Incidental thyroid carcinoma (ITC): a retrospective study in a series of 737 patients treated for benign disease

Roberta Gelmini, Chiara Franzoni, Erica Pavesi, Francesca Cabry, Massimo Saviano

Department of Surgery, Policlinico of Modena, University of Modena and Reggio Emilia, Modena, Italy

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AIM: *Aim of the study is to evaluate correlations between incidental thyroid carcinoma (ITC) and benign thyroid pathologies (BTP), to determine the most represented histotype and to point out the total thyroidectomy's possible advantages in terms of radicality, follow-up management and incidence of complications.*
MATERIALS AND METHODS: *During 10 years, 739 patients underwent thyroid surgery for BTP. Fine needle biopsy (FNAB) was negative in all cases; 503 total thyroidectomies(TT), 5 subtotal thyroidectomies(ST) and 231 emithyroidectomies(ET) were performed.*
RESULTS: *The specimens pathological examination revealed the presence of a ITC in 82 patients (11.1%); the prevalent histotype was the papillary one with a less than 1cm diameter in almost the totality of cases but with nodes metastasis in the 3.6% of cases. Complications were detected in 117 patients with a morbidity rate of 15.8%.*
DISCUSSION: *In our study the ITC prevalence was of 11.1% similar to literature with a higher incidence in patients affected by multinodular than uninodular goiter. No statistical significant differences were found between euthyroid and toxic pathologies. In our series hyperthyroidism doesn't seem to hold a protective role towards the ITC onset.*
CONCLUSIONS: *The ITC incidence is relevant; the prevalent histotype is papillary and nodes metastasis are present even if in a low percentage of cases. Besides, the complications of TT are similar to conservative procedures. The recurrence of goiter and ITC require a second surgical procedure, with a higher risk of complications. So we can claim that the standard surgical treatment of bilateral PBT would be represented by TT.*

KEY WORDS: Benign thyroid disease, Incidental thyroid carcinoma, Total thyroidectomy.

Introduction

Thyroid pathologies represent the most common endocrine disease. The incidence of thyroid carcinoma is about 1-3 cases in every 100,000 population [1] and, even if considered a relatively rare tumour, its increasing prevalence is of the order of 1% to 2%, and its mortality rate is estimated to be 0.5% of all deaths from neoplastic disease [2].
The increased incidence of thyroid carcinoma seems to be related to an improvement in the diagnostic approach. The more widespread employment of ultrasonographic and cytological techniques such as the application of FDG-PET\CT imaging systems ensures the early diagnosis of occult thyroid nodules [3-5].
The fine needle biopsy (FNAB) was first introduced during the 70's by US Authors and it is today considered the "first-line test" because of its diagnostic accuracy and reliability, its simple method of execution and a low incidence of complications. The wide diffusion of the FNAB has contributed towards achieving an early diagnosis and treatment of thyroid cancer [2].

The term "occult thyroid carcinoma" was introduced by Graham in 1928 to describe thyroid tumors that are clinically hidden but suspicious because of the presence of metastatic latero-cervical nodes [2,6]. Later, the term "occult" was extended to cover all thyroid cancers less than 15mm in diameter irrespective of their clinical presentation. Besides, in 1988 the Papillary Thyroid MicroCarcinoma (PTMC) was defined by the World Health Organization as a papillary carcinoma measuring 10mm or less in greatest diameter [7-9].

Nowadays, the term "incidental" identifies malignant tumors of the thyroid gland detected by postoperative pathological examination of the surgical specimens resected for benign disease, whereas the term "occult carcinoma" is used to describe thyroid cancer found on autopsy of patients who deceased for causes unrelated to thyroid disease [10-12].

The incidence of incidental thyroid carcinoma (ITC) ranges from 3% to 16% in different series [13-17] with the highest frequency in patients affected by multinodular goiter. ITCs typically present as small (less than 10mm in diameter) and papillary cancers [14].

These tumors, even if small, can metastasize to regional cervical nodes but the potential they have to cause significant morbidity and mortality is nowadays controversial [18].

