RESEARCH

Non-thyroidal second primary malignancy in papillary thyroid cancer patients

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Abstract

Introduction: The occurrence of non-thyroidal second primary malignancy (NTSPM) in patients with papillary thyroid cancer (PTC) is well documented, but epidemiological data are conflicting.
Objective: The aim of this study was to evaluate the incidence of NTSPM in a large series of patients with PTC and to assess its potential risk factors.
Methods: Single-center cohort study with retrospective data collection conducted on consecutive PTC patients diagnosed from 1988 to 2018 with a minimum follow-up time of 2 years. NTSPM was defined as any primary malignancy with histological confirmation occurring in an anatomical site other than the thyroid. According to the timing of occurrence, NTSPM were subdivided into anachronous, synchronous or metachronous (diagnosed >6 months before, within 6 months and >6 months after PTC diagnosis, respectively).
Results: We included 773 individuals (83.3% females), median age at PTC diagnosis was 47.0 (IQR: 37.0–58.0) years and median follow-up time was 9.9 (6.2–16.3) years. Incidence of NTSPM was 15.5% (n = 120) and its standard incidence ratio (SIR) was higher when compared to the general population (SIR: 2.70). Family history of malignancy and younger age at diagnosis were associated respectively with 206 and 4% increased risk of developing metachronous neoplasia (HR: 2.06 (95% CI: 1.10–3.86) and 1.04 (95% CI: 1.02–1.05), respectively).
Conclusion: In our series, the occurrence of NTSPM was not uncommon and its incidence was higher compared to the general population. First-degree family history of malignancy was a strong risk factor for multiple primary malignancies.

Key Words

- thyroid cancer
- papillary thyroid cancer
- second primary malignancy
- radioiodine therapy

Introduction

Differentiated thyroid carcinoma (DTC) is the most common endocrine gland malignancy, most frequently diagnosed among women between the ages of 45 and 54 years (1, 2). Despite the increasing incidence worldwide over the last years, thyroid cancer has an excellent prognosis with a 5-year disease-specific survival rate of over 95% (2).

Increased risk of non-thyroidal second primary malignancy (NTSPM) in DTC patients has been reported in several cancer epidemiological and registry studies (3, 4, 5, 6, 7, 8, 9, 10, 11). These individuals can present anachronous (antecedent), synchronous or metachronous NTSPM with a reported frequency ranging between 1 and 19% (3, 5, 6, 7, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23). This wide variability may reflect the conflicting methodology and different populations, with the best evidence emerging from population-based cancer registries (5, 6, 8, 9, 23) or multinational studies (7, 10).

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There is a long experience in the use of radioiodine for diagnostic and therapeutic purposes in thyroid pathology (24). Particularly, in DTC, radioiodine ablation after surgery can be recommended, according to the risk assessment, in order to eliminate residual normal or neoplastic thyroid tissue (24). Despite its safety, its use is not without risks. The most frequent adverse effects are mild and limited to time (e.g. nausea and sialadenitis) (23), but a potential carcinogenic effect is a long-term negative effect that has been described (3, 5, 11, 21, 23).

Studies about this topic in the Portuguese population are very scarce. A paper by Silva-Vieira *et al.* (3), in a cancer registry-based analysis of the South-Portuguese population, has found an increase in the risk of NTSPM (standardized incident ratio (SIR): 1.40) in papillary thyroid carcinoma (PTC) patients submitted to radioiodine ablation.

The primary aim of this study was to evaluate the incidence of NTSPM in a series of patients with PTC at our institution. Secondary aims were to assess the relative risk for NTSPM in PTC patients and its potential associated factors, namely, radioiodine therapy exposure.

Methods

Study design

A single-center population study with retrospective data collection was conducted using PTC patients followed at our institution. Consecutive patients from 1988 to 2018 with a minimum follow-up of 2 years and at least one thyroid cancer outpatient visit between January 2018 and December 2020 were selected. Patients with insufficient or missing relevant data were excluded. The study protocol was approved by the Ethics Committee at the authors' institution (study authorization 2021.052-042-DEFI/043-CE). Patient consent was waived by the Ethics Committee due to the retrospective nature of the study and full data anonymization.

