	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.

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A Retrospective Analysis of Postoperative Complications With or Without Para-aortic Lymphadenectomy in Endometrial Cancer

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Introduction: Although para-aortic lymphadenectomy (PALX) has not been accepted as a standard treatment for patients with endometrial cancer, it is possible that systematic lymphadenectomy including PALX has therapeutic significance for patients with intermediate-/high-risk endometrial cancer. On the other hand, a consensus regarding the safety of PALX has not been reached. The aim of this study was to compare the incidence rates of postoperative complications after pelvic lymphadenectomy (PLX) with or without PALX in patients with uterine corpus cancer.

Methods: A retrospective chart review was carried out for all patients with endometrial cancer treated at 2 tertiary centers between 1998 and 2004. Surgery at one institute included both PLX and PALX, whereas PLX alone was routinely performed at the other institute. A total of 142 patients underwent PLX + PALX and 138 patients underwent PLX alone. We evaluated postoperative complications including intraoperative injury, ileus, lymphedema, lymphocyst, and thrombosis.

Results: There was no fatal accident associated with surgery. Lymphedema was the most frequent complication. Comparing the PLX + PALX group and the PLX group, there were no significant differences in the rate of cases of lymphedema (23.2% vs 28.3%), lymphocyst (9.2% vs 9.4%), and thrombosis (4.9% vs 2.2%). The rate of cases of mild/moderate ileus in the PLX + PALX group was significantly higher than that in the PLX group (10.5% vs 2.9%; $P = 0.011$). However, no significant difference in the rates of cases of severe ileus was found between the 2 groups (1.4% vs 0.7%). There were also no significant differences between the 2 groups in the rates of intraoperative organ injury (2.8% vs 2.2%) and secondary operation for postoperative complications (4.9% vs 4.3%).

Conclusions: Para-aortic lymphadenectomy can be performed with an acceptable morbidity under the conditions in which it is performed by experienced surgeons, and measures to prevent complications are properly taken.

Key Words: Endometrial cancer, Para-aortic lymphadenectomy, Complication, Ileus, Lymphedema

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Para-aortic lymphadenectomy (PALX) has not been accepted as a standard treatment for patients with endometrial cancer for the following 2 reasons. First, a consensus regarding the therapeutic effect of PALX has not been reached. Second, PALX is time consuming and seems to have a high incidence of postoperative complications.

Recently, 2 large prospective randomized trials on pelvic lymphadenectomy in endometrial cancer failed to show any therapeutic benefits of lymphadenectomy.[1,2] However, both studies had limitations for drawing definite conclusions about the therapeutic role of lymphadenectomy because neither study included PALX. This would have negated the therapeutic impact of lymphadenectomy because more than half of patients with pelvic lymph node metastasis have para-aortic node metastasis,[3–5] and the para-aortic area is a critical site for sentinel nodes in endometrial cancer.[6–8]

We reported that systematic lymphadenectomy including PALX has therapeutic significance for patients with intermediate-/high-risk endometrial cancer.[9] Selective PALX does not increase morbidity.[10,11] Systematic PALX may also be a feasible and safe operative procedure[12] even in elderly patients.[13,14] However, a consensus regarding the safety of PALX has not been reached.[15,16] There has been no study in which complication rates were compared between a systematic lymphadenectomy with PALX cohort and a systematic lymphadenectomy without PALX cohort. We report here the incidence rates of postoperative complications after pelvic lymphadenectomy with or without PALX and discuss about the safety of PALX in patients with endometrial cancer.

MATERIALS AND METHODS

Study Population

We previously reported the results of the Survival Effect of Para-Aortic Lymphadenectomy in endometrial cancer (SEPAL) study in which a total of 860 patients with malignant tumors of the uterine corpus were treated at 2 tertiary centers, Hokkaido University Hospital (HUH) and Hokkaido Cancer Center (HCC), during the period from 1986 to 2004, and a total of 671 patients with endometrial carcinoma who underwent extensive surgical staging including lymphadenectomy were eligible for the study.[9] In that study, HUH used routine pelvic lymphadenectomy (PLX) with PALX, and HCC used routine systematic PLX without PALX.

During the first period of the SEPAL study, morbidity associated with PLX + PALX was a major problem. It took many years to achieve a stable surgical procedure. In 1998, active management including the use of intermittent pneumatic compression, postoperative administration of an anticoagulant, and preoperative storage of autologous blood was started at HUH. In this study, therefore, we focused on cases during the period from 1998 to 2004 in the SEPAL study. Data for a total of 280 patients, including 142 patients who underwent PLX + PALX and 138 patients who underwent PLX alone, were used for analysis in this study.

Surgery

Systematic PLX included resection of the internal iliac nodes, external iliac nodes, medial suprainguinal nodes, lateral suprainguinal nodes, obturator nodes, sacral nodes, and common iliac nodes. Suprainguinal nodes are the most distal external iliac lymph nodes and have been called circumflex iliac nodes.[17] Para-aortic lymphadenectomy included systematic resection of all nodes from the precaval and lateroacaval, interaortocaval, and preaortic and lateroaortic area up to the renal veins. At the end of surgery, the surgeon put 2 drainage tubes in the bilateral pelvic retroperitoneal spaces. Choice of drainage tube was at the surgeon's discretion. Drainage tubes were removed within 7 days after the operation.

Complications and Managements

Postoperative lower extremity lymphedema was defined as stage II or III lower extremity lymphedema related to lymphadenectomy. For determining staging of lymphedema, we used the consensus document of the International Society of Lymphology.[18] Therefore, we excluded from analysis data

TABLE 1. Clinical backgrounds of 280 patients with endometrial carcinoma who underwent surgical treatment including lymphadenectomy

	PLX + PALX (n = 142)	PLX Alone (n = 138)	*P*
Age, Median (IQR)	56 (51–64)	58 (53–63)	0.26
Body Mass Index, mean (SD)	24.8 (4.6)	24.7 (4.0)	0.88
Disease Stage (FIGO)			0.27
1	94	90	
2	9	18	
3	37	28	
4	2	2	
Histological Finding			0.60
Endometrioid	127	126	
Nonendometrioid	15	12	
Myometrial Invasion			0.63
<½	95	96	
≥½	47	42	
Adnexal Metastasis			0.16
Negative	130	132	
Positive	12	6	
Lymph Node Metastasis			0.44
Negative	120	121	
Positive	22	17	
Risk of Recurrence*			0.66
Low	39	30	
Intermediate	46	49	
High	57	59	

*Risk of recurrence: Low, FIGO stages IA and IB with grades 1–2 endometrioid adenocarcinoma and no lymph–vascular space invasion; High, FIGO stages III and IV; Intermediate, all other tumors.
IQR, interquartile range.

TABLE 2. Operative characteristics of 280 patients with endometrial carcinoma who underwent surgical treatment including lymphadenectomy

	PLX + PALX (n = 142)	PLX Alone (n = 138)	*P*
Lymph Nodes Removed, Median (IQR)	87 (68–107)	36 (28–47)	< 0.0001
Pelvic	61 (48–77)	36 (28–47)	< 0.0001
Para-aortic	25 (17–34)	0 (0–0)	< 0.0001
Operation Time, Mean (SD), min	393 (127)	167 (49)	< 0.0001
Blood Loss, Mean (SD), cc	1278 (1069)	748 (806)	< 0.0001
Allogenous Blood Transfusion			
Not done	108	97	
Done	34 (23.9%)	41 (29.7%)	0.28

for patients who had leg edema related to recurrent disease, progressive disease, deep vein thrombosis, and any other medical comorbidities.

