Development of endometrial cancer following radiation therapy for cervical carcinoma

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Summary

The clinical and histologic findings in five cases of endometrial cancer, which developed following radiation therapy for squamous cell carcinoma of the cervix, are described. The mean age at endometrial cancer diagnosis was 69 years and average latency period from initial therapy to development of endometrial carcinoma was 13.4 years. For endometrial cancer, one patient had Stage Ib, one patient had Stage IIIa, two patients had Stage IIIc, and one patient did not undergo laparotomy. The histological types were carcinosarcoma in two patients, endometrioid adenocarcinoma, grade 3 in one patient, and clear cell carcinoma in one patient. All patients died of disease within 33 months of diagnosis. Endometrial cancers that develop after radiation treatment have a preponderance of high-risk histological subtypes, and consequently have a poor prognosis. Long-term follow-up should be mandatory for patients surviving radiation therapy for cervical cancer in order to detect and effectively treat second malignancies.

Key words: Endometrial cancer; Radiation therapy; Cervical cancer; Second cancer.

Introduction

The carcinogenic effect of ionizing in humans has been well documented in studies investigating atomic bomb exposure and occupational exposure. However, the mechanism of carcinogenesis by radiation is still unclear. Furthermore, it is still controversial that the radiation emplyed in treating the primary lesion results in an excess of subsequent cancers, particularly in the irradiated area. With recognition of the importance of adjuvant therapy, the indication of radiation therapy for malignant neoplasm has increased. Women with cervical cancer have been selected for study because treatment is relatively successful and many patients survive long enough to be at risk of later complications from radiotherapy. A large number of studies have been carried out on second cancers following radiation therapy for cervical cancer. We describe five cases in which endometrial cancer occurred several years after the patients had received radiation therapy for cervical cancer.

Materials and Methods

In a review of endometrial carcinoma cases treated at Kitakyushu Municipal Medical Center from 1989 to 1997, we identified five patients who had histories of radiation treatment for squamous cell carcinoma of the cervix and developed subsequent endometrial cancer. We performed a retrospective chart review to obtain histories of prior irradiation, and to determine the latent period for the development of the subsequent endometrial carcinoma. From the clinical records, the modes of presentation, magnetic resonance (MR) image findings, treatments, and survival data were determined. Histologic examination of each case of endometrial cancer was performed.

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Results

Table 1 summarizes the characteristics of patients diagnosed with cervical carcinoma. The mean age at diagnosis of cervical cancer was 55.6 years (range 36-72). All women had more than two children. Three patients were postmenopausal, and none had a history of exogenous estrogen use. One patient had Stage Ib, two patients had Stage IIIa, and two patients had Stage IIIb carcinoma of the cervix. Radiation treatment was given by external beam (Lineac), or a combination of external beam and intracavitary application (RALS). Radiation treatment data from four patients were available. One patient received only external beam, and three were treated with a combination of internal cavitary and external beam. One patient received concurrent chemotherapy with radiation for cervical cancer. After completion of radiation therapy, none of the patients experienced a severe acute adverse event. No patient received hormonal therapy after radiation. One patient (case 3) developed lung metastasis

Table 1. — *Patient characteristics.*

	Cervical cancer			
Case No.	Age (yrs.)	Age at menopause	Stage	Dose of radiation therapy
1	50	50 (RI)	IIIb	Unknown
2	36	36 (RI)	IIIa	EBRT, 50Gy
				ICRT, 24Gy
3	61	50	IIIb	EBRT, 50Gy
				ICRT, 10Gy
4	59	53	Ib	EBRT, 50Gy
				ICRT, 15Gy
5	72	50	IIIa	EBRT, 45Gy

RI: radiation induced; EBRT: external beam radiation therapy; ICRT: internal cavitary radiation therapy.

Table 2.

				Endometrial cancer				
Case No.	Age	Presentating symptom	Complication	Interval from CC (yr)	Surgical stage	Histology	Treatment	Outcome (mos.)
1	74	Bloody discharge	HT Obese (24)	24	IIIc	Endometrioid adenocarcinoma, grade 3	RAH+BSO Chemotherapy	DOD at 24
2	56	Abdominal pain	Obese	20	IIa	Carcinosarcoma	RAH+BSO	DOD at 9
3	71	–	–	9.6	Ic	Clear cell adenocarcinoma	RAH+BSO	DOD at 33
4	66	–	DM Obese	6.8	IIIc	Carcinosarcoma	RAH+BSO RT for head	DOD at 12
5	79	Abdominal pain	HT	6.8	Unknown	Adenocarcinoma*	–	DOD at 10

CC: cervical carcinoma; *: endometrial curettage specimen; RAH: radical hysterectomy; BSO: bilateral salpingo-oophorectomy; RT: radiation therapy; DOD: dead of disease; HT: hypertension.

