

## ORIGINAL ARTICLE

## INCIDENTAL THYROID CARCINOMA IN A LARGE SERIES OF CONSECUTIVE PATIENTS OPERATED ON FOR BENIGN THYROID DISEASE

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**Background:** The diagnosis of incidental thyroid carcinoma (ITC) in patients operated on for a benign disease is frequent. This study aims to determine both its clinical effect and the possibility of identifying this class of patients preoperatively.

**Methods:** A total of 998 consecutive patients (697 women and 301 men; mean age, 49.5 years) undergoing surgery for benign thyroid pathology in a single institution were studied. The mean time between first diagnosis of thyroid disease and operation was 9.0 years (range, 0–50 years). All patients underwent at least one ultrasonography before surgery, and 678 patients underwent fine-needle aspiration cytology. Patients with undetermined cytology or follicular nodules were excluded from the study.

**Results:** Histology revealed an ITC in 104 patients (10.4%); 99 had a papillary carcinoma. Mean and median diameters of ITC were 1.4 and 0.7 cm, respectively (range, 0.1–7.5 cm). In 43 patients, the tumour size was greater than 1 cm, whereas it exceeded 2 cm in 25 patients. Tumours were multicentric in 19.8% of the patients and occurred in 8.2% of patients with nodular toxic goiter, 8.7% of patients with toxic diffuse goiter and 13.8% of patients with multinodular goiter.

**Discussion:** The results confirm the high frequency of ITC. ITC was more frequent in euthyroid patients than in thyrotoxic patients ( $P < 0.03$ ). Sex, age, thyroid volume and interval between diagnosis and surgery did not significantly influence its incidence. The majority of ITC was represented by microcarcinomas, but in approximately 25% of patients, the tumour size was greater than 2 cm. The role played by FNAC in excluding malignancies proved to be fairly inconclusive.

**Key words:** benign thyroid disease, fine-needle aspiration cytology, thyroid carcinoma.

Abbreviations: ETV, estimated thyroid volume; FNAC, fine-needle aspiration cytology; ITC, incidental thyroid carcinoma; TSH, thyroid-stimulating hormone; US, ultrasound.

## INTRODUCTION

The finding of incidental malignancies (incidental thyroid cancer (ITC)) among patients operated on for a benign thyroid disease is not infrequent. The incidence ranges between 3 and 16% according to case selection;<sup>1–4</sup> it also occurs in patients with a history of hyperthyroidism, who have long been believed to be protected against cancer by suppression of thyroid-stimulating hormone (TSH).<sup>5–8</sup> ITC are mainly small and differentiated papillary cancers. For both these reasons, they are considered of little clinical significance. Nevertheless, in several cases, the clinical effect of these tumours cannot be ignored once a correct staging has been carried out. Moreover, most of these patients have been treated by the endocrinologist for several years before undergoing surgery for a supposed benign disease. For this reason, we carried out an extensive prospective analysis of these cases to evaluate the possibility of better identifying all of the cases at risk of malignancy.

To analyse the profile of the population affected with ITC, we prospectively collected data from 998 consecutive patients suffering from benign thyroid disease, who had been referred to our department for surgery. In particular, we decided to analyse: (i) the time interval between diagnosis and surgical treatment;

(ii) the duration of suppressive therapy in patients with nontoxic goiter; (iii) the histological type and subtype; and (iv) the effect of cytological examination on dominant nodules. This study aims to identify any pattern of suspicion and to analyse any measure that might improve a correct preoperative diagnosis, at least in patients who present with malignancies other than microcarcinoma.<sup>9–12</sup>

## METHODS

Data were prospectively collected from February 2002 to November 2003 from 1535 consecutive patients affected with thyroid disease and referred to our department for surgical treatment. All cases with fine-needle aspiration cytology (FNAC) that was either inconclusive or revealed follicular nodules, as well as patients with cytological evidence of malignancy or those who had been previously exposed to irradiation on the neck area, were excluded from the study. According to our protocol, serum calcitonin measurement had been carried out before surgery in all patients in order to exclude the presence of medullary carcinoma. A total of 998 consecutive patients undergoing surgery for unequivocally benign thyroid disease were then selected for the study. The sample consisted of 697 women and 301 men with a mean age of 49.5 years (range, 14–77 years). Preoperative diagnosis is summarized in Table 1. All patients were preoperatively submitted to at least one ultrasound (US) examination in order to define thyroid morphology and to obtain the estimated thyroid volume (ETV). Among the 510 patients affected by nontoxic goiter, 270 (52.9%) had been treated with a TSH-suppressive dose of l-thyroxine for a mean duration of treatment of 7.3 years

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**Table 1.** Indications for operation in 998 patients with benign thyroid disease

	Thyroid pathology	n (%)
Nontoxic disease	Multinodular goiter	441 (44.2)
	Uninodular goiter	69 (6.9)
Toxic disease	Toxic multinodular goiter	255 (25.5)
	Toxic diffuse goiter	206 (20.6)
	Toxic uninodular goiter	27 (2.7)
Total		998 (100)

(range, 1–25 years). All patients with toxic thyroid diseases had been treated with antithyroidal drugs and were euthyroid at the time of surgery.

