

Natural history, diagnosis, treatment and outcome of thyroid microcarcinoma (TMC)

A mono-institutional 5 year experience



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Natural history, diagnosis , treatment and outcome of thyroid microcarcinoma(TMC). A mono-institutional 5 year experience

Thyroid microcarcinoma (TMC) it's a rare type of differentiated thyroid cancer, which according to the World Health Organization measures 10 mm or less. Accounting 7-16 % of all thyroid carcinomas, it occurs at any age, more frequently in men, with a female to male ratio of 1:3. More frequently histotype is the papillary subset, PTMC.

Aim of this study is to retrospectively evaluate the patients diagnosed with TMC in terms of their clinical and histopathological features. In our institution we collected 23 cases of TMC sampled on 338 plongeant being operated. All the tumors, in our study, were found incidentally during the treatment of benign thyroid diseases. All the sample were analyzed and prepared using the same frozen section technique. Surgical pathology identified 11 papillary microcarcinomas, 10 follicular microcarinomas, 1 oncocyary microcarcinomas and in 1 patient was found only a focal tireocitary transformation. TMC's prognosis and treatment is still a subject of controversy

We propose our approach consisting in total thyroidectomy (less than 5 gr residual thyroid tissue), being considered the low rate of post-operative complications, and recurrences: all patients are disease-free at the median follow-up of 78 months (range 96 to 30 months). We have considered either the less malignancy habit of this neoplasia either its well prognosis.

KEY WORDS: Microcarcinoma, Multinodular goiter, Thyroidectomy

Introduction

Multinodular goiter is a benign thyroid diseases, often consequence of hypertrofia/hyperplasia of follicular cells. In a low proportion of multinodular gotier surgical pathology can identified a TMC, a malignant tumor

measuring less than 1 cm. From 1927, when, Graham e Coll. ¹ described for the first time this subset of thyroid carcinoma, the incidence of thyroid cancers, particularly of PTMC, has been sharply increasing in Western countries for several years ². The relative rate of TMC has increased in patients with differentiated thyroid carcinoma mainly because of the improvements in the diagnostic instruments: high-resolution ultrasonography, fine-needle aspiration cytology (FNA cytology), computed tomography (CT) scan, magnetic resonance imaging (MRI) and their frequent use, as well as the accurate pathological examination of thin slices (1-2 mm) of specimens ^{3,4}.

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A large proportion of these tumors were found incidentally during the treatment of non-neoplastic thyroid diseases ⁴, most common histotype found is the papillary microcarcinoma ⁵⁻⁶, however even the medullary subset of thyroid cancer can occur in the microcarcinomas, (i.e. no larger than 1 cm) ⁷.

It occurs at any age with a higher prevalence in male. Most cases followed an indolent course with an excellent prognosis on the other hand, more aggressive behavior with regional and distant metastasis did occur. Since the treatment of patients with microcarcinoma is controversial, the present study will retrospectively summarize the clinical and histopathological characteristics of 23 TMC patients and will attempt to derive from the analysis a rationale for the appropriate diagnostic and therapeutic interventions.

Patients and Methods

Between february 2005 and December 2010, 424 patients with different thyroid pathology were operated on consecutively at our institution: 338 presenting with multinodular goiter, 22 with Basedow Disease, 64 with thyroid carcinoma.

Considering useful for a correct evaluation, we decided to include the 338 patients with a non-presenting carcinoma, who underwent thyroidectomy for benign disease, even because methodologically homogeneous as regards the histopathological study.

