ORIGINAL ARTICLE

Clinical–pathological changes in differentiated thyroid cancer (DTC) over time (1997–2010): data from the University Hospital "Maggiore della Carità" in Novara

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Abstract Differentiated thyroid cancer (DTC) is an important clinical entity in our population (Novara, Piedmont, Italy) which is characterized by important environmental influences, as iodine deficiency (ID) and subsequent supplementation, thyroiditis and occupational exposure. To evaluate the features of DTC in our population 20 years after the iodine-prophylaxis pondering the effects of the introduction of the new guidelines for diagnosis and management of DTC after 2005. 322 patients [244 females, age: mean (±SD) 53.8 ± 15.8 years] treated for DTC in a tertiary care center between 1997 and 2010 were retrospectively evaluated. Medical history, demographics, and pathological features were considered. Patients were subdivided into two groups: A ($n = 139$, diagnosis 1997–2005) and B ($n = 183$, diagnosis 2006–2010). The population of group A showed a mild ID, while normal iodine status was recorded in group B. A significant increase in histological tumor-associated thyroiditis was found from group A to B ($p = 0.021$). Recurrent or persistent diseases were found to be correlated with lymph nodes metastases and/or a distant disease at diagnosis, stimulated thyroglobulin levels at the first follow-up and an additional radioiodine therapy. Twenty percent of our patients were females employed in textile industries. The tumor-related inflammation and the occupational exposure should be considered as important factors in the pathogenesis of DTC. Further studies are required in order to confirm our findings.

Keywords Differentiated thyroid cancer ·
Environmental risk · Thyroiditis

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Introduction

The incidence of the differentiated thyroid carcinoma (DTC) has been increasing in many countries over the last 30 years. In United States, the incidence of thyroid cancer rose up from 4.9/100,000/year people in 1975 to 11.0/100,000/year people in 2006, with a 2.3-fold increase across all patients [1]. The same trend has been reported in Europe from 1973–1977 to 1998–2002, with an increase in the incidence rate ranging between 5.3% in Switzerland and 155.6% in France [2]. Data from the Italian Network of Cancer Registries report nearly 5.2 new thyroid cancers/100,000 males and 15.5/100,000 females each year. Incidence varies significantly across different Italian Regions, being the highest incidence in Emilia Romagna and the lowest documented in Trentino Alto Adige [3].

Data extrapolated from the urban Turin Cancer Registry show that the annual age-standardized incidence rate was 5.1/100,000/year in males and 15.4/100,000/year in females, from 2004 to 2006 [4].

On the other hand, mortality rates associated with DTC has been slowly decreasing in all countries. The coexistent increase in the incidence rate could therefore imply significant improvements in a better recognition of the smallest papillary thyroid cancers (PTC), as a result of the improved diagnostic accuracy achieved by neck ultrasound (US) and US-guided fine needle aspiration biopsy (US-FNAB). Currently, nearly 60–80% of thyroid carcinomas detected are micropapillary (<1 cm in size) and carry an excellent long-term prognosis [1, 5]. Despite the favorable prognosis of these tumors, with a 10-year survival rate exceeding 90.0%, rates of loco-regional and distant recurrences are 5.9 and 1.5%, respectively, and the cancer-related mortality is 1.0–2.0% [1, 6].

Considering the risk factors for DTC, literature data show the importance of environmental factors in the pathogenesis of this tumor [7–12]. In particular, cohort studies [8, 9] have investigated the correlation between iodine supplementation (with the exception of radioactive iodine) and the incidence of new PTCs in goiter endemic areas, with controversial results.

Based on the foregoing, aim of our study was to investigate the clinical and pathological trend of DTC followed in an Italian tertiary care center from 1997 to 2010 (University Hospital "Maggiore della Carità," Novara). Our center may be representative for an Italian iodine-deficient population 20 years after the start of iodine prophylaxis and exposed to undetectable radiation after the Chernobyl accident in 1986.

