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Radiation-induced thyroid changes: A retrospective and a prospective view

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ABSTRACT

Aim of the study: Incidental/therapeutic thyroid irradiation causes hypothyroidism and nodular disease. Increasing numbers of children are being cured of cancers by treatments that include radiation also involving the thyroid bed: these children warrant an early diagnosis and treatment of any radiation-related thyroid changes.

Methods: In 1998 we retrospectively evaluated thyroid parenchyma/function in all patients irradiated between 1975 and 1997; thereafter, we prospectively evaluated all patients given thyroid irradiation by means of thyroid ultrasound and serum fT3, fT4, TSH and thyroglobulin.

Results: Of 596 eligible patients, 468 agreed to the retrospective evaluation: 128/468 had one or more thyroid nodules, and 73 of these 128 had concomitant or previously untreated hypothyroidism, while 22/128 had a differentiated carcinoma. Another 144/157 patients treated between 1998 and 2004 were evaluated and any iatrogenic hypothyroidism was promptly treated: 19/144 had nodules, all smaller than 1 cm in diameter. The first patient group was studied retrospectively, so we have no precise record of the time of nodule occurrence or of their initial sizes. We found, however, that both the number of patients with nodules and the sizes of the nodules were significantly lower ($p < 0.01$) in the prospectively studied group (after a median follow-up of 81 months) than in the retrospectively studied group. Among all the patients with nodules, significantly more females developed cancer than males ($p < 0.04$).

Conclusions: Early treatment for hypothyroidism and ultrasound evaluation of the parenchyma are needed to limit nodule onset and growth.

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1. Introduction

The particular susceptibility of the thyroid gland to irradiation is well known. Exposure to radiation in childhood results in changes in thyroid endocrine function and increases the risk of both benign and malignant thyroid nodules.[1,2] As increasing numbers of children, adolescents and young adults are being cured of cancer after being treated with radiation therapy that has included the thyroid bed: it is important to understand whether early diagnosis and treatment of any radiation-related thyroid changes has an impact on their evolution and outcome.

Thyroid gland activity relies on the secretion of hypothalamic thyrotropin-releasing hormone into the pituitary gland, where it stimulates the secretion of thyroid stimulating hormone (TSH). TSH secretion results in thyroid cell hypertrophy and hyperplasia, with increased iodine trapping and thyroid hormone synthesis. TSH production is stimulated by reduced endogenous thyroid hormone levels and is inhibited by the administration of exogenous thyroid hormone or an increase in endogenous thyroid hormone synthesis. Inappropriate long-term stimulation by TSH is believed to correlate with the progression of thyroid nodules and thyroid hormone medication is frequently used to suppress TSH secretion with a view to controlling the growth of differentiated thyroid cancers and their metastases.[3,4]

We report data obtained from two studies of children treated for cancer with radiation fields involving the thyroid. In the first, retrospective study, we evaluated the incidence of both functional and structural abnormalities in the thyroid and established an approach to future management of such patients which we then evaluated in a second, prospective cohort. Preliminary data support the suggestion that early intervention with thyroid hormone medication may reduce the incidence of subsequently diagnosed malignant thyroid nodules.

2. Patients and methods

2.1. *Retrospective phase*

In 1998, all patients who had had treatment including radiation to the thyroid bed between 1975 and 1997, and who were currently in remission, were identified from our clinical archives and invited to take part in the study. Informed consent was obtained from patients or their parents/guardians. Patients underwent clinical examination, thyroid ultrasound and blood samples were obtained for thyroid function tests (serum free-triiothyronine (fT3), free-thyroxine (fT4), and TSH). The biochemical investigations were undertaken at our institution or at a facility closer to the patient's home. Thyroid function testing was then repeated every 6 months and thyroid ultrasound examination every other year. Patients were given a brief form documenting clinical history for the radiologist undertaking the ultrasound examination and, whenever possible, subsequent ultrasound examinations were requested at the same facility and with the same operator to limit inter observer variability in sequential assessments.

