Nippon Kayaku, and Ono Pharmaceutical. The other authors have no conflict of interest.

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Flexible hysteroscopy with narrow band imaging (NBI) for endoscopic diagnosis of malignant endometrial lesions

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Received October 14, 2010; Accepted December 3, 2010

DOI: 10.3892/ijo.2011.903

Abstract. Narrow band imaging (NBI) for detection of blood vessels and microstructures on the mucosal surface is used in gastrointestinal endoscopy since it can improve qualitative diagnosis and detection of lesion. However, there are no studies on flexible hysteroscopy using NBI. We performed flexible hysteroscopy with NBI for outpatients to investigate the sensitivity and specificity of endoscopic diagnosis of malignant endometrial lesions. Of patients who attended our hospital for suspected lesions in the uterine cavity between April 2009 and May 2010, 104 subjects underwent hysteroscopy with NBI, in addition to white light. Using the pathological diagnosis as the gold-standard, we evaluated the sensitivity and specificity of NBI hysteroscopy for detecting atypical endometrial hyperplasia (AEH) or carcinoma. The results were also compared with historical data (n=209) for conventional hysteroscopy using white light only in 2008. The sensitivities were 97.2% [95% confidence interval (95% CI): 90.3-99.7%] and 82.6% (95% CI: 74.4-89.0%) for NBI hysteroscopy and conventional hysteroscopy, respectively. The 95% CIs for the two methods did not overlap and the sensitivity of lesion detection was higher with NBI hysteroscopy. Specificities were comparable, 90.6% (95% CI: 75.0-98.0%) and 85.1% (95% CI: 76.3-91.6%) between the methods. NBI hysteroscopy has increased sensitivity for detection of atypical endometrial hyperplasia (AEH) or carcinoma. A comparison with historical data suggested that NBI may be useful for diagnosis of malignant endometrial lesions. As far as we are aware, this is the first evaluation of flexible hysteroscopy with NBI for diagnosis of malignant endometrial lesions.

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Key words: narrow band imaging, hysteroscopy, endometrial lesions

Introduction

Hysteroscopy. is an endoscopic examination of the uterine cavity using an endoscope for patients with suspected endometrial lesions and is used for patients with lesions detected by imaging, such as transvaginal ultrasonography, endometrial cytology or histology, and patients with hemorrhage, hypermenorrhea or infertility. Hysteroscopy has similar or better sensitivity than transvaginal ultrasonography, endometrial cytology or histology for detection of endometrial lesions (1-3). It is also useful for preoperative evaluation of lesions, identification of the occupation of tumors, or evaluation of the effect of high-dose medroxyprogesterone acetate (MPA) therapy. However, Lasmar *et al* have reported that the sensitivities of hysteroscopy for endometrial hyperplasia (EMH) and endometrial carcinoma are 56.3 and 80.0%, respectively (4). This suggests that diagnostic criteria based on morphological changes in an endometrial lesion are inadequate and a pathological examination is required for diagnosis of endometrial lesions.

Narrow band imaging (NBI) is an endoscopic imaging technology produced by shifting the light spectrum to a narrow band. NBI allows enhanced imaging of blood microvessels and microstructures in the surface layer. In the gastrointestinal field, NBI has contributed to improving qualitative diagnosis and detection of lesions (5). The visible light wavelength for humans is 400-700 nm, and different wavelengths appear as different colors. Light of 400 nm appears blue, that of 550 nm is green, and that of 600 nm is red, while light with a wide range of wavelengths of 400-700 nm appears white. In the NBI system, a filter inserted into the light path is positioned in front of a xenon lump, so that light of narrow bands at 415 and 540 nm reaches the mucosal surface. Oxidized hemoglobin in blood has an absorption spectrum with peaks at 415 and 540 nm, and absorbs most of the blue light emitted in the NBI system, resulting in blood vessels appearing as a dark green color. Other tissue scatters the light and appears as a bright color. Therefore, NBI distinguishes blood vessels in the mucosal surface from other tissue.

In this study, NBI was used in flexible hysteroscopy in outpatients for enabling visual identification of blood vessels with clear contrast. The objective of this study was to evaluate

the utility of NBI flexible hysteroscopy for endoscopic diagnosis of atypical endometrial hyperplasia (AEH) or endometrial carcinoma.

Patients and methods

Patients and procedures. The subjects were 104 patients with suspected endometrial lesions who were examined by NBI hysteroscopy in addition to conventional white light hysteroscopy from April 2009 to May 2010, and thereafter were pathologically diagnosed based on surgical specimens. The study was approved by the ethics committee of our hospital and was performed after obtaining the informed consent of the patients. Patients receiving high-dose MPA therapy and those with a history of this therapy were included in the study. Patients with a history of surgery including dilatation and curettage (D&C) and transcervical resection of the endometrium (TCRE), and those for whom hysteroscopy was required, were also included. Patients with voluminous genital hemorrhage, menstruation, possible pregnancy, endometritis and cervical neoplasia were excluded from the study.

Pathological diagnoses were made using specimens obtained in surgery, including D&C, TCRE, and hysterectomy. Based on these diagnoses, the cases were classified into four categories: benign lesion (normal endometrium, endometrial polyp, submucosal myoma, decidual change due to MPA therapy), EMH, AEH, and endometrial carcinoma. Endometrial lesions that did not fall into these categories were excluded. The sensitivity and specificity of hysteroscopy for diagnosis of AEH or endometrial carcinoma, for which high-dose MPA therapy or surgery are used, were examined for 104 subjects evaluated by NBI hysteroscopy from April 2009 to May 2010 and 209 subjects evaluated by white light hysteroscopy in 2008.

The instruments used in the study were a 3.1-mm flexible hysterofiberscope (HYF-XP) connected to a CCD digital camera (OTV-S7ProH-HD-12E), a VISERA Pro Xenon light source (CLV-S40Pro), and a VISERA Pro video processor (OTV-S7Pro) (all from Olympus Medical Systems Corp., Tokyo, Japan). An Olympus OEV-191H 19-in high-definition LCD monitor was used. Images were printed on an Olympus OEP-4 video printer and movies were recorded with a high-definition recorder (AG-HMR10; Panasonic Co., Osaka, Japan) and a DVD recorder (DMR-XP12; Panasonic Co.).

Patients were placed in the lithotomy position and the examinations were performed transvaginally with no kind of anesthesia. Physiological saline solution was dripped from a bag suspended 1 m above the patient to have a constant intrauterine pressure, and the scope was inserted into the uterus while the uterine cavity was distended.