Lymphocysts were classified into noninfected and infected lymphocysts, or symptomatic and asymptomatic lymphocysts. Lymphocysts associated with temporary abdominal distension were classified into asymptomatic lymphocysts. All patients underwent ultrasound examination or computed tomography for detection of a lymphocyst within 1 month after surgery. In this study, lymphocysts with a maximum diameter of 6 cm or more were identified and used for analysis. Management for asymptomatic lymphocysts was just observation regardless of size. In this study, we found no chylous ascites, and we therefore did not assess the morbidity in chylous ascites.

Severity of ileus was classified into 3 levels, which are mild (improvement by conservative management within 10 days and sufficient status to tolerate adjuvant treatment at 1 month after surgery), moderate (improvement by conservative management for more than 10 days and sufficient status to tolerate adjuvant treatment at 1 month after surgery), and severe (insufficient status to tolerate adjuvant treatment at 1 month after surgery).

Postoperative thrombosis included deep vein thrombosis and pulmonary thromboembolism and was classified into asymptomatic thrombosis and symptomatic thrombosis. Intermittent pneumatic compression devices were attached to the legs from the start of surgery to the first walking after surgery. Administration of an anticoagulant was started on the day after the surgery. Choice of anticoagulant and administration period were at the physician's discretion. Routine examination was not performed for diagnosis of thromboembolic events. For patients with any symptoms including leg edema and dyspnea, ultrasound examination, computed tomography, and/or pulmonary scintigraphy were performed. These examinations were also performed at the physician's discretion for patients who were obese or had abnormal laboratory results.

Analysis of Complication According to Type of Surgery

We conducted a retrospective chart review of all patients. Age, body mass index, International Federation of Gynecology and Obstetrics (FIGO) stage (1988), histological finding, grade, myometrial invasion, adnexal metastasis, lymph node metastasis, type of lymphadenectomy, number of resected lymph nodes, and adjuvant therapy were recorded as patients' characteristics. According to the type of lymphadenectomy, we evaluated operation time, blood loss, allogenous blood transfusion, intraoperative organ injury, second surgery for postoperative complications, postoperative ileus, postoperative lower extremity lymphedema, lymphocyst, and postoperative thrombosis. Unpaired numerical data were compared with Student unpaired *t* test. Proportional data were compared using the χ^2 test or the Fisher exact test. The statistical significance level was set at 0.05. Statistical analyses were performed with StatView J-5. 0 PPC (SAS Institute, Cary, NC).

RESULTS

The clinical and pathological characteristics of the 280 patients according to the type of lymphadenectomy are shown in Table 1. There was no significant difference in the distribution of each variable between the PLX + PALX group and the PLX group.

Table 2 shows invasiveness of the operation according to the type of lymphadenectomy. The median numbers of lymph nodes removed were 87 in the PLX + PALX group and 36 in the PLX group, the difference being statistically significant ($P < 0.0001$). Operation time and blood loss were 393 minutes and 1278 mL in the PLX + PALX group and 167 minutes and 748 mL in the PLX group. These differences were also statistically significant ($P < 0.0001$, respectively). The blood loss was 500 mL more in the PLX + PALX group than in the PLX group, but the difference in the percentages of patients who needed to have allogenous blood transfusion was not significant (23.9% vs 29.7%, $P = 0.28$).

Table 3 shows the incidence of postoperative complications according to the type of lymphadenectomy. There was no fatal accident associated with surgery.

Postoperative lower extremity lymphedema was the most frequent complication in this study. The rates of cases of lymphedema were 23.2% (n = 33) in the PLX + PALX group and 28.3% (n = 39) in the PLX group, the difference not being statistically significant ($P = 0.34$).

TABLE 3. Incidence of postoperative complication in 280 patients with endometrial carcinoma who underwent surgical treatment including lymphadenectomy

	PLX + PALX (n = 142)	PLX Alone (n = 138)	*P*
Lymphedema			
Negative	109	99	
Positive	33 (23.2%)	39 (28.3%)	0.34
Lymphocyst (≥6 cm)			
Negative	129	125	
Positive, noninfected	7 (4.9%)	8 (5.8%)	0.94†
Positive, infected	6 (4.2%)	5 (3.6%)	0.80‡
Positive, asymptomatic	5 (3.5%)	8 (5.8%)	
Positive, symptomatic	8 (5.6%)	5 (3.6%)	0.42§
Thrombosis			
Negative	135	135	
Positive, asymptomatic	2 (1.4%)	0	0.21‖
Positive, symptomatic	5 (3.5%)	3 (2.2%)	0.50¶
Ileus*			
Negative	125	133	
Mild	5 (3.5%)	4 (2.9%)	0.0094#
Moderate	10 (7.0%)	0	0.0021**
Severe	2 (1.4%)	1 (0.7%)	0.58††
Intraoperative Organ Injury			
No	138	135	
Yes	4 (2.8%)	3 (2.2%)	0.73
Second Operation for Postoperative Complication			
Not done	135	132	
Done	7 (4.9%)	6 (4.3%)	0.82

*Mild, improvement by conservative management within ten days and sufficient status to tolerate adjuvant treatment at 1 month after surgery; moderate, improvement by conservative management for more than ten days and sufficient status to tolerate adjuvant treatment at 1 month after surgery; severe, insufficient status to tolerate adjuvant treatment at 1 month after surgery.

†For negative versus positive.

‡For negative/positive, noninfected versus positive, infected.

§For negative/positive, asymptomatic versus positive, symptomatic.

‖For negative versus positive.

¶For negative/positive, asymptomatic versus positive, symptomatic.

#For negative versus mild/moderate/severe.

**For negative/mild versus moderate/severe.

††For negative/mild/moderate versus severe.

The rates of cases of postoperative lymphocyst with a maximum diameter of 6 cm or more were 9.2% (n = 13) in the PLX + PALX group and 9.4% (n = 13) in the PLX group, the difference not being statistically significant (P = 0.94). Among the 26 patients with lymphocyst, 10 patients (38.5%) needed secondary surgery.

The rates of cases of deep vein thrombosis or pulmonary thromboembolism were 4.9% (n = 7) in the PLX + PALX group and 2.2% (n = 3) in the PLX group, the difference not being statistically significant (P = 0.22). Among the 7 patients with thrombotic disease in the PLX + PALX group, 2 patients did not receive any perioperative preventive measures including wearing an elastic stocking, use of intermittent pneumatic compression, and administration of heparin.