Patients and methods

Patients

We retrospectively selected from the hospital chart all patients with thyroid cancer treated and followed at our institution (University Hospital "Maggiore della Carità," Novara, Italy) between July 1997 and July 2010, following as inclusion criteria: (1) patients who had an histological diagnosis of PTC or follicular thyroid carcinoma (FTC); (2) available information for age at diagnosis, gender, coexisting thyroid disease, and median urinary iodine concentration (UIC); (3) patients resident from birth in a iodine-deficient geographic area and were invited to adopt a iodized salt prophylaxis program in the last years [13]. Environmental and occupational exposures were identified through a direct interview.

Patients with history of neck irradiation, poorly differentiated, anaplastic, medullary carcinomas and secondary tumors were excluded from the database.

The population sample ($n = 322$) was subsequently divided into two groups: group A, patients with DTC diagnosed between 1997 and 2005; group B, patients with DTC diagnosed between 2006 and 2010. The rationale for the division into two groups was based on the introduction in the clinical practice of the new guidelines for the diagnosis and management of thyroid carcinoma after 2005 [14, 15]. The last date for the enrolment was July 30, 2010.

Moreover, in 103/322 patients we reported the short-term follow-up (defined as the first 5 years after diagnosis) data, because all the patients had the following inclusion criteria:

- thyroglobulin (Tg) evaluation, obtained after endogenous or exogenous stimulation with recombinant human thyroid stimulating hormone (rhTSH);
- neck US evaluation;
- information about the radioiodine therapy when performed;
- information about ^{18}F-fluoro-deoxyglucose-positron emission tomography (FDG-PET) uptake performing when patients showed detectable Tg levels, but negative US and total body scintigraphy (TBS) with I^{131} (TBS).

Patients were thus considered as disease free when Tg and antithyroglobulin antibodies (TgAb) were undetectable, and imaging studies were negative, during the endogenous or exogenous TSH stimulation. Recurrence was diagnosed on the evidence of disease status, documented at least 6 months after the previous definition of a disease free condition. Persistence condition was defined when Tg levels persisted at detectable levels and/or regional lymph nodes or distant metastases were present.

Methods

Cytology and histology

The cytology specimens were evaluated and classified according to the international guidelines [16].

Histological slides were reviewed by two independent pathologists for the purposes of this study. For all cases, tumor-associated thyroiditis was assessed. The tumor size, number of foci, focality, extension, presence of loco-regional, and/or distant metastases were reported and classified according to the 2002 tumor-node-metastases (TNM) system [17].

Thyroid function test and urinary iodine

Serum TSH, Tg, TgAb, and thyroid peroxidase (TPOAb) were measured with the amplified chemiluminescence method (Immunolite 2000, DPC, Los Angeles, USA). Tg assays had a functional sensitivity of 0.6 ng/ml.

All the analyses were automatically performed using "ADVIA Centaur" (Siemens) in the Hospital's chemistry laboratory.

Urine samples were kept covered at 4°C in deiodized tubes and analyzed within 30 days from the collection. UIC was determined by using methods recommended by World Health Organization (WHO) and International Council for Control of Iodine Deficiency Disorders (ICCIDD). Criteria used for assessing iodine deficiency (ID) were as follows [18]:

- Severe ID: UIC < 20 μg/l;
- Moderate ID: UIC = 20–9 μg/l;
- Mild ID: UIC = 50–99 μg/l;
- No deficiency: UIC ≥ 100 μg/l

Neck ultrasound

US was routinely performed in all patients.

The study was performed with a "Color Doppler Toshiba Apparatus" equipped with a linear transducer of 7.5 MHz. The hypoechogenicity, in the presence of an irregular peripheral halo, microcalcifications and an intranodular blood flow, were classified as US risk factors [19]. Cervical lymphadenopathies and their US features were also evaluated.

I^{131} total body scintigraphy

Therapeutic TBS was performed in other referral tertiary care centers using a total body scanner (E. CAM 180 dual detector γ camera, Siemens Medical System). A therapeutic dose of I^{131} (3,700–5,500 MBq) was administered, and repeated until post-therapeutic TBS, FDG-PET or US were negative, and until Tg levels were undetectable.

Diagnostic TBS was performed at the Service of Nuclear Medicine of our center, 2–3 days after the administration of rhTSH, using a diagnostic dose of I^{131} (74–185 MBq).

Scans were performed in anterior and posterior projection 5–7 days after administration of the radionuclide.