Table 3**. — *Diagnostic reliability of radiation-induced cancers following radiotherapy for malignant neoplasms.*

		Criteria			
		Histological type	Organ of origin	Latent period*	Site of origin
A (High)	1	Different	Different	More than 5 year	Within the irradiated
	2	Different	Same		
B (Medium)	1	Same	Different (non-continuous)	More than 5 years	Within the irradiated
	2	Same	Different (continuous)		
C (Low)	1	Same	Same (non-continuous)	More than 5 years	Within the irradiated
	2	Same	Same (continuous)		

*This criterion was excluded when leukemia developed as a second malignancy.
**Excerpt from reference #1.

four years after completion of radiation therapy, and underwent thoracotomy and subsequent radiation therapy for bilateral hilar lymphadenopathy.

The basic clinical courses after diagnosis of endometrial cancer are presented in Table 2. The mean interval between administration of radiation treatment and development of endometrial cancer was 13.4 years (range 6.8-24). The mean age at the time of diagnosis of endometrial cancer was 69 years (range 56-79). The presenting symptoms of endometrial cancer were abdominal pain in two cases, and bloody discharge in one. The remaining two patients were asymptomatic, and the endometrial cancer was detected on routine cervical cytology. Preoperative imaging with MR or computed tomography (CT) revealed an enlarged uterus in all cases (Figure 1). Preoperative SCC levels were within normal limits in all cases. One patient had elevated CEA levels (case 4; 37.9 ng/ml), and one had remarkably elevated CA125 levels (case 5; 9420 U/ml). An endometrial curettage was very difficult in all patients because of stenosis of the cervical os. Specimens of endometrial cytology were positive in all patients. One patient presented with clinical International Federation of Gynecology and Obstetrics (FIGO) Stage Ib endometrial cancer, three patients presented with Stage II, and one patient presented with Stage IVa. Four patients had radical hysterectomy and bilateral salpingo-oophorectomy. One patient with Stage IVa cancer had only a diagnostic dilation and curettage because of advanced disease at presentation. Retrospectively applying surgical FIGO classification of endometrial carcinoma (1988), one patient had Stage Ic disease, one patient had Stage IIa, two patients had Stage IIIc, and one patient had disease of unknown stage. One patient underwent postoperative chemotherapy of two cycles cyclophosphamide, doxorubicin, cisplatin (CAP). One patient received adjuvant external beam radiation therapy and one patient with brain metastases received radiation therapy for the head a month after surgery.

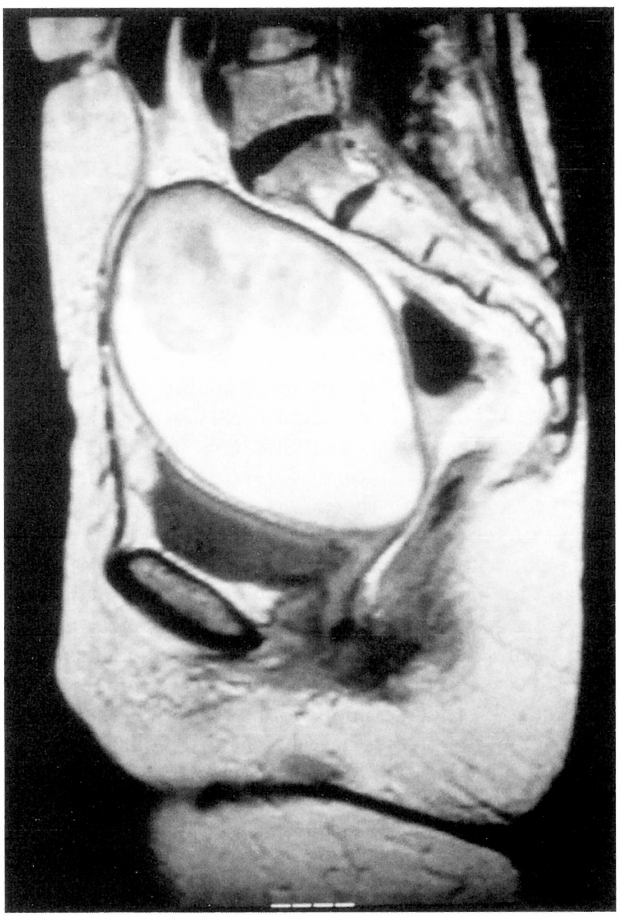


Figure 1. – MR imaging of case 1 revealed an enlarged uterus and pyometra (T_1-weighted image).

