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A retrospective study on combination therapy with ifosfamide, adriamycin and cisplatin for progressive or recurrent uterine sarcoma

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Abstract. There is currently insufficient evidence to recommend a specific chemotherapeutic regimen as standard treatment for uterine sarcomas. In this study, we investigated the toxicity and effectiveness of ifosfamide, adriamycin and cisplatin (IAP therapy) in patients with progressive and recurrent uterine sarcoma. A total of 11 patients with progressive or recurrent uterine sarcoma containing leiomyosarcoma (LMS), undifferentiated endometrial sarcoma (UES) or adenosarcoma, who were diagnosed at our institution, were retrospectively investigated. We recorded the adverse events, response rate and progression-free survival in these cases. The histological types included LMS (54.5%), adenosarcoma (27.3%) and UES (18.2%). Grade ≥3 leukopenia or neutropenia were observed in all the cases, febrile neutropenia developed in 45.5% of the patients and grade 4 thrombocytopenia developed in 3 cases (27.3%). With IAP therapy, the response rate was 36.4% and the disease control rate was 90.9%. Therefore, IAP therapy may be a viable option as chemotherapy for uterine sarcoma.

Introduction

Uterine sarcomas are extremely rare, non-epithelial malignant uterine tumors. Uterine sarcomas account for 8% of all malignant tumors of the corpus uteri and the most common histological types are carcinosarcoma (CS), leiomyosarcoma (LMS) and endometrial stromal sarcoma (ESS), in decreasing order of frequency (1). In Japan, it was reported that the most common histological types are CS (46%), LMS (36%) and ESS (13%) (2). CS is a malignant tumor consisting of an epithelial and a non-epithelial component, which mainly affects postmenopausal women. A combination tumor theory suggested that the majority of CSs originate from a single cell and differentiate into epithelioid-like and stromal-like components, whereas they are considered to exhibit cellular characteristics and progression similar to those of poorly differentiated endometrioid adenocarcinoma (3). Therefore, CSs tend to be treated in accordance with the treatment for epithelial endometrial cancer. However, LMS and ESS possess totally different properties compared to epithelial endometrial cancer.

LMS and ESS are malignant tumors that are mainly encountered during the perimenopausal period. Uterine leiomyomas may exhibit malignant transformation to LMS in 0.13-0.81% of the cases (4). These tumors are diagnosed based on the number of mitoses, degree of cellular atypia and presence of coagulation necrosis. ESS may be classified as low- or high-grade, based on the number of mitoses. However, these sarcomas are currently considered as different types of tumors. High-grade ESS, in particular, is referred to as undifferentiated endometrial sarcoma (UES). Total hysterectomy and bilateral salpingo-oophorectomy (BSO) are currently considered the first choice for the treatment of uterine sarcomas, although a consensus has not been reached regarding retroperitoneal lymphadenectomy (5,6). However, these tumors cannot be sufficiently controlled by surgical treatment alone, since a number of patients develop progression and recurrence of uterine sarcoma. As LMS often develops distant hematogenous metastases to the lungs and the liver, chemotherapy is commonly required as a systemic treatment. However, there is insufficient evidence to recommend a specific chemotherapeutic regimen as standard treatment for uterine sarcomas, as these are rare tumors and the number of reported cases is limited.

We administered a combination of ifosfamide (IFM), adriamycin (ADM) and cisplatin (CDDP) (IAP therapy) to patients with progressive and recurrent uterine sarcomas and retrospectively investigated treatment effectiveness and toxicity.

Patients and methods

Patients. We investigated 11 patients who were diagnosed with uterine sarcoma and treated with IAP between 1990 and 2010 at the Keio University Hospital, Tokyo, Japan.

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Total hysterectomy and BSO or tumorectomy were performed in our hospital. The pathological diagnosis in all the cases was LMS, UES or adenosarcoma. The median follow-up period was 298 days (range, 36-2,757 days). Remission induction chemotherapy was performed in all the cases, as 8 of the patients had progressive disease (PD) and 3 patients had recurrent disease.

This study was approved by the Keio University School of Medicine Ethics Committee (approval no. 20120236) and all the patients provided informed consent.

Treatment plan. The treatment schedule was based on a case report of uterine sarcoma that was treated with IAP (7,8). The administration was every 3 weeks as follows: IFM 1.5 g/body on days 1-5, mesna 900 mg/body on days 1-5, ADM 50 mg/m^2 on day 1 and CDDP 50 mg/m^2 on day 1, intravenously. Granulocyte colony-stimulating factor (G-CSF) was used according to the criteria of the American Society of Clinical Oncology. This treatment schedule was repeated every 3 weeks until disease progression or until discontinuation due to adverse events.

Evaluation of response and toxicity. The adverse events were assessed according to the Common Terminology Criteria for Adverse Events, version 4.0, based on the interviews and blood tests conducted once a week or more frequently after each cycle. The subsequent cycle was initiated after the adverse events were resolved. As regards hematotoxicity, if patients presented with grade 4 leukopenia or neutropenia for >7 days, grade 3-4 thrombocytopenia, or febrile neutropenia, we considered reducing the dose or withdrawing drugs for the subsequent cycle.

We assessed the overall response rate of 11 cases who had received remission induction therapy and had evaluable lesions in accordance with the World Health Organization evaluation criteria and recorded the progression-free survival. The tumors were measured by computed tomography after every 2 cycles. After the product of the two longest perpendicular diameters was calculated, the response was assessed as follows: complete response (CR), complete disappearance of all known lesions for a minimum of 4 weeks; partial response (PR), >50% reduction in the sum of the length x width of each measurable lesion for a minimum of 4 weeks; PD, >25% increase in the sum of the products of all measurable lesions or appearance of any new lesions; no change (NC), any outcome that did not qualify as response or progression.

Statistical analysis. SPSS software, version 20 (IBM-SPSS Software, Chicago, IL, USA) was used for statistical analysis, using Fisher's exact test. $P<0.05$ was considered to indicate a statistically significant difference. Kaplan-Meier curves were used for the estimation of progression-free survival and were compared with standard log-rank tests.

Results

Clinicopathological characteristics. The clinicopathological characteristics of the 11 cases who underwent IAP therapy are presented in Tables I and II. The median age at IAP therapy was 50 years (range, 34-72 years). The primary tumor sites were the uterus (10 cases, 90.9%) or the retroperitoneum (1 case, 9.1%). The histological types were LMS (6 cases, 54.5%), adenosarcoma (3 cases, 27.3%) and UES (high-grade ESS; 2 cases, 18.2%).

Table I. Clinicopathological characteristics of the 11 cases.

Characteristics	No.
Age (years)	
<50	5
≥50	6
Origin	
Uterus	10
Retroperitoneum	1
Histological type	
Leiomyosarcoma	6
Adenosarcoma	3
Undifferentiated endometrial sarcoma	2
Stage (FIGO 1988)	
I	4
II	0
III	1
IV	5
Other	1
Type of disease	
Progressive	6
Recurrent	5
Initial treatment	
Surgery	11
Chemotherapy	0
Type of surgery	
Hysterectomy + BSO (USO)	7
Other	4
Chemotherapy prior to IAP[a]	
None	9
CYVADIC[b]	1
DOC + GEM	1

[a]Ifosfamide, adriamycin and cisplatin. [b]Cyclophosphamide, vincristine, adriamycin and dacarbazine. FIGO, International Federation of Gynecology and Obstetrics; BSO, bilateral salpingo-oophorectomy; USO, unilateral salpingo-oophorectomy; DOC, docetaxel; GEM, gemcitabine.

Treatment. A total of 2 cases (18.2%) had received pretreatment; 1 case had received cyclophosphamide, vincristine, ADM and dacarbazine (DTIC) (CYVADIC therapy) and 1 case had received docetaxel (DOC) + gemcitabine (GEM).

The median number of cycles of IAP therapy was 6 (range, 1-8 cycles). In 72.7% of the cases, a dose reduction was required. Among cases who received >6 cycles, in particular, 71.4% required a dose reduction. The chemotherapy was interrupted after 1 to 2 cycles for the patients who requested treatment discontinuation due to intolerable adverse events.

Adverse events. The adverse events of IAP therapy are summarized in Table III. Hematotoxicity, particularly grade ≥3

Table II. Clinicopathological and treatment details of the 11 cases.