When abnormalities were identified, the recommended strategy for further follow-up and treatment was defined as follows:

(a) *normal thyroid ultrasound findings with high TSH and normal fT3/fT4* (subclinical primary hypothyroidism): if a second set of hormone tests confirmed the anomaly 2 months later, the patient was given L-thyroxine at an initial dose of 1–2 mcg/kg/day. Serial measurements (every 2 months) of the patient's hormone status enabled the euthyroid status to be reached. Follow-up continued with ultrasound scans every other year and hormone tests twice a year until puberty and then once a year thereafter;

(b) *abnormal thyroid ultrasound findings (one or more nodules) with or without abnormal hormonal levels*:

- *nodule(s) under 1 cm in size*: a confirmatory ultrasound was required 3 months later. L-thyroxine was generally prescribed, tailored to reach the individual's TSH-suppressive dose (<0.3 μM/ml). A first thyroid ultrasound scan was performed 4 months after achieving TSH suppression. If the nodule had shrunk or remained the same size, the diagnostic follow-up included thyroid ultrasound 6 months later, then annually, and blood hormone tests every 6 months. If the nodule increased significantly in size, the patient underwent hemithyroidectomy or total thyroidectomy (depending on number and extent of nodules). After surgery, TSH-suppressive hormone therapy was prescribed, as described above.
- *nodule(s) over 1 cm in size*: fine-needle aspiration biopsy (ultrasound-guided where necessary) was always required for cytohistological diagnosis. If this revealed benign disease, L-thyroxine therapy was given to reach a TSH-suppressive dose and the same follow-up was used as for nodules less than 1 cm in size. Surgery was recommended in the case of large (>2 cm) or symptomatic adenomas. If cytohistology diagnosed malignant tumour, or follicular cells of undetermined malignancy, patients always underwent surgery, after which TSH-suppressive hormone therapy was prescribed indefinitely, and the follow-up was as described in the previous sections.

2.2. *Prospective phase*

From 1998 onwards, children with primary cancer whose treatment involved irradiation including all or part of the thyroid parenchyma had a CT-based simulation and a computer-assisted three-dimensional treatment plan to precisely identify thyroid volume and related radiation isodose distributions. All patients were subsequently evaluated during their follow-up and treated as soon as any iatrogenic damage became evident, as explained for the retrospective part of the study.

2.3. *Statistics*

The chi-square test was used to compare the frequency of patient characteristics.[5] The *p*-value was considered statistically significant when <0.05.

3. Results

3.1. Retrospective phase

We identified 596 survivors of paediatric primary cancer whose treatment had involved partial or total thyroid parenchyma irradiation. Their diagnoses and treatments dated from 1975 to 1997. Due to the referral methods adopted at our institution, patients came from most parts of Italy, which ruled out any potential bias in the evaluation of the results due to iodine deficiency disorders (data not shown).[6] Of these 596 cases, 468 agreed to take part in this study. The main features of this cohort and the ones of patients evaluated in the prospective phase are given in Table 1. The primary cancer was Hodgkin's lymphoma in 54 cases, brain tumours in 20, non-Hodgkin's lymphoma in 18, neuroblastoma in 11, soft tissue sarcoma in 10, peripheral primitive neuroectodermal tumour (pPNET) in 2, and various other diagnoses in the other 13 cases. Fig. 1 shows the flow diagram of the evaluation of patients in the retrospective phase.

No ultrasound features were predictive of the histological diagnoses.

At the time the nodules were diagnosed, 94 patients were on daily thyroxine medication. In all, 128/468 (27%) patients were considered to have developed nodules, 22/58 biopsied patients (38%) were found to have malignant nodules. Transient or persistent hypothyroidism was documented in 57% of patients developing nodules.

3.2. Prospective phase

The patients considered in this report were diagnosed and treated for non-thyroid primary cancer from 1998 to the end of 2004, and actively followed up thereafter. The total number of patients warranting evaluation was 157, but only 144 completed all the tests. The results are up-to-date as on 30 June 2008 and the median follow-up for this series is 81 months (range 50–126 months) from radiation treatment. Table 1 summarises some of the results of this second series. All 144 patients were euthyroid at first diagnosis and their thyroid was nodule free. During the study, 19 (eight males and 11 females) developed nodules, all being with diameter $\leqslant$1 cm. These 19 patients had had primary brain cancers (eight patients), soft tissue sarcomas,[5] Hodgkin's lymphomas[4] and Ewing's sarcomas.[2] Three nodules were diagnosed as papillary adenocarcinoma (microcarcinoma in two cases), while all the other patients with nodules (below 1 cm diameter) were given TSH-suppressive thyroxine medication without any cytohistological evaluation.

The number and size of the nodules were significantly smaller among the prospectively evaluated patients than in the retrospectively evaluated series ($p < 0.01$ for both variables).

Table 1 – Characteristics of the retrospective and prospective series.

