original article

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Natural history and clinical outcome of differentiated thyroid carcinoma: a retrospective analysis of 1503 patients treated at a single institution

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Background: The study evaluates clinical presentation and outcome of differentiated thyroid cancer (DTC) on a large series of patients homogeneously managed.

Patients and methods: A cohort of 1503 DTC followed according to a standardized protocol entered the study. Main outcome measures were clinical presentation at the diagnosis, survival, morbidity and prognostic risk factors.

Results: Median age at diagnosis was 46 years. Papillary cancer and low pathological tumor–node–metastasis stages represented >80% of cases. Cancer specific survival at 5, 10 and 15 years was 98.6%, 94.7% and 87.4%; 10-year disease-free and progression-free survivals were 96.8% and 17.1%, respectively. Cancer-specific mortality rate was 2.5% [95% confidence interval (CI) 1.7% to 3.4%], recurrence rate was 0.6 % while morbidity rate was 12.6% (95% CI 11% to 14%). Response to radioiodine treatment is the strongest predictor of a good outcome in multivariate analysis (hazard ratio 211, $P < 0.0001$). Other independent predictor variables are sex, age, histology and distant metastases for survival and metastases for morbidity.

Conclusions: A rigorous initial therapeutic approach leads to a better survival and a very low morbidity. Patients who do not respond to radioiodine treatment have a worse prognosis.

Key words: morbidity, radioiodine therapy, survival, thyroid carcinoma

introduction

Despite its clinical impact, differentiated thyroid cancer (DTC) is a difficult topic for evidence-based decision making and management strategies are still largely empirical.

The indolent course of the disease requires very large cohorts of patients followed over several decades to confirm significant differences in prognostic factors and treatment efficacy [1]. Neither randomized clinical trials nor meta-analysis are available and evidence is based on a number of retrospective studies with multivariate analyses for mortality risk factors or data from national cancer registries [2–8]. Unfortunately, very remarkable differences in patients' selection, staging systems and clinical management affect the available studies, mainly those including a long period of observation [3–5]. In particular, radioiodine treatment is not routinely carried out in a standard manner and outcome results of different studies are thus not comparable.

In addition, during the last 10 years, there has, these patients are generally long survivors, plain survival is probably not the best gold standard end point of treatment, been a dramatic change in the natural history of the disease, with progressively increasing tumor incidence around the world, and in the clinical approach, with the continuous evolution of diagnostic modalities [9, 10]. In the mean time, DTC follow-up paradigms have progressively changed toward a standard care, balanced between achieving cure and minimizing overtreatment [11].

In this study, data from a large cohort of patients with DTC homogeneously treated and managed at the same institution in the last 15 years were retrospectively analyzed. The end points of the study were as follows: (i) pattern of DTC clinical presentation at the end of twentieth century; (ii) clinical outcome in patients treated by total thyroidectomy plus radioiodine therapy as primary treatment during long-term follow-up with both survival and morbidity as outcome measures and (iii) prognostic role of examined variables in relation to the selected outcome measures.

patients and methods

patients' cohort and study design

A retrospective analysis of a cohort of 1503 patients with DTC enrolled at Nuclear Medicine Division of 'Regina Elena' National Cancer Institute during the period January 1991–January 2006 was carried out. Among them, 1437 (95.6%) had a new cancer diagnosis and were referred for primary radioiodine treatment immediately after surgery while 66 (4.4%)

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Table 1. Clinical data of patients' cohort