^{18}F-fluoro-deoxyglucose-positron emission tomography

FDG-PET/CT scans were obtained by Biograph Hirez (pico-3D) PET/CT scanner (Siemens Medical Solutions). Patients were intravenously injected with 3–4 MBq/kg of ^{18}F-FDG according to standard protocols.

The examination was only performed if fasting blood glucose levels were <140 mg/dl. According to the body mass index of each patient, the average duration of the FDG-PET/CT image acquisition was about 15 min, followed by emission tomographic images reconstruction.

Statistics

Data were expressed as mean $\pm$ SD or percentages. The distributions of dichotomous variables were evaluated using the Chi-square test. The association between the factors for the variables significantly associated in the univariate analysis was assessed with the multinomial logistic regression using the stepwise method with 95% confidence intervals. p values <0.05 were considered significant. Computations have been performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical features

139 patients with DTC were included in group A and 183 in group B. The females gender was the most represented among the two groups; the mean age at diagnosis was 53.5 $\pm$ 15.8 years with any difference between the two groups.

Table 1 summarizes patients' epidemiological and clinical–pathological features.

Median UIC was 90.0 μg/l in group A, and 136.0 μg/l in group B, indicating mild and absence of deficiency, respectively.

Regarding patients' occupational exposures, a predominance of patients was females employed in textile industries (20.0%).

Goiter was the most common coexisting benign thyroid disease associated with DTC. It was found in 82.7% patients in group A and in 74.9% in group B. Detectable TPOAb levels were found in 14.4% patients in group A and 24.0% in group B.

Cytological examination was the first suspicion of malignancy (THY 4 and 5) then confirmed by histology in 28.0 and 36.6% of patients in group A and B, respectively; 7.3% underwent surgery for an indeterminate cytological diagnosis (THY 3) (5.7% group A, 8.7% group B).

In the 61.5% (66.3% group A, 54.7% group B) of patients the diagnosis of malignancy was made after surgery. In these cases, we reviewed the missing pre-operative diagnosis. In group A, FNAC was not performed in the 35.5% of patients, while the 30.8% of cases showed a non-diagnostic results by FNAC (THY1) because performed only by palpation without US help. In group B, FNAC was not performed in the 16.9% of patients undergoing surgical therapy for multinodular compressive goiter (defined as "incidentalomas"); the rate of non-diagnostic result (THY 1) is reduced to a 19.3% when US-guided FNAC was performed. In these cases, one of the main reasons for non-diagnostic specimens is the inclusion of aspirates arising from cysts. False negative (THY2) in these group was 8.3%. Again, 10.2% of malignancy found in the gland

Table 1 Epidemiological, clinical, and pathological features of the whole population studied

	All	Group A (1997–2005)	Group B (2006–2010)	p (Group A vs group B)
Number of patients	322 (100%)	139 (43.2%)	183 (56.8%)	0.253
Gender				
F (N/%)	244 (75.8%)	101 (72.7%)	143 (78.1%)	0.287
M (N/%)	78 (24.2%)	38 (27.3%)	40 (21.9%)	
Age at diagnosis				
≤45 years (N/%)	102 (31.7%)	43 (31.0%)	59 (32.2%)	0.726
>45 years (N/%)	220 (68.3%)	96 (69.0%)	124 (67.8%)	
Mean (years)	53.5 ± 15.8	53.2 ± 16.3	53.7 ± 15.4	0.320
Coexisting thyroid disease				
Goiter (N/%)	252 (78.3%)	115 (82.7%)	137 (74.9%)	0.081
Autoimmune thyroiditis (N/%)	64 (19.9%)	20 (14.4%)	44 (24.0%)	0.021
Toxic adenoma (N/%)	6 (1.8%)	4 (2.9%)	2 (1.1%)	0.176
Surgical therapy				
Total thyroidectomy and neck dissection (N/%)	84 (26.1%)	31 (22.3%)	53 (29.0%)	0.258
Total thyroidectomy (N/%)	214 (66.5%)	93 (66.9%)	121 (66.1%)	0.333
Lobectomy (N/%)	24 (7.4%)	15 (10.8%)	9 (4.9%)	0.069

outside the nodule analyzed by FNAC, consisting of papillary microcarcinoma (again defined as "incidentalomas"). Interestingly, lymphocytic thyroiditis was mainly observed in these patients.

