December 2004. Following normal clinical practice, patients were scheduled to undergo magnetic resonance imaging (MRI) of the pelvis in three phases of RT, namely before and at 3 to 4 weeks (early phase) and 6 to 7 weeks (late phase) after the start of RT. The accuracy and clarity of MRI in demonstrating cervical tumors has been confirmed (9, 10). Seven patients were excluded from the study because not all MR images were available or because the images did not clearly identify the tumor. Clinical disease stages according to the International Federation of Gynecology and Obstetrics staging system were IB1 (n = 1), IIB (n = 1), and IIIB (n = 10). Patients ranged in age from 37 to 81 years (median, 51 years).

Treatment

Radiotherapy consisted of external and intracavitary RT. External RT was performed with a 10-MV X-ray in 1.8-Gy fractions at 5 fractions per week. Clinical target volume was the pelvis (n = 5) or the pelvis plus para-aortic nodes (n = 7), with para-aortic nodes treated prophylactically. A conformal box-field technique was used for all but 1 patient, in whom anterior–posterior opposing portals were used. A central block was placed in the pelvic RT field for the start of intracavitary RT after a total dose of 45.0 Gy (stage IIIB) or 36.0 Gy (stages IB1 and IIB) was reached. Total dose to the pelvis ranged from 50.4 to 66.6 Gy (median, 54.0 Gy), including boost doses to parametrial induration or lymphadenopathy, and total dose to the para-aortic nodes was 45.0 Gy. Intracavitary RT was performed with a high-dose-rate remote afterloading system. The prescribed dosage to reference point A was 6.0 Gy per insertion at three (n = 10) or four (n = 2) weekly insertions per patient. One patient underwent an interstitial implant after three intracavitary insertions. Thus, overall RT treatment duration ranged from 42 to 63 days (n = 11; median, 50 days) and was 70 days for the patient treated by interstitial implant.

Ten patients were treated by concurrent chemotherapy with cisplatin, and 2 (both aged 81 years) were treated by RT alone. Cisplatin was given by single weekly i.v. administration at 35 mg/m^2 (n = 3), 30 mg/m^2 (n = 6), or 20 mg/m^2 (n = 1, aged 72 years) for 3–6 weeks, starting from the first (n = 5), second (n = 4), or third week (n = 1) of RT. Delayed chemotherapy (n = 5) was due to renal dysfunction caused by hydronephrosis, which was managed by nephrostomy.

Tumor measurement with MR images

Magnetic resonance imaging was performed with 1.5-T units. The preRT images were obtained from 1 to 26 days (median, 11 days) before RT, with early-phase images obtained from 18 to 34 days (median, 24 days) and late-phase images obtained from 36 to 59 days (median, 46 days) after the start of RT, the latter being before (n = 1) or during (n = 11) the intracavitary RT course. Tumors identified as high-intensity lesions on T2-weighted images were measured three-dimensionally by width, thickness, and length for each tumor, and tumor volume was calculated on the assumption that the tumor mass was ellipsoid. The volume of tumors that disappeared or were recognized as only a remnant was regarded as 0.01 cm^3, whereas that of those remaining as a small, high-intensity "scar" that was difficult to measure was regarded as 0.05 cm^3.

Radioresponse assessment

Estimated tumor volumes were plotted on a semilogarithmic graph, with the start of RT set as Day 0. The early-phase shrinkage curve was calculated from the preRT and early-phase volumes, the late-phase shrinkage curve from the early-phase and late-phase volumes, and the through-phase shrinkage curve from the preRT and late-phase volumes. The slope of the curve (day^{-1}) (i.e., the speed of shrinkage per day) was determined by fitting an exponential regression equation to the respective curve. Radioresponse was defined as the speed of shrinkage, with radioresponsive tumors thus characterized by steep slopes. With the equation of the through-phase shrinkage curve, the tumor volume at the end of RT (postRT volume) was duly calculated for each tumor and categorized according to the degree of shrinkage. For this, either shrinkage to $\leq$0.05 cm^3 or to <1% of the preRT volume was regarded as complete response, whereas shrinkage to <35% of the preRT volume and shrinkage confined to $\geq$35% of the preRT volume were defined as partial response and stable disease, respectively.

Statistical analysis

The early-assessed radioresponse was compared with the late-assessed and with the through-assessed radioresponse. Differences in response between phases were analyzed by the Wilcoxon signed rank test. Correlation between the early-assessed and through-assessed radioresponses was analyzed by regression analysis. Radioresponse was compared between the speed of shrinkage (through-assessed radioresponse) and the degree of shrinkage. StatView 5.0 (SAS Institute, Cary, NC) was used for all analyses. P values of <0.05 were considered statistically significant.

RESULTS

The preRT volume ranged from 2.3 to 301.6 cm^3 (median, 95.5 cm^3). Complete response was observed in the early phase in one tumor and in the late phase in two (Fig. 1). Radioresponse ranged from 0.001 to 0.106 day^{-1} (median, 0.021 day^{-1}) in the early phase, from 0.013 to 0.121 day^{-1} (median, 0.025 day^{-1}) in the late phase, and from 0.009 to 0.091 day^{-1} (median, 0.021 day^{-1}) in the through phase. Radioresponse did not differ significantly between the early and late phases or between the early and through phases (p = 0.1361 for both). When the tumor that achieved a complete response in the early phase was excluded, however, the difference in response between the early and late

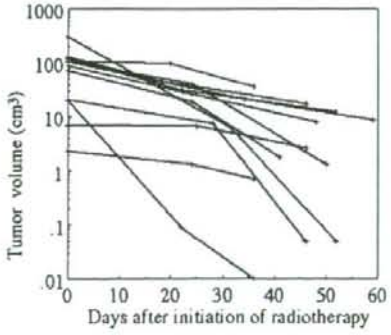

Fig. 1. Tumor shrinkage curves composed of three-phase volumes of preradiotherapy, early phase (3 to 4 weeks), and late phase (6 to 7 weeks) (n = 12).