Data collection

Demographic, clinical, anatomopathological and therapy management (radioiodine therapy (RAIT), date, number of treatments and total cumulative activity administered), as well as personal and family history of malignancy (defined as a history of malignancy in a first-degree relative) data, were retrieved from clinical records. Diagnosis of NTSPM was searched through institution clinical records and using the Portuguese Electronic Health Registry, a digital platform that merges clinical data and medical care contact (Public National Health Service with primary care and national public hospitals) for each patient. Electronic Health Registry and Primary Care data were used to determine the causes of death.

Papillary thyroid cancer treatment and follow-up

All patients underwent surgical treatment (total thyroidectomy or totalization of previous sub-total thyroidectomy) with prophylactic central compartment lymph node dissection with further lateral lymph node compartments' exploration based on loco-regional disease assessed by pre-operative cervical ultrasound. After surgery, levothyroxine therapy was started, and according to the risk and treatment response, some patients received RAI ablation treatment.

At our institution, the criteria for RAIT became more restrictive over time. More recently, it is reserved for remnant ablation in patients with high risk of local recurrence (based on the ATA Guidelines (24)) or to treat persistent disease. Patients were considered for RAIT 6 months after thyroidectomy with levothyroxine withdrawal or recombinant thyroid-stimulating hormone stimulation. The initial activity of RAI administered ranges from 50 to 150 mCi (1850–5550 MBq), depending on risk stratification with subsequent ^{131}I treatments performed, with a minimum 6-month interval, based on structural or biochemical evidence of disease. In the whole cohort, the total cumulative activity ranged from 50 to 750 mCi (1850–27,750 MBq).

For cohort analysis, several subgroups were considered, based on the presence or absence of RAI treatment (RAIT+ vs RAIT−, respectively), NTSPM occurrence and timing.

NTSPM definition

NTSPM was defined as any primary malignancy with histological confirmation occurring outside the thyroid gland. According to the timing of NTSPM occurrence with respect to PTC diagnosis, we subdivided NTSPM group into anachronous (diagnosed up to 6 months before PTC diagnosis), synchronous (within 6 months of PTC diagnosis) or metachronous (diagnosed more than 6 months after PTC). For patients who developed more than one NTSPM, the date of the earliest occurring malignancy were considered.

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Statistical analysis

For descriptive analysis, variables were presented as mean ± S.D. or median (interquartile range) according to normal or non-normal distribution. Categorical data were presented as *n* (%). We used independent *t-test* or the non-parametric Mann–Whitney test to analyse differences between two independent subgroups. The Pearson's chi-square test was used to evaluate differences in counts and frequency between groups for categorical variables.

Kaplan–Meyer 'time to event' method was used to generate the curves of cumulative incidence of NTSPM. Log-rank test was performed to test the difference between cumulative incidence and survival curves. To control for the potential confounding factors, multivariable analysis was conducted using the Cox proportional hazards model and the Fine and Gray regression model (25) for competing risk analysis to calculate the relative risk for the risk factors for NTSPM development. Results will be presented as hazard ratios (HRs) with 95% CIs. A P value <0.05 was considered statistically significant.

The incidence of NTSPM in the cohort and in both RAIT+ and RAIT− subgroups was compared with that of the general Portuguese population by calculating the standardized incidence ratios (SIRs) for all sites NTSPM (26). The SIR is the ratio of observed to expected cases in which the expected number is calculated for a reference cohort of identical age and gender. Portuguese National Oncology Registry (26) was used to retrieve the expected cases of malignancies, during the person-years at risk, on the basis of sex and age.

The statistical analysis was performed using SPSS Statistics for Windows, version 23.0 (2015, IBM Corp) and STATA Statistical Software, version 17.0 (2021, StataCorp).