Total thyroidectomy was performed in 92.6% of cases, with any difference between the two groups, even in the presence of malignant cytological diagnosis in nodule <1 cm.

Histo-pathological features

The histo-pathological features of the 322 cases of DTC are shown in Table 2.

PTC was the most frequent diagnosis in both groups (89.9% in group A and 86.9% in group B); in particular, the classical variant was the most represented histological type, with 42.4% in group A and 42.8% in group B. Relatively to the tumor size, microcarcinomas (<1 cm) represented the majority of cases in both groups (42.4% in group A, 43.2% in group B); small cancers (<2 cm) were more represented in group B than in group A (31.1 and 25.9%, respectively), but the increase in frequency was not significant.

We also found the lymphocytic infiltration associated to DTC, with a typical focal and peripheral zone distribution. This co-staining showed an interesting increase over years (14.4% in group A and 24.0% in group B, $p = 0.021$).

Short-term follow-up

After the initial surgery, all patients of group A and 60.0% of group B, considered at a moderate-high risk of recurrence, underwent radioiodine therapy ($p = 0.08$).

219/322 patients were lost at follow-up because they were followed in other centers or did not need a strict follow-up. Thus, 103 patients out of 322 (23 in group A and 80 in group B) are currently followed-up in our care center (months of follow-up: 37.3 ± 33.1; group A 90.0 ± 26.1 months; group B 22.4 ± 14.3 months). Detectable TgAb levels were found in 5.2% of patients in group A and 22.5% in group B ($p = 0.079$).

Considering the change in the follow-up management after 2005, the main differences between group A and group B concern:

(1) the method of choice for Tg stimulation at first follow-up. In fact, in group B in all patients were performed rhTSH stimulation vs 17.4% of group A ($p = 0.0001$);

(2) the progressive reduction in the use of diagnostic TBS during Tg stimulation (26.2% group B vs 91.3% group A) over the years ($p = 0.0001$). In particular, in group B, diagnostic TBS was performed for the evaluation of patients with AbTg positive (22.5%);

(3) an increase, though not significant, of new diagnostic techniques such as [18]FDG-PET (group B = 9.7% vs group A = 3.8%) in order to detect metastatic patients ($p = 0.382$);

(4) moreover since 2005, the preparation to perform radioiodine ablation is based on the administration of recombinant human TSH (rhTSH) while patients were on L-T4 therapy.

At the last follow-up, 79 patients (76.7%) were considered as disease free, 15 patients (14.6%) showed signs of recurrence, and 9 (8.7%) had a persistent disease (Fig. 1).

