Thyroid Carcinomas After Irradiation for a First Cancer During Childhood

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Background: The thyroid gland is among the most radiosensitive organs. However, little is known about the long-term risk of developing a thyroid tumor after fractionated external radiotherapy for cancer during childhood.

Objective: To study the long-term risk of developing a thyroid tumor in 4096 three-year survivors of childhood cancer treated between May 1942 and December 1985 in 8 centers in France and the United Kingdom, 2827 of whom had received external radiotherapy.

Methods: A wide range of radiation doses were given to the thyroid: 1164 children received less than 0.5 Gy and 812 received more than 5.0 Gy, the average dose being 7.0 Gy.

Results: After mean follow-up of 15 years (range, 3-45 years), 14 patients—all of whom had received radiotherapy—developed a clinical thyroid carcinoma. Within the cohort, the relation between radiation dose to the thyroid and risk of thyroid carcinoma and adenoma was similar to that observed in patients who received radiotherapy during childhood for other reasons, such as an excess relative risk per gray of 4 to 8, up to a few gray. In contrast, compared with thyroid cancer incidence in the general population, the standardized incidence of thyroid carcinoma was much higher than expected from the dose-response relationship estimated within the cohort and from patients who received radiotherapy during childhood for other reasons: a dose of 0.5 Gy was associated with a standardized incidence ratio of 35 (90% confidence interval, 10-87) and a dose of 3.6 Gy with a standardized incidence ratio of 73 (90% confidence interval, 28-153). We did not show a reduction in excess relative risk per gray with use of an increasing number of fractions.

Conclusion: Although we cannot estimate the exact proportion, it is probable that some or all children who are treated for cancer are predisposed to developing a thyroid carcinoma.

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The thyroid gland is among the most radiosensitive tissues.1 After irradiation, the excess relative risk (ERR) of a thyroid tumor per dose unit decreases with increasing age at the time of irradiation.1-5 During the first decades after irradiation, the ERR of developing differentiated carcinoma and adenoma was 3 to 12 for a dose of 1 Gy of external low–linear energy transfer (LET) radiation delivered during childhood in 1 or a few fractions.1-8 Twenty years after irradiation, the ERR decreases with time; however, absolute excess risk increases for at least 40 years after irradiation.2-9 After external low-LET radiation delivered at a high dose rate during childhood, the dose-response relationship is essentially linear—at least from 0.1 Gy to a few gray.1-3,6-8 Although this aspect has not been studied sufficiently, it seems that identified risk factors for thyroid cancer, including reproductive factors, iodine intake, and body mass index, could modify the dose-response relationships after external low-LET irradiation.10,11

Few studies12 have been published concerning thyroid tumors in patients who received external radiotherapy for cancer during childhood, even though they represent a population most at risk for developing thyroid cancer in Western countries.

In the absence of a substantial cohort of children who received high activities of radioiodine for medical reasons, a study of thyroid tumors occurring after a first cancer during childhood is a way to enhance epidemiological knowledge about the onset of thyroid tumors after administration of high doses of radiation to the thyroid during childhood. As illustrated by the Chernobyl disaster,13 such
PATIENTS, MATERIALS, AND METHODS

PATIENTS

A retrospective cohort of 4400 children treated in 8 centers in France and the United Kingdom constituted patients who were alive 3 years after a first solid cancer diagnosed before age 15 years and before 1986. All patients fulfilling these criteria in each participating center were included except in British centers, where patients treated for a retinoblastoma were excluded because they were included in a specific study. A general description of cohort characteristics has already been published,14 as have the results of all types of cancers together,15 osteosarcomas,13 and brain tumors.16

Of 4400 children, 36 had been treated for thyroid cancer as the first cancer and were excluded from the present analysis. Another 177 children were excluded because information about radiotherapy was not available or exploitable (radiotherapy outside participating centers, radiotherapy on arms, or technical and medical records lost), and 91 were excluded because they had received brachytherapy. The remaining 4096 children were included in this analysis, 2827 of whom received external beam radiotherapy.

Information about treatments was abstracted from the clinical notes and radiotherapy files of the participating centers, and the diagnoses of first and second malignant neoplasms were histologically confirmed. Only clinical thyroid tumors requiring surgery were taken into account.