Were considered eligible for surgical treatment 165 patients presenting with *plongeant* goiter, 203 with multinodular goiter, 51 simple goiter with involvement of both lobes, 3 with Hashimoto's thyroiditis, 2 with Plummer disease. A total of 276 women with an age range 18 to 87 (mean age 53.2 yrs) and 62 men with an age range of 19-86 yrs (mean age 52 yrs) were included in this study. Overall 270 underwent an almost total thyroidectomy, 66 a total thyroidectomy, in 2 cases a second surgery it was necessary due to a recurrent goiter. Total thyroidectomy was also performed in those patients in whom although presenting FNAB negative results for malignant cells, presenting suspicious nodules highlighted in other imaging techniques such as ultrasound hypoechoic nodules with microcalcifications and vascularization with pattern III or scintigraphically hypocaptant nodules I ³¹. All patients performed before surgery neck ultrasonography exam and a blood sample to assay thyroid hormone, 106 have performed an additional FNAB, as well as the previous, negative for malignant cells. Surgical specimen was prepared according standardized methods, was fixed with formalin and sent to the pathology department of our university. Only accurate pathological examination of specimens gives ultimate diagnosis of TMC, using the Rosai and Zampi criteria, that classify these tumors according to three parameters: characteristic nuclear, cytoplasmic and architectural characteristics.

TABLE I - Association between TMC and other benign thyroid pathologies

Benign Thyroid Pathologies	N°	%
Multinodular goiter	13	58
Plongeant Goiter	7	30
Hashimoto's thyroiditis,	1	4
Plummer Disease	1	4
Recurrence of multinodular goiter	1	4

A small proportion, (consisting in 23 patients) of these tumors were found incidentally during the treatment of benign thyroid diseases. Of the 23: 5 men with an age range of 16 to 63 (mean age 37 yrs) and 18 women with an age range of 20 to 67yrs (mean age 45.5 yrs) ; underwent thyroid surgery 13 of them for multinodular goiter (58%), 1 of them for Plummer adenoma, 1 of them for Hashimoto disease (4%), 1 of them for recurrent goiter (Table I).

Subsequently, all patients were treated with radionuclide therapy with I ¹³¹ at range doses 1,85 to 3,7 GBq; this because only in the absence of functioning thyroid tissue assay of thyroglobulin (Tg) in conditions of elevated TSH is a sensitive test for the presence of neoplastic cells.

The radio ablation allow the destruction of the remnant thyroid cells, that hesitate in cancer in a very high rate of cases. All patients received TSH-suppressive doses of L-thyroxine during the subsequent follow-up, in order to reduce either local recurrence either distant metastases. The recurrence rate is lower in terms of TSH ≤ 0.05 mU/ml. After just a year suppressive therapy can be reduced in the presence of obvious signs of disease remission (Tg/rhTSH ≤ 0.7 ng/ml).

The patients were followed-up at the time of ablation with radioiodine, 3 months later, and then after 6 months.

1 year after treatment with L-T4 and after TSH stimulation, repeating FT3, FT4, TSH, and Tg thyroglobulin antibodies, anti-TPO dosages and an ultrasonography exam of the neck.

Results

In our study all cases were found incidentally during the treatment of other thyroid pathology.

About histopathological features was found a prevalence of papillary histological pattern, according our experience. The diameter of the lesions varies from 0.1 cm to 1.5 cm in 11 patients; > 0.4 cm in 11; between 0.5 and 1.5 cm 1cm one case. 20 cases were found to be in unilateral, 2 multifocal localization and a 1 only case occurred bilaterally (Table II).

TABLE II - Morphological characteristics

Morphological characteristics		N°
Histological typing	Papillary	11
	Follicular	10
	Oncocytary	1
	Tireocytary	1
Size	<0.4 cm	11
	0.5cm -1 cm	11
	>1cm	1
Localization	Monolateral	20
	Bilateral	1
	Multifocal	2

Histopathological study showed papillary neoplasia in 11 cases (49%), follicular in 10 cases (43%), oncocytary in one case (4%), and in 1 patient was found only a focal tireocytary transformation. (4%) (Fig. 1).

All patients were disease free at the periodic post-operative follow-up 3, 6, 12, months.

Just in one case, a woman of 30 years, presenting with Plummer adenoma who underwent a first surgery for right lobectomy and isthmusectomy, we had to proceed with a further surgery, after surgical pathology positive for MCP.

All patients are at the moment disease free with neither local recurrence neither metastasis with a median follow-up 78 months (range 96 to 30 months).