Variable	Category	No. of patients	%
Sex	Male	322	21.4
	Female	1181	78.6
Age	<45	745	49.6
	≥45	758	50.4
Histology	Papillary	1282	85.3
	Follicular	221	14.7
Histological variants[a]	1	508	76.5
	2	44	6.7
	3	76	11.4
	4	36	5.4
Multifocality (>3 tumor foci)	No	1159	77.1
	Yes	344	22.9
Tumor size	pT1	678	45.1
	pT2	459	30.5
	pT3	52	3.5
	pT4	314	20.9
Node status	pN0	1205	80.2
	pN1	298	19.8
Metastases	M0	1472	97.9
	M1	31	2.1
Stage	I	1036	68.9
	II	201	13.4
	III	236	15.7
	IV	30	2
Node surgery[b]	Conservative	1176	78
	Aggressive	327	22
Clinical presentation	New diagnosis	1437	95.6
	Previous diagnosis	66	4.4
TWB	Thyroid remnant	1133	75.4
	Tumor evidence	370	24.6
oN	Negative	1051	69.9
	Positive	452	30.1
oM	Negative	1347	89.6
	Positive	156	10.4
Response to ^{131}therapy	CR	1281	85.2
	PR	165	10.9
	SD	21	1.4
	PD	36	2.3

[a]Histological variants of papillary carcinoma were categorized into four classes of increasing aggressiveness [19]: 1 = encapsulated, not otherwise specified, clear cell, oncocytic (oxyphilic), follicular; 2 = solid follicular, diffuse follicular, 3 = diffuse sclerosing, squamous cell, with exuberant stroma; 4 = tall cell, columnar cell, insular carcinoma. Hurtle cell carcinoma was also categorized as class 4.

[b]Node surgery was defined as follows: conservative, no node surgery or minimal lymph node plucking; aggressive, medial or lateral compartment lymphadenectomy.

TWB, ^{131}I post-therapy whole-body scan; oN, overall node metastases evidenced both at pathological tumor–node–metastasis (pTNM) and at TWB scan; oM, overall distant metastases evidenced both at pTNM and at TWB scan; CR, complete response after one or more radioiodine consecutive cycles (initial cure); PR, partial response (reduction of disease documented by ^{131}I DWB uptake, thyroglobulin values and radiological studies); SD, stable disease; PD, progressive disease.

Table 2. Characteristics of 37 cancer-related deaths

Variable	Category	Cancer deaths, *n*	Mortality rate of the specific category (%)
All cancer deaths	All population	37	2.5
Sex	Male	19	5.9
	Female	18	1.5
Age	<45	4	0.5
	≥45	33	4.3
Histology	Papillary	18	1.4
	Follicular	19	8.5
Histological variants[a]	1	14	2.7
	2	5	11.3
	3	7	9.2
	4	11	30.5
Tumor	pT1	6	0.9
	pT2	8	4.5
	pT3	6	30.7
	pT4	17	14.3
Node status	pN0	7	0.5
	pN1	30	10
Metastases	pM0	26	1.7
	pM1	11	35
Stage	I	5	0.5
	II	7	3.4
	III	14	5.8
	IV	11	37
Clinical presentation	New diagnosis	28	1.9
	Old diagnosis	9	13.6

[a]Histological variants of papillary carcinoma were categorized into four increasing aggressiveness classes [19]: 1 = encapsulated, encapsulated, not otherwise specified, clear cell, clear cell, oncocytic (oxyphilic), follicular; 2 = solid follicular, diffuse follicular; 3 = diffuse sclerosing, squamous cell, with exuberant stroma; 4 = tall cell, columnar cell, insular carcinoma. Hurtle cell carcinoma was also categorized as class 4.

were referred with a previous diagnosis and surgery (dating >2 years) and no previous radioiodine treatment.

All the patients included in the analysis had total or near-total thyroidectomy at different surgical institutions located in and around Rome, Italy. The node surgical management was on the contrary heterogeneous, ranging from no node surgery to systematic lymphadenectomy. The primary tumor was histologically classified according to the World Health Organization criteria [12] and staged according to the tumor–node–metastasis (TNM) classification (4th edition) for malignant tumors [13]. Histological variants of papillary carcinoma were also considered when available [14]. An internal re-evaluation of histological specimen was made by a senior pathologist, when histological reports were considered not completely addressing the required data. All patients after the admission to the study were submitted to radioiodine therapy and aftercare management in a standardized manner according the protocol described below.

