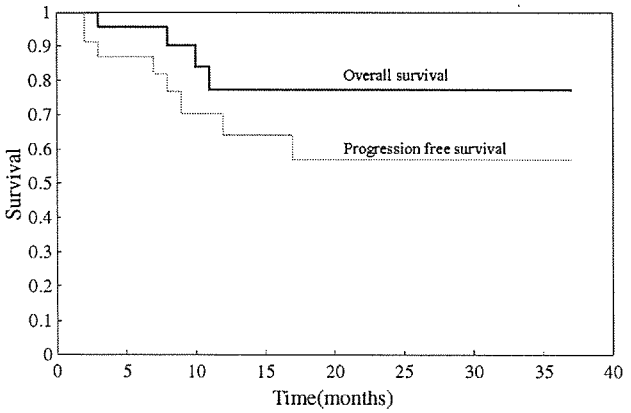

Fig. 1. Overall and progression-free survival time in patients with primarily advanced cancers.

Toxicity

There were no treatment-related deaths. The most common toxicity was hematologic (Table 3), with 59%, 86% and 11% of patients experiencing grade 3 or 4 leukopenia, neutropenia and thrombocytopenia, respectively. Three patients (8%) required granulocyte colony-stimulating factor (G-CSF) support. One patient (3%) had a platelet transfusion, and four (11%) had blood transfusions during the chemotherapeutic portion of the regimen. Non-hematologic toxic reactions consisted of grade 3 nausea and emesis in 2 patients (5%), peripheral neuropathy in 3 patients (8%), diarrhea in 1 patient (3%), general fatigue in 1 patient (3%) and dyspnea in 1 patient (3%). Alopecia was observed in all patients. A single patient encountered severe hypersensitivity reactions: this patient and one patient who suffered grade 3 peripheral neuropathy required to discard continuation of the chemotherapy.

Discussion

Both paclitaxel and carboplatin have been reported to have activity against endometrial carcinoma [4–6]. The purpose of this study was to evaluate the activity and toxicity of the combination of paclitaxel and carboplatin in women with primarily advanced or recurrent endometrial cancers. There are several studies which demonstrated activity of paclitaxel plus carboplatin in the treatment of endometrial cancer (Table 4) [7–11]: for example, Hoskins et al. reported the response rate being 61% in 46 patients with either advanced or recurrent disease treated by this chemotherapy regimen alone or with irradiation.

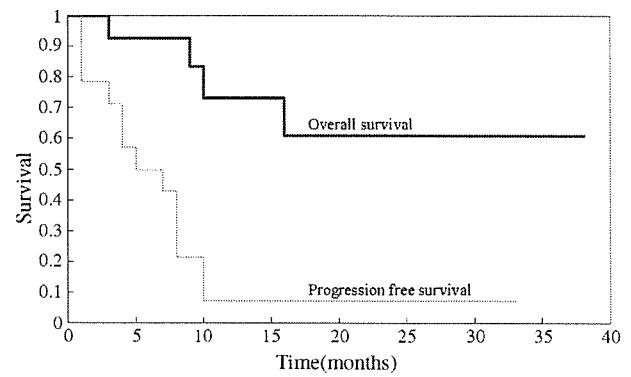

Fig. 2. Overall and progression-free survival time in patients with recurrent cancers.

Table 3
Hematologic toxicity

Toxicity	% of patients affected				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	0	14	27	51	8
Neutropenia	0	3	11	27	59
Anemia	0	19	57	16	8
Thrombocytopenia	48	41	0	11	0

In this study, we observed objective responses in 61% of patients, including complete responses in 6% of them. Our data about overall response rate were in line with other reports. One of the reasons for relatively lower rate of CR in our study was that 14 of 18 patients with measurable lesions were recurrent and that 10 of them had received prior chemotherapy. Considering these backgrounds of the patients, this combination chemotherapy with paclitaxel and carboplatin is highly effective against endometrial cancer. This study also supports the results of two other reports of secondary chemotherapy with paclitaxel and/or platinum in patients with endometrial carcinoma [15,16].

Toxicity with this regimen was tolerable, the most common one being hematologic side-effects. The fact that only limited number of patients required G-CSF support and/or blood transfusion supports the feasibility of this regimen in control of endometrial cancer. Only one patient who required discontinuation of this regimen due to grade 3 peripheral neuropathy was recurrent and had been treated with 9 cycles of cyclophosphamide, doxorubicin and cisplatin (CAP regimen) and 2 cycles of cyclophosphamide and cisplatin (CP regimen), prior to the entry into this study. Accumulation of neurotoxicity due to prior treatment with 11 cycles of chemotherapy using cisplatin might have a role in the occurrence of serious neuropathy. In addition, severe hypersensitivity reactions (HSRs) were observed in one patient though standard anti-allergic pretreatments had been given her. The incidence of severe HSRs to paclitaxel has been reported. Sendo et al. reported that in 105 patients with ovarian cancer during the chemotherapy of paclitaxel and carboplatin, the frequency of

Table 4
Chemotherapy results for primary advanced or recurrent endometrial carcinoma

	No. of patients	Response (%)		
		CR	PR	Total
Price [7]	8	0	63	63
Hoskins [8][a]	46	15	46	61
Nakamura [9]	11	45	27	73
Akram [10]	18	35	28	63
Michener [11]	17	41	41	82

[a] Included irradiation.

HSRs that led to cessation or discontinuation of the chemotherapy was 13.3% [17]. It has been reported that pemirolast is potentially useful for prophylaxis of paclitaxel-induced HSRs [18]. Revision of the current protocol for premedication is requisite.

Our current study included a case that the combination of paclitaxel and carboplatin was administered as neo-adjuvant chemotherapy. Her uterine body and cervix were enlarged and left hydronephrosis due to left ovarian metastasis was observed. In addition, there was a metastasis of the liver so that her clinical stage was IVB. After 4 cycles of paclitaxel and carboplatin, both the primary and metastatic lesions showed a marked decrease in size. She underwent complete surgery of total abdominal hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy and partial resection of liver. Adjuvant chemotherapy was performed and there is no evidence of disease so far. Though there is no consensus regarding to the neo-adjuvant chemotherapy as the treatment of endometrial carcinoma, the existence of such a case and higher responses of this combination chemotherapy suggest that neo-adjuvant chemotherapy with paclitaxel plus carboplatin is effective to advanced endometrial cancer.

The results of our study indicate that the combination of paclitaxel and carboplatin, alone or with irradiation, is effective against primarily advanced and recurrent endometrial cancer. Long-term follow-up and additional prospective randomized studies are necessary to be better able to predict the efficacy of the chemotherapy with this regimen.

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Endometrial Scraping Cytology in Women with Extragenital Malignancies

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Objective

To clarify the usefulness of endometrial scraping smears in women with extragenital malignancies.

Study Design

A total of 4,335 endometrial scraping smears were obtained during the 5-year period 1995–1999 at the National Kyushu Cancer Center and were retrospectively analyzed regarding extragenital malignancies.

Results

There were 88 cases of extragenital malignancies. Extragenital malignant cells were detected in endometrial smears in 13 cases. The cases consisted of 4 gastric cancers, 4 breast cancers, 2 lung cancers, 1 rectal cancer, 1 gastrointestinal stromal tumor of the small intestine and 1 case of adenocarcinoma of unknown origin. The patients' average age was 52.5 years. The symptoms and signs included abnormal vaginal bleeding, abdominal and lumbar pain, lower limb edema, abdominal mass and neck lymph node swelling. Both ascites and peritoneal dissemination were found in 8 cases. Ten of the 13 cases were diagnosed as of extrauterine origin based on the characteristic cancer cell appearance, the absence of cellular detritus among the poorly differentiated adenocarcinomas and, above all, the morphologic difference between normal endometrial cells and cancer cells.

Conclusion

Endometrial scraping smears are useful for detecting extragenital malignant cells that enter the uterine cavity. (Acta Cytol 2006;50:158–163)

Endometrial scraping smears, because of their simplicity and accuracy, are useful for detecting extragenital malignant cells that enter the uterine cavity.

Keywords: endometrial cancer, scraping cytology, endometrial smears.