. 2A

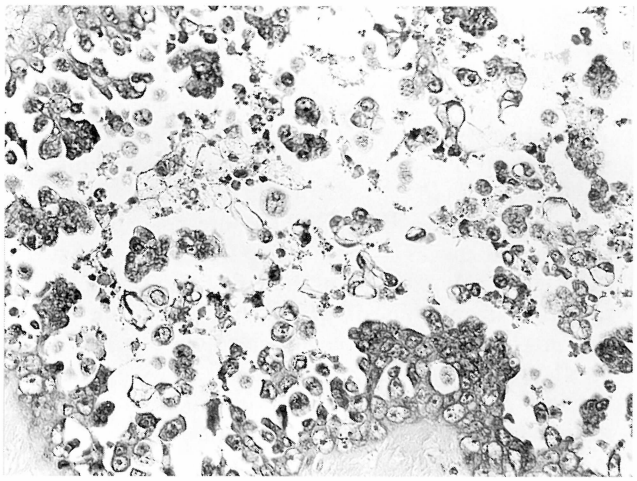
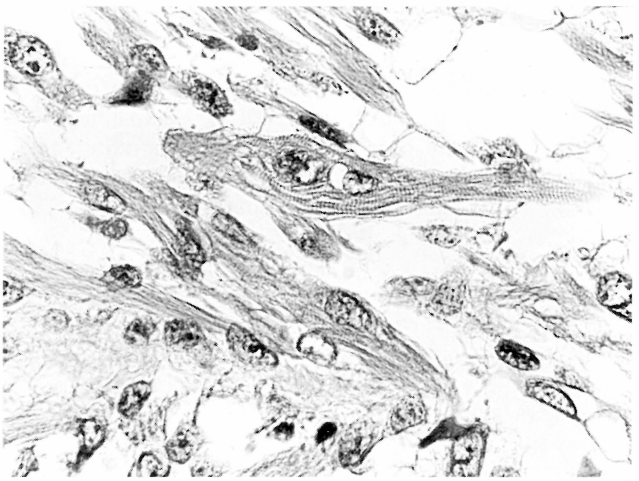


Fig. 2B



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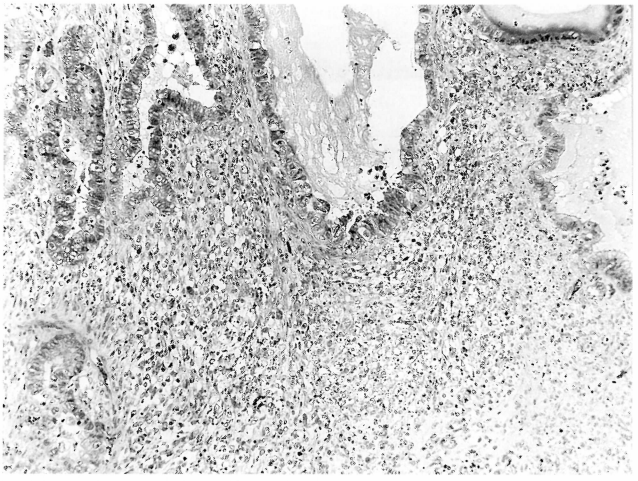
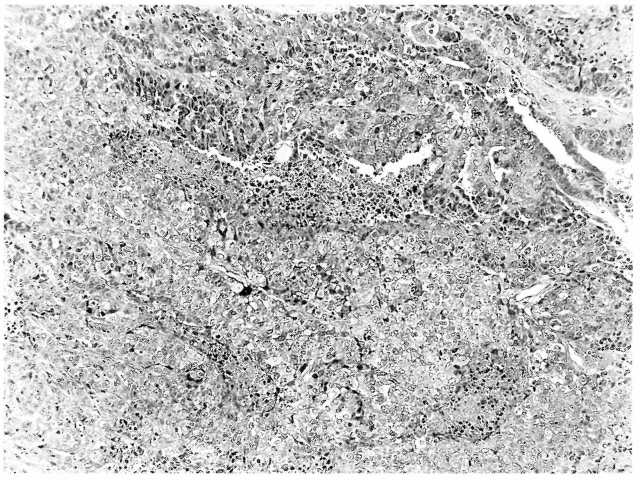


