

Incidental thyroid carcinoma in patients with TIR1, TIR2 and TIR3 FNA



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AIM: *The aim of our study was to evaluate the presence of incidental differentiated thyroid carcinomas, at final histological examination, in patients undergoing thyroidectomy or lobectomy for presumed benign pathology or in those with cytological diagnosis of indeterminate nodules (TIR3).*

MATERIAL OF STUDY: *457 patients who underwent surgery for benign disease and 179 patients with indeterminate FNA were included in our study.*

RESULTS: *77 out of 457 patients had the diagnosis of differentiated thyroid carcinoma. 29 out of 179 patients had the same diagnosis as previous ones, but not on the undetermined FNA nodule. In the most of the cases, the istotype was follicular variant of papillary carcinoma.*

DISCUSSION: *The incidence of incidental carcinomas, approximately the same in the two groups of patients, respectively 16.8% and 16.2%, shows that there is still a group of patients with benign thyroid disease escaping a careful ultrasound evaluation and therefore a targeted FNA. Even in patients with indeterminate cytology, the presence of an incidental carcinoma suggests that on the one hand there has been an overestimation and on the other a non-recognition of the really suspect nodule. Although in most cases it is a microcarcinoma, we must not overlook the presence of many tumors at stage T3.*

CONCLUSIONS: *Surely the analysis of the set of risk factors with a wider application of molecular biology surveys will in the future lead to better selection of patients to undergo surgery sooner than those that can be followed in follow up even for a longer period of time.*

KEY WORDS: Differentiated thyroid carcinoma, Fine needle aspiration, Incidental carcinoma.

Introduction

Thyroid diseases are extremely common and are significantly higher in goitrogenic areas but only a small percentage of these disease are represented by malignancies: approximately 1 nodule of 20 (5%) is a cancer ¹. Fine-

needle aspiration (FNA) has become the primary diagnostic tool in the initial evaluation of thyroid nodules with a sensitivity and specificity ranges between 80 and 100 % ². There are many classification systems based on the cytological features to evaluated thyroid nodules; the most used are the Bethesda system, a six-tired classification ³, and the SIAPEC-IAP a five-tired classification ⁴, by Italian Society for Anatomic Pathology and Cytology with the Italian Division of the International Academy of Pathology. The last "Italian consensus for the classification and reporting of thyroid cytology" ^{5,6} reviewed this classification and now distinguishes FNA cytology reported as indeterminate (Tir 3) into two dif-

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ferent subgroups: Tir 3A or low-risk indeterminate lesion (LRIL) and Tir 3B or high-risk indeterminate lesion (HRIL). In spite of the great specificity and sensitivity of FNA, in our experience there is still a high incidence of incidental carcinomas in patients whose FNA has given non-diagnostic, negative or indeterminate results.

Materials and Methods

From 2010 to 2016, 896 patients (705 females and 191 males) underwent thyroid surgery. The operation performed was total thyroidectomy in 846 cases and lobectomy in 58 cases. In these 58 cases there were 8 patients who had contralateral lobectomy by the presence of cancer at final histology, so for a total of 904 surgeries. Among the 896 observed patients 457 had a preoperative diagnosis of benign thyroid disease: goiter in 293 cases (259 multinodular, 34 uninodular), Plummer disease in 15 and Basedow disease in 149.

In 439 patients FNA cytology led to the diagnosis of cancer (131 pz) or suspicious malignant lesion (308 pz). The 457 patients who underwent surgery for benign disease and 179 patients with indeterminate FNA who underwent surgery were included in our study.

All patients with benign disease were studied by neck ultrasound prior to surgery and submitted to a CT scan of the chest in the case of plunging goiter. The surgical indication was due to the fact that the goiter had become symptomatic, or because thyroid function was compromised, or there was no response to medical therapy or this treatment could not be continued anymore. At the time of surgery all patients were euthyroid and almost all with no evidence of chronic thyroiditis. Routine pre-operative fibrolaryngoscopy were performed in each case.