protocols of treatment and follow-up

A 185 MBq ^{131}I diagnostic whole-body scan (DWB) was carried out 4 to 6 weeks after surgery followed after few days by in-patient ^{131}I therapy administration. The activity chosen for DWB does not be exceed suggested limit to minimize stunning effect, if any [15]. Therapeutic ^{131}I activity was

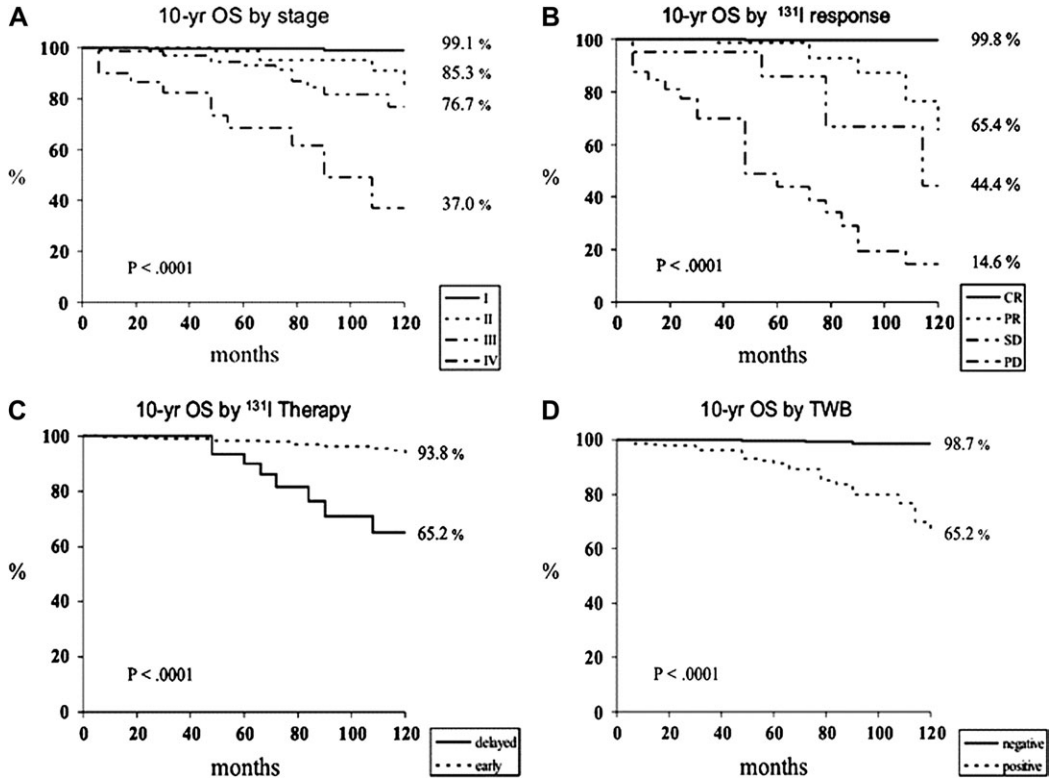

Figure 1. Ten-year overall specific cancer survival curves (OS) according to themain significant prognostic variables. (A) Stage (I/II/III/IV); (B) ^{131}I response [complete response (CR)/partial response (PR)/stable disease (SD)/progressive disease (PD)]; (C) ^{131}I therapy early and delayed; (D) TWB negative (i.e. only thyroid remnant)/positive (disease evidence).

estimated according to DWB ^{131}I uptake and ranged from 3700 MBq ± 10% for thyroid residual tissue ablation to 5500–9200 MBq for residual tumor or metastases treatment. A ^{131}I post-therapeutic whole-body scan (TWB) was carried out 5–7 days after therapy. All patients had stopped L-thyroxine and tri-iodothyronine 4–5 weeks and 15 days prior the first radioiodine procedure, respectively, in order to achieve a minimum of thyrotropin levels >30 mU/l on the day of ^{131}I administration. Hormonal therapy was then replaced 24 h after radioiodine treatment in all patients [16]. A low-iodine diet was also requested during the 10 days before the radioiodine administration.