Diagnostic criteria. For diagnosis with hysteroscopy, we took notice of protruding lesions, atypical vessels and necrosis. The evaluation of blood vessels based on NBI hysteroscopy was used for diagnosis other than that of white light hysteroscopy. Malignant lesions frequently have atypical blood vessels with an irregular, expanded, stenosed, interrupted, or zigzagged shape, and judgment of these atypical vessels was made with reference to Fig. 1. We prepared the following diagnostic criteria (Fig. 2), based on our own experience and criteria published elsewhere (6): Normal endometrium: endometrial mucosa with a smooth surface and no evident vascular network. Endometrial polyp: protruding lesion with a smooth surface and no evident vascular network. Myoma: protruding lesion with a smooth surface and clearly evident vascular network consisting of vessels branching from main vessels, but no atypical vessels. Decidual changes due to MPA therapy: decidual membrane lesion with a smooth surface and evident vascular network with a basal layer in the cavity. EMH: thick proliferated endometrium with none or minor blood vessel network on the surface. AEH: thick endometrium or protruding lesion with evident atypical blood vessels on the surface, but no evident necrosis. Endometrial cancer: protruding lesion with a rough surface including evident atypical vessels and necrosis.

Statistical analysis. Descriptive statistics were calculated for demographic characteristics in each group (white light plus NBI and white light only hysteroscopy). The pathological diagnosis [4-scales: benign lesion (normal, polyp, myoma, decidual change), EMH, AEH, and carcinoma] was used to indicate the true disease status. To evaluate the agreement of the hysteroscopic diagnosis with the pathological data, cross-tables were generated and weighted Kappa coefficients were estimated for each diagnostic test. Sensitivity and specificity were calculated with binary diagnostic data (disease defined as AEH or carcinoma). The 95% confidence intervals (CIs) for sensitivity, specificity and accuracy were estimated using the Clopper-Pearson (exact) method. All data were analyzed with SAS (version 9.1).

Results

Clinicopathological features of lesions. NBI hysteroscopy was performed in 104 subjects with no complications and observations were feasible in all cases. Cross tables of diagnostic results between each hysteroscopy and pathological diagnosis were summarized in Table I. Based on the pathological diagnoses, the subjects evaluated with NBI hysteroscopy included 25 benign lesions (24.0%; normal endometrium 3, endometrial polyp 7, myoma 6, decidual change 9), and 7 EMH (6.7%), 16 AEH (15.4%), and 56 carcinoma (53.8%) subjects. The 209 subjects examined conventionally in 2008 included 87 benign lesions (41.6%; normal endometrium 17, endometrial polyp 30, myoma 29, decidual change 11), and 7 EMH (3.3%), 32 AEH (15.3%), and 83 carcinoma (39.7%) subjects.

Comparison of visualization by conventional and NBI hysteroscopy. Compared with the conventional method, NBI hysteroscopy visualized blood vessels in the endometrium surface as a dark green color with clear contrast, resulting in easier inspection of the blood vessels and detection of atypical vessels (Fig. 3).

Sensitivity, specificity and accuracy of NBI and conventional hysteroscopy. In the 104 subjects examined by NBI hysteroscopy from April 2009 to May 2010, the hysteroscopic and pathological diagnoses were concordant in 92 subjects (accuracy 88.5%, 95% CI: 82.3-94.6%). For conventional hysteroscopy examined in 2008, the diagnoses were concordant in

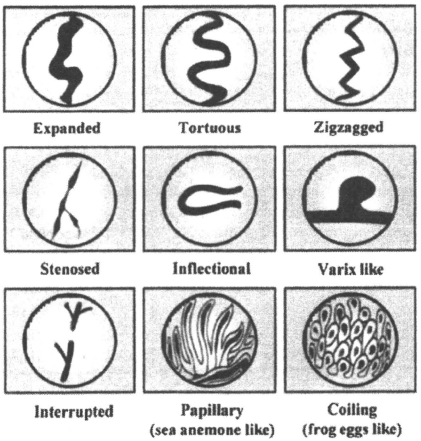

Figure 1. Atypical vessels. A variety of atypical blood vessels were observed in the mucosa of endometrial malignant lesions, including vessels with expanded, tortuous, and zigzagged shapes; variable diameter; inflectional, interrupted, papillary shapes; and sea anemone shapes.

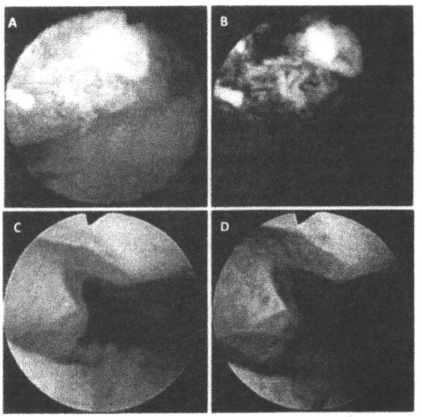

Figure 3. Comparison of visualization of endometrial lesions by conventional and NBI hysteroscopy. Endometrial carcinoma in conventional (A) and NBI (B) hysteroscopy. Evident necrosis and atypical blood vessels were found in the protruding lesion area. Atypical vessels were visualized more clearly by NBI. Endometrial hyperplasia in conventional (C) and NBI (D) hysteroscopy. Thick proliferated endometrial lesions were observed in the whole uterine cavity, but without observation of a prominent blood vessel network, even with NBI.

148 of 209 subjects (accuracy 70.8%, 95% CI: 64.6-77.0%). The weighted Kappa coefficients for the hysteroscopy and pathological diagnoses were 0.895 (95% CI: 0.835-0.955) and 0.663 (95% CI: 0.582-0.744) for NBI and conventional hysteroscopy, respectively. These results show that NBI hysteroscopy has better agreement with pathological diagnosis compared to the conventional hysteroscopy (Table I).

The sensitivities in detecting AEH or carcinoma for NBI and conventional hysteroscopy were 97.2% (95% CI: 90.3-99.7%) and 82.6% (95% CI: 74.4-89.0%), respectively, based on pathological diagnosis of AEH or endometrial carcinoma, which are endometrial lesions that require therapy of high-dose MPA or surgery. NBI hysteroscopy had a higher sensitivity, and the lower limit of the 95% CI for NBI hysteroscopy was higher than the upper limit for the conventional method. The specificities of the two methods were similar: 90.6% (95% CI: 75.0-98.0%) and 85.1% (95% CI: 76.3-91.6%), respectively (Table II and Fig. 4).

