Influence of Previous Radiation Exposure on Pathologic Features and Clinical Outcome in Patients With Thyroid Cancer

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Objective: To determine whether previous radiation exposure to the head and neck is related to less favorable pathologic and clinical outcome in patients after surgical management of thyroid cancer.

Design: Retrospective chart review.

Setting: Academic teaching hospital (referral center).

Patients: All patients with diagnosed thyroid cancer who had been exposed to radiation before surgical treatment were retrospectively identified from the thyroid cancer database at our institution (1963-2007). One hundred twenty-five patients (95 women and 30 men) were included. Inclusion criteria included surgical treatment for thyroid cancer and a history of exposure to radiation at least 3 years before diagnosis of the disease.

Main Outcome Measures: Pathologic features and data related to disease recurrence, distant metastasis, and survival.

Results: Mean (range) age at first exposure to radiation was 19.4 (1-65) years, and mean lag time to diagnosis of disease was 28.7 (3-60) years. Patients were treated surgically with either total or near-total thyroidectomy (83%) or partial or subtotal thyroidectomy (17%). Pathologic diagnoses included 111 papillary carcinomas (89%). Sixty-three percent of patients had multifocal disease, 12% had lymphovascular tumor invasion, and 26% had direct extrathyroid extension of disease. Twenty-five percent of patients had metastases to cervical lymph nodes, and 9% had distant metastases. Sixteen percent of patients experienced local recurrence of disease. At last follow-up, 86% of patients were alive and free of disease, 8% were alive with disease, 4% had died of thyroid cancer, and 2% had died of an unrelated cause. Compared with other patients with thyroid cancer, this radiation-exposed cohort was more likely to undergo total thyroidectomy, multiple operative procedures, and external radiotherapy. A higher percentage had multifocal disease, extrathyroid extension, stage IV disease, and distant metastases. At follow-up, fewer patients were free of disease, and more patients had died of thyroid disease.

Conclusion: Patients who have been exposed to radiation have more aggressive disease and worse clinical outcome compared with other patients with thyroid cancer.


HYPOID CANCER IS ONE OF the well-known malignant neoplasms associated with radiation exposure. It often induces characteristic histologic changes in thyroid tissue, and it is a well-established risk factor for both benign and malignant thyroid tumors. This is supported by epidemiologic studies in atomic bomb survivors and in children living in contaminated areas around Chernobyl, Ukraine, after the 1986 nuclear reactor accident. Studies in patients who received therapy because of external radiation also support the causative role of irradiation in the development of thyroid cancers; in Canada, benign childhood diseases of the head and neck were treated with external radiotherapy from the 1930s to the 1960s. The objective of this study was to determine whether patients with previous radiation exposure have thyroid cancer with more aggressive pathologic features and clinical behavior, and ultimately a worse clinical outcome, compared with patients with thyroid cancer without a history of radiation exposure.

METHODS

A retrospective medical record review of the thyroid carcinoma database at Mount Sinai Hospital, Toronto, Ontario, Canada (1963-2007) was undertaken to identify all surgical patients who had a history of exposure to radiation. Patients considered positive for a history of radiation exposure included those who at least 3 years before diagnosis of thyroid cancer had received direct external radiation to the head and neck for therapeutic purposes (eg, treatment of acne), direct external radiation to another body site (eg, treatment of breast cancer), occupational exposure (eg, unprotected radiography technician or dental assistant), diagnostic exposure (eg, repeated medical imaging of the head and neck), environmental exposure (eg, Chernobyl disaster), or therapeut-
One hundred twenty-five patients with thyroid cancer who had a history of radiation exposure were identified from the thyroid cancer database at the Department of Otalaryngology—Head and Neck Surgery, Mount Sinai Hospital. Mean (range) patient age was 48.2 (18-79) years. The patient group consisted of 95 women (76%) and 30 men (24%). Most patients (89%) had a clinically evident (palpable) thyroid nodule, whereas fewer patients had thyroid nodules that were noted at ultrasonography to be enlarging (7%) or had palpable cervical lymph nodes.

