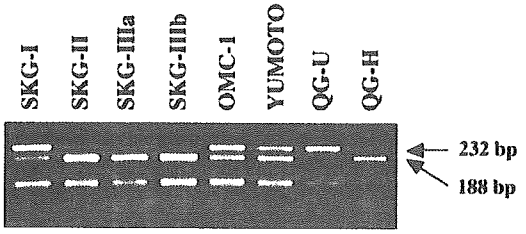

Fig. 2. Genotyping of Fas gene promoter −670 in 8 cervical squamous carcinoma cell lines by PCR-RFLP. The AA genotype was detected only for QG-U, whereas the GA genotype for SKG-I, OMC-1 and YUMOTO, and the GG genotype for SKG-II, SKG-IIIa, SKG-IIIb and QG-H cell lines, respectively.

neoplasm and reported that the frequency of A allele and AA genotype increased in accordance with the multi-step carcinogenesis from LSIL, HSIL to invasive squamous cell cancer. They stated that A allele and AA genotype, conferring an intact GAS element and more efficient Fas expression could be one of the mechanism that cells use to avoid carcinogenesis. In contrast, our present results using exfoliated cervical cell samples demonstrated that the frequency of GA + GG genotype or G allele increased from LSIL to HSIL. Moreover, there was an increased OR for GA + GG genotype in HSIL cases compared to controls among the patients with high-risk HPV. We also observed the opposite trend that AA genotype decreased in HSIL compared to LSIL and controls among the patients with or without high-risk HPV. Lai et al. [12] reported that HPV types 16 and 18, the most prevalent and aggressive types worldwide, are predominant in cases with GA or GG genotypes, whereas HPV type 58, prevalent in Southeast Asia, favors AA genotype. Very recently, Engelmark et al. [24] and Dybikowska et al. [25] have demonstrated that AA genotype in Fas gene promoter at −670 position may not be engaged in the development of cervical neoplasia in Swedish and Polish population, respectively. These discrepancies may be due to the ethnic variation of HPV prevalence and genotype frequency of Fas gene promoter in different geographical regions.

Previous studies [26,27] have demonstrated that high-risk HPV infection is inversely correlated with apoptosis of cervical epithelial cells and that a decrease of apoptosis is closely associated with higher histologic grade of SIL. In cervical cancer tissues and cell lines, significant decrease in the expression levels of Fas has been also reported [27,28]. The higher frequency of GA or GG genotype in HSIL cases in our series may result in a significant decrease in Fas gene expression and subsequent escape from apoptosis of the cells in high-risk HPV-related cervical carcinogenesis. Interestingly, 7 of 8 human cervical squamous carcinoma cell lines that possess high-risk HPV except for YUMOTO also showed GA or GG genotype. Further studies on the differential gene expression profiles between normal cervical keratinocytes and cervical cancer cell lines with or without G allele at −670 of Fas gene promoter may provide the better understanding for the effect of this SNP in the sequence of cervical carcinogenesis. Moreover, it might be of interest to further examine whether cultured cervical cancer cells with GA or GG genotype could escape from apoptosis in response to INF-γ stimuli through an abolishment of the GAS element and a decrease in the expression levels of Fas.

In the present study, we demonstrated the role of Fas gene promoter −670 polymorphism in cytologic materials or cell lines from women with premalignant or malignant cervical disease. Fas polymorphism may be closely associated with cervical carcinogenesis in a Japanese population particularly in high-risk HPV group. These observations are potentially important in managing SIL patients by cytologic examination and in understanding the pathogenesis of cervical cancer. It would be of interest to further evaluate whether this polymorphism could be used as a disease marker for the natural history of cervical neoplasias in a setting of longitudinal cohort study and for the determination of appropriate screening interval in patients with or without high-risk HPV.

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Lymph node pathway in the spread of endometrial carcinoma

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Summary

Objective: To elucidate the sentinel nodes of endometrial carcinoma, the spread pathway was clarified. The correlation between lymph node spread and other clinicopathological variables was also analyzed.

Methods: Dissected lymph node samples in 342 patients who underwent pelvic and selective paraaortic lymphadenectomy were reviewed. Pelvic and paraaortic node (PLN and PAN) status was compared with clinicopathological parameters.

Results: Lymph node metastasis was demonstrated in 52 patients, including 46 cases with PLN metastasis and six patients with independent PAN metastasis. The metastatic sites were most frequent in the obturator and internal iliac nodes. Eleven of 49 patients who underwent PAN dissection were positive for metastasis. Sixteen of 23 cases with parametrial metastasis also metastasized in the retroperitoneal lymph node.

Conclusion: The lymph node spread pathway in endometrial carcinoma consists of a major route via the obturator node or internal iliac node with or without parametrial involvement, and rarely a direct PAN pathway.

Key words: Endometrial carcinoma; Lymph node metastasis; Spread pattern; Prognostic factor; Staging laparotomy.

Introduction

The International Federation of Gynecology and Obstetrics (FIGO) has adopted surgical and pathological staging of endometrial carcinoma since 1988 [1]. In this classification, metastasis to the pelvic or paraaortic lymph node (PLN or PAN) should be staged as IIIc. This is based on the results of the Gynecologic Oncology Group (GOG) study, which reported PLN and PAN involvement in endometrial carcinoma in 9% and 5%, respectively [2]. Therefore, it is necessary to investigate lymph node status. Metastasis in PAN in endometrial carcinoma is reportedly more frequent than that in cervical carcinoma [2-5]. Recently, McMeekin *et al.* [6, 7] reported retroperitoneal lymph node metastasis, including PLN and PAN, in 8% of 607 patients of which 17% showed metastasis in PAN only, whereas Mariani *et al.* [8] reported that it accounted for 17.4% in 65 patients of which 7.7% was in PAN only. Many investigators have reported that patients with endometrial carcinoma had a poor prognosis if they revealed metastasis on PLN [9]. It is not, however, a reasonable method to dissect both PLN and PAN in all patients with endometrial carcinoma. Patients who should undergo lymphadenectomy of either PLN or PAN can be identified if spread patterns and pathways of lymph node metastasis in endometrial carcinoma are clarified. Holub *et al.* [10] tried to identify the sentinel node in endometrial carcinoma by using pre- or intraoperative dye and/or lymphoscintigraphy.

In this paper, we aimed to clarify the spread patterns of lymph node metastasis in endometrial carcinoma and analyze the correlation of lymph node metastasis with clinicopathological prognostic factors in a series of cases at Kitasato University Hospital.

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Patients and Methods

There were 342 patients with endometrial carcinoma who underwent complete surgical therapy, including systemic lymphadenectomy, treated during the period between 1971 and 1998. Radical hysterectomy in addition to bilateral salpingo-oophorectomy was basically performed for patients with clinical Stage II and III, and modified radical hysterectomy was done for those with Stage I. Pelvic lymphadenectomy was performed in all cases and PAN dissection was selectively performed for those who met the criteria such as enlarged PLN and PAN, myometrial invasion of more than one-third in the excised uterine specimen, adnexal metastasis, specific histological types including serous adenocarcinoma and clear cell adenocarcinoma, and positive peritoneal cytology.

Lymph node metastasis was carefully investigated and multiple metastatic lesions found in the same node region were classed as one metastasis. To investigate the spread pathway, the left or right pelvic nodes in each case were separately analyzed and expressed as a region calculated as a side. PAN was defined as one node. Metastasized nodes were mapped and the relationship among individual positive nodes was analyzed. In addition, relationships among lymph node status and various clinicopathological variables, including clinical stage, histopathological findings, myometrial invasion, lymphovascular space invasion (LVSI), cervical invasion, adnexal metastasis, parametrial involvement and peritoneal cytology were evaluated.

Statistical analysis was performed using the chi-square test and $p < 0.05$ was considered statistically significant.

Results

Incidence of lymph node metastasis

Among the 342 patients, 165 and 177 cases underwent modified radical hysterectomy and radical hysterectomy, respectively, and 46 were positive for PLN metastasis; Eleven of 49 who underwent both PLN and PAN dissection appeared positive, including six cases with positive PAN metastasis independently, without PLN metastasis. Consequently, 52 (15.2%) of 342 patients showed positive lymph node metastasis in PLN and/or PAN.