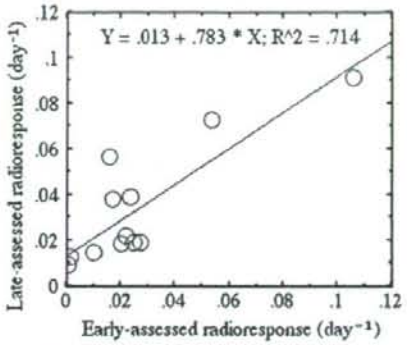

Fig. 2. Correlation between early-assessed and late-assessed radioresponse (n = 12, p = 0.0005).

phases approached significance, with radioresponse greater in the late (range, 0.013–0.121 day^{-1}; median, 0.022 day^{-1}) than in the early phase (range, 0.001–0.054 day^{-1}; median, 0.021 day^{-1}) (n = 11, p = 0.0505).

The early-assessed radioresponse correlated with the late-assessed radioresponse (Fig. 2; R^2 = 0.714, p = 0.0005). This correlation remained significant even when the tumor that achieved a near-complete response was excluded (n = 11, R^2 = 0.496, p = 0.0155).

The postRT volume ranged from 0.01 to 21.95 cm^3 (median, 0.41 cm^3) and was ≤0.05 cm^3 in three tumors. The postRT volume as a percentage ranged from 0 to 17.8% (median, 4.5%) of the preRT volume. Response category was complete response for five tumors and partial response for the remaining seven (Fig. 3). None was categorized as stable disease.

DISCUSSION

Characterization of radioresponse is particularly important for large tumors, from the standpoint of not only radiosensitivity but also dose delivery by intracavitary RT, which is characterized by steep dose fall-off within the tumor. Given that radioresponse normally implies generic radiosensitivity of tumor cells, tumors with low radioresponsiveness require larger doses for local disease control than those with high radioresponsiveness. Nevertheless, large tumors with low radioresponsiveness receive smaller target doses at the tumor periphery (minimum target doses) by intracavitary RT than large tumors with high radioresponsiveness, because the latter undergo significant shrinkage subsequent to the preceding external RT (11). Compared with large tumors, small tumors receive substantially higher minimum target doses irrespective of tumor shrinkage induced by external RT, and these high doses are considered to effectively overcome any radioresistance.

Tumors were categorized by the degree of shrinkage into either complete response or partial response only. Whereas complete response is characterized by shrinkage within a very narrow range (99–100% decrease), partial response is characterized by a wide range of shrinkage (65%–99% decrease) and is therefore not suitable for differentiating tumors at the respective ends of this range. In contrast, the speed of shrinkage is shown as a variable specific to the individual tumor and is therefore useful for differentiating partial response tumors by calculation, if the shrinkage is fitted well by a regression equation.

Our results showed that the early-assessed radioresponse corresponded with the late-assessed radioresponse, although not particularly closely. In contrast, Gong *et al.* (12), who used frequent, rigidly scheduled MRI (four to eight times per patient) and sophisticated tumor measurement methods, reported that the radioresponse of cervical tumors is exponential. Several possible reasons for this apparent discrepancy can be suggested.

First, Gong *et al.* investigated radioresponse during simple treatment with external RT alone, whereas our study involved complex treatment. Second, most of our tumors were treated by concurrent chemotherapy that was nevertheless not always simultaneous with the start of RT and by intracavitary RT that was performed in the late phase. The impact of our treatment might therefore have differed between phases, or even by week. In fact, we previously showed that the use of concurrent chemoradiotherapy tends to increase radioresponse over that achieved with RT alone (13). Further, radioresponse might have been underestimated in our three tumors that achieved a complete response because the response might have occurred before the time of observation. On these bases, we suggest that the lack of a clear exponential radioresponse in the present study was likely due to the complex treatment given, in addition to differences in the accuracy and frequency of tumor measurement.

Although exact correspondence was not obtained, our response assessment, conducted under conditions of stan-

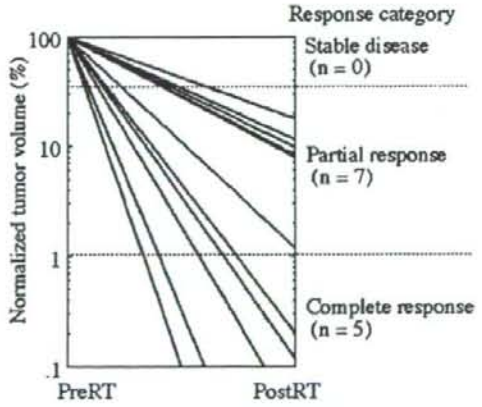

Fig. 3. Comparison of calculated radioresponse at the end of radiotherapy (RT) between the speed of shrinkage (curves) and the degree of shrinkage (response category). The postRT volume was calculated with the regression equation for each tumor at the end of RT for each individual (42–63 days from the start of RT).

dard clinical practice, is considered effective in the differentiation of highly (e.g., >0.05 day^{-1}) and poorly radioresponsive (e.g., <0.02 day^{-1}) tumors, which here represented the upper and lower quartiles of tumors by response, from those moderately radioresponsive, which made up the middle half of tumors. This is because the wide radioresponse seen facilitates the recognition of tumors at the respective ends of radioresponsiveness. Moreover, this finding is consistent between our results and those of Gong *et al.*: radioresponse range from 0.001 to 0.106 day^{-1} (early phase, 106-fold variation) and from 0.009 to 0.091 day^{-1} (through phase, 10-fold variation) in the present study and from 0.007 to 0.182 day^{-1} (26-fold variation, by planimetry) in Gong *et al.* (12).

