Radiation-Induced Well-Differentiated Thyroid Cancer: Disease Characteristics and Survival

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ABSTRACT: **Background:** Radiation exposure is a well-known risk factor for well-differentiated thyroid cancer (WDTC). However, disease characteristics, optimal treatment, time from exposure to disease appearance, and the effect of age at initial exposure on the outcome have yet to be determined.

Objectives: To identify the characteristics of radiation-induced thyroid carcinoma.

Methods: We retrieved the charts of all patients previously exposed to radiation who were diagnosed with WDTC between the years 1985 and 2013 in a tertiary referral center.

Results: Forty-four patients were reviewed. Median time from radiation exposure to diagnosis was 23 years. These patients had higher rates of aerodigestive symptoms and distant metastases on presentation than seen in non-radiated patients. Patients who were exposed to radiation before age 15 years tended to develop the disease at a younger age but had a longer latency period (34.7 ± 15.3 vs. 16.3 ± 10 years, $P < 0.001$) and none had significantly higher rates of vocal cord palsy, hoarseness on presentation, or aggressive variants on histology compared to patients exposed to radiation at an older age. Disease-specific survival (DSS) was the same for both groups and were similar to that seen in the general population (95% 20 year DSS).

Conclusions: Radiation-induced thyroid cancer has a more aggressive presentation and the age at exposure affects the presentation of disease. Nonetheless, appropriate treatment leads to a favorable prognosis.

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According to the National Cancer Institutes SEER* database, the incidence of thyroid cancer increased from 3.6/100,000 in 1973 to 8.7/100,000 in 2002. Research suggests that this finding reflects better medical surveillance, made possible by technological advances and earlier detection of small lesions [1,2]. Alternatively, it may represent a true rise in the occurrence of thyroid cancer, which is partly attributable to the growing exposure of the population to ionizing radiation, a well-known risk factor of thyroid cancer [3], from both medical and non-medical sources. Although radiation is no longer used in the treatment of benign conditions of the head and neck, such as tinea capitis, recurrent tonsillitis or hemangiomas, its diagnostic and therapeutic use in patients with malignancies is steadily increasing, along with dental diagnostic imaging, computed tomography and fluoroscopy [4,5]. The dose of radiation given during childhood to treat tinea capitis is believed to be 3.5–4.0 Gy; the average radiation dose absorbed in the thyroid area is 0.065 Gy [6]. The estimated relative risk of acquiring thyroid cancer is 15–53 times higher in the irradiated than the non-irradiated population, and it remains elevated even 30 years after exposure [7]. The sensitivity of the thyroid gland to the carcinogenic effect of ionizing radiation is highest in children; it diminishes with age but is never eliminated completely [8].

Radiation-induced thyroid carcinomas have been associated with the frequent occurrence of chromosomal rearrangements, such as RET/PTC [9,10]. However, it is still not clear whether radiation-induced thyroid carcinoma exhibits the same clinical behavior as sporadic thyroid carcinoma. While some authors reported a link between a history of radiation to the head and neck and a less favorable pathologic and clinical outcome [11], others did not support these findings [12]. The disease behavior has important implications for the type and aggressiveness of treatment needed, in terms of the extent of surgery and administration of radioactive iodine (RAI) and external beam radiation [13-15].

The aim of the present study was to identify characteristics distinguishing radiation-induced from de novo thyroid carcinoma and to evaluate the natural history of the disease.

PATIENTS AND METHODS

The study was approved by the institutional ethics committee. The study group included 44 patients with well-differentiated thyroid carcinoma (WDTC) and documented exposure to external ionizing radiation, who were diagnosed, treated

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and followed at Rabin Medical Center, a tertiary university-affiliated medical center, from 1985 to 2013. The individual medical records were reviewed for patients' age and gender, source of ionizing radiation, presenting symptoms, histologic diagnosis, treatment modalities, recurrence and survival. Persistence of disease was defined as biochemical (stimulated Tg > 2 ng) or structural (scintigraphic and/or radiographic with positive cytology) 1 year after primary treatment. Recurrence was defined by biochemical or structural evidence of disease detected after a minimum period of 1 year with no disease.

Data were analyzed with SPSS version 17.0. Survival was calculated with the Kaplan-Meier product limit estimate method. Variables were compared between groups by Fisher's exact test. A P value < 0.05 was considered statistically significant.

