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Original Research

Ultrasound surveillance for radiation-induced thyroid carcinoma in adult survivors of childhood cancer

Enrico Brignardello [a,*], Francesco Felicetti [a], Anna Castiglione [b], Marco Gallo [c], Francesca Maletta [d], Giuseppe Isolato [e], Eleonora Biasin [f], Franca Fagioli [f], Andrea Corrias [g], Nicola Palestini [h]

[a] *Transition Unit for Childhood Cancer Survivors, Department of Oncology, Città della Salute e della Scienza Hospital, Turin, Italy*
[b] *Unit of Clinical Epidemiology, University of Torino and Centre for Cancer Epidemiology and Prevention (CPO Piemonte), Turin, Italy*
[c] *Oncological Endocrinology Unit, Department of Oncology, Città della Salute e della Scienza Hospital, Turin, Italy*
[d] *Pathology Unit, Department of Medical Sciences, University of Torino, Turin, Italy*
[e] *Diagnostic Imaging Department, Città della Salute e della Scienza Hospital, Turin, Italy*
[f] *Pediatric Onco-Hematology, Città della Salute e della Scienza Hospital, Turin, Italy*
[g] *Pediatric Endocrinology Unit, Department of Pediatric Sciences, Città della Salute e della Scienza Hospital, Turin, Italy*
[h] *Department of Surgery, Città della Salute e della Scienza Hospital, Turin, Italy*

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Abstract ***Introduction:*** The optimal surveillance strategy to screen for thyroid carcinoma childhood cancer survivors (CCS) at increased risk is still debated. In our clinical practice, beside neck palpation we routinely perform thyroid ultrasound (US). Here we describe the results obtained using this approach.
Methods: We considered all CCS referred to our long term clinic from November 2001 to September 2014. One hundred and ninety-seven patients who had received radiation therapy involving the thyroid gland underwent US surveillance. Thyroid US started 5 years after radiotherapy and repeated every 3 years, if negative.
Results: Among 197 CCS previously irradiated to the thyroid gland, 74 patients (37.5%) developed thyroid nodules, and fine-needle aspiration was performed in 35. In 11 patients the cytological examination was suspicious or diagnostic for malignancy (TIR 4/5), whereas a follicular lesion was diagnosed in nine. Patients with TIR 4/5 cytology were operated and in all cases thyroid cancer diagnosis was confirmed. The nine patients with TIR 3 cytology also underwent surgery and a carcinoma was diagnosed in three of them. Prevalence of thyroid

* *Corresponding author*: Transition Unit for Childhood Cancer Survivors, AOU Città della Salute e della Scienza di Torino, Via Cherasco, 15 - 10126 Torino, Italy. Tel.: +39 011 6334531; fax: +39 011 6334703.
E-mail address: ebrignardello@cittadellasalute.to.it (E. Brignardello).

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cancer was 7.1%. Tumour size ranged between 4 and 25 mm, but six (43%) were classified T3 because of extra-thyroidal extension. Six patients had nodal metastases; in eight patients the tumour was multifocal. At the time of the study all patients are disease free, without evidence of surgery complications.

Conclusion: Applying our US surveillance protocol, the prevalence of radiation-induced thyroid cancer is high. Histological features of the thyroid cancers diagnosed in our cohort suggest that most of them were clinically relevant tumours.

1. Introduction

Childhood cancer survivors (CCS) are a continuously growing population, with unique health problems that physicians will be facing more in the future. Due to modern chemotherapy and radiation therapy techniques, the 5 year survival rate of children and adolescents affected by tumours has improved steadily and is now estimated to be about 80% [1]. It has become evident, however, that the cure brings the risk of serious late effects [2–4], including the onset of second malignant neoplasms (SMNs).

SMNs are the most frequent cause of mortality for CCS who survived for more than 20 years [5,6], and their occurrence also has a dramatic impact on survival and quality of life.

The thyroid gland is a highly radiosensitive organ. In CCS, the risk of developing a thyroid cancer is closely related to radiation therapy to the head, neck or upper thorax, persists for several decades after treatment and is higher in patients who received radiotherapy at a younger age [7,8] and/or treated with doses ranging between 10 and 30 Gy [7,9–11]. These observations suggest that surveillance might be useful for those CCS at increased risk of thyroid cancer [12,13].