The U.S. National Cancer Institute has recommended the concurrent use of RT and chemotherapy with cisplatin or cisplatin plus fluorouracil (as radiosensitizers) in place of the conventional use of RT alone to improve survival in patients with locally advanced cervical cancer (8), and the efficacy of this treatment has been confirmed by systematic review and meta-analysis (14). However, this recommendation is based on the assumption that the radioresponse of tumors is unknown. Early knowledge of the radioresponsiveness of tumors during treatment would allow the individualization of treatment. Given that a substantial proportion of patients have been cured by conventional RT treatment alone, those with highly radioresponsive tumors, so-called radiosensitive tumors, might not necessarily require concurrent chemotherapy. Conversely, patients with poorly radioresponsive tumors, so-called radioresistant tumors, might benefit from the intensification of treatment, such as the planned use of interstitial implants and the incorporation of a potent new radiosensitizer (gemcitabine) into concurrent chemotherapy (15).

In conclusion, the early-assessed radioresponse of uterine cervical squamous cell carcinoma corresponded with the late-assessed radioresponse, albeit not particularly strongly. Although it would be premature to incorporate these findings directly into local disease control, early determination might nevertheless be useful for identifying tumors at either extremity of the wide radioresponse range seen here.

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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

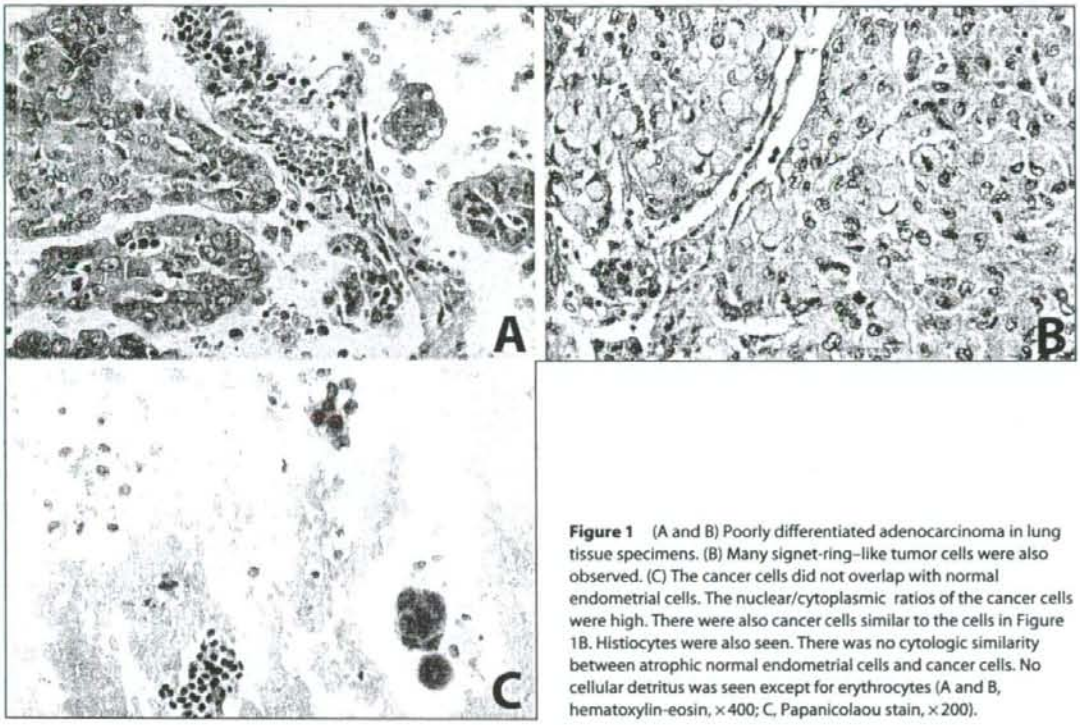

Figure 1 (A and B) Poorly differentiated adenocarcinoma in lung tissue specimens. (B) Many signet-ring–like tumor cells were also observed. (C) The cancer cells did not overlap with normal endometrial cells. The nuclear/cytoplasmic ratios of the cancer cells were high. There were also cancer cells similar 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]

