Development of Malignant Tumors following
Irradiation for Preexisting Tumors
—Study Based on Autopsy Cases of Double Cancer—

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Postirradiation cancer/Irradiation effect/Double cancer/Carcinogenesis/Pathology

Carcinogenesis is a significant matter among the late pathologic effects of therapeutic irradiation which is now used for malignant tumor. Accumulation and analysis of cancer cases following radiation therapy for malignant tumor seem necessary to search for ways to follow up such patients. For the purpose of screening secondary cancer cases following irradiation for a primary malignant tumor, we first selected 259 cases of double cancer from about 13,000 autopsied cases of Nagasaki University and its related hospitals, and reviewed probable cases of secondary carcinogenesis based on their clinical and autopsy records. The criteria used for selection of most probable cases were that 1) radiation therapy was performed for the first cancer, 2) the second cancer developed at the site of irradiation field, and 3) the interval from radiation therapy to detection or onset of the second cancer (latent period) was five years or more. We found 6 cases of most probable radiation induced cancer, all females. The first cancer was cervical cancer in 4 cases, thyroid cancer in 1 case and lymphosarcoma in 1 case. The radiation induced cancer was carcinoma in 4 cases, and sarcoma in 2 cases. The latent period ranged from 5 to 23 years, the mean being 13.3 years. The clinical and pathological features of these cases with special reference to radiation-carcinogenesis relationship are reported. Two A-bomb survivors were included among these 6 cases.

INTRODUCTION

Carcinogenesis is a particularly significant sequential event among the late pathogenic effects of therapeutic irradiation. Radiation therapy that had been used even for benign diseases such as tuberculous lymphadenitis, ankylosing spondylitis, and eczematous dermatitis is now being limited to malignant tumors.[1] Recently case reports on malignant neoplasms induced by irradiation for preexisting malignant tumor have increased.[2] Accumulation and analysis of cancer cases that developed following radiation therapy for previous malignancy seem

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necessary so as to consider how such patients should be followed up.

For collecting cancer cases due to previous radiation therapy for malignant tumor, we screened autopsy cases of multiple cancer and selected from them possible cases of secondary carcinogenesis on the basis of their clinical and autopsy records. The purpose of this report is to review the clinical and pathological features of these cases, with special reference to the relationship between radiation and carcinogenesis.

MATERIALS AND METHODS

On the basis of the Annual of the Pathological Autopsy Cases in Japan edited by the Japanese Pathological Society, 259 cases of multiple cancer were screened from the autopsy cases (approximately 13,000) of Nagasaki University and its related major hospitals. Using their autopsy records, review was made on the time of onset and/or detection of the first and second cancers, as to whether or not radiation therapy was performed for the first cancer, dose, if available, and the relation of the irradiated field and the site of the second cancer. Thus, cases of most probable radiation-induced cancer were selected. The criteria used for selection of most probable cases were that 1) radiation therapy was performed for the first cancer, 2) the second cancer developed at the site of irradiation, and 3) the interval from radiation therapy to the detection or onset of the second cancer (latent period) was five years or more. Cases of leukemia and those of possible recurrence or metastasis of the first cancer were discarded from this study. For the most probable cases thus selected, histological specimens were re-examined, and review was made of the histological diagnoses of the first and second cancers and histological changes caused by irradiation.

RESULTS

The analysis of 259 cases of double cancer is given in Table 1. Most probable radiation induced cancer was identified in 6 cases who were all females. Two of these cases have been reported elsewhere.[3,4] The first cancer was cervical cancer in 4 cases, thyroid cancer in 1 case and lymphosarcoma of neck in 1 case. The radiation induced cancer was carcinoma in 4 cases, and sarcoma in 2 cases. The latent period ranged from 5 to 23 years, the mean being 13.3 years.

Table 1. Analysis of double cancer cases

Total	259
Non-irradiation for 1st cancer	204
Irradiation for 1st cancer	55
2nd cancer in radiation field	13
5 years or more of latent period (most probable radiation-induced cancer)	6

Two A-bomb survivors were included among these 6 cases. A summary of these 6 cases is given in Table 2.

