Information

Radiation-Induced Cancer in Japan[†]

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1. Introduction

In 1961, the survey was carried out to study the induction of skin or head and neck cancer of patients who received radiation therapy of their benign disease. As the radiotherapy became conventional therapy for the treatment of cancer, it raised the issue of second cancer following the radiation therapy. The Ministry of Welfare, therefore, supported the survey of radiation-induced cancer to send questionnaires to hospitals in Japan in 1977. Surprisingly, the incidence of second cancer

was much higher than we had predicted, and then the second survey was proceed to conducted in 1984. Results of these two surveys were described elsewhere in detail ¹⁾⁻⁴⁾, and their statistical analysis was also presented in the 17th International Congress of Radiology by some of us in 1989.

Now, the induction of secondary cancer after the radiotherapy of malignant tumors have been studied exclusively. It has been common to select the therapeutic method for the treatment of any diseases including cancer. In 1960's, however, there were not many choices for the treatments in Japan, and therefore it was not strange that radiation was applied for the cases who are not applicable now. It was also not unreasonable not to concern of the secondary cancer after the treatment.

As mentioned above, there have been many reports that describe the possibility of secondary cancer after radiation therapy, but

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few works can be found dealing with the survey of this incidence in a big epidemiological scale. In addition, the cases of benign tumor who received radiation therapy have been decreased in the number. From these points, we have decided to summarize our survey here although they were done almost 20 years ago. We believe that this material would issue the warn to induction of secondary cancer following the radiotherapy of benign as well as malignant tumors.

2. Subjects and Analysis

In 1977 a questionnaire was conducted on a total of 672 university and general hospitals in Japan and the responses obtained from 357 hospitals indicated the actual status of radiation therapy in Japan at that time. The

results of this survey are summarized in Tables 1 and 2. The survey was classified into three periods, 1945 - 1955, 1956 - 1965, and 1966 - 1977. Table 1 shows radiation therapy to patients whose underlying disease was benign, while Table 2 shows the same for patients whose underlying disease was malignant. The survey was again performed in 1984 and a questionnaire survey on radiation induced malignant tumors 1977 and 1984 generated responses from 139 and 95 hospitals, respectively.

Exposure to large doses of radiation increases the risk of malignant tumors, but pathohistological or others means can differentiate radiation-induced from other causes of cancer. Therefore, cancer causes can only be evaluated by differences in incidence, and age of onset, as the latent period of

Table 1 Numbers of patients underlying benign disease who received radiation therapy from 1945 to 1977 in Japan

Underlying benign diseases	Period of radiation therapy			
	1945-1955	1956-1965	1966-1977	1945-1977(Total)
Lymphadenitis tuberculosis	1,527	1,271	380	3,178
Skin disease	461	1,486	1,829	3,776
Hemangioma	171	1,875	1,456	3,502
Thyroid disease	800	460	240	1,500
Others	7,350	4,168	2,144	13,662
TOTAL	10,309	9,260	6,049	25,618

Table 2 Numbers of patients underlying malignant tumors who received radiation therapy from 1945 to 1977 in Japan

Underlying malignant tumors	Period of radiation therapy			
	1945-1955	1956-1965	1966-1977	1945-1977(Total)
Uterine cancer	1,140	8,518	39,349	49,007
Breast cancer	1,436	5,553	20,982	27,971
Head & neck cancer	1,846	9,503	37,156	48,505
Others	5,708	17,506	73,191	96,405
TOTAL	10,130	41,080	170,678	221,888

radiation-induced tumors is comparatively short. We then reviewed the registration cards compiled on each occasion. Patients were classified according to sites of irradiation, then the number of tumors and their incidence were computed according to organ and site. From the observed morbidity rate by organ during the same period in the general population of Japan, the predicted values (E) was statistically calculated⁵⁾. When the ratio of the observed values (O) of our survey to the predicted values (E) was greater 3, the tumor was probably a radiation-induced malignant tumor.

3. Results

The application of radiation therapy for benign diseases tended to decrease, whereas that for malignant tumors remarkably increased by over fourfold during each 10-year period (Tables 1 and 2).