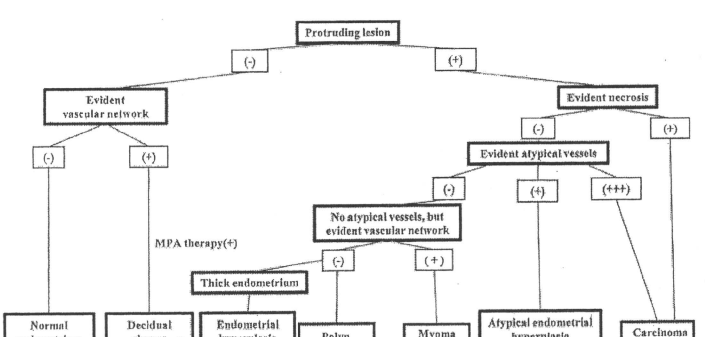

Figure 2. Diagnostic criteria for endometrial lesions detected by hysteroscopy.

Table I. Comparison of conventional and NBI hysteroscopy diagnoses with pathological findings.

	Pathological diagnosis				% Accuracy (95% CI)	Weighted Kappa (95% CI)
	Benign	EMH	AEH	Carcinoma		
Conventional hysteroscopy						
Benign	75	4	11	9		
EMH	0	1	0	0	70.8	0.663
AEH	12	1	11	13	(64.6-77.0)	(0.582-0.744)
Carcinoma	0	1	10	61		
NBI hysteroscopy						
Benign	23	0	1	0		
EMH	1	5	1	0	88.5	0.8949
AEH	1	2	12	4	(82.3-94.6)	(0.835-0.955)
Carcinoma	0	0	2	52		

Table II. Sensitivity and specificity of conventional and NBI hysteroscopy for diagnosis of AEH or carcinoma.

	Pathological diagnosis		% Sensitivity (95% CI)	% Specificity (95% CI)
	≥ AEH	< AEH		
Conventional hysteroscopy				
≥ AEH	95	14	82.6	85.1
< AEH	20	80	(75.6-89.5)	(77.9-92.3)
NBI hysteroscopy				
≥ AEH	70	3	97.2	90.6
< AEH	2	29	(90.3-99.7)	(75.0-98.0)

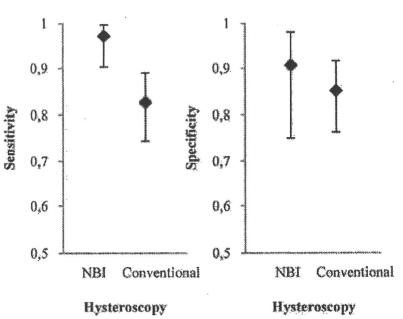

Figure 4. Sensitivity and specificity of NBI and conventional hysteroscopy for detecting atypical endometrial hyperplasia or carcinoma.

Discussion

This study provides a preliminary evaluation of NBI as image-enhanced endoscopic technique used in the gastrointestinal field for diagnosis of endometrial lesions. Development of NBI started in May 1999, and a NBI system was made available by Olympus Corp. in May 2006. This approach has been used effectively in the gastrointestinal field for endoscopic evaluation of the pharynx, esophagus, stomach, and large intestine, as shown in several studies. However, to our knowledge, only 7 reports (7-13) have described use of NBI in gynecology. This report is the first study to apply NBI flexible hysteroscopy to diagnosis of endometrial lesions in outpatients.

Improved visualization with NBI is achieved by shifting the light spectrum to narrow bands at 415 and 540 nm, which results in clear discrimination of lesions, microstructures and blood microvessels. Most blue light emitted in the NBI system is absorbed by oxidized hemoglobin in blood, resulting in visualization of blood vessels as a dark green color, in contrast to the light scattered by other tissue in the mucosal membrane. Neoplastic vessels tend to proliferate on the surface of cancerous lesions in the digestive tract, and this makes NBI very useful for qualitative diagnosis of malignant and benign lesions through clear visualization of microvessels (14). In the gynecological field, angiogenesis is also considered as a diagnostic marker of a malignant endometrial lesion (15,16), which suggests that NBI hysteroscopy may have a supplementary role in diagnosis of malignant endometrial lesions.

The choice of therapy for AEH and endometrial carcinoma is often high-dose progesterone and surgery including D&C and hysterectomy. A malignant lesion should be suspected when proliferation of neoplastic atypical vessels is observed, and therefore identification of the atypical vessel using NBI is important for diagnosis and therapy. However, diagnosis with hysteroscopy tends to be subjective. For this reason, we defined diagnostic criteria for objective assessment based on classification of the atypical vessel (Figs. 1 and 2).

The correct diagnostic rate were compared using data collected in two different periods. The sensitivity with NBI hysteroscopy of 88.5% (95% CI: 82.3-94.6%) was higher than that with the conventional hysteroscopy 70.8% (95% CI: 64.6-77.0%), and the lower limit of the confidence interval with NBI was higher than the upper limit with conventional hysteroscopy (Fig. 4). This result indicates that NBI hysteroscopy may improve the diagnostic accuracy compared with the conventional method. Furthermore, the weighted Kappa coefficient between NBI hysteroscopy and pathological diagnosis was as high as 0.8949 (95% CI: 0.835-0.955), which indicates that the agreement of these diagnosis was high. The sensitivity and specificity of NBI hysteroscopy for detection of AEH or carcinoma were 97.2% (95% CI: 90.3-99.7%) and 90.6% (95% CI:75.0-98.0%), respectively, compared with 82.6% (95% CI: 74.4-89.0%) and 85.1% (95% CI: 76.3-91.6%), respectively, for conventional hysteroscopy. Therefore, NBI hysteroscopy had higher sensitivity and similar specificity to those of the conventional method. This result suggests that NBI improves detection of malignant endometrial lesions, resulting from easier inspection of atypical vessels. The higher sensitivity but similar specificity compared to the conventional method suggests that NBI emphasizes vessel visualization, but does not increase the false positive rate. Overall, our results suggest that NBI hysteroscopy has superior sensitivity and accuracy compared with conventional hysteroscopy, and is useful for diagnosis of endometrial lesions.

Despite the promising results, our study has some limitations. This study involved only small number of patients and was conducted at a single institution. It was not performed as a randomized comparison, but as an exploratory comparison of NBI hysteroscopy with historical data obtained using conventional hysteroscopy. This design could lead to biases in the two groups based on the differences in time period, patients and operators, or sampling scheme. However, the sensitivity and specificity in the two groups are not influenced by sampling scheme, and data were collected from the two groups in the same hospital with an interval of only one year. It is unlikely that there are major biases in the data, but a crossover randomized study is required to confirm the results.

The high sensitivity of NBI hysteroscopy is likely to be clinically useful for judging whether an endometrial lesion is malignant or not, based on the following points. First, biopsy or endometrial histology may not be required for all patients with a suspected endometrial lesion, resulting in a decrease in unnecessary and invasive examinations. Second, judgment of the effect of therapy with high dose progesterone may be made by NBI hysteroscopy without the need for D&C. Third, NBI hysteroscopy may improve the diagnostic accuracy and sensitivity of detection of endometrial lesions.