For this purpose, available guidelines [12,14,15] recommend annual palpation of the thyroid and restrict the use of ultrasound (US) to the characterisation of palpable nodules. Although the sensitivity of neck palpation to detect thyroid cancer is low, particularly in early stages, this approach is supported by the observation that radiation-induced thyroid carcinomas are usually well differentiated (i.e. papillary and, less frequently, follicular), generally behaving non-aggressively and with excellent survival rates in adults as well as in children [11,16]. Moreover, there is no evidence to date that an early diagnosis obtained by screening procedures is effective to reduce mortality for thyroid cancer in CCS.

On the other hand, it should be considered that radiation-induced thyroid cancer is suspected to be more aggressive [17,18]. American Association of Clinical Endocrinologists (AACE)–Associazione Medici Endocrinologi (AME)–European Thyroid Association (ETA) guidelines suggest to perform thyroid US in all patients with risk factors for thyroid malignancy (which include a history of head and neck irradiation), even if results of palpation are normal, and recommend fine-needle aspiration (FNA) biopsy for nodules of any size in patients with a history of neck irradiation in childhood or adolescence (grade designation B; best evidence level 3) [19]. American Thyroid Association (ATA) guidelines states that FNA may be warranted even in subcentimeter nodules of patients with a history of head and/or neck irradiation, since they have a greater potential to be clinically significant cancers [20].

Thus, while the international community is working to develop international survivorship follow-up guidelines [21], currently there is no consensus on the optimal surveillance strategy for thyroid cancer after radiotherapy in CCS and this issue is still matter of debate.

In 2008 we proposed neck US surveillance for CCS previously irradiated to the head, neck or upper thorax [22]. Here we describe the results obtained using this protocol in a cohort of young adults previously treated with radiotherapy for a childhood cancer and now enrolled in a long term follow-up program.

2. Methods

2.1. Study population

We considered all patients referred to the 'Transition Unit for Childhood Cancer Survivors' (part of the 'Città della Salute e della Scienza' Hospital in Turin, Italy) from November 2001 to September 2014. All clinical information (cancer diagnosis, therapies, relapses, second tumours, late toxicities, etc) of our CCS are recorded during follow-up. Data about demographic and treatment characteristics of this cohort have been previously published [23,24].

To the purpose of this study we selected all subjects who satisfied the following criteria: a) age at paediatric cancer diagnosis <18 years; b) at least 5 years of survival; c) at least one visit after the 18th birthday; d) previous radiotherapy involving the thyroid gland (i.e. radiation therapy to the head, neck or upper thorax) at age <18 years. Patients with a paediatric cancer diagnosis before 1985 were excluded from the analysis, to reduce the possible selection bias of the cohort.

During follow-up visits at our centre all patients received a complete physical examination, including neck palpation. Moreover, CCS who had received radiation therapy to the head, neck or upper thorax underwent thyroid US examination, according to a previously described protocol [22]. Thyroid US, which is always performed by a specialist of our working group (GM, IG) with high expertise in the specific field of cancer survivors [25], starts between the fifth and the sixth year after the completion of radiotherapy (i.e. at the first follow-up visit done 5 years after the end of radiotherapy) and is repeated every 3 years, if negative. Thyroid nodules are taken into consideration when solid at US and with major diameter ≥0.5 cm. If a nodule is found, thyroid US is repeated every 12 months (or less) or FNA is performed on nodules bearing the combination of US characteristics associated with increased risk of malignancies (hypoechoic pattern and/or irregular margins, a more tall-than-wide shape, microcalcifications, or chaotic intranodular vascular spots) [20]. FNA procedure includes a bedside evaluation of the sample, with repeated aspiration if needed.

Cytological diagnosis was formulated according to the five cytological categories reported by the Working Group SIAPEC-IAP for the Consensus on Classification of Thyroid Cytology (TIR 1: non-diagnostic; TIR 2: negative for malignant cells; TIR 3: inconclusive/indeterminate – follicular proliferation; TIR 4: probably malignant; TIR 5: positive for malignant cells) [26]. The present classification was adopted in 2009; for FNAs performed before this date, the original diagnosis was converted in the corresponding TIR category.

After surgery, the specimen was submitted for histopathological examination: tumours were classified by pTNM staging, according to the AJCC VII edition [27]. Tumour characteristics included histology, grade, tumour focality, tumour size, lymph node status and distant metastases at presentation. Histological subtypes of papillary thyroid cancer were classified according to the World Health Organisation classification [28].