A DWB was repeated 6–12 months after the therapy and reablation was considered if persistent uptake was observed. Initial cure (disease-free status) was defined by all the following criteria: absence of pathological ^{131}I uptake on DWB, undetectable serum thyroglobulin (Tg) value measured on thyroid hormone withdrawal, normal anti-Tg antibody value, no evidence of residual disease at neck ultrasonography and other clinical or radiological examinations.

Follow-up program was based on periodical clinical controls and a series of investigations, including serial assessment of Tg and anti-Tg antibody, neck ultrasonography and DWB, all carried out at our institution. Patients with persistent or recurrent disease after radioiodine therapy were submitted to additional cancer treatment as appropriate.

data analysis

All patients data records were collected on an internal centralized database by dedicated nuclear medicine physicians with clinical experience on thyroid disease.

Among all the collected data, the main prognostic variables chosen and the relative categorizations used for the present analysis are illustrated in Table 1. Final disease status at last follow-up (dead or alive, alive with or without disease) and cause of death were also considered for the analysis. Tumor recurrence was defined as a new evidence of locoregional disease or distant metastases occurring >6 months after successful primary therapy, while morbidity was defined as overall evidence of disease, both recurrent and persistent. Disease-free survival (DFS) and progression-free survival (PFS) were considered also as indexes of morbidity, respectively, in patients who had initial cure and in patients with recurrent or persistent disease.

statistical methods

Survival curves, i.e. overall survival, cancer specific survival, DFS and PFS, were estimated by the Kaplan–Meier product-limit method. The log-rank test was used to assess difference between subgroups. Significance was defined at $P < 0.05$ level. The hazard risk and the confidence limits were estimated for each variable associated with cancer-specific mortality and morbidity using the Cox univariate model and adapting the most suitable prognostic category as a reference group. A multivariate Cox proportional hazard model was also developed using stepwise regression (forward selection) with predictive variables which were significant in the univariate analyses. Hazard risks <1 indicated improved outcome and those >1 indicate a worsened outcome. Enter and remove limits were $P = 0.10$ and $P = 0.15$, respectively. Chi-square test was also used for proportion analysis. The SPSS (11.0) statistical package was used for analysis.

results

clinical presentation of the cohort

Detailed data on the cohort are illustrated in Table 1. The median age of the cohort at diagnosis was 46 years (range 10–85

years) with only a little difference between the sexes (48 years for male and 45 years for female). Female/male ratio was 3.6 : 1 while papillary/follicular ratio was 5.8 : 1. Data on the histological variants were available in 664 patients only, with less aggressive variants representing 84% of cases. Over 80% patients presented low pathological tumor–node–metastasis (pTNM) stages (stages I and II); metastases prevalence at the study entry was 19.8% for node metastases and 2.1% for distant metastases, respectively. The DWB and TWB demonstrated post-surgery tumor evidence in 14.4% and 24.6% of the cohort, respectively. Accordingly, the true initial metastases prevalence, considering both pTNM and TWB evidence, was 30.1% for node metastases (oN—overall node metastases) and 10.4% for distant metastases (oM—overall distant metastases). Median follow-up was 60 months with a minimum follow-up of 24 months.

No significant differences in baseline clinical presentation (sex, age, surgery, histology and pTNM) were observed in the group of 66 patients with previous diagnosis versus the larger group of patients with new diagnosis. Median time from initial surgery to nuclear medicine admission in these patients was 5 years (range 2–25 years) while in the patients with new diagnosis it was 2 months (range 1–6 months). Over 35% of patients with previous diagnosis presented at the entry to the study evidence of radiologically documented locoregional recurrence. The prevalence of disease increased to 53% with TWB study, which was significantly higher than the 23% observed in the group of patients with new diagnosis ($P < 0.0001$).

survival

Forty-six of 1503 patients died during the whole observation period. Thirty-seven deaths were cancer related, yielding a cancer specific mortality rate of 2.5% (95% CI 1.7% to 3.4%) for the whole cohort. Cancer deaths are detailed in Table 2.

