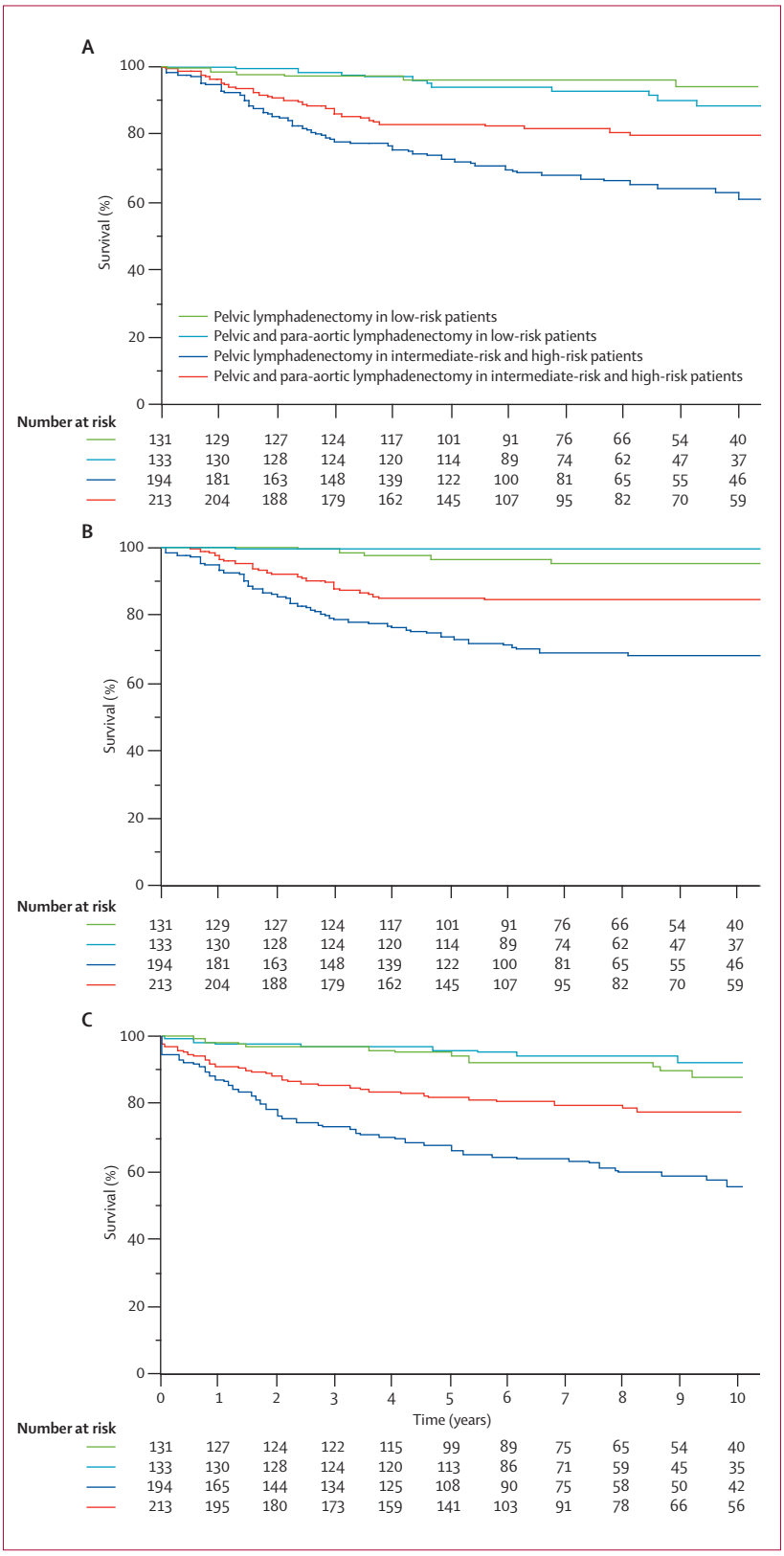

Figure 3: **Kaplan-Meier analysis of overall (A), disease-specific (B), and recurrence-free (C) survival for patients with endometrial carcinoma according to type of lymphadenectomy and risk of recurrence**