Table 2 Histo-pathological features of the 322 patients

	Total series N (%)	Group A (1997–2005) N (%)	Group B (2006–2010) N (%)	p (Group A vs group B)
Total	322 (100%)	139 (43.2%)	183 (56.8%)	0.253
Histotype				
PTC	284 (88.2%)	125 (89.9%)	159 (86.9%)	0.397
Classical variant	121 (42.6%)	53 (42.4%)	68 (42.8%)	
Follicular variant	103 (36.2%)	44 (35.2%)	59 (37.1%)	
Classical and follicular variant	38 (13.4%)	20 (16%)	18 (11.3%)	
Hurthle cell variant	11 (3.9%)	6 (4.8%)	5 (3.1%)	
Tall cell variant	7 (2.5%)	1 (0.8%)	6 (3.8%)	
Sclerosant variant	4 (1.4%)	1 (0.8%)	3 (1.9%)	
FTC	34 (10.6%)	11 (7.9%)	23 (12.6%)	
Minimally invasive	32 (94.1%)	11(100%)	21 (91.3%)	
Invasive	2 (5.9%)	0	2 (8.7%)	
PTC and FTC	4 (1.2%)	3 (2.2%)	1 (0.5%)	
Dimension				
≤1 cm	138 (42.9%)	59 (42.4%)	79 (43.2%)	0.333
>1 cm to ≤2 cm	93 (28.9%)	36 (25.9%)	57 (31.1%)	
>2 cm to ≤4 cm	67 (20.8%)	34 (24.5%)	33 (18.0%)	
>4 cm	24 (7.4%)	10 (7.2%)	14 (7.7%)	
T (TNM 2002)				
T1	200 (62.1%)	81 (58.3%)	119 (65%)	0.078
T2	47 (14.6%)	22 (15.8%)	25 (13.7%)	
T3	56 (17.4%)	23 (16.5%)	33 (18%)	
T4	19 (5.9%)	13 (9.4%)	6 (3.3%)	
Node metastasis (N)				
NX	238 (73.9%)	108 (77.7%)	130 (71.0%)	0.390
N0	36 (11.2%)	12 (8.6%)	24 (13.1%)	
N1	48 (14.9%)	19 (13.7%)	29 (15.9%)	
Distant metastasis (M)				
Mx	317 (98.5%)	139 (100%)	178 (97.3%)	0.059
M1	5 (1.5%)	0	5 (2.7%)	
Extrathyroid invasion				
No	265 (82.3%)	111 (79.9%)	154 (84.1%)	0.195
Yes	57 (17.7%)	28 (20%)	29 (15.9%)	
Multifocality				
No	225 (69.9%)	93 (66.9%)	132 (72.1%)	0.188
Yes	97 (30.1%)	46 (33.1%)	51 (27.9%)	
Bilaterality				
No	242 (75.2%)	101 (72.7%)	141 (77%)	0.221
Yes	80 (24.8%)	38 (27.3%)	42 (23.0%)	
Staging AJCC 2005 [20]				
I	235 (73.0%)	102 (73.4%)	133 (72.7%)	0.389
II	28 (8.7%)	9 (6.4%)	19 (10.4%)	
III	35 (10.9%)	14 (10.1%)	21 (11.5%)	
IV	24 (7.4%)	14 (10.1%)	10 (5.4%)	
Thyroiditis tumor-associated				
No	258 (80.1%)	119 (85.6%)	139 (76%)	0.021
Yes	64 (19.9%)	20 (14.4%)	44 (24.0%)	

Fig. 1 Clinical outcomes of the 103 patients, subdivided into the two groups. Panel **a** disease free, panel **b** relapsing disease, and panel **c** persistence disease
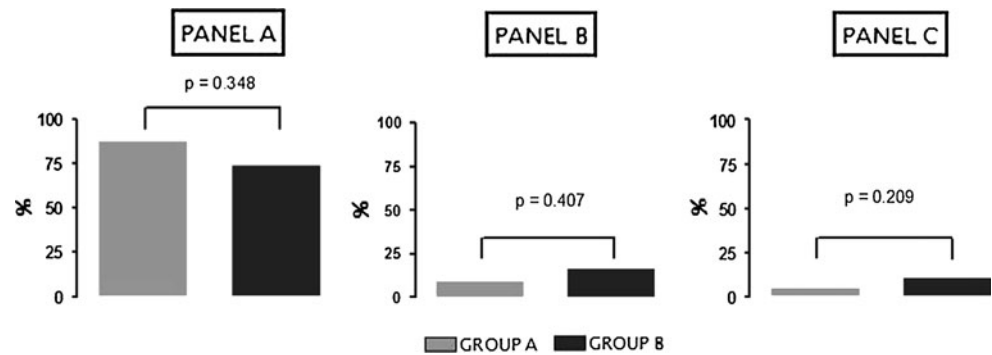
Interestingly, all relapsed patients of group A had a micro or small cancers. In group B, among those who had relapsed/persisted in loco-regional lymph nodes, 14/17 patients (82.3 %) presented a micro or small cancer.

No patients died because of thyroid cancer.

Correlation analysis

Tables 3 and 4 summarize correlation analysis.

Recurrence and/or persistence of the disease was correlated with the presence of lymph node metastases and/or a distant disease at diagnosis, as well as with stimulated Tg values at the first follow-up and following radioiodine therapy. No correlation was found between a recurrent disease and a tumor-associated thyroiditis.

In the multivariate analysis, both tumor relapse and/or persistence were independently predicted by Tg values after stimulation at the first follow-up, also when weighted for the time of follow-up.

Discussion

The first objective of our study was to analyze features of DTC in a homogeneous population over years time-frame analysis. Then, we subdivided these consecutive series of DTC into two groups according to the year of the diagnosis; the rationale for choosing the year 2005 as a cut-off was related to the introduction into clinical practice of the new guidelines for the diagnosis and management of thyroid cancers [14, 15].