Over 10% of cancer-specific deaths was represented by patients who had <45 years at the time of initial diagnosis and treatment with five patients (13.5%) in stage I. All younger patients died by local invasion. Interestingly, 24.3% of cancer deaths were represented by patients with previous diagnosis who received a delayed radioiodine therapy after surgery. Mortality rate in this group was 13.6% and was significantly higher compared with that observed in patients with new diagnosis and early treatment (1.9%, $P < 0.0001$).

Overall survival by Kaplan–Meier curves was 98.4%, 93.7% and 83.5% at 5, 10 and 15 years, respectively, while cancer-specific survival was 98.6%, 94.7% and 87.4% at 5,10 and 15 years, respectively. Cancer-specific survival curves at 10 years according to the main prognostic variables are illustrated in Figure 1.

A significant better likelihood of survival over time ($P < 0.0001$ by log-rank test) was observed in females, younger patients, papillary tumors, patients without distant metastases and patients showing only thyroid remnants at TWB. Also significant differences were observed according to pT size, TNM stages and clinical response to radioiodine therapy. Patients with new diagnosis and early radioiodine therapy had a significant better likelihood of survival over time than the group of patients with delayed radioiodine therapy after surgery ($P < 0.0001$ by log-rank test).

No significant difference was observed by log-rank test between unifocal and multifocal tumors ($P = 0.14$) and node surgical approach (p = 0.83).

morbidity

During the whole observation period, 190 patients lived with the disease: only eight had a cancer recurrence after the initial cure while in the remaining 182 cases, there was a persistent disease. Accordingly, the overall morbidity rate was 12.6% in the whole cohort (95% CI 11% to 14%). Overall recurrence rate in the cohort of patient who had initial cure (1281 patients) was only 0.6%. Locoregional recurrence was observed in six patients while lung metastases occurred in two patients. Median time to recurrence after initial cure was 54 months (range 36 to 120 months).

Overall DFS and PFS at 10 years are illustrated in Figure 2.

prognostic analysis

Univariate and multivariate analysis results for cancer mortality and morbidity are illustrated in Tables 3 and 4.

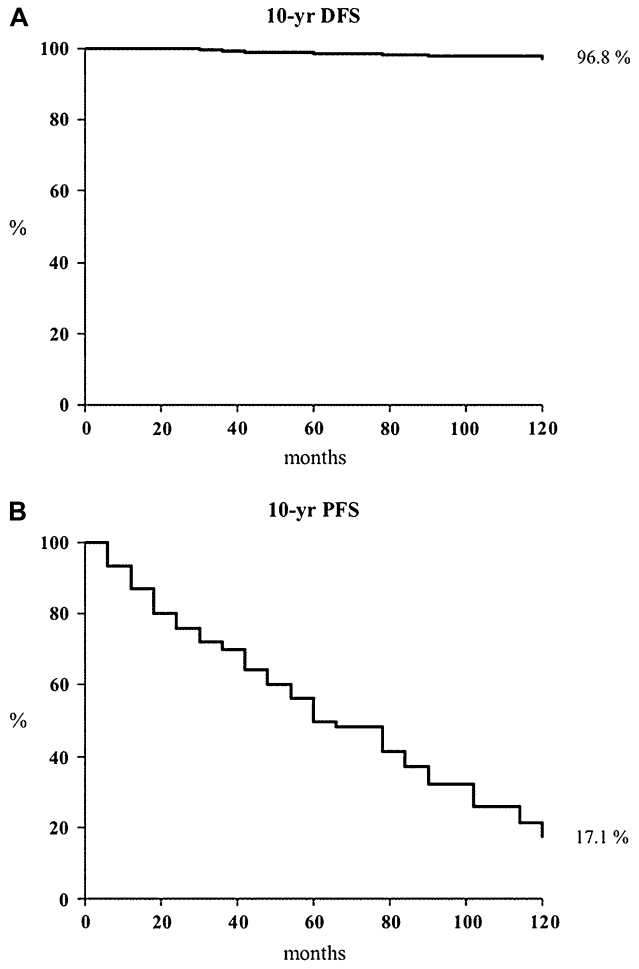

Figure 2. Ten-year overall disease-free survival (DFS) curve (A) and 10 year overall progression-free survival (PFS) curve (B).