The distribution of patient characteristics was summarised using percentages and frequencies.

Table 1
Patients and treatments characteristics.

	Total (N = 197)		Patients without thyroid cancer (N = 183)		Patients with thyroid cancer (N = 14)		Chi-square p-value
	No.	%	No.	%	No.	%	
Gender							
Female	84	42.64	79	43.17	5	35.71	0.587
Male	113	57.36	104	56.83	9	64.29	
Age at paediatric cancer diagnosis							
0–4	37	18.78	31	16.94	6	42.86	0.064
5–9	48	24.37	46	25.14	2	14.29	
≥10	112	56.85	106	57.92	6	42.86	
Age at thyroid cancer diagnosis							
10–19	4	2.03			4	28.57	
20–29	8	4.06			8	57.14	
≥30	2	1.02			2	14.29	
Paediatric cancer diagnosis era							
1985–1989	30	15.23	28	15.3	2	14.29	0.393
1990–1999	94	47.72	85	46.45	9	64.29	
2000–2007	73	37.06	70	38.25	3	21.43	
Paediatric cancer diagnosis							
Haematologic malignancies	144	73.1	132	72.13	12	85.71	0.138
ALL	58	29.44	51	27.87	7	50.00	
Hodgkin Lymphoma	61	30.96	57	31.15	4	28.57	
NHL	7	3.55	7	3.83	0	0	
AML	18	9.14	17	9.29	1	7.14	
Brain tumours	39	19.8	38	20.77	1	7.14	
Sarcomas	11	5.58	11	6.01	0	0	
Others	3	1.52	2	1.09	1	7.14	
Paediatric cancer treatments							
Radiation therapy (dose)[a]							
Total body	56	28.43	49	26.77	7	50.00	0.063
Cranial	72	36.55	67	36.61	5	35.71	0.946
Neck/upper thorax	91	46.19	87	47.54	4	28.57	0.170
Chemotherapy	189	95.94	175	95.63	14	100.00	0.424
Haematopoietic stem cell transplantation	72	36.55	65	35.52	7	50.00	0.278

ALL = acute lymphoblastic leukaemia; AML = acute myeloblastic leukaemia; NHL = Non-Hodgkin Lymphoma.
[a] Each patient received one of more of this radiation therapy type.

3. Results

3.1. Screening results

In our cohort, 197 patients were treated with radiotherapy involving the thyroid gland (Table 1). Using US surveillance a differentiated thyroid cancer was diagnosed in 14 (7.1%) of them. Demographic and clinical characteristics of included patients are detailed in Table 1. The median follow-up after radiotherapy involving the thyroid gland was 15.19 years (range: 5.43–30.06).

During follow-up, 74 CCS (37.5%) developed thyroid nodules, with FNA performed in 35 patients (Table 2). In 11 patients the cytological examination was suspicious (TIR 4, n = 4) or diagnostic (TIR 5, n = 7) for malignancy, whereas a follicular lesion (TIR 3) was diagnosed in other nine patients.

3.2. Treatment

Patients with TIR 4/5 cytology were operated. For these patients, according to the internal protocol of our hospital, surgical treatment included total thyroidectomy and central neck node dissection. Lateral neck dissection was performed in five cases (bilateral in two of them), due to cytological evidence or US suspect of nodal metastases. In all cases, thyroid cancer diagnosis was confirmed by histological examination, always performed at the pathology department of our hospital by a high experienced pathologist (Table 3). The nine patients with TIR 3 cytology also underwent surgery (total thyroidectomy), because of the high risk of thyroid carcinoma due to the previous radiotherapy, and a papillary thyroid carcinoma was diagnosed in three of them. In subjects diagnosed with thyroid cancer, the male/female ratio was 9/5. Thirteen out of these 20 operated nodules were not palpable at the time of surgery (7/11 TIR 4–5 and 6/9 TIR 3).

Two patients with TIR 2 cytology also underwent surgery, due to the large volume of the goitre. In one case the histological examination showed a well differentiated thyroid tumour of unknown malignant potential; in the other patient, the diagnosis of nodular goitre was confirmed.

The median elapsed time between radiation therapy for paediatric cancer and the thyroid cancer diagnosis was 13.08 years (range 8.22–23.65 years; interquartile range 10.03–18.26 years).

