

Radiation-induced Tumors
—Study Based on Biopsied and Surgical Materials—

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ABSTRACT

So-called radiation-induced tumor cases following radiation therapy have been collected for the purpose of elucidation the relationship between ionizing radiation and carcinogenesis. Presented in this paper is a summary of cases obtained from biopsied and surgical materials. Materials were 64,082 cases with tumor or tumor-like lesion registered to the Nagasaki Tumor Tissue Registry during a 12-year period from 1973 to 1984. The criteria used for determination of radiation-induced tumor were 1) the past history of radiation therapy, 2) the evidence of tumor developing at the site of irradiation and 3) the latent period of five years or more. As a result, 6 male cases and 26 female cases, totalling 32 cases, of radiation-induced tumor were detected. These 32 cases were compiled after being classified into four categories of 1) malignant tumor developing after radiation therapy for malignant tumor, 2) malignant tumor after radiation therapy for benign condition, 3) benign tumor after radiation therapy for malignant tumor, and 4) benign tumor after radiation therapy for benign condition.

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INTRODUCTION

As to the cancer of various organs, precancerous lesions such as dysplasia in cervical cancer, adenoma in colonic cancer, etc., have been proposed. It has been evident that ionizing radiation induces cancer in human, from epidemiological study proving the higher incidence of cancer of various organs in atomic bomb survivors¹⁻⁶⁾ and many reports of cancers after radiation therapy⁷⁻¹⁰⁾. However, there have hardly been morphological (histopathological) studies on the relationship between ionizing radiation and carcinogenesis, and hence it is unknown as to what type of precancerous lesion would result in a cancer. For the morphological study on the relationship between radiation and cancer, we have collected tumor cases that developed after radiation therapy and undergone histopathological examinations. Six cases of postirradiation tumor found in autopsy cases were reported previously¹¹⁾. This paper reports a summary of radiation-induced tumor cases detected from biopsied and surgical materials.

MATERIALS AND METHODS

For the purpose of detecting cases with radiation-induced tumor, we reviewed 64,082 cases with tumor or tumor-like lesion registered to the Nagasaki Tumor Tissue Registry (NTTR) during 12 years from 1973 to 1984 covering the central and southern areas of Nagasaki prefecture (Table 1). The criteria used for selection of radiation-induced tumor were 1) the past history of radiation therapy, 2) the evidence of tumor or tumorous lesion at the site of irradiation, and 3) the long interval of five years or more from radiation therapy to detection or onset of the tumor (latent period).

In addition to the cases with the past history of radiation therapy, the cases with possibility of previous irradiation, for example, the cases with the past history of operation for uterine cancer, breast cancer or the like, were also reviewed with the aid of protocols. Cases of leukemia and those of possible recurrence or metastasis of the treated tumor were discarded from this study.

Table 1. Number of Cases Registered to Nagasaki Tumor Tissue Registry (1973-1984)

Year	Male	Female	Total
1973	889	1654	2543
1974	1202	2085	3287
1975	1327	2238	3565
1976	1729	2589	4318
1977	1684	2844	4528
1978	1777	2856	4633
1979	2168	3942	6110
1980	2186	3613	5799
1981	2695	4136	6831
1982	2871	4096	6967
1983	3023	4467	7490
1984	3240	4771	8011
Total	24791	39291	64082

RESULTS

32 cases of possible radiation-induced tumor consisting of 6 males and 26 females were selected. The diseases or conditions treated with radiation as well as the induced tumors were classified into benign lesions and malignant tumors, respectively, resulting in the classification of the 32 cases into four groups.

1) Malignant tumor developing after radiation therapy for previous malignant tumor (Table 2)