The rates of cases of postoperative ileus were 12.0% (n = 17) in the PLX + PALX group and 3.6% (n = 5) in the PLX group, the difference being statistically significant (P = 0.0094). However, the rates of cases of postoperative severe ileus were 1.4% (n = 2) in the PLX + PALX group and 0.7% (n = 1) in the PLX group, the difference not being statistically significant (P = 0.58). None of the 9 patients with mild ileus needed nasogastric intubation, and they could all

TABLE 4. Incidence of postoperative ileus in 280 patients who underwent surgical treatment including lymphadenectomy

	Postoperative Ileus (Mild to Severe)		
	n/N	Percent (%)	*P*
Age, yrs			
<65	16/222	7.2	
≥65	6/58	10.3	0.43
BMI, kg/m^2			
<26	16/185	8.6	
≥26	5/94	5.3	0.32
FIGO Surgical Stage (1988)			
I/II	18/211	8.5	
III/IV	4/69	5.8	0.61
Type of Lymphadenectomy			
PLX	5/138	3.6	
PLX + PALX	17/142	12.0	0.0094
Adjuvant Chemotherapy			
Not done	12/161	7.5	
Done	10/119	8.4	0.77
Adjuvant Radiation Therapy			
Not done	22/270	8.1	
Done	0/10	0.0	>0.9999

take meals after 3 to 7 days of fasting. Of the 10 patients with moderate ileus, 2 (20%) patients needed nasogastric intubation. The median postoperative day for taking a meal was day 20 (range, days 14–23) in patients with moderate ileus. Drip treatment was stopped within 7 days from the day for taking a meal. Among the 3 patients with severe ileus, one in the PLX + PALX group had secondary surgery 2 years after the initial surgery. The remaining 2 patients did not need surgery but needed nasogastric intubation, and it took more than 1 month to improve. Age, body mass index, and FIGO stage were not significantly associated with postoperative ileus (Table 4).

The rates of cases of intraoperative organ injury were 2.8% (n = 4) in the PLX + PALX group and 2.2% (n = 3) in the PLX group, the difference not being statistically significant ($P = 0.73$). The organs injured were the ureter in 2 cases and the bladder, small bowel, sigmoid colon, obturator nerve, and inferior mesenteric artery each in one case.

The rates of patients requiring secondary operation for postoperative complications were 4.9% (n = 7) in the PLX + PALX group and 4.3% (n = 6) in the PLX group, the difference not being statistically significant ($P = 0.82$). Among the 13 cases, the most frequent reason for reoperation was infected lymphocyst in 8 cases. Other reasons were noninfected lymphocyst in 2 cases, hydronephrosis in one case, ileus in one case, and sigmoid colon injury in one case. Eleven patients underwent the secondary operation within 2 months after the initial operation, and 2 patients had the reoperation more than 2 years after the initial surgery.

DISCUSSION

According to recent prospective randomized trials, lymphadenectomy is not needed for patients with low-risk endometrial cancer.[1,2] On the other hand, systematic lymphadenectomy including PALX might have therapeutic significance for patients with high-risk endometrial cancer.[9] It has been reported that the 5-year survival rates were relatively high (79%–85%) for patients with FIGO stage III endometrial cancer who had been treated at tertiary hospitals in which systematic PALX was routinely performed.[19,20] On the other hand, the 5-year survival rate was 65% for patients with FIGO stage III endometrial cancer who had been treated at tertiary hospitals in which systematic PALX was not performed,[21] and this rate is similar to the 5-year survival rate of 62% for FIGO stage III in the 26th FIGO annual report.[22]

Whether selective lymphadenectomy increases morbidity or not is controversial. The A Study in the Treatment of Endometrial Carcinoma (ASTEC) trial showed that selective lymphadenectomy increases morbidity,[1] whereas other studies showed that it does not increase morbidity.[10,11] On the other hand, systematic lymphadenectomy needs a longer operation time and increases postoperative complications. Kodama et al[16] reported that 25.1% of patients with a median number of 46 lymph nodes removed had at least one complication. According to that report, the most frequent complication was lymphedema (8.1%) and the second most frequent complication was ileus (6.2%), but no serious complication was found. The incidence rate of lower extremity lymphedema that originates in systematic lymphadenectomy has been reported to be 23.4% to 37.8%.[23–25] We could clarify that PALX did not increase lymphedema in this study.

The incidence rate of ileus that originates in systematic PLX and PALX has been reported to be 8.4% to 50.0% in patients with a malignant gynecologic tumor.[12–14] In retrospective studies, the incidence rates of ileus were 8.4% to 12.9%, being relatively low.[12,13] In a prospective study, the incidence rate of ileus was 50.0%.[14] Fujita et al[12] reported that severe ileus occurred in 1.4% of patients with PALX and concluded that PALX is a feasible and safe operative procedure. Gol et al[13] reported that the incidence of ileus in patients aged 65 years or older was 8.0% and that no difference was found between patients aged 65 years or older and those aged 64 years or younger. Fagotti et al[14] reported that the incidence of ileus in patients with PALX was 50.0% and that severe ileus occurred in 10.7% of patients with PALX, but all patients recovered with only conservative management. Regarding the definition of severity of ileus, we drew a line between moderate and severe according to whether a patient is able to tolerate adjuvant treatment at 1 month after surgery or not. In the present study, the incidence of mild/moderate ileus in the PLX + PALX group was significantly higher than that in the PLX group. On the other hand, there was no difference in the incidence of severe ileus between the 2 groups. The former result, however, might not be entirely due to PALX because the numbers of pelvic lymph nodes

harvested in the PLX + PALX group was significantly larger than that in the PLX group. Our study has a limitation about this issue. The latter result suggested that the incidence of unmanageable ileus does not depend on addition of PALX.

A few reports have shown that the incidence rates of thrombosis originating in systematic PLX and PALX were 1.2% to 5.6%.[13,14] However, there has been no discussion in any report of whether PLX + PALX causes postoperative thrombosis more frequently than does PLX alone. In the present study, the rate of patients with postoperative thrombosis in the PLX + PALX group was slightly higher than that in the PLX group, the difference not being statistically significant (4.9% vs 2.2%; $P = 0.21$). Among the 7 patients in the PLX + PALX group, 2 patients did not receive any preventive measure. Management to prevent perioperative thrombosis would be very important for patients with PLX + PALX because lymphadenectomy with PALX needs a longer operation period. Although no difference in the rates of cases of postoperative thrombosis was found in our study, this result may be due entirely to appropriate management, including use of intermittent pneumatic compression or postoperative administration of low-dose heparin.

In conclusion, systematic PLX + PALX does not increase the occurrence of lymphedema, lymphocyst, thrombosis, severe ileus, intraoperative organ injury, and reoperation for postoperative complications compared to systematic PLX. We should emphasize that PLX + PALX has been performed by experienced surgeons with active management including use of intermittent pneumatic compression, postoperative administration of an anti-coagulant, and preoperative storage of autologous blood. Para-aortic lymphadenectomy can be performed with an acceptable morbidity under the conditions in which it is performed by experienced surgeons, and measures to prevent complications are properly taken.

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ORIGINAL PAPER

Identification of potential serum markers for endometrial cancer using protein expression profiling

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Abstract

Objectives Screening method of endometrial cancer (EC) has not been established yet. Our study was to explore serum biomarkers of EC patients using surface-enhanced laser desorption and ionization-time-of-flight mass spectrometry (SELDI-TOF MS).

Methods Serum samples from 65 EC patients and 40 controls were analyzed by SELDI-TOF MS (training set). Single- and multi-variant analyses were performed to compare protein profiles in serum of EC patients and healthy controls. Subsequently, blind test set including 40 EC patients and 40 controls were analyzed for validation.