Analysis of positive node lesions

Ninety-nine nodes were positive in 52 patients, including 11 in PAN, 13 in the common iliac node, 19 in the external iliac node, 29 in the internal iliac node, 22 in the obturator node, four in the suprainguinal node and one in the sacral node. Single metastasis in unilateral PLN or PAN regions was found in 47 patients (55 sides), of which nine cases developed multiple node metastasis in the contralateral node regions. Multiple metastases were found in the bilateral sides in four cases and in the unilateral side in one case. As a result, multiple node metastasis was found in 14 cases (18 sides).

In 55 sides with single metastasis in unilateral PLN or PAN, lymph node metastasis was most frequent in the internal iliac and obturator nodes revealing 30.9%, followed by the external iliac node in 18.2% (Table 1).

Table 1. — *Single lymph node metastasis in 55 sides (47 cases) with endometrial carcinoma.*

	Metastatic nodes (%)
Paraaortic*	6 (10.9)
Common iliac	2 (3.6)
External iliac	10 (18.2)
Internal iliac	17 (30.9)
Suprainguinal	2 (3.6)
Obturator	17 (30.9)
Sacral	1 (1.8)
Total (sides)	55 (100.0)

*: without distinction of the side.

Forty-four nodes were positive in 14 cases that suffered multiple metastases in 18 sides of PLN and PAN. Metastasis in the internal iliac node and/or obturator node was found in 16 sides (88.9%). Metastasis in the internal iliac node was found on 12 sides, of which five and seven cases were also metastasized in the external and common iliac nodes, respectively. Of these, four cases metastasized into PAN with or without common iliac node metastasis. Metastasis in the obturator node, where single metastasis was frequently found, occurred on five sides, of which additional metastases were found in one of the internal iliac nodes and two in PAN. Additional metastasis, both in the external and the common iliac nodes was seen on two sides, one of which also metastasized in to PAN. Five (22.7%) of 22 sides with positive obturator nodes, 11 of 29 with positive internal iliac nodes and six of 19 with positive external iliac nodes had more metastasis in the distant cranial nodes, whereas only two with both negative obturator or internal iliac nodes were positive in the external iliac and/or suprainguinal node.

In 49 patients who underwent PLN and PAN dissection, 11 were positive for PAN metastasis. Thirteen cases were found to have metastasis in PLN, whereas 36 were not. The incidence of metastasis in PAN was 38.5% and 16.7%, respectively. Six cases that developed PAN metastasis without metastasis in PLN are listed in Table 2. Cancer lesions occupied the whole endometrium; there was also deeper myometrial invasion and frequent LVSI. No additional adnexal metastasis nor positive peritoneal cytology was determined.

Table 2. — *Cases with paraaortic node metastasis and without pelvic node metastasis.*

Case	Clin. Stage	Histology	Myometrial invasion	Cervical involvement	LVSI	Peritoneal cytology	Adnexal metastasis	Pm. metastasis
1	III	adenosq	outer 1/3	+	+	negative	–	–
2	II	clear cell	inner 1/3	+	–	negative	–	–
3	II	clear cell	middle 1/3	+	–	negative	–	–
4	II	G2 em	outer 1/3	+	+	negative	–	–
5	II	carcinoma	serosa	–	+	negative	–	+
6	III	G3 em	serosa	+	+	negative	–	–

Clin: clinical; LVSI: lymph vascular space invasion in the myometrium; Pm: parametrium; adenosq: adenosquamous cell carcinoma; clear cell: clear cell carcinoma; em: endometrioid adenocarcinoma; carcinosa: carcinosarcoma.

Parametrial metastasis was found in 23 of 342 cases (29 sides). Metastasis both in the parametrium and the lymph nodes was found in 16 cases (Table 3) and one of those 16 cases had a single metastasis in PAN. Ipsilateral PLN involvement was found in 13 cases or in 17 of 28 sides and contralateral node metastasis was also found in five sides. In two cases (2 sides), metastasis was found in only the contralateral lymph node. Among 17 sides with ipsilateral involvement, 14 were found to have metastasis either in the internal iliac node or obturator node. Single metastasis in PLN was recorded in nine sides with ipsilateral parametrial involvement, and seven were involved either in the internal iliac node or obturator node.

Table 3. — *Lymph node state of 15 patients with both parametrial and pelvic lymph node metastasis.*

	Number	Sacral	Suprainguinal	Obturator	Internal iliac	External iliac	Common iliac
Ipsilateral	17 sides*	1	2	3 (2)	11 (5)	4 (1)	6 (1)
Contralateral	7 sides**	–	1	2 (2)	4 (2)	3	2

( ): case number with single node metastasis; *: three sides had both pelvic and paraaortic node metastasis; **: one side had both pelvic and paraaortic node metastasis.

Correlation with clinicopathological parameters

Lymph node metastasis was statistically higher in patients with advanced clinical stage, unusual histologic type including adenosquamous cell carcinoma, higher grade of endometrioid carcinoma, deeper myometrial invasion, LVSI, cervical invasion, adnexal metastasis, parametrial involvement and positive peritoneal cytology (Table 4).

Discussion

In this study series, 15.2% of patients with endometrial carcinoma developed retroperitoneal lymph node metastasis. The most frequent metastatic single region was the internal iliac node and obturator node in 61.8%, and multiple metastasis also involved either of these nodes in 88.9%. Frequent lymph node metastasis in the internal and external iliac nodes has been reported in the literature [11]. However, we speculate from our results that metastasis originates either in the internal iliac or obturator node region and spreads further to the cranial and distant lymph nodes (Table 2). Therefore, the internal iliac and obturator nodes could be sentinel nodes of endometrial carcinoma.

Parametrial metastasis in endometrial carcinoma has a poorer prognosis [12]. Metastasis either in the internal

Table 4. — *Frequency of lymph node metastasis in 342 patients with endometrial carcinoma.*

		Overall	Positive (%)		p value
Clinical stage	I	176	13 (7.4)		< 0.01
	II	157	33 (21.0)		
	III	9	6 (66.7)		
Histological type	Endometrioid	276	32 (11.6)	*, **	
	Adenocanthoma	24	4 (16.7)		
	Adenosquamous	9	5 (55.6)	*	
	Serous	9	2 (22.2)	**	
	Mucinous	7	1 (14.3)		
	Clear	6	3 (50.0)		
	Carcinosarcoma	11	5 (45.4)		
Grade (Endometrioid)	G1	139	11 (7.9)		n.s
	G2	109	17 (15.6)		
	G3	28	4 (14.3)		
Myometrial invasion	Intra-endometrial	69	0		< 0.01
	Inner 1/3	142	8 (5.6)		
	Middle 1/3	63	9 (14.3)		
	Outer 1/3	56	26 (46.4)		
	Serosa	12	9 (75.0)		
LVSI	Positive	106	42 (39.6)		< 0.01
	Negative	236	10 (4.2)		
Cervical invasion	Positive	82	30 (36.6)		< 0.01
	Negative	260	22 (8.5)		
Adnexal metastasis	Positive	19	9 (47.4)		< 0.01
	Negative	323	43 (13.3)		
Parametrial metastasis	Positive	23	16 (69.6)		< 0.01
	Negative	319	35 (11.0)		
Peritoneal cytology	Positive	45	11 (24.4)		< 0.05
	Negative	212	26 (12.3)		

LVSI: lymph vascular space invasion in the myometrium; *, **: $p < 0.01$.

iliac or obturator node was highly correlated with that in the parametrium in 61.1%. Consequently, there may be a pathway via lymphatic lesions in the parametrium in addition to direct spread to PLN.

Direct spread to PAN was observed in 16.7% as well as the pathway via the pelvic lymph node in 38.5 in this study. When 293 patients who were not indicated to undergo PAN dissection were calculated as negative, the incidence of PAN metastasis was 1.8%, similar to that reported by Mariani *et al.* [8]. The incidence of metastasis both in PLN and PAN was reported to be 3% to 16% [2, 5], and that in PAN without coexisting pelvic node metastasis was from 0% to 2% [2, 5]. Thus, there may be two spread patterns to PAN, including a major pathway via PLN, and a rare direct pathway.