Mean age at first exposure to radiation was 19.4 (1-65) years, and mean (SD) lag time to diagnosis of thyroid disease was 28.7 (3-60) years. Patients with exposure occurring less than 3 years before diagnosis of the disease were excluded from the study. Most patients (56%) had a history of direct external radiation to the head and neck, often as therapeutic radiotherapy to treat benign conditions. Other exposures included direct external radiation to other body sites (6%), occupational or diagnostic exposures (eg, unprotected radiography technicians, dental assistants, or patients exposed to repeated radiographic imaging of the head and neck) (23%), environmental exposure (eg, the Chernobyl disaster) (11%), and radioactive iodine treatment (4%). Patient and radiation exposure data are given in Table 1.

All patients underwent surgical treatment of thyroid cancer including total or near-total thyroidectomy in 83% and subtotal or partial thyroidectomy in 17%. Thirty-eight percent of patients underwent formal neck dissection, and 23% of patients required at least 1 additional operative procedure. Of these procedures, 50% were neck dissections, 25% were completion thyroidectomies, 14% were both completion thyroidectomies and neck dissections, 7% were excisions of single lymph nodes, and 4% were repeated resections of disease in the thyroid bed combined with neck dissection. Seventy-four percent of patients underwent adjuvant radioactive iodine ablation, and 6% underwent adjuvant external radiotherapy. Treatment data are given in Table 2.

Final surgical pathologic results revealed that 89% of patients had papillary thyroid carcinoma. Fewer patients had follicular (6%), Hurthle cell (2%), or medullary (2%) carcinomas; 1 patient had a hyalinizing trabecular tumor. In terms of histologic variants, 72% of tumors exhibited a classic pattern. There were also follicular (22%), diffuse sclerosing (5%), and insular (1%) variants represented in this patient population. No tall cell or columnar variants were reported.

Mean (range) tumor size was 1.8 (0.1-7.0) cm. Sixty-three percent of patients had multifocal disease, with a mean (range) of 1.94 (1-7) foci. Twelve percent of tumors demonstrated lymphovascular invasion, and 26% demonstrated extrathyroidal spread. Lymph nodes were positive for disease in 25% of cases; of these, 36% exhibited extranodal invasion. Pathologic data are given in Table 1.
Patients were followed up for a mean (range) of 10.6 (0.08-35.10) years. Clinical stage (American Joint Commission for Cancer) and clinical outcome data are given in Table 2. MACIS scores were calculated for all patients with papillary thyroid carcinoma. Most patients had stage I disease (64%) and MACIS scores lower than 6 (81%). Sixteen percent of patients had local recurrence of disease, and 9% had distant metastases. At last follow-up, most patients (86%) were alive and free of disease; fewer patients were alive with local recurrence (4%) or distant metastases (4%). Four percent of patients had died of thyroid cancer, and 2% had died of an unrelated cause.

This patient cohort was compared with a group of general thyroid cancer patients, that is, patients who were not identified on the basis of previous radiation exposure. This group included 574 patients who were similar for age and sex distribution and were identified from the same thyroid cancer database located in our department. Treatment, pathologic findings, and clinical outcome data for the 2 groups are given in Table 3.

Although statistical calculations are impossible, there are some notable results evident with this type of comparison. The radiation-exposed group was more likely to undergo total or near-total thyroidectomy (83% vs 38%) and more likely to require additional operative procedures (23% vs 2%) compared with the general thyroid cancer group. In addition, these patients were more likely to require adjuvant external radiotherapy for treatment of malignant lesions of the thyroid gland (6% vs <1%). The radiation-exposed patients were more likely to have multifocal tumors (63% vs 36%) and tumors exhibiting extrathyroid spread (26% vs 8%). More radiation-exposed patients had stage IV disease compared with the general thyroid cancer group (16% vs 5%); they were also more likely to have distant metastases (9% vs 2%), to have disease at follow-up (8% vs 3%), or to have died of thyroid malignant neoplasm (4% vs 1.5%).