Results A panel of four biomarker candidates were selected in training set analysis. These markers could also distinguish stage I patients from controls. Among them, two biomarkers were purified and identified as apolipoprotein A1 and a modified form of apolipoprotein C1. Screening for blind test set using dual-biomarker analysis yielded a sensitivity of 82% and a specificity of 86%.

Conclusions Involvement of apolipoproteins with EC is first suggested in this study. In addition to possibility of screening method for EC, findings of these new biomarkers might be related with carcinogenesis or predisposition to EC.

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Keywords Endometrial cancer · Screening · Proteomics · Serum biomarker · Apolipoprotein

Introduction

Endometrial cancer (EC) is the most common malignancy of the female reproductive tract and its incidence is increasing in North America and Europe (Amant et al. 2006; Shang 2006). There are numerous reports regarding screening methods for EC. Elevation of CA125 has been detected in a number of gynecologic diseases including EC (Jacobs and Bast 1987). However, raised serum levels of CA125 (>35 U/ml) have been reported in only 11–33.9% of the patients of this disease, and elevation of CA125 was closely related with only advanced disease (Gadducci et al. 2004). Additionally, elevation of other tumor-associated markers, such as CA19-9, CEA, and CA15-3, were detected in only one-fourth of the patients (Cherchi et al. 1999). Although the utilities of ultrasound or hysteroscopy in combination with biopsy and cytology significantly improved the screening efficacy of EC (Emoto et al. 2002; Minagawa et al. 2005; Tabor et al. 2002; Mutter et al. 2000), some cases would still be missed with false-positive test results.

Surface-enhanced laser desorption/ionization mass spectrometry (SELDI-MS) is a proteomic technique which enable to identify multiple differentially expressed proteins in a large set of samples. The ProteinChip SELDI system (Bio-Rad Laboratories; Hercules, CA) has been applied for the discovery of new biomarkers in many diseases. In the present study, we have attempted to find out novel biomarkers for EC. Through the proteomic analysis of ProteinChip SELDI system, two biomarkers related with metabolism of lipid, were discovered. In addition to application for the detection of EC, these findings may be closely related with the carcinogenesis of the tumors.

Materials and methods

Patient and serum sample preparation

Serum samples from pathologically confirmed endometrial cancer (EC) patients were obtained after written informed consent. The study was performed after approval of each institutional review board. Between April of 2005 and October of 2006, all patients were treated in collaborating hospitals in Japan; National defense medical college hospital, Ohki memorial Kikuchi cancer clinic for women, Teikyo university hospital, Tottori university hospital, Hokkaido university hospital, Sasaki research institute Kyoundo hospital, Iwate medical university hospital, Tohoku university hospital, Osaka city general hospital, Seto hospital. Further, blood samples from age-matched healthy controls were obtained with written informed consent. For the training set, we analyzed serum samples of 40 healthy controls and 65 EC cases; 50 stage I, 7 stage II, and 8 stage III tumors. Next, 40 endometrial cancers and 40 healthy controls ware analyzed for the validation study for blind test set analysis (Table 1). Endometrial cancer group of training set included 49 cases of endometrioid grade 1 (stage I 40, stage II 5, stage III 4), 11 cases of endometrioid grade 2 (stage I 7, stage II 2, stage III 2), and 5 cases of endometrioid grade 3 or other carcinoma (stage I 3, stage III 2). Endometrial cancer group of blind set group included 28 cases of endometrioid grade 1 (stage I 20, stage II 3, stage III 5), 9 cases of endometrioid grade 2 (stage I 6, stage II 1, stage III 2), and 3 cases of endometrioid grade 3 or other carcinoma (stage I 2, stage III 1). Approximately 8 ml of blood was drawn by venipuncture and placed on ice. The samples were centrifuged at 3,000 rpm for 20 min within 2 h and serum was aliquoted and stored at −80° until use.

Table 1 Number of the patients in training set and blind test set

Group	Training set	Blind test set
Control group	40	40
Endometrial cancer group	65	40
FIGO stage		
Stage I	50	28
Stage II	7	4
Stage III	8	8
Histology		
Endometrioid, grade 1	49	28
Endometrioid, grade 2	11	9
Endometrioid, grade 3 or others	5	3

FIGO The International Federation of Gynecology and Obstetrics

SELDI ProteinChip array

Serum samples endometrial cancer patients and controls were denatured by 9 M urea, 2% CHAPS, 50 mM Tris–HCl, pH 9 and were pre-fractionated into six fractions using strong anion exchange resin by reducing of buffer pH. Obtained fractions were incubated in three different chip conditions; CM10, H50, and IMAC30 arrays (Bio-Rad Laboratories). Pretreatment with binding and washing buffers was performed according to the manufacture's instruction. All sample pre-fractionation and chip profiling process was performed by Biomek2000 robot (Beckman Coulter, Inc., Fullerton, CA). Briefly, arrays were incubated with 150 µl binding buffer [100 mM Sodium Acetate (pH4) and 50 mM HEPES (pH7) for CM10 chip, 50 mM HEPES (pH7) for H50 chip, and 100 mM Sodium Phosphate (pH7)/0.5 M NaCl for Copper immobilized IMAC30 chip] for 5 min followed by application of 10 µl of pre-fractionated

serum samples and 90 μl binding buffer to each spot. After incubation for 30 min at room temperature, spots were washed three times with binding buffer for 5 min and rinsed with distilled water. After air drying, 0.5 μl of a saturated solution of sinapinic acid or of a 50% saturated solution of α-cyano-4-hydroxycinnamic acid)in 0.5% trifluoroacetic acid and 50% acetonitrile was applied onto each bait surface of arrays. Following a final air drying, protein profiles were read using SELDI-TOF MS (ProteinChip SELDI System, Bio-Rad Laboratories) on the same day. All samples were run in duplicate to confirm the consistency of assay.

Statistical analysis and SELDI-TOF mass spectra

All of the duplicated spectra were complied, and the protein peak intensities were normalized using ProteinChip Data Manager Software (Bio-Rad Laboratories). The mass range from 3,000 to 10,000 *m/z* was measured as a low mass range, and the mass range of 10,000 to 30,000 *m/z* was measured as a high mass range. Maximum measured mass range was 200,000 *m/z*. Next, peak clustering was generated, and single- and multi-marker analyses were performed to compare protein profiles in serum of endometrial cancer patients and healthy controls. Receiver operating characteristics (ROC) curves was constructed to evaluate the predictive power for each peak, and Mann–Whitney test were used for statistical analysis. A P value of <0.05 was considered significant. Further multi-marker analysis such as classification analysis were performed by ProteinChip Pattern Analysis Software (Bio-Rad Laboratories).

Protein Identification

After purification of the marker candidates, they were excised from the polyacrylamide gel stained with Colloidal Blue Staining Kit (Invitrogen Japan K.K., Tokyo, Japan). The extracts were applied to NP20 ProteinChip arrays and reanalyzed with the ProteinChip Reader to confirm *m/z* values of the excised/extracted proteins. After treatment with trypsin, peptide identification was performed using the tandem mass spectrometer equipped with a PCI-1000 ProteinChip Interface (Ciphergen Biosystems, Inc.). MS/MS spectra were submitted to the database mining tool (Mascot; Matrix Sciences) for identification.