In the digestive tract, NBI as image-enhanced endoscopic technique has been used in magnifying endoscopy for evaluation of blood microvessels and surface microstructure, with the goals of qualitative diagnosis and evaluation of invasion depth. Magnifying NBI endoscopy is referred to as 'optical biopsy', and a classification based on magnifying NBI for each internal organ has been proposed (17-21). Improvements in endoscopic imaging technology also allow clear visualization of cells and nuclei using endocytoscopy and endomicroscopy (17,22,23). These methods may allow evaluation as cytology and histology of biopsy specimens. We plan to investigate the diagnostic utility of the new imaging technology by applying NBI to magnifying hysteroscopy for evaluation of the microstructure and blood microvessels in endometrial lesions.

In conclusion, NBI hysteroscopy improved the diagnostic sensitivity for AEH or endometrial carcinoma, compared with conventional hysteroscopy. This increased sensitivity was achieved by application of NBI to enhance the contrast between vessels and other tissue in the lesion area, which resulted in easier detection of atypical vessels. Our results suggest that NBI hysteroscopy may be a useful supplementary endoscopic method for diagnosis of endometrial lesions. However, the study was performed as a historical comparative study of two groups, and large-scale, multicenter, prospective randomized controlled studies are required to establish the utility of NBI hysteroscopy for the diagnosis of endometrial lesions.

Acknowledgments

We thank Mr. Takashi Saga, Tomoharu Sanada and Kenji Matsushima of Olympus Medical Science Sales Co., Ltd. for technical assistance during the study. We also thank Drs Tai Ohmori and Tomohiko Nishi for advice on the NBI system. This study was supported by the Japan Society for the Promotion of Science (JSPS) through a Grant-in-Aid for Scientific Research (KAKENHI); a Grant-in-Aid for Scientific Research (C) (22591866); the Takeda Science Foundation; the Foundation for Promotion of Cancer Research; and the Japanese Foundation for Research and Promotion of Endoscopy (JFE) Grant.

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original article

Annals of Oncology 22: 636–642, 2011
doi:10.1093/annonc/mdq401
Published online 9 August 2010

Randomized phase II study comparing docetaxel plus cisplatin, docetaxel plus carboplatin, and paclitaxel plus carboplatin in patients with advanced or recurrent endometrial carcinoma: a Japanese Gynecologic Oncology Group study (JGOG2041)

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Received 12 December 2009; revised 6 June 2010; accepted 8 June 2010

Background: The purpose of this study is to assess the efficacy and safety of treatment with taxane plus platinum in combination therapies for advanced or recurrent endometrial carcinoma.

Patients and methods: Patients with measurable disease derived from histologically confirmed stage III/IV or recurrent endometrial carcinoma were randomly assigned to receive docetaxel plus cisplatin (DP), docetaxel plus carboplatin (DC), or paclitaxel plus carboplatin (TC) every 3 weeks until disease progression or adverse events prohibited further therapy. Among these regimens, the study evaluated the tumor response rate as the primary end point as well as toxicity.

Results: Ninety patients were enrolled. Of them, 88 were eligible and consequently 29, 29, and 30 patients were randomly assigned to DP, DC, and TC, respectively. Tumor response rates were 51.7%, 48.3%, and 60.0% in DP, DC, and TC, respectively ($P = 0.65$). The following toxic effects were observed: grade 3/4 neutropenia in 83.3%, 90.0%, and 76.6%; febrile neutropenia in 10.0%, 6.7%, and 3.3%; grade 3/4 thrombocytopenia in 6.7%, 10.0%, and 10.0%; grade 3/4 diarrhea in 13.3%, 3.3%, and 0%, respectively; and grade 3 neurotoxicity in 10.0% of TC. These toxicity profiles were not significantly different.

Conclusion: The taxane plus platinum combination therapies could be candidates in further phase III trials for endometrial carcinoma.

Key words: advanced, endometrial carcinoma, recurrent, taxane plus platinum combination

introduction

Endometrial carcinoma is the most common gynecologic neoplasms in recent years. The disease is frequently diagnosed at an early stage, and in many cases, a cure can be expected from surgery alone, with an overall 5-year survival rate for patients with endometrial carcinoma of 80.0% [1]. In contrast, advanced-stage disease in stage III or IV is diagnosed in ~16% of all patients, for whom the prognosis is poor, with the 5-year survival rates for stages III and IV being 61.9% and 21.1%, respectively [1]. Furthermore, stage III and IV endometrial carcinoma recurs in about 52% of cases despite postoperative adjuvant therapy [2], and the prognosis is extremely poor for patients with recurrent endometrial carcinoma, with a 2-year survival rate of 19%–24% [3, 4].

Treatment of advanced or recurrent endometrial carcinoma most commonly involves chemotherapy, but the fact remains that chemotherapy for endometrial carcinoma may be no more than a palliative measure. The drugs for which efficacy has been studied in monotherapy for endometrial carcinoma include cisplatin, carboplatin, doxorubicin, epirubicin, and 5-fluorouracil, for which the reported response rates are 4%–42% [5–7], 28%–33% [8, 9], 37% [10], 26% [11], and 41% [12], respectively. Of these, it is presently considered that

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cisplatin and doxorubicin, which have relatively high response rates, and which have been studied extensively, are the key drugs for endometrial carcinoma. As well, doxorubicin monotherapy and cisplatin/doxorubicin (AP) combination therapy for advanced or recurrent endometrial carcinoma have been compared by Gynecologic Oncology Group (GOG) 107 study and European Organization for Research and Treatment of Cancer (EORTC) 55872 study [13, 14]. At present, AP is generally acknowledged to be the standard chemotherapy for advanced or recurrent endometrial carcinoma in Japan.

The efficacy of taxanes in advanced or recurrent endometrial carcinoma has also been studied. The response rate reported for paclitaxel is 36% [15], and that for docetaxel 31% [16], and taxanes are considered to be one of the effective class of drugs for the treatment of endometrial carcinoma [17–19]. In the GOG 163 study, doxorubicin/paclitaxel (AT) + granulocyte colony stimulating factor (G-CSF) therapy was compared with AP in advanced or recurrent endometrial carcinoma [20]. The differences between AP and AT were not significant, thus this report did not conclude that AT is a useful substitute for AP. The GOG 177 study compared paclitaxel/doxorubicin/cisplatin (TAP) + G-CSF combination therapy against AP [21]; TAP was significantly superior to AP with survival; however, from the perspectives of toxicity and tolerability, the conclusion that TAP could be the standard therapeutic choice was not supported. In this matter, combination chemotherapy approaches that include taxanes are presently under scrutiny as the standard regimen for endometrial carcinoma.