2.1 Radiation induced malignant tumors following radiation therapy for benign disease

The number of patients with benign diseases

in whom radiation induced malignant tumors after radiation therapy was 150 in the first survey (1977) and 86 in the second (1984), for a total of 236 (Fig.1).

The underlying diseases treated with radiation therapy were classified by site of radiation into head and neck, trunk, and extremities. Disease of the head and neck are shown in Fig. 2. The underlying disease with the highest frequency in the head and neck was cervical lymphadenitis tuberculosis (125 patients), followed by hemangioma (22) and thyroid disease (20). The most frequent radiation induced malignant tumor was malignant tumor of the pharynx (80 patients), followed by cancer of the larynx (26), malignant tumor of the thyroid gland (22), cancer of the esophagus (219), and skin cancer (21). To determine whether or not the relationship between primary disease treated with radiation therapy and induced malignant tumors, the chi square test was performed. The correlation of underlying benign disease to induced malignant tumor for head and neck disease was highest between cervical

Fig. 1 The number of patients with benign diseases in whom radiation induced malignant tumors after radiation therapy.

Fig. 2 The number of patients with benign diseases in whom radiation induced malignant tumors after radiation therapy in head and neck.

* $p=0.05$ and ** $p=0.01$ by Chi-square-test

Fig. 3 The ratio of the observed values (O) to the predicted values (E) patients with benign diseases in whom radiation induced malignant tumors after radiation therapy in head and neck.

lymphadenitis tuberculosis and tumor of the pharynx (67 patients), followed by cancer of larynx (19) and malignant tumor of the thyroid gland (11). Thyroid diseases and malignant

tumors of the thyroid gland were also correlated (8), as were hemangioma and skin cancer (7), skin disease and skin cancer (8).

The O/E ratio (Fig. 3) was the highest with

Fig. 4 The number of patients with malignant tumors in whom radiation induced secondary malignant tumors after radiation therapy.

cancer of the pharynx(118), followed by cancer of the parotid gland(42), skin cancer (31), cancer of the esophagus(22), malignant tumor of the thyroid gland(21) and cancer of the larynx(16). These ratios were significantly high, indicating radiation induced cancers.

2.2 Secondary malignant tumors following radiation therapy for malignant tumors

Of the 221 888 malignant tumor patients given radiation therapy in the years between 1945 and 1977, the number of reported secondary malignant tumors induced by radiation according to the results of the two surveys conducted in 1977 and 1984 were 140 in 1977 and 108 in 1984 for a total of 248 as shown in Fig. 4.

We could not directly investigated the survival of all of these patients. However, reports from many large hospital indicated the 5-year survival rate of patients with malignant tumors undergoing radiation therapy at the time. The number of patients with secondary malignant tumors from uterine cancer was 106,

that from breast cancer patients was 32, and that from malignant tumors of the head and neck was 80. The total number was 248. Despite the far larger dose of radiation administered to patients with malignant tumors than to those with benign disease, the incidence of secondary malignant tumors was 1/3 of that in the latter, suggesting that the induction cancer with radiation requires an optimal dose.

The irradiated sites were classified into head and neck(Fig. 5), chest(Fig. 6), abdomen(Fig. 7), and entire body including the extremities(Fig. 8). Head and neck cancer(Fig. 5) included malignant tumors of the larynx(21), the oral cavity(16, 0.4%), and of the maxilla(13). When examined according to secondary malignant tumors, the largest number was accounted for 14 of the pharynx, followed by 12 of the maxilla, 11 of the larynx and 8 of the tongues among malignant tumors of the oral cavity(19 cases). The correlation between primary malignant to induced tumors was highest between oral cavity - oral cavity (13)larynx - larynx(8), larynx - pharynx(7)

Fig.5 The number of patients with malignant tumors in whom radiation induced secondary malignant tumors after radiation therapy in head and neck.

*p = 0.05 and **p = 0.01 by Chi-square-test

Fig.6 The number of patients with malignant tumors in whom radiation induced secondary malignant tumors after radiation therapy in chest.

and maxilla - maxilla (6).

Breast cancer was the most frequent malignancy of the chest (Fig.6), followed by

lung cancer (8). Of the induced malignant tumors, cancer of the esophagus was the most predominant (11), followed by soft tissue

Fig.7 The number of patients with malignant tumors in whom radiation induced secondary malignant tumors after radiation therapy in abdomen.