Fig. 4



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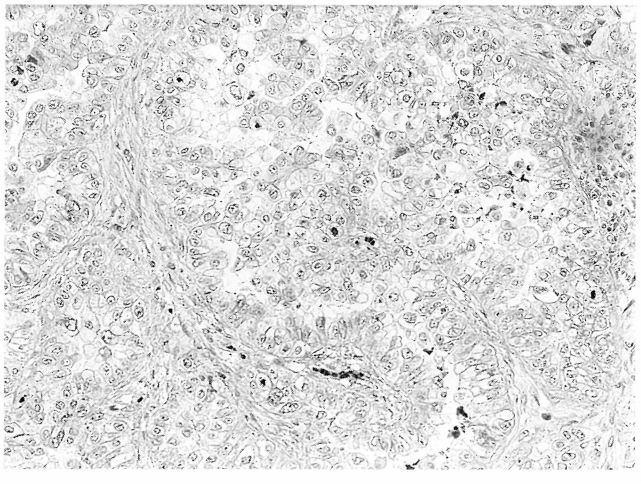

Figure 2A. – Carcinomatous element of carcinosarcoma (case 4) showing serous adenocarcinoma.

Figure 2B. – Sarcomatous element in case 4 demonstrating rhabdomyosarcoma.

Figure 3. – Carcinosarcoma (case 2) composed of endometrioid adenocarcinoma and sarcoma (non-specified).

Figure 4. – Endometrioid adenocarcinoma, grade 3 (case 1).

Figure 5. – Clear cell adenocarcinoma composed mainly of clear cells (case 3).

Histological examination of the hysterectomy specimens revealed carcinosarcoma in two cases. One of these cases had serous carcinoma as a part of a carcinomatous lesion (Figure 2A), and rhabdomyosarcoma as a part of a sarcomatous lesion (Figure 2B). The other case had endometrioid adenocarcinoma (grade 3) and unspecified sarcoma (Figure 3). Moreover, we observed endometrioid adenocarcinoma (grade 3) in one case (Figure 4), and clear cell adenocarcinoma in one case (Figure 5). The endometrial curettage specimen in the patient who did not undergo laparotomy revealed endometrioid adenocarcinoma. Significant myometrial invasion was present in all hysterectomy specimens.

All patients died of disease from nine to 33 months following diagnosis of endometrial cancer. The mean survival period was 17.6 months. Disease was present in both pelvic and extrapelvic sites at the time of death in all five cases.

Discussion

Over the past half century radiotherapy has emerged as an acceptable alternative to radical surgery, primarily because of improvements in technique. With improvement of treatment results, a considerable number of studies have been carried out on a radiation-induced second cancer, which is a late complication due to the initial radiation therapy.

Although there are many reports on radiation-induced cancer, it is very difficult to distinguish a radiation-induced second cancer from late recurrences. In this study, we diagnosed radiation-induced cancer according to Sakai *et al's.* classification, which was made on the basis of the report by Warren and Gates [1, 2]. From a pathological point of view, the second cancer was defined as having a different histologic type from cancer of the primary site, and we excluded adenocarcinomas of the cervix. If a second cancer had the same histologic type as the primary cancer in the uterus, it was classified by the above definition as a recurrence, regardless of the length of period after therapy.

There are some epidemiologic surveys for second cancers following radiation treatment for cervical cancer. Boice *et al.* conducted an international cooperative research for second cancers based on a large population, and reported that there was a relative risk for developing cancer in organs close to the cervix that had received high radiation exposures including the uterine corpus [3]. Arai *et al.* reported that there was a significantly higher incidence of a second cancer in the rectum, bladder, and lung as well as leukemia, and that there was a significantly smaller incidence of a second cancer in the uterus [4]. However, in the case of uterine cancer, a significant decrease in risk was noted up to 15 years, after which a rather significant increase became evident. Fehr and Prem [7] observed 2,294 patients who were irradiated for squamous cell carcinoma of the cervix, and found 12 patients with proven endometrial cancer – an incidence of 52%. This was more than double the expected annual spontaneous incidence of endometrial cancer. In their study, the average latency period was 11.3 years. In other previous studies on endometrial cancer following radiation therapy for cervical cancer, the latency period from the initial diagnosis of cervical cancer to the development of endometrial cancer was more than ten years in most cases [5, 6, 8-12]. Therefore, based on these previous studies, ten years after radiation therapy for cervical cancer the possibility of a second cancer in the uterine corpus should be investigated in addition to follow-up for primary cervical cancer.