Another platinum-containing drug, carboplatin, has demonstrated equivalent efficacy to cisplatin monotherapy for endometrial carcinoma [8, 9]. Nevertheless, cisplatin is still used in numerous combination therapy regimens, and the role of carboplatin in combination therapy is yet to be clearly defined.

Given the above background, the Japanese Gynecologic Oncology Group has planned a study to investigate the efficacy and safety of various combination chemotherapy regimens including taxanes and platinum for patients with advanced or recurrent endometrial carcinoma. Excluding paclitaxel/cisplatin (TP) in light of its neurotoxic adverse reactions [19], three groups were selected for combined regimens of taxanes plus platinum drugs: docetaxel/cisplatin (DP), docetaxel/carboplatin (DC), and paclitaxel/carboplatin (TC). The objective of this clinical study is to evaluate whether they are eligible as a candidate for a future phase III randomized clinical study.

patients and methods

patients

The inclusion criteria for the patients in this study were as follows: primary lesion histologically confirmed to be endometrial carcinoma; International Federation of Gynecology and Obstetrics (FIGO) stage III, stage IV, or recurrent cancer; maximum measurable diameter at computed tomography (CT) or magnetic resonance imaging at least 20 mm; or a maximum measurable diameter at helical CT of at least 10 mm. Prior chemotherapy was permitted and there was no limitation to the number of prior chemotherapy regimens. Other inclusion criteria were Eastern Cooperative Oncology Group performance status 0–2, at least 6 months since last treatment with other chemotherapeutic agents, at least 4 weeks since prior radiotherapy, at least 2 weeks since prior treatment with antimetabolic drugs, hormone therapy, or immunotherapy; age ≥20 and <75 years; adequate hematologic and major organ function preserved, with an absolute granulocyte count ≥2000/mm^3, platelet count ≥100 000/mm^3, hemoglobin ≥9.0 g/dl, aspartate aminotransferase ≤100 U/l, alanine aminotransferase ≤100 U/l, bilirubin ≤1.5 mg/dl, serum creatinine ≤1.2 mg/dl, creatinine clearance ≥60 ml/min, normal electrocardiogram, and provision of written consent to participate in this study.

The exclusion criteria in this study were the presence of sarcomatous components; apparent infection; serious complications; active multiple cancers; apparent interstitial pneumonia or pulmonary fibrosis; pleural effusion or ascites requiring continuous drainage; grade 2 or higher peripheral neuropathy or grade 2 or higher edema; a history of hypersensitivity to preparations containing polysorbate 80, polyoxyethylene castor oil, or hardened castor oil; and patients judged by the investigator to be ineligible for other reasons.

The protocol was reviewed and approved by the institutional review boards of each participating institute. Written informed consent was obtained from all patients before registration.

study design and treatment

The study treatments were DP (docetaxel 70 mg/m^2 + cisplatin 60 mg/m^2, day 1, every 3 weeks), DC (docetaxel 60 mg/m^2 + carboplatin area under the curve (AUC) 6 mg/ml·min, day 1, every 3 weeks), or TC (paclitaxel 180 mg/m^2 + carboplatin AUC 6 mg/ml·min, day 1, every 3 weeks), each regimen to be given until disease progression or adverse events prohibited further therapy. The stratified factors used to adjust allocation to treatment were prior chemotherapy with taxanes and presence of a measurable lesion in the previously irradiated region. Patients were randomly allocated to three groups at a rate of 30 per group by the minimization method (Figure 1).

If any of the adverse events listed below were seen during treatment in the previous cycle, the dose for the subsequent cycle was to be reduced in the following instances: occurrence of febrile neutropenia, grade 4 neutropenia persistent for at least 5 days, or grade 3 or higher non-hematological toxicity with docetaxel and paclitaxel; creatinine clearance <60 ml/min with cisplatin; and grade 4 thrombocytopenia, bleeding tendency due to grade 3 thrombocytopenia, or platelet transfusion with carboplatin. In case of febrile grade 3 neutropenia or grade 4 neutropenia, the administration of G-CSF was permitted.

assessments

The primary end point was the response rate, and the secondary endpoints were the frequency of adverse events, the treatment completion rate, and progression-free survival (PFS). Objective tumor assessments were evaluated every two cycles in accordance with the RECIST guidelines, and complete response and partial response were confirmed at least 4 weeks

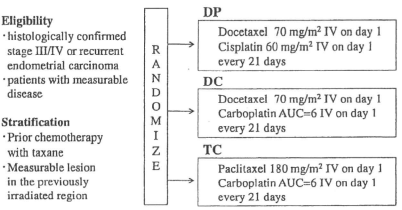

Figure 1. Study design.

after the initial responses. The response rate was defined as a total of complete response and partial response. Adverse events were classified and evaluated by grade in accordance with the National Cancer Institute–Common Toxicity Criteria (Version 2). Treatment completion was defined as being able to appropriately commence treatment and administer at least three cycles.

statistical analysis

In the GOG 177 study, the response rate for doxorubicin + cisplatin therapy (AP) in chemonaive patients was 34% [21]. In the present study, the threshold response rate for combination therapy was set at 25% for each group, in accordance with the lower bound of 26% for the 95% confidence interval (CI) (26% to 43%) for AP, and it was hypothesized that the rate would not fall below this 25% level in any group. Assuming an expected response rate of 50%, α error = 0.05, and β error = 0.20, a calculation using Simon's optimal two-stage design indicated that the required number of patients in each group would be 24. Making allowances for dropouts, the target number of patients per group was set at 30. A single interim analysis was planned with the objective of early termination of any group with obviously inferior efficacy. Based on Simon's two-stage design, the interim analysis was to be carried out when nine patients had been accumulated in the full analysis set (FAS) for each group.

results

patient characteristics

Between December 2003 and May 2005, 95 patients were registered in the study, and of these, 5 were deemed to be ineligible due to violation of the inclusion or exclusion criteria. Therefore, a total of 90 patients were admitted to the study, comprising 30 in each group. Negligible deviations from the protocol were reported for 43 patients, meanwhile serious deviations were deemed to have occurred in 3 patients. For the evaluation of efficacy, the analysis set was the FAS, from which two patients were excluded after it was ascertained following enrolment and randomization that they did not have measurable lesions. Since the study treatment had been given at least once to each of the above three patients, the tabulation and analysis of safety were done for the randomized groups. The distribution of stratified factors in the FAS analysis population (history of prior taxane chemotherapy or presence of a measurable lesion in the previously irradiated region), FIGO stage, performance status, histological type, age, and prior therapy (surgery, radiotherapy, or chemotherapy) is shown in Table 1.