	Retrospective series	Prospective series
Total no. patients studied	468	144
No. with nodules (%)	128 (27%)	19 (13%)
No. with solitary nodules	60 (47%)	19 (100%)
M:F	67:61	8:11
Median age at RT (range) years	9 (1–19)	10 (4–32)
Median latency after RT (range)	14 (3–28)[a]	4.5 (1.9–10)
Median RT dose to thyroid (Gy)	32 (2.5–75)	25 (19.2–70.4)
Thyroid function		
Euthyroid	54	10
Previously hypothyroid	37	Not applicable
Treated hypothyroid	36	9
Hyperthyroid	1	0

a Latency in the retrospective series is estimated from the time of examination.

3.3. Malignant tumours

The characteristics of the malignant tumours recorded in both the series studied are given in Table 2.

Of the 612 patients studied (retrospectively and prospectively) after irradiation, adenocarcinomas were diagnosed in 25 cases (eight males and 17 females); 22 of these cases were diagnosed in the retrospectively studied group and three in the prospectively studied group. The primary tumours involved had been lymphoma in 10 cases, neuroblastoma in four, sarcoma in four, brain tumours in three, Wilms tumour in two, and Langerhans histiocytosis in two. The median interval from irradiation to thyroid cancer diagnosis was 10 years (range 4–23 years), with no difference between the patients in the two series.

Among all patients developing nodules, significantly more females developed secondary cancers than males ($p < 0.04$), while the two populations were homogeneously distributed in terms of other risk factors, such as age at irradiation, doses administered to the thyroid and hypothyroidism.

Specific results and details of the treatment for post-irradiation thyroid tumours will be the object of another report.

4. Discussion

Any irradiation involving more than 0.5 Gy to the thyroid during childhood should be viewed with concern. Exposure to 1–7 Gy during the first 3–4 years of life has been associated with a 1–7% incidence of thyroid cancer 10–30 years later.[7–9]

Many studies have demonstrated that the risk of hypothyroidism increases proportionally with the dose of radiation,[10–12] whereas the risk of developing a thyroid malignancy peaks at relatively low doses and then levels off with increasing doses.[13]

The pathophysiology of radiation-induced thyroid damage is related to the inhibition of follicular epithelial function and subsequent progressive alteration of the endothelium, from cell degeneration and necrosis with follicular disruption to vascular degeneration and thrombosis, to acute and chronic inflammation, fibrous organisation and partial epithelial regeneration.[14,15] The effects of radiation apparently also depend on circulating TSH concentrations, which govern the size and shape of the thyrocytes,

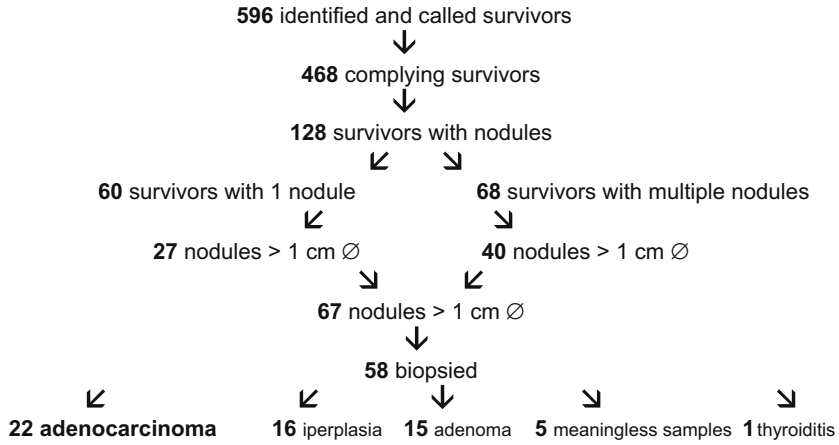

Fig. 1 – Flow diagram of the study of the retrospective series.

Table 2 – Flow diagram of the malignant tumour diagnosis.