Results

Patient characterization

Among the 773 individuals with PTC included in the analysis, 83.3% ($n=644$) were females. Median (interquartile range) age at PTC diagnosis was 47.0 (37.0–58.0) years. Median tumour size was 12.0 (7.0–20.0) mm, and 95.0% ($n=734$) of the patients underwent total thyroidectomy. First-degree family history of malignancy was present in 137 (27.4%) of the 500 individuals with available information. Over a median follow-up time of 9.9 (6.2–16.3) years, there were 21 deaths, where 0.3% (2/773) were related to PTC. Other clinical characteristics of the study group are shown in Table 1.

Regarding radioiodine therapy, 48.9% ($n=378$) of the patients underwent at least one treatment with a median cumulative activity administered of 100.0 (100.0–150.0) mCi. More than half of the patients in the RAIT+ group were treated with a total cumulative activity up to 100 mCi, and 28.3% ($n=107$) were treated with higher activities. In the RAIT+ group, patients were significantly younger at PTC diagnosis and presented larger tumours and longer follow-up time, compared to individuals not submitted to RAIT (Table 2). Family history of malignancy (25.8% vs 28.8%, $P=0.44$) was similar in both RAIT+ and RAIT− groups (Table 2).

Non-thyroidal second primary malignancy

A total of 134 non-thyroidal second primary malignancy (NTSPM) were observed in 120 patients. The overall incidence of NTSPM was 15.5% (120/773) with similar rates in RAIT+ and RAIT− patients (14.6% vs 16.5%, $P=0.46$). When we observed the timing of the NTSPM occurrence compared with PTC diagnosis, of the 134 NTSPM, 29.9% ($n=40$) were anachronous, 5.0% ($n=7$) were synchronous and 64.9% ($n=87$) were metachronous. Twelve patients (12/120, 10.0%) had two or more NTSPM; therefore, the total number of malignancies is higher than the number of patients.

In the group of patients with NTSPM, PTC diagnosis was made later in life (49.0 (40.0–61.8) years vs 47.0 (36.0–57.0) years, $P=0.009$) and overall mortality was significantly increased (10.8% vs 1.2%, $P<0.001$) when compared to the group of patients with no NTSPM. Although there was no difference concerning the proportion of patients submitted to RAIT, patients with an NTSPM had been submitted to higher ^{131}I cumulative activities (43.6% vs 25.7% treated with more than 100 mCi, $P=0.008$). There was also a trend for more frequent first-degree family history of malignancy in patients with an NTSPM (34.9% vs 25.8%, $P=0.09$), but it did not reach statistical significance (Table 3).

The most frequent second tumours were breast, colon–rectal and skin cancer. The site and prevalence of the distinct NTSPM are shown, by timing of occurrence, in Supplementary Table 1 (see section on supplementary materials given at the end of this article).

Metachronous NTSPM and potential risk factors

Like the whole group of patients with NTSPM, individuals with a metachronous NTSPM were more frequently treated with ^{131}I cumulative activities superior to 100 mCi and presented increased mortality when compared to those

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Table 1 Clinical and pathological features of the cohort.

	Total (***n*** = 773)
Female sex (*n*, %)	644 (83.3)
Age at PTC diagnosis (years)	47.0 (37.0–58.0)
Tumour size (mm)	12.0 (7.0–20.0)
Tumour size ≤10 mm (*n*, %)	328 (42.4)
Type of surgery (*n*, %)	
Total thyroidectomy	734 (95.0)
Hemithyroidectomy	38 (4.9)
Lateral neck lymphadenectomy only	1 (0.1)
Radioiodine treatment (*n*, %)	378 (48.9)
Radioiodine cumulative activity (categories of mCi)	
<100	77/378 (20.4)
100	194/378 (51.3)
>100	107/378 (28.3)
First-degree family history of malignancy (*n*, %)	137/500 (27.4)
Follow-up (years)	9.9 (6.2–16.3)
PTC treatment response status at last follow-up (*n*, %)	
Excellent response	574 (74.3)
Biochemical incomplete response	33 (4.3)
Structural incomplete response	20 (2.6)
Indeterminate response	145 (18.8)
Overall mortality (*n*, %)	21 (2.7)
Causes of mortality	
PTC	2/21 (9.5)
NTSPM	7/21 (33.3)
Other	12/21 (57.1)

NTSPM, non-thyroidal second primary malignancy; PTC, papillary thyroid cancer.

without an NTSPM; additionally, a longer follow-up period was observed (14.8 (8.7–21.6) years vs 9.8 (6.1–15.9) years in the group with no NTSPM, $P=0.004$), as shown in Supplementary Table 2.