There have been several studies regarding extrauterine malignant cells detected in cervical smears,[1-9] and about 50% of such cells have been reported to come from cancers of the ovary and fallopian tube.[3,9] However, few reports have been published on endometrial smears concerning extrauterine malignant cells, especially extragenital ones.[10-14] Endometrial aspiration cytology has been used in previous reports,[10-14] and the positive rate of extrauterine malignant cells is higher for endometrial aspiration smears than for cervical smears.[12,13] One of the routes by which extrauterine carcinoma cells move to the

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uterine cavity and cervix is via the fallopian tube.[3,8] Therefore, endometrial smears might be more useful than cervical smears in this regard.

There are no reports regarding endometrial scraping smears in cases of extragenital malignancies, and we therefore elucidated this topic in this study. In order to evaluate the usefulness of cytologic examination of the uterus in extragenital malignancies, we retrospectively studied cases of extragenital malignancies in which endometrial smears were examined. We identified 13 positive endometrial smears, which included rare cases of lung cancers and small intestinal gastrointestinal stromal tumor (GIST). An evaluation of the primary sites, cytologic and clinical features in the endometrial smears was performed.

If malignant cells are seen on endometrial scraping smears and no cytologic similarities are observed between normal endometrial cells and cancer cells, one should consider the possibility that an extrauterine/extragenital malignant tumor exists....

Materials and Methods

During the 5-year period from 1995 to 1999, 4,335 smears of the endometrium were obtained at the outpatient clinic of the gynecology service and evaluated in the cytology laboratory of the National Kyushu Cancer Center. The endometrial smears were obtained using the Endocyte device (Laboratoire CCD, Paris, France). The Endocyte has 2 propellerlike tips covered with elastic material. In addition, there is a small ball-shaped end attached to one of the tips. The Endocyte was inserted into the uterine cavity, and its elastic cover was pulled off. The propellerlike tips were then turned clockwise and/or counterclockwise several times. The cells on the tips were then spread onto glass slides after cutting the ball-shaped end. Endometrial slides were placed in 95% ethanol and then were processed by Papanicolaou stain. A total of 13 patients whose endometrial cell samples contained malignant tumor cells of extragenital origin were analyzed. The primary sites, extent and distribution of the tumors and the presence of peritoneal fluid collection were evaluated. Primary gynecologic origins were ruled out based on clinical and histopathologic examinations in all cases and thus were excluded from the study. In 1 case, immunohistochemical staining with polyclonal rabbit antihuman antibody against c-kit (Dako Cytomation, Inc., Carpinteria, California, U.S.A.) was carried out.

Results

Endometrial smears were obtained in 4,335 cases during the study period, and there were 54 cases with untreated extragenital malignancies and 34 with recurrent extragenital malignancies. Two of them had no diagnosis regarding the primary site of malignancy at the time of consultation. These 88 cases were referred for a gynecologic evaluation in our department. Endometrial smears were obtained from all of them. In 13 cases, malignant cells were detected in an endometrial smear: 0.30% of endometrial smears (13 of 4,335) and 14.8% of extragenital malignancies (13 of 88). As for the untreated cases, positive endometrial smears were found in 3 of 54 cases (5.6%). In recurrent cases, positive endometrial smears were found in 10 of 34 cases (29.4%).

The clinical characteristics are summarized in Table I. The cases with a positive endometrial smear consisted of 4 gastric cancers, 4 breast cancers, 2 lung cancers, 1 rectal cancer, 1 GIST of the small intestine and 1 case of adenocarcinoma of unknown origin. Ten of the 13 cases had recurrent diseases. The average age was 52.5 years.

The symptoms and signs included abnormal vaginal bleeding in 5 cases, abdominal and lumbar pain in 1, abdominal pain in 1, lower limb edema in 1, abdominal mass in 1 and neck lymph node swelling in 1.

Table I *Clinical Characteristics of the Patients*

Characteristic	No. of patients
Age (yr) (average)	52.5 ± 8.4
Primary site	
Stomach	4
Breast	4
Lung	2
Rectum	1
Small intestine (GIST)	1
Unknown	1
Symptom	
Vaginal bleeding	
+	5
–	8
Involved organ/process	
Ascites	9
Peritoneal dissemination	9
Ovary and/or tube	5
Pleural effusion	3
Bone	2
Lung	2
Lymph nodes	2
None	2

Table II *Detection of Extragenital Malignant Cells or Tissue by Histologic Examination in Cases of Positive Endometrial Smears*

Case no.	Endometrial biopsy	Hysterectomy specimen
1	–	None
2	–	Cervix, myometrium
3	+	Cervix, endometrium
4	ND	ND
5	+	ND
6	–	Cervix, myometrium
7	ND	ND
8	–	None
9	–	ND
10	–	ND
11	+	ND
12	–	ND
13	+	None

ND = not done.

Ascites and peritoneal dissemination were found in 9 cases each, and both were found in 8. There were 13 untreated or recurrent cases with ascites in 88 extragenital malignancy cases, and 9 (69.2%) of them demonstrated positive endometrial smears. Adnexal lesions were clinically found in 5 of 11 cases.

Uterine lesions, except for serosal dissemination, were detected in 6 cases either pathologically or surgically (Table II). An endometrial biopsy was obtained from 11 of the 13 cases with positive endometrial smears, and 4 of the 11 revealed malignant tissue or cells. In addition, 6 cases either underwent a hysterectomy at the time of surgery for primary cancer or were examined at autopsy. Three cases had a histologically proven metastatic lesion in the uterus.

Table III shows the cytologic characteristics of the endometrial smears of extragenital malignancies. There were 5 cases with distinctive cytologic characteristics of extrauterine malignant cells, while 4 cases had signet-ring cell type gastric cancers (cases 1–4). In the case of small intestinal GIST, mesenchymal malignant cells were found on the endometrial smears (case 12).

Among the 13 positive endometrial smear cases, 10 cases of endometrial smears were obtained from postmenopausal women (cases 1–3, 6–9, 11–13). In 9 of these cases, the normal endometrial cells were atrophic, and clear morphologic differences were easily recognized between cancer cells and normal endometrial cells (cases 1–3, 6–9, 12, 13). There was no cytologic similarity between them. Most of the malignant cell groups were small and separately arranged among the groups of normal endometrial cells.

There were 8 cases of poorly differentiated adenocarcinoma (cases 1–5, 7, 9, 13). Regarding the presence of tumor diathesis in these 8 patients, except for erythrocytes, only necrotic cellular detritus was seen in 2 of the 8 cases (cases 2, 5). Consequently, among the 13 positive endometrial smear cases, 10 were diagnosed as possibly of extrauterine origin based on the characteristic cancer cell appearance, morphologic difference between normal endometrial cells and cancer cells, and absence of cellular detritus among the poorly differentiated adenocarcinomas (cases 1–4, 6–9, 12, 13).

One of the lung cancer cases is shown in Figure 1 (Table III, case 9), and a small intestinal GIST case is shown in Figure 2 (Table III, case 12).

Discussion

The malignant tumor cells observed in cellular samples obtained from the cervical canal usually originate in primary uterine neoplasms and less frequently from extrauterine cancers. About half the extrauterine can-

Table III *Endometrial Cytology Diagnoses of Extragenital Malignancies*

Case no.	Age (yr)	Primary site	Diagnosis of extrauterine origin	Normal atrophic endometrial cells	Cellular detritus	Tumor differentiation
1	52	Stomach	+	+	–	Poor: signet-ring cell
2	59	Stomach	+	+	+	Poor: signet-ring cell
3	49	Stomach	+	+	–	Poor: signet-ring cell
4	46	Stomach	+	–	–	Poor: signet-ring cell
5	38	Breast	–	–	+	Poor
6	57	Breast	+	+	–	Moderate
7	61	Breast	+	+	–	Poor
8	52	Breast	+	+	–	Moderate
9	53	Lung	+	+	–	Poor
10	36	Lung	–	–	+	Moderate
11	59	Rectum	–	–	+	Moderate
12	60	Small intestine	+	+	–	GIST
13	61	Unknown	+	+	–	Poor