	Low risk		Intermediate or high risk	
	Pelvic lymph-adenectomy (n=131)	Pelvic and para-aortic lymphadenectomy (n=133)	Pelvic lymph-adenectomy (n=194)	Pelvic and para-aortic lymphadenectomy (n=213)
Overall survival				
Died	13 (10%)	6 (5%)	70 (36%)	43 (20%)
3 years	98·4%	97·0%	78·1%	86·2%
5 years	94·2%	96·2%	72·6%	83·2%
8 years	93·1%	96·2%	66·0%	79·8%
Disease-specific survival				
Died	5 (4%)	1 (1%)	60 (31%)	33 (15%)
3 years	99·2%	99·2%	78·6%	87·9%
5 years	96·7%	99·2%	73·0%	84·9%
8 years	95·5%	99·2%	68·8%	84·1%
Recurrence-free survival				
Relapsed or died	14 (11%)	8 (6%)	80 (41%)	46 (22%)
3 years	96·9%	97·0%	70·9%	84·4%
5 years	92·7%	95·3%	64·8%	80·7%
8 years	92·7%	94·4%	59·7%	79·0%

Data are number of patients (%) or percentage survival. Numbers of patients were recorded at least 5 years after treatment completion. Percentage survival at 3 years, 5 years, and 8 years was estimated by Kaplan-Meier analysis (figure 3).

Table 4: **Overall, disease-specific, and recurrence-free survival of patients with endometrial carcinoma according to type of lymphadenectomy and risk of recurrence**

	Hazard ratio (95% CI)	p value
Age-group (years)		
≤56	1·00	..
>56	1·81 (1·23–2·67)	0·0028
Tumour type		
Grade 1–2 endometrioid adenocarcinoma	1·00	..
Grade 3 endometrioid adenocarcinoma and non-endometrioid carcinoma	1·87 (1·29–2·70)	0·0010
Lymph node metastasis		
Negative	1·00	..
Positive	3·07 (2·10–4·46)	<0·0001
Type of lymphadenectomy		
Pelvic	1·00	..
Pelvic and para-aortic	0·44 (0·30–0·64)	<0·0001

Table 5: **Multivariate analysis of prognostic factors in overall survival for patients with endometrial carcinoma of intermediate or high risk of recurrence (n=407)**

	None	Radiotherapy	Chemotherapy
Intermediate risk (n=240)			
Pelvic lymphadenectomy (n=124)	26 (21%)	56 (45%)	42 (34%)
Pelvic and para-aortic lymphadenectomy (n=116)	33 (28%)	1 (1%)	82 (71%)
High risk (n=167)			
Pelvic lymphadenectomy (n=70)	5 (7%)	19 (27%)	46 (66%)
Pelvic and para-aortic lymphadenectomy (n=97)	15 (15%)	1 (1%)	81 (84%)

Data are number (%).

Table 6: **Distribution of adjuvant therapy across patients with endometrial carcinoma of intermediate or high risk of recurrence**

lymph node dissection, to obtain complete removal of lymph nodes that had or could have had endometrial carcinoma metastasis. Such lymphadenectomy is needed to ensure complete tumour eradication in the lymph nodes, and improve survival in patients at high risk of lymph node metastasis. The study also benefited from a large patient population, with few (<5%) lost to follow-up, and a long follow-up period (median >90 months).

Findings from several studies have suggested that the therapeutic effect of pelvic[13,16] and para-aortic lymphadenectomy[15] depends on risk of recurrence. More than half of patients with pelvic lymph node metastasis have para-aortic lymph node metastasis, and about 10% of lymph node metastases occur exclusively in the para-aortic region.[18,19] Furthermore, from sentinel lymph node investigation, the para-aortic region has been shown to be a important site of sentinel nodes in endometrial cancer, with 47% of para-aortic sentinel nodes located above the inferior mesenteric artery.[20] Therefore, both pelvic and para-aortic lymph nodes must be removed to eradicate microscopic and macroscopic tumour involvement, and achieve sufficient therapeutic effect in patients at risk of lymph node metastasis. Removal of the para-aortic lymph nodes could explain the significant survival effect of para-aortic lymphadenectomy in endometrial carcinoma of intermediate or high risk. We recorded a reduced occurrence of both extrapelvic and para-aortic node recurrence in patients who underwent pelvic and para-aortic lymphadenectomy, which suggests that para-aortic lymphadenectomy was effective for eradication of subclinical para-aortic node metastasis.