CASES

Case. 1. 68 years, female

The patient recalled that she had received radium therapy for 4 years after the diagnosis of cervical cancer in 1942. The dose and method are unknown. In 1945, she was exposed to the A-bomb at 3.5 km from the hypocenter in Nagasaki and entered the hypocenter area 2 days later. In 1964, general fatigue, edema, diarrhea, and genital bleeding developed, and the recurrence of cervical cancer (Stage IV) was pointed out. After developing left hydrothorax and intensified edema, the patient died of uremia.

Autopsy findings: Reddish skin scars of 6 cm in diameter seemingly due to percutaneous irradiation were observed in the lower abdominal and sacral regions. Fibrous adhesion was marked in the intrapelvic organs. The uterine cervix was replaced with a tumor and the cancer lesion invaded the uterine cervix, vaginal wall, urinary bladder and ureter. The ureter was bilaterally stenosed because of this invasion, and the kidneys showed hydronephrosis and pyelonephritis. Histologically, the cervical cancer was squamous cell carcinoma with a marked trend of keratinization. The rectum was intensively adhered to the vaginal region, uterus and vaginal wall. The rectal wall was thickened fibrously. On the anterior wall, an ulcerous tumor
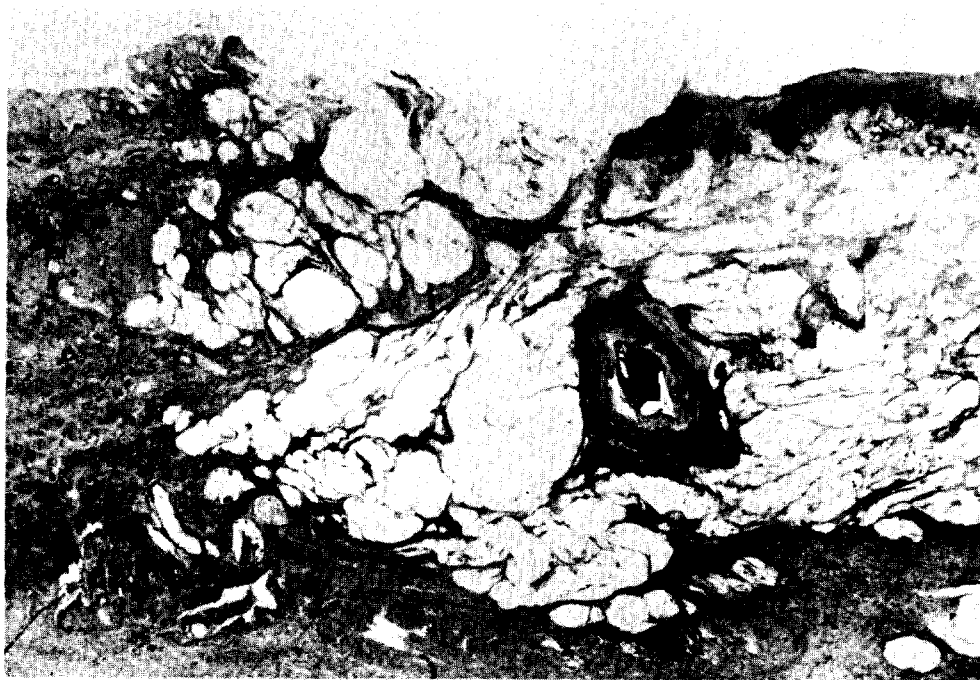

Fig. 1. Case 1. Mucinous adenocarcinoma in the anterior wall of the rectum.

Table 2. Summary of radiation-induced cancer

No.	Age at death / Sex	Original cancer Site	Histology	Onset or detection	Irradiation Method	Dose	Latent period	Radiation-induced cancer Site	Histology	Onset or detection	A-Bomb
1	68 F	Uterine cervix	SCC	1942	Radium	unknown (for 4 years)	23	Rectum	Muc	1964 (at autopsy)	At 3.5 km and entered to hypocenter 2 days after
2	46 F	Uterine cervix	SCC	1965	Telecobalt	70 Gy	8	Retroperitoneum to head of femur	MFH	1973	At 3.2 km
3	70 F	Uterine cervix	SCC	1969	Telecobalt Intracanal	60 Gy 4,000 mCi	13	Retroperitoneum	Leiomyo-sarcoma	1982	—
4	68 F	Uterine cervix	SCC	1959	Telecobalt	unknown	22	Urinary bladder	TCC	1981	—
5	73 F	Thyroid	Pap	1965	Telecobalt Telecobalt	unknown (in 1967) 22 Gy (in 1971)	5	Tongue	SCC	1972	—
6	45 F	Neck	Lymphsarcoma	1963	unknown	unknown	9	Thyroid	Pap	1972 (at autopsy)	—