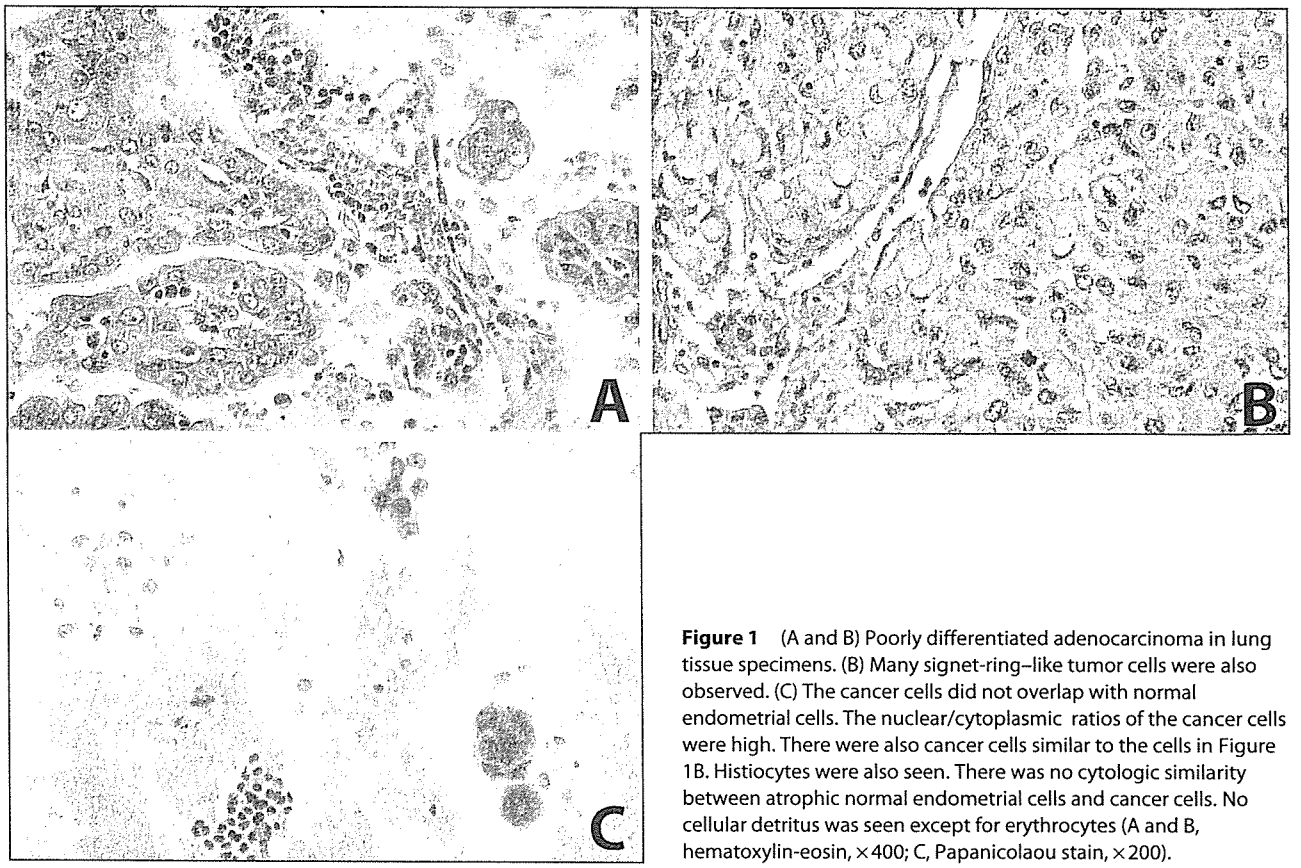

Figure 1 (A and B) Poorly differentiated adenocarcinoma in lung tissue specimens. (B) Many signet-ring–like tumor cells were also observed. (C) The cancer cells did not overlap with normal endometrial cells. The nuclear/cytoplasmic ratios of the cancer cells were high. There were also cancer cells similar to the cells in Figure 1B. Histiocytes were also seen. There was no cytologic similarity between atrophic normal endometrial cells and cancer cells. No cellular detritus was seen except for erythrocytes (A and B, hematoxylin-eosin, ×400; C, Papanicolaou stain, ×200).

cers are carcinoma of the ovary and the fallopian tube.[3] In rare cases, a Pap smear can serve as a diagnostic tool in the evaluation of extrauterine malignancies.[9] McGill et al reported a case in which the cervical cytology findings led to a diagnosis of gastric cancer.[6]

In patients with known extrauterine cancer, the presence of malignant cells in uterine samples provides information regarding the extent of the neoplasm,[3] and Pap smears are therefore best utilized as an adjunct to tumor staging and patient management.[9]

There have been few reports in the English-language literature on extrauterine malignancies detected by endometrial aspiration cytology, and most such reports are related to ovarian cancer.[11-14] Takashina et al reported 19.3% of their cases to have cervicovaginal smears positive for ovarian cancer cells, while 41.9% of the endometrial aspiration smears they analyzed were positive in 114 preoperative patients with ovarian cancer.[12] According to Jobo et al, the positive rate of endometrial aspiration cytology was 100% in patients with endometrial invasion and 15.9% in cases without invasion among preoperative patients with ovarian carcinoma.[13] These results suggest that endometrial aspiration cytology is more effective than cervical cytology for detecting ovarian cancer cells. Endometrial aspiration cytology has also been suggested to be more effective than endometrial biopsies because endometrial smears can detect ovarian cancer cells without endometrial invasion, while endometrial biopsies detect ovarian cancer tissues only when endometrial invasion is found.

The fallopian tube is an important pathway through which extrauterine malignant cells appear in cervical cytology.[3,9] In endometrial aspiration cytology, the fallopian tube also seems to be an important pathway through which ovarian cancer cells appear because endometrial aspiration cytology can be positive without endometrial invasion, and the positive rate increases when ascites and/or peritoneal carcinomatosis are found.[12,13]

Regarding extragenital malignancies, Miyagi et al reported 16 cases of gastric cancer detected by endometrial aspiration cytology. In 9 patients, adenocarcinoma cells were present in both the cervical and endometrial aspiration cytology specimens. Twelve of the 16 cases were investigated for uterine metastases, and 5 cases had metastatic foci in the uterus. Primary gastric cancer was diagnosed as a result of positive endometrial aspiration smears in 3 patients.[10]