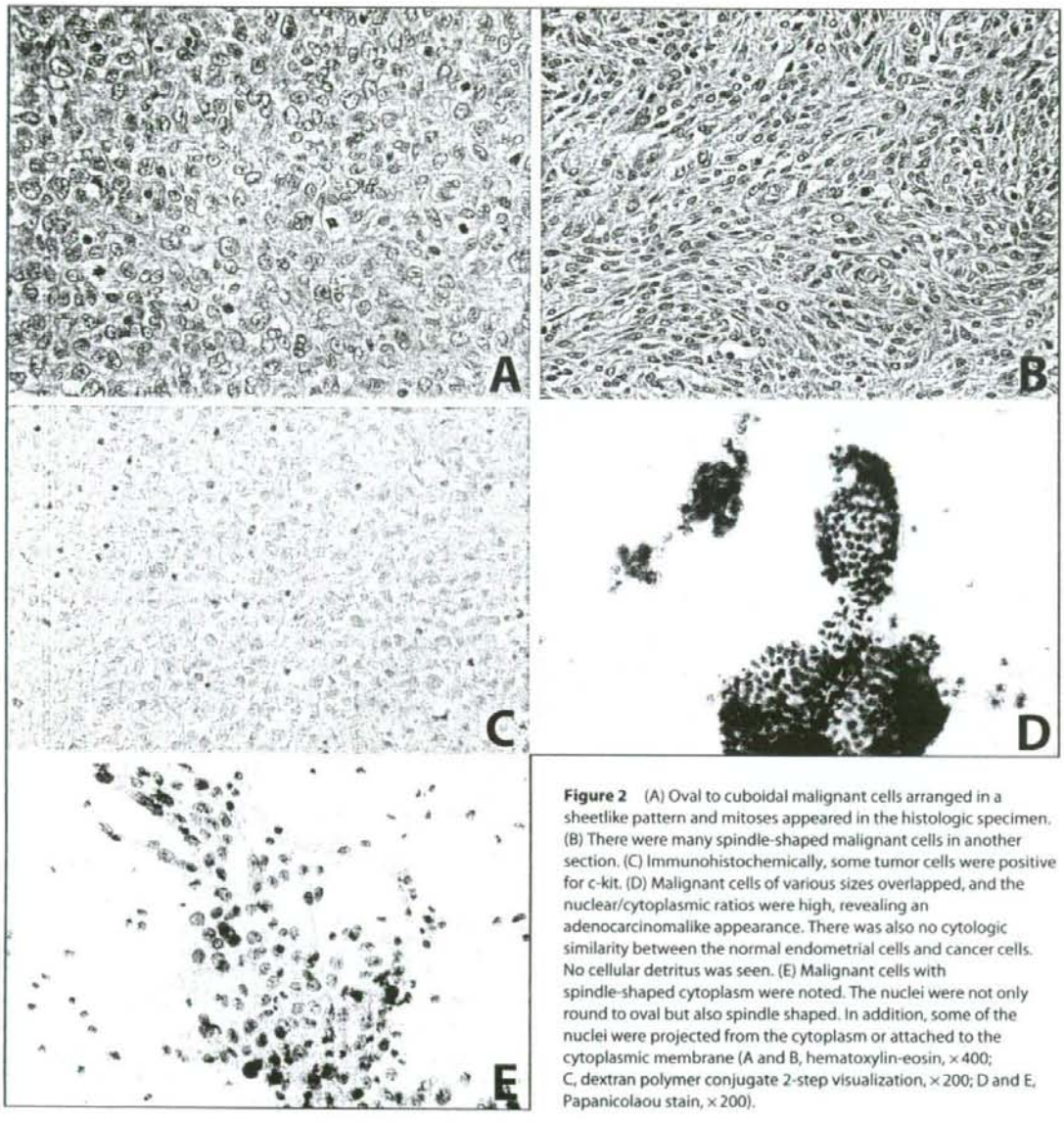

Figure 2 (A) Oval to cuboidal malignant cells arranged in a sheetlike pattern and mitoses appeared in the histologic specimen. (B) There were many spindle-shaped malignant cells in another section. (C) Immunohistochemically, some tumor cells were positive for c-kit. (D) Malignant cells of various sizes 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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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

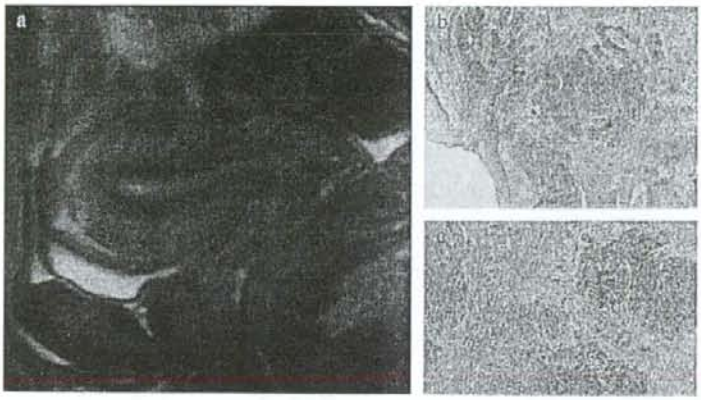

Figure 1. a) T2-weighted MRI of a stage IA2 cervical carcinoma patient (case no. 10 in Table 1). Tumor was not evident by MRI. b) Photomicrograph of the patient at low magnification. Tumor cells invaded the stroma to a depth of approximately 5 mm (×50). c) Higher magnification. Desmoplastic stromal reaction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

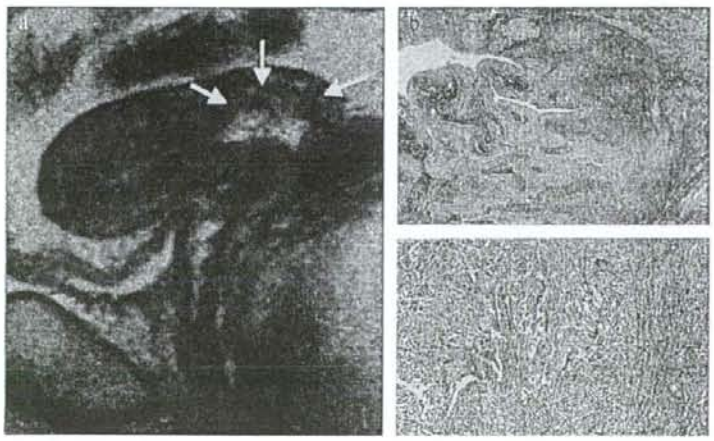

Figure 2. a) T2-weighted MRI of a stage IB1 cervical carcinoma patient. Tumor is clearly detected by MRI with increased signal intensity (arrows). b) Photomicrograph at low magnification. Stromal invasion is noted with an intact outer layer of the cervix (×40). c) Higher magnification. Tumor cells are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