The mortality rate is reported to be 0-1% [8] even if Hay, in a wide retrospective series, has observed a rate of recurrence of 6% at 20 years after the diagnosis [19]. Moreover, data from many studies show no significant difference in the rate of postoperative complications associated with total thyroidectomy compared with subtotal thyroidectomy. The data also suggest an increased risk for malignancies among patients with benign thyroid disease [20-21]. In such patients total thyroidectomy is to be considered a definite treatment for thyroid cancer and a permanent cure associated with no risk of disease recurrence and repeat surgery, which may be burdened with a higher rate of postoperative complications [22-23]. For these reasons total thyroidectomy and hemithyroidectomy prove to be valuable surgical options for the treatment of benign thyroid disease.

Materials and methods

From January 1998 to December 2008, at the Department of General Surgery of Policlinico of Modena, 1,331 patients underwent a surgical treatment of benign thyroid disease; 77.8% were female, while 22.2% were male, with a median age of 52.3 years (range 15-87 years).

Preoperatively, all patients underwent thyroid function tests, measurements of serum calcitonin level (to exclude any medullary carcinoma hotbeds), and a laryngoscopy to evaluate the motility of the vocal cords.

A standard chest X-ray was performed in patients older than 40 years either affected by respiratory diseases or with mediastinal goiter. A swallow X-ray was reserved for patients with dysphagia and dyspnea due to compression.

All patients underwent thyroid ultrasonography associated with ecocolordoppler test to check the morphology of nodules, vascularization and thyroid volume; whereas, scintigraphy was performed only in patients with hyperfunctioning thyroid nodules.

However, the research did not consider patients from whom a FNAB wasn't taken preoperatively, along with those who were suspected of or tested positive for malignancy, e.g. patients previously exposed to radiation in the neck and facial area.

On the basis of these exclusion criteria, we selected 737 patients with preoperative diagnosis of: multinodular goiter (n=380; 51.6%), uninodular goiter (n=206; 28%), multinodular toxic goiter (n=107; 14.5%), uninodular toxic goiter (n= 30; 4%), and Grave's disease (n=14; 1.9%).

The surgical procedures performed included: 501 total thyroidectomies (68%), 231 hemithyroidectomies (31.3%), and 5 sub-total bilateral thyroidectomies (0.7%) (Table I.).

The thyroid gland weight was higher than 100g in 53 patients (7.2%); the goiter was mediastinal in 33 cases (4.5%) and recurrent in 28 (3.8%).

In all cases the surgical procedure was carried out through a median collar incision, while respecting the integrity of the anterior neck muscles; a sternotomy was

TABLE I - *Preoperative diagnosis and surgical treatment*

Preoperative diagnosis	Total thyroidectomy	Subtotal thyroidectomy	Hemi-thyroidectomy	Tot
Multinodular goiter	380	0	0	380 (51,6%)
Uninodular goiter	0	2	204	206 (28%)
Toxic multinodular goiter	107	0	0	107 (14,5%)
Toxic uninodular goiter	0	3	27	30 (4,1%)
Toxic diffuse goiter	14	0	0	14 (1,8%)
Total	501	5	231	737

TABLE II - *ITC incidence related to preoperative diagnosis*

Preoperative Diagnosis	N°(% of cases)	ITC n° cases (%)	% ITC of the whole series
Toxic diffuse goiter	14 (1,9)	3 (21,4%)	0,4
Multinodular Goiter	380 (51,6)	48 (12,6%)	6,5
Toxic multinodular goiter	107 (14,5)	14 (13,1%)	1,9
Uninodular Goiter	206 (28)	14 (6,8%)	1,9
Toxic uninodular goiter	30 (4)	1 (3,3%)	0,1
Totale	737	80	10,8