Table 3. Univariate and multivariate analysis by Cox proportional model related to cancer-specific mortality

Variable	Description	HR	95% CIs	*P*
Univariate				
Patients				
Sex	Male versus female	4.92	2.57–9.41	0.0001
Age	≥45 versus <45	11.19	3.95–31.69	0.0001
Tumor				
Histology	Follicular versus papillary	5.34	2.73–10.44	0.0001
Multifocality	No versus yes	2.39	0.73–7.83	0.14
pT	T3–T4 versus T1–T2	6.16	3.16–12.01	0.0001
	T2–T3–T4 versus T1	4.48	1.87–10.75	0.001
	T2 versus T1	1.91	0.66–5.5	0.23
pN	N1 versus N0	0.80	0.36–1.71	0.58
pM	M1 versus M0	19.15	9.40–39.01	0.0001
Stage	III–IV versus I–II	13.08	6.31–27.04	0.0001
Histological variants	4 versus 1–2–3	3.48	1.12–10.82	0.03
	3–4 versus 1–2			n.s.
	2–3–4 versus 1			n.s.
TWBS	Tumor evidence versus only thyroid remnant	17.78	6.90–45.92	0.0001
oN	Overall N1 versus overall N0	2.28	1.18–4.42	0.01
oM	Overall M1 versus overall M0	11.99	6.16–23.32	0.0001
Treatment				
Node surgery	Conservative versus aggressive	1.27	0.60–2.71	0.52
^{131}Therapy	Delayed versus early	1.80	0.76–4.22	0.17
^{131}I response	No versus yes	211	n.e.	0.0001
Multivariate				
Patients				
Sex	Male versus female	3.88	1.93–7.82	0.0001
Age	≥45 versus <45	6.76	2.23–20.46	0.001
Tumor				
Histology	Follicular versus papillary	3.76	1.88–7.52	0.0001
pM	M1 versus M0	2.15	0.96–4.781	0.06
TWB	Tumor evidence versus only thyroid remnant	12.34	4.20–36.27	0.0001
Treatment				
^{131}I response	No versus yes	211	n.e.	0.0001

HR, hazard ratio; CI, confidence interval; n.s., not significant; TWB, ^{131}I post-therapy whole-body scan; oN, overall node metastases evidenced both at pathological tumor–node–metastasis (pTNM) and at TWB scan; oM, overall distant metastases evidenced both at pTNM and at TWB scan; no, no complete response after radioiodine (including progression of disease, stable disease and partial response); yes, complete response; n.e., not evaluable because of the high number of events (deaths) in patients with no response.

The strongest predictor of increased risk of cancer-related death is an unsuccessful radioiodine treatment (hazard ratio 211, $P < 0.0001$). Other independent predictor variables for cancer death confirmed at multivariate analysis are sex, age and histology. When the radioiodine response was excluded from the analysis, distant metastases at diagnosis (pM) and TWB evidence of tumor disease appeared also as independent predictors for cancer mortality.

Multivariate analysis confirmed as independent predictor variables of increased risk of cancer morbidity-only node and distant metastases when the radioiodine response was excluded from the analysis.

discussion

The analysis of our DTC cohort, evaluated with a standardized protocol, evidences a number of interesting epidemiological and clinical topics that can be useful to refocus the therapeutic approach.

A first important point to note is the relative distribution of papillary and follicular carcinoma, strongly unbalanced in favour of papillary forms (about six times more frequent). This result probably reflects an increasing peak of papillary carcinoma in the last 15 years in Europe according to the similar observation registered in the United States in the corresponding years [2, 5, 10]. Median age and female/male ratio were well comparable with the European range [17–19] while the peak age at diagnosis resulted lower and more homogeneously divided between the sexes than recently reported in Surveillance, Epidemiology and End Results (SEER) program: 40–50 versus 65–69 years for male and 35–45 versus 40–44 years for female, respectively [20]. Most tumors were represented by stage I patients (68.9%); this result is in the upper range of literature data ranging from 44% to 74%

Table 4. Univariate and multivariate analysis by Cox proportional model related to cancer specific morbidity.