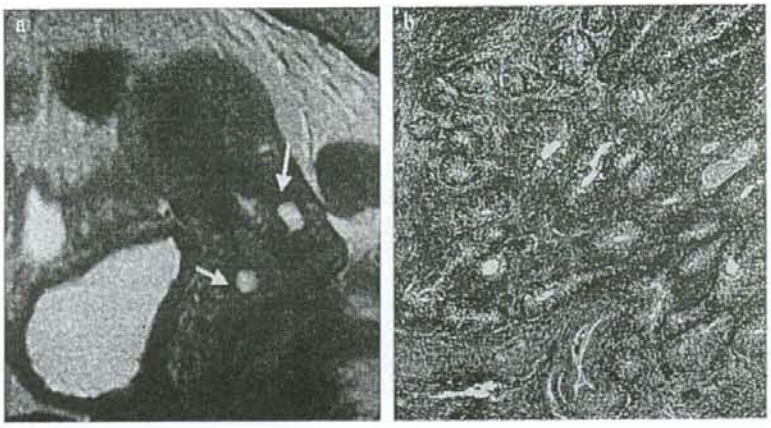

Figure 3. a) T2-weighted MRI of a stage IB1 cervical carcinoma patient. Arrows indicate Nabothian cysts, and the tumor is not detected. b) Photomicrograph of the case. Carcinoma cell nests are invading deeply into the stroma, and almost all the cervical tissue is replaced by cancer tissue. In this case,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

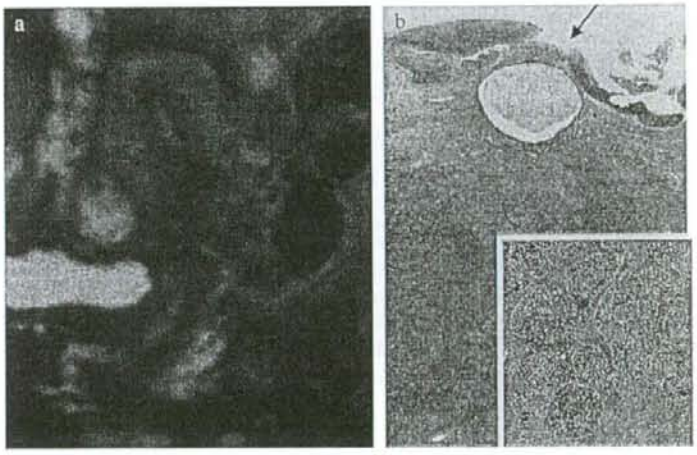

Figure 4. a) T2-weighted MRI of a stage IB1 patient. The tumor image is not evident. b) Photomicrograph at low magnification (×40). Squamous cell carcinoma is observed on the surface of the cervix (arrow), and nests of adenoid cystic carcinoma have invaded the stroma (asterisk). The desmoplastic reaction 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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Table 1
The incidence of ovarian metastasis

FIGO stage	Squamous cell carcinoma	Adenocarcinoma
Stage Ib	4/1784 (0.22%)	14/376 (3.72%)
Stage IIa	3/402 (0.75%)	2/38 (5.26%)
Stage IIb	16/739 (2.17%)	13/132 (9.85%)

therefore, analyzed a large number of cervical cancer patients with stage Ib to IIb cervical cancer who underwent radical hysterectomy including bilateral salpingo-oophorectomy. To our knowledge, the present study is the largest series of patients with ovarian metastasis from cervical cancer.

Material and methods

A total of 3471 patients with International Federation of Gynecology and Obstetrics (FIGO) stage Ib to IIb cervical cancer who underwent radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection (type III) at Hyogo Medical Center for Adults, Aichi Cancer Center Hospital, Jichi Medical School, National Defense Medical College, Saga University Hospital, and Tottori University Hospital between 1981 and 2000 were enrolled in this study. Data were collected from the patients' medical records. Of 3471 patients with cervical cancer, 52 patients (1.50%) had ovarian metastasis. The mean age was 49.9 years old (range 29–73 years). Twenty-six patients were premenopausal women. Tumor size was evaluated with magnetic resonance imaging (MRI) or ultrasonography, and bulky tumor was defined as a maximum diameter over 4 cm. Among 52 patients with ovarian metastasis, 22 patients received radiation alone, 11 patients chemotherapy alone, and 15 patients both radiation and chemotherapy after radical hysterectomy. Four patients did not receive additional treatment after surgery.

Patient survival distribution was calculated using the Kaplan–Meier method. The significance of the survival distribution in each group was tested by a log-rank test. The Chi-square test was used to compare any associations of prognostic factors. Additionally, univariate analysis was done with Stat view Version 4.5-J program (Hulinks Inc, Tokyo Japan) to fit a Cox proportional hazards model. A value of $P < 0.05$ was considered statistically significant.

Results

The incidence of ovarian metastases is shown in Table 1. Patients with ovarian metastases were distributed as follows: 6 in stage Ib1 (3 for squamous cell carcinoma and 3 for adenocarcinoma), 12 in stage Ib2 (one for squamous cell carcinoma and 11 for adenocarcinoma), 5 in stage IIa, and 29 in stage IIb. Twenty-three patients had squamous cell carcinoma, and 29 had adenocarcinoma including adenosquamous cell carcinoma. Ovarian metastasis were more frequently observed in patients with adenocarcinoma than in those with squamous cell carcinoma (5.31% vs. 0.79%, $P < 0.01$).