RADIATION DOSIMETRY

Radiation doses were estimated in the middle of the 2 lobes and in the isthmus of the thyroid for each of the 2827 patients who received radiotherapy. Doses at 148 other anatomic sites, including the thymus, spleen, gonads, and 91 sites of the skeleton, were also estimated. A computer program (Dos_EG; Institut Gustave Roussy, Villejuif, France) was developed for these calculations and is described elsewhere.17,18

To establish the effects of fractionation, we considered all treatment given on the same day as 1 fraction. This definition was acceptable because there was no hyperfractionated treatment in the cohort. Mean dose received by the active bone marrow was estimated as a weighted mean of the doses received at 91 sites of the skeleton, using published age-dependent coefficients.19

Among 2827 patients who received external radiotherapy, 70% had received 1 treatment course, 21% had received 2, 6% had received 3, and 3% had received between 4 and 8. The interval between the beginning of the first course and the end of the last was less than 1 year for 2804 patients and more than 3 years for 10 patients.

Mean dose of radiation administered to the thyroid for 2827 patients who received external radiotherapy was 7.0 Gy, but the median dose was only 0.8 Gy (range, <0.001-75.000 Gy) (Figure 1 and Table 1). Doses received by the thyroid were higher for cobalt 60 and high-energy x-rays than for orthovoltage or electrons (Table 1). Because of variations in treatment machines and the type of first cancer, the mean dose to the thyroid varied considerably according to the calendar period: 2.9 Gy before 1960, 5.3 Gy between 1961 and 1969, 8.6 Gy between 1970 and 1979, and 6.4 Gy between 1980 and 1985.

CHEMOTHERAPY MEASUREMENT

Chemotherapy doses could not be found for 104 of 2949 patients who had received chemotherapy. Drugs were grouped into 5 classes according to their known mechanism of action in the cell: electrophil agents, spindle inhibitors, inhibitors of nucleotide synthesis, topoisomerase II inhibitors, and other drugs. To quantify the total amount of drug administered in each class, we chose to convert the dose of each cytotoxic agent to moles per square meter rather than to milligrams per square meter. However, we also analyzed the data assuming equivalent carcinogenic effects per milligram per square meter to ascertain whether this affected our conclusions. A detailed description of the chemotherapy received by the cohort has been published elsewhere.14

STATISTICAL METHODS

The cohort analysis was scheduled to end on January 1, 1992, for patients treated in French centers, and January 1, 1991, for those treated in British centers. Cumulative incidence of thyroid tumors was estimated by the Kaplan-Meier method.20 To estimate the expected number of thyroid cancers by sex, 5-year calendar period, and 5-year age class, we used data from the Danish Cancer Registry.21 Because of the rarity of thyroid cancer in age classes exposed in our studies, the reference registry had to be long-term, well-established, and cover a sufficiently large population. French registries dating back 20 years cover a too limited population and could not be used for our purpose. If Iceland is excluded, the differences in thyroid cancer incidence in Europe are small before age 45 years,22 the maximum age attained in our cohort during follow-up. Among the European national cancer registries that have long been established, the Danish Cancer Registry covers the largest population and was hence chosen. Standardized incidence ratio (SIR) was defined as the ratio between observed and expected numbers of thyroid carcinomas. Relative risk (RR) was defined in a similar manner, with expected number of thyroid carcinomas being estimated from a given reference category within the cohort.

Because there is no incidence registry for thyroid adenomas, the benign tumor analysis was performed internally, and the 1269 children not submitted to radiotherapy were considered as the reference category. The SIR of thyroid carcinoma and the RR of thyroid carcinoma and adenoma were modeled, assuming that the number of thyroid cancers followed the Poisson distribution. Statistical tests were carried out using the deviance of nested models.23 We modeled variations in the thyroid tumor risk with time since irradiation as a power function of the time since irradiation, as previously described.14 These analyses were done using AMFIT software.24 Because of the small number of thyroid tumors in our cohort, 90% confidence intervals (CIs) were estimated for variables using the methods of maximum of likelihood.25
detailed knowledge could be a critical determinant in radiation protection.

We report the results of a cohort study designed to evaluate the long-term risk of developing thyroid tumors after administration of fractionated high doses of external beam radiotherapy to the thyroid. Radiation doses were estimated for each child.

Mean follow-up was 15 years after diagnosis of the first cancer (Table 2); 985 persons were followed up for 20 years or longer, 750 of whom had received radiotherapy. Three to 29 years after the first cancer diagnosis, 14 patients developed a clinical thyroid carcinoma requiring surgery, and 44 developed an adenoma. Histological size (main diameter of the larger nodule) of the carcinomas ranged from 1.0 to 4.0 cm, and that of the adenomas ranged from 1.5 to 4.0 cm. Of 14 carcinomas, 10 presented locoregional involvement or distant metastasis at the time of diagnosis. Histological type of the carcinomas was papillary (11 patients) or well-differentiated follicular (3 patients). All carcinomas and all but 1 adenoma occurred in patients who had received radiotherapy for their first cancer. Cumulative incidence of differentiated thyroid carcinoma 30 years after radiotherapy was 1.5% (95% CI, 0.6%-2.3%), and that of thyroid adenoma was 5.4% (95% CI, 3.3%-7.4%).