We performed a sub-analysis of the individuals with metachronous neoplasia, regarding ^{131}I exposure (Table 4). In this sample, there were 40 individuals (42 malignancies) treated with RAIT and 38 individuals (40 malignancies) not submitted to RAIT. There were no differences between groups regarding sex, age at PTC diagnosis or latency time between PTC and NTSPM diagnosis. The only significant difference between groups was the duration of follow-up, with a longer period in the RAIT group.

The results of the multivariable analysis exploring the association between RAIT, first-degree family history of malignancy and metachronous NTSPM are presented in Table 5. In Fine and Gray model, adjusted for sex, with death treated as a competitive event, family history of malignancy was associated with a 206% increase in the hazard risk of metachronous NTSPM (HR: 2.06, 95% CI: 1.10–3.86, $P=0.02$). Younger age at PTC diagnosis was also associated with a higher risk of metachronous NTSPM with a 4% risk increase at each additional year (HR: 1.04, (95% CI: 1.02–1.05), $P<0.001$). In contrast, we did not find an increased risk associated to RAIT or to total ^{131}I cumulative activity – data not shown.

Table 2 Patients and tumour characteristics according to radioiodine treatment.

	^{131}I treatment (RAIT+) (***n*** = 378)	**No ^{131}I treatment** (RAIT−) (***n*** = 395)	***P*-value**
Female sex (*n*, %)	301 (79.6)	343 (86.8)	0.007
Age at diagnosis (years)	44.0 (33.0–55.3)	49.0 (39.0–60.0)	<0.001
Tumour size (mm)	18.0 (11.0–30.0)	9.0 (4.0–14.0)	<0.001
First-degree family history of malignancy (*n*, %)	60/233 (25.8)	77/267 (28.8)	0.44
All NTSPM (*n*, %)	55 (14.6)	65 (16.5)	0.46
Metachronous only (*n*, %)	40/55	38/65	0.24
Age at NTSPM (years)	56.0 (45.0–64.0)	55.0 (46.5–64.0)	0.78
Follow-up (years)	11.4 (7.1–20.1)	8.8 (5.3–14.6)	<0.001

NTSPM, non-thyroidal second primary malignancy.

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Table 3 Patients and tumour characteristics according to occurrence of NTSPM.

	Patients with NTSPM (*n* = 120)	Patients with no NTSPM (*n* = 653)	*P*-value
Female sex (*n*, %)	96 (80.0)	548 (83.9)	0.18
Age at PTC diagnosis (years)	49.0 (40.0–61.8)	47.0 (36.0–57.0)	0.009
Tumour size (mm)	12.0 (7.0–21.5)	12.0 (8.0–20.0)	0.68
Tumour size ≤10 mm (*n*, %)	56 (46.7)	272 (41.7)	0.31
Type of surgery (*n*, %)			0.17
Total thyroidectomy	117 (97.5)	617 (94.5)	
Hemithyroidectomy	3 (2.5)	35 (5.4)	
Lateral neck lymphadenectomy only	–	1 (0.2)	
Radioiodine treatment (*n*, %)	55 (45.8)	323 (49.5)	0.47
Radioiodine cumulative activity (categories of mCi)			0.008
<100	5/55 (9.1)	72/323 (22.3)	
100	26/55 (47.3)	168/323 (52.0)	
>100	24/55 (43.6)	83/323 (25.7)	
First-degree family history of malignancy (*n*, %)	30/86 (34.9)	107/414 (25.8)	0.09
Follow-up(years)	11.2 (6.7–19.9)	9.8 (6.1–15.9)	0.17
PTC treatment response status at last follow-up (*n*, %)			0.06
Excellent response	97 (80.8)	477 (73.0)	
Biochemical incomplete response	4 (3.3)	29 (4.4)	
Structural incomplete response	6 (5.0)	14 (2.1)	
Indeterminate response	13 (10.8)	132 (20.2)	
Overall mortality (*n*, %)	13 (10.8)	8 (1.2)	<0.001
Causes of mortality			0.008
PTC	2/13 (15.4)	–	
NTSPM	7/13 (53.8)	–	
Other	4/13 (30.8)	8/8 (100)	