The 5-year survival rate was 18.0% for patients with adenocarcinoma and 43.5% for those with squamous cell carcinoma, but the difference was not statistically significant (Fig. 1). The 5-year survival rate was 46.6% for stage Ib, 37.5% for stage IIa, and 18.0% for stage IIb. FIGO stage was not significantly related to the prognosis for patients with cervical cancer having ovarian metastasis.

Pathological review could be confirmed in 50 subjects for lymph node involvement and 51 subjects for parametrial invasion. The incident of lymph node involvement and parametrial invasion was 72.0% and 70.5%, respectively. Ovarian metastases did not correlate with lymph node involvement or parametrial invasion (Tables 2, 3). Deep stromal invasion, defined as less than 3 mm from the serosa, could be confirmed in 50 subjects. Endometrial invasion and tumor size could be evaluated in 47 and 44 subjects, respectively. The incidence of deep stromal and endometrial invasion was 80.0% and 55.3%, respectively. Bulky tumor was observed in 54.5% of patients with ovarian metastasis. Parametrial invasion was only the risk factor in patients with ovarian metastasis (Table 4).

Forty patients (76.9%) (16 for squamous cell carcinoma and 24 for adenocarcinoma) had a recurrence: 10 intrapelvic, 23 extrapelvic, 3 both intrapelvic and extrapelvic, and 4 unknown site. Among extrapelvic recurrence, a distant (extraabdominal) recurrence was observed in 18 patients (9 for squamous cell carcinoma and 9 for adenocarcinoma). Three intraabdominal lesions (peritonitis carcimoatosa) occurred among the extrapelvic recurrence. Distant recurrent sites were 7 in bone, 6 in

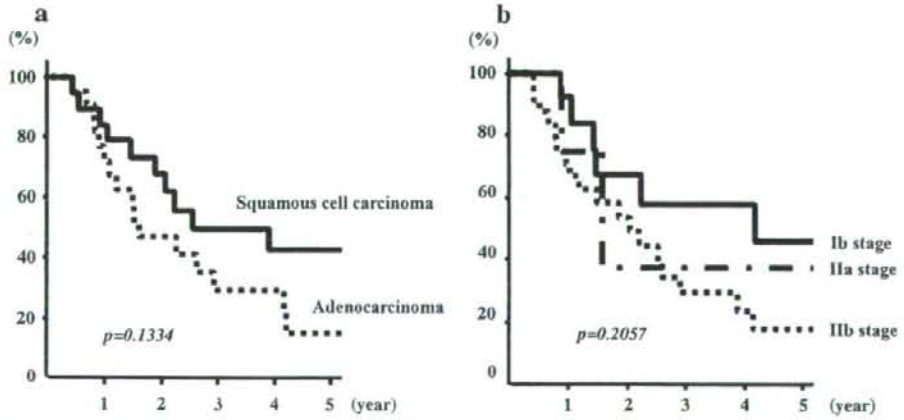

Fig. 1. The survival rate for patients with cervical cancer who have ovarian metastasis. (a) The outcome for patients with adenocarcinoma was worse than that of patients with squamous cell carcinoma, but the difference was not significant. (b) The 5-year survival rate was 46.6% for stage Ib, 37.5% for stage IIa, and 18.0% for stage IIb. FIGO stage did not significantly affect the outcome for patients with cervical cancer having ovarian metastasis.

Table 2
Pelvic lymph node involvement and ovarian metastasis

	Ovarian metastasis		
	Bilateral (n = 21)	Right (n = 11)	Left (n = 18)
Bilateral (n = 30)	16	6	8
Unilateral (n = 6)	1	0	5 (2)
Negative (n = 14)	4	5	5

( ): the same site of ovarian metastasis.

lung, 3 in liver, and 2 in skin. Of 9 distant recurrence patients with squamous cell carcinoma, 8 patients recurred in extra-pelvic lymph node (5 para-aortic lymph node, 2 cervical lymph node, and one inguinal lymph node). Two of 9 distant recurrence patients with adenocarcinoma showed para-aortic lymph node recurrence and remaining 7 had hematogenous metastasis.

Discussion

A review of published studies indicated that the incidence of ovarian metastasis from uterine cervical cancer is less than 0.5% of squamous cell carcinoma and 1.4% of adenocarcinoma [13]. However, the details are not clear due to the small number of subjects studied. Toki et al. reported that one of 525 (0.19%) patients with squamous cell carcinoma and 2 of 36 (5.5%) patients with adenocarcinoma had ovarian metastasis [12]. No patients with stage Ib had ovarian metastasis. Other authors found ovarian metastasis in 9 of 82 (11%) patients with adenocarcinoma (1/40 for stage Ib, 1/5 for stage IIa, and 7/37 for stage IIb) [9]. The largest study until now is Sutton et al.'s [14]. In their study, 990 patients with stage Ib were examined, and ovarian metastasis was identified in 4 of 770 (0.5%) patients with squamous cell carcinoma and 2 of 121 (1.7%) patients with adenocarcinoma [14]. Even their study could not conclude that a significant difference occurred in the incidence of ovarian metastasis between adenocarcinoma and squamous cell carcinoma. In the present study, the incidence of ovarian metastasis from adenocarcinoma of 5.31% (29/546) was significantly higher than that of squamous cell carcinoma (29/2925, 0.79%). Furthermore, we describe the distribution of patients with ovarian metastasis in each stage.