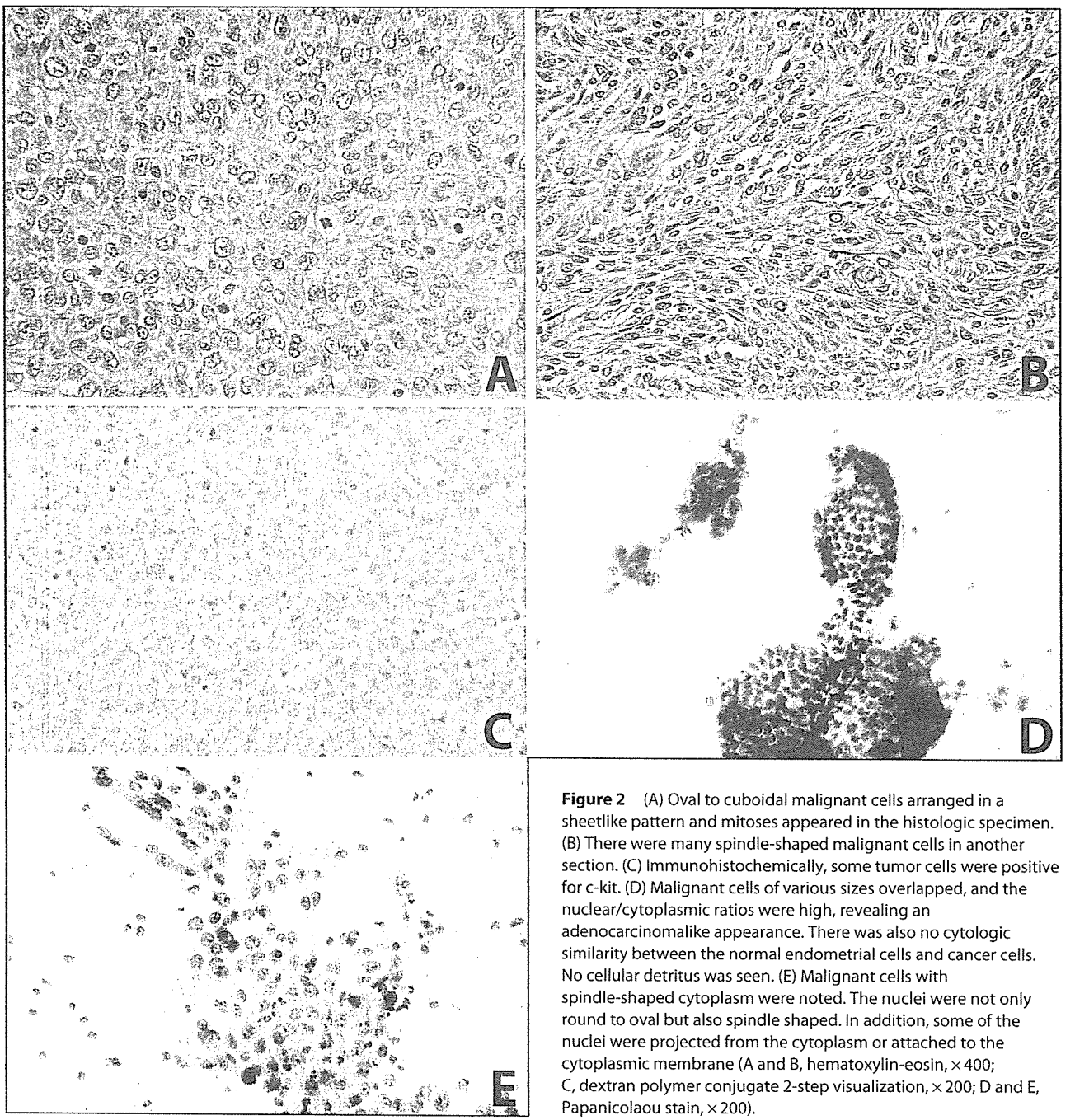

Figure 2 (A) Oval to cuboidal malignant cells arranged in a sheetlike pattern and mitoses appeared in the histologic specimen. (B) There were many spindle-shaped malignant cells in another section. (C) Immunohistochemically, some tumor cells were positive for c-kit. (D) Malignant cells of various sizes overlapped, and the nuclear/cytoplasmic ratios were high, revealing an adenocarcinomalike appearance. There was also no cytologic similarity between the normal endometrial cells and cancer cells. No cellular detritus was seen. (E) Malignant cells with spindle-shaped cytoplasm were noted. The nuclei were not only round to oval but also spindle shaped. In addition, some of the nuclei were projected from the cytoplasm or attached to the cytoplasmic membrane (A and B, hematoxylin-eosin, ×400; C, dextran polymer conjugate 2-step visualization, ×200; D and E, Papanicolaou stain, ×200).

The above reports suggest that endometrial aspiration cytology also detects extragenital malignancies more frequently than cervical cytology and endometrial biopsies. In addition, in some cases, endometrial aspiration cytology is thus suggested to accurately diagnose extragenital malignancies.

To our knowledge, this is the first English-language report on extragenital malignant cells detected by endometrial scraping smears in a fairly large number of cases. In this study there was no case in which endometrial scraping smears led to a diagnosis of extragenital malignancy, but the smears were helpful in avoiding unnecessary surgery in 1 case of gastric cancer with a small amount of ascites before treatment because peritoneal dissemination was indicated by a positive endometrial scraping smear.

Our findings regarding histologic examinations of the uterus indicate that endometrial scraping smears tend to detect extragenital malignancies more often than do endometrial biopsies. It is difficult to detect

extragenital malignant tissue or cells in endometrial biopsy specimens when there are no endometrial lesions because the endometrium is scraped several times. However, endometrial scraping smears wipe a large part of the endometrial surface with propeller-shaped tips, and it is therefore easier to detect extrauterine malignant cells if they are in the uterine cavity.

Tumor diathesis consists of exudate and/or transudate, erythrocytes, fibrin and necrotic cellular detritus.[3,9] Several investigators reported that a lack of tumor diathesis on cervical smears was not a characteristic finding in metastatic carcinoma.[8,9] Regarding poorly differentiated adenocarcinoma, however, Ng et al stated that lack of tumor diathesis was an important sign of extrauterine malignancies.[3] Tumor diathesis of poorly differentiated adenocarcinoma was evaluated in our study; among the factors only necrotic cellular detritus, except for erythrocytes, was seen in 2 of 8 poorly differentiated adenocarcinoma cases. In these 8 cases, 5 had no endometrial lesions, and necrotic cellular detritus was seen in only 1 of the 5 cases. Consequently, when poorly differentiated adenocarcinoma without necrotic cellular detritus is seen on endometrial scraping smears, there is a possibility that extrauterine/extragenital malignant tumors exist.

In 1 ovarian cancer case reported by Jobo et al, small clusters of serous adenocarcinoma cells and normal endometrial cells were coincidentally obtained and demonstrated no structural relationship to each other.[13] In many of our cases, extragenital malignant cells appeared between the normal endometrial cells, and no cytologic similarity was seen. In addition, most of the extragenital malignant cell groups were relatively small and solitary. Especially in cases of postmenopausal women, normal endometrial cells were atrophic, and the difference between normal endometrial and cancer cells was clear.

Endometrial cells are rarely seen on cervical smears, and almost no relationship between malignant cells and normal endometrial cells could be observed. However, when using endometrial scraping smears, such a relationship could be clearly observed, making endometrial scraping smears superior to cervical smears in this regard.

We found that endometrial scraping smears, because of their simplicity and accuracy, are useful for detecting extragenital malignant cells that enter the uterine cavity. If malignant cells are seen on endometrial scraping smears and no cytologic similarities are observed between normal endometrial cells and cancer cells, one should consider the possibility that an extrauterine/extragenital malignant tumor exists, especially in specimens with poorly differentiated adenocarcinoma cells not demonstrating cellular necrotic detritus.

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特集 今，改めて“子宮がん”を考える

再発子宮頸がんとその治療

Treatment of recurrent carcinoma of the uterine cervix

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再発子宮頸癌をその再発パターンにより近年のエビデンスのある治療法を記述した．再発癌の治療は困難であるが，一部には長期生存や治癒可能な症例も存在する．治療方針の決定にあたっては再発パターンによる症例の個別化が必要である．諦めない姿勢，対象例の再発状態をよく吟味すること，また集学的治療を考慮したチーム医療など婦人科腫瘍学の粋をつくした対応が必要である．

Key Words 子宮頸癌，再発，手術，放射線治療

はじめに

子宮頸癌の治療成績は長期間大きな改善を認めていない．再発を可能な限りおこさない適切な初回治療とともに再発時の有効な治療の導入が子宮頸癌の長期予後の改善には必要である．しかし，初回治療に関する種々の解析や新しい試みに比べ，再発子宮頸癌に対する検討や治療の試みに関する研究はまだまだ不十分である．再発子宮頸癌の治療を述べる際の難しさは再発パターンの多様性にある．初回治療の治療法，放射線治療の有無と線量，組織型，再発までの期間，再発部位，孤在性か多発性か，年齢，などの因子を考慮しなければならない．この多様な再発様式についてそれぞれ個別に最良の治療方法を考える必要があるからである．本稿では，すべての再発パターンについて述べつくすことはできないが基本的ないくつかの観点から再発子宮頸癌の治療について言及する．

再発の診断について

治療を行う前に，すべての子宮頸癌再発についてはその再発様式を明らかにすべきである．発見された再発病巣のみでなく，ほかに再発・転移巣がないかを十分に検討する．近年，CT, MRIに加えてPET，或いはPET/CTが再発病巣の同定には有用であることが分かっている．微細な転移をすべて知ることはできないが，ほかの診断法より検出感度は高いと考えて良さそうである[1)2)]．これらの検査により再発病巣が孤在性であるのか多発性であるかを知ることは治療戦略を考えるうえで極めて重要である．

われわれが再発子宮頸癌の予後因子を多変量解析により検討した結果によれば，再発が孤在性であるか多発性であるかが最も予後に影響を与えている因子であった[3)]．また，初回治療から再発までの期間が長い程，予後が良好である傾向が認められる．孤在性再発では長期生存の可能性がある