After surgery, radioactive iodine (^{131}I; RAI) thyroid remnant ablation was administered in 12/14 patients, at doses ranging between 30 and 100 mCi. Two patients with a recent diagnosis of thyroid cancer did not receive RAI for remnant ablation, due to the favourable stage of disease. The whole body RAI scanning demonstrated extra-thyroidal uptake (lung) in one patient who required a subsequent dose of RAI (100 mCi). At the last follow-up visit, all patients were disease free (i.e. absence of residual disease detectable by neck US, undetectable basal and recombinant human Thyroid Stimulating Hormone (TSH)-stimulated serum thyroglobulin levels). As far as regards surgery complications, no patient had recurrent laryngeal nerve paralysis nor definitive hypoparathyroidism.

3.3. Histopathological findings

Histopathological findings of patients with thyroid cancer are detailed in Table 3. All cancers but one were papillary, classical variant being the most frequent. One case was a mixed papillary and follicular thyroid cancer. Tumour size ranged between 4 and 25 mm, but six were classified T3 because of extra-thyroidal extension. Six patients had nodal metastases at diagnosis; moreover, in eight patients the tumour was multifocal.

Table 2
Clinical characteristics.[a]

	Patients without thyroid cancer (N = 183)		Patients with thyroid cancer (N = 14)		Total (N = 197)	
	No.	%	No.	%	No.	%
Thyroid function						
Normal	125	68.31	12	85.71	137	69.54
Hypothyroidism	58	31.69	2	14.29	60	30.46
Nodules						
No	123	67.21	0	0	123	62.44
Yes	60	32.79	14	100	74	37.56
FNA						
No	162	88.52	0	0	162	82.24
Yes	21	11.48	14	100.00	35	17.76
TIR 2	15		0		15	
TIR 3	6		3		9	
TIR 4	0		4		4	
TIR 5	0		7		7	

FNA = fine-needle aspiration.
[a] For operated patients, data refer to the last available visit before thyroidectomy.

4. Discussion

Applying the US surveillance protocol followed at our centre [22], during a long follow-up after radiotherapy (median = 15.16 years) a thyroid cancer was diagnosed in 14 out of 197 CCS (7.1%). This result could appear surprising if compared to a lower prevalence of second thyroid malignancies reported in previously published large epidemiological studies [9,11,29], but is probably explained by the fact that all our CCS received US examination (resulting in a higher detection rate of thyroid nodules). Indeed, our finding confirms the observations made by other studies performed in clinical cohorts of CCS [30–32]. The prevalence of thyroid cancer was higher in younger patients at the time of radiation therapy and our data also confirm the quite long latency period between radiation exposure and the onset of thyroid cancer [7].

Table 3
Patients with thyroid cancer.

Patient	Sex	Paediatric cancer	Age at paediatric cancer	Radiotherapy (Gy)	Cytology	Histology	Variants	Size (mm)	Multifocality	Vascular invasion	Extra-thyroidal extensiom	*T*	*N*	*M*
1	Male	HL	13.7	Mantle (20)	TIR 5	PTC	Classical	16	Yes	Yes	Yes	3	1b	0
2	Female	ALL	1.3	Cranial (18)	TIR 3	PTC	Classical	13 + 5	Yes	No	No	1b	0	0
3	Male	HL	11.4	Mantle (20)	TIR 5	PTC	Classical	9	No	No	No	1a	0	0
4	Male	ALL	10.1	Cranial (18)	TIR 4	PTC	Classical	13	No	No	No	1b	0	0
5	Male	Neuroblastoma	3.5	TBI (14)	TIR 4	PTC	Classical + solid	23	Yes	Yes	Yes	3	1b	1
6	Female	ALL	8.8	Cranial (18) + TBI (14)	TIR 3	PTC	Classical + follicular	19 + 3 + 2	Yes	No	Yes	3	X	X
7	Male	AML	12.6	TBI (12)	TIR 4	PTC	Classical	7 + 6	Yes	Yes	Yes	3	1b	0
8	Male	ALL	3.4	Cranial (18) + TBI (12)	TIR 5	PCT + FTC	Classical	25 (PTC) 4 (FTC)	Yes (PTC) No (FTC)	Yes	No	1a (PTC) 2 (FTC)	0	0
9	Female	HL	17.3	Cervical (21,6)	TIR 5	PTC	Classical	9	No	No	No	1a	X	0
10	Male	ALL	2.4	TBI (12)	TIR 4	PTC	Follicular	7 + 3 + 8 + 5 + 2	Yes	Yes	No	1a	1a	0
11	Female	HL	18.2	Mediastinal (40)	TIR 5	PTC	Sclerosing	13	No	Yes	Yes	3	1a	0
12	Female	ALL	7.5	TBI (12)	TIR 5	PTC	Classical	25 + 21	Yes	Yes	Yes	3	1b	0
13	Male	ALL	3.2	TBI (12)	TIR 3	PTC	Classical	4	No	No	No	1a	0	X
14	Male	Ependymoma	4.7	Cranial (59,4)	TIR 5	PTC	Follicular	8	No	No	No	1a	X	X