Age at diagnosis (years)	Age at IAP[a] therapy (years)	Histological type	Disease status	Initial treatment	Prior chemotherapy	No. of cycles	Effectiveness	Recurrence after IAP[a] therapy	PFS (days)
33	34	Leiomyosarcoma	Recurrent	ATH + BSO	CYVADIC[b]	8	SD	Yes	1,321
67	72	Adenosarcoma	Recurrent	ATH + BSO	-	2	SD	No	-
51	51	Leiomyosarcoma	Recurrent	Tumorectomy + BSO	-	3	CR	Yes	213
62	62	Leiomyosarcoma	Progressive	Tumorectomy	-	8	SD	Yes	125
57	56	ESS, high-grade	Progressive	Virchow LN biopsy	-	1	SD	Yes	307
43	43	Adenosarcoma	Progressive	ATH + BSO + PLN + OMT + tumorectomy	-	6	SD	Yes	44
50	50	ESS, high-grade	Progressive	ATH + BSO	-	2	SD	Unknown	-
40	40	Leiomyosarcoma	Progressive	ATH + BSO + PLN + tumorectomy	-	8	PD	Yes	25
38	39	Adenosarcoma	Progressive	ATH + tumorectomy	-	6	PR	Yes	80
35	35	Leiomyosarcoma	Progressive	ATH + BSO	DOC + GEM	6	CR	No	-
56	57	Leiomyosarcoma	Progressive	Tumorectomy	-	6	CR	Yes	1,539

[a]Ifosfamide, adriamycin and cisplatin. [b]Cyclophosphamide, vincristine, adriamycin and dacarbazine. PFS, progression-free survival; ESS, entometrial stromal sarcoma; ATH, abdominal total hysterectomy; BSO, bilateral salpingo-oophorectomy; LN, lymph node; PLN, pelvic lymphadenectomy; OMT, omentectomy; DOC, docetaxel; GEM, gemcitabine; SD, stable disease; CR, complete response; PD, progressive disease; PR, partial response.

leukopenia or neutropenia, developed in all the cases during the first cycle. Febrile neutropenia developed in 45.5% of the cases and resolved with administration of antibiotics and G-CSF. Grade 4 thrombopenia developed in 3 cases (27.3%), one of which required a platelet transfusion. Non-hematological adverse events other than anorexia, nausea and vomiting were not reported. Hemorrhagic cystitis or cardiotoxicity, which are adverse events characteristic of IFM and ADM, were also not reported.

Effectiveness. The therapeutic effects of remission induction chemotherapy are presented in Fig. 1. The sum of CR + PR was 36.4% (95% CI: 8.0-64.8%) and that of CR + PR + NC was 90.9% (95% CI: 73.9-100%). The median progression-free survival was 307 days (95% CI: 168-446 days).

Table III. Adverse events following IAP[a] therapy.

Adverse events	Grade	N	%
Hematological			
Leukopenia	3	2	18.2
	4	9	81.8
Neutropenia	3	2	18.2
	4	9	81.8
Febrile neutropenia	3	5	45.5
Thrombocytopenia	4	3	27.3
Non-hematological	3	0	0
	4	0	0

[a]Ifosfamide, adriamycin and cisplatin.

Discussion

Although several chemotherapeutic options for uterine sarcoma were previously suggested, the number of large-scale studies on uterine sarcomas is limited, as this type of tumor is relatively rare. The overall rate of response to single-agent chemotherapy is presented in Table IV. The response rate for ADM, IFM and gemcitabine (GEM) was 25.0, 17.0 and 21.0%, respectively (9-11); these are considered to be the key drugs in the treatment of uterine sarcoma. However, the response rate with paclitaxel and CDDP was 9.0 and 3.0%, respectively (12,13); thus, these drugs are considered to be less effective.

The efficiency of multi-agent chemotherapy for uterine sarcoma is summarized in Table V. Omura *et al* (9) investigated the efficiency of ADM + DTIC therapy and reported that, among 66 cases with measurable lesions of uterine sarcoma, 16 (24.2%) achieved a remission (CR + PR). Specifically, the response rate was 30.0% (6/20) in cases with LMS.

Sutton *et al* (14) investigated ADM + IFM therapy in 33 patients with LMS. As regards adverse events, grade >3 neutropenia developed in 17 cases (48.6%), of which 2 developed febrile neutropenia. Grade ≥3 thrombocytopenia was observed in 2 cases and nephrotoxicity in 1 case. There were 2 reported deaths due to the development of severe adverse events, specifically sepsis and cardiotoxicity. CR was achieved in 1 case and PR in 9 cases. The overall response rate was 30.3% and the disease control rate (CR + PR + SD) was 82.0%.

Piver *et al* (15) investigated CYVADIC therapy in 26 patients with intrapelvic sarcoma. As regards adverse events, neurotoxicity was observed in 8 cases (30.7%), including 6 mild-to-moderate and 2 severe cases. No patient developed cardiotoxicity. However, sepsis developed in 4 cases (15.3%) and 1 patient succumbed to the complications. The effectiveness was determined in 10 uterine sarcoma cases. The overall response rate and disease control rate were 20.0 and 60.0%, respectively.

Table IV. Overall rate of response to single-agent chemotherapy.

Agents	Dose and regimen	Response rate (%)	First author	Refs.
ADM	60 mg/m^2 day 1	25	Omura	(9)
Etoposide	100 mg/m^2 day 1-3	11	Slayton	(19)
CDDP	50 mg/m^2 day 1	3	Thigpen	(13)
Ifosfamide	1.5 g/m^2 day 1-5	17	Sutton	(10)
Paclitaxel	175 mg/m^2 day 1	9	Sutton	(12)
Gemcitabine	50 mg/m^2 day 1, 8 and 15	21	Look	(11)
Liposomal doxorubicin	50 mg/m^2 day 1	14	Sutton	(20)
Topotecan	1.5 mg/m^2 day 1-5	11	Miller	(21)
Trabectedin	1.5 mg/m^2 day 1	10	Monk	(22)

ADM, adriamycin; CDDP, cisplatin.

Table V. Overall rate of response to multi-agent chemotherapy.

Agents	Dose and regimen	Cases	Response rate (%)	Disease control rate (%)	First author	Refs.
ADM + DTIC	ADM 60 mg/m^2 day 1 DTIC 250 mg/m^2 days 1-5	20	30.0		Omura	(9)
IFM + ADM	IFM 5 g/m^2 day 1 ADM 50 mg/m^2 day 3	33	30.3	81.8	Sutton	(14)
CYVADIC	CPA 400 mg/m^2 day 2 Vicristine 1 mg/m^2 days 1-5 ADM 40 mg/m^2 day 2 DTIC 200 mg/m^2 days 1-5	10	20.0	60.0	Piver	(15)
GEM + DOC	GEM 900 mg/m^2 day 1 DOC 100 mg/m^2 days 1 and 8	42	35.8	62.0	Hensley	(16,17)
MAID	Mesna 1.5 g/m^2 days 1-4 IFM 1.5 g/m^2 days 1-3 ADM 15 mg/m^2 days 1-3 DTIC 250 mg/m^2 days 1-5	6	33.3	50.0	Pearl	(18)
IAP	IFM 1.5 g/body days 1-5 ADM 50 mg/m^2 day 1 CDDP 50 mg/m^2 day 1	11	36.4	90.9	Present study	

ADM, adriamycin; CPA, cyclophosphamide; GEM, gemcitabine; DTIC, dacarbazine; DOC, docetaxel; IFM, ifosfamide; CDDP, cisplatin.

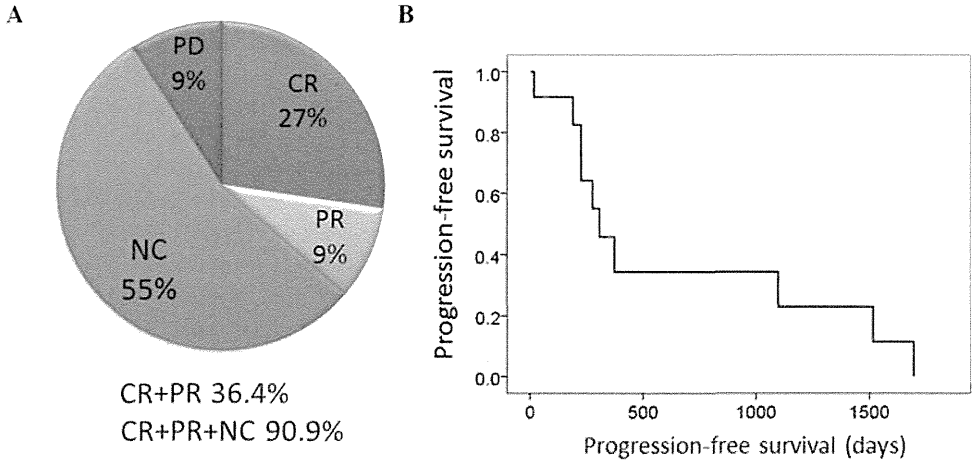

Figure 1. Therapeutic effects of remission induction chemotherapy. (A) The overall response rate was 36.4% and the disease control rate, including NC, was 90.9%. (B) The median progression-free survival was 307 days (95% CI: 168-446 days). NC, no change; CR, complete response; PR, partial response; PD, progressive disease.

Hensley *et al* (16,17) investigated docetaxel (DOC) + GEM therapy in 42 patients with uterine LMS. The adverse events were grade ≥3 neutropenia in 17.0%, grade ≥3 anemia in 24.0% and grade ≥ thrombocytopenia in 14.5% of the cases. Grade 3 allergic reactions and grade 4 pulmonary toxicity developed in all the patients. As regards effectiveness, the overall response rate was 35.8% and the disease control rate was 62.0%.