RESULTS

Patients' demographic and clinical data are presented in Table 1. The present study included 30 females (68%) and 14 males. Mean age at exposure to radiation was 16.8 years (1–60 years) and mean age at diagnosis of WDTC 46 years (14–76 years). Mean time from radiation exposure to diagnosis was 28 years and median 23 years (2–71 years). Twenty-nine patients (66%) were treated with radiation during childhood for benign conditions of the head and neck such as tinea capitis or recurrent tonsillitis, 7 (16%) were irradiated as part of an oncological treatment protocol, and 8 (18%) were residents of Chernobyl, Ukraine, during the nuclear power plant disaster in 1986. Since most of the patients did not have cancer, the actual amount of radiation exposure was difficult to estimate.

Table 1. Characteristics and prognosis of patients with radiation-induced thyroid carcinoma compared to a previous cohort at our center

Characteristic	Radiation-induced thyroid carcinoma
Age at diagnosis (yr), mean	46
No. of females, n (%)	30 (68)
Presenting symptoms, n (%)	
Central neck mass	22 (50)
Distant metastases	8 (18)
Aerodigestive symptoms	7 (16)
Treatment	
Total thyroidectomy, n (%)	44 (100)
Hemithyroidectomy, n (%)	0
Lateral & central neck dissection, n (%)	20 (45)
Central neck dissection, n (%)	4 (9)
RAI, n (%)	40 (91)
EBRT, n (%)	11 (25)
Prognosis	
Overall survival,%	83
Recurrence/persistence rate,%	34

RAI = radioactive iodine, EBRT = external beam radiotherapy

PRESENTING SYMPTOMS

Twenty-two patients (50%) presented with a central neck mass, 4 (9%) with a lateral neck mass, 4 (9%) with hoarseness or vocal cord paralysis, 2 (4%) with dysphagia, and 1 patient with hemoptysis; the remaining 11 patients (25%) were diagnosed incidentally. Eight patients (18%) had distant metastases diagnosed during the first year after surgery, mostly to the lungs.

SURGICAL PROCEDURES

All patients underwent total thyroidectomy. Twenty patients (45%) had lateral and central neck dissection with the primary procedure, 5 (11%) had a hemithyroidectomy followed by completion thyroidectomy, and 4 (9%) had level 6 neck dissection along with total thyroidectomy. None of the patients underwent hemithyroidectomy alone.

HISTOLOGY

On pathology, 28 patients (62%) had classic papillary thyroid carcinoma (PTC); 9 (20%) had PTC-follicular variant; and the remainder had insular thyroid carcinoma, columnar variant and tall cell variant. Average nodule size was 16 mm. Thirty-three patients (75%) had multiple foci of tumor, and 5 (11%) had lymphocytic infiltrates in the thyroid gland. Extrathyroid extension was detected in 52% of patients: trachea in 7 (16%), larynx in 1 (2%), esophagus in 2 (4%), and recurrent laryngeal nerve in 3 (6%). Thirty-two percent had an extension to fat and muscle tissue adjacent to the thyroid gland. Eighteen patients (40%) had positive regional lymph nodes.

POSTOPERATIVE TREATMENT

Whole-body scan was performed in all patients. Residual thyroid tissue was found in 40 patients (89%), all of whom were treated with radioiodine ablation at a dose of 100–200 mCi. The median total dose was 175 mCi. The median number of treatments per patient was 1, and the mean number of treatments 1.9. In 25% of patients, postoperative treatment included external beam radiation. Indications for external beam radiation were aggressive variant and significant extrathyroidal extension.

FOLLOW-UP

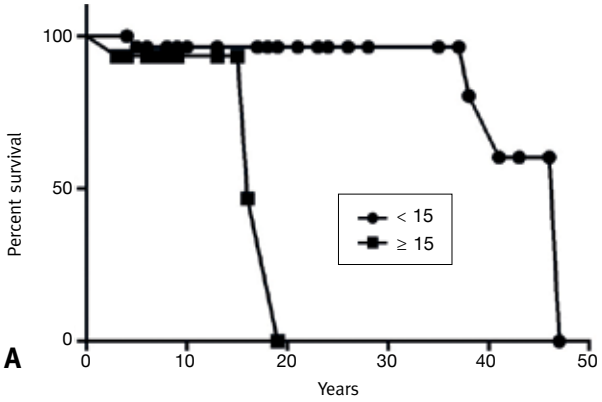
Mean duration of follow-up was 17.4 years (median 14 years, range 3–47). Follow-up consisted of clinical examination in all patients, neck sonogram in 40 patients (91%), and measurement of blood levels of thyroglobulin and thyroglobulin antibodies in 41 patients (93%). Fifteen patients (34%) had recurrent/persistent disease: in the lateral neck in 73%, distant metastases in 45%, and in the gland bed in 2% (percentage exceeds 100% due to the presence of disease at multiple sites). Forty-two percent of the patients required more than one treatment with radioiodine, 11% required repeated surgery, and 5% required another course of radiotherapy, all due to recurrence of disease or elevated thyroglobulin levels.