tumor response

A single interim analysis was carried out when nine FAS patients had been accumulated in each group, but since this showed that there were at least three patients with an effective response in each group, the study progressed to the second stage without meeting the predetermined early termination criteria. Furthermore, the final analysis was carried out when 24 FAS patients had been accumulated in each group. Since there were at least 10 patients with an effective response in each group and the predetermined efficacy criteria had not been contravened, it was not concluded that any of the therapies was ineffective. The response rates for DP, DC, and TC for all FAS patients overall and their 95% CIs were 51.7% (15/19) (32.5% to 70.6%), 48.3% (14/29) (29.4% to 67.5%), and 60.0% (18/30) (40.6% to 77.3%), respectively (Table 2). Statistically, it did not appear that the efficacy rates in the three groups were nonuniform ($P = 0.6492$). The odds ratios of the compared two groups were 1.1480 (0.4098–3.2156) (DP versus DC), 0.7143 (0.2546–2.0038) (DP versus TC), and 0.6222 (0.2218–1.7455) (DC versus TC).

adverse events

Table 3 shows the adverse events and the frequencies of grade 3 or higher events and its 95% CI observed in the first three cycles, as stipulated in the study protocol. The major adverse events produced after treatment with the investigational products were hematological toxic effects in every group. Leukopenia or neutropenia was seen in nearly all patients, and adverse events of grade 3 or higher occurred at a high incidence of >80%. Febrile neutropenia was reported in four patients (13.3%) in DP and in two patients each (6.7%) in DC and TC; infection associated with grade 3–4 neutropenia was reported in two patients in DP and one patient in TC. Grade 3 motor neuropathy occurred in two patients (6.7%) in TC, and sensory neuropathy occurred in one patient (3.3%) in TC only, but in all instances, the differences were not statistically significant at the 5% level. Other grade 3 or higher adverse events that occurred at high frequency were the gastrointestinal symptoms of anorexia, diarrhea, and nausea. The serious adverse events reported as the Expedited Report were pseudomembranous colitis, febrile neutropenia, and allergic reaction/hypersensitivity in DP; pulmonary thromboembolism and hydronephrosis in DC; and hypokalemia in TC.

treatment completion rate

The specified three cycles of treatment could not be completed for eight patients in DP, nine patients in DC, and three patients in TC. The main reason was obvious progression of disease (11 patients in total, comprising 3 in DP, 7 in DC, and 1 in TC). The medians of treatment cycles were 4 (1–11), 4 (1–10), and 6 (1–13) in DP, DC, and TC, respectively. The treatment completion rate for three or more cycles was 72.4% (95% CI 52.8% to 87.3%) in DP, 69.0% (95% CI 49.2% to 84.7%) in DC, and 90.0% (95% CI 73.5% to 97.9%) in TC (Table 4). Statistically significant differences at the 5% level, two sided, were not detected.

survival

The PFS curve, as estimated by the Kaplan–Meier method for the patients in the FAS, is shown in Figure 2. Three patients were lost to follow-up. The median PFS was 232, 238, and 289 days in DP, DC, and TC, respectively. The median overall survival was 629, 731, and 854 days, respectively. Analysis of uniformity of hazard for the three groups and of hazard for DC or TC relative to DP did not yield any significant differences.

discussion

In this study, we treated patients with advanced or recurrent endometrial carcinoma with combination therapy comprising taxane and platinum, and investigated the

Table 1. Patients characteristics

Characteristics	DP (n = 29)	DC (n = 29)	TC (n = 30)	Total (n = 88)	P value
Prior chemotherapy with taxane					0.9161
No	26	26	26	78	
Yes	3	3	4	10	
Measurable lesion in the previously irradiated region					0.7590
No	28	27	29	84	
Yes	1	2	1	4	
Disease status					0.2919
Stage III	9	6	5	20	
Stage IV	9	6	13	28	
Recurrent	11	17	12	40	
ECOG performance status					0.3717
0	23	24	19	66	
1	5	5	9	19	
2	1	0	2	3	
Histology					0.5705
Adenocarcinoma	1	2	1	4	
Endometrioid adenocarcinoma	18	19	14	51	
Endometrioid adenocarcinoma with squamous differentiation	4	3	5	12	
Serous adenocarcinoma	2	2	6	10	
Clear cell adenocarcinoma	0	2	0	2	
Mucinous adenocarcinoma	0	0	1	1	
Squamous cell carcinoma	0	0	0	0	
Mixed carcinoma	2	1	2	5	
Undifferentiated carcinoma	1	0	1	2	
Others	1	0	0	1	
Age (years)					
Median (range)	64.0 (39–74)	66.0 (51–73)	61.0 (49–74)	62.5 (39–74)	
Prior surgery					0.7510
No	8	9	11	28	
Yes	21	20	19	60	
Prior radiotherapy					0.9372
No	25	25	25	75	
Yes	4	4	5	13	
Prior chemotherapy					0.0714
No	24	16	19	59	
Yes	5	13	11	29	
Regimens of prior chemotherapy					
Taxane/platinum	2	3	4	9	
Anthracyclin/platinum	2	9	8	18	
Taxane/anthracyclin/platinum	1	0	1	2	
Platinum	0	2	0	2	
Hormone	0	0	1	1	
Others	0	1	0	1	

DP, docetaxel plus cisplatin; DC, docetaxel plus carboplatin; TC, paclitaxel plus carboplatin; ECOG, Eastern Cooperative Oncology Group.

efficacy and safety of the various forms of combination therapy, with the objective of evaluating the appropriate arms for a proposed phase III study.

In the combination of taxane and platinum, we adopted DP, DC, and TC. We excluded paclitaxel/cisplatin combination by the reason of severe neurotoxicity than others [22]. Although not in a randomized Phase III study, for advanced endometrial carcinoma, the response rates obtained with TC were reported to be 50–78% [23, 24]. On the other hand, there are no comparative studies involving docetaxel in combination therapy for endometrial carcinoma. Markman et al. [25] carried out phase II study of the combination therapy of docetaxel 60 mg/m^2 and carboplatin AUC 6 for ovarian cancer. Aoki et al. [26] carried out phase II study of the combination therapy of docetaxel 70 mg/m^2 and cisplatin 60 mg/m^2 for ovarian cancer. They reported adequate efficacy and tolerability, and these doses were recommended. On the basis of the above-mentioned reports, we consider that the doses

of taxane plus platinum combinations in this study are also effective for patients in endometrial carcinoma.