Results

Discovery of endometrial cancer-specific serum biomarker in training set

Initially, a total of 9,175 peaks were detected in SELDI-TOF MS analysis in the *m/z* region of 1,000–10,000.

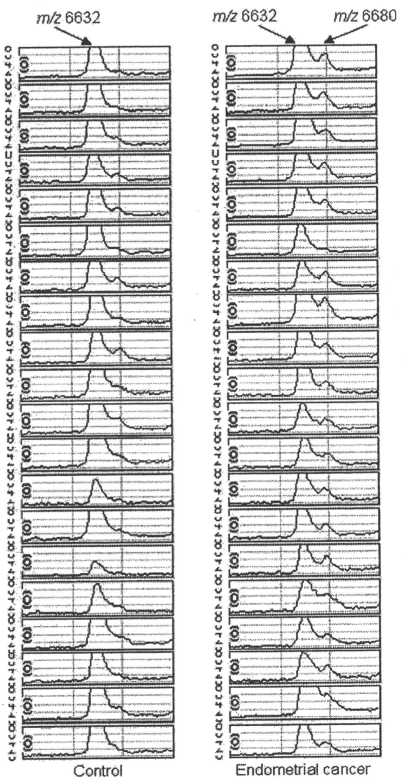

Fig. 1 Representative differential SELDI-TOF mass spectra of serum samples of endometrial cancer patients and healthy control. The mass spectrographic profile reveals upregulation of *m/z* 6,680 peak in endometrial cancer patients

Among these peaks, the spectra generated from control group and endometrial cancer group were analyzed using ProteinChip Pattern Analysis Software. In these peaks, eight peaks were discovered for the discrimination of endometrial cancer and non-cancer control. Finally, four markers were selected as candidates after reproducibility check. These four peaks corresponded to *m/z* of 3,340, 6,680, 9,300, 28,000 (Table 2). The peaks at *m/z* ratio of 3,340, 6,680 were upregulated, and the peaks at *m/z* ratio of 9,300, 28,000 were downregulated in the cancer group. Peak intensity of the candidate at *m/z* of 6,680 was increased in

Table 2 Peak intensity and area under the curve (AUC) of receiver operating characteristics (ROC) analysis for biomarker candidates

Biomarker candidate (*m/z*)	Peak intensity	EC/control	AUC	*P* value
6,680	9.37 ± 1.83	1.13 ± 0.22	0.88	0.00001
3,340	7.43 ± 1.17	1.16 ± 0.18	0.92	0.00000017
28,000	0.21 ± 0.05	0.72 ± 0.17	0.86	0.000056
9,300	0.49 ± 0.09	0.88 ± 0.16	0.88	0.000015

EC Endometrial cancer

endometrial cancer patients compared with control (Fig. 1), and the differences was also significant for the stage I patients only (mean value; 9.57 vs. 8.31, $P = 0.00003$). Serum level of the candidate at *m/z* of 28,000 was significantly decreased in endometrial cancer patients compared with control, and the difference was still significant when the cases were limited in the stage I patients (mean value; 0.20 vs. 0.29, $P = 0.0003$). ROC curves of the biomarker candidates at 6,680 *m/z* and at 28,000 *m/z* are shown in Fig. 2. The AUC of the ROC plot was 0.88 at *m/z* of 6,680, and 0.86 at *m/z* of 28,000, respectively.

There were no significant differences of mean peak intensities of four biomarkers between grade 1/2 endometrioid adenocarcinoma cases and grade 3 endometrioid adenocarcinoma/other carcinomas (data not shown).

Identification of the candidates

The *m/z* 28,000 peak was purified and identified as apolipoprotein A1. All five tryptic digested peptides were sequenced by tandem mass spectrometry and confirmed this finding. The *m/z* 9,300 peak was identified triple charge of *m/z* 28,000 peak, apolipoprotein A1.

Peaks at *m/z* ratio of 6,632 were neighboring on the peaks at *m/z* 6,680, and higher than the peaks. There was no statistical significant difference of *m/z* 6,632 peak intensity between control and EC group (data not shown). The molecular weight (MW) of the 6,680 Da peptide and neighboring peptide (6,632 Da) were searched against SWISS-PROT using TagIdent that predicts protein/peptide by MW and pI. The neighboring peptide at 6,632 Da was predicted as apolipoprotein C1. To confirm *m/z* 6,680 is apolipoprotein C1 related protein or not, the interaction assay was established by using PS10 Chip (Bio-Rad Laboratories) attaching anti-human antibody of apolipoprotein C-1 (abcam plc., Cambridge, UK) or control antibody were prepared for interaction analysis. The *m/z* 6,632 peak located close to the present candidate at *m/z* 6,680 was identified apolipoprotein C-1 through SELDI-TOF MS interaction study. Target peak at *m/z* 6,680 as well as peak at *m/z* 6,632 (apolipoprotein C-1) was detected through the ProteinChip attaching anti-apolipoprotein C-1 antibody, but the peak was not detected by the ProteinChip attaching control immunoglobulin G (Fig. 3). This candidate protein was identified as a modified form of apolipoprotein C1. The peak at *m/z* ratio of 3,340 was identified as double charge of candidate protein showing peak at *m/z* 6,680.

Validation analysis for screening of endometrial cancer in blind test set

The efficacy of these biomarkers for detection of EC was summarized in Table 3. From the efficacy of the training set analysis, cut off point of peak intensity level was determined as 0.2 for *m/z* 28,000, and 9.8 for *m/z* 6,680, respectively. In training set analysis, dual-marker analysis of these two biomarkers yielded a sensitivity of 78% and a specificity of 90%. In the analysis for blind test set, dual-marker analysis of two peaks yielded a sensitivity of 82% and a specificity of 86% (Table 3).

Discussion

Using ProteinChip techniques, many studies have isolated serum biomarkers of malignancy for the detection of early stage tumors. However, there have been few reports analyzing

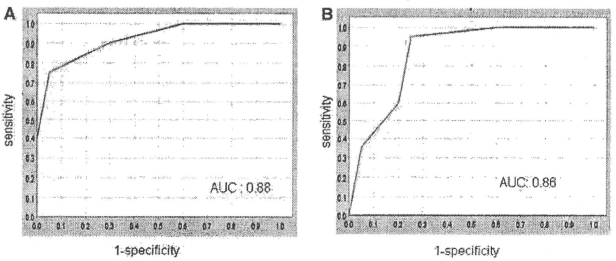

Fig. 2 Receiver operating characteristics (ROC) curves of the biomarker candidates at 6,680 *m/z* (**a**) and at 28,000 *m/z* (**b**). The area under the curve (AUC) of the ROC curve was 0.88 at 6,680 *m/z* and 0.86 at 28,000 *m/z*