Lymph node metastasis in endometrial carcinoma is correlated with clinical stage, histological type of the carcinoma, grade of endometrioid adenocarcinoma, myometrial invasion, LVSI, cervical invasion, adnexal metastasis, parametrial involvement and positive peritoneal cytology. Correlations with these clinicopathological variables have been reported in the literature [2, 5, 13, 14]. However, Creasman *et al.* [2] and Girardi *et al.* [13] reported that lymph node metastasis was not correlated with histological type. Four cases (4%) of endometrial carcinoma with pelvic lymph node metastasis and without myometrial invasion were reported by Takeshima *et al.* [15]. Boronow *et al.* [3] also denied a link between the grade of endometrioid adenocarcinoma. Creasman *et al.* [2] demonstrated that positive peritoneal cytology in endometrioid carcinoma was correlated with metastasis both at PLN and PAN, whereas in our series PAN metastasis was not correlated with positive cytology (data not shown). Lymph node metastasis was found in 69.9% of the cases with parametrial involvement in our series, which was significantly higher than the 11.0% of parametrial negative patients (Table 4). Tammusino *et al.* [16] reported supporting data with a limited number of 24 cases.

In cases of clinical Stage I, well-differentiated adenocarcinoma and shallow myometrial invasion, and sentinel node dissection of the internal iliac and obturator nodes could be substituted for total systemic PLN and PAN dissection.

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Small-cell carcinoma of the uterine cervix: a clinicopathologic study of 11 cases

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Abstract. Tsunoda S, Jobo T, Arai M, Imai M, Kanai T, Tamura T, Watanabe J, Obokata A, Kuramoto H. Small-cell carcinoma of the uterine cervix: a clinicopathologic study of 11 cases. *Int J Gynecol Cancer* 2005; 15:295–300.

We report the clinical profiles and immunohistochemical features of small-cell carcinoma of the uterine cervix. Eleven cases that we have encountered at the Department of Gynecology, Kitasato University Hospital, between 1971 and 2003 are presented. Of 1370 invasive carcinomas of the uterine cervix, the incidence of small-cell carcinoma was 0.8%. Patient ages ranged between 32 and 65 years, with a mean age of 46.3 years. The clinical stages at diagnosis were Ib in four patients, IIb in three, IIIb in three, and IVb in one. All patients presented with abnormal vaginal bleeding. Two patients who are alive with no evidence of disease for 12 years and 3 years 6 months, while eight patients died of primary carcinoma between 4 and 25 months after treatment. Histopathologic findings showed solid nests with marked peripheral palisading pattern and rosette formation. Small tumor cells with scant cytoplasm demonstrated a very high nuclear/cytoplasm ratio and indistinct cell borders. The nuclei were round to oval and demonstrated increased but fine granular chromatin. Nucleoli were indistinct in all cases. Immunohistochemical findings were positive in 81.8% each for neuron-specific enolase and protein gene product 9.5, 72.7% for synaptophysin, 63.6% for chromogranin A, and 54.5% for neural cell adhesion molecule. All specimens were positive for at least one of the above. In conclusion, small-cell carcinoma of the uterine cervix revealed poor prognosis. Making an accurate diagnosis of small-cell carcinoma before performing treatment is of great significance but often difficult. Immunohistochemical analysis using several kinds of neuroendocrine markers is helpful in establishing the correct diagnosis in addition to focusing on characteristic histo- and cytopathologic features.

KEYWORDS: immunohistochemical study, neuroendocrine feature, small-cell carcinoma, uterine cervix.

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Small-cell carcinoma is a tumor commonly seen in the lung, with characteristic histologic findings, but it has been reported to develop in many other organs, including the stomach, rectum, breast, and ovary[1–4]. Rarely, it develops in the uterine cervix[5–10] and is known to metastasize to the lymph nodes within the early stage, promoting a poor prognosis. The term small-cell carcinoma was not used in the General Rules of Clinical and Pathological Management of the Uterine Cervix[11] published in 1982, and the disease was classified as undifferentiated carcinoma. However, because of the poor prognosis due to rapid clinical progression as well as characteristic histopathologic findings, it has been classified as an independent disease under the name small-cell carcinoma in the General Rules of Clinical and Pathological Management of the Uterine Cervix revised in 1997[12]. However, clinical and pathologic features of small-cell carcinoma of the uterine cervix have not yet been fully elucidated due to its low incidence. Therefore, we report small-cell carcinoma of the uterine cervix in a series of 11 cases, focusing on the clinicopathologic, histopathologic, and cytopathologic characteristics, including immunohistochemical features.

Materials and methods

Between July 1971 and December 2003 at the Department of Gynecology, Kitasato University Hospital, the tumor registry recorded 1370 patients with invasive carcinoma of the uterine cervix, including 11 cases of small-cell carcinoma, indicating an incidence of 0.8%. The clinical profiles of these cases, including age, symptoms, stage, treatment methods, and prognosis, were investigated. Patients were clinically staged according to the FIGO classification. The follow-up period ended in December 2003 or when patients died. One case was transferred to other hospital and was lost to follow-up.

The diagnosis was made based on histologic criteria for small-cell carcinoma in the General Rules of Clinical and Pathological Management of the Uterine Cervix[12], using pathologic specimens prepared by hematoxylin–eosin stain. Paraffin–block embedded specimens after formalin fixation were sectioned 3 μm thick. Additional specimens were placed for immunohistochemical search, with informed consent. Immunohistochemical stainings were performed using the labeled streptavidin–biotin method with the following antibodies: mouse anti-human neuron-specific enolase (NSE) monoclonal antibody (DAKO, Glostrup, Denmark; 1:1000), rabbit anti-human chromogranin A polyclonal antibody (DAKO; 1:200), rabbit anti-human synaptophysin polyclonal antibody (DAKO; 1:100), mouse anti-cd-56 (neural cell adhesion molecule [NCAM]) monoclonal antibody (Nihonkayaku, Tokyo, Japan; 1:400), and rabbit anti-human protein gene product 9.5 (PGP9.5) polyclonal antibody (Ultraclone, Cambridge, UK; 1:100).

The positivity criteria were as follows: −, when less than 5% of cells were stained; +, when 5–25% of cells were stained; ++, when 25–50% of cells were stained; and +++, when more than 50% of cells were stained.

Results

Patient ages ranged widely between 34 and 65 years, with a mean age of 46.3 years. All patients presented with abnormal vaginal bleeding. Presumptive diagnosis of small-cell carcinoma was made by cytology in only two cases (18.1%), although findings were positive for malignant cells in all cases. Likewise, preoperative histologic examination accurately diagnosed small-cell carcinoma in only four cases (36.4%) that we encountered recently. Three patients were diagnosed as having adenocarcinoma and three as having small-cell nonkeratinizing squamous cell carcinoma (SCC). Four patients were clinically staged in Ib, three in stage IIb, three in IIIb, and one in IVb with liver and bone metastases (Table 1). None of the patients demonstrated any clinical evidence of abnormal hormone production. Four patients with stage Ib and two with stage IIb underwent radical hysterectomy and bilateral salpingo-oophorectomy with pelvic lymphadenectomy. Postoperative chemotherapy (four to six courses of cisplatin 50 mg/m^2 and etoposide 100 mg/m^2) was given to two patients in stage Ib. Radiation therapy (Linac 50Gy) was given postoperatively to

Table 1. Clinical features of the patients with small-cell carcinoma of the uterine cervix

Case	Age	Stage	Therapy	Prognosis
1	34	Ib	RH	DOD at 12 months
2	47	Ib	RH + PE	A & W at 144 months
3	55	Ib	RH + PE	A & W at 44 months
4	32	Ib	RH	Lost to follow-up[a]
5	50	IIb	RH + radiotherapy	DOD at 14 months
6	52	IIb	RH + radiotherapy	DOD at 16 months
7	48	IIb	SIP[b] + SH + PE	DOD at 11 months
8	65	IIIb	Radiotherapy + PP	DOD at 9 months
9	36	IIIb	PE + RH	DOD at 13 months
10	42	IIIb	PE + radiotherapy	DOD at 7.6 months
11	48	IVb	Radiotherapy + PP	DOD at 4 months

RH, radical hysterectomy; SH, simple hysterectomy; PE, cisplatin + etoposide; PP, cisplatin + peplomycin; SIP, nedaplatin + ifosfamide + peplomycin; DOD, died of disease; A & W, alive and well.
[a]Transferred to other hospital.
[b]Treated with two courses of chemotherapy preoperatively.