Pearl *et al* (18) investigated MAID therapy in 23 patients with gynecological sarcoma, including uterine LMS and adenosarcoma. The overall response rate was 33.3% and the disease control rate was 50.0%.

The number of studies on IAP therapy for uterine sarcoma is currently limited. Yamawaki *et al* (6) reported that IAP was effective in a case with progressive UES. Yamaguchi *et al* (23) also reported that the rate of PR with IAP therapy for uterine sarcomas was 40.0% in the first-line and 9.1% in the second-line chemotherapy setting.

In this study, IAP therapy achieved an overall response rate of 36.4% and a disease control rate, including NC, of 90.9%. Our results were comparable to those of IFM + ADM or DOC + GEM therapy. The adverse events recorded in the present study were mainly hematological, with grade ≥3 leukopenia and neutropenia in all the cases. However, these adverse events were manageable with dose reduction and G-CSF administration for severe hematotoxicity. Only one patient experienced severe thrombocytopenia requiring platelet transfusion. The median number of administered cycles was 6. There were no severe non-hematological complications or treatment-related deaths in the present study.

In conclusion, taking into consideration the abovementioned findings, IAP therapy may be a feasible chemotherapeutic option for progressive or recurrent uterine sarcoma.

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Original Article

The efficacy of preoperative positron emission tomography-computed tomography (PET-CT) for detection of lymph node metastasis in cervical and endometrial cancer: clinical and pathological factors influencing it

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Abstract

Objective: We studied the diagnostic performance of ^{18}F-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography in cervical and endometrial cancers with particular focus on lymph node metastases.

Methods: Seventy patients with cervical cancer and 53 with endometrial cancer were imaged with ^{18}F-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography before lymphadenectomy. We evaluated the diagnostic performance of ^{18}F-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography using the final pathological diagnoses as the golden standard.

Results: We calculated the sensitivity, specificity, positive predictive value and negative predictive value of ^{18}F-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography. In cervical cancer, the results evaluated by cases were 33.3, 92.7, 55.6 and 83.6%, respectively. When evaluated by the area of lymph nodes, the results were 30.6, 98.9, 55.0 and 97.0%, respectively. As for endometrial cancer, the results evaluated by cases were 50.0, 93.9, 40.0 and 95.8%, and by area of lymph nodes, 45.0, 99.4, 64.3 and 98.5%, respectively. The limitation of the efficacy was found out by analyzing it by the region of the lymph node, the size of metastatic node, the historical type of tumor in cervical cancer and the prevalence of lymph node metastasis.

Conclusion: The efficacy of positron emission tomography/computed tomography regarding the detection of lymph node metastasis in cervical and endometrial cancer is not established and has limitations associated with the region of the lymph node, the size of metastasis lesion in lymph node and the pathological type of primary tumor. The indication for the imaging and the interpretation of the results requires consideration for each case by the pretest probability based on the information obtained preoperatively.

Key words: positron-emission tomography, diagnostic imaging, lymphatic metastasis, gynecology, clinical oncology

Introduction

Positron emission tomography (PET) is used in more than 300 institutes in Japan (1) and is becoming common for preoperative examination and diagnosis of recurrence of gynecological cancer. PET-computed tomography (CT), in which PET and CT images are overlaid to improve anatomical accuracy, has also become common. In patients of reproductive age, ^{18}F-fluoro-2-deoxy-D-glucose (FDG) is taken up by the ureter and ovaries physiologically. PET-CT can discriminate between this uptake and abnormal accumulation in pelvic lymph nodes based on anatomical information in the CT images.

Lymph node metastasis (LNM) is a major factor in treatment planning and prediction of prognosis in gynecological cancer. PET-CT allows precise anatomical and metabolic imaging, but the diagnostic accuracy of PET-CT for LNM has varied among studies (2). For example, Park et al. (3) reported that, the efficacy for endometrial cancer, sensitivity was 69.2% and specificity was 90.3% by region; and Sironi et al. (4) reported that for cervical cancer, sensitivity was 72% and specificity was 99.7% by region. However, in the clinical situation, we could not observe such high efficacies and considered that there would be some factors influencing it.

The efficacy of PET-CT may be overestimated in certain clinical situations, in part because PET evaluates metabolic features of tumor cells and may be influenced by tissue type (5). There may also be differences in diagnostic efficacy among pathological types of cervical cancer. The importance of the amount of tumor tissue in a metastatic lymph node, including micrometastases (MM) and isolated tumor cells (ITCs), is now recognized in many cancers, including gynecological cancer (6). The efficacy of PET-CT may be affected by the size of the target tumor, and thus PET-CT may be limited for the detection of small lesions (4).

In this study, the diagnostic accuracy of PET-CT was examined retrospectively based on the final pathological diagnosis. Clinical information was also used to define approaches that improve preoperative interpretation of PET-CT findings.

Patients and methods

Subjects

The subjects were patients who were diagnosed with cervical or endometrial cancer histopathologically and underwent PET-CT for treatment planning in our department. Data were collected and evaluated retrospectively and sampling was performed consequently. Pelvic and paraaortic systematic lymph node dissection was performed based on the medical indication and the patients' consent. Patients who did not undergo surgery including systemic lymph node dissection in our institute were excluded. In addition, the patients who were included in other clinical trials on LNM were also excluded because the pathological evaluation of LNs was different from usual (6,7).

Since this research was a retrospective study based on existing clinical data, informed consent was not obtained from each participant. Instead, the scheme of our research was disclosed on the website, and by excluding those who refused to participate, the voluntariness of one's participation was guaranteed. The study was conducted with the approval of the ethics committee of our university (approval number: 20130289).

The study included 70 patients with cervical cancer and 53 with endometrial cancer who underwent preoperative PET-CT and surgery including lymph node dissection in the gynecological department of our hospital from September 2012 to March 2014. Patients with a history of sarcoidosis and one patient who could not complete PET-CT due to mental illness were excluded. A flow diagram of the study is shown in Fig. 1. There were no adverse events associated with PET-CT.

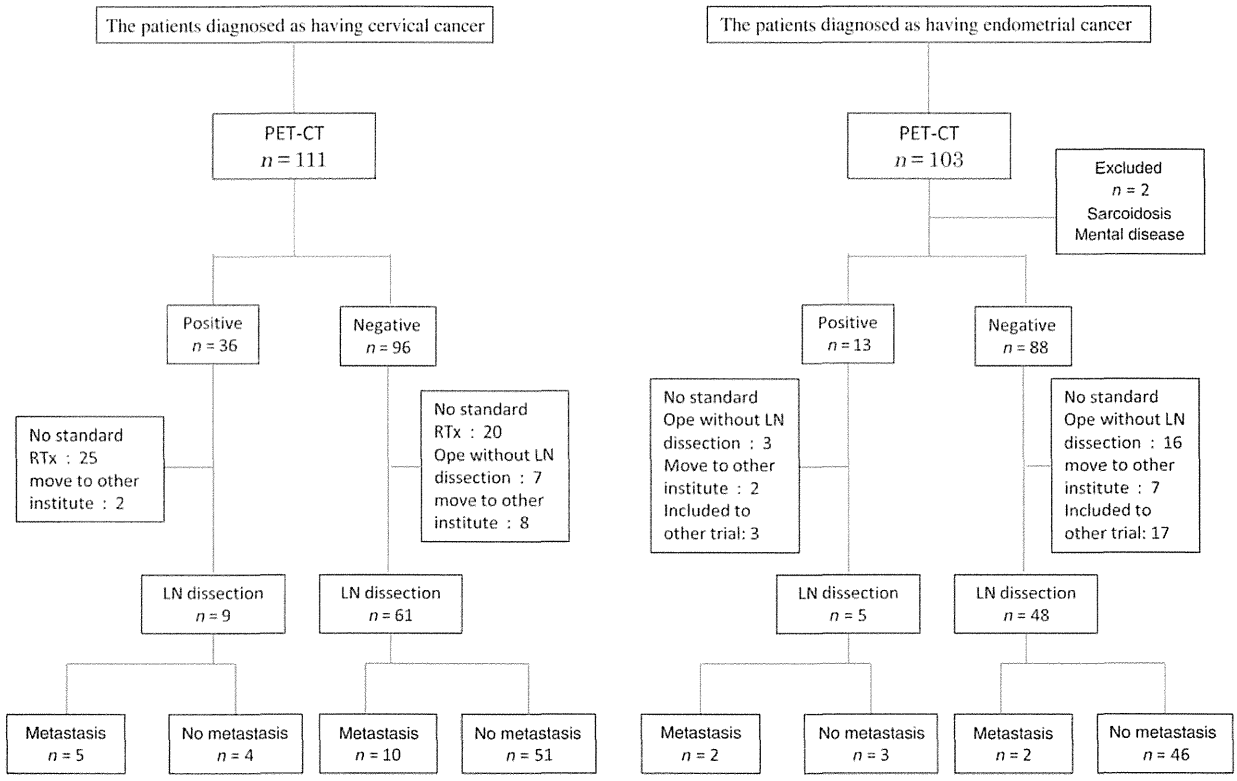
The characteristics of the patients are shown in Table 1. For patients with cervical cancer, the mean age was 38.8 ± 8.5 years, the pathological type was mainly squamous cell carcinoma (SCC) (58.6%) and the common FIGO 2008 stage was IB1 (74.3%). For those with endometrial cancer, the mean age was 58.7 ± 11.4, and the main histological type, grade and stage were endometrioid adenocarcinoma (83.0%), Grades 1 and 2 (30.1% each), and IA (47.2%), respectively.

