



## Original research

## Incidental carcinoma of the thyroid



Angela Pezzolla <sup>a</sup>, Rinaldo Marzaioli <sup>a</sup>, Serafina Lattarulo <sup>a,\*</sup>, Giovanni Docimo <sup>b</sup>,  
Giovanni Conzo <sup>c</sup>, Anna Ciampolillo <sup>a</sup>, Graziana Barile <sup>a</sup>, Ferdinando Massimiliano Anelli <sup>a</sup>,  
Andrea Madaro <sup>a</sup>

<sup>a</sup> Department of Emergency and Organs Transplantation, University of Bari, Policlinico di Bari, P.zza Giulio Cesare 11, Bari, Italy

<sup>b</sup> Department of Surgery, Second University of Naples, Italy

<sup>c</sup> Department of Anesthesiologic, Surgical and Emergency Sciences, VII Division of General and Endocrine Surgery, Second University of Naples, Italy

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## ABSTRACT

The diagnosis of incidental thyroid carcinoma in patients submitted to thyroidectomy for a benign disease is quite frequent. A retrospective analysis was performed on 455 patients submitted to surgical intervention in order to establish the incidence of this kind of carcinoma. Two hundred fifty-six patients (56%) were affected by benign disease (176 multinodular goiter, 12 uninodular goiter, 1 Plummer disease and 67 Basedow disease) and 202 (44%) by carcinoma. In 28 of 256 patients (11%), affected by benign disease, occurred a histological diagnosis of thyroid carcinoma, (10 papillary carcinoma, 1 follicular carcinoma, 29 papillary carcinoma follicular variant). In this study it's considered incidental thyroid carcinoma the one occurred in patients who never underwent Fine Needle Aspiration (FNA) and there were no suspicious features in all exams that may suggest the presence of carcinoma. Twenty-three of the 40 incidental carcinoma (57.5%) were microcarcinomas. Ten patients had a synchronous carcinoma. Actually, these patients are still in a follow up program and no recurrency of disease is occasionally observed. This study shows that the only way to put doubts on the real benignity of the disease is the fine needle aspiration; there are no other instruments that could identify the occurrence of the carcinoma. Moreover in the majority of cases the incidental carcinoma is a microcarcinoma, it doesn't reach significant volume, may be not centered by a FNA, but in most cases it's not really biologically aggressive.

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## 1. Introduction

Thyroid nodular disease is extremely common; the incidence in the adult population of the United States varies from 2% to 4%, but is significantly higher in goitrogenic areas [1].

Nodules may occur as single or multiple lesion, some may be hypofunctioning compared to normal thyroid tissue, while others show a normal activity or develop an autonomous functioning, not subject to physiological regulation of the hypothalamic-pituitary-thyroid axis [2].

A small percentage of thyroid nodules is represented by malignancies: approximately 1 nodule of 20 (5%) is a cancer.

Carcinomas of the thyroid are about 1% of all malignancies [3,4], their annual incidence is 0.004% [4]. They are more frequent in females, and although the main age of onset is between 40 and 60 years, they can also arise in childhood and youth [3].

The incidence of thyroid carcinoma – particularly the follicular histotype – is higher in goitrogenic regions, while papillary forms are more common in areas where there are no conditions of iodine deficiency.

The incidental finding of thyroid carcinoma in goiters is, without doubt, an occurrence more common than in the past, due to the improvement of diagnostic imaging [5], greater accuracy of the histological technique and above all to the increased number of thyroid diseases needing surgical treatment.

## 2. Materials and methods

From January 2010 to June 2013, 455 patients (363 females and 92 males, mean age 56.98 years, range 15–83) underwent thyroid surgery. The operation performed was total thyroidectomy in 429 cases, lobectomy in 29.

Among the 455 observed patients 256 had a preoperative diagnosis of benign thyroid disease: goiter in 188 cases (176 multinodular, 12 uninodular), Plummer's disease in 1, and Basedow disease in 67. In 202 patients cytology led to the diagnosis of cancer

\* Corresponding author.

E-mail address: [s.lattarulo@virgilio.it](mailto:s.lattarulo@virgilio.it) (S. Lattarulo).

or suspicious malignant lesion. Only the 256 patients who underwent surgery for benign disease were included in this study.

All patients were studied by neck ultrasound prior to surgery, and submitted to a CT scan of the chest in the case of plunging goiter. In 11 patients a fine needle aspiration (FNA) was performed, excluding malignancy.

At the time of surgery all patients were euthyroid, and almost all with no evidence of chronic thyroiditis.

The histological examination of the specimen confirmed the diagnosis of benign disease in 228 patients (89%). In 28 patients (11%) the presence of 40 incidental carcinomatous lesions was detected (10 patients with synchronous carcinoma).

The majority of patients with incidental carcinoma underwent total thyroidectomy (27/28). In those previously submitted to lobectomy (1/28), completion thyroidectomy was performed.

Histology detected a papillary cancer in 10 patients (25%), follicular carcinoma in 1 (2.5%), follicular variant of papillary carcinoma in 29 (72.5%).

Referring to the “T” of TNM classification, we had 23 microcarcinoma, 2 T1 carcinoma, 3 T2 carcinoma and 12 T3 carcinoma. One of 12 patient with T3 carcinoma was T3N1.

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 0.2–0.5 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.

### 3. Discussion

The thyroid carcinoma usually occurs as nodular disease. The etiology is likely to be multifactorial, resulting from the complex interaction between genetic, individual, and environmental risk factors.

