

Latency Period until the Development of Thyroid Cancer in Young Patients Submitted to Radiotherapy: Report of 10 Cases

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Key Words

Cancer survivors · Radiotherapy · Radiation-related cancer · Thyroid cancer

Abstract

Background: Radiotherapy increases the risk of thyroid cancer (TC); patients submitted to this treatment should undergo a long-term follow-up. Our aim is to describe the features and outcomes of young patients who developed TC after radiotherapy. **Methods:** At our center, patients undergoing radiotherapy directly or indirectly involving the thyroid are regularly followed up in order to detect early dysfunction or nodules. Herein, we report the cases of 10 patients who were submitted to radiotherapy and developed TC. **Clinical Findings:** Seven patients were irradiated in the neck and 3 in nearby regions. The mean age at the last radiotherapy session was 10 ± 5.5 years. The average time until the appearance of the first thyroid nodule was 14 ± 4.7 years. The mean size increment of the nodules was 2.4 ± 1.6 mm/year. On the first cytology, only 2 results were suspicious of papillary thyroid cancer (PTC). All patients presented a histology of PTC. Eight were in stage I and 2 in stage II. The median follow-up from primary diagnosis to TC and beyond was 20 and 3 years, respectively. **Conclusions:** In these patients, cytologies may be difficult to interpret due to persistent benign results. The threshold for surgical indication may be anticipated, considering the increased risk of TC. We report the evolution of these nodules over time, from the end of primary oncological treatment.

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Introduction

Nowadays, the survivors of malignancy during youth demonstrate a long survival, mainly due to the treatments that they were submitted to, such as chemo- and radiotherapy. Therefore, these patients should undergo a long-term follow-up, also from an endocrinological point of view. As the thyroid represents one of the most radiosensitive tissues in the human body, it is known that external beam radiation promotes the development of nodules and, subsequently, thyroid cancer (TC). This association between radiation and thyroid carcinoma was first described in 1950 [1]. Recently, some publications from the Childhood Cancer Survivor Study [2, 3] have corroborated this association and have also shown that this risk decreases with increasing age at exposure, increases after exposure to radiation at doses of 10–30 Gy, but is reduced with doses greater than 30 Gy. However, this risk remains elevated for decades, requiring a long follow-up [4]. Radiation-related TC appears to be greater when combined with chemotherapy [5]. To our knowledge, there are not many published studies that demonstrate the evolution of these patients since the end of their treatments for the primary disease. With this work, we intend to describe the features and outcomes of the patients who developed benign nodules and TC after undergoing radiotherapy.

Patients and Methods

At our center, childhood cancer survivors are referred to and followed up by endocrinologists differentiated in this area as soon as they conclude their oncologic treatments. The endocrine risks of these patients are initially identified, and they are regularly monitored according to their specific risk. Patients undergoing radiotherapy directly or indirectly involving the thyroid are regularly followed up in order to detect early dysfunction, nodules and, subsequently, TC.

We report the clinical evolution of 10 patients who developed TC, thyroid nodules and subsequently carcinoma after radiotherapy. Cytologies were performed on dominant nodules, and the results were classified according to the Bethesda system [6]. The initial results of colloid nodules were later reviewed by an experienced pathologist from our center (Portuguese national reference for TC).

Clinical Findings

Primary Diagnosis and Treatment

Seven out of 10 patients were female. Their mean age at primary diagnosis was 9 ± 5.6 years. Five patients were initially diagnosed with Hodgkin's lymphoma, 1 with abdominal lymphosarcoma, 3 with acute lymphoblastic leukemia (ALL) and 1 with medulloblastoma. One patient was submitted to cervical radiotherapy, 4 were irradiated in the neck and mediastinum, 1 in the abdomen (3-year-old patient with abdominal lymphosarcoma), 1 was submitted to total body irradiation, 2 were irradiated in the central nervous system (CNS) (5- and 6-year-old patients with ALL) and 1 in the CNS and neuroaxis. The mean age at the last radiotherapy treatment was 10 ± 5.5 years. Nine patients were also submitted to chemotherapy.

Evolution of Thyroid Nodules

None of the patients developed thyroid dysfunction. The average time until the appearance of the first thyroid nodule was 14 ± 4.7 years (range 6–22). In 7 patients, only 1 dominant nodule was observed, and 3 showed ≥ 2 nodules on ultrasound; the mean size increment of the nodules was 2.4 ± 1.6 mm/year. The first cytology results demonstrated 6 colloid nodules (table 1 shows the evolution of these nodules) and 1 follicular neoplasm, 2 were suspicious of papillary thyroid carcinoma (PTC), and in 1 patient, the result was unknown. Review of the colloid nodule cytologies found no atypia suggestive of malignancy (they were similar to those without a history of radiotherapy).