As a result, the incidence of ovarian metastasis in patients with squamous cell carcinoma was less than 1% for stage Ib–IIa, but 2.17% for stage IIb. In contrast, the incidence of ovarian metastases in patients with adenocarcinoma was high in all stages. The incidence of ovarian metastasis in stage Ib patients with adenocarcinoma was the same as in stage IIb patients with squamous cell carcinoma.

Table 3
Parametrial invasion and ovarian metastasis

	Ovarian metastasis		
	Bilateral (n = 20)	Right (n = 13)	Left (n = 18)
Bilateral (n = 16)	6	5	5
Unilateral (n = 20)	8	3 (1)	9 (4)
Negative (n = 15)	6	5	4

( ): the same site of ovarian metastasis.

Table 4
Pelvic lymph node involvement and ovarian metastasis

Risk factor	Numbers	5-year survival rate (%)	P value
Lymph node involvement			
Positive	36	19.6	0.094
Negative	15	46.3	
Paramatrial invasion			
Positive	36	16.4	0.034
Negative	14	58.3	
Deep stromal invasion			
Positive	40	18.2	0.090
Negative	10	44.9	
Endometrial invasion			
Positive	26	35.0	0.525
Negative	21	24.2	
Bulky tumor			
<4 cm	24	33.8	0.921
>4 cm	20	30.7	

Preserving the ovaries is an important issue when deciding about surgery for cervical cancer in young women. In our series, the incidence of ovarian metastasis in stage Ib–IIa patients with squamous cell carcinoma is very low (0.22% for stage Ib and 0.75% for stage IIa). This finding is nearly identical to that of Baltzer et al. (4/745, 0.5%), Singleton et al. (1/258, 0.4%), and Sutton et al. (0.5%) [13–15]. We also recommend preserving the ovaries in stage Ib and IIa patients with squamous cell carcinoma. One author reported that it was reasonable to conserve normal appearing ovaries in young women undergoing radical hysterectomy for treatment of stage Ib cervical adenocarcinoma [9]. On the contrary, another author indicated that ovarian preservation was contraindicated for patients with adenocarcinoma because of its high incidence of ovarian metastasis [12]. We found that the incidence of ovarian metastasis was 3.72% even in stage Ib patients with adenocarcinoma.

In the literature, several risk factors have been proposed, including lymph node involvement, deep stromal invasion, endometrial invasion, and tumor size [7–10,13,16]. The present study showed that the incident of those risk factors ranged from 55% to 80%, and that two patients who had no lymph node involvement, no stromal invasion, no endometrial invasion, and no bulky tumor had ovarian metastasis. Determining whether the patient has ovarian metastasis during surgery is difficult. Our study was unable to detect a predictor of ovarian metastasis; ovarian metastases did not correlate with lymph node involvement or parametrial invasion.

In FIGO report, the 5-year survival rate for patients with cervical cancer was 80.7% for stage Ib, 76.0% for stage IIa, and 73.3% for stage IIb [17]. The current study found that the 5-year survival rate for patients with ovarian metastasis was 46.6% in stage Ib, 37.5% in stage IIa, and 18.0% in stage IIb. Although 48 patients (92.3%) received adjuvant therapy, including radiotherapy and/or chemotherapy after radical hysterectomy, 40 patients had recurrences. Furthermore, 26 of 40 patients (65%) showed distant recurrences,

and the incidence of distant recurrence was more frequent than that of local relapse. The outcome for patients with ovarian metastasis is very poor, indicating that ovarian metastasis is the prognostic factor in patients with cervical cancer. Additionally, the present study revealed that most of the risk factors, such as histology, FIGO stage, and lymph node involvement, were not significant in patients with ovarian metastasis. Parametrial invasion was only the risk factor in patients with ovarian metastasis.

Routes of spread to the ovarian involvement in cervical cancer have been controversial. Wu et al. suggested that lymphatic spread and transtubal implantation might be possible pathways of metastases from cervix to the ovaries [11]. On the other hand, Tabata et al. reported that ovarian metastasis might occur via hematogenous spread of cervical carcinoma [8]. Interestingly, we found that 8 of 9 distant recurrent patients with squamous cell carcinoma showed lymphatic spread. In contrast, 7 of 9 those patients with adenocarcinoma had hematogenous metastasis. Our results suggest that the route of spread to ovarian metastasis from cervical cancer might be different by histological type, while the further study is necessary to draw the conclusion of routes of spread to the ovary.

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Urodynamic study on postsurgical bladder function in cervical cancer treated with systematic nerve-sparing radical hysterectomy

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Abstract. Todo Y, Kuwabara M, Watari H, Ebina Y, Takeda M, Kudo M, Yamamoto R, Sakuragi N. Urodynamic study on postsurgical bladder function in cervical cancer treated with systematic nerve-sparing radical hysterectomy. *Int J Gynecol Cancer* 2006;**16**:369–375.

The objective of this study was to assess the postsurgical bladder function by urodynamic study in patients with cervical cancer treated with nerve-sparing radical hysterectomy. A total of 27 consecutive patients were included in the study. Of the 27 patients, autonomic nerves had been completely preserved at least on one side in 22 patients (group A), and autonomic nerves could not be successfully preserved in five patients (group B). In group A, there was no significant difference in compliance at the moment of strong desire to void, maximum flow rate, and residual urine volume between before the operation and at 12 months after the operation. However, abdominal pressure at maximum flow had significantly increased in patients of group B than of group A. Detrusor contraction pressure at maximum flow had significantly decreased in patients of group B than of group A. Bladder sensation was diminished in three cases (60%) of group B but preserved in all the patients of group A. Although it is still preliminary, our surgical technique described in this report is thought to be effective for preservation of bladder function. For further evaluation of the efficacy of nerve-sparing radical hysterectomy in terms of quality of life and survival of patients, a prospective randomized trial needs to be performed.