SCC: Squamous cell carcinoma, Pap: Papillary carcinoma, Muc; Mucinous carcinoma, TCC: Transitional cell carcinoma, MFH: Malignant fibrous histiocytoma.

measuring 3 x 3 cm was present, which, histologically, was mucinous carcinoma characterized by much mucin production and accumulation in the atypical gland (Fig. 1). Invasion or metastasis of this rectal cancer to other organs was not noted. On the rectal wall around the cancer, changes such as fibrosis of the submucosal tissue, and thickening, tortuosity, hyalinization and teleangiectasia of the blood vessels that seemed to be caused by irradiation, were observed.

Case 2. 46 years, female

The patient was exposed to the A-bomb at 3.5 km from the hypocenter at age 15 in Nagasaki. Early 1965, genital bleeding was noted. In July 1965, a diagnosis of invasive squamous cell carcinoma Stage II was made from a biopsy of the uterine cervix and complete hysterectomy (Okabayashi's method) was performed. During September–November 1965, she received cobalt teletherapy abdominally and dorsally with a total dose of 70 Gy a radiation field of 14 x 15 cm. After treatment, she complained of constipation, abdominal pain and incontinence of urine. In 1973, she was admitted since edema developed in both legs, particularly the right leg, and pain which was intensified at coughing also developed. A large tumor was found in the right inguinal region and its vicinity. Recurrence of cervical cancer was suspected but it could not be demonstrated. She died in November 1976.

Autopsy findings: A large tumor measuring 12 x 19 cm in size was present in the region from the head of the right femur to the right lower retroperitoneum. The cut surface of the tumor showed almost complete hemorrhagic necrosis. Metastasis was not observed. Histologically, the tumor consisted of spindle and polygonal cells occasionally showing a typical storiform pattern (Fig. 2). Giant cells were also seen occasionally. A diagnosis of malignant fibrous histiocytoma was made. No findings of residual or recurrent cervical cancer were observed.

The formation of rectovesical fistula (Fig. 3) and the presence of ulcerous proctitis were suggestive of radiation effects.

Case 3. 70 years, female

In February 1965, a diagnosis of cervical cancer Stage II was made. Biopsy disclosed invasive squamous cell carcinoma. During February – May 1965, she received cobalt teletherapy dorsally and abdominally with a total dose of 60 Gy, and also cervical and canal irradiation with a total of 4006 mCi.

In August 1982, numbness and pain extending from the lumbar region to the left leg occurred. She was admitted in January 1983 and diagnosed radiologically as having metastatic tumors at L5 and L6. In April, the tumors became palpable in the right lower abdominal region. Thereafter, the entire lower abdominal region became swollen and a diagnosis of lower retroperitoneal tumor was made. In spite of symptomatic therapy, she fell into a state of ileus and died in December 1983.