TABLE III - *Postoperative complications*

Preoperative diagnosis	Temporary unilateral nerve palsy	Definitive unilateral nerve palsy	Transient symptomtic hypocalcemia	Definitive hypcalcemia
Uninodular goiter	3 (1,4% exposed nerves)	1 (0,5% exposed nerves)	9 (4,4%)	0
Multinodular goiter	17 (2,2% exposed nerves)	2 (0,3% exposed nerves)	44 (11,6 %)	11 (2,9%)
Toxic multinodular goiter	4 (1,9% exposed nerves)	1 (0,5% exposed nerves)	18 (16,8%)	5 (4,7%)
Toxic diffuse goiter	0	0	6 (42,8%)	2 (14,3%)
Toxic uninodular goiter	0	1 (3% exposed nerves)	1 (3,3%)	0
Total	24 (1,9% exposed nerves)	5 (0,4% exposed nerves)	80 (10,8%)	18 (2,4%)

TABLE IV - *Postoperative complications according to surgical treatment*

Surgical treatment	Temporary unilateral nerve palsy	Definitive unilateral nerve palsy	Transient symptomtic hypocalcemia	Definitive hypcalcemia
Total thyroidectomy	18 (1,8% exposed nerves)	3 (0,3% exposed nerves)	75 (10,2%)	18 (3,6%)
Subtotal thyroidectomy	1 (10% exposed nerves)	0	1 (20%)	0
Hemithyroidectomy	5 (2,1% exposed nerves)	2 (0,9% exposed nerves)	4 (1,7%)	0
Total	24 (1,9% exposed nerves)	5 (0,4% exposed nerves)	80 (10,8%)	18 (2,4%)

never necessary, neither was it performed in cases of huge and mediastinal goiters.

The identification of the inferior laryngeal nerves and of the parathyroid glands was systematically carried out.

Continuous normally distributed variables were compared using the T-test while non-normally distributed variables were compared by means of the Mann-Whitney test; differences in categorical variables were analyzed using the χ^2-test or Fisher's exact test where appropriate. We conducted all data statistical analyses using the software package STATA Intercooled, version 9.0 (StataCorp LP, College Station, TX, USA) and report the 2-sided p-values at the 0.05 significance level.

Results

The postoperative pathological examination of the surgical specimens showed the presence of incidental thyroid carcinomas in 80 cases (10.8%). Of the total number of patients 58 were female (72.5%) and 22 were male (27.5%) with a median age of 53.41 years (range 15-87 yrs).

The incidentally detected carcinomas were of papillary histotype in 50 cases (62.5%), follicular in 2 cases (2.5%), papillary with a follicular variant in 21 cases (26.25%), and medullary in 1 case (1.25%); in 1 case (1.25%) a papillary carcinoma was associated with a medullary carcinoma, and in 4 cases (5%) a papillary carcinoma coexisted with a papillary carcinoma follicular variant. In the remaining case (1.25%) a papillary carcinoma was associated with a metastatic renal cells carcinoma.

In 8 cases (1.1%), all initially treated by hemithyroidectomy, a second operation was performed. The pathological examination of the surgical specimens revealed multiple neoplastic nodules (papillary follicular variant histotype) in one case (12.5%), and no signs of disease in 7 cases (87.5%).

In 57 cases (71.25% of ITC) the tumor was unifocal, whereas in 23 cases (28.75%) it was multifocal and characterized by the presence of 2 nodules in 13 cases, 3 nodules in 9 and more than 3 foci in the remaining case.

The mean diameter of the incidental carcinomas (81 cases in 80 patients) was 8.73mm; more than 10mm in 19

cases (23.5%), and less than 1cm in 62 cases (76.5%). In all cases of multifocal tumor, we have considered the diameter of the largest nodule.

The thyroid capsular invasion was detected in 15 cases (18.5%) and in 5 of these (6.2%) it was found to be associated with vascular invasion. In 1 case of papillary histotype (1.2%) ipsilateral juxta-jugular lymph node metastases were diagnosed (these lymph nodes were removed during the surgical procedure but without complete dissection of the central compartment).

In line with the preoperative diagnosis incidentally detected carcinomas were found in (Table II):
– 48 patients with multinodular goiter (12.6%);
– 14 patients with toxic multinodular goiter (13.1%);
– 14 patients with uninodular goiter (6.8%);
– 3 patients with toxic diffuse goiter (Grave's disease) (21.4%);
– 1 patient with toxic uninodular goiter (3.3%).