KEYWORDS: autonomic nerve, bladder function, cervical cancer, nerve-sparing, radical hysterectomy, urodynamic study.

The quality of life (QoL) of patients who have undergone radical hysterectomy is deteriorated by physical and mental stress caused by difficulty in urination after the operation. The reported incidence of impaired bladder function at 12 months after radical hysterectomy is as high as 63% for sensory loss, 55% for stress incontinence, and 85% for urination with abdominal pressure (Pabd) as well as 63% for abnormal compliance[1]. Various attempts for preserving urinary function, including recently proposed autonomic nerve-preserving radical hysterectomy techniques, have been reported[2–6].

Several studies have been carried out on urodynamics after radical hysterectomy, but the results are discrepant. The reason for this discrepancy is thought to be differences in operations and periods of examination. There have been very few reports in which the type of operation and the time of examination has been clearly stated and in which preoperative and short-term as well as long-term postoperative data are compared. In this study, we assessed urodynamic results of radical hysterectomy with autonomic nerve preservation in patients with uterine cancer.

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Materials and methods

A total of 27 patients who underwent radical hysterectomy during the period from January 2000 to December 2002 and in whom urodynamic examinations were performed before radical hysterectomy and at 1 month and 3, 6, and 12 months after the operation were included in this study. Of these 27 patients, data for 22 patients (group A) in whom autonomic nerves had been completely preserved at least on one side and

data for five patients (group B) in whom the autonomic nerves had not been successfully preserved were used for analysis. The clinical backgrounds of the 27 patients are shown in Table 1. The ages of the 22 patients of group A ranged from 35 to 60 years (median age: 43 years) and those of the five patients of group B ranged from 31 to 64 years (median age: 46 years). In group A, there were six patients with stage IB1, six with stage IB2, three with stage IIA, and seven with stage IIB uterine cervical cancer. For stage IIB patients, nerve-sparing procedure was employed for only the uninvaded side. In group B, there were four patients with stage IB1 and one patient with stage IIB uterine cervical cancer. None of the patients underwent radiation therapy before the operation, but radiation therapy was performed in three patients of group A postoperatively. None of the patients took cholinergic agents or α1 blocker during the observation period.

Operative procedure

Nerve-sparing radical hysterectomy was performed as described in the preceding report. Briefly, the following surgical procedure was used, which is based on the anatomical consideration for autonomic nerves innervating urinary bladder[6]. Before hysterectomy, the pelvic lymph nodes were removed. The hypogastric nerves and the proximal part of the pelvic plexus were identified and lateralized during the dissection of the uterosacral ligament and rectovaginal ligament. After lateralizing the hypogastric nerves and the proximal part of the pelvic plexus, the nerve tissue in this part could be preserved by selective resection of the exposed uterosacral and rectovaginal ligaments. We carefully attempted to avoid dissecting pelvic splanchnic nerves together with the vascular part of the cardinal ligament during resection of the cardinal ligament. In this part of the technique, first, the cardinal ligament nodes were dissected to clearly skeletonize the deep uterine vein using suction apparatus. The uterus was then pulled up in the direction perpendicular to the operating table to expose two separate parts: the cardinal ligament that contains vessels, fat, and loose connective tissue and the dorsomedial part below the cardinal ligament that contains nerve fibers. The anterior segment of the vesicouterine ligament was dissected after developing the ureteral tunnel. Since vesical vein was draining from bladder to deep uterine vein coursing through the posterior part of the vesicouterine ligament, separation and cutting of the vesical vein was required for resection of the uterus. The fatty connective tissue of the posterior part of the vesicouterine ligament was resected while leaving the vesical nerve branches of the pelvic plexus. This enabled identification of the plain between the pelvic plexus and the paracolpium. The blood vessels of the cardinal ligament were resected at the origin of the vessels from internal iliac vein. The careful rubbing of the deep uterine vein in an upward (ventral) direction to its point of attachment to the paracolpium enabled sparing of the

Table 1. Clinical profile of 27 patients with cervical cancer who underwent radical hysterectomy

	Group A ($n = 22$)	Group B ($n = 5$)	P value
Age (in years)	35–60 (median: 43)	31–64 (median: 46)	0.41
Stage			
IB1	6	4	
IB2	6	0	
IIA	3	0	
IIB	7	1	0.15
Tumor diameter (mm)	11–70 (median: 39)	12–50 (median: 34)	0.57
Length of resected vagina (mm)	20–45 (median: 30)	25–35 (median: 35)	0.30
Adjuvant Tx			
None	4	2	
RT	1	0	
CHT	15	3	
RT + CHT	2	0	0.82
Symptoms at 12 months			
Incontinence	0	3	0.0034
Abnormal sensation	2 (increased sensation)	3 (decreased sensation)	0.030
Recurrence	1[a]	0	>0.99
Duration of DFS (months)	13–48 (median: 30)	12–36 (median: 32)	0.90

Tx, treatment; RT, radiation therapy; CHT, chemotherapy; DFS, disease-free survival.
[a]Patient was in stage IIB, and recurrence occurred in the pelvis 13 months after surgery, which was treated with radiation therapy, and she is alive with no evidence of disease at the moment of preparing this article.