PET-CT protocol

PET-CT was performed using a Biograph mCT system (Siemens Medical Solutions, Knoxville, TN, USA). The patient received 3.7 MBq/kg FDG and underwent scanning at 60th minute after FDG administration. Data were transferred to an AZE workstation (AZE Ltd, Tokyo, Japan). A PET-CT-positive case was defined as an abnormal FDG uptake in the lymph node region, regardless of the size of the lymph node on CT images, as described in previous studies (8–10). The diagnosis of an abnormal uptake in lymph node region was made by the radiologist, by comparing/observing the higher uptake than the background and the opposite region. With regard to anatomical position, the CT image helped in differentiating peritoneal dissemination from urinary tract or ovary. Regions of positive lymph nodes were recorded to match with dissected tissues, and SUV_{max} was determined in the early and delayed phases. Abnormal FDG uptake in lymph node regions was evaluated by radiologists with experience of >8 years. A retrospective review was performed by a radiologist specialized in nuclear medicine imaging with 28 years' experience and who was blinded to the pathological results.

Surgery

The range of lymph node dissection was based on our institutional criteria. In cervical cancer, cases from Stage IA2–IIB in FIGO clinical staging underwent pelvic lymph node dissection. In endometrial cancer, pelvic and paraaortic lymph node dissection was performed in cases with a high risk of recurrence, >50% myometrial invasion, or a histopathological type of serous, clear cell, Grade 3 endometrioid adenocarcinoma and carcinosarcoma. Intermediate risk cases underwent pelvic lymph node dissection only. Lymph nodes were dissected separately by region (Fig. 2). Pelvic nodes were divided into 13 regions: bilateral common iliac, external iliac, suprainguinal, internal iliac, obturator, parametrial and sacral nodes; and paraaortic nodes were divided into six regions: three columns divided by the right and left edges of the aorta and two rows divided by the height of the inferior mesenteric artery. Matching between dissected tissue and images was performed based on clinical and operative records and images of mapping of dissected nodes, and was reviewed by a certified gynecological oncologist with experience of 21 years.



Abbreviation: PET-CT, positron emission tomography – computed tomography / RTx , radiotherapy / Ope, operation / LN, lymph node

Figure 1. The flow diagrams of cases of cervical and endometrial cancers.

Pathological evaluation

Dissected lymph nodes were fixed and stained with hematoxylin and eosin to test for the presence of LNM. Routine pathological evaluation of lymph nodes is usually based on one or two sections (11). Diagnoses were made by two experienced general pathologists and were reviewed retrospectively by one pathologist who was blinded to the PET-CT results with 8 years' experience in gynecological tumor imaging . For each lymph node found to have metastatic tumor, the short axis (SA) of the lymph node and the maximum metastasis diameter (MMD) were measured on the slide. False-positive lymph nodes were also examined to determine the reason for FDG accumulation.

Magnetic resonance imaging (MRI)

MRI findings for myometrial invasion were used to stratify the risk of LNM in endometrial cancer because this information is available to evaluate the PET-CT result preoperatively. MRI is most useful for preoperative depth assessment of MI (12,13). MRI was performed in 38 patients (71.7%) in our hospital and in 14 patients (26.4%) at other institutes. One patient did not undergo MRI. In our institute, pelvic MR examination was performed on a 1.5-T clinical scanner using the following sequence: (i) T_2-weighted fast spin-echo images (TR/effective TE = 4000/90 msec), (ii) high b-value (b = 1000 s/mm^2) single-shot echo-planar diffusion-weighted images (TR/TE = 5000/68 ms) and (iii) fat-suppressed 3D-T_1 weighted images (TR/TE = 4.4/2.2 ms) after the administration of gadolinium-based contrast material (0.1 mmol/l per kg of body weight) in cases without contraindication. MRI findings were classified into three groups: (i) no myometrial invasion, (ii) <50% invasion and (iii) 50% or more invasion. Diagnosis of myometrial invasion was based on disruption or discontinuation of a junctional zone or subendometrial gadolinium enhancement if this procedure was performed. Diagnosis was performed by experienced general radiologists and reviewed retrospectively by one radiologist with 20 years' experience in gynecological imaging, who was blinded to pathological data and PET-CT results.

Statistical analysis

Diagnostic accuracies of PET-CT for detection of LNM were calculated for all cases, for cases of cervical and endometrial cancer, and for different tissue types in cervical cancer. Ninety-five percent confidence intervals were obtained using the Clopper–Pearson (exact) method. Data were analyzed using SPSS (ver. 21, New York, NY, USA).

Results

The MRI findings of myometrial invasion and the periods to surgery from PET-CT are also given in Table 1. The periods did not show significant difference by analysis of variance (ANOVA) between the groups of PET-CT results: true positive, false positive, true negative and false negative.

The diagnostic accuracies of PET-CT for detecting LNM are given in Table 2 by cases and by regions for both cancers, and by tissue type in cervical cancer. We calculated the sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio positive (LR+) and likelihood ratio negative (LR−). In the

Table 1. The characteristics of the patients

	Cervical cancer		Endometrial cancer	
Number		70		53
Age, years mean ± SD		38.8 ± 8.5		58.7 ± 11.4
Historical type *n* (%)	Squamous cell carcinoma	41 (58.6%)	Endometrioid adenocarcinoma	
			Grade1	16 (30.1%)
	Mucinous adenocarcinoma	20 (28.6%)	Grade2	16 (30.1%)
	Adenosquamous cell carcinoma	2 (2.9%)	Grade3	12 (22.6%)
	Endometrioid adenocarcinoma	3 (4.3%)	Serous papillary adenocarcinoma	2 (3.8%)
	Glassy cell carcinoma	2 (2.9%)	Clear cell carcinoma	3 (5.7%)
	Serous adenocarcinoma	1 (1.4%)	Carcinosarcoma	4 (7.5%)
	Endometrioid +	1 (1.4%)		
Clear cell carcinoma	Undifferentiated	0 (0%)		
	Undifferentiated	0 (0%)		
FIGO Stage				
Included patients	IA1	4 (5.7%)	IA	25 (47.2%)
	IA2	1 (1.4%)	IB	11 (20.8%)
	IB1	52 (74.3%)	II	5 (9.4%)
	IB2	10 (1.4%)	IIIA	4 (7.5%)
	IIA1	2 (2.9%)	IIIB	2 (3.8%)
	IIA2	0 (0%)	IIIC1	1 (1.9%)
	IIB	1 (1.4%)	IIIC2	3 (5.7%)
			IVA	0 (0%)
			IVB	2 (3.8%)
Excluded patients	IA1	6 (9.7%)		
	IA2	0 (0%)		
	IB1	17 (27.4%)		
	IB2	7 (11.3%)		
	IIA1	7 (11.3%)		
	IIA2	2 (3.2%)		
	IIB	15 (24.2%)		
	IIIA	0 (0%)		
	IIIB	5 (8.1%)		
	IVA	0 (0%)		
	IVB	2 (3.2%)		
	Unclassified	1 (1.6%)		
MRI finding of myometrial invasion			a (no invasion)	22 (42.3%)
			b (1/2>)	11 (21.2%)
			c (1/2≦)	19 (36.5%)
Period between PET-CT and surgery (days, mean ± SD)		True positive	37.4 ± 14.9	*P* = 0.106 by ANOVA
		False negative	32.7 ± 17.0	
		False positive	43.7 ± 14.7	
		True negative	48.2 ± 23.8	

FIGO, The International Federation of Gynecology and Obstetrics; PET-CT, positron emission tomography-computed tomography; MRI, magnetic resonance imaging.

analysis for cervical cancer, sensitivity and specificity were 33.3 and 92.7% by cases, respectively, and 30.6 and 98.9% by regions. In the analysis for endometrial cancer, sensitivity and specificity were 50.0 and 93.9% by cases, and 45.0 and 99.4% by regions, respectively.

The sensitivities according to pelvic region for both cancers are added and are shown in Fig. 3. No metastatic lymph nodes were detected by PET-CT in the internal iliac and parametrial regions.

The sizes of lymph nodes (short axis) and the MMD according to the PET-CT result are shown in Fig. 4. SA did not show significant difference between PET-CT results, but MMD did. The 14 false-positive lymph nodes showed histiocytic infiltration of sinusoids ($n = 4$), follicular hyperplasia ($n = 6$), granuloma ($n = 1$), peritoneal dissemination ($n = 1$) and no findings ($n = 2$) (Fig. 5).

