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MALIGNANT NEOPLASMS AMONG ATOMIC BOMB SURVIVORS FOLLOWING RADIATION THERAPY

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Follow-up observations of the Hiroshima and Nagasaki atomic bomb (A-bomb) survivors have provided a major share of the knowledge of the effects of radiation exposure in man. Exposure of survivors to ionizing radiation from other sources, however, such as from diagnostic and therapeutic radiology, is a potential source of bias in the investigations of radiation effects attributable to the A-bombs.

A previous report described members of a large, fixed cohort of A-bomb survivors who received radiation therapy for a variety of benign and malignant conditions. Several cases of malignant neoplasms which subsequently developed in or near treatment fields were documented. The current status of this group is now described, together with new cases in which malignancies which occurred may have been related to previous radiation therapy.

Materials and Methods

The focus of the present investigation was the Radiation Effects Research Foundation (RERF) Adult Health Study (AHS), a fixed sample of the Hiroshima and Nagasaki populations, originally numbering 20000 subjects (BELSKY et coll. 1973). The AHS, jointly sponsored by the United States and Japanese governments, is a long-term clinical investigation for detecting late effects of the A-bombs, whose participants are provided complete physical examinations and laboratory tests biennially. Postero-anterior stereoscopic and lateral chest

films are included; other radiography and fluoroscopy are performed as clinically indicated.

At the time of these examinations all subjects are routinely interviewed to determine whether they received any diagnostic or therapeutic radiologic exposures, and the times and locations thereof. All hospitals at which subjects reported receiving radiation therapy were visited, and their records reviewed to confirm the reported exposures. The technical data were recorded on forms, and included numbers of courses and daily treatments, doses incurred, types of radiation source used, locations and sizes of fields employed, and the diagnosis for which treatment was administered. The radiation output of each therapy unit was measured using a Victoreen Condenser R-meter (Model 570) and ionization chambers of appropriate capacities.

The RERF medical records of all confirmed radiation therapy cases, including those previously reported (RUSSELL & ANTOKU 1976) were reviewed. The information sought included clinical diagnoses, particularly those of malignancy, information on radiation sequelae, dates and causes of deaths, and autopsy information.

Results

Review of the medical records of 72 Hiroshima and 20 Nagasaki AHS participants who reported having received radiation therapy from 1970 through 1979 revealed 41 Hiroshima and 14 Nagasaki sub-

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Table 1*Radiation therapy reported and confirmed by city*

	Hiroshima			Nagasaki		
	Survey		Total	Survey		Total
	First	Second		First	Second	
Subjects surveyed*						
Inside city**	329	67	396	66	20	86
Outside city	25		25	6		6
Subtotal	354	67	421	72	20	92
Actual number of subjects	323	66	389	69	20	89
Subjects excluded	98	6	104	41	2	43
Total	452	73	525	113	22	135

* Some subjects reported radiation therapy at more than one hospital.

** One Hiroshima hospital bordering the city was included.

Table 2*Distribution of confirmed subjects by city and sex*

Sex	Hiroshima			Nagasaki			Total
	Survey		Total	Survey		Total	
	First	Second		First	Second		
Male	21	7	28	10	4	14	42
Female	81	34	115	23	10	33	148
Total	102	41	143	33	14	47	190

jects. The data thus obtained were pooled with those of the previous investigation of radiation therapy exposures received by AHS subjects before 1970 (RUSSELL & ANTOKU).

The distribution of subjects who reported receiving radiation therapy is shown in Table 1. For the 525 Hiroshima and 135 Nagasaki subjects reporting such exposures, 421 and 92 follow-up examinations were made, respectively. Some subjects reported receiving therapy at more than one institution. No survey was made of 104 Hiroshima and 43 Nagasaki cases, most frequently because the institutions reported to be responsible were not clearly identified by the subjects. Radiation therapy was confirmed for 190 patients including 42 males and 148 females, and of the total, 143 were in Hiroshima (Table 2).