The major postoperative complications (recurrent nerve palsy and hypocalcemia) reported in 127 cases and recorded in 117 subjects (15.9%), included (Table III):
– temporary unilateral recurrent nerve palsy in 24 cases (1.9% of exposed nerves);
– permanent unilateral recurrent nerve palsy in 5 cases (0.4% of exposed nerves);
– transient symptomatic hypocalcemia in 80 cases (10.8% of patients);
– permanent hypocalcemia in 18 cases (2.4% of patients).

Permanent bilateral reccurrent nerve palsy didn't occur in any patient.

According to the operation performed, the postoperative complications can be subdivided as follows (Table IV):
– 18 cases of temporary unilateral palsy (1.8% of exposed nerves) and 3 of permanent one (0.3% of exposed nerves), together with 75 cases of symptomatic transient hypocalcemia (10,2%) and 18 of definitive one (3.6%) all occurred in the group of 501 patients who underwent total thyroidectomy;
– 1 case of unilateral temporary unilateral palsy (10% of exposed nerves) and 1 case of transient symptomatic hypocalcemia (20%) were reported in the 5 patients who underwent subtotal thyroidectomy;
– 5 cases of temporary unilateral palsy (2.1% of exposed nerves) and 2 of permanent one (0.8% of exposed nerves), along with 4 cases of transient symptomatic hypocalcemia (1.7%) occurred in the 231 patients subjected to hemithyroidectomy (8 of these procedures were converted to total thyroidectomy).

Discussion

Papillary carcinoma, which accounts for some 85% of cases, is the most common histotype of thyroid cancer. Its prognosis is good with a mortality rate below 5% at 10 years after the diagnosis [10]. The papillary thyroid microcarcinoma is a particular variant of papillary carcinoma and it is characterized by a small diameter, low levels of aggression and a very low frequency of distant metastases, which could theoretically justify a less aggressive therapeutic approach than is necessary to treat other types of thyroid carcinoma [24].

This type of tumor often remains clinically unknown and in fact the papillary thyroid microcarcinoma (PTMC) is also the most common malignant thyroid tumors detected incidentally (ITC), both in the course of ultrasound tests and surgery.

Recent studies show a significant incidence of ITC in patients undergoing surgery for benign thyroid disease; therefore, our research, which revealed a prevalence rate of the phenomenon estimated at 10.8%, is in accordance with literature data [20,25-27].

With reference to the type of benign lesion [28], or preoperative diagnosis, patients with multinodular disease, both toxic and euthyroid, were those with a greater incidence of ITC in cotrast with patients with uninodular disease. A comparative analysis of the cases of incidental thyroid cancer in multinodular goiters and in uninodular goiters demonstrated that in the first group they were 48 out of 380 (12.6%), whereas in the second group they were 14 out of 206 (6.8%). This difference was significant; the p-value of the test χ^2 was <0.002. Specifically, the difference could be attributed to the fact that in patients with multinodular goiters FNAB was performed on a benign nodule. Hence the need to select the nodules for FNAB on the basis of their vascular patterns, sonographic features, and not just their volume [14]. An examination of US high-resolution, in fact, allows the detection of lesions up to 2mm in diameter and to assess carefully their characteristics [29-30].

Patients with bilateral goiter also underwent a more radical treatment, which allowed not simply a more accurate histological exam [31] but also the detection of undiagnosed diseases. Nevertheless, we have to acknowledge that widespread multinodular diseases may actually increase the likelihood of developing a focus of malignancy.

A comparative examination of the incidence of ITC among the whole series of our study showed that there were about 62 out of 586 cases (10.6%) of ITC in the group of patients operated for euthyroid disease (uninodular goiter and multinodular goiter), and 18 out of 151 cases (11,9%) among patients surgically treated for hyperfunctioning diseases (toxic mutinodular goiter, diffuse toxic goiter and toxic goiter uninodular). This difference was not significant; the p-value of the test χ^2 was 0.72. Data in the literature are conflicting; indeed, in large published series [32-35], the incidence of ITC in hyperfunctioning goiters is not significantly different from that in euthyroid goiters, while in others [14], this impact is significantly higher. Regardless of the conflicting results, we claim that hyperthyroidism itself is not to be considered a protective factor against differentiated thyroid carcinoma.