Discussion

The efficacy of PET-CT in detecting LNM was less than that reported;. therefore, we analyzed the factors that seem to influence this. Considering the theory of PET, first we focused on size and region.

The size of the tumor in the metastatic lymph node, including MM and ITCs, is important in many cancers, including gynecological cancer (6). The efficacy of PET-CT may be affected by the size of the target tumor, as PET cannot detect small lesions. The SA of metastatic lymph

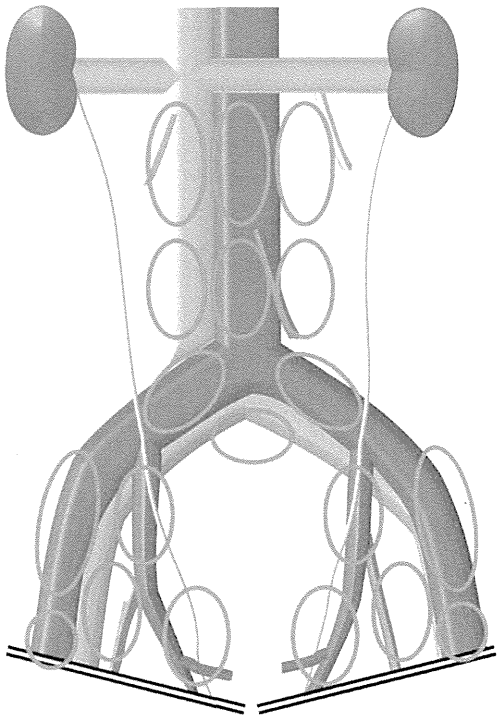


Figure 2. The map of pelvic and paraaortic lymph nodes. Pelvic nodes were divided into 13 regions: bilateral common iliac, external iliac, suprainguinal, internal iliac, obturator, parametrial and sacral nodes; and paraaortic nodes were divided into six regions: three columns divided by the right and left edges of the aorta and two rows divided by the height of the inferior mesenteric artery.

nodes has been used for analysis in cervical cancer (4,14,15), but we focused on the MMD as a measure of tumor size that may be more suitable for PET-CT features. The MMD on the section is not equal to the true maximum diameter of a metastatic lesion but only an approximation ; its usefulness has been reported (16). The definitions of MM and ITC are based on the MMD. The MMD of metastasis-positive lymph nodes identified by PET-CT were longer than that of non-identified nodes ($P = 0.017$ by t test). However, the SA did not show a significant difference ($P = 0.17$ by t test). Our study indicates that MMD relates more strongly to PET-CT efficacy than SA.

It seems likely that sensitivity should increase with an increased MMD, but a strong correlation was not found (OR = 1.091, $P = 0.024$, by univariate logistic regression). Thus, other factors may also affect the efficacy of PET-CT. The sensitivity was 40.9% in metastatic lymph nodes with MMD >2 mm and 52.9% in those with MMD >5 mm. The sensitivity was 41.7% for metastatic lymph nodes with a short axis >5 mm. The clinical impact of MM or ITCs is unclear in gynecological cancer, but there is a limitation in detecting these lesions by PET-CT.

Differences in the diagnostic sensitivity of PET-CT were observed for lymph nodes in different regions. The sensitivities for the interiliac and parametrial regions were both 0%. These regions are close to the uterus, and thus close to the primary tumor, and FDG accumulation in the primary tumor may hide the abnormal FDG uptake in the LNM. A similar situation was reported in urological cancers (17).

Obturator, interiliac, parametrial and common iliac lymph nodes are frequent regions of cancer metastasis (18,19). In this study also, these were the frequent regions of metastasis in both cancers. Low sensitivities in these regions would be a problem. The pelvic regions except for the interiliac and parametrial regions showed reasonable sensitivity in endometrial and cervical cancer and the PET-CT result and MMD showed a better correlation (Fig. 3, OR = 1.194, $P = 0.011$, by univariate logistic regression). Although these might be classification error of lymph nodes in surgical techniques, these results show that the lymph node region can strongly affect the efficacy of PET-CT.

Next, we analyzed the histopathological tumor type, because the utility of PET is dependent on the metabolic features of tumor cells and might be influenced by the pathological type of the tumor. SUV_{max} of primary tumors differs between SCC and non-SCC (5), but differences in diagnostic efficacy have not been examined. In the current study in a population with a relatively high percentage of non-SCC cases, the diagnostic accuracy tended to be higher in non-SCC cases, despite the previous finding of a tendency for a higher SUV_{max} in SCC cases (5). However, there was no significant difference in logistic regression analysis using variables of pathological type and MMD (OR = 3.4, $P = 0.175$).

Compared with the previous studies, Park et al. (3) reported better efficacy for endometrial cancer and Sironi et al. (4) reported better efficacy for cervical cancer. In the report of Park, the pathological evaluation of LNs, that is the standard examination, was performed on only suspected LNs. Because systemic dissection was not performed and they would overlook suspicion on small lesions, sensitivity might be overestimated. Actually, in the report of Kitajima et al. (8), which was performed in a similar setting to the present study, the efficacy was similar. Kitajima et al. mentioned about the size of LNs but did not analyze the region. In the report of Sironi, the protocol was similar and we could not exactly find the reason for the difference in results. There might be the influence of a difference of pathological evaluation and study population.

One of the limitations of this study was the subject population. In this study, the patients with cervical cancer were younger, included a higher percentage of non-SCC cases and had a tendency to be at a lower stage compared with general Japanese epidemiological data (20). These differences may arise from a difference in surgical indication. The cases of endometrial cancer were representative of the general Japanese data. We did not determine the surgical indication based on PET-CT, but more PET-CT-positive cases tended to be chosen for radiotherapy. This might be a limitation of studies due to/depending on the accuracy of the imaging procedure, with the results of the standard examination being unclear in some cases. High-risk cases of cervical cancer with LNM could not be known especially in those that tend to undergo radiotherapy, and this decreased prevalence in the study population, which may cause a bias toward a lower positive-predictive value and a higher negative-predictive value. Speaking about the periods from PET-CT to surgery, they did not differ between the groups based on the PET-CT result. Though a longer period would lead to a false negative in theory, we do not have to think much about the influence from that factor.

Though PET-CT is increasingly used in gynecological cancer preoperatively, the results described above indicate that PET-CT has a relatively low diagnostic efficacy for LNM. Thus, we should consider about the indication of this examination. LNMs were relatively rare, especially in low-risk cases. PPV and NPV are influenced by prevalence, which means that they are calculated from prevalence and LR+ and LR−. We limited our study to high-risk cases, cervical cancer of clinical stage IB1 or higher and endometrial cancer with >50% myometrial invasion in MRI findings. This information can be obtained preoperatively,

Table 2. The diagnostic efficacy of PET-CT for detecting lymph node metastasis in cervical and endometrial cancer, by cases and by regions

	PET-CT	Pathological evaluation			Sensitivity, % (95% CI)	Specificity, % (95% CI)	Accuracy, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	LR+ (95% CI)	LR− (95% CI)
		Lymph node metastasis	No metastasis	Total							
Cervical cancer											
SCC											
By regions	+	2	6	8	16.7 (2.09–48.4)	98.8 (97.3–99.5)	96.8 (94.8–98.2)	25.0 (3.19–65.1)	98.0 (96.3–99.0)		
	−	10	481	491							
	Total	12	487	499							
Non-SCC											
By regions	+	9	3	12	37.5 (18.8–59.4)	99.1 (97.3–99.8)	94.8 (92.0–96.9)	75.0 (42.8–94.5)	95.5 (92.8–97.5)		
	−	15	322	337							
	Total	24	325	349							
All cases											
By cases	+	5	4	9	33.3 (11.8–61.6)	92.7 (82.4–98.0)	80.0 (68.7–88.6)	55.6 (21.2–86.3)	83.6 (71.9–91.8)	4.58 (1.40–15.0)	0.72 (0.50–1.04)
	−	10	51	61							
	Total	15	55	70							
By regions	+	11	9	20	30.6 (16.3–48.1)	98.9 (97.9–99.5)	96.0 (94.4–97.2)	55.0 (31.5–76.9)	97.0 (95.6–98.0)	27.6 (12.2–62.3)	0.70 (0.57–0.87)
	−	25	803	828							
	Total	36	812	848							
Endometrial cancer											
All cases											
By cases	+	2	3	5	50.0 (6.76–93.2)	93.9 (83.1–98.7)	90.6 (79.3–96.9)	40.0 (6.27–85.3)	95.8 (85.7–99.5)	8.17 (1.88–35.5)	0.53 (0.20–1.42)
	−	2	46	48							
	Total	4	49	53							
By regions	+	9	5	14	45.0 (23.1–68.5)	99.4 (98.5–99.8)	98.0 (96.7–98.8)	64.3 (35.1–87.2)	98.6 (97.5–99.3)	69.3 (25.5–188)	0.55 (0.37–0.82)
	−	11	765	776							
	Total	20	770	790							

SCC, squamous cell carcinoma; PPV, positive predictive value; NPV, negative predictive value; LR+ likelihood ratio positive; LR−, likelihood ratio negative.