two patients in stage IIb. One patient in stage IIb with coexisting SCC underwent simple hysterectomy and bilateral salpingo-oophorectomy, followed by chemotherapy (two courses of nedaplatin 80 mg/m^2/day 1, ifosfamide 1.5 g/body/days 1–5, and peplomycin 5 mg/body/days 1–6). Two patients in stage IIIb and one in IVb received radiation therapy (Linac 50Gy and ^{60}CO-RALS 30Gy in the vagina) in combination with chemotherapy (two to three courses of cisplatin 50 mg/m^2 and peplomycin 5 mg/body/day). One patient with stage IIIb underwent radical hysterectomy and right salpingo-oophorectomy, followed by chemotherapy (three courses of cisplatin 50 mg/m^2 and etoposide 100 mg/m^2). Of the 11 patients, including one who was lost to follow-up, only two with stage Ib are currently alive without any symptoms of recurrence, and both had received adjunctive chemotherapy postoperatively. These two patients have survived for 12 years and 3 years 6 months. Eight patients died of primary cancer between 4 and 25 months, with a mean surviving interval of 13.5 months. Four of seven patients who had undergone surgery developed recurrence, and the relapsing sites included the pelvic cavity in one patient (case 1), brain in two (cases 6 and 9), and multiple organs, including liver, kidney, and lung, in one (case 5). The interval before recurrence was 0.5–12 months. Recurrences were treated with radiation therapy and chemotherapy, including cisplatin and etoposide, none of which was effective and patients proceeded rapidly to death due to primary tumor. Four patients in stage III or IV who received combined chemoradiation therapy responded poorly and died between 4.4 and 13 months without a disease-free period.

Tumors in the extirpated uterus ranged from 3 to 4 cm in diameter. Histopathologic findings demonstrated marked lymph vascular space invasion in six of seven patients (Table 2). Metastasis to the obturator node was observed in two cases in stage IIb and that to the para-aortic node in one patient in stage IIb. Lymph node metastasis was not found in any patients in stage Ib.

Hematoxylin-eosin–stained specimens showed small tumor cells forming solid nests of various sizes with diffuse infiltrative proliferation (Fig. 1). A peripheral palisading pattern around the border of the nests was a typical feature (Fig. 1). In 9 of the 11 cases, rosette formation was observed (Fig. 1). The tumor cells were small with scant cytoplasm, showing a high nuclear/cytoplasm ratio and indistinct cell borders. The nuclei were round to angulated, with increased fine granular chromatin (Fig. 2). Nucleoli were inconspicuous in all cases. Mitosis is frequently observed, demonstrating more than 10 mitotic figures per 10 high-power fields. In addition to small-cell carcinoma,

Table 2. Pathological findings of the extirpated uterus

Case	Coexisting lesion	Lymphovascular space invasion	Metastasized lymph node
1	Adenocarcinoma	–	–
2	Squamous cell carcinoma	+	–
3	—	+	–
4	—	+	–
5	—	+	Right obturator
6	Squamous cell carcinoma	+	Bilateral obturator
7	Adenocarcinoma, squamous cell carcinoma	+	Para-aortic

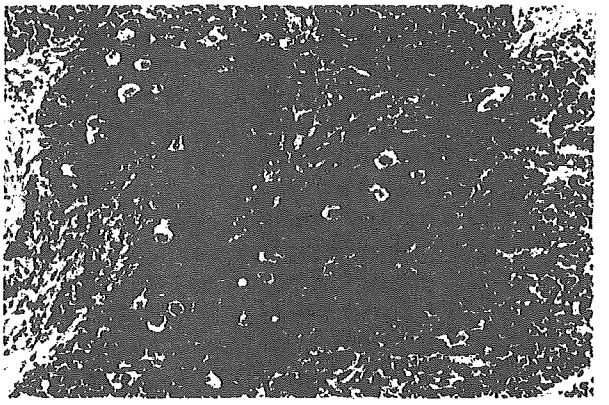

Figure 1. Small and large cancer nests with rosettes formation and peripheral palisade arrangement (H&E, 5 × 4).

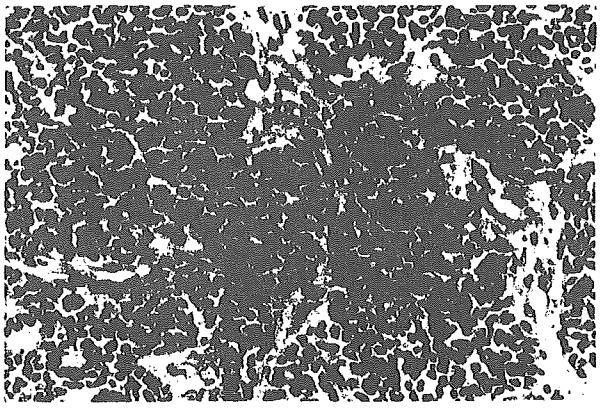

Figure 2. Tumor cells arranging in solid sheets with round, hyperchromatic nuclei and scanty cytoplasm (H&E, 5 × 20).

Table 3. Immunohistochemical results

Case	NSE	NCAM	PGP9.5	Chromogranin A	Synaptophysin
1	+++	+++	+++	+++	++
2	+	−	++	++	−
3	++	+	++	−	++
4	−	++	++	++	+++
5	++	−	−	++	++
6	++	−	++	++	−
7	+	++	+	−	++
8	++	++	++	++	+
9	−	++	++	−	++
10	+++		++	++	++
11	+++	−	−	−	

NCAM, NCC-Lu-243.

SCC coexisted in two cases, adenocarcinoma in one, and SCCand adenocarcinoma in one.

Immunohistochemical findings are shown in Table 3. Nine cases (81.8%) showed immunoreactions for NSE and PGP9.5, eight (72.7%) for synaptophysin, seven (63.6%) for chromogranin A, and six (54.5%) for NCAM. All specimens were positive for either of these neuroendocrine markers (Fig. 3).

Discussion

Small-cell carcinoma of the uterine cervix was first reported under the name carcinoid by Albores-Saavedra *et al.*[13] in 1972. Thereafter, various authors have reported on this entity as a tumor-expressing neuroendocrine differentiation[5–10,14] and numerous names besides carcinoid, eg, small-cell carcinoma, argyrophil cell carcinoma, small-cell tumor with neuroendocrine feature, neuroendocrine carcinoma, small-cell undifferentiated carcinoma, and small-cell neuroendocrine carcinoma. In Japan, it has been classified as small-cell carcinoma and distinguished from undifferentiated carcinoma in the General Rules of Clinical and Pathological Management of the Uterine Cervix in the 1997 revision[12].

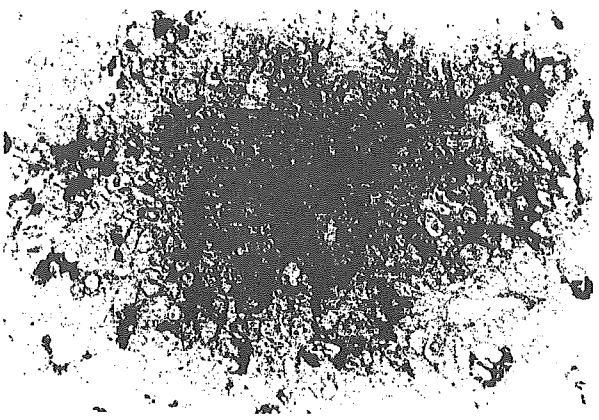

Figure 3. Immunohistochemically positive for chromagranin A (× 160).

The incidence of small-cell carcinoma is very low in 0.31–2% of the invasive carcinoma of the uterine cervix[5–10,15]. In our experience of 1 370 cases of invasive carcinoma, only 11 were small-ell carcinomas, showing an incidence of 0.80%. According to the literature, patient ages range widely from the 2nd to the 10th decade of life[5–8,10,15–22], with mean ages mostly in the forties. A mean age of 46.3 years in our study is consistent with previous reports. Ambros *et al.*[23] and Sheridan *et al.*[21] have reported that small-cell carcinoma is characterized by a number of cases showing juvenile onset. Sixty percent of patients in our series were in their thirties or forties.