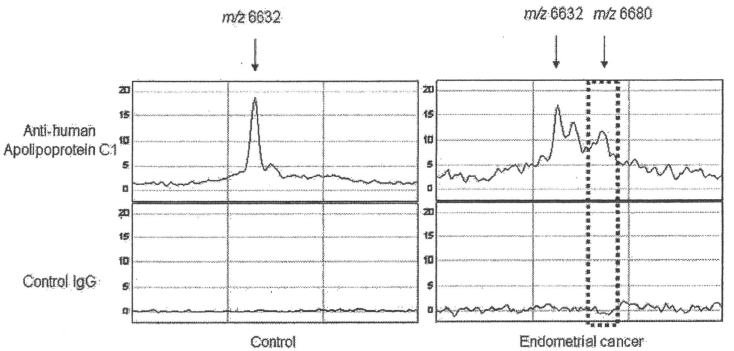

Fig. 3 Representative SELDI-TOF MS profiles of interaction study for serum samples of endometrial cancer patients and controls. Target peak at *m/z* 6,680 as well as peak at *m/z* 6,632 (apolipoprotein C-1) was detected through the ProteinChip attaching anti-apolipoprotein C-1 antibody, but the peak was not detected by the ProteinChip attaching control immunoglobulin G

Table 3 Efficacy of candidate biomarkers for detection of endometrial cancer

Group of analysis	Single marker analysis (28,000 *m/z*)			Dual-marker analysis
	Cut off of average peak intensity			28,000* and 6,680 *m/z*
	0.2	0.235	0.25	
Training set				
Sensitivity (%)	48	58	69	78
Specificity (%)	95	70	60	90
Blind test set				
Sensitivity (%)	55	68	75	82
Specificity (%)	90	75	68	86

*Cut off of average peak intensity was 0.2 of 28,000 *m/z*

serum biomarkers for endometrial cancer (EC). In the present study, two candidate serum markers were discovered using this proteomic analysis. One marker was downregulated, and the other was upregulated in patients with EC.

Many authors have described on the pathogenesis of EC. Alteration of *PTEN* appeared to be the earliest and most fundamental genetic change, and observed in up to 80% of EC tumors (Mutter et al. 2000, 2001; Kanamori et al. 2001, 2002; Salvesen et al. 2004). Mutations of *K-ras* were observed in up to 30% of the EC tumors (Lagarda et al. 2001; Lax et al. 2000; Enomoto et al. 1995). Alterations of *p53* were not commonly observed in tumors of ECs, whereas grade 3 EC tumors harbored the mutations of *p53* (Lax et al. 2000; Kolasa et al. 2006; Feng et al. 2005). Recently, the extracellular-regulated kinase and PI3K pathway had been reported as another important pathway related to carcinogenesis and prognosis of EC patients (Mori et al. 2007; Mizumoto et al. 2007; Velasco et al. 2006). Through the global expression analysis by proteomics, other distinct biomarkers have been discovered. Using SELDI-TOF MS technology, a study has shown increased expression of chaperonin 10, a member of heat shock protein, in tissue samples of EC (Yang et al. 2004). Further, the authors have identified calgranulin A as another biomarker for EC. Calgranulin A is a member of S100 family of calcium binding protein and might be involved in inflammation caused by malignant tumors (Guo et al. 2005). Yoshizaki et al. (2005) have investigated that EC tumors showed increased peak level at *m/z* 9,600 and decreased expression level at *m/z* 11,300 by SELDI-TOF MS analysis. These biomarkers discovered by proteomic analysis have not been clearly implicated in EC; however, the findings would facilitate the pathogenic analysis of EC and be expected for new clinical markers of screening or monitoring EC.

Two biomarkers discovered in the present study belong to apolipoproteins. Downregulation of serum apolipoprotein A1 has been observed in several cancers including ovary

(Zhang et al. 2004; Gadomska et al. 2005; Kozak et al. 2005; Moore et al. 2006), breast (Huang et al. 2006; Chang et al. 2007), pancreas (Ehmann et al. 2007). Apolipoprotein A1 is the major lipoprotein found in high density lipoprotein (HDL), and has been found to have potent anti-inflammatory and antioxidant properties (Navab et al. 2007). Considering the concept that inflammation is a critical component for tumor progression has been widely accepted (Coussens and Werb 2002), it is possible that apolipoprotein A1 might be related with predisposition of the host to EC.

Recently, the clinical and pathological effects of apolipoprotein C-1 upon malignancy have been elucidated (Takano et al. 2008). Apolipoprotein C-1 was highly expressed in pancreas cancer cells, and is also detected in the culture medium of the pancreatic cancer cell line in vitro, suggesting that cancer cells secrete apolipoprotein C-1. Also, apolipoprotein C-1 is related with cell proliferation and cell apoptosis in vitro, and with the aggressiveness of pancreatic cancer in vivo. Furthermore, RELN pathway through signaling via the very low density lipoprotein (VLDL) receptor, to which apolipoprotein C-1 is known to bind, influences cell motility in pancreatic cancer (Sato et al. 2006). The *m/z* 6,680 peak detected in the present study was identified as a modified form of apolipoprotein C-1, but the modification of the protein has not been elucidated yet. The identification of the modification would facilitate further understanding of the pathogenesis or host reaction to EC tumors.

In the blind test set analysis for EC screening, the sensitivity of single marker test using apolipoprotein A-1 (*m/z* 28,000) yielded up to 75%, and dual-marker analysis showed a sensitivity of 82%. However, the specificity was 68–90% in single marker test with apolipoprotein A-1 and 86% in dual-marker analysis. The cut off points for cancer screening should be selected to maximize sensitivity, but that would lead to lower specificity. Further discovery of new biomarkers or new imaging technology might contribute to maximal screening effects in combination with the present biomarkers. For the successful application of these biomarkers, apolipoprotein A-1 and a modified form of apolipoprotein C-1, additional work to assure consistency of measured peak intensities without institutional bias and sample bias is needed and the investigation should be confirmed in the prospective analysis for EC.

Conflict of interest statement We declare that we have no conflict of interest.

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原　著

子宮内膜間質肉腫18例の臨床病理学的検討

Clinicopathological study of 18 cases of endometrial stromal sarcoma

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概要：3施設において経験した子宮内膜間質肉腫(ESS)症例を臨床病理学的に検討し報告する．診断・治療を行ったESS症例は18例(low-grade 11例，high-grade 6例，grade不明1例)で年齢は32～69歳(平均51.5歳)であった．主訴は，不正性器出血が最も多く44.4%（8/18）認めた．術前診断は子宮筋腫が38.9%（7/18）であり，術前にESSと診断された症例は11.1%（2/18）であった．腫瘍マーカーでLDHの上昇を認めた症例が62.5%（5/8）であった．手術療法を行った症例は15例，化学療法のみ行った症例は2例であった．術後療法として抗癌剤投与（IAP療法3例，CYVADIC療法3例，TC療法1例，DC療法1例），MPA内服6例，放射線療法1例，経過観察3例であった．転帰に関しては，原病死が4例，無病生存が13例，不明が1例(観察期間1～192カ月，中央値24カ月)であった．ESSは稀な疾患であり，今回の検討では術前の正診率も低く管理方法も一貫性がなかった．多施設での症例の集積と解析により治療方法の確立が望まれる．

Synopsis: Clinicopathological studies on patients with endometrial stromal sarcoma (ESS) who were managed at 3 facilities are reported below.