No thyroid carcinoma and only 1 adenoma occurred 3 to 5 years after radiotherapy. Peak incidence of thyroid carcinoma was 15 to 19 years after radiotherapy (Table 3).

Thirty-seven thyroid tumors (29 adenomas and 8 carcinomas) developed among 1370 women who received radiotherapy; 20 thyroid tumors (14 adenomas and 6 carcinomas) developed among 1257 men. Incidence of thyroid carcinoma was 1.6-fold higher (95% CI, 0.6-4.5) in women than in men, and that of adenoma was 2.5-fold higher (95% CI, 1.3-4.7). These ratios remained similar after adjustment for radiation dose received by the thyroid.

Within the cohort, the ERR per gray of thyroid carcinoma and adenoma was between 4 and 8, depending on the adjustments made. For doses greater than a few gray, the RR still increased but more gradually (Table 4). A model with a linear term plus a negative exponential term for cell killing because of high radiation doses given to the thyroid fitted the data more adequately than did a purely linear model ($\chi^2_1 = 4.3; P = .04$ for the carcinomas and $\chi^2_1 = 4.8; P = .03$ for the adenomas).

Five of 14 thyroid carcinomas and 12 of 43 thyroid adenomas developed among 302 patients who received radiotherapy for a neuroblastoma (Figure 2), even though the dose received by the thyroid was lower than that received by other patients: 3.5 vs 7.4 Gy. The 25-year cumulative incidence of thyroid tumors in 54 patients treated for a neuroblastoma whose thyroid received 5 Gy or more was 60% (95% CI, 28%-92%). Whatever the dose given to the thyroid, patients treated for neuroblastoma had a higher risk of developing a thyroid carcinoma than did other patients (Table 5). When adjustment was made for dose given to the thyroid, age at diagnosis of first cancer, sex, and country of treatment, the RR of thyroid carcinoma was 5.6-fold higher (95% CI, 1.7-16.0) for patients treated for neuroblastoma than for others. Similar results were obtained for adenomas.

Two of 15 thyroid carcinomas and 13 of 43 thyroid adenomas developed in 323 patients treated for Hodgkin disease whose thyroid had received a mean dose of 24.0 Gy, well above that received by other patients (4.9 Gy). None of these 15 thyroid tumors occurred more than 20 years after diagnosis of Hodgkin disease (Figure 2). When radiation dose was taken into account, the risk of developing a thyroid carcinoma or a thyroid adenoma was similar in patients treated for Hodgkin disease and in those treated for another first cancer.

After controlling for the total radiation dose to the thyroid, the number of fractions was not found to have a significant effect on the risk of thyroid cancer or adenoma ($P > .5$ for all).

We did not show any effect of chemotherapy, any type of drug, or any specific drug (whether analyzed on a positive or negative basis or by moles per square meters of body area) on the risk of developing a thyroid carcinoma or adenoma.

Of 628 patients who received more than 20 Gy to the spleen or had a surgical splenectomy, 3 developed a thyroid carcinoma and 17 developed a thyroid adenoma. No evidence for a spontaneous higher risk of thyroid tumor or modification of the relationship between radiation dose to the thyroid and risk of developing a thyroid tumor was found to be imputable to this factor. Similarly, no modification of the risk of thyroid cancer was evidenced among 629 patients who received a mean dose higher than 10 Gy to the active bone marrow, 235 girls who received doses higher than 15 Gy to both ovaries, 189 girls who received 10 Gy or more to both breasts, or 157 boys who received doses higher than 6 Gy to both testes. Such an analysis was not possible for doses given to the thymus, which was found to be strongly linked to the thyroid dose because of its proximity.

Overall, the 2827 patients who received radiotherapy had an 80-fold higher risk (90% CI, 50-120) of...
developing a thyroid carcinoma than expected from data concerning the general population. In the general population, the incidence of thyroid cancer is about 3-fold higher in women than in men. Hence, the SIR of thyroid carcinoma was 1.9-fold higher (95% CI, 0.6-5.5) in men who received radiotherapy (SIR, 121; 95% CI, 48-245) than in women (SIR, 63; 95% CI, 29-118). This ratio remained similar after adjustment for the radiation dose given to the thyroid.