Overall survival was 39.4 years. The 20 year disease-specific survival was 95%. Two patients died of the disease: one after 5 years due to metastases to the brain and the other after 16 years due to metastases to the lungs.

AGE AT EXPOSURE

In order to evaluate the effect of age at exposure to radiation on outcome, we compared patients who were exposed to radiation from birth until the age of 15 years to patients who were exposed at an older age [Figure 1]. Twenty-nine patients were exposed when they were less than 15 years old and 15 were exposed later in life. Patients who were exposed to radiation before the age of 15 developed thyroid carcinoma on average 11 years earlier as compared to patients who were exposed at an older age (P = 0.016). The mean age at diagnosis was 42 ± 15.3 years in the first group and 53.7 ± 13.3 years in the other. However, a longer latency period was observed in patients exposed at a younger age (34.7 ± 15.3 vs. 16.3 ± 10 years, $P < 0.001$).

Figure 1. [A] Overall survival for patients grouped according to age of radiation exposure. Patients exposed before the age of 15 had an overall survival of 42.8 vs. 16.5 years for patients exposed at an older age (P = 0.04)



[B] Disease-specific survival was 44.5 years in patients exposed before the age of 15 compared to 17.5 years in patients exposed at an older age (P = 0.25). Data were influenced by the significant difference in age of diagnosis

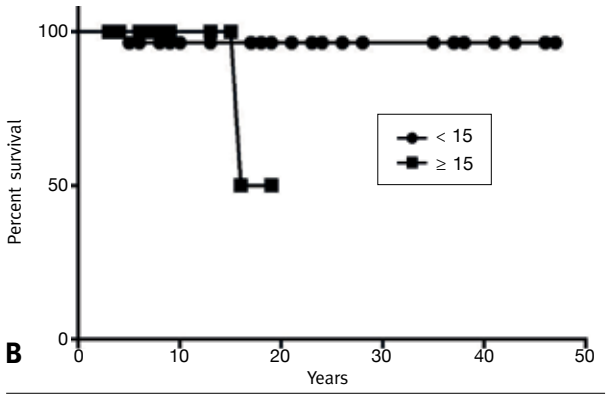


Table 2. Characteristics and prognosis of patients grouped according to age at radiation exposure

Patient exposure to radiation	Before age 15	After age 15	*P* value
No. (n)	29	15	
Age at diagnosis (years)	42 ± 15.3	53.7 ± 13.3	0.016
Time to diagnosis (years)	34.7 ± 15.3	16.3 ± 10	< 0.001
Vocal cord paralysis as a presenting symptom, n (%)	3 (10)	1 (6)	1
Aggressive variants on histology, n (%)	5 (17)	2 (13)	1
Recurrent/persistent disease, n (%)	10 (34)	5 (33)	1

Patients who were exposed to radiation at a younger age developed cancer 11 years before those who were exposed to radiation after age 15

Regarding disease characteristics, the earlier age group had more aggressive disease: of the four patients who presented with vocal cord paralysis, three were exposed to radiation before age 15. Seven patients had aggressive variants on histology, five in the group exposed before the age of 15 and two in the older group. Ten of the 15 patients who had recurrent/persistent disease were exposed before the age of 15. Clinical and demographic data comparing the two groups are summarized in Table 2. The 20 year disease-specific survival was 95% for the two groups.

DISCUSSION

Our study describes patient and tumor characteristics, natural history of the tumor, and treatment outcome in patients with WDTC and a history of radiation exposure. Our results suggest that radiation exposure leads to more extensive disease. Patients who were exposed at a younger age seem to be more affected than patients exposed during adulthood. Nevertheless, there was no difference in survival of both groups.

We compared our cohort to a previous study conducted in our center by Segal and co-authors [16] which included 728 patients with WDTC from the general population who were diagnosed, treated and followed from 1954 to 1994. Despite the different years of treatment and diagnosis and the possibility of bias due to the retrospective nature of both studies, we believed the findings could provide perspective on the presentation and characteristics of radiation-induced thyroid cancer.

The cohort in both groups was characterized by a female predominance and mean age in the mid-fourth decade. Despite the similar demographics, however, analysis of the clinical disease parameters yielded a significantly higher rate of aerodigestive symptoms, such as dysphagia, dyspnea and hemoptysis (15% vs. 4%, P = 0.009, Fisher's exact test) and distant metastasis (18% vs. 3%, $P < 0.001$, Fisher's exact test) in irradiated patients.