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ことから，このような症例に対しては治癒を目的として積極的に個別化した集学的治療を行うことも考慮すべきである．一方において多発性再発に対する基本的な治療法は化学療法であるが，現段階では化学療法のみにより再発子宮頸癌の治癒を期待することはできない．したがって，症状緩和や若干の延命効果を期待することが治療の目的となる．

■■■ 手術後の骨盤内再発

早期癌に対する広汎性子宮全摘出術などの術後の骨盤内再発に対しては根治的放射線治療が有効であることは古くからエビデンスのある事実である[4)5)]．Ciatto らはこの再発についてさらに以下の３つに分類している[4)]．１）腟或いは傍腟組織に限局した再発で骨盤壁には到達していない，２）一方の傍子宮結合織に病巣があり骨盤壁に達している，３）両側の傍子宮結合織に病巣があり骨盤壁に達している．１）２）の状態に対して放射線治療は最も適しており，その５年生存率は30～70%と報告されている．45－50Gy の全骨盤外部照射と腔内照射を併用するのが通常である．腟壁下1/3までの進展があれば，鼠径リンパ節を含む照射範囲が必要である．大きな病巣ではさらに範囲を限定した照射を追加して64－66Gy の線量を得る必要がある．本邦では腔内照射は高線量率照射が行われることが多く，Ito らが腟断端再発90例を治療した報告を行っている[6)]．その結果によると，全体の10年生存率は52%で，腫瘍のサイズが統計学的に有意な予後因子であった．すなわち，3 cm 以上は０%，3 cm 以下は48%，明らかな腫瘤のないものは72%の結果であったとしている．

Wang らは扁平上皮癌の遅発性再発73例の腟再発の治療結果を報告しており，それによれば，40%の５年生存率が得られたとしている[7)]．彼らは腟用の mold を用いて，３～５回に分割して20－40Gy を照射している．低線量率，高線量率いずれの治療法も可能であるとしている．しかし，それでも25%の例で合併症が発生し，瘻孔形成は12%に認めている．

上記のように，手術後の骨盤内再発は放射線治療が最も考慮されるが，膀胱や直腸との瘻孔を形成しているような再発症例では，放射線治療を行っても瘻孔形成により人工肛門や尿路変更を余儀なくされるため，骨盤除臓術が選択されても良いと考える．

■■■ 根治的放射線治療後の骨盤内再発

１．放射線再照射

残念ながら，再度の放射線治療は一般的に治療効果が少ないのが事実である．例えば，Prasasvinichai らは照射後の再発症例51例を再照射し，17.6%の５年生存率しか得られなかったとしている[8)]．しかし，一方で腟や子宮の再発で病巣が小さな場合は腔内照射や組織内照射でコントロールできる場合もあることはよく知られた事実である．Puthawala などはこのような再発例10例に対して組織内照射を行い，７例において腫瘍のコントロールができ，80%の症例で症状が改善できたとしている[9)]．また，Randall などは，13例を治療し，69%の完全寛解と46%の２年生存を得たことを報告している[10)]．これらの治療で有効例となるのは，病巣が小さいことのほかに，再発までの期間が長いこと，扁平上皮癌であることがあげられている．

再照射に伴う重要な問題は周囲組織の障害の率も高くなり，直腸腟瘻，膀胱腟瘻といった高度な障害も多くなることである．しかし，これらの障害は，前回治療からの期間が長ければ軽度に留まる傾向があり，治療に際してこの要因も十分考慮する必要がある．

本邦においては，組織内照射の治療例は学会報告などで散見されるが，まだ一般的に考慮されている治療法ではない．放射線照射後ということで諦めることなく，上記のような予後良好因子をもつ症例に対しては，熟練した放射線治療医による工夫された照射が考慮されてもよいと思われる．

2．手術療法

1）骨盤除臓術

放射線治療後の中央再発に対して，治癒をめざした治療法として最もエビデンスがあるのは，骨盤除臓術である．よく選択された症例の5年生存率は30～60%で，手術関連死亡率も近年では10%以下と報告されている[11)-14)]．骨盤除臓術で問題となるのは術後のQOLの低下であるが，除臓後の再建術の発達により，この問題に対する改良が行われている[15)16)]．膣の再建は，大腿薄筋皮弁，大殿筋皮弁，腹直筋皮弁等，を用いた方法が開発されている．また，尿路変更術については，Indiana, Miami, Mainz pouchなどの尿貯留能を有する術式が欧米では選択されるようになってきた．人工肛門を回避するために，超低位での直腸・大腸吻合を行うのみでなく，さらに便貯留能を有するJ型結腸嚢やtransverse coloplasty pouchを作成する吻合方法なども用いられるようになっている．これらの比較的新しい技術を導入することにより，患者は術後のストーマ装具の装着や外見上の劣等感から解放され，比較的自然に近い状態で生活できるようになるため，骨盤除臓術の術後QOLは従来に比し，格段と向上すると報告されている[17)]．

2）広汎子宮全摘出術

非常によく選択された小病巣の中央再発には骨盤除臓術の代わりとしてこの術式が用いられることもある[18)19)]．Rubinらは，194例の検討を行って，5年生存率は62%と報告している[19)]．しかし，この治療法での合併症率は極めて高く，48%の瘻孔形成や手術関連死亡も2例あったことは，治療法の選択として躊躇させるものである．

■■ 再発例に対する化学療法

遠隔転移を伴う再発や多発病巣の再発例では局所療法による癌の制御はもはや困難であり化学療法が治療選択肢となる．しかし，残念ながら，化学療法は子宮頸癌再発について治癒を目的とした治療法とはいまだ成り得ていない．あくまで，症状緩和或いは生存期間の延長を目的として用いられるべきである．薬剤としてはcisplatinが単剤で最も有効であることは十分なエビデンスが得られている[20)]．また，cisplatinの量は50mg/m^{2}を100mg/m^{2}としても奏効率の上昇が見られるのみで，無増悪期間，全生存期間いずれも改善しないことも分かっている[21)]．

一般的には併用化学療法が単剤の治療よりも有効とされているが，従来の併用化学療法でCisplatin単剤の効果を凌駕するものはなかった．現在までに行われた前方視的ランダム化比較試験の結果を表に示している[22)-27)]（表1）．これらの結果をみても，全生存期間を著明に改善する治療法はないことが分かる．GOG169で行われたCDDP単剤とCDDP/Paclitaxel併用療法を比較した結果では，全生存期間に差はなかったものの，無増悪生存期間の中央値が2.8カ月と4.8カ月と併用群が有意に上回り（$p<0.01$），なおかつCDDP単剤に比し毒性の増強がほとんどなかった[27)]．このことから，CDDP/Paclitaxel併用療法はCDDP単剤に対して優る併用療法として，現在では欧米での標準治療と位置付けられている．本邦では，卵巣癌治療としてCDDP/Paclitaxel併用療法が十分使用される以前にCBDCA/Paclitaxelが標準治療として普及した経緯から，一般臨床においてCBDCA/Paclitaxelが子宮頸癌でも使用されていることが多い．この2者の治療法の前方視的比較を行うために日本臨床腫瘍研究グループ（JCOG）では，Ⅳb期および再発子宮頸癌に対するCDDP/Paclitaxel併用療法vs. CBDCA/Paclitaxel併用療法のランダム化比較試験が実施されている．この結果により，CBDCA/Paclitaxel併用療法の真価が明らかになるとともに，本邦における標準治療が確立するものと思われる．

■■ 肺転移に対する手術療法

肺転移例に対する外科的切除の試みは以前より報告が散見されてきた．本邦においても後方視的多施設共同研究として山本らが肺転移症例29例の

表1　子宮頸癌に対するシスプラチンを有する多剤併用療法のランダム化比較試験

治療薬	症例数	CR (%)	PR (%)	CR＋PR (%)	生存期間の中央値（月）
MMC/VCR/BLM/CDDP	54	7	15	22	6.9
vs					
MMC/CDDP	51	4	21	25	7
vs					
CDDP	9	11	22	33	17
DVA/BLM/MMC/CDDP	143	8	23	31	10
vs					
CDDP	144	6	14	19	9.4
DBD/CDDP	153	9	12	21	7.3
vs					
IFM/CDDP	155	12.5	18.5	31	8.3
vs					
CDDP	146	6.5	11.5	18	8
BLM/IFM/CDDP	50	26	26	52	8
vs					
CDDP	56	10	20	29	6
BLM/IFM/CDDP	141			32.1	8.4
vs					
IFM/CDDP	146			32.2	8.5
PTX/CDDP	130	15	21	36	9.7
vs					
CDDP	134	6	13	19	8.8