The conditions for which subjects were treated are given in Table 3. The majority of treatments was for malignant disease, but a substantial portion

(35%) was for various benign conditions, the most frequent being eczema (48%). Proportionally, more benign conditions were treated in Nagasaki (44%) than in Hiroshima (31%). Among malignant diseases, the most frequently treated were uterine corpus and cervix carcinoma (32%), followed by carcinoma of the breast (27%). These frequencies reflect the greater number of females in the AHS sample, the female : male ratio being approximately 3 : 2. Radiation therapy for gastric carcinoma was relatively infrequent among AHS subjects, accounting for only 9 (7%) cases in the malignant disease group. No radiation therapy was administered for lung or gastric carcinoma in Nagasaki.

Among the patients reviewed who received radiation therapy before 1970, 7 cases of malignancies possibly related to previous radiation therapy were found. In 4 of these, a second primary malignancy developed following radiation therapy for a first pri-

Table 3*Diseases for which radiation therapy was administered by city*

Disease	Hiroshima	Nagasaki	Total
Malignant			
Uterine corpus and cervix carcinoma	39	3	42
Breast carcinoma	26	9	35
Thyroid carcinoma	6	6	12
Lung carcinoma	9	—	9
Stomach carcinoma	9	—	9
Others	11	12	23
Subtotal	100	30	130
Benign			
Eczema	21	12	33
Keloid	2	3	5
Tuberculosis	4	1	5
Others	18	8	26
Subtotal	45	24	69
Total	145	54	199

mary. In 3 cases a malignancy developed following radiation therapy for a benign condition. These 7 cases are summarized in Table 4.

In addition a case in which a probably benign ovarian tumour occurred following radiation therapy was encountered. In 1963, a Nagasaki female, at age 60, received 5 160 R (approximately 49 Gy) ⁶⁰Co teletherapy to the lower abdomen and pelvis for invasive squamous carcinoma of the cervix. In 1977, a mucinous cystadenoma of the ovary, probably benign, was resected. Follow-up examination in 1977 revealed no evidence of residual tumour. The scatter dose to the ovaries was estimated to have been 63 Gy. Her A-bomb dose is unknown (MF No. 007753).

Discussion

The present results strengthen the previous conclusion that exposure to therapeutic irradiation must

Table 4*Malignancies associated with previous radiation therapy*

Case No.	Sex	Age ATB* (years)	Age at time of initial radiation therapy (years)	A-bomb dose (Gy)	Diagnosis	Sites treated	Total dose or exposure	Post-irradiation neoplasm	Age at diagnosis of post-irradiation neoplasm	Latent period (years)
1	M	39	58	3.11	Retro-peritoneal tumour	Abdomen	49.4 Gy	Squamous carcinoma	65	7
2	F	16	36	0	Cervical carcinoma	Pelvis	70.0 Gy	Malignant fibrous histiocytoma	47	11
3	F	42	60	0	Gastric ulcer	Abdomen	1 320 R (approx. 12.5 Gy)	Carcinoma	73	13
4	F	39	60	0.69	Cervical carcinoma	Abdomen and pelvis	4 800 R (approx. 45.6 Gy)	Squamous carcinoma	66	6
5	M	53	66	0.05	Carcinoid	Abdomen	2 160 R (approx. 20.5 Gy)	Carcinoma	84	18
6	M	42	65	Unexposed	Eczema	Hip	450 R (approx. 4.3 Gy)	Transitional cell carcinoma	69	4
7	M	29	45-53	0	Tinea pedis	Foot	Unknown (multiple courses, low voltage roentgen rays)	Squamous carcinoma	61	8-16

* ATB—At the times of the A-bombs.

Cases 1 to 7: MF Nos 001460, 082364, 226225, 294149, 430952, 853670, 202287.

be taken into account when assessing the effects of radiation received from A-bomb exposures. Previously (RUSSELL & ANTOKU), 5 cases of malignancies occurred in members of the AHS sample who had received radiation therapy, and which were thought possibly to have been related to the radiation therapy. Two of those cases, both women who developed acute granulocytic leukemia following irradiation for breast carcinoma, have recently been reported in more detail. In the present series, 8 instances of neoplasms which developed in or near a field of previous radiation therapy have been described. Although it is not possible to state with certainty the cause of any individual neoplasm in this group, in reports of neoplasms developing in the fixed samples of A-bomb survivors at RERF, knowledge of previous radiation therapy may influence the assignment of affected cases to exposure categories. In Case 2, for example, a malignant fibrous histiocytoma was diagnosed 11 years following 70 Gy ^{60}Co teletherapy to the pelvis for carcinoma of the cervix. This sarcoma occurred in the irradiated area. Although the A-bomb dose in this instance was 0 Gy, obviously, it would seem improper to assign this case to the 0 Gy or control group in an analysis of sarcomas—which might otherwise occur if the history of previous radiation therapy was not known. This problem would not arise in an analysis of carcinomas of the cervix, however, since in this instance (Case 2) the neoplasm occurred before the administration of the radiation therapy. This unusual case of a postirradiation malignant fibrous histiocytoma was reported in detail by PINKSTON & SEKINE (1980).