Abnormal vaginal bleeding is the most common symptom, as being reported to comprise all cases[10,17,19–21]. Asymptomatic cases are very rare, 5.5%[17] and 6.7%[19]. The prognosis of patients with small-cell carcinoma is considered unfavorable[9,18–22] because of its high rate of lymph node metastasis[21] and early systemic metastasis, including to the lung[18,20]. In our study, only two patients in stage Ib currently remain alive without evidence of disease. Sevin *et al.*[24] reported that the overall 5-year disease-free survival rate of 12 patients, including 1 in stage Ia, 10 in stage Ib, and 1 in stage IIa, was 36.4%, which was significantly lower than that of 71.6% for other histologic types of carcinoma of the cervix.

Albores-Saavedra *et al.*[25] have classified neuroendocrine tumors of the uterine cervix into four categories: the typi3cal carcinoid, atypical carcinoid, large-cell neuroendocrine tumor, and small-cell carcinoma. The criteria for small-cell carcinoma are as follows. (1) Tumor cells are small round or fusiform, with scanty cytoplasm. (2) Nuclear chromatin is hyperchromatic and finely granular. Nucleoli are inconspicuous with nuclear molding. (3) The neoplastic cells may grow in a diffuse manner or may be arranged in nests, trabeculae, or cords. Peripheral palisading and a prominent perivascular concentration of cells are often seen. (4) Necrosis is a constant feature. The coexistence of adenocarcinoma or SCC is reported in 21–77% of the cases[9,17–20,26].

Immunohistochemically, tumor cells are positive for neuroendocrine markers. We performed an immunohistochemical study using NSE, NCAM, PGP9.5, chromogranin A, and synaptophysin. Although there were differences in positivity rates of antibodies, all cases reacted to at least one of the five neuroendocrine

markers. Thus, we can immunohistochemically verify the presence of cells with neuroendocrine differentiation. Similar results were reported in the literature[5,9,17–19]. However, Albores-Saavedra *et al.*[25] indicated that not all of the neuroendocrine markers need to be present to make the diagnosis because 60% of small-cell carcinomas are negative for chromogranin A and synaptophysin and 30% for NSE. Yamawaki *et al.*[9] have also reported that small-cell carcinoma can be diagnosed when tumor cells are positive for two or more of the neuroendocrine markers such as chromogranin A, NSE, and grimelius. In addition, Ambros *et al.*[23] indicated that small-cell carcinoma may be diagnosed when tumor cells are positive for neuroendocrine markers such as NSE, chromogranin A, and synaptophysin, and negative for keratin. Likewise, immunohistochemistry may be considered highly useful in diagnosing such confusing cases[16].

It is often difficult[21] to make a preoperative diagnosis of small-cell carcinoma. In our study, only 2 of the 11 patients had an accurate diagnosis of small-cell carcinoma by cytology and four by preoperative histology. Kim *et al.*[17] reported that histologic type could be presumed by cytology in 79% of 18 cases of small-cell carcinoma based on the findings, including nuclear molding, nuclear smearing effect, salt and pepper chromatin pattern with minimal cytoplasm, and cell clusters without a typical architectural pattern. Furthermore, inconspicuous nucleoli and isolated or loose cell aggregates are also described as cytologic features of small-cell carcinoma[9,27]. As Zhou *et al.*[28] have pointed out, it is often important in clinical practice to consider the differential diagnosis from follicular cervicitis, endometrial cells, adenocarcinoma of the uterine cervix, small-cell type SCC, and lymphoma.

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Phase II trial of docetaxel in advanced or metastatic endometrial cancer: a Japanese Cooperative Study

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The purpose of this study was to determine whether docetaxel has antitumour activity in patients with advanced or recurrent endometrial carcinoma. Chemotherapy-naïve or previously treated patients (one regimen) with histopathologically documented endometrial carcinoma and Eastern Cooperative Oncology Group performance status ⩽2 entered the study. Docetaxel 70 mg m^{-2} was administered intravenously on day 1 of a 3-week cycle up to a maximum of six cycles. If patients responded well to docetaxel, additional cycles were administered until progressive disease or unacceptable toxicity occurred. Of 33 patients with a median age of 59 years (range, 39–74 years) who entered the study, 14 patients (42%) had received one prior chemotherapy regimen. In all, 32 patients were evaluable for efficacy, yielding an overall response rate of 31% (95% confidence interval, 16.1–50.0%); complete response and partial response (PR) were 3 and 28%, respectively. Of 13 pretreated patients, three (23%) had a PR. The median duration of response was 1.8 months. The median time to progression was 3.9 months. The predominant toxicity was grade 3–4 neutropenia, occurring in 94% of the patients, although febrile neutropenia arose in 9% of the patients. Oedema was mild and infrequent. Docetaxel has antitumour activity in patients with advanced or recurrent endometrial carcinoma, including those previously treated with chemotherapy; however, the effect was transient and accompanied by pronounced neutropenia in most patients.

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Most patients with endometrial cancer are diagnosed at an early stage when surgery alone may result in cure. However, the outcome for women with advanced stage or recurrent disease is poor and rarely curable. Both single-agent and combination regimens of chemotherapy have been studied in women with advanced endometrial carcinoma. Currently, no standard chemotherapy regimen for endometrial cancer exists, but single-agent doxorubicin is active, with responses observed in up to one-third of previously untreated patients (Moore *et al*, 1991). Other single agents with modest activity include cisplatin (Thigpen *et al*, 1984a, 1989) and carboplatin (van Wijk *et al*, 2003). Although the response rates with the combination doxorubicin–cisplatin appear to be higher than those achieved with either agent alone, there is no evidence that survival is any longer with combination therapy. In the Gynecologic Oncology Group (GOG) trial comparing doxorubicin alone with doxorubicin–cisplatin, the response rates and progression-free survival were better with the combination regimen (42 *vs* 25%, 5.7 *vs* 3.8 months, respectively), but overall survival (OS) had not significantly improved (Thigpen *et al*, 2004).

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The taxanes, paclitaxel and docetaxel, are potent chemotherapeutic agents that block tubulin depolymerisation, leading to the inhibition of microtubule dynamics, and have significant clinical efficacy for various solid tumours. Paclitaxel has been evaluated as an active agent for endometrial cancer (Ball *et al*, 1996; Lissoni *et al*, 1996; Lincoln *et al*, 2003). However, preclinical data show that docetaxel has increased potency and an improved therapeutic index compared with paclitaxel (Bissery *et al*, 1995), and its short 1-h infusion time offers a substantial clinical advantage over the prolonged infusion durations required with paclitaxel. Docetaxel and paclitaxel also have substantially different toxicity profiles. In particular, docetaxel has a significant lower incidence of neurotoxicity in comparison to paclitaxel (Hsu *et al*, 2004).

The present phase II trial was designed to evaluate the clinical efficacy and tolerability of docetaxel 70 mg m^{-2} in patients with advanced or recurrent endometrial cancer.

PATIENTS AND METHODS

Eligibility criteria

Eligible patients aged between 20 and 74 years, with a life expectancy in excess of 3 months, and Eastern Cooperative

Oncology Group (ECOG) Performance Status (PS) of 0–2 had histologically documented primary stage III, IV or recurrent endometrial carcinoma. Tumours were staged according to the International Federation of Gynecology and Obstetrics criteria. All patients had measurable disease according to the response evaluation criteria in solid tumours (RECIST) (Therasse *et al*, 2000). Measurable lesions defined unidimensionally were $\geqslant 20$ mm using conventional imaging, or $\geqslant 10$ mm with spiral computed tomographic scan. Patients were either chemotherapy-naive or had received one prior chemotherapy regimen for endometrial cancer, with 4 weeks between prior therapy and study treatment. Prior treatment with a taxane was not allowed. Adequate organ function was required for study entry: neutrophil count $\geqslant 2000\,\mu l^{-1}$, platelet count $\geqslant 100\,000\,\mu l^{-1}$, haemoglobin $\geqslant 9.0\,g\,dl^{-1}$, serum bilirubin level $\leqslant 1.5\,mg\,dl^{-1}$, normal hepatic function (asparate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels $\leqslant 2.5$ times upper limit of the institutional normal (ULN)), serum creatinine level $\leqslant 1.5\,mg\,dl^{-1}$, PaO_2 $\geqslant 60$ mmHg and normal electrocardiogram. Patients with any of the following conditions were excluded from the study: sarcoma component, active infection, severe heart disease, interstitial pneumonitis, past history of hypersensitivity, peripheral neuropathy, malignant or benign effusions requiring drainage, active brain metastasis, or active concomitant malignancy. All patients gave informed consent before entering this study, which was approved by the institutional review boards at all participating institutions.