Variable	Description	HR	95% CIs	*P*
Univariate				
Patients				
Sex	Male versus female	1.88	1.22–2.88	0.004
Age	≥45 versus <45	2.04	1.35–3.1	0.001
Tumor				
Histology	Follicular versus papillary	2.18	1.39–3.43	0.001
Multifocality	Yes versus no	1.39	0.88–2.19	0.15
pT	T3–T4 versus T1–T2	4.47	2.9–6.69	0.0001
	T2–T3–T4 versus T1	3.54	2.14–5.86	0.0001
	T2 versus T1	1.96	1.07–3.50	0.02
pN	N1 versus N0	1.72	1.12–2.64	0.01
pM	M1 versus M0	9.29	5.41–15.94	0.0001
Stage	III–IV versus I–II	6.47	4.32–.67	0.0001
Histological variants	4 versus 1–2–3	5.35	2.58–11.08	0.0001
	3–4 versus 1–2	3.37	1.85–6.13	0.0001
	2–3–4 versus 1	2.68	1.51–4.79	0.001
TWB	Tumor evidence versus only thyroid remnant	15.93	9.67–26.24	0.0001
oN	Overall N1 versus overall N0	4.30	2.83–6.54	0.0001
oM	Overall M1 versus overall M0	7.61	5.03–11.51	0.0001
Treatment				
Node surgery	Aggressive versus conservative	1.30	0.94–2.00	0.23
^{131}Therapy	Delayed versus early	4.82	2.92–7.98	0.0001
^{131}I response	No versus yes	211	n.e.	0.0001
Multivariate				
Tumor				
pN	N1 versus N0	2.38	1.39–7.17	0.001
pM	M1 versus M0	3.39	1.61–7.17	0.001
oN	Overall N1 versus overall N0	4.81	2.67–8.87	0.0001
oM	Overall M1 versus overall M0	2.08	1.20–3.56	0.009
Treatment				
^{131}I response	No versus yes	211	n.e.	0.0001

HR, hazard ratio; CI, confidence interval; TWB, ^{131}I post-therapy whole-body scan; oN, overall node metastases evidenced both at pathological tumor–node–metastasis (pTNM) and at TWB scan; oM, overall distant metastases evidenced both at pTNM and at TWB scan; no, no complete response after radioiodine (including progression of disease, stable disease and partial response); yes, complete response; n.e., not evaluable because of the high number of events (progressions) in patients with no response.

[5, 6,17–19]. Prevalence of node metastases (19.8%) and distant metastases (2.1%) at pTNM staging was in the lower range compared with previous reports (up to 60% and 10%, respectively) [21, 22]. All these figures together probably reflect the modern trend toward an early diagnosis [9, 19].

Another important point to focus is that the prevalence of metastases at the initial conventional pathological staging was underestimated. In fact, 25% of patients had residual disease after surgery, both locoregional and/or distant, mostly unexpectedly observed only at TWB. Using a corrected staging system (pTNM plus TWB evidence), the overall node involvement resulted 30.1% while overall distant metastases disease prevalence was 10.4% instead of 19.8% and 2.1%, respectively. Over 7% patients classified as stage I and 8% pT1 patients unknown distant metastases at TWB. In these patients, radioiodine therapy determined an important disease upstaging.

Analyzing survival, we observed an overall cancer-specific survival that is better than previously reported over the world and particularly in Europe. In fact, the 10-year survival rates for overall DTC in large American series range from 87% to 94% (92%–94% and 81%–92% for papillary and follicular, respectively) [2, 6,23–25] while the European average 5-year survival in 1990s is 83% (72%–74% for men and 80%–85% for women) [26–28].