Similarly, there was not any significant difference between the incidence of ITC in hyperfunctioning multinodular disease and the hyperfunctioning diffuse one, as reported in the literature [36-37]. In detail, our series showed a marked incidence of ITC in hyperfunctioning diffuse goiters (21.4%), but given the small sample size (14 patients), we do not consider it as particularly significant. The comparison of the average age of patients with and without ITC (respectively 54.5±12.2 years and 52.1±13.4 years) did not provide any evidence of a statistically significant difference (p-value = 0.1172). Even by comparing the distribution of sexes in each group, the difference turned out not to be substantial (p-value = 0202).

The analysis of their size showed that 23.5% of ITC exceed one centimeter in diameter and as such they are not to be regarded as microcarcinoma. The relatively high incidence of these non-PTMC tumors could be justified by the fact that needle aspiration cytology is not always adequate in detecting cancers, especially when contained within large nodules. Thus, it would be more appropriate to take multiple samples of tissue from larger nodules by performing a greater number of needle aspirations.

Most of the ITC are papillary microcarcinomas, whose prognosis is absolutely favorable, although the biological behavior is influenced by a histological variant of the same cancer. The incidence of metastatic disease in the thyroid is low, accounting for less than 1% of thyroid neoplasms [38]. In our series there was a case of metastatic renal cell carcinoma associated with a focus of papillary carcinoma (0.1% of total cases and 1.25% of incidental cancer). Furthermore, as regards the incidence of postoperative complications after total thyroidectomy and hemithyroidectomy, and in particular temporary unilateral palsy of the recurrent laryngeal nerve and the permanent lesion in both groups (total thyroidectomy and hemithyroidectomy), the difference was not statistically significant (p=0.70; p=0.24). Finally, if we consider the postoperative hypocalcemia, the comparative study of the incidence of this complication in the group of patients who underwent total thyroidectomy, and in those subjected to subtotal thyroidectomy (5 cases), did not reveal any substantial difference. In conclusion, the incidence of postoperative complications reported in our study is in agreement with literature data for both temporary and permanent recurrent paralysis [39-42], and definitive hypocalcemia [40-42].

as in case of large yet single nodule. Our data also highlight that ITC can be multifocal and bilateral. Based on these considerations, the most effective treatment for benign thyroid disease is suggested to be the most radical possible one, namely total thyroidectomy. Among the Authors, the choice of the most appropriate surgical treatment has not reached any consensus yet. In fact, the surgical procedure can vary from a radical approach such as total thyroidectomy to a more conservative one such as the hemithyroidectomy [43-44]. The reasons for the adoption of one of the different approaches can be attributed mainly to residual functional management of patients undergoing non-radical surgery, and the risk of complications related to the extension of the surgery itself (hypoparathyroidism and laryngeal nerve injury, temporary or definitive) [45-46]. On the other hand, the possibility of developing either a recurrence in the residual gland or a cancer in the context of spared parenchyma over time, which has been reduced by the use of suppressive drug treatment, often requires reoperation to "radicalize" thyroidectomy. This procedure is inevitably linked to a higher complication rate than the first surgery[47]. Worthy of note is also the high percentage of ITC detected in parenchyma and removed for benign disease, which may exhibit a totally unpredictable, yet highly aggressive, biological behaviour [48]. Because the tools available today (e.g. ultrasound) do not allow both the identification of the morphological features predictive of aggressive PTMC and the retrieval of molecular information on the possible natural history of cancer, a total thyroidectomy is always highly recommended [49]. This operation, which can sometimes seem overwhelming to treat benign thyroid disease, enables the complete removal of the parenchyma and reduces the risk of recurrent benign tumors (full recovery), the occurrence of residual tumor on the gland (secondary prevention), and the risk of iatrogenic injury from surgical reintervention[50]. Furthermore, total thyroidectomy improves the diagnostic accuracy of assay of serum thyroglobulin in the follow-up of thyroid neoplasms. A criticism that can be made of total thyroidectomy may be the replacement therapy which is required by postoperative patients in their remaining lifetime. However, not to be forgotten is the fact that even patients who undergo a "non-total" resection of the gland may require replacement therapy with L-thyroxine for at least one year, which even when administered for prolonged periods does not lead to any substantial degradation in performance and quality of life[51].