MMC：mitomycin C, VCR：vincristine, BLM：bleomycin, CDDP：cisplatin, DVA：vindesine, DBD：dibromodulcitol, IFM：ifosfamide, PTX：paclitaxel

外科的切除療法の結果を報告している[28]．それによれば，無病5年生存率は全体で32.9%，1～2個の転移例では42.2%，3個以上の転移例では0%であった．孤在性肺転移では，考慮されるべき治療法と考えられる．われわれの症例も含まれており，一部の症例では諦めることなく治療することにより長期生存が可能であったことを他誌に紹介している[29]．

大動脈周囲リンパ節転移のみの再発例

大動脈周囲リンパ節に限局性に再発する症例は稀に経験するものである．このような再発パターンに対する報告は今までほとんどなかったが，近年少数例ではあるがまとまった報告を散見する．

Grigsbyらは，放射線治療後の大動脈周囲リンパ節転移再発症例20例に対して，放射線外部治療を行った結果を報告している[30]．2年以内に全例死亡するという惨憺たる結果ではあったが，45Gy以上の照射例，再発までの期間が24カ月以上の例で生存期間の延長が見られるという希望もあった．さらに近年では外部照射に化学療法を併用した結果が報告されている．Kimらは超多分割照射に主にpaclitaxelを併用して治療した12例の結果を報告しており，再発までの期間が24カ月以上の症例では生存期間の中央値が45カ月と良好であったとしている[31]．さらに，Chouらは PAN 転移に対して大動脈周囲への外部照射と cisplatin-base の化学療法を併用した14例では5年生存率は51.2%と極めて良好であったことを報告している[32]．

以上のことから，大動脈周囲リンパ節への孤在性の再発は，再発までの期間が2年以上ある場合，十分量の放射線照射を行うことや化学療法を併用するなどの工夫をすることで治癒の可能性のある再発であることが分かってきた．われわれは大動脈周囲リンパ節に限局した再発例は後で述べる術中照射の良い適応であると考えている．

術中照射

骨盤内再発病巣やリンパ節転移再発病巣に対する放射線治療法として，腸管などの周囲臓器への照射量を増加させることなく高い病巣照射量を得ることができる点で術中照射が一部の施設で行われている[33]．残念ながら，再発のみに限れば症例数が少ないこと，対象が一定していないこと，また，実際の治療成績は決して良好ではないことなどから十分な評価を得ていない．Abeらは再発例の術中照射の予後因子を検討し，中央再発例，とくに放射線治療癌のないものやあっても同時に外科的病巣切除が施行されたものが良い対象となることを示している[34]．われわれは，過去の再発例に対する術中照射を検討した結果，骨盤内再発よりも大動脈周囲への孤在性再発に対して最も有用であると考えている[35]．

Chemoradiation

進行子宮頸癌を含む子宮頸癌に対するchemoradiationの放射線治療単独治療に対する優位性の確立から，再発癌の放射線治療についても当然chemoradiationの効果が期待されるところである．実際，すでに再発癌の放射線治療に際しては，日常臨床としてchemoradiationが行われている．しかし，従来の治療に比し，真に治癒率の向上や生存期間の延長に寄与するか否かは今後の検討課題と思われる．また，どのような方法が最も妥当であるかに関しても今後さらに検討の余地がある．

最後に

再発子宮頸癌の一部には長期延命，治癒可能な症例が含まれており，決して簡単に諦めることや安易に化学療法に走るべきではない．しかし，積極的に治療する際には，前治療の詳細な検討，十分な癌の広がり診断，予後因子の検討を行い，治療方針を個別に考えることが重要である．また，単独の治療では良い結果が得られないことから，他分野の専門医の協力を得た集学的治療が必要である．

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Correlation between MRI and histopathologic findings in stage I cervical carcinomas: influence of stromal desmoplastic reaction

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Abstract. Itoh K, Shiozawa T, Ohira S, Shiohara S, Konishi I. Correlation between MRI and histopathologic findings in stage I cervical carcinomas: influence of stromal desmoplastic reaction. *Int J Gynecol Cancer* 2006;**16**:610–614.

Although the effectiveness of magnetic resonance imaging (MRI) in depicting cervical carcinoma has been reported, whether MRI can detect early-stage or stage IB "occult"-type cervical carcinoma remained undetermined. We examined the correlation between MRI and pathologic findings in 38 stage I (IB 28 cases, IA 10 cases) cervical carcinoma patients, with special reference to the influence of desmoplastic stromal reaction around the tumor. The results demonstrated that the tumor was detected by MRI in none of stage IA patients but in 21 (75%) stage IB patients. The image was clearly demonstrated in 15 of 18 (83%) tumors of more than 2 cm in diameter and in 6 of 10 (60%) tumors of 2 cm or less. The tumor image was evident in 21 of 22 (95%) tumors with prominent (>200 μ) stromal reaction but in none of 6 tumors with minimal (≦200 μ) stromal reaction. These findings suggest that MRI is not useful for the detection of stage IA tumors. In stage IB tumors, however, the stromal reaction rather than the size of the tumor may influence the tumor's image in MRI.

KEYWORDS: cervical carcinoma, desmoplastic reaction, diagnosis, MRI.

Detection of the tumor and a precise assessment of stage in uterine cervical cancer is essential to determine the treatment modalities. Although the detection and diagnosis of cervical carcinoma with the use of cervical cytology followed by cervical biopsy in combination with other conventional examinations including bimanual examination, nephrography, and cystoscopy have been established[1], magnetic resonance imaging (MRI) has been reported to have made the detection of the tumor and the evaluation of the tumor's characteristics such as size and microenvironment more accurate[2–5]. Especially in cases with advanced-stage cervical carcinomas like stage II or higher[2,6], MRI has been reported to be a potent tool to assess the tumor size and extrauterine extension such as parametrial involvement. Although diagnosis of early-stage cervical carcinoma has been made using cone biopsy, its procedure is technically sometimes difficult for older patients with atrophic cervices, and MRI seems to be an alternative approach for the detection of early-stage carcinoma in such cases. However, it remains undetermined whether MRI is useful for the detection of early-stage tumors such as stage IA. In addition, detection of stage IB "occult"-type tumors, ie, those invading higher portion of the cervix or deep in the stroma is often difficult even with MRI. Moreover, we have encountered patients whose invasive cervical tumors were not clearly detectable in MRI in clinical practice. With regard to the factors which may impair the accuracy of MRI in the detection of disease, a few reports pointed out a possible adverse effect of stromal edema, which may lead to a false-positive or false-negative result[7,8]. However, effects of stromal edema on the diagnosis of early-stage cervical carcinoma are not fully understood. This background prompted us to examine the precision of MRI in the diagnosis of stage I uterine cervical carcinoma, as well as the influence of the desmoplastic stromal reaction which is histologically characterized by an edematous change of the connective tissues in the stroma with/without inflammatory infiltrations[9], on the diagnosis of cervical carcinoma. In this study, therefore, we retrospectively examined the correlation between MRI and pathologic findings especially with regard to the desmoplastic reaction in patients with stage I cervical carcinoma and analyzed

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the accuracy and limitation of MRI in the detection of early or occult cervical tumors.

Materials and methods

We examined the preoperative MRI scans and postoperative pathologic specimens of 38 patients with stage I cervical carcinoma (IA1, 8 cases; IA2, 2 cases; IB1, 24 cases; and IB2, 4 cases), who underwent surgery (simple hysterectomy with pelvic lymph node dissection, 8 cases and radical hysterectomy with pelvic lymph node dissection, 30 cases) at Shinshu University Hospital. MRI was conducted within 4 weeks of the surgery. The histologic type was squamous cell carcinoma in 29 cases, squamous cell carcinorma with adenoid cystic carcinoma in 1, adenocarcinoma in 6, adenosquamous carcinoma in 1, and small-cell carcinoma in 1. The maximal diameter of the tumor was measured in MRI figures and pathologic slides. In addition, we examined the degree of desmoplastic stromal reaction with or without lymphocytic infiltration around the tumor, which was classified as either prominent if the reaction reached beyond 200 μ or minimal if 200 μ or less.