The subjects were 18 patients with ESS who underwent diagnosis and treatment. There were 11 of the low-grade, 6 of the high-grade, one of an unknown grade. Their ages ranged from 32 to 69 years (mean; 51.5). The most frequent major complaint was irregular vaginal bleeding (8 patients, 44.4%). Pre-operative diagnoses included ESS (2 patients, 11.1%), Elevation of serum LDH, a tumor marker, was noted in 5 (62.5%) of 8 patients. Surgical procedures were applied to 15 patients, while 2 patients received only chemotherapy. For postoperative treatment, 8 underwent chemotherapy (IAP for 3, CYVADIC for 3, TC and DC for one each); Oral MPA was given to 6 patients; one underwent radiotherapy; and 3 remained under observation. The outcome of the diseases was recorded as follows: 4 succumbing to the original disease; 13 enjoying a disease-free status; and one lost to follow-up (observation period: 1 to 192 months; median, 24 months).

ESS is a rare disease: the current study found that its preoperative diagnosis lacked accuracy and a therapeutic approach without uniformity. It is desired that through the accumulation of more clinical data at a larger number of facilities and their analyses, a system may be established to delineate more appropriate therapeutic modalities.

Key words: uterine body, clinicopathologica study, endometrial stromal sarcoma

はじめに

子宮内膜間質肉腫（endometrial stromal sarcoma；ESS）は子宮体部悪性腫瘍中約0.5%であり[1]，非上皮性悪性腫瘍の中でも約10%と稀な疾患である[2]．悪性度の低いlow-gradeと悪性度の高いhigh-gradeに大別（新しいWHOの分類ではundifferentiated endometrial sarcoma；UES）され，低悪性度が全体の80%を占める．low-gradeは比較的長期予後が期待できるが，high-gradeは進行した状態で発見されることが多く，また，再発率も高いため予後が不良である．治療法として手術療法が一般的であり，化学療法は奏効率が悪く，有効な治療法はいまだ確立されていない．

今回3大学病院において経験したESS症例を臨床および病理学的所見を中心に解析したので報告する．

対象と検討方法

聖マリアンナ医科大学7例（1998年から2006年まで），北里大学5例（1971年から2005年まで），東海大学6例（1975年から2006年まで）の18例を対象とした(表1)．症例は各大学で診断された病理学診断をもとに集積した．

臨床所見および病理学的所見を中心に後方視的に検討した．検討した項目に関しては，年齢・発症時期・主訴・LDH値・術前診断・病理結果・臨床進行期・初回治療・後治療・転帰・免疫染色について集積した．

結　果

臨床所見と術前診断を表2に示す．

ESS 18症例の内訳は，low-grade 10例，high-grade 7例，grade不明が1例であった．low-gradeの発症年齢は平均47.9歳high-gradeが57.0歳であり約10歳の差を認めた．low-gradeは閉経前発症が7例，閉経後発症が3例，またhigh-gradeの閉経前発症が3例，閉経後発症が4例であった．

主訴は不正性器出血が44.4%（8/18）と最も多く，過多月経および腹部膨満感が11.1%（2/18）であった．術前の診断では子宮筋腫と診断した症例が最も多く38.9%（7/18）であり，術前にESSと診断された症例は11.1%（2/18）と低い結果となった．また，術前に測定したLDHで上昇を認めた症例は62.5%(5/8)であり，ESSの腫瘍マーカーになる可能性が示唆された．初回治療で術前化学療法（Neoadjuvant chemotherapy；NAC）を行った症例は1例，手術療法は15例，化学療法は2例であった．NACの1症例はIAP（ifosfamide＋adriamysin＋cisplatin）療法を施行した(表3)．手術療法は腹式子宮全摘術（total abdominal hysterectomy；TAH）を行った症例が12例あり，骨盤内リンパ節郭清を行った症例は2例あった．子宮筋腫の診断で筋腫核出術，子宮内膜全面掻爬を行った症例が各1例であった（表4)．

術後の後療法に関してはESS low-gradeはホルモン療法としてmedroxyprogesteron acetate（MPA）内服が6例と最も多く，化学療法を行った例が4例（IAP療法2例，CyVADIC（cyclophosphamide＋vincristine＋adriamycin＋dacarbazine）療法2例）であった．また，再発に対して放射線療法を行った症例を1例認めた（表5）．ESS high-gradeの術後療法は4例化学療法（IAP療法1例，CyVADIC療法1例，TC（paclitaxel＋carboplatin）療法1例，DC（docetaxel＋carboplatin）療法1例）を行ったが（表6），施行したレジメンに一貫性はなかった．

ESS low-gradeの転帰は原病死が1例，無病生存例が8例（観察期間9～192カ月，中央値22カ月），不明が1例であった．ESS high-gradeに関しては原病死が3例，無病生存例が4例（観察期間1～108カ月，中央値45カ月）であった．

集積した症例に古い症例もあり，免疫染色のデータが不十分で症例数が少ないが，集積した免疫染色の結果を示す．子宮内膜間質細胞表面の中性の膜蛋白であるCD10が陽性を示す症例は100%（6/6），間質系マーカーであるvimentinも100%（6/6）であった．上皮系細胞のマーカーであるcytokeratinは14.2%（1/7），ERは50%（5/10），PRは70%（7/10）に陽性であった（表7）．

考　察

ESSの平均発症年齢は45歳前後と言われており[3]，今回の検討でもlow-gradeの発症年齢は平均47.9歳，high-gradeが57.0歳と約10歳の差を

表1　3施設における症例数

施設名	期間	症例数
聖マリアンナ医科大学	1998年から2006年まで	7
北里大学	1971年から2005年まで	5
東海大学	1975年から2006年まで	6

表2　臨床所見と術前診断

	年齢	閉経前・後	主訴	LDH (IU/ml)	術前診断
1	64	後	帯下異常	201	肉腫疑い
2	58	後	不正性器出血	209	肉腫疑い
3	49	前	不正性器出血	2,707	肉腫
4	50	前	不正性器出血	300	筋腫
5	46	前	腹部膨満感	182	卵巣腫瘍疑い
6	49	前	不正性器出血	257	筋腫
7	53	後	不正性器出血	327	筋腫
8	65	後	不正性器出血	1,261	肉腫疑い
9	39	前	過多月経	—	ESS, low-grade
10	69	後	下腹部痛	—	肉腫疑い
11	56	前	不正性器出血	—	ESS, high-grade
12	49	不明	検診目的	—	卵巣腫瘍疑い
13	43	前	筋腫分娩	—	子宮筋腫
14	36	前	過多月経	—	粘膜下筋腫
15	63	後	下腹部腫瘤感	—	卵巣癌
16	41	前	腹部膨満感	—	子宮筋腫
17	32	前	不正性器出血	—	子宮筋腫
18	65	後	子宮腫大指摘	—	肉腫疑い

表3　病理結果および治療

	病理	臨床進行期	初回治療	後治療	転帰
1	low-grade	IVb	TAH + BSO	MPA内服	N.E.D.（20M）
2	low-grade	I	TAH + BSO	—	N.E.D.（16M）
3	high-grade	IVb	CBDCA単剤DIV	—	死亡（初回治療より1M）
4	low-grade	I	TAH + BSO	—	N.E.D.（117M）
5	low-grade	IVb	TAH + BSO + OMT	MPA内服	N.E.D.（9M）
6	low-grade	I	TAH	不明	不明
7	low-grade	I	semi-radical + BSO + PLN	Rx CyVADIC	死亡（初回治療より31M）
8	high-grade	不明	IAP後，TAH + BSO	IAP	N.E.D.（88M）
9	low-grade	IIIa以上	TAH + BSO + OMT	IAP	N.E.D.（123M）
10	high-grade	Ib	TAH + BSO	DC	N.E.D.（1.5M）
11	high-grade	不明	IAP	—	死亡（初回治療より4M）
12	grade不明	IV	TAH + BSO	IAP, MPA	N.E.D.（34M）
13	low-grade	IIIa	TAH + BSO + Tumorec	CyVADIC MPA	N.E.D.（192M）
14	low-grade	Ia	D&C	MPA	N.E.D.（24M）
15	high-grade	Ib	TAH + BSO	CyVADIC	N.E.D.（108M）
16	low-grade	Ib	TAH + BSO + PLN	MPA	N.E.D.（12M）
17	high-grade	Ib	myomectomy	—	死亡（初回治療より24M）
18	high-grade	不明	TAH + BSO	TC	N.E.D.（1M）