The histological examination of the specimen confirmed the diagnosis of benign disease in 380 patients. In 77 patients (16,8%), 63 female and 14 male, the presence of incidental carcinomatous lesions was detected. By the diagnosis of synchronous carcinoma in 19 patients, 105 was the total number of carcinomas. In 32 patients a fine needle aspiration was performed in preoperative time, excluding malignancy and their FNA were non diagnostic (TIR1) or negative (TIR2) by 2007 SIAPEC-IAP classification. In 17 patients there was a condition of hyperthyroidism (Plummer or Basedow) and 24 patients had chronic thyroiditis as evidenced by the ultrasound and the presence of autoantibodies. The majority of patients with incidental carcinoma underwent total thyroidectomy (72/77). In those previously submitted to lobectomy (5/77), completion thyroidectomy was performed. Histology detected 22 papillary cancer, 10 follicular carcinoma, 73 follicular variant of papillary carcinoma and confirmed chronic thyroiditis by the presence of lymphocyte infiltration.

Referring to the "T" of TNM classification, we had 38

microcarcinoma, 4 T1 carcinoma, 5 T2 carcinoma and 30 T3 carcinoma. One of 30 patient with T3 carcinoma was T3N1.

Our study also involved 179 patients with indeterminate FNA (TIR3) 2007 SIAPEC-IAP classification. In these patients final histology confirmed the initial FNA diagnosis in 48 cases (carcinoma on the same nodule subjected to FNA); in 29 patients there was a carcinoma, but in other side of the thyroid and in any case not on the nodule subjected to FNA, so even these carcinomas can be considered incidental (16,2%). All the patients had been subjected to total thyroidectomy. Also in these cases, at final histology, most of carcinomas was follicular variant of papillary carcinoma. Referring to the "T" of TNM classification there were 8 T3 carcinomas and in 5 patients there were synchronous incidental carcinomas.

None of all the patients of this study had long term complication related to the surgical procedure like permanent dysphonia (over 6 months) and persistent hypocalcaemia (over 6 month).

Post-surgical treatments were entrusted to the endocrinologist consultant on the basis of the histological result. All the patients underwent to radioiodine metabolic therapy and were submitted to follow-up: in the first year after surgery annually dosage of thyroglobulin (TG), cervical ultrasound, and a progressive reduction of L-T4 dose leading from fully suppressive to half-suppressing effect (TSH levels maintained at 0.2e0.5 mU/l); further evaluation of TG after stimulation test with recombinant human Thyroid-Stimulating Hormone (rhTSH) was scheduled after 2 years. At the moment, all patients are alive, apparently without local recurrence or systemic progression of disease, and are still in the course of follow-up.

Discussion

Despite the improvement and more extensive employ of preoperative diagnostic techniques, particularly the fine needle aspiration and its cytological interpretation, the percentage of incidental carcinomas is an increase if compared to the data collected in our study a few years ago, (16,8 vs 11%). Most incidental thyroid cancers reported in literature are microcarcinomas. This term refers to a malignant lesion, predominantly papillary, smaller or equal to 1 cm in diameter.⁷

It is not yet been clarified whether the microcarcinoma is a distinct clinical entity characterized by a lower aggressiveness and lesser growth potential, or instead it represents a subgroup of differentiated thyroid carcinoma, diagnosed by chance when it is smaller than 1 cm, during its evolution towards a clinically evident cancer.⁸

The prevailing current opinion is that the papillary microcarcinoma is a tumor characterized by an indolent trend of growth and a very favorable prognosis; despite

the uncertainty about its natural history has caused the lack of univocal and standardized therapeutic approach^{9,10}. Nevertheless in some authors' opinion, the papillary microcarcinoma is a neoplastic disease characterized by a heterogeneous

clinical behavior, ranging from the small neoplastic out-break accidentally discovered after surgery for benign thyroid diseases, to that of a cancer that is clinically manifested by the only presence of metastasis to lymph nodes of the neck or at a distance. The tumor, however, has a good prognosis. Recurrences are mainly loco- regional and occur usually within the first 10 years of follow-up, with a prevalence oscillating between 1 and 10%. The rate of mortality for microcarcinoma is very low, and reported with a prevalence ranging between 0.2 and 2.2%¹¹.

Our experience confirms this data: in patients with pre-operative benign disease and in those with indeterminate FNA, incidental carcinomas were mostly microcarcinomas, in the most of the cases the histological type was follicular variant of papillary carcinoma, as in other studies¹², there weren't loco- regional recurrences and all our patients after radioiodine metabolic therapy are submitted to follow-up and are all alive.