NTSPM, non-thyroidal second primary malignancy; PTC, papillary thyroid cancer.

NTSPM in patients with PTC and RAIT

Figure 1 shows the cumulative incidence of NTSPM in the RAIT+ and RAIT− groups. The 5-year cumulative incidence rates in the RAIT+ and RAIT− groups were 3.0% (95% CI: 1.6–5.4%) and 3.8% (95% CI: 2.2–6.3%), respectively. The 10-year cumulative incidence rates were 5.5% (95% CI: 3.6–8.4%) and 6.8% (95% CI: 4.6–10.0%), respectively, in the RAIT+ and RAIT− groups. Neither statistically significant difference was found between the two groups nor when total radioiodine cumulative administered activity was considered.

SIR of NTSPM

The SIR of NTSPM was higher in the whole PTC group compared to the general population (SIR: 2.70 (95% CI: 2.58–2.82), $P < 0.001$) (Table 6). There was also a difference

Table 4 Individuals with metachronous neoplasia and relation to RAIT.

	Metachronous neoplasia with RAIT (*n* = 40)	Metachronous neoplasia with no RAIT (*n* = 38)	*P*-value
Female sex (*n*, %)	31 (77.5)	34 (89.5)	0.16
Age at diagnosis (years)	44.0 (34.5–55.6)	48.5 (40.0–61.3)	0.08
Age at NTSPM diagnosis (years)	56.1 ± 14.9	59.4 ± 13.3	0.31
Latency period to NTSPM (years)	10.1 (4.8–17.3)	6.7 (3.1–12.8)	0.06
First-degree family history of malignancy (*n*, %)	7 (29.2)[a]	9 (30.0)[b]	0.95
Follow-up time (years)	18.7 (11.5–25.9)	10.8 (7.7–19.0)	0.002
Overall mortality (*n*, %)	4 (10.0)	5 (13.2)	0.66
Causes of mortality (*n*, %)			
PTC	1(2.5)	–	
NTSPM	1(2.5)	–	
Other	2 (5.0)	5 (13.2)	0.20

[a]24 individuals with available information; [b]30 individuals with available information.
NTSPM, non-thyroidal second primary malignancy; PTC, papillary thyroid cancer.

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Table 5 Association between radioiodine treatment, family history of malignancy and metachronous NTSPM, controlling for age and sex.

Covariates	**Cox regression model** (no competitive risk)			**Fine and Gray regression model** (competitive risk)		
	Relative risk	95% CI	*P*-value	Relative risk	95% CI	*P*-value
Sex						
Female vs male	1.47	0.66–3.31	0.35	1.41	0.67–2.97	0.36
Age at PTC diagnosis						
Each additional year	1.05	1.03–1.07	<0.001	1.04	1.02–1.05	<0.001
First-degree family history of malignancy						
Yes vs no	2.11	1.14–3.90	0.02	2.06	1.10–3.86	0.02
RAIT						
Yes vs no	0.73	0.41–1.28	0.27	0.72	0.42–1.26	0.25

RAIT, radioiodine therapy; PTC, papillary thyroid cancer.

between the RAIT+ (SIR: 1.57 (1.48–1.66), $P=0.01$) and RAIT− (SIR: 1.74 (1.65–1.84), $P=0.002$) groups and the general population.

Overall survival

The overall 10-, 20- and 30-year survival rate for all PTC patients in our study was respectively 98.1, 95.9 and 90.7% with a mean (±S.D.) survival of 37.2 ± 0.5 years.