Conclusion

The results of this study suggest that ITC is to be considered a relevant entity in terms of frequency in patients undergoing surgery for benign thyroid disease. It seems to be more frequent in cases of multinodular disease probably because of the objective difficulty to detect a neoplastic focus with FNAB within multiple nodules sich

Riassunto

Le malattie tiroidee rappresentano la più frequente patologia endocrina e il carcinoma tiroideo ha una prevalenza dell'1-2%, in progressivo aumento, con una mortalità pari allo 0,5% di tutti i decessi per neoplasia. Un ruolo importante per la sua affidabilità diagnostica è svol-

to dall'agobiopsia, metodica semplice, pressochè priva di complicanze, che consente una diagnosi precoce delle neoplasie tiroidee il cui approccio terapeutico è essenzialmente chirurgico. Con il termine di carcinoma occulto della tiroide si definiscono quelle neoplasie clinicamente non apprezzabili, di diametro inferiore al centimetro; con il termine incidentaloma, invece, si identificano quelle neoplasie maligne riscontrate casualmente durante l'esame istologico in pazienti sottoposti ad intervento chirurgico per patologia benigna. Dal gennaio 1998 al dicembre 2008 sono stati sottoposti ad intervento chirurgico per patologia tiroidea 1331 pazienti. Da questo campione sono stati selezionati 737 pazienti sottoposti, preoperatoriamente, ad agoaspirato con diagnosi di patologia tiroidea benigna, precisamente 380 casi di gozzo multinodulare, 206 di gozzo uninodulare, 107 di gozzo tossico multinodulare, 30 di gozzo tossico uninodulare e 14 di patologia tossica diffusa (Grave's). Gli interventi chirurgici eseguiti sono stati: 501 tiroidectomie totali, 231 loboistmectomie e 5 tiroidectomie subtotali. L'esame istologico ha diagnosticato 80 casi di carcinoma tiroideo (incidentaloma), di cui 76 a istotipo papillare, 3 follicolare, 1 midollare, 1 presentava in concomitanza un istotipo papillare e uno midollare e 1 che presentava, in concomitanza a un istotipo papillare, metastasi plurifocali da carcinoma renale. In 8 casi si è reso necessario un secondo intervento di radicalizzazione. Per quanto riguarda le complicanze, verificatesi in 117 pazienti, si sono avute 24 paralisi temporanee monolaterali del nervo ricorrente, 5 paralisi definitive monolaterali del nervo ricorrente, 80 ipocalcemie sintomatiche transitorie e 18 ipocalcemie permanenti. Gli incidentalomi hanno una frequenza che varia dal 3 al 6%, e nella maggior parte dei casi hanno istotipo papillare, a bassa aggressività e con scarsa tendenza alla metastatizzazione. La maggior incidenza di tale patologia è riscontrata in pazienti con patologia multinodulare, sia tossica che eutiroidea, nonostante in letteratura i dati siano discordanti (secondo alcuni autori nei gozzi iperfunzionanti l'incidenza di tale neoplasia è nettamente superiore). Normalmente la scelta del trattamento chirurgico delle patologie benigne della tiroide varia a seconda della gestione funzionale residua del paziente e al rischio di complicanze legate all'estensione dell'atto chirurgico. D'altra parte il rischio di una ripresa della malattia o l'evenienza di comparsa, a distanza di tempo, di una neoplasia nel contesto del parenchima residuo, spesso impone un reintervento allo scopo di radicalizzare il pregresso intervento.

Considerando inoltre la rilevante percentuale di incidentalomi diagnosticati nel parenchima ghiandolare asportato e il fatto che possono assumere un atteggiamento anche aggressivo reputiamo che la tiroidectomia totale debba essere considerata come il trattamento gold-standard della patologia tiroidea benigna, in grado di garantire la completa rimozione del parenchima, quindi minor rischio di recidive e un minor rischio di lesioni iatrogene legate al reintervento.

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