Fig.8 The number of patients with malignant tumors in whom radiation induced secondary malignant tumors after radiation therapy (irradiated sites).

tumors(9). The correlation between primary malignant and induced tumors was highest between breast cancer and soft tissue tumors

(9), skin cancer(7) and cancer of the esophagus(6).

Figure 7 shows that cancer of the uterine

Fig. 9 The ratio of the observed values (O) to the predicted values (E) patients with malignant tumors in whom radiation induced secondary malignant tumors after radiation therapy.

cervix accounted for the largest number of abdominal malignancies with 97 patient, followed by cancer of the uterine body (9) and of the external genitalia (skin 6). Among induced malignancies, soft tissue tumors predominated (28), followed by cancer of the rectum (17), leukemia (16), cancer of the uterine cervix (14), cancer of the external genitalia (skin, 9) and cancer of the uterine body (8). With respect to correlations between primary cancer and secondary malignant tumors, that of uterine cancer to soft tissue tumor accounted predominated (26), followed by that to cancer of the rectum (13), to vaginal cancer (8) and that to cancer of the external genitalia (skin, 7).

Tumors involving all sites of body included soft tissue and skin tumors as well as leukemia. These are summarized in Fig. 8. Tumors of the extremities were very rare. Bone sarcoma and soft tissues tumors were listed, but as the

number was small, we excluded them from this study. Soft tissue tumors accounted for the largest number 41, among which 28 were located in the abdomen and 28 were leukemia, mostly located in the abdomen. Skin cancers were largely located in the abdominal region with the majority developing in the external genitalia (scrotum, vulva, etc.) and their periphery.

The O/E ratio was also calculated in secondary malignant tumors caused by radiation therapy to primary tumors (Fig. 9). Among malignancies of the head and neck, the highest O/E ratio was in cancer of the pharynx 9.5, followed by the cancer of the tongue 5.4 and soft tissue tumors 4.8. In the chest, the ratio to soft tissue tumors was 15.5 and that of skin cancer 5.1. In the abdomen, the ratio was highest in vaginal cancer 30.3, followed by soft tissue tumors 28.6 and skin cancer 3.5 in that order. The ratio of cancer of the rectum was 1.1,

and that of bladder cancer was 1.2, both showing no significant difference.

3. Conclusion

Until about 1965, radiation therapy was extensively administered even to benign diseases, but thereafter, the frequency suddenly decreased. It was most frequently applied to patients with tuberculosis and was often applied to those with skin diseases and hemangioma. Malignant tumors developed in 3.93% of patients with tuberculosis following radiation therapy. Tuberculosis was followed by skin disease, thyroid disease, and hemangioma. The most frequent were malignant tumors of the pharynx, followed by those of the larynx, esophagus and thyroid gland.

The use of radiation therapy of malignant tumors has remarkably increased over the years and despite the increased irradiation dose, the incidence of induced secondary malignant cancers has not significantly increased. Changes have developed in the use of radiation for primary diseases, namely, orthovoltage radiation or the use of small shield sources or radioisotopes for benign diseases and mostly supervoltage radiation for primary malignant tumors.

Of the primary malignant tumors treated by radiation, uterine cancer was the most frequent followed by breast cancer. Various organs were involved in malignant tumors of the head and neck. Among the secondary malignant tumors considered to be induced by radiation, those developing from uterine cancer were the most frequent, followed by cancers of the breast, larynx, and pharynx. Among secondary malignant tumors, soft tissue tumor were the most frequent, followed by leukemia,

skin cancer, tumor of the oral cavity, cancer of the rectum and of the pharynx.

The incidence was remarkably higher when compared with the predicted cancer incidence among Japanese. The tumors of which the incidence was significantly elevated were those of soft tissue and skin cancer, but leukemia did not significantly differ. In the head and neck region, many organs are located adjacent to each other. Induced cancers showing a significant increase in frequency were those of the pharynx, tongue, maxilla, and larynx.

In conclusion, our survey indicated that radiation therapy to benign tumor should be considered very carefully and that radiation to malignant tumors should be well managed by taking of tumor sites, age of patients, and radiation dose into the count.

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