Autopsy findings: Whitish tumors measuring 13 x 10 x 5 cm, 4 x 4 x 4 cm and 4 x 4 x 4 cm were found in the left lower part, median part and right side of retroperitoneum, respectively. Histologically, each of the tumors was leiomyosarcoma consisting of quite atypical
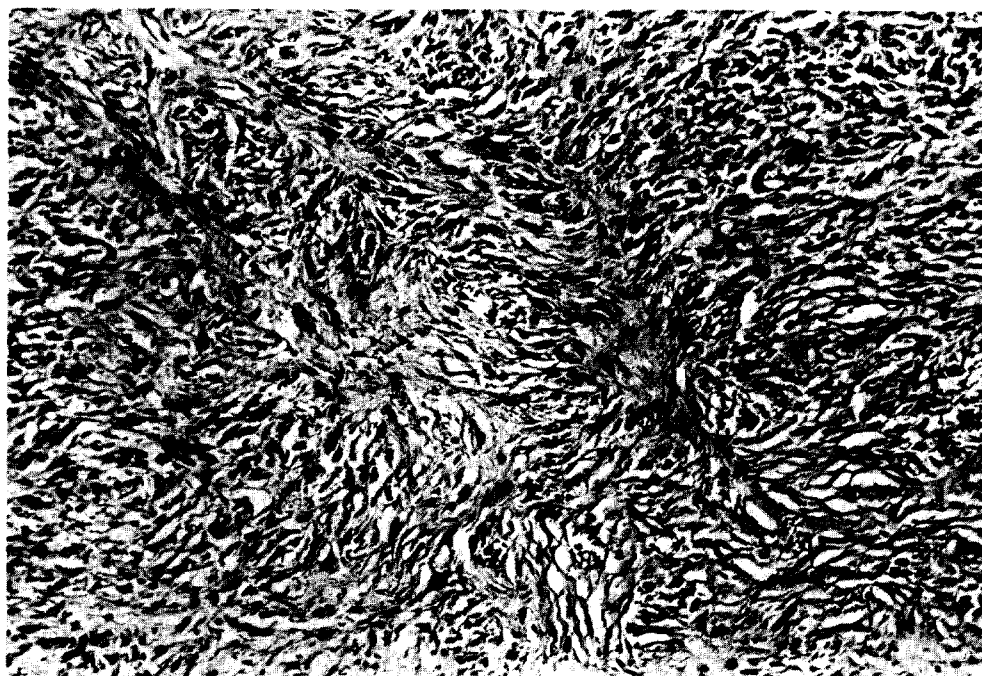
Fig. 2. Case 2. Malignant fibrous histiocytoma of the retroperitoneum of head of femur. Proliferation of atypical spindle cells with typical storiform pattern.

Fig. 3. Case 2. Rectovesical fistula was seen as a complication of irradiation.

spindle cells (Fig. 4). The small and large intestines showed intensive fibrous adhesion. The histological picture of the lower half of the small intestine revealed chronic irradiation enteritis.

Case 4. 68 years, female

In 1959, complete hysterectomy (Okabayashi's method) was performed at the Kyushu University Hospital with a diagnosis of cervical cancer, and postoperatively cobalt teletherapy was given. However, the irradiation method and dose are unknown. Subsequently, loss of right renal function was noted. In 1980, macrohematuria developed and diagnoses of irradiation cystitis and hydropyeloureter were made. In 1981, urine cytology was Class V. In 1982, left nephrostomy was performed. In 1983, an ulcer was noted in the urinary bladder and marked vesical hemorrhage developed. Telecobalt irradiation of 40 Gy was performed. The patient died of cerebral hemorrhage in April 1984.

Autopsy findings: Recurrence of cervical cancer was not seen. Pelvic organs showed intensive fibrous adhesion. The vesical wall was remarkably thickened. A tumor mass with hemorrhagic and necrotic changes was formed within the wall. Histologically, it was a transitional cell carcinoma associated with glandular metaplasia.

Case 5. 73 years, female

In 1965, a swelling of the left neck was noted and, in 1967, a tumor of the neck was extirpated. After the operation, remote cobalt irradiation was performed but the method and
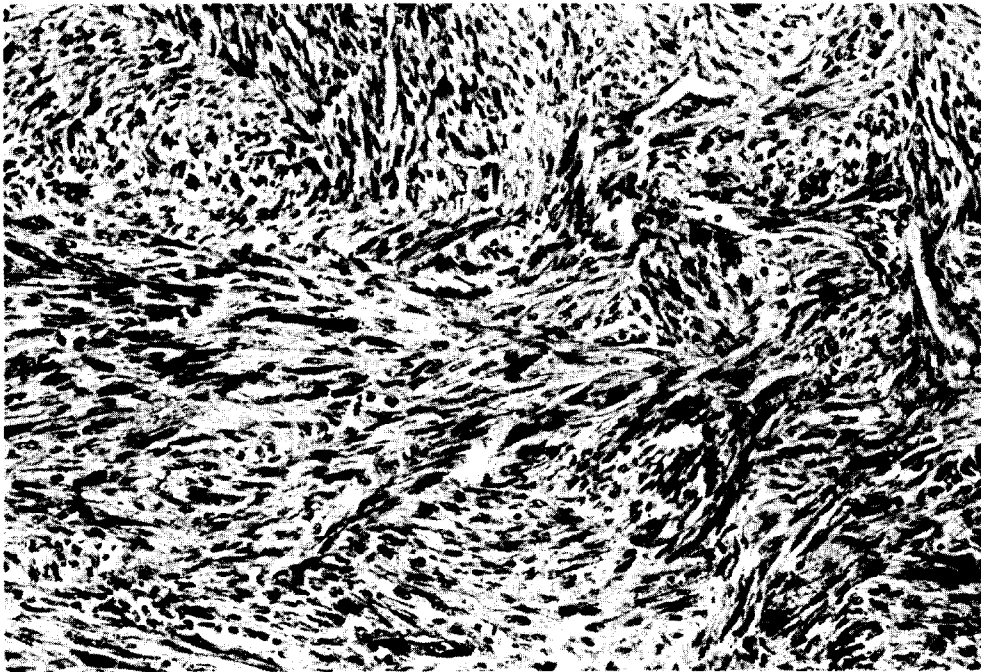