As shown in Fig. 2, the mean survival in patients with PTC who developed an NTSPM was significantly inferior to the group of patients with only PTC (32.0 ± 1.2 (28.8–35.3) years vs 38.4 ± 0.3 (37.9–38.9) years, $P<0.001$). The increase in mortality risk in patients with NTSPM was nearly 13-fold (HR: 12.5, 95% CI: (5.2–30.4), $P<0.001$); further adjustment for age and sex was made but had little effect on the HR (HR: 12.5, 95% CI: (5.1–30.2), $P<0.001$).

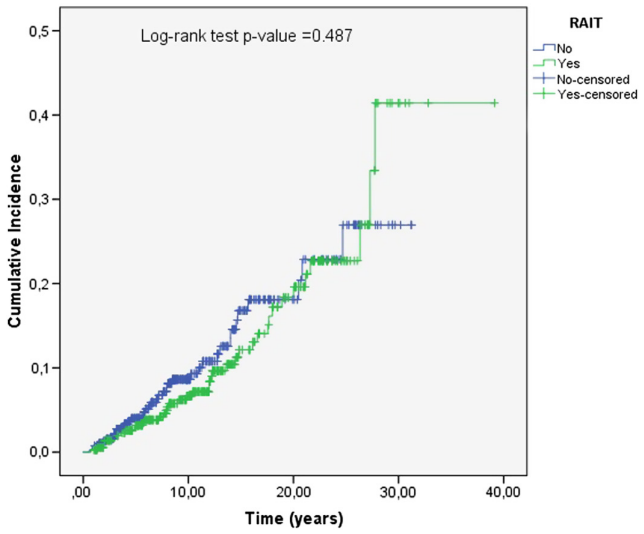

Figure 1
Cumulative incidence of metachronous NTSPM (patients with a first antecedent neoplasia (n = 35) or with a synchronous neoplasia (n = 7) were excluded from this analysis), according to RAIT.

Discussion

A retrospective cohort study was conducted to investigate the incidence of NTSPM in patients with PTC, including 773 individuals with a median follow-up time of 10 years. Approximately, 16% of PTC patients were diagnosed with another primary malignancy either prior, simultaneously or more frequently, after PTC detection. According to our data, the incidence of NTSPM in our PTC patient population was higher when compared to the general Portuguese population. First-degree family history of malignancy and younger age at PTC diagnosis, but not RAIT exposure, were associated with higher risk of metachronous NTSPM.

Published studies on the prevalence of NTSPM in thyroid cancer cohorts mostly consider papillary, follicular and medullary thyroid cancer as a whole group. The prevalence of NTSPM in these patients ranges from 1 to 19% (3, 5, 6, 7, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23), with most studies reporting from cross-matched local

Table 6 Standardized incidence ratio of NTSPM.

Comparison of the incidence of NTSPM	Standardized incidence ratio	CI	*P*-value
All PTC patients vs general population	2.70	2.58–2.82	<0.001
RAIT+ patients vs general population	1.57	1.48–1.66	0.01
RAIT− patients vs general population	1.74	1.65–1.84	0.002

PTC, papillary thyroid cancer; RAIT, radioiodine therapy.

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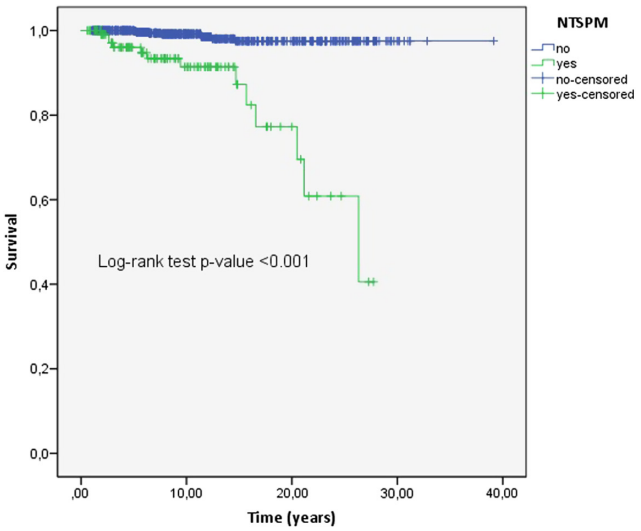