In this study, the response rate for all patients in the FAS was 51.7% in DP, 48.3% in DC, and 60.0% in TC. By the randomized allocation procedure, there were no substantial biases for patient characteristics in each treatment group. The response rate of AP was reported as 42% in GOG 107 study [13] or 43% in EORTC 55872 study [14]. In combination therapies using taxane, the response rate of AT + G-CSF therapy was 43% in GOG 163 study [20] and that of TAP + G-CSF combination therapy was 57% in GOG 177 study [21].

Table 2. Tumor response rates

	CR	PR	SD	PD	NE	Response rate (95% CI)
DP (n = 29)	0	15	7	4	3	51.7 (32.5–70.6)
DC (n = 29)	4	10	4	8	3	48.3 (29.4–67.5)
TC (n = 30)	2	16	7	4	1	60.0 (40.6–77.3)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; CI, confidence interval; DP, docetaxel plus cisplatin; DC, docetaxel plus carboplatin; TC, paclitaxel plus carboplatin.

This study concluded that the response rates of all taxane plus platinum regimens did not fall below 25% as the threshold response rate. Although the patients in this study were selected by the inclusion or exclusion criteria and the results might be better than what we achieved in a non-selected population, the results did suggest that the efficacy of taxanes and platinum was higher than that of AP or combination therapies using taxanes previously reported.

The main adverse events observed in this study were pancytopenia and other myelosuppression-related events. In particular, grade 3 or higher leukopenia or neutropenia occurred in >80% of patients. Moreover, febrile neutropenia and infection associated with grade 3 or higher neutropenia occurred at rates of ≤20% in all groups. Other grade 3 or higher adverse events with an incidence of ≥10% were gastrointestinal symptoms, such as anorexia, diarrhea, and nausea. The main reason for dropping out was obvious progression of disease. Based on the above results, it was considered that all the three regimens, compared with conventional AP, presented no concerns with respect to the degree of adverse events or tolerability.

Thus, our results obtained suggest the usefulness of combination therapy using taxane and platinum, but the

Table 3. Adverse events observed by three cycles

Toxic effects	DP (n = 30)				DC (n = 30)				TC (n = 30)			
	Grade			Grade 3–4 (%) (95% CI)	Grade			Grade 3–4 (%) (95% CI)	Grade			Grade 3–4 (%) (95% CI)
	1	2	3		1	2	3		1	2	3	
Hemoglobin	15		1	3.3 (0.1–17.2)	13	5	1	16.7 (5.6–34.7)	14	3	2	16.7 (5.6–34.7)
Leukocytes	7	15	7	73.3 (54.1–87.7)	3	21	5	86.7 (69.3–96.2)	8	13	2	50.0 (31.3–68.7)
Neutrophils (ANC)	4	9	16	83.3 (65.2–94.4)	2	8	19	90.0 (73.5–97.9)	3	11	12	76.6 (57.7–90.1)
Platelets	1	2		6.7 (0.8–22.1)	4	3		10.0 (2.1–26.5)	2	3		10.0 (2.1–26.5)
AST	1				2	1		3.3 (0.1–17.2)		1		3.3 (0.1–17.2)
ALT					3	1		3.3 (0.1–17.2)	3			
Allergic reaction	1		1	3.3 (0.1–17.2)	1	1		3.3 (0.1–17.2)				
Anorexia	10	5		16.7 (5.6–34.7)	7	3		10.0 (2.1–26.5)	6	3		10.0 (2.1–26.5)
Diarrhea	6	3	1	13.3 (3.8–30.7)	1	1		3.3 (0.1–17.2)	2			
Nausea	12	3		10.0 (2.1–26.5)	12	2		6.7 (0.8–22.1)	5	3		10.0 (2.1–26.5)
Motor neuropathy					1					2		6.7 (0.8–22.1)
Sensory neuropathy									3	1		3.3 (0.1–17.2)
Febrile neutropenia		2	1	10.0 (2.1–26.5)		2		6.7 (0.8–22.1)		1		3.3 (0.1–17.2)

DP, docetaxel plus cisplatin; DC, docetaxel plus carboplatin; TC, paclitaxel plus carboplatin; CI, confidence interval; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 4. Treatment completion rate

		DP (n = 29)	DC (n = 29)	TC (n = 30)
Dropout cases	First course	2	1	2
	Second course	6	8	1
	Total	8	9	3
Completion rate (%) (95% CI)		72.4 (52.8–87.3)	69.0 (49.2–84.7)	90.0 (73.5–97.9)
Median of treatment cycles (minimum–maximum)		4 (1–11)	4 (1–10)	6 (1–13)

DP, docetaxel plus cisplatin; DC, docetaxel plus carboplatin; TC, paclitaxel plus carboplatin; CI, confidence interval.

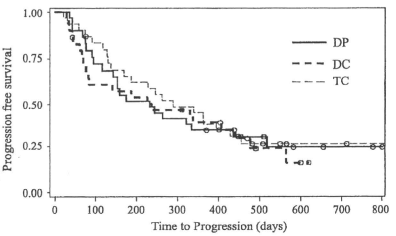

Figure 2. Kaplan–Meier curve of estimated progression-free survival. DP, docetaxel plus cisplatin; DC, docetaxel plus carboplatin; TC, paclitaxel plus carboplatin.

optimal drugs to be used together in combination therapy remain uncertain. Since it was not an objective of this study to statistically compare effects in different therapy groups, it is difficult to conclude with an adequate power of detection that the response rate in any group was the highest. There were three interested regimens as taxane plus platinum regimen and each regimen would be a candidate of phase III study for endometrial carcinoma. There are phase III evidences in TC for ovarian cancer, but it has yet no phase III evidences for endometrial carcinoma. However, TC is used clinically and widely for endometrial carcinoma, in fact. Thus, we think a proper scientific inspection for TC is necessary and other taxane plus platinum combinations that are effective in ovarian cancer should be equally compared. On the other hand, since there are no comparative studies involving docetaxel in combination therapy, its efficacy is yet to be clarified. According to a systematic review and practice guideline for non-small-cell lung cancer (NSCLC), paclitaxel or docetaxel combined with cisplatin is recommended as one of a number of chemotherapy options for the first-line treatment of advanced NSCLC patients [27]. Of the taxane–platinum combinations, DP yielded survival and response rates superior to another platinum combination and demonstrated broad quality of life benefits [28]. As our use of taxane–platinum combination expands for endometrial carcinoma, there may be a need to study the significance to combine docetaxel with cisplatin. In addition, it is considered that the role of carboplatin in combination therapy is yet to be defined [29]. DC represents an alternative first-line chemotherapy regimen for ovarian cancer patients; however, longer follow-up was not carried out for a definitive statement on survival [30]. Although there was no statistical significant difference, the response rate of DC was lowest among three groups in this study. We think DC may not be adequate for a candidate of phase III study.