Treatment schedule

Docetaxel $70\,mg\,m^{-2}$ was infused over a 1–2-h period. The treatment was repeated every 3 weeks unless there was documented disease progression or unacceptable toxicity. Prophylactic medications for nausea, vomiting or hypersensitivity reactions were given if these symptoms occurred. No routine premedication was given for hypersensitivity reactions and fluid retention during the first cycle of treatment. The patient's physician identified all hypersensitivity reactions and, if deemed necessary, the investigator administered premedication drugs.

Treatment was delayed for up to 3 weeks in the event of toxicity, but was restarted when the neutrophil count was $\geqslant 1500\,\mu l^{-1}$, platelet count $\geqslant 100\,000\,\mu l^{-1}$, AST/ALT/ALP levels $\leqslant 2.5$ times ULN, and neuropathy or oedema $\leqslant$ grade 1. Docetaxel dosage was reduced by $10\,mg\,m^{-2}$ if febrile neutropenia occurred, if there was bleeding with grade 3–4 thrombocytopenia requiring a platelet transfusion, or if a patient experienced any grade 3–4 nonhaematologic toxicities except nausea, vomiting, anorexia, fatigue, alopecia or hypersensitivity.

Response and toxicity evaluation

The tumour response was assessed according to the standard RECIST criteria (Therasse *et al*, 2000). Target lesions included all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total. Complete response (CR) was defined as the complete disappearance of all target and nontarget lesions, with no development of new disease. Partial response (PR) was defined as a reduction by $\geqslant 30\%$ in the sum of the longest diameter of target lesions. Complete response or PRss were confirmed by repeat assessments performed no less than 4 weeks after the criteria for response were first met. Progressive disease (PD) was defined as an increase by $\geqslant 20\%$ in the sum of the longest diameter of all target lesions, or the appearance of one or more new lesions and/or unequivocal progression of existing, nontarget lesions. Stable disease (SD) was defined as neither sufficient lesion shrinkage to qualify for a PR, nor sufficient increase to qualify for PD. Best response was defined as the most CR achieved by a patient (thus, each patient had a single best response: CR, PR, SD or PD), and the date of best response was the date it was first detected. Time to progression (TTP) was defined as the time from the first medication to the date of a PD event or death (due to endometrial cancer or study drugs). All tumours were radiographically assessed for response every 6 weeks. An independent response review committee (IRRC) evaluated all tumour responses after the investigators had completed their judgement.

Toxicities were evaluated with respect to incidence and severity using National Cancer Institute common toxicity criteria (NCI-CTC, version 2.0) (Trotti *et al*, 2000).

Statistical consideration

Assuming a response rate of 20%, the study was designed with 80% power such that the lower limit of the 95% confidence interval (CI) for the estimate of the response rate was greater than 0.05. A sample size of 32 evaluable patients was required.

The primary end point was overall tumour response (determined by the IRRC) with the corresponding 95% CI using the exact binominal method for the evaluable population. The secondary end point of this study was safety. The Kaplan–Meier (KM) method was used to determine the TTP and median survival time (MST) in the evaluable population.

RESULTS

Patient characteristics

A total of 33 patients were enrolled on the study from April 2001 to October 2003 and one patient was unevaluable as a result of having received prior treatment with paclitaxel and doxorubicin–platinum regimens. The median age of the intent to treat (ITT) population ($n = 33$) was 59 years (range 39–74) and 70% patients had ECOG PS 0 (Table 1). Several patients had unfavourable histologic characteristics: adenosquamous features (three) and uterine papillary serous cancers (two). Most patients (88%) had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy, and one-third of patients had prior radiotherapy. Of those patients who had received prior chemotherapy ($n = 14$), 10 had received combination doxorubicin–platinum in combination, three had received platinum alone and one had received oral fluorouracil. All 33 patients were evaluated for toxicity and survival, while 32 patients were evaluated for response and TTP.

Treatment delivery

Overall, 32 patients received a total of 133 cycles of docetaxel and the median number of cycles of docetaxel was four (range, 1–13). Five patients (15%) experienced dose reductions for the following reasons: two patients experienced febrile neutropenia (in one patient this occurred twice) and three patients had grade 3 nonhaematologic toxicities: diarrhoea (occurred twice in one patient), hyperglycaemia, hyperkalaemia and supraventricular tachycardia.

Response

Table 2 presents the assessment of response to treatment. Two patients, one who was chemotherapy-naïve and the other who had received prior therapy, were not assessable for response because they had received only one cycle of treatment. Before evaluation by the IRRC, primary physicians had reported two CRs and nine PRs. The IRRC judged one CR as a PR, two PR as SD and one SD as a PR. Therefore, the overall response rate for 10 of 32 patients was 31% (95% CI, 16.1–50.0%). Of 13 patients who had prior chemotherapy, three (23%) achieved a PR: two had received doxorubicin–platinum and one platinum alone. The histologic analysis revealed responses among the following tumour types:

endometrioid adenocarcinoma (6 of 25 patients), squamous differentiated adenocarcinoma (1 of 3), papillary serous (2 of 2) and undifferentiated cancer (1 of 1). The median time for the onset of effect was 2.0 months (range, 0.7–4.5) and the median duration of response was 1.8 months (range, 0.9–4.6). The median follow-up time was 17.6 months (range, 1.7–36.3) and median TTP was 3.9 months (95% CI, 1.5–10.2 months) (Figure 1). Median survival time was 17.8 months (95% CI, 7.4–22.0 months).

Safety and toxicity

In all, 33 patients were assessable for toxicity (Table 3). Also, 31 (94%) patients experienced grade 3 or 4 neutropenia, and three (9%) developed febrile neutropenia. Nonhaematologic toxicities included grade 3 anorexia and vomiting experienced by some patients (18 and 9%, respectively). One patient experienced grade 3 peripheral neuropathy (sensory and motor) after five treatment cycles. Three patients terminated the study as a consequence of the following toxicities: infection with *Mycobacterium avium* complex (one), grade 4 hypersensitivity reaction despite premedication with dexamethasone (one) and grade 3 oedema with pleural effusion after six treatment cycles (one). All three patients recovered after receiving recommended medical treatment. There were no treatment-related deaths.

Table 1 Patient characteristics

Characteristic	No. of patients ($n = 33$)
Age, years	
Median	59
Range	39–74
ECOG performance status	
0	23
1	9
2	1
Disease status	
Stage III, IV	9
Recurrent	24
Histology	
Endometrioid	26
Adenocarcinoma with squamous differentiated	3
Papillary serous	2
Adenocarcinoma, unspecified	1
Undifferentiated	1
Tumour grade	
1	11
2	11
3	6
Unknown	5
Prior treatment	
Surgery	29
Radiotherapy	9
Hormonal therapy	5
Prior chemotherapy	
None	19
Doxorubicin and platinum	9
Platinum alone	3
Others	2

ECOG = Eastern Cooperative Oncology Group.

DISCUSSION

At initial diagnosis, only a small percentage of endometrial cancer patients have recurrent or advanced disease with distant metastases, and therefore a multicentre trial is essential for the accrual of patients. This multicentre phase II trial, although relatively small in sample size, clearly demonstrated that docetaxel is active in the treatment of endometrial cancer. Toxicity was manageable and predominantly haematologic.