The risk of endometrial carcinoma following radiation therapy for cervical cancer should be interpreted carefully. However, there is almost definite evidence as far as uterine carcinosarcoma is concerned. A history of pelvic irradiation was present in 5-29% of patients [13, 14]. A study from the Institute of Warsaw of over 8,000 patients treated with pelvic radiotherapy for cervical carcinoma found the risk of uterine sarcoma to be 5.4 times that of the control population [5]. With regard to the pathologic findings, there is a study suggesting that the heterologous mixed mesodermal tumor (MMT) is the most frequent type [6]. However, Crement and Scully reported that the relationship between sarcoma and antecedent pelvic radiation therapy seems to involve only malignant epithelial-nonepithelial tumors, such as carcinosarcoma and adenosarcoma [15].

It is still unclear from the literature not only whether endometrial cancer is more likely to develop in patients exposed to pelvic radiation therapy, but also the role of radiation in the genesis of this tumor even in uterine sarcoma. Parkash *et al.* have pointed out that it is possible that the obliteration of the cervical os by previous radiation therapy favored the development of an inflammatory process in the uterine cavity, which might have led to necrosis and cancer [8]. However, the risk of cancer in other organs in the radiation field (bladder, rectum etc.) is more likely than that of endometrial cancer. Theoretically, radiation therapy might have a stimulating effect on the multipotential cells, and has been implicated as a carcinogenic factor in the development of second cancers in many studies. Therefore, inflammation of the uterine cavity or exogenous estrogen intake may not be a definitive cause of carcinogenesis, and irradiation itself might have a strong influence on carcinogenesis.

The prognosis of patients who develop endometrial cancers is very poor. Radiation-induced cervical stenosis may prevent early symptoms and complicate efforts to obtain a diagnosis. Unlike other patients with endometrial cancer whose first symptom it typically vaginal bleeding, the patients in this series usually presented with symptoms of an enlarged uterus and pelvic pain, indicating relatively advanced disease. Furthermore, patients who develop endometrial cancer after radiation are also much more likely to have aggressive histological subtypes of adenocarcinoma. Parkash *et al.* reported six cases of uterine papillary serous carcinomas (UPSC) [8]. All of the patients had an early menopause, which was induced by radiation therapy in three of them, and the median patient age at the time of diagnosis of UPSC was lower than that reported for UPSC unrelated to radiation therapy. In this study, although only one patient had an early menopause induced by radiation therapy, all patients had aggressive histological subtypes of adenocarcinoma. Bochman proposed that endometrial carcinoma could be classified into two types from clinical characteristics [6]. Type I with features of hyperestrogenism and Type II, which is unassociated with hyperestrogen. In this study, all cases fell into the latter classification including a carcinomatous lesion of carcinosarcoma. The same observation applies to other studies [8, 9]. This finding is consistent with the hypothesis that radiation contributes to the genesis of Type II tumors in particular.

Recently, the combination of radiation therapy and chemotherapy has been applied frequently for cancer patients. Significant reductions in the risk of relapse and death are observed. Chemotherapeutic agents, in particu-

lar cisplatin, have also been associated with the occurrence of treatment-related second cancers. It is likely that the risk of a second cancer increases when chemotherapy is added to radiation therapy, and increased risks have already been reported [17]. In several studies about non-Hodgkin lymphoma and leukemia after chemotherapy, the incidence increased when radiation therapy was taken together [18, 19]. Smith observed radiation-induced sarcoma in bone, and demonstrated that a combination of chemotherapy made the latent period shorter than radiation only [20]. In chemoradiation therapy for cervical cancer, the combination of cisplatin and 5-FU has been widely selected. Currently, treatment-related second cancers from this study have not been reported because there has not been sufficient time for a second cancer to develop. However, cisplatin and 5-FU have both been associated with the occurrence of second cancers [21-23]. Therefore, more attention should be given to chemoradiation in occurrence of a second cancer. The latent period should be shorter, namely within ten years.

This study again points out the need for prolonged routine follow-up examination in all patients treated for cervical cancer and for adequate evaluation of symptoms and masses found on examination. Whether these tumors are coincidental second malignancies or whether they are radiation-induced is a question that cannot be answered by this study. Further research is needed to understand the molecular genetic alteration in these tumors.

Conclusions

1. The clinical findings in five patients with endometrial cancer following radiation therapy for cervical carcinoma were as follows. The mean latency period was 13.4 years. First, the symptom was abdominal pain rather than genital bleeding, which is seen in typical endometrial cancer. The prognosis was very poor with a mean survival period of only 17.6 months.

2. All patients had aggressive histological subtypes of adenocarcinoma, which were classified into Type II. Two patients (40%) had carcinosarcoma.

3. The role of radiation in the genesis of radiation-induced second cancer and epidemiological evidence for the incidence of this tumor are still unclear.

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