Among combination chemotherapy options involving taxanes and platinum for advanced or recurrent endometrial carcinoma, the results of the present study suggested that the three regimens of DP, DC, and TC may have efficacy and tolerability that surpass those of AP reported in the past. It is concluded that these combination therapy regimens can become the appropriate study arm in the planned phase III clinical study.

funding

Health Labour Sciences Research Grant for Clinical Cancer Research from the Ministry of Health Labour and Welfare of Japan.

acknowledgements

The participating institutions for all studies described in this report are listed in Appendix 1. The authors would like to thank the Kitasato University Research Center for Clinical Pharmacology, Clinical Trials Coordinating Center (CTCC), especially Ms Miwa Nonaka for the data management, and Ms Keiko Abe for the study fund management.

disclosure

DA received honoraria from Sanofi Aventis and Bristol-Myers Squibb; NK received honoraria from Sanofi Aventis, Kyowa Hakko Kirin, Chugai Pharmaceutical, Yakult, and Nippon Kayaku.

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appendix 1

The following member institutions participated in this study: Aichi Cancer Center Hospital, Asahikawa Medical College Hospital, Japan Labour Health and Welfare Organization Chugoku Rosai Hospital, Fujita Health University Hospital, University of Fukui Hospital, Fukuoka University Hospital, Hokkaido University Hospital, Iwate Medical University Hospital, The Jikei University Aoto Hospital, The Jikei University Daisan Hospital, Kagoshima City Hospital, Keio University Hospital, Kinki University School of Medicine, Kitasato University Hospital, Kushiro Rosai Hospital, Miyagi Cancer Center, Morioka Red Cross Hospital, National Cancer Center Hospital, National Hospital Organization Saitama National Hospital, National Kyushu Cancer Center, Niigata Cancer Center Hospital, Niigata University Medical & Dental Hospital, Nikko Memorial Hospital, Osaka City General Hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka Medical College Hospital, Saga Prefectural Hospital Koseikan, Saiseikai Suita Hospital, Shikoku Cancer Center, Showa University Hospital, Saitama Social Insurance Hospital, Shinshu University Hospital, St Marianna University School of Medicine Yokohama City Seibu Hospital, Tohoku University Hospital, Tokyo Dental College Ichikawa General Hospital, Tonami General Hospital, and Tottori University Hospital.

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

Yukiharu Todo, Hidenori Kato, Masanori Kaneuchi, Hidemichi Watari, Mahito Takeda, Noriaki Sakuragi

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

This online publication has been corrected. The corrected version first appeared at TheLancet.com on August 20, 2010

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**

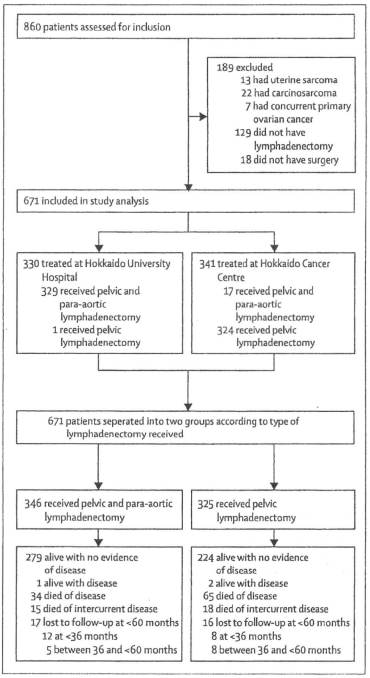

Figure 1: **Study design**

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 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**

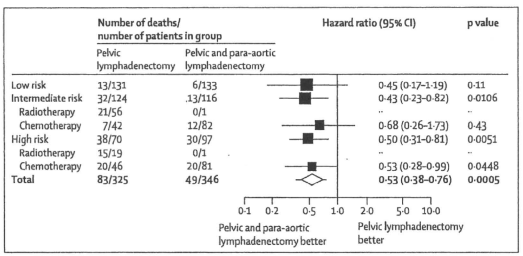

Figure 2: Cox regression analysis of overall survival with pelvic and para-aortic lymphadenectomy compared with pelvic lymphadenectomy alone according to risk of recurrence
..=data not available.

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			0·141
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			0·27
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			0·32
Negative	148 (76%)	151 (71%)	..
Positive	46 (24%)	62 (29%)	..
Adjuvant therapy			0·101; <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

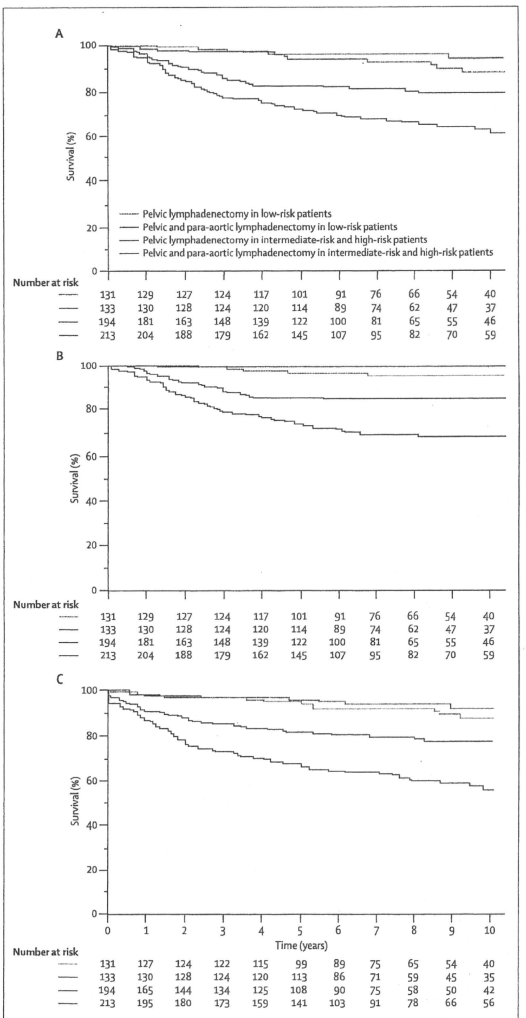

Figure 3: Kaplan-Meier analysis of overall (A), disease-specific (B), and recurrence-free (C) survival for patients with endometrial carcinoma according to type of lymphadenectomy and risk of recurrence

	Low risk		Intermediate or high risk	
	Pelvic lymphadenectomy (n=131)	Pelvic and para-aortic lymphadenectomy (n=133)	Pelvic lymphadenectomy (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