Our study has been conducted in an industrial area (Piedmont) known to be iodine-deficient [21], where population has undergone a food education campaign [13] in order to promote the use of iodized salt during the last 20 years. Despite being related only to a single clinical center, our data confirm the trend toward an increase in the incidence of the thyroid cancer as reported in recent years [1]. This evidence may represent a real increase in the pathology, although a greater diagnostic accuracy may also play a role [22]. However, despite the high clinical and

scientific interest for the growing number of thyroid cancer diagnosed, few is known about recognized risk factors for thyroid cancer, apart from ionizing radiation both in childhood and in adulthood and a medical history of goiter or thyroid nodules.

In our population, we found that goiter was the most common coexisting benign thyroid disease in the whole population, but its frequency decreased from group A to group B though not significantly; conversely, the evidence of thyroid autoimmune disease increased over the years with a clear significativity; as a matter of fact, positive serum TPOAb were greatly detected in group B than in A. Some authors simply report that this trend of rising is tied up to the increased attitude to measure serum thyroid autoantibodies during the work-up of a thyroid disease [23]. Instead, other studies [24, 25] show a real increase in the annual incidence of Hashimoto's thyroiditis in Italy, proposing a number of environmental factors as endocrine disrupters. Regarding this, we suspect, in our geographic area, a possible role of iodine supplementation in exacerbating thyroid autoimmunity. This hypothesis is supported by some literature data indicating an evolution of the thyroid autoimmune markers during the course of iodine prophylaxis [26]. However, a limitation of our study is that we defined the ID only on the basis of median UIC such as an extemporaneous evaluation of the iodine intake, while effects of an ID over time may be determined [27]. Further studies methodologically closer to ours will be required to confirm these hypotheses.

Interestingly, we also observed a significant increase of lymphocytic infiltration, mostly focal, associated to DTC from group A to group B at histological analysis.

A role for the lymphocytic infiltration co-expressed with thyroid cancer was hypothesized after the Chernobyl accident [28]; this interpretation is in keeping with the observation that thyroid autoimmune reactions may be related to radiation exposure. Moreover, after the radioactive event (April 26, 1986), the occurrence of thyroid carcinoma in children reached its peak in 1993, with a trend to a plateau in the following years [28]; however, this evidence does not exclude the possibility of a second peak

Table 3 Univariate analysis of epidemiological, clinical, and histo-pathological features of the whole population

	χ^2	Exp (B) (95% CI)	p value
Gender			
F	1.00		
M	0.485	1.467 (0.488–4.411)	0.486
Age			
≤45 years	1.00		
>45 years	0.128	1.179 (0.480–2.893)	0.721
Histotype			
FTC	1.00		
PTC	2.253	0.319 (0.074–1.380)	0.133
Dimension			
≤2 cm	1.00		
>2 cm	2.964	0.300 (0.064–1.403)	0.085
TNM			
T1–T2	1.00		
T3–T4	2.895	0.402 (0.141–1.142)	0.093
Lymph node metastases			
N0	1.00		
N1	6.210	6.375 (1.384–30.142)	0.013
Distant metastases			
Mx	1.00		
M1	11.178	350.8 (350.5–352.5)	0.011
Extrathyroid invasion			
No	1.00		
Yes	2.132	0.412 (0.128–1.322)	0.144
Bilateral foci			
No	1.00		
Yes	0.267	1.312 (0.472–3.648)	0.606
Multifocality			
No	1.00		
Yes	0.039	1.103 (0.419–2.900)	0.843
Associated thyroiditis			
No	1.00		
Yes	0.180	0.789 (0.260–2.395)	0.672
Tg			
Undetectable	1.00		
Detectable (≥1 ng/ml)	7.388	0.288 (0.115–0.721)	0.0070
Radioactive iodine			
Yes	1.00		
No	5.511	3.150 (1.144–8.674)	0.019

Dependent variables: recurrence and/or persistence of disease

Table 4 Multinomial logistic regression of epidemiological, clinical, and histo-pathological features of the whole population