Fig. 4.   Case 3. Leiomyosarcoma in the retroperitoneum. Spindle cells with atypism are arranged as fascicles.

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dose are unknown. In 1969, the left neck was swollen again and esophageal passage was disturbed. In September 1971, biopsy was performed and a diagnosis of papillary carcinoma seemingly primary at thyroid was made. Telecobalt irradiation of 16 Gy was performed. In February 1972, an ulcer appeared at the left edge of tongue, which was disclosed by biopsy in May as squamous cell carcinoma. During May — July 1972, 19 Gy of radium was irradiated by needle insertion. In July 1972, 6 Gy was irradiated to the left neck also, but the both cancers gradually proliferated and the patient died in August 1972.

Autopsy findings: The thyroid was replaced with a bilateral tumor mass, which had invaded the surrounding tissues including the trachea and esophagus. Histologically it was a papillary carcinoma. In the tongue, an ulcer was located on the left exterior side, which histologically was a squamous cell carcinoma.

Case 6. 45 years, female

In 1963, swelling of lymphnodes in the left neck was noted and a diagnosis of lymphosarcoma was made by biopsy. X-ray irradiation was performed but details are unknown. Motor paralysis of the four extremities developed beginning with the left side since 1965 and she died of general hyposthenia in 1972.

Autopsy findings: A burn scar was noted at the nape of the neck. The spinal cord of the neck was atrophic, and there was particularly marked atrophic degeneration of anterior corneal cells (Fig. 5). A diagnosis of irradiation myelitis was made. The thyroid was atrophic and hard, and histologically, latent cancer (papillary carcinoma) was found (Fig. 6) scattered
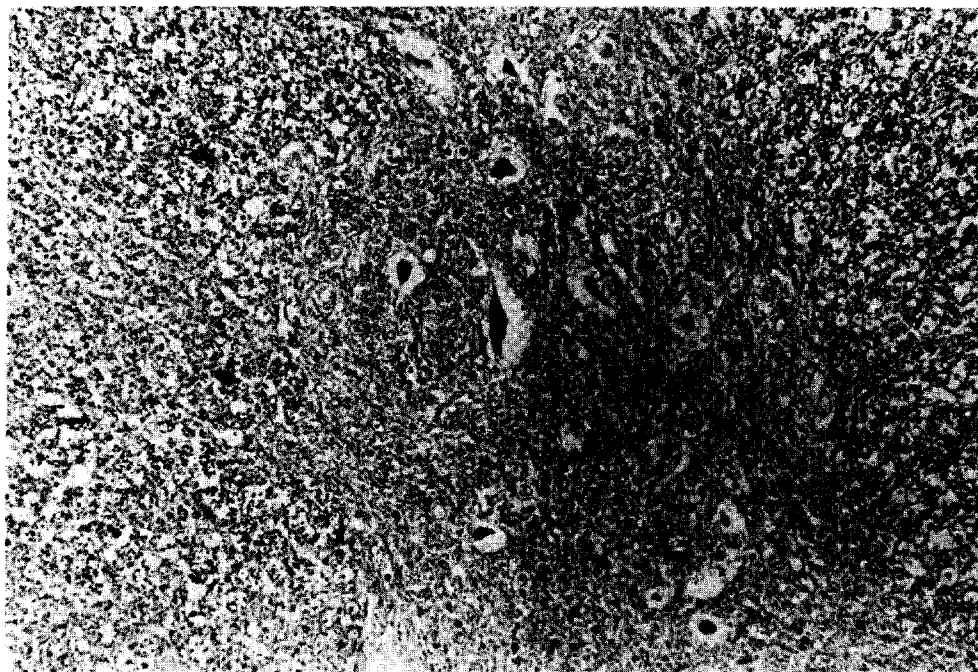