Overall a mention deserves the case of a man of 41 years free of any thyroid disease who underwent a prophylactic total thyroidectomy following familial medullary thyroid carcinoma diagnosis; we look for and found for the RET mutation after the incidentally found of medullary microcarcinoma in both two brothers of the patients. Before surgery, this patient was carefully supervised in

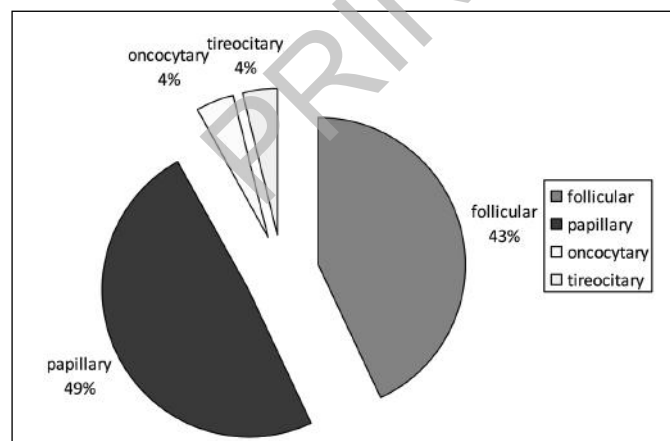


Fig. 1. Histological findings.

close collaboration with endocrinologists. He has performed all instrumental examinations and routine blood examination, ultrasonography thyroid gland exam and a thyroid scan, with no evidence of thyroid disease. The only significant fact to report is a slight rise of Calcitonin: 19.3 pg / ml. Surgical pathology showed, in the left lobe, a micronodule of diameter of approximately 1 mm thick solid carcinoma pattern partially encapsulated to report as medullary carcinoma T1 G1. After 20 days after surgery the patient has performed blood exam dosages for FT3, FT4, TSH and Calcium, after 3 months further examinations were performed, in particular a MIBG scintigraphy and octreotide in order to exclude other associated pathologies such as MEN II, and was examined serum calcitonin in basal conditions and after stimulation (the pentagastrin test), all exam showed undosable levels.

Discussion

According WHO definition for thyroid microcarcinoma (TMC) is a malignant tumor with a diameter not exceeding 10mm⁸, furthermore it is possible distinguish a “tiny” form with a diameter between 5 and 10 mm and a “minute” form of less than 5 mm.

In addition the TMC can be found as incidental if it is discovered accidentally by a histological study performed for other thyroid disease, latent if it is found during autopsy studies for not thyroid pathology, occult if it occurs during a metastatic spread to the lateral cervical lymph node chain without thyroid manifestation^{9,10}. The number of microcarcinomas reported in the literature has increased substantially. The incidence is 7-16% although^{11,12} some authors as Yamashita et al reported a prevalence of 30%; continuous progress of diagnostic imaging, the attention paid to these tumors during the specimens examinations even in the case of benign thyroid disease, can corroborate the increasing clinical encounter^{13,14}.

The nosological classification and the surgical treatment of choice for this neoplasia, is still controversial. Furthermore it is still unclear if the TMC is an initial morphological appearance of unconcealed thyroid tumors or if it represents the very early stage of a cancer destined during years to a more or less rapid growth, which is a nosography entity, genetically different. The hypothesis that the thyroid microcarcinoma may represent an early stage of papillary carcinoma has been reported time after time in the literature, however, only a small part evolves into a papillary carcinoma “mature” and this is the basis of the current debate on surgical treatment planning.

Therefore the possible role of the RET protooncogene in the appearance of microcarcinoma has been studied to establish whether its rearrangement can be used as useful markers to prognosis¹⁵. The data of Corvi¹⁶ et

all. showed a high frequency of RET rearrangement in the TMC, expression of an early stage of tumorigenesis but not enough nor necessary for further tumor progression. Some authors have identified risk factors for this cancer associated with goiter such as the presence of cervical adenopathies, advanced age, male gender, family history of thyroid cancer, cervical pain, the presence of dysphagia and odynophagia or residence in areas of endemic goiter¹⁷, which can help to identify patients presenting a high risk. However, the "goodness" or "malignancy" of such a tumor, depends not only on the size or other characteristics symptomatic but also by its local oncodynamic, by multifocality and histologic type. Even the studies of molecular biology, such as the evaluation of the positivity to Galectin 3, neoplastic markers considered selective, addresses the diagnosis towards a benign or malignant neoplasia¹⁸.