	χ^2	Exp(B) (95% CI)	p value
Overall	14.636		0.0059
Tg levels	4.194	0.369 (0.141–0.966)	0.041
Lymph node metastases (N1)	3.703	1.551 (0.377–6.385)	0.157
Radioactive iodine	1.991	2.151 (0.725–6.384)	0.158

Dependent variables: recurrence and/or persistence of disease

environmental exposures, except ionizing radiation, no occupational risk factors for thyroid cancers have been consistently identified so far, with the exception of a Chinese study [12] documenting an association between thyroid cancer and a long-term employment in textile industry, where an exposure to formaldehyde and benzene can be considered. Interestingly our data seems to confirm these findings. In fact, when we reviewed occupational status of our cohort of patients, the majority of our cohort was employed in textile industries; in particular, female sex was found to be an important variable, though not statistically significant, for development of malignant thyroid pathologies in exposed groups.

However, further epidemiological studies in larger and detailed cohorts are required in order to characterize and confirm the latter evidence. All together, these data could hypothesize that environment features create an inflammatory trigger that facilitates tumor promotion.

In our cohort of patients, we found an higher percentage of tumors not diagnosed before surgery with FNAC, than literature show [30, 31]. Most of these patients were in group A, the older diagnosed, when false negative and non-diagnostic FNAC and a clinical practice not focused on guidelines where evidenced in our institution.

However, the real meaning of high prevalence of incidentalomas, and of its link with lymphocytic thyroiditis, in the occupational exposed group requires a longer observation of these subjects with larger database.

Moreover, we found an increase in the diagnosis of micro or small intrathyroidal carcinoma over the years. This pattern has been reported in other series recently published [23, 32], where some authors raising the question whether the reduced tumors size could be due to an early diagnosis, or to an identification of persistently small thyroid carcinomas, that would have never become clinically evident. In agreement with the first hypothesis, we found that most of recurrences in group B occurred in micro/small, often incidental, carcinomas during the first years after initial treatments, though they were initially considered at low risk.

Notably, we found an increased prevalence of cancers N0 and N1 in group B, as a consequence of the reduction of

occurring in following decades and having a longer latency period, similarly to that observed after external radiation [29]; in fact the majority of our patients was older than 45 years and was affected by a classical variant of PTC with a mean latency period exposure to Chernobyl accident and diagnosis of 16.0 ± 2.5 years and 22.5 ± 1.3 years in group A and B, respectively. Regarding other

Nx stage, as well as a greater number of patients with metastatic disease. This evidence can be correctly interpreted as the results of an improvement in the diagnostic accuracy (rhTSH introduction in clinical practice, FNAB, US and other imaging techniques as ^{18}FDG-PET) in the last years, more than a worse clinical profile in group B. Our data fit with others in scientific literature [33, 34].

When we consider the changes in the follow-up and outcome management in our patients, we found that, in agreement with other data in literature [35–37], the presence of loco-regional or distant metastases at the time of diagnosis were principal predictors of recurrence or persistence of the disease. Particularly, Tg levels at the first postsurgical evaluation, after L-tiroxine withdrawal or exogenous rhTSH stimulation, were the strongest predictor of the outcome, as reported by Castagna et al. [38]. In our experience, radioiodine therapy showed to be related to a better outcome, also in microcarcinomas. However, the benefit to perform radioiodine therapy even in low risk patients remains unclear, given that the disease-specific mortality rate on DTC patients is very low. Speculations on alternative outcome markers in a longer follow-up should be considered. This concept has been recently validated by Tuttle [39] that proposed a dynamic risk assessment that can be used to tailor more effectively, ongoing follow-up recommendation.

In conclusion, our data show that after the introduction of the new guidelines in 2006 earlier diagnosis and more effective treatments for DTC was present in our patients' population. We speculate that an early identification of the tumor (and its recurrences) is the reason of a better outcomes together with the introduction of the new guidelines in clinical practice with a better stratification through the new TNM staging. In our population, we can speculate that the inflammation induced by the iodine prophylaxis might accelerate the tumor progression in patients submitted to an iodine supplementation in adulthood. Other variables, such as occupational factors and the fallout influence of Chernobyl, could help to individualize the follow-up and indentify populations needing more aggressive treatments.

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