TAH；total abdominal hysterectomy, BSO；bilateral salpingo-oophorectomy, OMT；omentectomy, PLN；pelvic lymphadenectomy, semi-radical；modified radical hysterectomy, MPA；medroxyprogesteron acetate, IAP；ifosfamide + adriamysin + cisplatin, CyVADIC；cyclophosphamide + vincristine + adriamycin + dacarbazine, TC；paclitaxel + carboplatin, DC；docetaxel + carboplatin, Rx；radiation, N.E.D；non evidence of disease

表4　初回治療（手術症例）

TAH + BSO	7例
TAH + BSO + OMT	2例
TAH	1例
TAH + BSO + PLN	1例
TAH + BSO + tumorectomy	1例
Semi-radical + BSO + PLN	1例
myomectomy	1例
全面掻爬	1例
合計	15例

TAH；total abdominal hysterectomy, BSO；bilateral salpingo-oophorectomy, OMT；omentectomy, PLN；pelvic lymphadenectomy, semi-radical；modified radical hysterectomy

表5　ESS low-gradeの後療法

治療		症例数	効果
ホルモン療法	MPA内服	6	CR 6例
化学療法	IAP療法	2	CR 2例
	CyVADIC療法	2	CR 1例　PR 1例
放射線療法		1	
経過観察		2	

MPA；medroxyprogesteron acetate, IAP；ifosfamide + adriamysin + cisplatin, CyVADIC；cyclophosphamide + vincristine + adriamycin + dacarbazine, CR；complete response, PR；partial response

表6　ESS high-gradeの後療法

治療		症例数	効果
化学療法	IAP療法	1	CR 1例
	CyVADIC療法	1	CR 1例
	TC療法	1	不明
	DC療法	1	不明
経過観察		1	

IAP；ifosfamide + adriamysin + cisplatin, CyVADIC；cyclophosphamide + vincristine + adriamycin + dacarbazine, TC；paclitaxel + carboplatin, DC；docetaxel + carboplatin, CR；complete response

表7　免疫染色

CD10陽性	100%（6/6）
vimentin陽性	100%（6/6）
cytokeratin陽性	14.2%（1/7）
ER陽性	50%（5/10）
PR陽性	70%（7/10）

認め，low-gradeの閉経前発症が7例（70%）と高い傾向を示した．初発症状として過多月経や不性器出血が多く[3]，われわれの検討でも不正性器出血が44.4%（8/18）と最も多く，過多月経および腹部膨満感が11.1%（2/18）と続いた．術前診断は困難であり，術後の病理学的診断で初めてESSと診断される場合がほとんどである．ドップラー超音波が診断に有効であるとの報告もあるが[4]，画像上肉腫の診断は困難で，子宮筋腫の術前診断で手術が行われる例が多い[3]．術前診断がつきにくい理由として，腫瘍組織が子宮内膜から主に筋層内に浸潤・進展し内腔に突出することが少ないことや，リンパ管を中心に脈間内に進展することが挙げられる．腫瘍が子宮筋層内を圧排性に浸潤するため，子宮筋腫あるいは子宮腺筋症と診断されることがほとんどで，術前の子宮内膜細胞診・組織診で診断されることは稀である．今回の検討でも術前にESSと診断された症例は11.1%（2/18）と低い結果となり，術前診断が困難であることが示唆された．

免疫組織学検討で子宮内膜間質細胞表面の中性の膜蛋白であるCD10が陽性を示すと報告されている[5)~7)]．今回の検討でもCD10陽性が6例中6例（100%）であったことより，ESSの診断確定に有用であることが示唆された．

初回治療としては手術療法が一般的で子宮全摘術および両側付属器摘出術が行われている[8)]．症例によっては骨盤内リンパ節郭清も追加する必要があるといわれているが一定の見解は得られていない[8)9)]．18症例中初回治療で手術療法を行った15例中リンパ節郭清を行った症例は2症例のみであった．

ESS low-gradeの発育は緩徐で，子宮の限局する症例が60%で，びまん性あるいはポリープ状に発育する[10)]．Piver et al.の報告では，52例のESS low-gradeのうち初回治療後3~274カ月（平均34カ月）に約50%の症例が再発している[11)]．今回の検討でESS low-gradeは10症例認めたが，原病死

1例，無病生存8例（観察期間9～192カ月，中央値22カ月），不明が1例であった．今後，再発に関して慎重に経過をみていく予定である．

ESSの臨床病理学的検討としてChang et al.は109例の検討を行っている[12]．ESSのI期症例で36%に再発を認め，III期およびIV期症例は72.7%，83%と高い再発率を認めた．今回の検討ではI期症例が9例（low grade 6例，high grade 3例），III期症例が2例（low grade 2例），IV期症例が3例(low grade 2例，high grade 1例），不明4例であったが，観察期間が短いこともあり再発症例は認められなかった．

ESS low-gradeは約70～80%の症例でエストロゲン受容体（ER），プロゲステロン受容体（PR）の性ステロイド受容体を発現している[11][13]．ESS low-gradeにおけるER陽性が83.3%，PR陽性が100%であったことから（表7），ホルモン療法の適応の可能性が再認識された．今回，後療法としてmedroxyprogesteron acetate（MPA）投与したが，6例全例ともCRであった．これより，ESS low-gradeの後療法としてホルモン療法の重要性が示唆された．

ESS high-gradeは，閉経後に発症することが多く，無症状で子宮腫大から発見されることが多い．治療は手術療法が第一選択となり，一般的な術式は腹式単純子宮全摘術および両側付属器摘出術であり，リンパ節郭清の意義は今のところ不明である[14]．術後追加治療としてホルモン療法，放射線療法および化学療法などが行われているが，進展の早いESS high-gradeに対してホルモン療法の効果は期待し難いとされており[15]，外科的に病巣を摘出することが非常に重要である．しかしながら，完全摘出例であっても再発することが多く，予後は極めて不良である．ESS high-gradeに対してTC療法[16]，IAP療法[17]の有効性例，isosfamide投与による33%の有効率[18]が報告されているが，有効な治療法が確立されていない．今回検討したESS high-gradeの4例の後療法においてもIAP療法1例，CyVADIC療法1例，TC療法1例，DC療法1例と一貫性がなかった．IAP療法ではCRが1例，CyVADIC療法はCRが1例であった．今回の検討では，症例数が少ないためhigh-gradeにおける有用なレジメンを決めることができなかった．更なる症例の集積と解析により治療法を確立する体制が望まれる．

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