Compared with the general population, the SIR of thyroid carcinoma ranged from 5.0 (90% CI, 0.5-21.0) for a mean dose of 0.04 Gy to 141.0 (90% CI, 33.0-376.0) for a mean dose of 41.00 Gy after adjustment for the type of first cancer (Figure 3 and Table 4). Table 5 and Figure 4 show the SIRs of thyroid carcinomas according to the radiation dose given to the thyroid and the type of first cancer (neuroblastoma vs another).

Cumulative risk of thyroid carcinoma 30 years after radiotherapy in our cohort was small: 1.5%. Nevertheless, if the 798 patients (about one quarter of the children in our cohort) who received more than 5 Gy to the thyroid are considered specifically, the 30-year cumulative risk is clearly higher: 5.9%.

**COMMENT**

Based on a cohort of 2827 three-year survivors of cancer during childhood who received fractionated external radiotherapy (mean number of fractions, 27) leading to a wide range in the dose given to the thyroid (<0.001-75,000 Gy), we found that the dose-response relationship between the dose given to the thyroid and the risk of developing a thyroid carcinoma was linear up to a few gray. Risk increased for higher doses, but more gradually. Within this cohort, the ERR of developing thyroid carcinoma for a dose of 1 Gy ranged from 4 to 8 according to the adjustments, a value comparable to that observed after irradiation during childhood in 1 or a few fractions for other reasons. In contrast, compared with thyroid cancer incidence in the general population, the standardized incidence of thyroid carcinoma was much higher than that expected from the dose-response relationship estimated within the cohort and that expected from cohorts of patients who received radiotherapy during childhood for other reasons.

Our results have to be confirmed by larger studies, given the small number of patients with thyroid carcinoma. Indeed, the CIs of our SIRs and RRs are broad, and our results are sensitive to small variations in the number of patients.

Although the number of patients who underwent radiotherapy in our study was relatively limited (n = 2827), the range of doses available for investigation of a dose-response relationship was wide: 20% of patients received less than 0.2 Gy to the thyroid, and 10% received more than 26 Gy. This range is higher than in other cohort studies, yet we were unable to detect a decline in risk per unit for the lower doses. Likewise, we did not demonstrate a reduction in risk according to a fractionation of doses, which agrees with similar studies. In addition, our study was not informative for doses below 0.1 Gy. For such low doses of external low-LET radiation, some studies suggest a reduction in the risk of developing a tumor with decreasing dose rate.

Our result concerning an excess of thyroid tumors after diagnosis of neuroblastoma confirms previous findings based on a small part of the present study, and could signify a still unknown mechanism common to neuroblastoma and differentiated thyroid tumors after irradiation. Currently, this result has not been confirmed by...
another study, to our knowledge. Such a question could only be investigated in a cohort study that includes a dose estimation for each child who receives radiotherapy, and not just patients with thyroid cancer but also controls matched on the first cancer type.12

We found much higher SIRs when comparing the thyroid carcinoma incidence per dose category with the general population than with patients within the cohort who received no radiotherapy or a very low dose to the thyroid, even after controlling for neuroblastoma as a first cancer. Our SIR estimates were higher than those estimated for all cohort studies2,3,6-8 of thyroid cancer after irradiation during childhood, which range from 4 to 10 for 1.0 Gy—much lower than our estimate of 35 (95% CI, 10-87) for a thyroid dose of 0.5 Gy. Only the Tinea Capitis study26 found risks comparable to ours: an SIR

Table 3. Occurrence of Thyroid Tumors According to Time Since Radiotherapy in 2827 Patients Who Received External Radiotherapy During Childhood

<table>
<thead>
<tr>
<th>Time Since Radiotherapy, y</th>
<th>Patients Still Followed Up, No.</th>
<th>Differentiated Thyroid Carcinomas</th>
<th>Thymus Adenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Annual Incidence, ( \times 10^6 )</td>
<td>Standardized Incidence Ratio*</td>
</tr>
<tr>
<td>3-9</td>
<td>2827</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>10-14</td>
<td>2001</td>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>15-19</td>
<td>1301</td>
<td>6</td>
<td>120</td>
</tr>
<tr>
<td>( \geq 20 )</td>
<td>746</td>
<td>3</td>
<td>63</td>
</tr>
<tr>
<td>( \geq 3 )</td>
<td>2827</td>
<td>14</td>
<td>39</td>
</tr>
</tbody>
</table>

*Compared with the general population.