A total of 678 patients (67.9%) had undergone FNAC on dominant nodules revealing benign disease in all cases. All diagnostic evaluations except FNAC (to avoid performing such an unpleasant procedure a second time) were repeated on all patients who came to our endocrinology department from other institutions.

Surgical operation consisted of either hemithyroidectomy or total thyroidectomy, according to the involvement of one or both lobes, respectively.

Differences between mean age, mean diagnosis–operation time and mean ETV were computed by a paired sample *t*-test. Statistical analysis was carried out using SPSS/PC+ 11.5 statistical software.

## RESULTS

Total thyroidectomy was carried out on 902 patients, whereas hemithyroidectomy (total lobectomy with isthmusectomy) was carried out on 96 patients; no other surgical procedure was associated to thyroidectomy.

Final histology revealed ITC in 104 patients (10.4%). This group included 71 women and 33 men with a mean age of 48.5 years (range, 21–79 years); 39 patients were younger than 45 years of age at the time of diagnosis, whereas 65 patients were 45 years or older.

When considering the functional status of the gland, the cases of ITC were 66/510 (12.9%) in nontoxic thyroid disease and 40/488 (8.2%) in toxic thyroid disease. This difference was significant using a  $\chi^2$  test ( $P < 0.03$ ).

Patients were divided into two groups according to final histology: patients presenting with an ITC (ITC group) and patients with benign disease (BD group). The two groups were compared for: mean age, time between diagnosis and operation, and ETV. No statistical difference was found between the two groups for these parameters (Table 2).

In patients belonging to the ITC group who were affected with nontoxic thyroid diseases and had been treated with L-thyroxine at suppressive doses, the mean period of treatment was 5.9 years (range, 1–15 years) compared with 7.4 years in the case of patients belonging to the BD group (range, 1–25 years).

Final histology is shown in Table 3. No medullary carcinoma was found in this series.

The mean diameter of the neoplastic nodule was 1.4 cm and the median diameter was 0.7 cm (range, 0.1–7.5 cm). The cancer was multifocal in 20 patients (19.2%) and 16 of these patients

**Table 2.** Comparison between patients with benign thyroid disease and incidental thyroid carcinoma (ITC)<sup>†</sup>

	BD group (n = 894)	ITC group (n = 104)	P
Mean age	49.7 years (14–77)	48.5 (21–79)	NS
Mean time diagnosis–operation	9 years (0–50)	8.7 (1–45)	NS
Mean ETV	60 cc (70–217)	59.6 (16–200)	NS

<sup>†</sup>Differences between data from the BD and ITC groups were computed by using a *t*-test and analysed with SPSS/PC+ 11.5 statistical software.

BD group, patients with benign disease; ETV, estimated thyroid volume; ITC group, patients presenting with an ITC; NS, not significant.

exhibited two foci, three patients exhibited three foci and one patient exhibited four localizations.

A classification of patients with regard to tumour size is reported in Table 4. Twenty-five patients had a tumour with a diameter of larger than 2 cm. Among them, FNAC revealed false benign diagnosis in 22 patients (it was carried out on malignant nodules, but diagnosis was incorrect); in two patients FNAC was carried out on benign nodules (tumours were found in different nodules from those biopsied), and it was not carried out in one patient. Mean ETV in patients affected with a carcinoma larger than 2 cm in diameter was 59.3 mL (range, 22–200), and it was not significantly different to that of the general sample (60 mL; range, 7–217).

The staging following the 6th edition of International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) (TNM) yielded 91 patients with stage 1 disease (87.5%), eight patients with stage 2 disease (7.7%), two patients with stage 3 disease (1.9%) and three patients with stage 4 disease (2.9%). Table 5 summarizes the current UICC/AJCC (TNM) staging and staging of patients with ITC. It is noteworthy that all patients younger than 45 years of age were at the first stage of the disease.

Table 6 shows the incidence of ITC according to preoperative diagnosis. Interestingly, all of the 18 patients with toxic diffuse goiter had tumours of less than 2 cm in diameter, with a mean size of 0.6 cm (range, 0.2–1.8 cm).

## DISCUSSION

The incidence of malignancy in patients undergoing surgery for benign thyroid disease is quite relevant, and data from the literature are confirmed by our large consecutive prospective study carried out during a short period of time in a single institution. Our data suggest that age, sex, thyroid volume and time interval between diagnosis and operation cannot be considered as indicators of risk of thyroid carcinoma.