HL = Hodgkin lymphoma; ALL = acute lymphoblastic leukaemia; AML = acute myeloblastic leukaemia; TBI = total body irradiation; PTC = papillary thyroid carcinoma; FTC: follicular thyroid carcinoma.

Moreover, we diagnosed more thyroid carcinomas in males than in females. This unexpected result could be explained considering that we analysed a population with a strong risk factor for thyroid carcinogenesis (i.e. radiation), and the effect of this factor likely prevails over that due to the sex.

Since the excess of thyroid cancer diagnosis in our cohort is likely related to the high sensitivity of US in the early detection of thyroid nodules it follows that our surveillance strategy must be discussed analysing the advantages and disadvantages of anticipating the thyroid cancers diagnosis.

Differentiated thyroid cancer (i.e. papillary and, less frequently, follicular carcinoma) generally behave in a non-aggressive way, with excellent survival rates, and this is the reason why in general population US screening for thyroid cancer is not considered cost effective and should be avoided.

Nevertheless, some evidences have suggested that radiation-induced thyroid cancers have more aggressive biological features [17,18], possibly due to *RET* gene rearrangements [33–35]. Moreover, it has been recently reported that adolescents and young adults who develop thyroid cancer as an SMN have a significantly decreased overall survival compared to those with primary thyroid cancer [36].

In our series, about 60% of thyroid tumours were multifocal and 43% were staged pT3 because of thyroid capsule infiltration. It should be highlighted that multifocality, which is a histological feature frequently observed in radiation-induced thyroid carcinomas, has been identified as a risk factor for recurrence [37]. Moreover, despite the small size of most of the tumours, 6 out of 14 patients showed nodal metastases at diagnosis and one had also lung involvement.

These clinical features suggest that thyroid cancers diagnosed in our cohort, even if the majority were not palpable, were clinically relevant tumours. It could be supposed that, in these patients, the early diagnosis obtained by this high sensitivity surveillance modality led to a less extensive surgery and to a reduced need of repeated radio-iodine treatments. The systematic review of literature recently published by Clement et al. [38] is in agreement with this hypothesis.

Due to the unique features of this population, to avoid a high number of unnecessary FNA procedures (also resulting in an increased psychological stress), thyroid US in CCS should be performed by 'committed' specialists with high experience in the field of thyroid malignancies and late effects of cancer therapies [25]. In our experience, if CCS are correctly informed by the clinician about the advantages/disadvantages of the procedure, FNA is generally well accepted by the patients. Moreover, even if the use of FNA may be supposed to induce anxiety, a benign cytology can reassure the patient about the risk of thyroid cancer.

One half of our CCS with thyroid nodules was submitted to FNA, and more than 30% of them had a thyroid cancer. This result indicates the good efficacy of our surveillance program for the selection of patients to be operated. Moreover, the absence of relevant surgery complications and the low rate of unnecessary interventions (<30%, all in subjects with TIR 3 cytology) indicate the overall safety of this approach.

The lack of a control group to perform outcomes comparison (CCS previously irradiated to the thyroid gland and not submitted to US surveillance) represents the main limitation of this study and hamper definitive conclusions. Moreover, patients included in the study were treated for different cancer types and in a wide period, resulting in a broad variety of therapeutic protocols. For all patients, we know the type of radiation (as reported in Table 1) and the cumulative doses, but unfortunately we have not sufficient information to calculate the dose delivered to the thyroid gland.

In conclusion the histological features of carcinomas diagnosed in our cohort suggest that, in the specific context of CCS, the use of US for early diagnosis of radiation-induced thyroid cancer may be suitable. Nevertheless, routine US screening in irradiated CCS can actually not be recommended; in this regard, the results of International Guidelines Harmonization Group (www.ighg.org) will have to be awaited.

Conflict of interest statement

None declared.

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