Figure 2
Survival curves of patients with PTC and a NTSPM.

and national cancer registries where demographic and personal and family history data as well as the percentage of PTC patients included are not consistently available. Our findings were within the reported range, although it includes solely PTC patients. It is possible that previously published studies may even underestimate NTSPM prevalence by including patients with lower expected survival, namely, the ones with medullary thyroid carcinoma and by excluding antecedent or synchronous malignancies.

In our paper, we also explored the possibility of a relationship between NTSPM and RAIT exposure. Although the group of patients with metachronous NTSPM were treated with significantly higher ^{131}I cumulative doses (vs patients with no metachronous NTSPM), there was no difference in the observed cumulative incidence between the two groups (even when total ^{131}I cumulative activity was considered). There was a longer follow-up in the RAIT group, which may be explained by their high-risk disease, and the RAIT was also not associated to an increased risk of metachronous NTSPM. Published studies on the influence of RAIT in the development of NTSPM have shown conflicting data. Similar to our observation, some authors (12, 17, 18, 20, 27, 28, 29) have observed no association between RAIT and NTSPM. With comparable follow-up times, Hirsch *et al.* (12) and Cappagli *et al.* (20) neither find an association between RAIT and an increased risk in NTSPM nor a dose–response relationship. The population in both studies, like ours, was mostly low-risk DTC patients in whom limited amplitudes of ^{131}I activity were administered (40–60% of the patients treated with ^{131}I total cumulative activity ≤ 100 mCi). On the other hand, previous studies (3, 5, 11, 21, 23) reported an increased incidence of NTSPM in DTC patients submitted to RAIT. A study in a south-country Portuguese population (3) found a trend for cumulative incidence of NTSPM with higher RAIT activities with statistical significance reached for activities superior to 200 mCi. It is important to highlight that our median ^{131}I total cumulative activity was lower (100 (100–150) mCi) when compared to the proposed published ^{131}I cumulative activity cutoffs associated with risk of NTSPM, ranging from 150 to 540 mCi (3, 11, 21).

It has often been discussed that other factors besides RAIT can be associated with NSTPM in PTC patients. Factors like sex (11, 28), age at PTC diagnosis (4, 5, 11, 17, 28) or genetics (5, 7, 18) could be related to the overall risk of NSTPM in this population. We found a two-fold increase in the risk of metachronous NTSPM in PTC patients with family history of neoplasia in a first-degree relative, as well as a significant increase in the risk in patients with younger age at PTC diagnosis. Concerning age at PTC diagnosis, Brown (5), Teng (11) and Berthe *et al.* (30) found an increased overall risk of second primary malignancy in patients with PTC diagnosed from ages 25–40 years old. Conversely, in the study by Lang *et al.* (4), age at PTC diagnosis ≥50 years emerged as an independent risk factor for the development of NTSPM. Our findings may suggest that a PTC diagnosis earlier in life might reflect a potential genetic predisposition (with consequent higher risk for developing malignancies with each passing year); a surveillance bias in this context, with more frequent screenings, may also apply. In this regard, some authors have suggested the role of certain genes in increasing the susceptibility to multiple primary malignancies development and specific association with DTC. Checkpoint kinase 2 (*CHEK2*) (31), *RET*, *BRAF*, *RAS*, *PTEN* and mismatch–gene repair mutations as seen in Lynch Syndrome (32) have been described as increasing the risk of a second malignancy. Concerning first-degree family history of neoplasia, to the best of our knowledge, our work is the first to point up its role as a predictor of NTSPM incidence. In our study, 30% of the NTSPM were diagnosed prior to the diagnosis of PTC. This raises the possibility of a putatively shared genetic or environmental risk factors, namely, undiagnosed hereditary cancer syndromes or susceptibility, that add on to the increased risk of cancer found in these patients.