A total of 19 cases (1 male and 18 females) were included in this group. The mean age at the time of pathological diagnosis of the radiation-induced tumor was 63.8 years. The primary cancer for which radiation therapy had been performed was uterine cancer in 12 cases, breast cancer in 5 cases, lymphoepithelioma in 1 case and rectal cancer in 1 case. The radiation-induced malignant tumor was adenocarcinoma of colon and rectum in 6 cases, transitional cell carcinoma of bladder in 2 cases, adenoid cystic carcinoma of epipharynx, papillary carcinoma of thyroid, adenocarcinoma of stomach, squamous cell carcinoma of anus, squamous cell carcinoma of vulva, adenocarcinoma of vagina and adenocarcinoma of endometrium of uterus in 1 case each, and sarcoma in 2 cases consisting of fibrosarcoma in 1 case and malignant fibrous histiocytoma in another. The method and dose of radiation therapy were unknown in 11 cases. The mean latent period in 6 cases of colorectal cancer, 2 cases of bladder cancer, 7 cases of other cancer, 2 cases of basal cell epithelioma and 2 cases of sarcoma was 18.3, 18.5, 11.9, 15.0 and 13.5 years, respectively, the

Table 2. Malignant Tumors after Irradiation for Malignant Tumor
(NTTR, 1973-1984)

Case	Age	Sex	Primary cancer	Radiation therapy	Latent period	Year at diagnosis	Location	Induced tumor
1 H. M.	77	F	Uterine ca.	Linac 60Gy Int. Co 4, 010mchi	5	1981	Coecum	Adenoca.
2 T. S.	65	F	Uterine ca.	Radium 7,200mchi X-ray 3.06Gy x 16	10	1974	Rectum	Adenoca.
3 S. K.	56	F	Uterine ca.	+	19	1976	Rectum	Adenoca.
4 I. M.	72	F	Uterine ca.	Radium 5,875mg	22	1976	Rectum	Adenoca.
5 M. X.	69	F	Uterine ca.	+	27	1980	Rectum	Adenoca.
6 T. H.	73	F	Uterine ca.	+	27	1983	Sigmoid colon	Adenoca.
7 I. M.	68	F	Uterine ca.	Tele Co	10	1975	Bladder	T.C.C.
8 F. S.	66	F	Uterine ca.	+	27	1980	Bladder	T.C.C.
9 S. C.	67	M	Epipharynx Lymphoepithelioma	Tele Co 50Gy Tele Co 2mon.	14	1982	Epipharynx	Adenoid cystic carcinoma.
10 T. T.	62	F	Breast ca.	+	19	1979	Thyroid	Papillary ca.
11 H. M.	59	F	Breast ca.	Tele Co 60Gy	10	1983	Stomach	Adenoca.
12 N. S.	71	F	Uterine ca.	+	16	1977	Anus	S.C.C.
13 K. A.	70	F	Uterine ca.	Betatron	5	1981	External genitalia	S.C.C.
14 K. M.	57	F	Cervical ca.	+	5	1983	Vagina	Adenoca.
15 M. M.	46	F	Rectal ca.	+	14	1982	Endometrium	Adenoca.
16 B. S.	60	F	Breast ca.	Electrons 2mon.	6	1980	Chest wall	B.C.C.
17 H. Y.	62	F	Breast ca.	+ 40days	24	1982	Chest wall	B.C.C.
18 F. T.	45	F	Uterine ca.	+	8	1976	Buttock	Fibrosarcoma
19 F. S.	67	F	Breast ca.	+	19	1976	Chest wall	M.F.H.

Adenoca.: Adenocarcinoma, T.C.C.: Transitional cell carcinoma, S.C.C.: Squamous cell carcinoma,
B.C.C.: Basal cell carcinoma M.F.H.: Malignant fibrous histiocytoma

mean of the 19 cases being 15.0 years (Table 3).

2) Malignant tumor developing after radiation therapy for benign condition (Table 4)

This group involved 3 males and 2 females, totalling 5 cases with the mean age of 65.6 years. The lesions for which radiation therapy had been performed were skin lesions such as tenia pedis, pustulosis, keratosis and sycosis vulgaris, and wound after lymphadenectomy. The method of radiation therapy was regional irradiation in 2 cases and unknown in 3 cases. The mean latent period was 31.6 years.

3) Benign tumor developing after radiation therapy for malignant tumor (Table 5)

Five female cases with the mean age of 56.2 years belonged to this group. The primary malignancy for which radiation therapy had been performed was breast cancer in 2 cases and uterine cancer in 3 cases. The method or dose of radiation therapy known was 150 Gy in 1 case, Linac 30 times in 1 case and telecobalt therapy in 1 case. The mean latent period was 12.0 years. The tumors developing after radiation therapy were epidermal cyst of chest wall, lymphangioma of vulva, nerve sheath myxoma of chest wall, squamous papilloma of chest wall and adenoma of rectum.