Taxanes have shown activity in this setting previously, with paclitaxel demonstrating overall response rates of 27–37% when used as a single agent in endometrial cancer (Ball *et al*, 1996; Lissoni *et al*, 1996; Lincoln *et al*, 2003). Combination chemotherapy with paclitaxel and carboplatin or cisplatin has resulted in response rates of 50–56% (Dimopoulos *et al*, 2000; Hoskins *et al*,

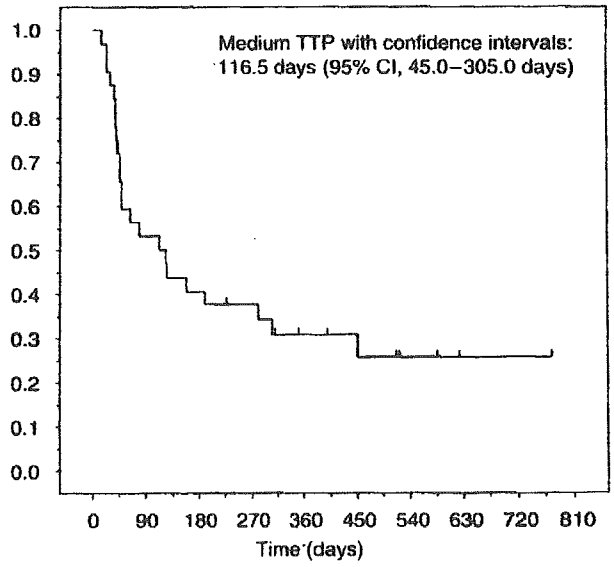

Figure 1 KM curve of estimated TTP.

Table 2 Best response (RECIST criteria) to docetaxel

	Prior chemotherapy ($n = 13$)		No prior chemotherapy ($n = 19$)		Total ($n = 32$)	
Response	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**
Complete response	0	0	1	5	1	3
Partial response	3	23	6	32	9	28
Stable disease	4	31	5	26	9	28
Progressive disease	5	38	6	32	11	34
Not assessable	1	8	1	5	2	6
ORR (95% CI)		23 (5.0–53.8)		37 (16.3–61.6)		31 (16.1–50.0)

ORR = overall response rate; CI = confidence interval.

Table 3 Adverse effects

	NCI-CTC grade ($n = 33$)									
	1		2		3		4		3–4	
Toxicities	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Neutrophils	1	3	0	0	10	30	21	64	31	94
Haemoglobin	11	33	11	33	1	3	1	3	2	6
Lymphopenia	1	3	14	42	11	33	—	11	33	
Platelets	6	18	1	3	0	0	0	0	0	0
Alopecia	5	15	26	79	—	—	—			
Fatigue	13	39	7	21	3	9	0	0	3	9
Anorexia	12	36	5	15	6	18	0	0	6	18
Nausea	16	49	6	18	2	6	—	2	6	
Vomiting	7	21	3	9	3	9	0	0	3	9
Diarrhoea	14	42	3	9	3	9	0	0	3	9
Constipation	2	6	10	30	4	12	0	0	4	12
Stomatitis	3	9	5	15	1	3	0	0	1	3
Febrile neutropenia	—	—	3	9	0	0	3	9		
Infection	0	0	3	9	0	0	0	0	0	0
Oedema	7	21	3	9	1	3	0	0	1	3
Neuropathy-motor	1	3	0	0	1	3	0	0	1	3
Neuropathy-sensory	9	27	2	6	1	3	0	0	1	3
Supraventricular arrhythmia	0	0	0	0	1	3	0	0	1	3
Allergic reaction	3	9	0	0	0	0	1	3	1	3
Rash/desquamation	6	18	5	15	1	3	0	0	1	3
Injection site reaction	5	15	2	6	0	0	0	0	0	0
Nail changes	4	12	0	0	—	—	—			
AST	9	27	3	9	0	0	0	0	0	0
ALT	8	24	2	6	0	0	0	0	0	0
Hypokalaemia	0	0	—	3	9	0	0	3	9	

NCI-CTC = National Cancer Institute common toxicity criteria; AST = asparate aminotransferase; ALT = alanine aminotransferase. Present NCI-CTC grade 3–4 in >5% patients and breakdown if possible by whether patient had prior chemotherapy.

2001; Scudder *et al*, 2005). However, a GOG randomised trial of women with advanced or recurrent endometrial carcinoma, in which the combination paclitaxel–doxorubicin was compared with doxorubicin–cisplatin, showed that the paclitaxel arm did not result in an improved outcome (Fleming *et al*, 2000). A subsequent GOG study, in which the combination paclitaxel, doxorubicin and cisplatin (TAP) with G-CSF was compared with doxorubicin–cisplatin, showed that the TAP arm yielded a better response (57 *vs* 34%; $P<0.01$), progression-free survival (median, 8.3 *vs* 5.3 months; $P<0.01$) and OS (median, 15.3 *vs* 12.3 months; $P=0.037$) than the control arm. However, more grade 3 neuropathy (12 *vs* 1%) and congestive heart failure were observed with TAP than with doxorubicin–cisplatin (Fleming *et al*, 2004). In light of this imbalance between efficacy and toxicity, TAP has not been accepted as the standard chemotherapy regimen in routine clinical practice.

Docetaxel has a toxicity profile that is different from paclitaxel. In particular, neurotoxicity occurs at a low incidence with docetaxel. In our study, only one patient developed grade 3 neuropathy-sensory and recovered in several weeks. While fluid retention is a distinctive toxicity of docetaxel, this can be prevented using premedication (Piccart *et al*, 1997); in our trial, one patient developed pleural effusion since the routine pre-medication with corticosteroids was not applied.

Several studies have reported on second-line chemotherapy for endometrial cancer. Two phase II trials of second-line paclitaxel report response rates of 27% (12 out of 44) and 37% (7 out of 19) (Lissoni *et al*, 1996; Lincoln *et al*, 2003). An older report describes a 30% response rate to second-line high-dose cisplatin (3 mg kg^{-1}) among 13 patients (Deppe *et al*, 1980). With the exception of these studies, response rates to second-line chemotherapy are uniformly less than 20% and most are less than 10% (Slayton *et al*, 1982, 1988; Stehman *et al*, 1983; Thigpen *et al*, 1984b, 1986; Homesley *et al*, 1986; Asbury *et al*, 1990; Muss *et al*, 1991, 1993; Sutton *et al*, 1994; Rose *et al*, 1996; Muggia *et al*, 2002). In our study, 23% of pretreated patients (3 out of 13) had a PR to docetaxel, suggesting that it too is active as second-line therapy.

In conclusion, this multicentre phase II trial shows that docetaxel is active in the treatment of chemotherapy-naïve and chemotherapy pretreated patients with advanced or recurrent endometrial cancer and possesses a manageable toxicity profile; however, the effect was transient and accompanied by pronounced neutropenia in most patients. The exploration of the efficacy of docetaxel combinations in phase III studies for the treatment of endometrial cancer is of great interest and will be initiated.

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Appendix

The following institutions (with principal investigators) participated in this study: Sapporo Medical University, Sapporo, Satoru Sagae; Niigata University, Niigata, Kenichi Tanaka; Tochigi National Hospital, Utsunomiya, Masaaki Kikuchi; National hospital Organization Saitama Hospital, Wako, Mikio Mikami; National Cancer Center Hospital, Tokyo, Noriyuki Katsumata; Tokyo Women's Medical University, Tokyo, Hiroaki Ohta; School of medicine, Keio University, Tokyo, Daisuke Aoki; St. Marianna University School of Medicine, Kawasaki, Kazushige Kiguchi; Kitasato University, Sagamihara, Hiroyuki Kuramoto; Nagoya City University, Nagoya, Atsushi Arakawa; Fujita Health University, Toyoake, Yasuhiro Udagawa; Aichi Cancer Center Hospital, Nagoya, Kazuo Kuzuya; Osaka Medical College, Takatsuki, Ken Ueki; Kinki University, Osakasayama, Hiroshi Hoshiai; Hyogo Medical Center for Adults, Akashi, Ryuichiro Nishimura; Wakayama Medical University, Wakayama, Katsuji Kokawa; Okayama University, Okayama, Junichi Kodama; Okayama Red Cross General Hospital, Okayama, Kohei Ejiri; Kawasaki Medical School, Kurashiki, Ichiro Kohno; National Kyushu Cancer Center,

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ハイリスク症例に対する後療法には adjuvant radiotherapy か adjuvant chemotherapy か

—adjuvant radiotherapy＋chemotherapy の立場から

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はじめに

子宮頸癌に対する術後放射線治療は，主として，術後の病理組織学的検索をもとに，予後不良とされる因子を持つ症例を選んで，経験的に施行されてきた．そのため，術後照射の有用性を支持する根拠のほとんどは，後方視的研究結果によるものであり，よく計画された探索的な臨床試験の結果に基づくレベルの高いエビデンスは少ない．したがって，術後照射を行うことによって最終的に患者の予後が改善するかどうかは，未だ明らかではない．ハイリスク症例とは，一般的に骨盤リンパ節転移陽性例，脈管浸潤陽性例，子宮傍組織浸潤例，切除断端陽性例，腫瘍径の大きい症例などを指すが，その定義は施設あるいは研究ごとに様々である．