Results

Cervical carcinoma was identified as a high signal intensity on T2-weighted images compared to the cervical stromal tissues. The intensity was slightly weaker when cancerous tissues contained fibrous tissues. The results indicated that the MRI did not exhibit an image of the tumor in any of the ten stage IA patients, including two stage IA2 carcinomas, although these two cases showed an invasion of 4 and 5 mm in depth with a prominent desmoplastic stromal reaction (Table 1; Fig. 1).

Table 1. Tumor detection by MRI—depth of invasion and desmoplastic reaction of stage IA cervical carcinomas

Case no.	Age (years)	Stage	Depth of invasion	Desmoplastic reaction	Tumor detection by MRI
1	34	IA1	<3 mm	Minimal	Negative
2	61	IA1	<3 mm	Minimal	Negative
3	31	IA1	<3 mm	Minimal	Negative
4	67	IA1	<3 mm	Minimal	Negative
5	50	IA1	<3 mm	Minimal	Negative
6	64	IA1	<3 mm	Minimal	Negative
7	28	IA1	<3 mm	Minimal	Negative
8	44	IA1	<3 mm	Minimal	Negative
9	63	IA2	4 mm	Prominent	Negative
10	43	IA2	5 mm	Prominent	Negative

In stage IB tumors, MRI demonstrated clearly the tumor in 21 of 28 cases (75%) (Table 2; Fig. 2) but failed to show the image in the remaining 7 cases (25%) (Figs. 3, 4). The image was clearly demonstrated in 15 of 18 (83%) tumors of more than 2 cm in diameter and in 6 of 10 (60%) tumors of 2 cm or less. The tumor image was evident in 21 of 22 (95%) tumors with a prominent stromal reaction but none of the 6 tumors with a minimal stromal reaction. There was no apparent tendency in the sensitivity and accuracy of detection among histologic types.

Discussion

This study demonstrated that MRI is not useful for the detection of stage IA cervical carcinoma including stage IA2 tumors. It must be taken into account that both of the IA2 cases were associated with prominent stromal reactions. Togashi *et al.* reported difficulty in detecting superficially invasive lesions using T2-weighted MRI[2]. Fujiwara *et al.* also reported that neither T2-weighted images nor dynamic images can detect invasive tumors of less than 5 mm[10]. These reports are consistent with our results. In contrast, Seki *et al.* reported the usefulness of T2-weighted MRI in detecting tumors invading the stroma to a depth of 3–5 mm[11]. In their study, although they could not detect lesions with 1.0- to 3.0-mm stromal invasion, the detection rate for 3.1- to 5.0-mm stromal invasion was 23% with T2-weighted MRI, and interestingly, 92% with dynamic MR images. However, we could not perform the dynamic study in this study.

In this study, the detection rate of stage IB tumors with T2-weighted MRI was 75%. In the previous reports, the detection rate of stage IB tumor with T2-weighted images was 76–90%[2,12–15], being similar to our result. Interestingly, our data showed that the detection rate for stage IB tumors more than 2 cm in diameter was 83% (15/18), whereas the rate for tumors with a prominent desmoplastic reaction was 95% (21/22). In addition, of the seven tumors not detected by MRI in this study, six lacked a desmoplastic reaction. More notably, all three tumors more than 2 cm in diameter that were not detected by MRI were devoid of a desmoplastic reaction. These findings suggest that the presence or absence of a stromal reaction rather than the size of the tumor influences the appearance of the tumor in MRI even in cases of stage IB cervical carcinomas. Cervical carcinomas, in general, exhibit a high signal intensity on T2-weighted images, whereas fibrous cells have low signal intensity on both T1- and T2-weighted images[2–4]. In addition, tissue edema surrounding the cancer tissue also shows high signal

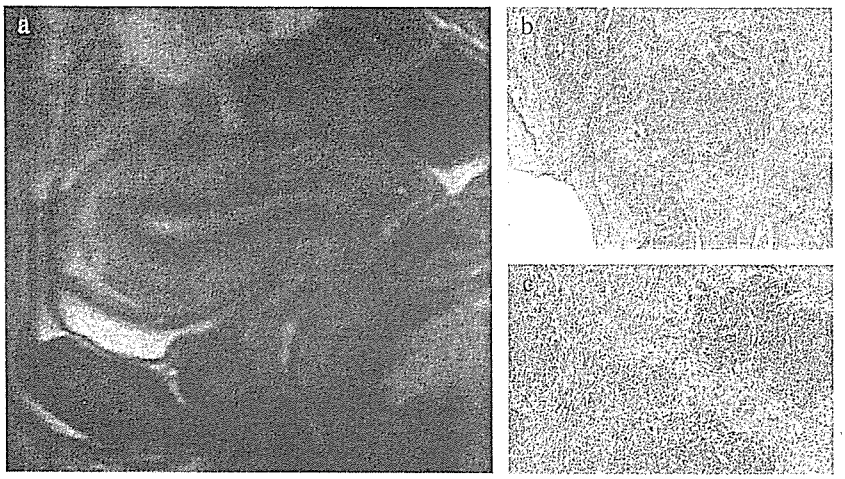

Figure 1. a) T2-weighted MRI of a stage IA2 cervical carcinoma patient (case no. 10 in Table 1). Tumor was not evident by MRI. b) Photomicrograph of the patient at low magnification. Tumor cells invaded the stroma to a depth of approximately 5 mm (×50). c) Higher magnification. Desmoplastic stromal reaction is prominent (×150).

Table 2. Tumor diameter, stromal reaction, and MRI findings in 28 cases of stage IB cervical carcinoma

Tumor diameter	Stromal reaction	MRI: tumor (+)	MRI: tumor (−)	Total
2 cm or less	Prominent	6	1	7
2 cm or less	Minimal	0	3	3
>2 cm	Prominent	15	0	15
>2 cm	Minimal	0	3	3
Total		21	7	28

intensity on T2-weighted images. Sheu *et al.* and Tsuda *et al.* reported that the staging error of cervical carcinoma by MRI can occur in cases associated with surrounding tissue edema[7,8]. Hatano *et al.* also pointed out the possibility of an overdiagnosis of recurrent cervical cancer after radiation therapy, since the inflammation and edema associated with acute radiation change also show high signal intensity on T2-weighted images[16]. One important tissue component that contributes to high signal intensity in T2-weighted images is tissue fluid[17]. Desmoplastic reaction, considered marker of stromal invasion, is characterized by loose connective tissues with abundant fluid in the intercellular space[9]. Therefore, in the early stage of invasive cervical cancer such as stage IB, the tumor may be detected by identifying not only carcinoma cells but also the surrounding desmoplastic reaction. In this context, cases without a stromal reaction may tend to be overlooked even if the tumor is more than 2 cm in diameter.

For the three stage IB tumors more than 2 cm in diameter which were not detected by MRI, it must be taken into account that the tumor tissue itself did not show high T2-signal intensity. It has been reported that carcinoma cells which contain relatively ample fibrous cells have less intense signal[18]. In this study, as indicated in the case in Figures 3, 4 where the tumor was not detected by MRI, tumor cells form

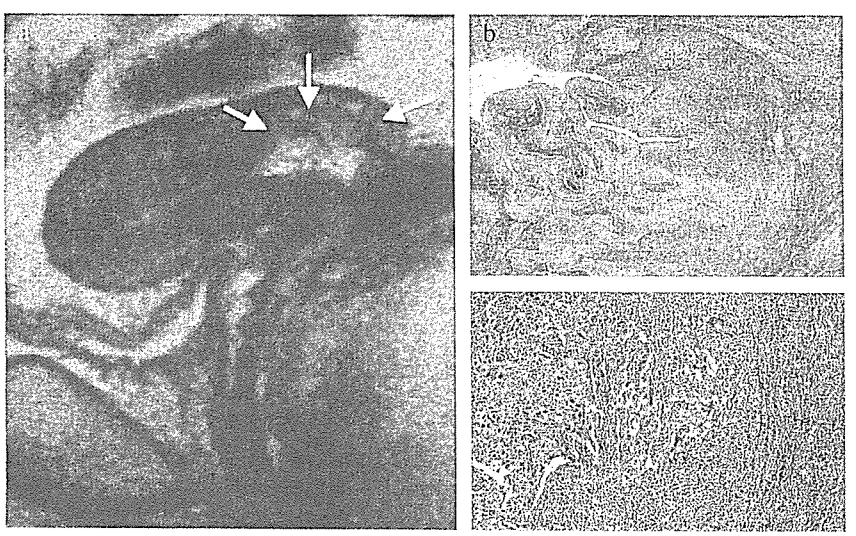

Figure 2. a) T2-weighted MRI of a stage IB1 cervical carcinoma patient. Tumor is clearly detected by MRI with increased signal intensity (arrows). b) Photomicrograph at low magnification. Stromal invasion is noted with an intact outer layer of the cervix (×40). c) Higher magnification. Tumor cells are accompanied by a prominent desmoplastic reaction (×200).