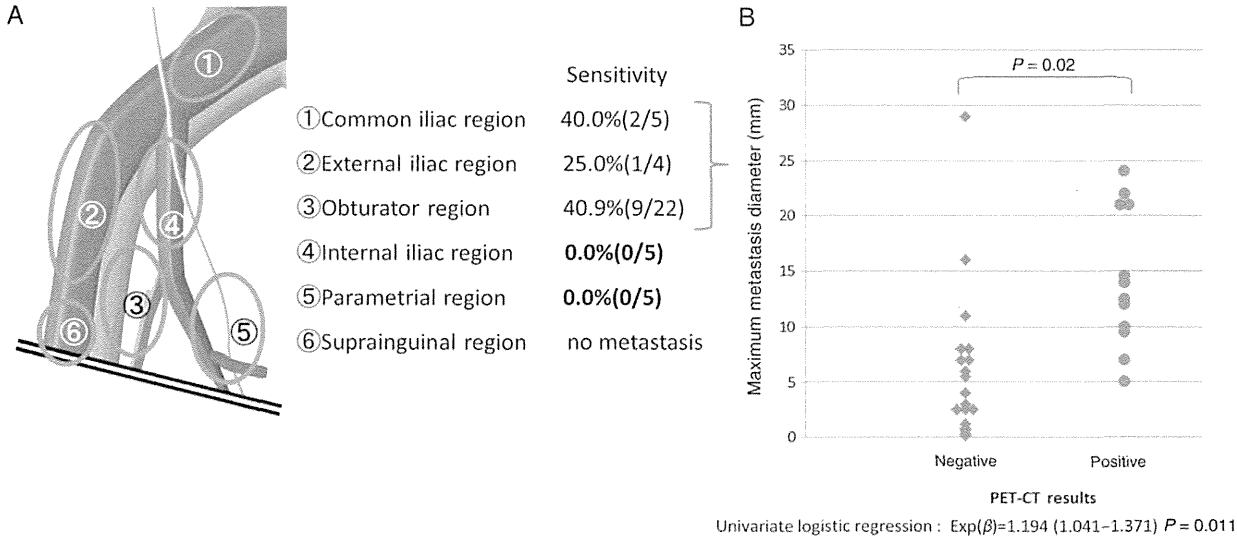


Figure 3. (A) The sensitivity according to the pelvic regions of the lymph node. (B) The comparison of the size of metastatic lymph nodes limited in common iliac, external iliac and obturator regions between PET-CT results.

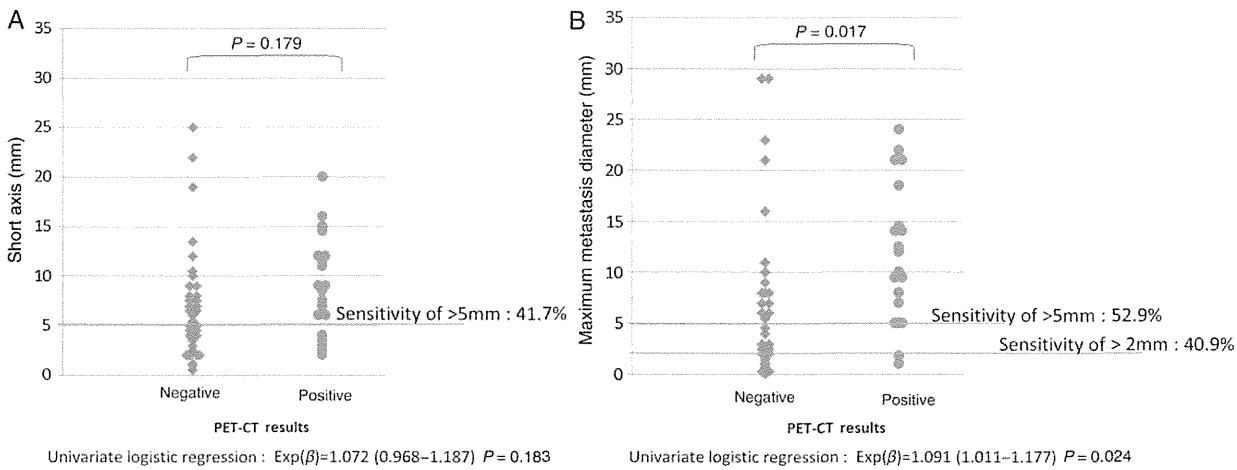


Figure 4. The comparison of the size of metastatic lymph nodes between PET-CT results and the sensitivity according to size: (A) by short axis and (B) by maximum metastasis diameter.

consistent with the goal of using PET-CT for preoperative evaluation. Even when limited to high-risk cases, the frequencies of LNM are 23.1% in cases with cervical cancer and 20.0% in cases with endometrial cancer. Our results indicate that PET-CT is less suitable for low risk cases in detecting LNM, and therefore, should not be performed routinely. We suggest that its indication be carefully considered. Here we discuss only about its use in predicting LNM preoperatively and the accuracies for other measurements such as the malignancy of the primary tumor or distant metastasis have to be discussed separately. This study does not mention about post-operative PET-CT. Generally, resurgery would be performed only in a limited situation when recurrence is indicated by imaging. Then we have no choice but to take the decision based on the most reliable imaging procedure. The diagnostic accuracy of PET-CT is better than preexisting imaging modalities like CT or MRI for detecting recurrence (21–23). Moreover, as PET-CT can detect metabolic change, we could achieve an effect of therapy even when the lesion size did not change (24).

On the other hand, preoperative usefulness of this procedure might increase when considering the therapy of limited high-risk cases. Actually, such a tentative plan was reported (25). When considering the plan in cervical cancer, it would be suitable to analyze by case because the presence of LNM may affect initial treatment. In endometrial cancer, however, our true concern is identification of the region of LNM, because the standard treatment is surgery (26) and systemic lymph node dissection has not been proved to be beneficial for overall survival (27). We require methods for precise preoperative identification of LNM to consider the range of lymph node dissection. Limited to cases who underwent paraaortic lymph node dissection in endometrial cancer, we calculated the diagnostic accuracy for the detection of the presence of paraaortic LNM. The sensitivity was 50.0% (2/4 cases, 6.8–93.2%) and specificity was 100% (26/26 cases 89.1–100%). The sample size became small ($N = 30$) but when limited to a high pretest probability, it seems relatively efficient to consider the indication of paraaortic dissection based on PET-CT results because of a high PPV.

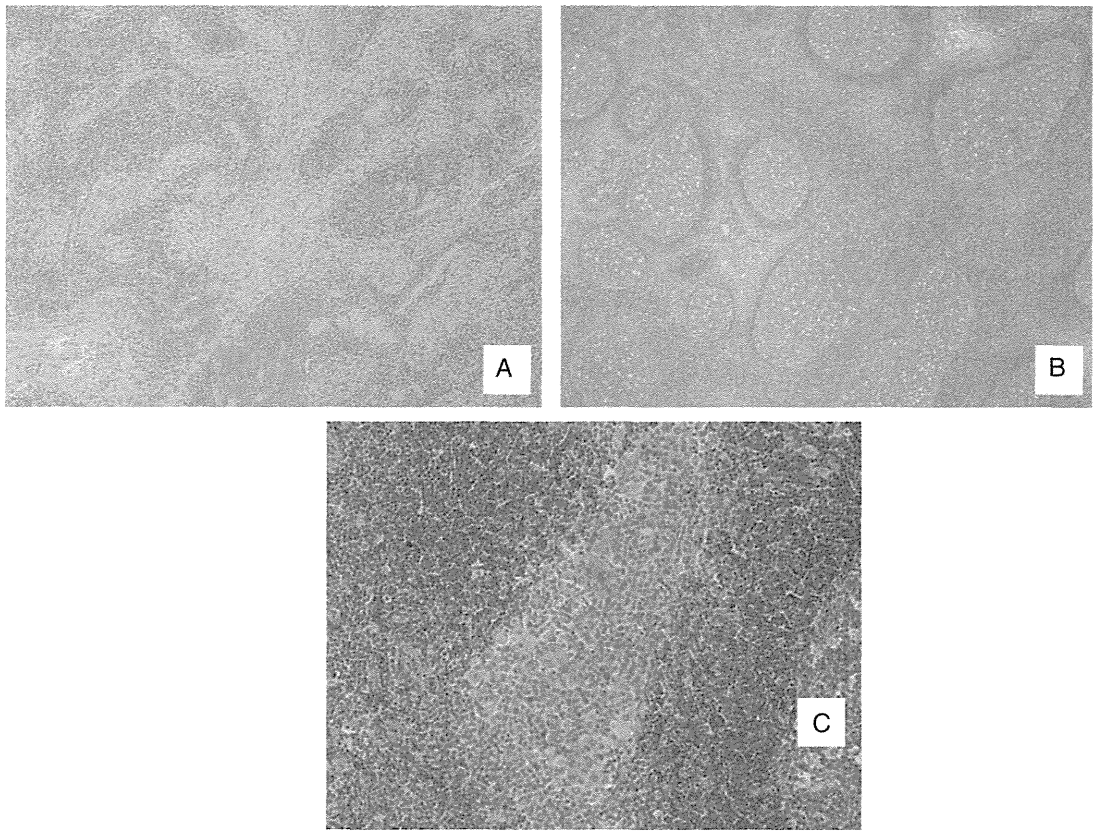


Figure 5. The findings of false-positive lymph nodes. (A) Histiocytic infiltration of sinusoids by hematoxylin and eosin (H&E) ×40 magnification; (B) follicular hyperplasia H&E ×40 magnification; (C) granuloma H&E ×200 magnification.