The large prevalence of lower pTNM stages in our cohort cannot be the only explanation of the observed better survival. In fact, our results are better than those obtained by Loh et al [6] in a cohort of 700 DTC with a similar distribution of TNM stages, i.e. 74% of stage I patients (94.7% versus 92%, cancer-specific survival at 10 years).

This point is confirmed by the specific cancer mortality rate observed in our cohort (2.5%) which is the lowest reported in literature until now. In fact, cancer-specific deaths reported in similar large series range from 5% to 8.4% for a 10- to 30-year period [2, 6].

Older age, more advanced stages III and IV, locally advanced T4 tumors and distant metastases explain most of the cancer deaths while partition among papillary and follicular forms is

quite similar. Nearly 1% of microcarcinomas died of the disease as 0.5% of stage I patients: very small, but not completely trivial numbers. Multivariate analysis confirms as independent predictor variables for cancer-specific survival only sex, age, histology, distant metastases (pM1) and TWB evidence of disease. These results are substantially confirming literature data with the added value of TWB result [4, 10, 29]. The strongest predictor of a good outcome is, however, the response to radioiodine treatment.

Results presented for morbidity are equally very encouraging: in our cohort, initial cure was obtained in a very large percentage of patients (85.2%) with only a 0.6% cumulative recurrence rate over 15 years which is the lowest reported to date in the literature. In fact, a 15%–30% recurrence rate over 30-year period is generally reported with just over half of all recurrence occurring within 5 years from the initial diagnosis [1, 6]. DFS curve shows that the likelihood of a definitively cure, in patients with initial complete response (no evidence of disease), is over 96% at 10 years (figure 2A). It is possible that the rigorous criteria adopted in our follow-up protocol minimize the chance of misclassification of minimal persistent disease as late recurrence. Nevertheless, our recurrence findings are unequivocal better than reported in other series, probably due to radioiodine treatment carried out routinely after total thyroidectomy.

If survival is an obvious outcome index, morbidity is not less important for its impact on individual quality of life and on social health issues. However, recurrence rate is not a comprehensive index of morbidity considering that there is no negligible number of patients not cured and long living with disease. A better working index for morbidity might be recurrent or persistent disease with treatment strategies aiming at minimizing both eventualities. Unfortunately, despite a wealth of evidence on recurrence rate and DFS, no studies are focused on morbidity in thyroid cancer. In our series of 1503 patients, overall morbidity rate resulted 12.6% including both recurrence after initial cure and residual disease not completely cured by the therapy. This means that of the 25% of patients with post-surgery evidence of residual metastatic disease, only about an half can be definitely cured by radioiodine while the other half is either partially controlled or not responding at all to the therapy. PFS curve shows that, in patients with persistent disease after surgery and radioiodine or recurrent disease, the likelihood of living with stable disease (less than a 50% reduction and less than a 25% increase in the sum of the products of two perpendicular diameters of all measured lesions and the appearance of no new lesions) is only 17.1 % at 10 years (Figure 2B). Prognostic risk factors for morbidity are the presence of metastases both nodal and at distance: factors having nothing to do with sex, age at diagnosis and histology. These data stress the importance of an optimal surgery at initial presentation routinely followed by a radioiodine therapy and subsequent staging including radioiodine scans, as recently suggested in another large retrospective study [30].

In conclusion, the results of this study can be summarized as follows:

(i) a progressively changing trend in DTC natural history characterized by an increasing prevalence of papillary carcinoma, a lower age of initial diagnosis in male sex and a greater prevalence of lower pTNM stages is deploying and is probably at least in part due to an earlier diagnosis; the likelihood of death is low but not negligible even in young patient and in low stages.

(ii) an initial therapeutic approach including radioiodine therapy leads to a very low recurrence rate and decreased cancer death justifying new simplified and less distressing follow-up algorithms in patients with initial cure; patients who do not respond to radioiodine treatment and who have a worse prognosis deserve increased efforts in follow-up and tentative alternative therapeutic approaches.

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