4) Benign tumor or tumorous lesion developing after radiation therapy for benign condition (Table 6)

Two male cases and one female case were found to be in this group. The mean age was 44.7 years. The primary lesion for which radiation therapy had been performed was tenia pedis in 2 cases and papilloma of tongue in 1 case. The method of radiation therapy in two cases was x-ray and isotope, respectively. A mere description of radiation therapy for two years was available for one case. The mean latent period was 27.0 years. The tumors developing after radiation therapy were hyperkeratosis of plantar skin, papilloma of tongue, and pseudocarcinomatous hyperplasia of plantar skin. Although the term 'hyperkeratosis' is a term for pathological findings and not for the diagnosis of a tumor or a tumor-like lesion, this case was listed since it appeared macroscopically as a tumorous

Table 3. Summary of Malignant Tumors after Irradiation for Malignant Tumor (NTTR, 1973~1984)

Primary tumor	Induced tumor	Latent period
Uterine ca.	12 Rectocolonic ca.	6 18.3
Breast ca.	5 Bladder ca.	2 18.5
Epipharyngeal ca.	1 Other ca.	7 11.9
Rectal ca.	1 B. C. C.	2 15.0
	Sarcoma	2 13.5

lesion. The case of papilloma of tongue might possibly be a recurrent case, but this was taken up since the tumor developed in a long-term cure state after radiation therapy.

Table 4. Malignant Tumors after Irradiation for Benign Condition (NTTR, 1973-1984)

Case	Age	Sex	Radiated disease	Radiation therapy	Latent period	Year at diagnosis	Location	Induced tumor
1 F.M.	73	F	Tinea pedis	Ultra soft X-ray (2 or 3 year)	15	1983	Planta	S.C.C.
2 N.T.	57	M	Pustolosis	Ultra soft X-ray	20	1982	Planta	S.C.C.
3 K.K.	44	F	Keratosis	+	20	1984	Palm	S.C.C.
4 O.M.	80	M	Sycosis vulgaris	+	53	1982	Face	S.C.C.
5 O.K.	80	M	Wound after lymphadenectomy	+	50	1982	Neck	Bowen disease

Table 5. Benign Tumors after Irradiation for Malignant Tumor (NTTR, 1973-1984)

Case	Age	Sex	Primary tumor	Radiation therapy	Latent period	Year at diagnosis	Location	Induced tumor
1 U.T.	50	F	Breast ca.	150Gy	5	1976	Chest Wall	Epidermal cyst
2 M.T.	56	F	Uterine ca.	Linac (30 times)	7	1984	Vulva	Lymphangioma
3 Y.K.	44	F	Breast ca.	Tele Co	9	1977	Chest Wall	Nerve sheath myxoma
4 H.S.	73	F	Breast ca.	+	12	1975	Chest Wall	Squamous papilloma
5 U.T.	58	F	Uterine ca.	+	27	1983	Rectum	Adenoma

Table 6. Benign Tumors or Tumor Like Lesions after Irradiation for Benign Condition (NTTR, 1973-1984)

Case	Age	Sex	Radiated disease	Radiation therapy	Latent period	Year at diagnosis	Location	Induced tumor or tumor like lesion
1 S.Y.	42	M	Tinea pedis	X-ray	7-8	1979	Planta	Hyperkeratosis
2 G.C.	28	M	Papilloma, tongue	Isotope	19	1979	Tongue	Papilloma
3 M.T.	64	F	Tinea pedis	+ (2 years)	54	1979	Planta	Pseudocarcinomatous hyperplasia

DISCUSSION

A summary of radiation-induced tumor or tumorous lesion in 32 cases (6 males and 26 females) detected from biopsied and surgical materials is reported (Table 7).