Our results indicate that the efficacy of PET-CT for detecting LNM have the limitation relating to size and region. The possible methods to improve the sensitivity might be optimizing the dose of FDG and the development of scanning devices or methods and so on. Otherwise, the possible methods to improve the specificity might be evaluation of the sequential change of FDG uptake, the dual time scanning, for example. Further research is required on this issue.

Conclusion

The efficacy of PET-CT regarding the detection of lymph node metastasis in cervical and endometrial cancer is not established and has limitation associated with clinical and pathological factors. The indication for the imaging and the interpretation of the results requires consideration for each case based on the information obtained preoperatively.

Conflict of interest statement

None declared.

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Clinical Study

Evaluation of Endometrial Cytology: Cytohistological Correlations in 1,441 Cancer Patients

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Key Words
Endometrial cancer · Endometrial cytology · Endometrial screening · Endometrial pathology

Abstract
Background: Endometrial cytology by direct intrauterine sampling is the most common test for an initial evaluation of the endometrium in Japan. However, its diagnostic value for endometrial cancer remains unknown. Here, we assess the correlation between cytopathology and histopathology to evaluate the diagnostic value of cytology for endometrial cancer. ***Methods:*** Patients with histologically confirmed endometrial cancer and controls with a normal endometrium confirmed by hysterectomy had all undergone preoperative endometrial cytology between 2001 and 2010 at our eight institutions and were retrospectively analyzed. The cytological results were compared by clinical stage, histological type, differentiation, and sampling instrument. ***Results:*** We analyzed 1,441 endometrial cancer and 1,361 control cases. Endometrial cytology detected cancer in 1,279 (916 positive and 363 suspicious) cases with a sensitivity (positive plus suspicious cases) of 88.8% and a specificity of 98.5%. The positive rate was high in advanced-stage, nonendometrioid, and undifferentiated cases, but there was no significant difference in sensitivity between these clinical conditions. ***Conclusion:*** Endometrial cytology shows a relatively high sensitivity and specificity for endometrial cancer, and neither statistical measure is significantly affected by clinical stage, histological type, differentiation, sample numbers, or sampling instrument. These findings form a superior dataset for evaluating the efficacy of endometrial cytology.

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Introduction

Endometrial cancer is the most common gynecological cancer in Western countries [1]. In Japan, its prevalence has been increasing in recent years, with more than 9,000 cases in 2007, and after cervical cancer, it has become the most frequent cancer type [2]. The prognosis for early-stage endometrial cancer is relatively good, but it is poor for advanced stages. Therefore, it is crucial to diagnose endometrial cancer early. In Japan, endometrial cytology by direct intrauterine sampling is the most common test for an initial evaluation of the endometrium [3]. This method is less invasive than histological biopsy, but its precision for detecting endometrial cancer is still unclear. Most previous studies of endometrial cytology reported its sensitivity and specificity in patients with various backgrounds, from asymptomatic cases to high-risk groups for uterine cancer [4, 5]. Consequently, insufficient numbers of uterine cancer cases were reported for stringent analyses of the effectiveness of cytodiagnostics. Furthermore, there have been no retrospective studies that showed separate results for preoperative endometrial cytology performed once or several times. In this study, a large number of histologically confirmed endometrial cancer cases were examined retrospectively, with results of the first of multiple samples evaluated separately to assess the usefulness of cytology for detecting endometrial cancer.

Methods

Patients with histologically confirmed endometrial cancer by hysterectomy who had undergone preoperative endometrial cytology between 2001 and 2010 at eight institutions of the Gynecologic Oncology Trial and Investigation Consortium of North Kanto (GOTIC) were retrospectively analyzed (GOTIC-007). The institutions are identified in the affiliations at the beginning of this report and are located within three prefectures in central Japan: Gunma, Saitama, and Tochigi. A prefecture is a subnational political entity equivalent to a state in the USA and a province in other countries. The results of the preoperative endometrial cytology as well as clinical information such as clinical stage (FIGO 1988), histological type, differentiation, and sampling instrument were investigated.

The control cases had undergone preoperative endometrial cytology before hysterectomy for benign gynecological disease and were confirmed to be without abnormal findings in the endometrium. When preoperative cytopathology had been performed more than once, both the first and the subsequent test were analyzed. The reasons for multiple cytological testing of a patient within 1 year are varied and include a patient's request, routine testing following an exceptional test, a physician's desire for confirmation before more invasive testing is performed, referral from another institution, and a development of suspicious symptoms after an initial negative test.

In this study, 'preoperative cytology' was defined as cytological examination performed within 1 year before surgery. The pathological and cytological diagnoses were made by pathologists and cytotechnologists at each institution. The results of cytology were classified into three groups: negative, suspicious, or positive. Negative and positive suggested a normal endometrium and malignancy, respectively. Suspicious specimens were equivalent to cytology suggestive of, but not conclusive for, malignancy, such as atypical endometrial hyperplasia and endometrial hyperplasia. Additional histological workup by biopsy or curettage must be considered when the results of endometrial cytology are positive or suspicious. Therefore, the sensitivity of endometrial cytology was defined as the number of positive plus suspicious cases divided by the total number of cases examined. Cases in which the cytology results had been reported as 'inadequate specimens' were excluded from the analyses of both the malignant and the control group. As this was a retrospective observational study, informed consent was not obtained from each patient; instead, this study was carried out with approval of the IRB of each institution. McNemar's test was used for statistical analysis of multiple examinations of the same patients, while the χ^2 test was used for other comparisons.

Table 1. Background characteristics of the patients and controls

Patients (n = 1,441)	
Median age (IQR), years	58 (13)
Stage (FIGO 1988), n	
I	922 (64.0%)
IA	273 (18.9%)
IB	490 (34.0%)
IC	159 (11.0%)
II	124 (8.6%)
III	320 (22.2%)
IV	75 (5.2%)
Histology, n	
Endometrioid	1,297 (90.0%)
Serous	45 (3.1%)
Mucinous	13 (0.9%)
Clear cell	23 (1.6%)
Other (mixed)	34 (2.4%)
CS/ESS	29 (2.0%)
Grade (endometrioid), n	
1	788 (60.8%)
2	346 (26.7%)
3	163 (12.6%)
Controls (n = 1,361)	
Median age (IQR), years	46 (7)
Diagnosis, n	
Myoma	1,136 (83.5%)
Adenomyosis	135 (9.9%)
Myoma + adenomyosis	64 (4.7%)
Ovarian tumor	5 (0.4%)
Others	21 (1.5%)

CS/ESS = Carcinosarcoma/endometrial stromal sarcoma.

Results

There were 1,452 endometrial cancer and 1,385 control cases reported from our eight institutions. Eleven cancer and 24 control cases were omitted from the study as they yielded insufficient specimens for cytology; thus, there were 1,441 cancer and 1,361 control cases left for analysis. The patients' background characteristics are shown in table 1. The median age was 58 and 46 years for the endometrial cancer and the control group, respectively.

The results of the first and the subsequent cytology examination are shown in figure 1. The first cytology detected cancer in 1,279 (916 positive and 363 suspicious) cases in the cancer group, which equals a sensitivity of 88.8%. In this group, 202 patients (14.0%) had undergone multiple endometrial cytology examinations, and 62 of these were upgraded from negative to positive or suspicious after secondary testing. The positive rates were not significantly different, but the sensitivity increased to 93.1% ($p < 0.001$) when the results of the reexamination were added.