Moreover, adjuvant chemotherapy, which was used most frequently in the pelvic and para-aortic lymphadenectomy group, might have had a therapeutic effect on occult metastasis in distant organs. Multivariate analysis showed that para-aortic lymphadenectomy and adjuvant chemotherapy was associated with improved survival in patients at high risk of recurrence. This effect corresponds with the Japanese Gynecologic Oncology Group study,[21] in which a subgroup analysis in the group with high-intermediate risk showed that chemotherapy was related to improved survival. However, the survival effect of chemotherapy was not shown in high-risk patients. Maggi and colleagues[22] reported similar survival outcomes after adjuvant chemotherapy and radiotherapy for patients with high-risk endometrial cancer: chemotherapy seemed to prevent or delay distant relapses, and radiotherapy tended to prevent or delay local relapses. Randall and colleagues[23] showed that chemotherapy results in superior progression-free and overall survival compared with whole abdominal radiotherapy in FIGO stage III or IV disease. Future studies might need to incorporate para-aortic lymphadenectomy and adjuvant chemotherapy to establish the optimum therapy for patients.

Our study of adjuvant therapy was limited by the lack of uniformity in the type of therapy used. The two institutes had different protocols for use of adjuvant

	Hazard ratio (95% CI)	p value
Age-group (years)		
≤56	1·00	..
>56	1·93 (1·26–2·97)	0·0024
Tumour type		
Grade 1–2 endometrioid adenocarcinoma	1·00	..
Grade 3 endometrioid adenocarcinoma and non-endometrioid carcinoma	2·05 (1·36–3·09)	0·0006
Lymph node metastasis		
Negative	1·00	..
Positive	2·56 (1·68–3·89)	<0·0001
Type of lymphadenectomy		
Pelvic	1·00	..
Pelvic and para-aortic	0·48 (0·29–0·83)	0·0049
Adjuvant therapy		
Radiotherapy	1·00	..
Chemotherapy	0·59 (0·37–1·00)	0·0465

Table 7: **Multivariate analysis of prognostic factors in overall survival for patients with intermediate-risk or high-risk endometrial carcinoma who were treated with adjuvant radiotherapy or chemotherapy (n=328)**

therapy—one used chemotherapy exclusively, and the other offered both chemotherapy and radiotherapy—and very few patients in the pelvic and para-aortic lymphadenectomy group received radiotherapy. Exclusion of patients who received adjuvant radiotherapy could have been an option for an alternative analysis. However, because each cohort was prospectively treated and followed up, we believed that exclusion of such patients could have brought some bias into the analysis.

Inclusion of only two tertiary centres in our study could mean that the benefit of para-aortic lymphadenectomy to survival could be related to the clustering effect of surgeries. The presence of such an effect suggests that surgeries for patients with endometrial cancer who are at risk of lymph node metastasis should be centralised at specialised hospitals and done by experienced gynaecological oncologists. A randomised trial, which would usually include many institutions, is judged to be the most reliable method to obtain strong evidence for the effectiveness of a treatment. However, in the specialty of surgical oncology, a randomised trial might need to incorporate specialised hospitals and well experienced surgeons.

Lymphadenectomy in the ASTEC trial[4] and Benedetti-Panici and colleagues' study[5] was not systematic, and did not remove important regional lymph nodes for endometrial cancer[24]—ie, para-aortic lymph nodes. The para-aortic region needs to be cleared of lymph nodes that harbour metastatic tumours to achieve the maximum therapeutic effect from lymphadenectomy, and we have shown that the combination of pelvic and para-aortic lymphadenectomy can significantly improve survival in patients at intermediate and high risk of recurrence.

Contributors
YT and NS contributed equally to the study design and writing of the report. HK, MK, HW, and MT contributed to collection of data. YT did the data analysis and search for published reports. NS did the data interpretation and prepared the figures.

Conflicts of interest
We declare that we have no conflicts of interest.

Acknowledgments
We thank Sharon Hanley, Japanese Red Cross Hokkaido College of Nursing, for English editing of the report. This study was partly supported by grants-in-aid for scientific research from the Japanese Foundation for Multidisciplinary Treatment of Cancer, and the Japan Society for the Promotion of Science.

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