Thyroid Cancer

Seven patients underwent isolated total thyroidectomy and 3 total thyroidectomy plus lymph node dissection; the mean age at surgery was 27.9 ± 9.2 years. All patients presented a histology of PTC (histological characteristics are shown in table 2). Microcarcinoma was found in only 1 patient. Eight were in stage I and 2 in stage II. Radioactive iodine (RAI) therapy was performed in all patients. One patient presented lung metastases in post-RAI whole-body scintigraphy, which disappeared after the fourth RAI therapy; histologically, he presented a follicular variant of PTC (18 mm) with angioinvasion and cervical lymph node metastases. Currently, all the patients are in remission. The median follow-up from primary diagnosis to histological diagnosis of PTC was 20 years (10–25), and the median follow-up since TC was 3 years (0.5–24).

Discussion

TC is a late complication of radiotherapy, even when the gland is not directly irradiated, as was observed in our patients. These cancer survivors must be regularly monitored once these nodules are at high risk of becoming malignant.

The time elapsed between the end of radiotherapy and the development of nodules was similar to that previously reported [7], and so was the period between radiotherapy and the diagnosis of PTC [8, 9]. The majority of patients also underwent chemotherapy, which supports the notion that this treatment can influence the development of radiation-related TC, as observed by other authors [5]. Similar to what has been published, most patients did not manifest previous thyroid dysfunction [7], and PTC was the most common finding in the histology [10].

Some of these nodules would have remained clinically irrelevant if they had not been subjected to echo-guided cytology. However, 1 patient developed lung metastases and demonstrated some poor prognostic histological features such as angioinvasion and cervical lymph node metastases, whereby the risk of aggressiveness of these tumors should not be disregarded. It has also been reported that 10% of patients with TC < 10 mm had local recurrence [11]. Furthermore, it was previously proven that the likelihood of malignancy of a nodule in a patient previously submitted to radiotherapy is independent of its size and of the presence of other nodules [12]. We consider that nodules should undergo cytology as soon as technically possible. Patients with a benign result should be closely followed up, considering that these nodules may become suspicious, even when they do not show a marked growth over the years (only 1 patient demonstrated a colloid nodule with significant growth in 6 years).

The fact that, in our sample, 44% of the tumors were multifocal reinforces the recommendation that these patients should be submitted to total thyroidectomy, even when there

is just a solitary nodule on the ultrasound. Furthermore, there is still persistence of radiation-related TC risk in the remaining lobe if this is not the chosen surgical procedure.

Previous studies [11] have demonstrated the advantage of detecting these cancers by screening (i.e., regular ultrasound/scan in radiation-exposed individuals considering their augmented risk of TC) versus by routine medical care. It was observed that, in the latter group, tumors were larger, had lymph node metastases, were multifocal and bilateral and showed invasion, but the only statistically significant difference was the positivity for lymph node involvement.

These patients were followed up prospectively, i.e., they were regularly monitored since they concluded radiotherapy treatments, taking into account their increased risk of developing thyroid nodules and, subsequently, TC. Therefore, we could report the real evolution of these nodules over time since the end of cancer treatment.

We admit that the true incidence of radiation-related thyroid nodules may be underestimated, since there are no widely used protocols for the follow-up of these patients. As we have been following up our patients on this basis, according to our center's experience and also to the Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers [13], we and other authors [7, 14] recommend: cervical ultrasound ab initio for later comparisons; annual thyroid palpation; cervical ultrasound 2–3 years after the primary diagnosis and annually thereafter if there are nodules or every 2 years in the absence of nodules. Cytology must be performed in nodules <10 mm when technically possible, according to published criteria [15]. Cytology results may be difficult to interpret due to persistent results of colloid nodules in slow growing nodules. However, this procedure must be repeated in these nodules, and the threshold for surgical indication may be anticipated, taking into account their increased risk. Total thyroidectomy may be the most suitable surgical approach if there are no recognized lymph node metastases. These patients must undergo a long-term follow-up, as their risk remains increased for several decades after the primary diagnosis.

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Table 1. Evolution of the thyroid nodules whose first cytology result was 'colloid nodule'

Patient No.	1st cytology		Interval, years	2nd cytology		Interval, years	3rd cytology	
	size, mm	result		size, mm	result		size, mm	result
1	13	CN	1	17	follic. neopl.			
2	15	CN	7	16	susp. of malign.			
3	17.7	CN	1	17.7	CN	2	19	follic. neopl.
4	15	CN	6	33	CN			
5	10	CN	4	14	follic. neopl.			
6	15	CN	1	19	CN; lymph node cytology susp. of PTC			

CN = Colloid nodule; follic. neopl. = follicular neoplasm; susp. = suspicious.

Table 2. Histological characteristics of TC

PTC	100%
Medium size, mm	16.6±8.13
Variants: classical/follicular/diffuse sclerosing	40%/50%/10%
Multifocality	44%
Angioinvasion	12.5%
Extrathyroidal extension	22%
Lymph node metastases	22%