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Original research

Clinical outcome in differentiated thyroid carcinoma and microcarcinoma

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ABSTRACT

Introduction: Due to the frequent use of neck ultrasonography, the incidence of differentiated thyroid microcarcinoma (DTMC), defined as a lesion with greatest dimension ≤1 cm, is increasing worldwide. Although DTMC generally has a lower aggressivity and a better prognosis than differentiated thyroid carcinoma (DTC), some cases of clinically aggressive DTMC were found. The aim of this study is to compare the rate of recurrence in DTMC and DTC, during a 3-year follow-up.

Methods: Patients with differentiated thyroid carcinoma, who underwent total thyroidectomy and postoperative ^{131}I-RAI ablation, were stratified according to lesion diameter (DTC for diameter > 1 cm or DTMC ≤ 1 cm). After surgery, patients underwent a 3-year follow-up. Recurrent disease was defined on the basis of positive biochemical (Tg > 2 ng/ml under TSH-suppression or after rhTSH-stimulation) and/or imaging (US, WBS, CT, PET/CT) findings.

Results: 449 patients have been included in the final analysis. Linfoadenectomy rate and RAI ablative dose were significantly higher in DTC than in DTMC (32.7% vs. 22.4%, $p = 0.018$ and112.3 ± 21 vs. 68.3 ± 24.1 mCi, $p < 0.001$). During the follow-up, 50 carcinoma recurrences occurred, more frequent in DTC than in DTMC (15.6% vs. 7.6%, $p = 0.010$). After adjustment for gender, age, rate of lymph node dissection and 131I dose of RAI treatment, the difference in the risk of recurrence was no longer significant among DTC and DTMC patients (HR: 1.585, 95% CI 0874–2877, $p = 0.130$).

Conclusions: The prediction of disease severity cannot be based exclusively on lesion diameter. A more careful therapeutic approach and follow-up should be recommended in DTMC patients.

1. Introduction

Differentiated thyroid carcinoma (DTC) accounts for about 95% of the endocrine tumors [1], with a mortality rate of 0.5/100.000 cases [2] and persistence/recurrence of the disease of 15–27% [3,4]. DTC has a multifactorial etiology, that includes environmental factors (low-iodine areas, ionizing radiations, family history of thyroid cancer, female sexual hormones) and genetic factors (BRAF, RET/PTC, RAS, PAX8/PPARγ) [5]. According to the World Health Organization classification system for thyroid tumors, differentiated thyroid microcarcinoma (DTMC) is defined as a differentiated thyroid carcinoma measuring ≤10 mm in its greatest dimension [6]. The incidence of DTMC is increasing worldwide [7–9], along with the frequent use of neck ultrasonography (US) [10,11]. Some data suggest that DTMC has a lower aggressivity and has a better prognosis than DTC [11]. However, some DTMC cases were found to be clinically aggressive and the local recurrence rate is widely variable in different literature reports [12]. Accordingly, there is not common agreement about DTMC's treatment. ATA's recommendation for the treatment of low-risk, unifocal intrathyroidal papillary microcarcinoma, without cervical lymph nodes metastasis, is lobectomy; however, in presence of multifocality, contralateral or distant metastasis, family history of DTC or earlier neck region irradiation, it is recommended to perform total or near-total thyroidectomy [13]. Nevertheless, since some DTMC show an aggressive behavior, several studies suggest total thyroidectomy in patient with DTMC [14–18]. Radioactive iodine-131 (RAI) treatment is performed after surgery to remove any iodine-avid residue and to

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reduce the recurrence risk. According to ATA's guidelines, very low risk patients (lesion with greatest dimension ≤1 cm, surgical radicality, classical variant of papillary thyroid carcinoma), RAI ablation is not indicated as it has not effective benefit [13]. However, recent studies show many patients affected by DTMC and not treated with RAI have an increased recurrence risk [19]. Given the high variability in literature recommendations, we performed this study with the specific aim to compare the rate of recurrence in DTMC and DTC, during a 3-years follow-up.

2. Methods

Between 2002 and 2007, 449 consecutive patients, were enrolled in our study; they had histological diagnosis of differentiated thyroid carcinoma and underwent total thyroidectomy (with or without linfoadenectomy) and postoperative RAI ablation.

Study population has been stratified according to lesion major diameter as DTC in the presence of a lesion diameter >1 cm, or DTMC for lesion diameter ≤1 cm.

Lesions were classified based on focality (unifocal/multifocal) and according to pTNM staging (Tumour Node Metastasis, AJCC Cancer Staging Manual, Seventh Edition), which evaluates parameters such as lesion diameter, capsular invasion, extrathyroidal structures extension, presence of lymph node metastases at diagnosis, as well as ATA classification system [13]. Moreover it was recorded if they underwent lymphadenectomy of the central compartment (level VI), as well as of lymph node levels II, III and IV. All enrolled patients underwent post-operative RAI ablation with ^{131}I and received TSH-suppressive therapy with L-thyroxine (L-T4).