Fig. 5. Case 6. Cervical spinal cord was diagnosed as irradiation myelitis in which anterior corneal cells disclosed marked atrophy and degeneration.
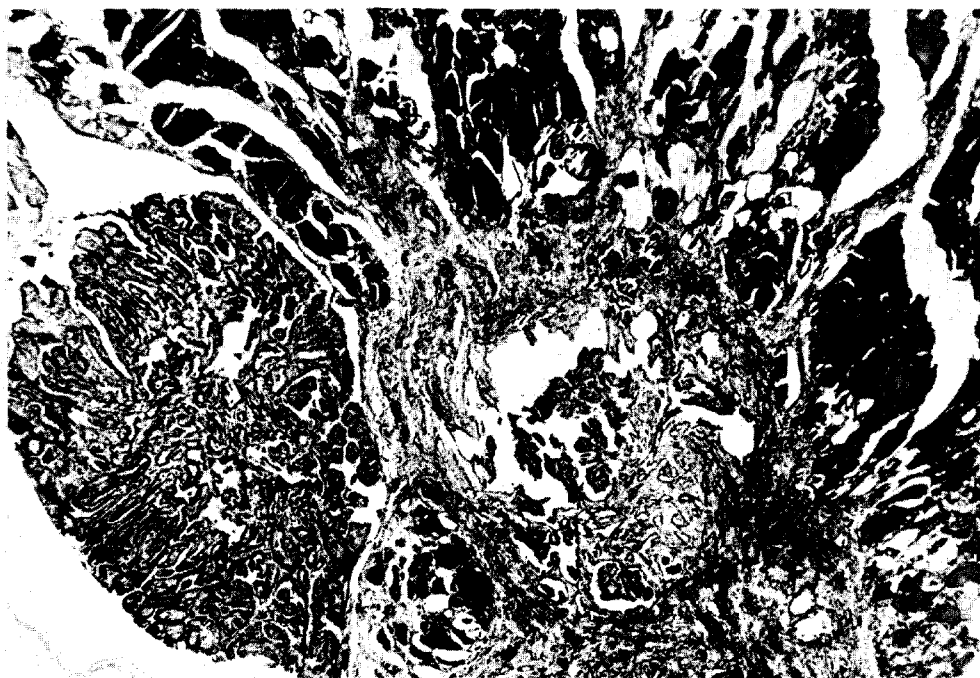
Fig. 6. Case 6. Papillary carcinoma (latent cancer) in the thyroid gland in which atrophy and psammoma bodies formation were marked.

psammoma bodies as well as fibrosis were seen.

DISCUSSION

As a means to find cancer cases induced by irradiation of a previous malignant tumor from approximately 13,000 autopsy cases, we first collected cases of multiple cancer on the basis of autopsy diagnosis, and then confirmed the clinical history in autopsy records as to whether or not radiation therapy was performed for the first cancer. However, there is a great possibility that some cases were overlooked for the following reasons: 1) Part of the history taken by the clinician was insufficient. 2) Description of the first cancer was missing in the clinical history which is presented from the clinician to the pathologist. 3) When the first cancer had been cured, the pathologist fails to describe the past history of the first cancer in the autopsy records and thus he also fails to indicate multiple cancer in autopsy diagnosis. Hence, it was considered dangerous to make a statistical analysis about the incidence on the basis of 6 cases out of 259 double cancer cases among 13,000 autopsy cases. Our impression, after examining 13,000 autopsy cases, was that carcinogenesis induced by radiation therapy is very rare. Seydel[5] reported that adenocarcinoma of the endometrium occurred in 3 cases or 0.85% of 354 5-year survivors treated for squamous cell carcinoma of the cervix with an average dose of 81 Gy, and adenocarcinoma of the colon and/or rectum occurred in 3 cases or 0.85% of 5-

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year survivors also treated for squamous cell carcinoma of the cervix, the latent period being 10 to 20 years in the same group. However, he did not present any data that radiation therapy promoted carcinogenesis.