The 5 previously reported cases and the present 7 cases bring to 12 the total number of malignancies possibly related to previous radiation therapy which have developed in AHS subjects. Since the AHS sample constitutes only about 20 per cent of the much larger Life Span Study (LSS) extended sample (BEEBE & USAGAWA 1968), the number of neoplasms which may be related to previous radiation therapy and which are occurring in members of the LSS extended sample is probably substantial. This is especially important because dose estimates have been made for most of its members, and since the LSS extended sample is a commonly used source for assessing dose-related radiation effects. In any investigation seeking to relate ionizing radiation effects to doses received from the A-bombs, radiation for medical reasons, particularly

that resulting in relatively high doses, such as in radiation therapy, must be properly accounted for. The extent to which diagnostic roentgen ray exposure may pose a similar problem is a subject now under active investigation (RUSSELL 1975).

During the present investigation, several trends were observed reflecting the general progress made in radiation therapy during recent years. Megavoltage beams have to a greater extent replaced medium voltage roentgen ray sources for treatment of deep-seated tumours. Doses have generally been more accurately measured and recorded as absorbed dose (rad, later Gy), and the fields employed have been more clearly delineated. This no doubt reflects the institution of procedures by the Japanese Association of Radiological Physicists. The ratio of malignant to benign diseases treated by irradiation continues to increase as the indications for radiation therapy for benign disease proportionately decreases.

The present results have important implications for the epidemiology of malignant tumours. Of 190 subjects who received radiation therapy 12 (6.3%) subsequently developed malignancies which might have been related to the therapy. Sixty-nine (35%) were treated for benign conditions. It is remarkable that radiation therapy has even in recent years been advocated in the treatment of benign diseases (DEWING 1965). Several previous long-term series of persons exposed to therapeutic irradiation for benign and malignant conditions have shown an increased incidence of various malignancies. HEMPELMANN *et coll.* (1975) noted increased incidences of benign and malignant tumours in a group of persons irradiated in infancy for thymus enlargement compared with unirradiated siblings. COURT-BROWN & DOLL (1965), noted increased incidences of leukemia and solid tumours in persons irradiated for ankylosing spondylitis. Present knowledge concerning the radiation induction of malignancies in man has recently been summarized (UNSCEAR 1977).

The role of radiation therapy in the treatment of malignant disease continues to increase with improved techniques and greater versatility of the various modalities used. For patients with some types of malignancies, cure is now the rule rather than the exception, and for those not cured, survival is often measured in years. These trends will undoubtedly continue as diagnosis and treatment steadily improve. The long-term adverse effects of treatment, including radiation carcinogenesis, are likely to in-

crease. Arguments for and against the documentation of medical radiation exposures have been reviewed, and such documentation advocated (EASON & BROOKS 1972). Continuing efforts must be exerted to document such exposure among A-bomb survivors, so that any effects attributable to atomic irradiation will not be unduly biased. In addition, in epidemiologic investigations on malignant tumours, recognition that these trends must be taken into account is to be emphasized.

SUMMARY

A second follow-up survey for radiation therapy exposure among a fixed cohort of A-bomb survivors originally numbering 20000 persons identified 55 more who had received radiation therapy, and 7 more therapy-associated malignancies. In the previous and present investigations, 12 postirradiation malignancies were identified among 190 cohort members (6%) who received radiation therapy. This investigation underscored the necessity for documenting exposures to ionizing radiation for medical reasons, especially exposures incurring relatively high doses, among persons at relatively high risk of developing neoplasms, such as A-bomb survivors, and in malignancy epidemiology to exclude bias in estimates of risk.

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