After 6–12 months from thyroidectomy, all patients underwent a complete assessment including clinical, biochemical and instrumental examination. During the follow-up, in all patients laboratory tests were performed on venous blood samples with an electrochemiluminescence immunoassay (Elecsys E170, Roche Diagnostics, Mannheim). TSH (0.3–4.2 μU/ml), FT3 (2.0–4.4 pg/ml), FT4 (0.9–1.7 ng/dl), Tg (0–50 ng/ml), Tg-Abs (0–115 IU/ml) levels were measured at baseline and after stimulation with recombinant human TSH (rhTSH). The hormone assay was practiced with the patient fasted for at least 8 h and before taking the daily dose of L-T4. Patients received two injections of 0.9 mg of rhTSH in two consecutive days with Tg measurement on the fifth day, in accordance with standard protocols [20]. Since the presence of Tg-Abs interferes with Tg assay, patients were always checked for the presence of Tg-Abs high levels in order to avoid false positive or false negative results.

A positive stimulated Tg at follow-up was defined by a value >2 ng/ml in the absence of Tg-Abs.

As imaging assessment, all patients underwent periodic neck US, performed by the same operator and using the same instrument (Esaote MyLab 25), with a probe from 8 to 10 MHz.

Tg under TSH-suppressive L-T4 therapy and US were evaluated throughout the follow-up period at 6–12 months intervals; while stimulated Tg was measured in all patients at 1 year from RAI therapy and was repeated when necessary. WBS, computed tomography (CT) and fluorodeoxy-D-glucose-positron emission tomography/CT (FDG-PET/CT) were performed when indicated, usually when the Tg was elevated and neck US was negative.

Recurrent disease was defined on the basis of positive biochemical (Tg under TSH-suppression or after rhTSH-stimulation) and/or imaging (US, WBS, CT, PET/CT) findings.

Statistical analysis was performed with the SPSS 16 system (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean ± SD; categorical variables were expressed as %. In case of values with a skewed distribution, Kolmogorov–Smirnov test was used to compare means. The chi-square test was employed to analyze categorical data. When the minimum expected value was <5, the Fisher's exact test was used.

A Kaplan–Meier survival model (with the Log-Rank test) was adopted to evaluate the cumulative disease-free survival according to the type of carcinoma (DTC vs. DTMC) and each patient has been censored at the time of the first recurrence. To adjust for all the other variables found to be associated with disease-free status at univariate analyses and to evaluate the risk of disease recurrence in DTC and DTMC, a COX regression analysis (stepwise method) was adopted. Multi-collinearity effect in multivariable regression models was excluded by a stepwise approach with each variable included for $p < 0.05$ and excluded for $p > 0.1$. All the results are presented as 2-tailed values with statistical significance if p values < 0.05.

3. Results

449 patients (102 males and 347 females) have been included in the final analysis of the study, after excluding 23 patients because of

Table 1
Clinical and demographic characteristics of the study population.

	Whole sample ($n = 449$)	DTC ($n = 199$)	DTMC ($n = 250$)	p
Age – years[a]	41.9 ± 13.6	42.6 ± 13.7	41.8 ± 13.6	0.609
Male gender – n (%)	102 (22.7)	49 (24.6)	53 (21.2)	0.428
Mean diameter – mm	13.3 + 9.1	20.8 + 8.9	7.3 + 2.2	<0.001[b]
Histological type- n (%)				
Papillary (common type)	291 (64.8)	130 (65.3)	161 (64.4)	0.934
Follicular variant	87 (19.4)	35 (17.6)	52 (20.8)	
Sclerosing variant	11 (2.4)	5 (2.5)	6 (2.4)	
Tall cell variant	5 (1.1)	3 (1.5)	2 (0.8)	
Follicular (common type)	53 (11.8)	25 (12.6)	28 (11.2)	
Hurtle cell variant	2 (0.4)	1 (0.5)	1 (0.4)	
Multifocal lesions – n (%)	101 (22.5)	53 (26.6)	48 (19.2)	0.069
Stage – n (%)				
1	378 (84.2)	147 (73.9)	231 (92.4)	<0.001
2	52 (11.6)	37 (18.6)	15 (6.0)	
3	13 (2.9)	11 (5.5)	2 (0.8)	
4	6 (1.3)	4 (2.0)	2 (0.8)	
Lymphadenectomy – n (%)	121 (26.9)	65 (32.7)	56 (22.4)	0.018
RAI dose – mCi[a]	87.8 ± 32.2	112.3 ± 21.6	68.3 ± 24.1	<0.001

$p \leq 0.05$ was considered statistically significant.
DTC: differentiated thyroid carcinoma; DTMC: differentiated thyroid microcarcinoma.
[a] Mean value ± standard deviation.
[b] Kolmogorov–Smirnov Test.