But we want to focus our attention on something that seems relevant to us: both in TIR3 patients and in those with preoperative benign disease, there are respectively 8/29 and 30/77 (including a patient with also node involvement, T3N1MX) T3 carcinomas for the infiltration of capsule and not for the size; this data affects not so much on prognosis as on patient follow-up.

Another data we considered: the percentage of incidental carcinomas in patients treated for presumed benign pathology without FNA, in those with *non diagnostic* or negative FNA, is similar to that of patients with indeterminate (TIR3) cytological examination, respectively 16.8 vs 16,2%; this means that a slight margin of improvement is still possible because in these patients we had on the one hand the difficulty in recognizing in a multinodular goiter those ultrasound and vascular aspects that may indicate the most suspicious nodule on which to perform the cytology and on the other, the data of cytopathologist who has overestimated the cytological analysis.

Ultimately, the two classes of patients are at the same risk of incidental carcinoma at the definitive histological diagnosis.

Despite the major and persistent limit of the ultrasound investigation remaining an operator-dependent procedure, thyroid ultrasound has been recognized as the main imaging examination, because of its sensitivity, simplicity, and noninvasiveness¹².

Number and size of the nodules have no predictive value of neoplasia –we have many T3 incidental carcinoma by capsule infiltration and not by size –; more frequently associated with thyroid tumors are the solid structure, the shape taller rather than wider, hypoechoic,

irregular or blurred margins, the absence of halo, the presence of fine calcification and only or predominantly intranodular vascularization. However none of these characteristic has high sensitivity and high positive predictive value. Although the ultrasound examination of the nodule completed with doppler has a higher diagnostic accuracy in detecting the presence of central vascularization, its validity is still controversial, since no type of flow allows certainty diagnosis or rule out the presence of cancer¹².

Very promising, but still validated, elastography, an emerging ultrasound technique which measures tissue rigidity properties, showed higher stiffness indices for thyroid cancers compared with benign nodules^{13,14}.

The ultimate goal of ultrasound, ultrasound with doppler, and elastography is to focus attention on the nodule, or thyroid nodules, deserving of further diagnostic deepening by FNA, but the same FNA may not be decisive, as in our TIR1, TIR2 and TIR3 patients with one or more incidental cancer at finally histology. Recent studies on thyroid lesions detected incidentally at PET or PET/CT in the course of follow-up for non-thyroid neoplasms, showed higher Fluorine-18 fluorodeoxyglucose (18F-FDG) uptake in neoplastic compared to benign nodules¹.

Age, familiarity, thyroglobulin, TSH, thyroid hormone, the presence or absence of chronic thyroiditis were taken into account by the various authors, but to date are not considered sure predictors of malignancy; on the other hand, the coexistence of a hyperfunctional disease does not exclude the possible presence of a cancer (17 our patients). Only the male sex is a negative prognostic factor¹⁵.

BRAF mutational analysis is commonly used to assess the malignancy of thyroid nodules but unfortunately, in some cases, it still leaves indeterminate diagnoses, because only positive results can be used to guide the decision for surgery.

Galectin-3, telomerase, thyroid peroxidase, RET-PTC, and p53 showed relatively high accuracy for detecting malignancy in thyroid nodules, but unfortunately many of these molecular markers are too complex or expensive for routine clinical use or are still poorly standardized, so their use is reserved only to some patients with indeterminate FNA¹⁶.

Clusterin protein isoforms, sCLU and nCLU, play an important role in the regulation of proliferation and cell death.

We have studied the regulation of the expression of isoforms of CLU in a system consisting of biopsies of tissue thyroid cancer (and corresponding normal tissue) and fine needle aspiration, in a series of patients with indeterminate thyroid nodules. Immunohistochemical analysis showed a general up-regulation of CLU in papillary carcinoma. In particular, a specific increase of sCLU was observed in papillary carcinoma, compared with a decrease of nCLU and although preliminary, our results

show a specific alteration of the relationship sCLU/nCLU during the progression from normal to malignant cell¹⁷. Finally, in the presence of inconclusive cytology, clinical decision concerning the excision or a conservative approach should be taken on the basis of the available epidemiological, clinical and instrumental data. Limits, risks and benefits of therapeutic options should never be overlooked, but always explained and discussed with the patient.

In this context, collaboration between surgeon, endocrinologist, radiologist, pathologist and nuclear medicine specialist to improve diagnostic accuracy that could permit a better definition of thyroid diseases lead to the better treatment, medical or surgical and, in the latter case, support the choice of the most suitable procedure for the patient.