Table 4. Thyroid Tumors According to the Radiation Dose Given to the Thyroid in 4096 Patients Treated for a First Cancer During Childhood, of Whom 2827 Received External Radiotherapy

<table>
<thead>
<tr>
<th>Radiation Dose to the Thyroid, Gy</th>
<th>No.</th>
<th>Adenomas</th>
<th>Thyroid dose, mean, Gy</th>
<th>Neuroblastoma as first cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>None or ( \leq 0.25 ) (n = 2011)</td>
<td>3</td>
<td>5</td>
<td>0.52</td>
<td>3/498 160 (51-365)</td>
</tr>
<tr>
<td>0.25 to ( \leq 1.0 ) (n = 775)</td>
<td>1</td>
<td>3</td>
<td>5.0 (2.9-8.6)</td>
<td>10 (1.9-31)</td>
</tr>
<tr>
<td>1.0 to ( \leq 10.0 ) (n = 683)</td>
<td>3</td>
<td>13</td>
<td>2.3 (3.5-50)</td>
<td>11 (2.3-123)</td>
</tr>
<tr>
<td>10.0 to ( \leq 30.0 ) (n = 411)</td>
<td>5</td>
<td>13</td>
<td>4.0 (2.3-141)</td>
<td>153 (36-4062)</td>
</tr>
<tr>
<td>( \geq 30.0 ) (n = 216)</td>
<td>1</td>
<td>2</td>
<td>0.5 (0.5-21)</td>
<td>117 (36-4062)</td>
</tr>
</tbody>
</table>

Relative risk (90% confidence interval, stratified for first cancer type (neuroblastoma and others), age at first cancer (0-1.9, 2.0-4.9, 5.0-9.9, and \( \geq 10 \) y), sex, country of treatment (United Kingdom or France), and follow-up (0-9.9, 10.0-14.9, 15.0-19.9, and \( \geq 20 \) y) as compared with cohort patients who did not receive radiotherapy or who received \( \leq 0.25 \) Gy to the thyroid.

†Reference category.

‡Standardized incidence ratio (90% confidence interval) compared with the general population, adjusted for first cancer type (neuroblastoma and others).

Table 5. Thyroid Carcinomas According to the Radiation Dose Given to the Thyroid in 4096 Patients Treated for a First Cancer During Childhood, of Whom 2827 Received External Radiotherapy

<table>
<thead>
<tr>
<th>Radiation Dose to the Thyroid, Gy</th>
<th>No.</th>
<th>Neuroblastoma as first cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>None or ( \leq 5 )</td>
<td>3/498</td>
<td>2/2800 11 (1.9-31)</td>
</tr>
<tr>
<td>( \geq 5 )</td>
<td>160 (51-365)</td>
<td>7/745 157 (78-277)</td>
</tr>
</tbody>
</table>

*Standardized incidence ratio (90% confidence interval), compared with the general population of the same attained age and sex.

Figure 2. Standardized incidence ratio (SIR) of thyroid carcinoma according to the radiation dose given to the thyroid.
We also investigated the role of radiation dose; these findings are consistent with those reported in a careful investigation of the population that received radiotherapy. Neuroblastoma survivors are the children most susceptible to developing a thyroid carcinoma after irradiation, but other such groups may exist. This hypothesis is not currently supported by other observations, to our knowledge. Indeed, the various RET/PTC rearrangements shown to be more frequent in radiation-induced thyroid tumors have not been reported in pediatric tumors, and no RET mutations have been observed in neuroblastoma.

On the other hand, radio-induced thyroid tumors have not been shown to present more frequently RAS and P53 mutations, which have been linked to pediatric tumors. Of 48 thyroid tumors that developed in our cohort, 8 were included in a study showing that RET rearrangements observed in thyroid tumors that occurred many years after external irradiation were RET/PTC1.39 as opposed to RET/PTC3 rearrangements observed in thyroid tumors a few years after the Chernobyl accident.34 Of the 8 tumors, 3 were negative for RET/PTC1 (thyroid dose: 0.6, 3.5, and 9.1 Gy) and 5 were positive (thyroid dose: 1.4, 7.2, 9.4, 17.9, and 29.2 Gy). All occurred more than 10 years after irradiation. Recently, we performed a familial study, including 649 children from the present study, that showed an increase in the risk of a second cancer according to the number of cancers in other young members of the same family, after controlling for the dose to the site of the second cancer and all types of second cancer being pooled. Only 2 second thyroid cancers were included in this family study. We are, therefore, unable to confirm these findings for thyroid tumors considered alone.

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