Regarding NTSPM sites, breast, colon–rectal and skin were the most frequently affected sites with no difference in site distribution or incidence found when RAIT was considered. This tumour site distribution was also

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frequently reported in other DTC populations (3, 7, 12, 18, 20). A bidirectional relationship between thyroid and breast cancer has been long recognized (33) with strong evidence of a relationship between the two as survivors of either cancer are at increased risk for the development of both tumors when compared with the general population (34). Many driver mutations are similar in both cancers, and the most studied is Cowden syndrome, associated with *PTEN* mutations (34); additionally, germline mutations in *PARP4* and *CHEK2* (35) were also identified in women treated for both cancers (36). Regarding colon–rectal cancer, aberrantly methylated *RET*, a well-established oncogene in thyroid cancer, has been identified in colon–rectal cancers and this might explain the link between the two tumours (37). Finally, a high rate of $BRAF^{V600E}$ mutational background in both thyroid cancer and melanoma unravels a possible common genetic pathway in the pathogenesis of these cancers (38).

Regarding population SIR for cancer, our findings are similar to the study of Silva-Vieira *et al.* (3) that observed an increased risk of NTSPM in the DTC patient's cohort (SIR: 1.32 (95% CI: 1.10–1.57)) when compared to the general population. However, while in their work there was a higher incidence of NTSPM only in the RAIT+ group (SIR: 1.40 (1.15–1.69)), our study found an increased incidence in both RAIT+ and RAIT− groups. This observation was further validated by the multivariable analysis that found no role for RAIT in the development of NTSPM and rather highlighted the importance of family history of malignancy. Regional variability and a higher ^{131}I cumulative activity in Silva-Vieira cohort may explain the observed differences concerning the incidence of NTSPM and RAI treatment status.

Concerning survival, PTC patients with at least one NTSPM had a significantly lower mean survival when compared to patients with no NTSPM during follow-up. Confirming that PTC has a very good prognosis, mortality in this group was also exclusively associated with the non-thyroid primary malignancy. Although few studies have explored survival in PTC patients with NTSPM, all have shown that survival outcomes were higher in the group with only PTC when compared to PTC patients who developed a NTSPM (6, 14, 15).

The retrospective nature of our study and the bias associated with a single-center study are its main limitations. Other potential confounders (occupational radiation exposure, smoking habits and comorbidities) were not available, and missing data concerning family history of malignancy in 273 patients could also underpower our conclusions. On the other hand, a surveillance bias may be present as patients with a previous malignancy may be more likely to seek routine medical care. Additionally, high-risk patients are submitted to longer follow-up periods, and therefore, NTSPM is more prone to be recognized in these patients.

In conclusion, our work explored the incidence of NTSPM and its risk factors in a fairly large series of PTC patients with a median follow-up time of 10 years at the same institution, assuring clinical continuity and coherence in patients' treatment. Furthermore, our comprehensive retrieval of information guarantees that any second primary malignancy diagnosed in Portuguese health centers was included in the analysis, data that could be missed when national cancer registries are used. To the best of our knowledge, this is the first single institution report that evaluated NTSPM in a Portuguese PTC patients' cohort and second only to the cancer registry-based analysis of Silva-Vieira *et al.* Our work has shown that although the incidence of NTSPM in PTC survivors is not uncommon, the risk of subsequent malignancies is higher when compared to the Portuguese general population and that radioiodine treatment was not associated with increased risk of NTSPM. Patients' genetic background, accessed by cancer family history, was raised as a potential risk factor to be further studied in the development of a multiple primary malignancies in PTC patients.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/ETJ-22-0018.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Statement of ethics

This study protocol was reviewed and approved by the Ethics Committee at the authors' institution (study authorization 2021.052-042-DEFI/043-CE) and written patient consent was waived.

Author contribution statement

D B D conceived the study. D B D and V B S wrote the manuscript. G A, A C C and C F revised the manuscript. All authors reviewed and approved the final manuscript.

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