The highest percentage of incidental carcinomas we studied in recent years is certainly due to increased surgeries for thyroid pathology. Surgery is necessary in a short time in all TIR 3 cases because, at the moment, we have no other parameters to select malignant from benign nodule and in our last experience the TIR3A and TIR3B classification does not give us more certainty of malignancy to the histological examination⁶. On the other hand, the patients with benign disease are followed a long time in follow up before surgery. We have said how the surgical indication was due to the fact that the goiter had become greater and then symptomatic or because thyroid function was compromised (hypofunction or hyperfunction) or there was no response to medical therapy or this treatment could not be continued (hepatotoxicity, pregnant women).

Then we put the question of which is the best surgical timing in patients in endocrinological follow up for benign thyroid disease.

It's really that aggressive nodules grow faster than benign lesions and their wider size can predict malignancy,¹⁵ but in our opinion, we have to make some considerations about the interventions delayed for so long.

First of all the frequency of incidental carcinomas: in these years, we expected a decrease in the percentage of carcinomas due to a greater knowledge of thyroid pathology and the patient's anamnesis, to improvement of imaging techniques, to a more precise indication of FNA and a more precise cytological diagnosis, but results were not the desired ones.

Secondly, we must point out the changes that have occurred in the surgical approach to thyroid disease. Modern surgery is relatively safe in expert hands and in this we are comforted by the lack of long-term complications in our patients. Surgeons' experience is an important factor which can influence the onset of these complications; the use of ultrasonic dissector can only help surgical action but cannot replace the experience of the surgeon. Thyroidectomy is a poorly demolitive procedure, well standardized (identification of the recurrent nerves, preservation of the parathyroid glands), and pos-

sibly, in selected cases, may be performed a mini-invasive video assisted approach or recently, trans axillary approach robot-assisted. Thanks to these recent techniques, in addition to a magnificent vision of vessels, nerves and parathyroids we obtain a great aesthetic result because cervicotomy is extremely small in the miniinvasive procedure and is absent in robot-assisted procedures. Finally it should be considered the possibility of an easy replacement therapy. On the other hand, the incidental neoplastic lesion is almost always a small cancer or a microcarcinoma, has poor biological aggressiveness and is susceptible to radioiodine metabolic therapy. On the basis of these data and according to our experience, we believe in the collaboration between surgeons and endocrinologists or more generally in a multidisciplinary team in patients with benign thyroid disease, aimed to the early detection of malignancies.

Riassunto

Scopo del nostro studio è stato valutare la presenza di carcinomi differenziati incidentali della tiroide, all'esame istologico definitivo, in pazienti sottoposti a tiroidectomia o lobectomia per presunta patologia benigna o in pazienti con diagnosi citologica di nodulo indeterminato (TIR3).

457 pazienti sottoposti a chirurgia per presunta patologia benigna e 179 pazienti con FNA indeterminato sono stati inclusi nel nostro studio.

77 su 457 pazienti hanno avuto diagnosi istologica di carcinoma differenziato della tiroide. 29 su 179 pazienti con FNA indeterminato hanno avuto la stessa diagnosi di quelli precedenti ma non sul nodulo precedentemente sottoposto a FNA. Nella maggior parte dei casi, l'istotipo è stato di carcinoma papillare, variante follicolare.

L'incidenza dei carcinomi incidentali, approssimativamente la stessa nei due gruppi di pazienti, rispettivamente del 16,8% e del 16,2%, dimostra che esiste ancora un gruppo di pazienti con patologia tiroidea benigna che sfugge ad un'attenta valutazione ecografica e quindi a un FNA mirato. Anche in pazienti con citologia indeterminata, la presenza di un carcinoma incidentale suggerisce che ci sia da un lato una sovrastima, e dall'altro un non riconoscimento del nodulo davvero sospetto. Sebbene nella maggior parte dei casi si tratti di un microcarcinoma, non dobbiamo trascurare la presenza di molti tumori allo stadio T3.

Sicuramente l'analisi dell'insieme dei fattori di rischio unito ad una più ampia applicazione delle indagini di biologia molecolare porterà a una migliore selezione dei pazienti da sottoporre a intervento chirurgico in tempi brevi, rispetto a quelli che possono essere seguiti in follow-up anche per un periodo più lungo.

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