In an effort to determine whether the type of previous radiation exposure had an effect on tumor pathologic findings or clinical outcome, the radiation-exposed patients were divided into 5 subgroups according to type of radiation exposure. These subgroups were compared for age at exposure, cancer stage, MACIS score, local recurrence, distant metastases, and likelihood of death from disease. The subgroup exposed to direct external radiotherapy to the head and neck accounted for 56% of all patients with stage IV disease and 60% of all patients with MACIS scores higher than 8. In addition, this subgroup accounted for 63% of patients who experienced local recurrence, 55% of those with distant metastases, and 80% of those who died of thyroid cancer. This subgroup also represents most patients (36%) in the current study. Further, these patients were exposed to radiation at a statistically significant younger age (mean age, 14.9 years) than each of the other subgroups (mean age, 36.3, 28.7, and 34.2 years) (P < .005) except the group exposed to occupational or diagnostic sources of radiation (mean age, 19.9 years) (Table 4).
Most patients with well-differentiated thyroid cancer can expect good disease-specific outcomes. Age and sex are important prognostic factors, as is family history. Other factors such as distant metastasis, completeness of resection, local invasion, and tumor size are used in prognostic scoring systems such as the MACIS score. The objective of the present study was to investigate whether, in addition to being a risk factor for thyroid malignant neoplasms, radiation exposure is also related to more aggressive tumor pathology and, ultimately, worse prognosis.

This relationship has been investigated in other studies, and it has been suggested that tumors in radiation-exposed patients are more likely to involve both thyroid lobes and demonstrate extrathyroid spread. Some have suggested an increase in multifocality and incidental micrcarcinomas. In contrast, others have reported no difference in multifocality or lymph node disease and have suggested that radiation-exposed patients have smaller tumors. Even those studies reporting differences in pathologic features have not reported a difference in clinical outcome for local recurrence, distant metastases, or survival.

The results of the present study suggest that there are different pathologic features in radiation-exposed patients. Although there were not an unexpectedly high number of aggressive variants of thyroid cancer, more multifocal disease and extrathyroid spread was noted. More patients underwent total or near-total thyroidectomy compared with a general population of patients with thyroid cancer. Further, more patients required additional operative procedures, most commonly neck dissection. This is in contrast to a previous study that suggested that the extent of thyroid surgery was similar in these 2 populations. Although the distribution of MACIS scores in the present study was similar to that noted in the original MACIS patient cohort, radiation-exposed patients in the present study were more likely to have stage IV disease and, thus, distant metastases compared with the general thyroid cancer group. Fewer patients were free of disease at follow-up, and more patients had died of thyroid cancer. This is in contrast to previous studies that reported no difference in clinical outcome between patient groups exposed or not exposed to radiation. In addition to the well-documented association in children between radiation exposure at Chernobyl and worse pathologic and clinical outcome, to our knowledge, the present study is the first to suggest worse prognosis in radiation-exposed patients. It is possible that this difference can be explained, at least in part, by the relatively larger number of radiation-exposed patients included in the present study compared with other recent studies.

The present study further sought to determine whether the type of previous radiation exposure was related to more aggressive pathologic features and worse clinical outcome. A wide variety of exposure types were included in this study, such as exposure to radioactive iodine for therapeutic purposes. While some have proposed that this exposure does not increase the risk of thyroid carcinomas, the number of patients exposed during vulnerable times such as childhood has been too small for firm conclusions to be drawn. Similarly, in the present study, this was the smallest subgroup of patients, and most were not exposed during childhood.

The subgroup of patients exposed to direct external radiotherapy to the head and neck accounted for most patients in the current study with stage IV disease, MACIS scores higher than 8, local recurrences, distant metastases, and death from thyroid disease. However, this observation needs to be interpreted with caution because this

### Table 4. Effect of Various Types of Radiation Exposure on Clinical Outcome in Subgroups of Patients With Thyroid Cancer