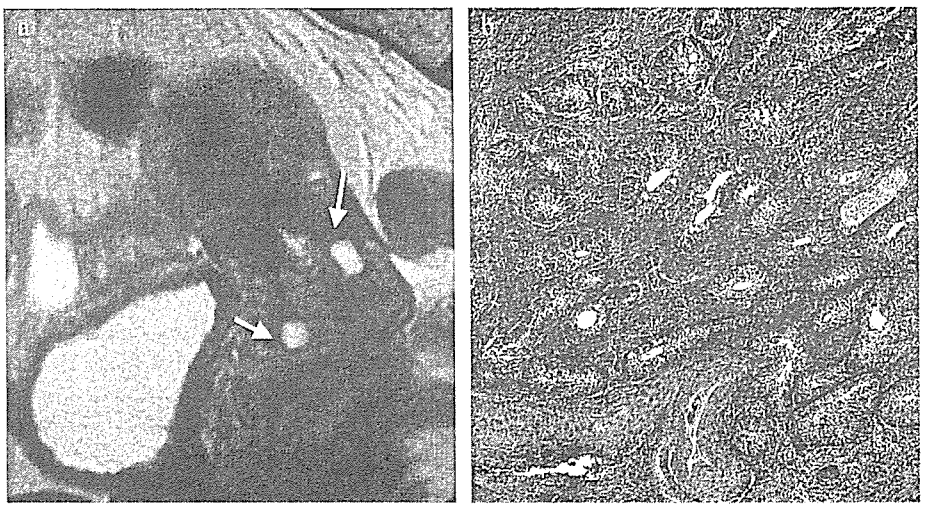

Figure 3. a) T2-weighted MRI of a stage IB1 cervical carcinoma patient. Arrows indicate Nabothian cysts, and the tumor is not detected. b) Photomicrograph of the case. Carcinoma cell nests are invading deeply into the stroma, and almost all the cervical tissue is replaced by cancer tissue. In this case, the desmoplastic reaction is minimal or negative (×100).

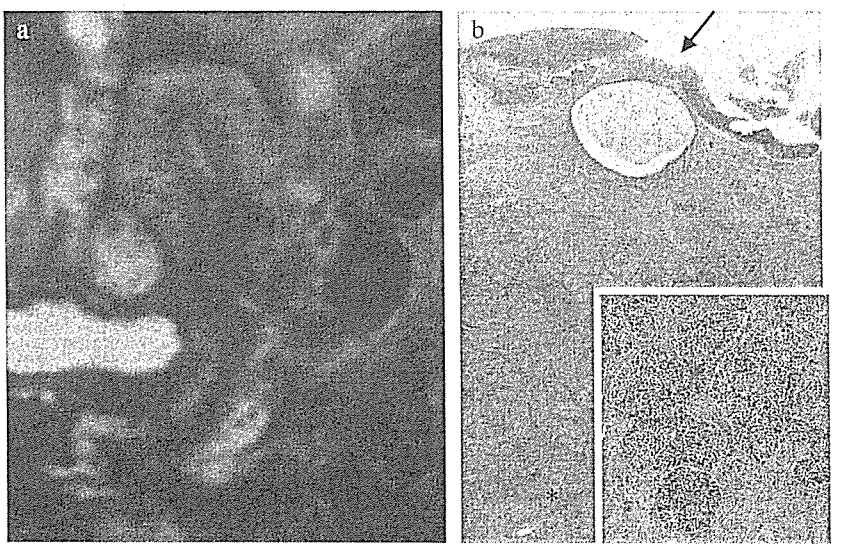

Figure 4. a) T2-weighted MRI of a stage IB1 patient. The tumor image is not evident. b) Photomicrograph at low magnification (×40). Squamous cell carcinoma is observed on the surface of the cervix (arrow), and nests of adenoid cystic carcinoma have invaded the stroma (asterisk). The desmoplastic reaction is minimal or negative. c) A higher magnification of the nest of the adenoid cystic carcinoma (×250).

small cancer-cell nests, and these nests invaded a relatively thick and dense stroma that lacked a desmoplastic reaction. This histologic pattern may be an example of cervical carcinoma which can be underdiagnosed by MRI.

In conclusion, this study demonstrated that MRI is not useful for the detection of stage IA cervical carcinoma including stage IA2 tumors. However, the presence or absence of a stromal reaction rather than the size of the tumor may influence the appearance of the tumor in MRI even in cases of stage IB cervical carcinomas. Further studies are needed to clarify the factor that regulated the desmoplastic reaction as well as to develop more sensitive techniques, including dynamic imaging.

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Ovarian metastasis in carcinoma of the uterine cervix

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Abstract

Background. The present study was conducted to determine the frequency and clinicopathological features of ovarian metastasis in a large population of patients with stage Ib–IIb cervical cancer.

Methods. The study population consisted of 3471 patients with stage Ib to IIb cervical cancer who underwent radical hysterectomy, including pelvic lymphadenectomy and bilateral salpingo-oophorectomy, at our six institutions between 1981 and 2000. To our knowledge, this study is the largest review of patients with ovarian metastasis from cervical cancer. We reviewed the patients' medical records to determine clinicopathological features.

Results. Fifty-two patients (1.50%) had ovarian metastases: 6 in stage Ib1, 12 in stage Ib2, 5 in stage IIa, and 29 in stage IIb. The mean age of patients with ovarian metastasis was 49.9 years (range: 29–73 years). The incidence of ovarian metastasis in patients with cervical cancer was 0.22% for stage Ib, 0.75% for stage IIa, and 2.17% for stage IIb with squamous cell carcinoma, and 3.72%, 5.26%, and 9.85%, respectively, in adenocarcinoma. Ovarian metastasis occurred more frequently among patients with adenocarcinoma than among those with squamous cell carcinoma (5.31% vs. 0.79%). Outcome for patients with ovarian metastasis was very poor and not related to FIGO stage and histological type. The presence of ovarian metastasis did not correlate with lymph node involvement or parametrial invasion.

Conclusion. Study results indicate that ovaries can be preserved in patients with stage Ib–IIa squamous cell carcinoma but removed in all patients with adenocarcinoma.

Keywords: Uterine cervical cancer; Ovarian metastasis; Radical hysterectomy; Squamous cell carcinoma; Adenocarcinoma

Introduction

Although concurrent chemoradiotherapy results in a good outcome for patients with cervical cancer [1,2], exposure to radiation can lead to early ovarian failure [3]. In the literature, radiation doses of less than 3 Gy to the ovary led to ovarian failure in 11% of women, more than 3 Gy in 60% of women, and over 5 Gy were sufficient to sterilize the ovary [4]. On the other hand, surgical treatment that preserves the ovaries benefits premenopausal women with cervical cancer. Ovarian transposition is reportedly useful to avoid damage to ovaries from radiation exposure [5].

Radical hysterectomy is generally considered a therapeutic option for patients with stage Ib to IIa cervical cancer [6], whereas, in Japan, most patients with stage Ib to IIb are treated with radical hysterectomy. Many authors have proposed risk factors for ovarian metastasis in cervical cancer to facilitate the decision to preserve the ovaries during radical hysterectomy [7–12]. However, the number of studies and size of patients population have been too small to substantiate the frequency and clinicopathologic features of ovarian metastasis. We,

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