The results of the first endometrial cytology according to clinical stage are shown in figure 2. The positive rate increased as the stage progressed. The sensitivity was higher for stage III than for stage I, but there were no significant differences between the other stages. We have no empirical evidence to explain why the sensitivity for clinical stage III is the highest. However, since the proportion of well-differentiated adenocarcinoma in which the cellular morphology resembles normal cells is high in early stages, one might expect a skewing of

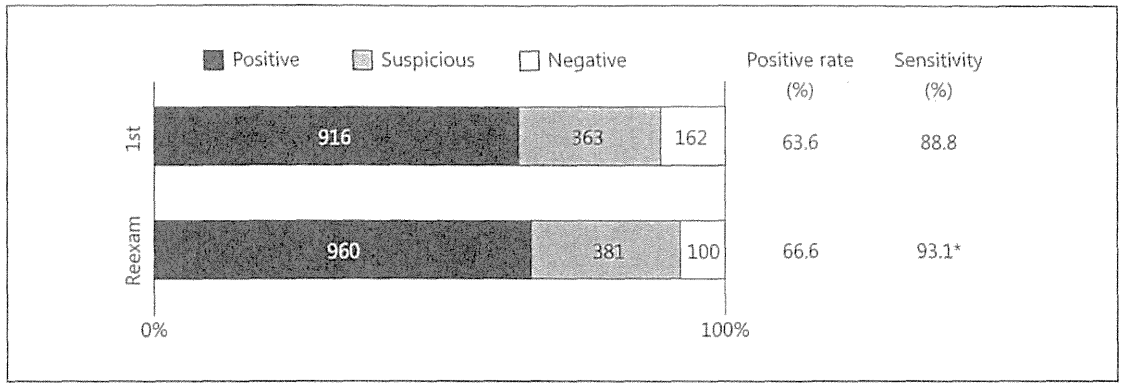

Fig. 1. Proportional results of endometrial cytology for the first examination (1st) and for the reexamination (Reexam). The numbers of cases are presented in the bars (total n = 1,441). * $p < 0.001$ vs. 1st (McNemar's test).

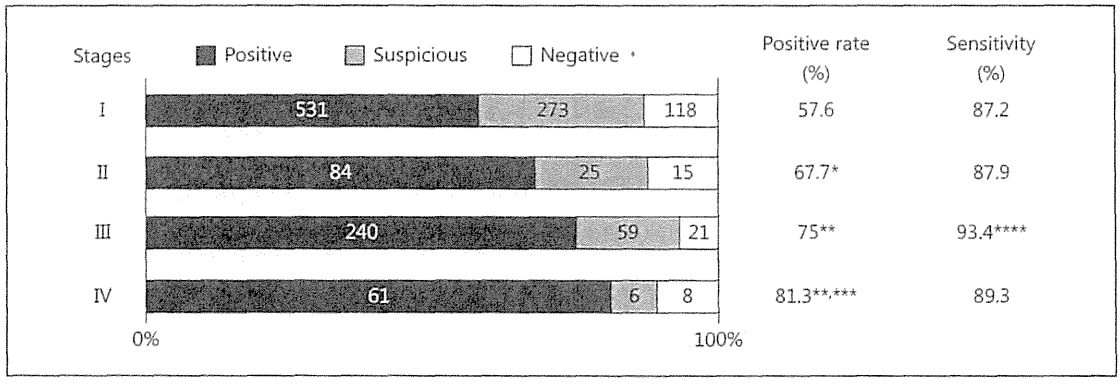

Fig. 2. Proportional results of endometrial cytology by stage (FIGO 1988). The numbers of cases are presented in the bars. * $p < 0.05$ vs. stage I, ** $p < 0.001$ vs. stage I, *** $p < 0.05$ vs. stage II, **** $p < 0.005$ vs. stage I.

sensitivity to a lower value than the one found for later stages. More data are needed to confirm this in future studies.

Figure 3 shows the results of endometrial cytology by histological type. The positive rate was higher for nonendometrioid than for endometrioid adenocarcinoma, but there were no significant differences in sensitivity between the two groups. Figure 4 shows the results of endometrial cytology by histological differentiation of the endometrioid adenocarcinoma. The positive rate increased along with the degree of differentiation, but there was no significant difference between the three groups in sensitivity.

Figure 5 shows the results of endometrial cytology according to the sampling instrument used. In the eight GOTIC institutions, three different sampling instruments (fig. 6) were used: a Soft Cyto sampler (Soft Medical Co. Ltd., Tokyo, Japan), an Endocyte sampler (Laboratoire CCD, Paris, France), and Honest Uterine Brush sampler (Honest Medical Co. Ltd., Tokyo, Japan). The positive rate was lower for the Soft Cyto sampler than for the other instruments, but there was no significant difference between the instruments in sensitivity.

Of the 1,361 control patients included for the purpose of examining specificity, there were 5 positive, 15 suspicious, and 1,341 negative cases. The number of negatives divided by

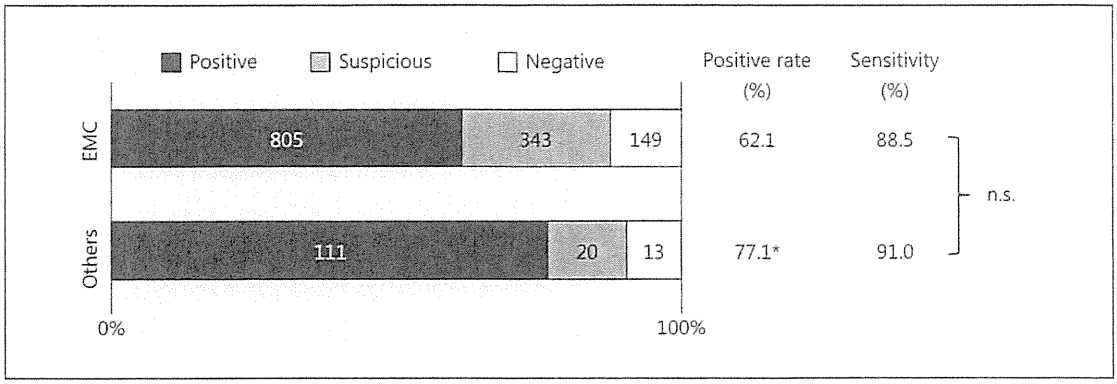

Fig. 3. Proportional results of endometrial cytology by pathology. The numbers of cases are presented in the bars. EMC = Endometrioid adenocarcinoma; n.s. = not significant. * $p < 0.001$ vs. EMC.

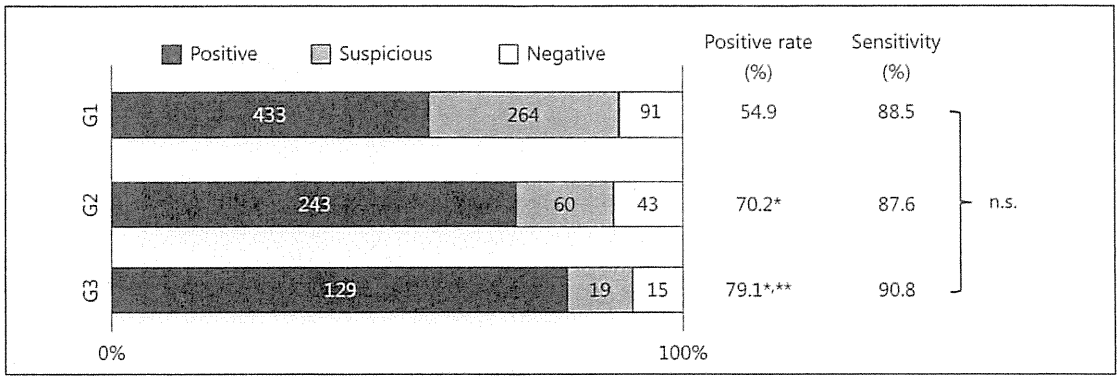

Fig. 4. Proportional results of endometrial cytology by histological differentiation. The numbers of cases are presented in the bars. G = Grade; n.s. = not significant. * $p < 0.001$ vs. G1, ** $p < 0.05$ vs. G2.

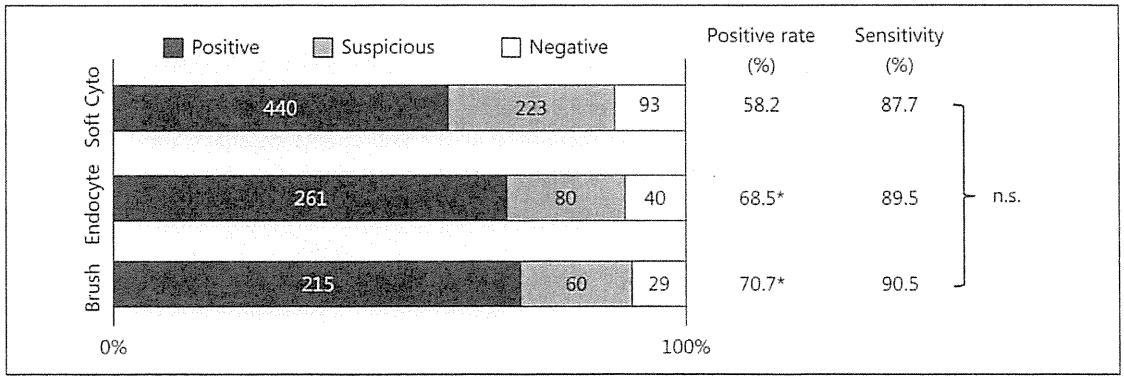

Fig. 5. Proportional results of endometrial cytology by sampling device. The numbers of cases are presented in the bars. Brush = Honest Uterine Brush; n.s. = not significant. * $p < 0.001$ vs. Soft Cyto.