<table>
<thead>
<tr>
<th>Radiation Exposure</th>
<th>Age at Exposure, Mean (Range), y</th>
<th>AJCC Stage</th>
<th>MACIS Score</th>
<th>Local Recurrence</th>
<th>Distant Metastases</th>
<th>Died From Disease</th>
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<tr>
<td>External radiotherapy to head and neck (n = 70)</td>
<td>14.9 (1-30)</td>
<td>1 (56)</td>
<td>&lt;6-51</td>
<td>63</td>
<td>55</td>
<td>80</td>
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<td></td>
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<td>2 (56)</td>
<td>&lt;7-63</td>
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<td></td>
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<td>3 (43)</td>
<td>&lt;8-25</td>
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<td></td>
<td></td>
<td>4 (56)</td>
<td>&gt;8-60</td>
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<tr>
<td>External radiotherapy to site other than head and neck (n = 7)</td>
<td>36.3 (8-65)</td>
<td>1 (3)</td>
<td>&lt;6-6</td>
<td>5</td>
<td>9</td>
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<td>2 (11)</td>
<td>&lt;7-0</td>
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<td>3 (7)</td>
<td>&lt;8-0</td>
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<td>4 (6)</td>
<td>&gt;8-0</td>
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<td>Occupational or diagnostic (n = 29)</td>
<td>19.9 (10-34)</td>
<td>1 (26)</td>
<td>&lt;6-28</td>
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<td>9</td>
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<td>4 (11)</td>
<td>&gt;8-0</td>
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<td>Environmental (n = 14)</td>
<td>28.7 (5-52)</td>
<td>1 (12)</td>
<td>&lt;6-14</td>
<td>5</td>
<td>18</td>
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<td>4 (17)</td>
<td>&gt;8-20</td>
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<td>Radioactive iodine ablation (n = 5)</td>
<td>34.2 (14-46)</td>
<td>1 (3)</td>
<td>&lt;6-1</td>
<td>11</td>
<td>9</td>
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<td>4 (11)</td>
<td>&gt;8-20</td>
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Abbreviations: AJCC, American Joint Commission for Cancer; MACIS, metastases, age, completeness of resection, invasion, and size.
was also the largest subgroup in the study and the young-
est at the time of radiation exposure. It is known that ra-
diation-induced thyroid tumors are associated with a strong
inverse correlation with age at the time of exposure. 3,5

There are several other limitations to this study that are
important. The heterogeneity of patient exposures to
radiation limits the ability to draw conclusions about the
risk of various types of exposures. Previous studies have
reported that the lowest dose with an observed risk is 10
cGy. 1 However, with retrospective patient data, it is dif-
ficult to determine the radiation exposure dose. Other
limitations include treatment by multiple surgeons and
nonstandardized reporting by multiple pathologists. Most
important, although the present study design enabled in-
clusion of a large number of radiation-exposed patients, it
does not permit statistical comparisons. Despite this,
the differences observed between groups (Table 4) must
be taken seriously, and they suggest the need not only
for further careful study but also for consideration of more
aggressive treatment of malignant thyroid nodules in pa-
ients who were exposed to radiation compared with those
who were not.

It is interesting to speculate on the mechanism by
which radiation exposure may cause more aggressive tu-
mor behavior and, ultimately, worse clinical outcome. The re-
t proto-oncogene (ret/PTC) (OMIM 188550) is unique to papillary carcinomas of the thyroid gland 19 and has been
observed in significantly higher frequency in radiation-associated thyroid cancers. 17,18 These rearrange-
ments, in turn, have been associated with more aggres-
sive tumor behavior, 19 which suggests a possible expla-
nation for the more aggressive pathologic features and
worse clinical outcome noted in radiation-exposed pa-
patients in the present study.

CONCLUSIONS

Compared with other patients with thyroid cancer, pa-
tients who have a history of exposure to radiation are more
likely to be treated surgically with total thyroidectomy, mul-
tiple operative procedures, and external radiotherapy com-
pared with the general thyroid cancer patient population.
A higher percentage of radiation-exposed patients have mul-
tifocal and extrathyroid extension of disease, stage IV dis-
ease, and distant metastases. At follow-up, fewer of these
patients are free of disease and more have died of thyroid
disease. Therefore, this study suggests that patients who
have been exposed to radiation have more aggressive dis-
ease and worse clinical outcome than other patients with
thyroid cancer and, therefore, may require more aggres-
sive treatment.

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sis. Study concept and design: Seaberg and Freeman. Acqui-
dition of data: Seaberg and Eski. Analysis and interpretation
of data: Seaberg and Freeman. Drafting of the manuscript:
Seaberg and Freeman. Critical revision of the manuscript for
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