The difficulty of the surgical choice in fact, depends on the biological behavior of the tumor which may present a slow evolution or aggression expressed by the presence of multicentric foci and / or early metastatic diffusion. Surgical treatment may opt for a radical or conservative choice. From the therapeutic point of view most of the authors is in agreement on the need for Total Thyroidectomy in patients with so-called "high risk" even though Taylor¹⁹ and coll. and more recently Wanebo²⁰ et al. report that the Total Thyroidectomy does not significantly improve survival. According to some authors, however, for this type of cancer characterized by a slow evolution, we must consider the time of the disease-free instead of the survival range, and therefore the Total Thyroidectomy would be the treatment of choice that can offer the best oncological radicality and the absence of disease recurrence^{21,22}. Hay⁶ et al. have identified in the extension of thyroidectomy and the presence of lymph node metastases the only significant risk factors for recurrence of the disease, supporting the need for a Total Thyroidectomy of principle.

Ardito²³ et al recommended total thyroidectomy in the presence of infiltration of the capsule, solid character of the lesion and multifocal. While these authors conclude on the usefulness of radical treatment, we must consider that relapses occur in a small percentage of cases and does not really influence the prognosis^{21,24}.

A radical surgical approach, however, does not offer real advantages in terms of survival and is burdened with a complication rate, higher than a nearly total thyroidectomy, although currently very low in experienced surgeons²⁵. The high incidence of TMC in autopsy studies, about 35%, suggesting that most of them has a benign behavior; demonstrating that it is not a cause of morbidity and mortality statistically significative²⁶ and can remain undetected for a lifetime. For these reasons, some schools advocate a conservative surgery.

In our experience, including the 22 patients with microcarcinoma, treated with a nearly total thyroidectomy, survival was 100% and the recurrence rate was zero. Our

attitude is to perform a nearly total thyroidectomy leaving a residue of less than 5g, considering the low incidence of recurrence and hypothyroidism which provides adequate post-operative therapy with L-thyroxine. Everything is supported by the fact that the TMC is a cancer with a moderately malignant behavior and a good prognosis.

Riassunto

Il microcarcinoma tiroideo è un tipo raro di tumore tiroideo differenziato, che secondo il WHO misura 10 mm o meno. Costituisce il 7-16% di tutti i carcinomi tiroidei, e insorge a qualsiasi età, più frequentemente negli uomini, con un rapporto femmina-maschio di 1:3. Più frequentemente l'istotipo è il tipo papillare. Scopo di questo studio è di valutare in maniera retrospettiva i pazienti con microcarcinoma tiroideo rispetto alle loro caratteristiche cliniche e istopatologiche. Nel nostro istituto abbiamo raccolto 23 casi di microcarcinoma tiroideo campionati su 338 gozzi operati. Tutti i tumori nel nostro studio sono stati trovati incidentalmente durante il trattamento di patologie benigne della tiroide. Tutti i campioni sono stati analizzati e preparati usando la stessa tecnica su sezioni congelate. All'esame istologico sono stati identificati 11 microcarcinomi papillari, 10 microcarcinomi follicolari e in 1 paziente è stata ritrovata solo una trasformazione focale tireocitaria. La prognosi e il trattamento del microcarcinoma tiroideo è ancora oggetto di controversia. Noi proponiamo il nostro approccio che consiste nella tiroidectomia totale (meno di 5gr di tessuto tiroideo residuo), che viene considerata a basso tasso di complicanze post-operatorie e recidiva: tutti i pazienti sono liberi di malattia per un follow up medio di 78 mesi (range tra 30 e 96 mesi).

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