612 Complying study patients
↓
147 Survivors with nodules
72 Females 75 Males
17 Adenocarcinomas 8 Adenocarcinomas
$p < 0.04$

25 Patients with adenocarcinoma		
Age at irradiation:	7 years	Range: 1–13 years
Estimated latency after radiation	10 years	Range: 4–23 years
Radiation dose to thyroid	25 Gy	Range: 8–38 Gy

Thyroid function	hypothyroid	9
	adequately treated	8.
	incomplete anamnesis	8

as well as providing an indication of thyroid cell function as a whole, and serving as the most sensitive marker of thyroid damage.[16] Animal studies have demonstrated that high levels of TSH in irradiated thyroid tissue lead to the onset of thyroid carcinoma.[17]

When beginning to assess our patients in the retrospective phase of the study, we carefully optimised the treatment of subclinical hypothyroidism beginning with higher TSH levels. In a similar retrospective report on paediatric patients treated for Hodgkin's lymphoma, abnormal TSH levels were seen in 80% of patients at a median follow-up of 35 months.[18] In an evaluation of 2109 patients of all ages treated for Hodgkin's lymphoma at Stanford University, the actuarial risk of having overt or subclinical hypothyroidism was 44% after 25 years of receiving 30 Gy to the thyroid.[19] The same authors reported that most palpable abnormalities and all thyroid cancers seen in their patients had occurred in those not given thyroxine, who had subclinical or overt hypothyroidism. Evaluation and treatment protocols similar to ours had therefore already been launched[20–22] with a view to containing the occurrence or recurrence of benign or malignant thyroid nodules. The percentage of nodules (27%) and malignancies (38%) in our retrospective series is consistent with previous reports.

The rationale for prescribing TSH-suppressive doses of thyroxine to control nodule growth stems from other experiences documenting significant volume reductions even with 'low-level' suppressive doses (keeping TSH to 0.4–0.6 mIU/ml) of thyroxine.[23,24]

Our experience spans 15 years of research and around 30 years of patient accrual, including more than 600 patients followed up for the specific purpose of assessing radiation-induced thyroid changes. As soon as we started the retrospective evaluation, we also launched a prospective assessment of newly accrued patients, gathering information on 144 patients treated for cancer by the end of 2004 (92% of the157 cases eligible for the study). Early evaluation disclosed a median time to the discovery of nodules of 54 months – far less than the 14 years found in the retrospective series. The patient advantage – possibly due to the earlier treatment of subclinical hypothyroidism – in the prospective series consisted of lower nodule occurrence and smaller nodule dimensions, which was statistically evident after a median follow-up

beyond 6 years. This advantage has yet to be demonstrated for the occurrence of malignant tumours; it seems likely that the fewer and smaller nodules, and their precocious identification will also mean fewer cases of adenocarcinoma in the longer term.[25]

The median dose of radiation to the thyroid in patients who subsequently developed malignant tumours was 25 Gy, consistent with the maximal dose at which the linear ratio between increase in dosage and cases of cancer is maintained[26]; higher doses can have a cell-killing effect that may balance the carcinogenic effect. This median dose is typically administered in Hodgkin's lymphoma cases that in our study, as in other series, had a prevalence attributable to the radiation modality (fields and doses).[27] The interval from irradiation to the onset of secondary cancer was a median 10 years, but early cases developed already after 4 years, as early as those documented after the Chernobyl incident.[28]

As other authors have also underlined, the number of secondary malignant tumours was significantly higher among females: this is also true of primary thyroid tumours after puberty,[29] suggesting a correlation with sex hormones. In our series of secondary cancers, the prevalence of females did not correlate with puberty, more frequent hypothyroidism or relatively early exposure to radiation,[28,30,31] suggesting that female gender *per se* might be a risk factor.

Early age at irradiation is a known risk factor, as seen in our 25 patients with secondary malignant tumours, who had received radiation at a median 7-year-old, as opposed to the median 10 years of the irradiated group as a whole.[27]

New radiotherapy techniques, such as three-dimensional conformal irradiation and proton therapy, could allow a better dose distribution with lower doses spreading to the non-targeted organs.[32] Apart from conformal radiotherapy, which should reduce the volume of normal tissue exposed to high doses and subsequent iatrogenic effects, proton radiotherapy should reduce the incidence of second malignancies and hypothyroidism, in patients treated for parasellar tumours for example.[33] A longer follow-up is needed, however, to evaluate the risk of radiotherapy-induced thyroid disorders when new treatment techniques are employed. With intensity modulated radiation therapy (IMRT), in fact, where a larger volume of normal tissue is exposed to lower doses and a total body exposure is higher (due to leakage radiation), there may be an increased of secondary tumours.[34]

In a previous paper,[35] we showed that TSH suppression during craniospinal irradiation for medulloblastoma can protect patients against hypothyroidism for as long as 7 years. In this report, we have also shown that careful surveillance of irradiated patients (with the early treatment of hypothyroidism and ultrasound of the parenchyma) is useful in monitoring any onset of nodules. After a longer follow-up, we shall see if this is true of malignant transformation too.

Conflict of interest statement

None declared.

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