The high prevalence of ITC in patients affected with hyperfunctioning diseases shows that hyperthyroidism per se does not

**Table 3.** Histological classification of 104 patients with incidental thyroid carcinoma

Histology	No. patients	%
Papillary	99: classic (59), follicular (36), tall cells (2) and oxyphilic (2)	95.2
Follicular	4: classic (2) and oxyphilic (2)	3.8
Poorly differentiated	1	1.0

**Table 4.** Classification of 104 patients with incidental thyroid carcinoma with regard to tumour diameter

Tumour diameter (cm)	n (%)
<0.5	38 (36.5)
0.5–0.9	23 (22.1)
1.0–1.9	18 (17.3)
2.0–3.9	14 (13.5)
4.0	11 (10.6)
Total	104 (100)

prevent the possibility of developing thyroid cancer. However, it is noteworthy that in most cases of previously nontoxic goiter, hyperthyroidism developed after a long period of TSH stimulation. It is conceivable that the mutations inducing thyroid cancer were already present before the development of hyperthyroidism.

In our series of patients, the duration of therapy is shorter in the ITC group with respect to the BD group (5.9 vs 7.4 years). Nevertheless, the role of L-thyroxine-suppressive therapy in preventing the occurrence of thyroid carcinoma is still under debate.<sup>13–17</sup> L-T4-suppressive therapy can prevent the development of new nodules and the growth of pre-existing ones, but has no effects on blocking tumorigenesis when this has already started; another relevant point is TSH suppression adequacy and continuity. In contrast, TSH is the main, but not the only growth factor for the follicular thyroid cells.

Incidental thyroid carcinomas are equally distributed in non-autoimmune and autoimmune thyroid diseases, thus suggesting that thyroid autoimmunity does not affect tumorigenesis.<sup>18</sup>

In our series of patients, the majority of ITC (58.6%) were microcarcinomas. Tumour size ranged between 1 and 2 cm in 18 patients (17.3%), and in 25 patients (24.1%) it was larger than 2 cm. When considering the new TNM staging for thyroid carcinoma, 13 patients (12.5%) were at stages higher than the first. The relatively high incidence of large tumours might be explained by the fact that single-needle aspirations are more likely to be inadequate to detect malignancies on large thyroid nodules than on small thyroid nodules. It might be more appropriate to draw several samples from bigger nodules, performing more than a few punctures.

**Table 5.** Tumour size (T) and stage of patients with ITC, aged 45 years or older, following the 6th edition of UICC/AJCC (TNM)†. All patients younger than 45 years of age were at the first stage of the disease

	T1 ( $\varnothing \leq 2$ cm)	T2 ( $\varnothing > 2, \leq 4$ )	T3 ( $> 4$ )	T4 (beyond thyroid capsule)
Patients (n = 66)	53	8	2	3
Stage	I	II	III	IVa

†The staging for papillary and follicular thyroid cancer is calculated as follows. (a) For patients younger than 45 years of age, stage I includes any T, any N and M0, whereas stage II includes any T, any N and M1. (b) For patients 45 years or older, stage I is T1, N0 and M0; stage II, T2, N0 and M0; stage III, T1–3, N0–N1a and M0; stage IVa: T1–4a, N0–1b and M0; stage IVb: T4b, any N and M0; stage IVc: any T, any N, M1.

ITC, incidental thyroid carcinoma.

**Table 6.** Relative incidence of ITC in different benign thyroid diseases

Thyroid pathology	Cancer incidence with regard to the indications for surgery (n/total) (%)
Multinodular goiter	63/441 (14.3)
Toxic multinodular goiter	21/255 (8.2)
Toxic diffuse goiter	18/206 (8.7)
Uninodular goiter	1/69 (1.4)
Toxic uninodular goiter	1/27 (3.7)
Total	104/998

ITC, incidental thyroid carcinoma.

Moreover, in a few patients, FNAC was performed on a benign nodule instead of on the malignant one: this should suggest the need for selecting more carefully the nodules to aspirate on the basis of their pattern at US scan rather than on their volume only.

Evidence that the majority of ITC in patients with toxic diffuse goiter were either microcarcinomas (83%) or smaller than 2 cm probably reflects the precocious medical approach due to the thyrotoxic status. The typical pattern of this disease at the US scan and the small size of the nodules may explain why malignant nodules were not observed.

Although more than 95% of the patients with ITC presented with a papillary thyroid carcinoma, it is important to stress that only 59 of the 99 had the classic variant, whereas the others presented variants, which, in some cases, had a more aggressive behaviour.

It is not surprising that no case of medullary thyroid carcinoma was found in this series: it is now an established fact that calcitonin screening on all patients undergoing surgery for thyroid disease is able to exclude the possibility of facing unexpected medullary carcinoma.<sup>19,20</sup>

The results of this study confirm that the frequency of ITC in patients undergoing surgery for benign thyroid diseases is not negligible, being more frequent in euthyroid patients than in thyrotoxic ones. Our data also indicate that the possibility of missing a malignant neoplasm exists in cases of large nodules in the context of multinodular goiter. This finding may provide support for the recommendation to perform multiple FNAC not only in dominant nodules, but also in all other nodules appearing suspicious at clinical examination or at US.<sup>21</sup>

At present, our data suggest that ITC can have clinical relevance, at least in terms of stage. Although a larger follow up is needed to draw definitive conclusions in terms of prognosis.

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