Skin cancer was first noted as the carcinogenesis after radiation therapy. Many cases of skin cancer have been reported developing after radiation therapy for benign lesions such as wart, dermatitis, tenia, hemangioma, tuberculous lymphadenitis, ankylosing spondylitis, etc.¹²⁾⁻¹⁵⁾

SLAUGHTER (1957) reported for the first time nine cases of mucosal carcinomas of hypopharynx, tongue, esophagus, colon, etc.¹⁶⁾ Since 1960's, the diagnostic and therapeutic methods for malignant tumor have advanced and long-survival cases of malignant tumor have increased in number. As a result, the occurrence of a malignant tumor after radiation therapy for a previous malignant tumor has become a matter of interest⁷⁾. Among a number of radiation-induced tumors reported, the major objects of radiation therapy were uterine cancer¹⁷⁾⁻²⁰⁾, breast cancer²¹⁾, laryngeal cancer²²⁾⁻²⁴⁾, bone sarcoma²⁷⁾, etc., and the major induced tumors were leukemia¹⁹⁾⁻²⁵⁾, rectosigmoid cancer⁷⁾⁹⁾²⁰⁾²⁶⁾, bladder cancer¹⁰⁾²⁰⁾, uterine cancer²⁰⁾, soft tissue sarcoma²⁷⁾²⁸⁾, osteosarcoma²⁹⁾, skin cancer³⁰⁾, etc.

Recently, an international collaborative work by 8 countries on second cancer following radiation for cervical cancer was reported²⁰⁾. In Japan, a nation-wide questionnaire survey by TAKAHASHI on 1961-1962 yielded a report "A statistical study on human cancer induced by medical radiation"³¹⁾. In that study, 63 cases were collected as radiation-induced cancer. Of these, 54 cases were skin cancer or neck cancer (including 29 cases of thyroid cancer). Irradiation had been given to about a half of the cases for tuberculous

Table 7. Summary of All Cases (NTTR, 1978-1984)

Radiated condition		Induced tumor	Cases	Male	Female	Latent period
Malignant	—	Malignant	19	1	18	15.0
Benign	—	Malignant	5	3	2	31.6
Malignant	—	Benign	5	0	5	12.0
Benign	—	Benign	3	2	1	27.0
Total			32	6	26	18.3

lymphadenitis and to the remainders for skin disease and goiter. Only two cases (3.7%) occurred after radiation therapy for malignant tumor. Subsequently, "A survey on radiation-induced cancer following radiotherapy in Japan" by K. SAKAI *et al.* on 1978-1979 was reported²⁵⁾. Collected in this report were 150 cases of tumors developing after radiation therapy for benign condition and 140 cases of tumors seen after radiation therapy for malignant tumor. In the latter study, 79 cases were considered to be highly possible radiation-induced tumor, demonstrating an increase of the cases of carcinogenesis by radiation therapy for malignant tumor.

In the present study, induced malignant tumor was detected in 19 cases after radiation therapy for malignant tumor and in 5 cases for benign condition. In contrast to the fact that all the induced malignancy in all the cases in the latter was squamous cell carcinoma or in situ carcinoma, the former group was comprised of 6 cases of colorectal cancer, 2 cases of bladder cancer, 6 cases of other solid cancer, 2 cases of basal cell epithelioma and 2 cases of sarcoma. The 4 cases of rectal cancer³²⁾, 1 case of basal cell epithelioma³⁰⁾, and 1 case of malignant fibrous histiocytoma³³⁾ have already been reported. It is interesting to note that, whereas the induced cancer after radiation therapy for benign condition was squamous cell carcinoma or in situ carcinoma in all the five cases, the induced tumor in both of the two cases after radiation therapy for malignant tumor was basal cell epithelioma³⁰⁾.

The mean latent period for the tumor induced after radiation therapy for malignant tumor was 15.0 years and that for the tumor induced after radiation therapy for benign condition was 31.6 years being approximately twice as long. This was in conformity with the results of other reports²⁷⁾³¹⁾. This seemed due to the difference in quality, method, dose and times of irradiation.

In the present study, cases of benign tumor or tumor-like lesion developing after radiation therapy were also selected in addition to the cases of radiation-induced cancer. Benign tumors developing after radiation therapy have been paid little attention and such reports have been scarce. However, when it is considered that the hyperkeratosis or pseudo-carcinomatous hyperplasia of skin as a precancerous state of skin cancer and that rectal adenoma as a precancerous state of rectal cancer, it may provide good materials for discussion of radiation and carcinogenesis.

Efforts will have to be made using these detected cases and various histopathological methods to study further the relationship between radiation and carcinogenesis and the character of such radiation-induced tumor.

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