Accordingly, all our patients underwent total thyroidectomy and nearly half required lateral neck dissection, whereas the corresponding rates in the group studied by Segal et al. [16] were 80% and 20% respectively. Together, these results suggest that thyroid cancer may be more aggressive in patients with a history of radiation exposure. Variability in treatment of thyroid cancer was assessed by Hilly et al. [17] and wide differences in treatment recommendations of treating physicians were reported. Accordingly, our results could be biased by the physicians' tendency towards more extensive surgery in post-irradiated patients.

Histopathologically, rates of PTC and multiple foci of disease were similar in both cohorts. The rate of follicular variant of PTC was considerably lower in Segal's group, with a high rate of follicular carcinoma, apparently because their analysis was performed before the follicular variant of PTC became widely recognized [18].

It is also noteworthy that in our study, over a third of irradiated patients had extra-thyroidal extension, including muscular, tracheal, laryngeal and esophageal involvement. Another study from our medical center that included 1200 patients with WDTC reported only a 5% rate of extra-thyroidal involvement in patients in the general population [19]. Most of these patients had a diagnosis of PTC and demonstrated a more aggressive form of the disease. The higher rates of extra-thyroidal involvement in irradiated patients correlate with the higher rates of aerodigestive symptoms and indicate a more aggressive disease than sporadic PTC.

Postoperative therapy consisted of radioiodine ablation in nearly all irradiated patients but was less indicated in Segal's group. RAI treatment is believed to be beneficial in terms of recurrence and survival in high risk patients. This might explain the high rate of ablation treatments in our cohort. Until recently this procedure required thyroid hormone withdrawal for 3–4 weeks, resulting in hypothyroidism in some patients; however, use of recombinant human thyroid-stimulating hormone (rhTSH) injections prior to the ablation prevents hypothyroidism, has a good outcome, and can be applied in high risk patients who need RAI treatment [19].

External beam radiation was administered in 27% of irradiated patients and only 7% of cases in the Segal cohort. In the past, external beam radiation was not included in the therapeutic protocol of WDTC on the assumption that the tumors were a consequence of radiation exposure and that treating them with radiation would aggravate the disease. Today, radiation is indicated for aggressive variants of WDTC and positive margins, although reports of its effectiveness are conflicting. Nonetheless, we do irradiate some patients with thyroid cancer.

Recurrence rates were higher in our group than in the other cohort group (24% vs. 17%), also suggesting a more aggressive form of disease. Nevertheless, overall survival in both irradiated and control group patients was high (83%) and 20 year disease-specific survival was 95%. Samaan et al. [21] reported an equally good overall survival in their comparison of thyroid carcinoma in patients who did or did not experience head and neck irradiation in childhood.

Regarding the time and radiation dose that causes the disease, Greenspan [22] reported a positive correlation between the incidence of thyroid cancer and the radiation dose to the thyroid gland from 6.5 to 1500 rads, and also stated that the peak occurrence of thyroid tumors occurs between 5 and 30 years after exposure to radiation. We found that the mean time from radiation exposure to diagnosis was 28 years (median 23 years), but since most of the patients did not have cancer the actual dose of radiation exposure for the whole cohort was difficult to estimate. The sensitivity of the thyroid gland to the carcinogenic effect of ionizing radiation is highest in children [8,23]. Our results demonstrate higher rates of extension of disease to the trachea, larynx and esophagus along with higher rates of aggressive variants of WDTC in patients exposed to radiation before the age of 15. This might suggest that exposure during childhood years is associated with a shorter latency and a disease with more aggressive features. However, survival does not seem to be affected by these findings.

CONCLUSIONS

This review of our experience with WDTC shows that a history of exposure to radiation leads to more extensive disease compared to sporadic thyroid carcinoma. Age of exposure affects disease onset: people who were exposed at a younger age presented with WDTC earlier than others. However, appropriate treatment results in a good overall survival, disease-specific survival and prognosis similar to that in non-irradiated patients. Nonetheless, the presence of more extensive disease requires closer follow-up to detect recurrence in affected patients.

In general, radiation is a double-edged sword: its high therapeutic impact is associated with major short and long-term adverse effects. Thus, when planning a radiation protocol, great care must be taken to protect the thyroid gland. The importance of minimizing the amount of radiation to the thyroid tissue should be emphasized. Future genetic and biomolecular studies are needed to better define the unique characteristics of radiation-induced thyroid cancer and to develop individually targeted treatment approaches.

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