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1．対象となる臨床病期 —欧米の研究対象との相違

欧米と日本とでは，そもそも切除の対象となる臨床病期に大きな違いがみられる．欧米では，根治的手術はIB，IIA期までの病変を対象としている．したがって，後療法としてのadjuvant radiotherapyは「再発危険因子を持つIIAまでの早期例に対する治癒切除後の補助療法」という位置づけである[1]．一方，日本では，IIB期までは切除対象とされるため，後療法の検討には主にIB～IIB期までが含まれている[2~4]．また，III期症例であっても，導入化学療法後に切除を行った症例は術後照射の対象としている．つまり日本では，adjuvant radiotherapyとは「病期は問わず手術後に行われる放射線照射」という考え方である．一般に，IIB期以上では，再発危険因子を持つハイリスク症例がほとんどである．子宮頸癌の取り扱い規約によれば，これらの症例のほとんどは後療法の対象となり，術後照射あるいは術後化学放射線治療が行われる場合が多い．したがっ

て，どうしても手術と放射線治療の両方が必要となり，放射線治療単独あるいは化学放射線療法よりも晩期毒性が強くなる．そのため欧米では，はじめからIIB期を手術対象外の進行例としている．つまり，術後照射の有用性についての多くの議論は，欧米ではIB～IIAまでの早期例を対象として進められてきた．IIB期以上の症例の後療法についての報告は，主にアジアを中心とした地域からの後方視的研究であることに注意が必要である．後述の米国の臨床試験はIB～IIAを対象として行われたものであり，その結果を我が国におけるIIB期の術後症例に当てはめられるかどうかは不明である．

2．再発危険因子の決定過程

再発危険因子は，切除後の病理組織学的所見と再発様式とを対比することによって，主に症例数の多い後方視的研究で抽出されてきた[5~7]．腫瘍径，骨盤リンパ節転移，リンパ節転移の個数，筋層浸潤の程度，脈管侵襲，病理組織型など様々な因子が挙げられてきた．しかし，腫瘍径，筋層浸潤の程度とリンパ節転移の有無との間には関係があるなど，再発危険因子相互の間には相関関係が報告されている[8,9]．したがって，統計学的検討が制限されることもあり，再発危険因子の重要度に順位をつけることはきわめて難しいと考えられてきた．このような状況で，ThomasとDemboは，同様に大規模な遡及的研究をすることによって，再発危険因子と主要な再発部位とを検討した[10]．彼らによると，リンパ節転移が陽性の場合は，骨盤内再発の有無にかかわらず遠隔転移が主要な再発となり予後不良である．そのため，生存率の向上には全身化学療法が必要となる．一方，術後の骨盤照射が有用なのは，再発が骨盤内に限局されやすい症例，つまり，リンパ節転移以外の再発危険因子を持つ症例であるとしている．これに対して，FIGO分類にリンパ節転移の有無が勘案されていないこともあり，一般には，早期子宮頸癌のもっとも重要な予後因子として腫瘍径が挙げられている[11]．腫瘍径は，現行のFIGOの病期分類にも取り入れられている．また，根治的放射線治療が行われた症例における遠隔転移を規定する因子としても知られている[12]．したがって，リンパ節転移の有無のみで，再発危険因子の重要度を分けてしまう考え方には無理がある．しかし，手術症例における後方視的研究の多くで，もっとも重要な予後因子は，骨盤内リンパ節転移の有無であることが示されてきた[5,7,13,14]．実際，IB期におけるリンパ節転移陽性例の5年生存率は50～60％程度である[15,16]．これらの経緯から，現在，IB～IIA期の手術症例におけるもっとも重要な再発危険因子は骨盤リンパ節転移であるとする考え方が主流となりつつある．米国Gynecologic Oncology Group (GOG) では，骨盤リンパ節転移陽性例をハイリスク症例としている．なお，癌遺残がある場合の後療法は，本来の術後補助療法の定義とは異なる．切除断端陽性を再発危険因子に含めているかどうかは研究ごとにまちまちであり，注意が必要である．

3．術後照射の適応

IB～IIA期子宮頸癌に対する術後放射線照射の適応は，上述のような再発危険因子を症例ごとに検討したうえで決定する必要がある．近年，これらの因子を組み合わせて検討することで，放射線照射を必要としない症例，術後照射によって骨盤内制御率が上昇し，ひいては予後の向上につながる可能性のある症例，および全身化学療法を併用すべき症例に分類する努力がなされている．

GOGの基準によれば，骨盤リンパ節転移が陰性で，腫瘍径が4 cm未満，リンパ管侵襲がなく，筋層浸潤が1/3未満のものは，骨盤内再発の

可能性がきわめて低いとされ，術後照射の適応外とされる．骨盤リンパ節転移陰性の症例のうち，リンパ管侵襲があるものでは，間質浸潤が外側1/3に及ぶ，中間1/3で腫瘍径が2 cm以上，内側1/3までで腫瘍径が5 cm以上，のいずれかの場合，あるいは，リンパ管侵襲がないものでは，腫瘍径4 cm以上かつ間質浸潤が中間1/3以上の場合は（**表1**），根治術後の経過観察のみでは，骨盤内制御率が不十分とされ，これらを中等度再発危険因子群としている[9]．GOGでは広汎子宮全摘術および骨盤リンパ節廓清が行われたIB期子宮頸癌の中等度再発危険因子群に対して，術後骨盤照射の有用性を検討するランダム化比較試験を行った（GOG 92）．照射群では再発率が47％減と有意に低下し，2年無再発率は照射群88％に対して非照射群79％（p＝0.008）であった[17]．この研究により，中等度再発危険因子群では骨盤照射によって再発率が有意に低下することが示された．しかし，この試験には，経過観察が不十分で生存率の解析がまだ行われていない，術後例にもかかわらず客観性を欠く術前の双合診で決定された腫瘍径を用いた，放射線治療のコンプライアンスが低い，減少したものの骨盤再発が照射群で13％とまだ高かった，消化管障害，下肢の浮腫など重要な晩期有害事象について検討されていないなどの様々な問題点があった．したがって，今のところ，中等度再発危険因子群に対して術後骨盤照射が生存率を向上させるかどうかについてのエビデンスは十分ではない．

一方，骨盤リンパ節転移陽性例では，遠隔転移出現の可能性が高く，術後照射を行っても，他の因子によって術後照射が施行されたリンパ節転移陰性群と比較して，生存率は有意に低い（**表2**）[18-22]．米国では，骨盤リンパ節転移陽性例を85％含むIA2～IIA期の再発危険因子群を対象とした大規模なランダム化比較試験（SWOG 8797）が行われた．全身化学療法としてCDDPと5-FUの同時併用による化学放射線療法群で4年生存率が81％であり，術後照射単独群の71％を有意に上回った[23]．術後の治療方針の違いが生存率に有意な差をもたらすことを示した最初の大規模な探索的臨床試験となった．しかし，そもそも有用性の証明されていない骨盤照射が両群に施行されていて，研究デザイン自体に問題があった．化学放射線療法群は補助化学療法単独群とも比較される

表1 Gynecologic Oncology Groupによる中等度再発危険因子群（文献9より）

脈管侵襲	筋層浸潤	腫瘍径
あり	外側1/3	すべて
あり	中間1/3	2 cm以上
あり	内側1/3	5 cm以上
なし	中間1/3以上	4 cm以上

表2 IB～IIA期子宮頸癌に対する術後照射
—骨盤リンパ節転移の有無による治療成績

著者（発表年）	骨盤リンパ節転移	症例数	5年生存率
Gonzalez[18]（1989）	なし	43	85％
	あり	89	60％
Frigerio[19]（1994）	なし	98	88％
	あり	39	44％
Garipagaoglu[20]（1999）	なし	67	95％
	あり	33	65％
Yeh[21]（1999）	なし	113	81％
	あり	66	53％
Tsai[22]（1999）	なし	150	87％*
	あり	72	71％*

著者名の肩付け番号は引用文献番号
*無病生存率