The possibility that the development of the second cancers in the present study was incidental irrespective of radiation therapy is cannot be denied at present. The diagnostic criteria for radiation induced cancer are not necessarily definite. For example, Cahan's[6] criteria for radiation induced sarcoma have been widely applied. Sakai et al.[7] classified the cancers occurring in the irradiated area after more than 5 years of latent period by the identity with or difference from the first cancer in histological type and the organ affected. We used three criteria, i.e., (1) history of high dose irradiation to the first cancer, (2) occurrence of the second cancer in the irradiated area, and (3) latent period of over 5 years. In our cases, since the histological type were completely different between the first and second cancers, there was no need for reviewing recurrence or metastasis of the first cancer. As to radiation induced leukemia, the latent period is been known to be short[8] and therefore other criteria should be applied.

As to the radiation dose, the records were not available in some cases because of long period of time before the onset of the second cancer. In Case 1, the method of irradiation and dose are unknown though the patient recalled that radium therapy had been performed for 4 years. However, it was speculated that a high dose was irradiated percutaneously and absorbed onto the rectal wall in view of the intensive fibrous adhesions in the pelvis and intensive fibrous change of the rectal wall. In Case 4, telecobalt irradiation was performed after the operation for cervical cancer and the irradiation was estimated to have amounted to 60 Gy. In Case 6, the actual state of radiation therapy for lymphosarcoma is unknown, but the burnlike scar and radiation induced myelitis which was the cause of death, suggest a high irradiation dose. These records support the argument that the records of medical radiation exposure should be preserved for a sufficient period of time.[9]

Yoshizawa et al. after reviewing the literature, estimated minimal doses required for carcinogenesis in individual tissues; 40 Gy for laryngopharyngeal cancer,[10] 1–10 Gy for uterine cancer,[11] 14.7 Gy for breast cancer,[12] 4.6 Gy for digestive tract,[13] and 8–18 Gy for bone tumor.[14] In four cases of the present study, the irradiated dose which was recorded or estimated for the first cervical cancer was as high as 60 Gy or more.

Carcinogenesis induced by therapeutic irradiation has been shown to be proportional to the radiation dose. In comparison with carcinoma, the development of sarcoma seems to require much higher doses.[15, 16]

In recent years, carcinogenesis due to therapeutic irradiation has become a matter of interest in Japan. Increased case reports and an overall questionnaire survey[7] have drawn attention of those concerned to this field. However, pathological studies in this field are scarce, and especially the morphological changes such as dysplasia and/or precancerous state related to carcinogenesis are not evident.

The second cancer of Case 1 was mucous adenocarcinoma of the rectum. In contrast to the fact that the rate of mucous adenocarcinoma in the usual cancer of the large intestine is

about 10%, that of radiation induced cancer was 58%, which, together with the complication of radiation induced proctocolitis, is considered to be the histological characteristics.[17] In Case 2, malignant fibrous histiocytoma was seen, for which only a few cases have been reported.[3] There were no findings to support the occurrence of malignancy due to irradiation. However, the changes in the region of rectovesical fistula and in the submucosal tissue of proctocolitis suggested a strong effect of irradiation also on the mesencymal tissue at the region. Pathological examination of therapeutic radiation induced cancers may be divided into two major categories as described above, i.e., the characteristics of induced cancer itself and the background changes caused by irradiation. Particularly in the background changes, recognition of precancerous lesions can be expected, and it is desired that many specimens be prepared from the irradiated area in search for the relationship between irradiation and carcinogenesis at autopsy of those cases.

The second cancer of Case 6 was thyroid cancer. In an autopsy series of thyroid cancer, so-called occult cancer is 97%[18] and, together with that of prostate cancer, has a great weight in autopsy diagnosis of multiple cancers. In this case, there is a high possibility of incidental occurrence but yet it is speculated that the thyroid was irradiated with a large dose in view of severe atrophy with fibrosis of the noncancerous thyroid tissue.

Of the 259 cases of multiple cancer in this study, 100 cases were A-bomb survivors including early entrants to the city, and 15 cases of these had received some sort of radiation therapy. It is also possible that the dose of diagnostic irradiation was large because of malignant tumor. The irradiation in these cases may possibly cause a bias in health study and life-span study of A-bomb survivors based on the A-bomb radiation dose, and it seems essential to incorporate such a medical dose into the total dose the patient received. Also, as it was reported that heavily irradiated A-bomb survivors showed the tendency to develop multiple cancers,[19] attention should be paid in these studies.

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