Although the pathogenetic role of the ionizing radiations is currently well recognized [6], there is no significant correlation with prior radiotherapy if the thyroid tumor develops after the age of 35, since the carcinogenic potential of the radiation treatment, if performed at a later age, seems to decrease [7].

In about 3–5% of patients with thyroid carcinoma a family history for cancer of the thyroid is referred. Case in point is the association of medullary thyroid carcinoma with other endocrinopathies in MEN-2 polyglandular syndrome [8,9].

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 [10].

In the last years a significant increase of this kind of neoplasm has been detected, probably due to the widespread of ultrasound examination as a first-level diagnostic tool in the study of thyroid diseases [11].

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 [12].

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 [13,14].

Nevertheless in some authors' opinion, the papillary microcarcinoma is a nosological entity characterized by a heterogeneous clinical behavior, ranging from the small neoplastic outbreak 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% [15].

Therefore, in patients at low risk of recurrence, as those with incidental microcarcinoma, cervical ultrasonography and, to a lesser extent, the basal dosage of serum TG may ensure a suitable surveillance, even in the absence of ablation of residual thyroid tissue. Moreover it is advisable to include in the protocol of controls clinical examination, serum dosage of FT3, FT4, TSH, TG and anti-TG antibodies (TGAb), in progress of hormone therapy [16–18].

In patients with medium/high risk of recurrence who underwent to ablative treatment of thyroid remnants, at a distance of approximately 12 months after the demonstration of complete ablation of thyroid tissue and undetectability of TG after maximum stimulation of the hypophysis, is advisable to perform a cervical ultrasound and the dosage of serum TG after stimulation of endogenous TSH or – even better – after exogenous stimulation with rhTSH.

The long-term follow-up of these patients shows that the risk of recurrence is less than 2%, and the relapsing lesion may be early detected by an ultrasonography of the neck [16].

Whilst our previous study showed a percentage of incidental carcinomas (18.2%) – higher than that of other experiences [19] – the current data, despite the greater number of patients (455 vs 240) report a lower value: 11%. This is due to the improvement and more extensive employ of preoperative diagnostic techniques, particularly the fine needle aspiration and its cytological interpretation.

This points out the importance of an accurate clinical and instrumental diagnostic of thyroid nodules to differentiate benign from malignant pathology.

For this purpose TSH, thyroid hormone, thyroglobulin, the presence or absence of autoantibodies are ineffective [20].

Other biomarkers are provided by clinical and laboratory research, aimed to the management of patients with thyroid neoplasms, applied in settings that vary from preoperative selection of thyroid nodules for surgery to postoperative follow-up.

In particular molecular markers of thyroid tumors, derived from genomic and proteomic methods, have been developed, but many of these are too complex or expensive for routine clinical use or are still poorly standardized [21–25].

One of the most interesting applications of biomarkers refers to the employ on needle aspiration specimens. Fifty potential thyroid tumor markers have been tested and five of these (galectin-3, telomerase, thyroid peroxidase, RET-PTC, and p53) showed relatively high accuracy for detecting malignancy in thyroid nodules with indeterminate FNAB findings [26].

Galectin-3, the only submitted to wide multicenter studies [27,28], usually is not expressed in normal thyroid tissue, while is over-expressed in thyroid malignancy. Therefore it is considered an accurate marker of early malignant transformation.

The highest value of specificity for galectin-3 to diagnose thyroid cancer nodules (97.2%) was shown using large needle aspiration (LNA), that ensures to the analysis a larger tissue substrate

compared to FNA, and employing the recently standardized galectin-3 immunodetection method [29,30].

Therefore, the use of LNA and galectin-3 detection on the aspirate specimen, represents a promising way to optimize the pre-operative selection of thyroid nodular lesions [25].

Further clinical trials are needed to determine the most cost-effective protocol to utilize these diagnostic tools.

Thyroid ultrasound has been recognized as the main imaging examination, because of its sensitivity, simplicity, and non-invasiveness. It is the first-line investigation, in the case of nodular thyroid disease, as confirmed in our experience. The use of “small parts” probes at high frequency (12–15 MHz) achieves an excellent representation of the anatomy of thyroid and surrounding structures, and may detect very small lesions (2–3 mm) [31]. Unfortunately, despite of its high sensitivity in identifying lesions, the thyroid ultrasound demonstrated an extremely low specificity. Therefore it cannot be used for the final discrimination between benign and malignant nodules [32].

The nodular features that are usually assessed in the ultrasound scan are the number, size, shape, echogenicity, structure, presence of punctate calcifications or shell calcifications, perilesional halo, margins and hematic flow at echocolordoppler scan (ECDS). In addition, are examined the regional lymph nodes, and can be checked their dimensional changes over time.

Number and size of the nodules have no predictive value of neoplasia; more frequently associated with thyroid tumors are the relief of solid structure, anteroposterior diameter greater than the latero-lateral one, 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 [31,33].

Although the ultrasound examination of the nodule completed with ECDS 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 cancer [31].

Elastography, an emerging ultrasound technique which measures tissue rigidity properties, showed higher stiffness indices for thyroid cancers compared with benign nodules. Although promising as adjunctive tool for the diagnosis of thyroid malignancy, especially in indeterminate nodules on cytology, larger and prospective studies are needed to validate this new technique [34,35].

At present nor scintigraphy nor CT scan are able to solve the problem of differential diagnosis of malignant and benign thyroid nodules.

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 nodules [36], especially at a threshold of 3.3 or more of maximum standardized uptake value (SUVmax) [37]. In these patients the metabolic tumor volume (MTV) measured by F-FDG PET/CT seems able to predict malignancies, and better results are obtained referring to the combination of SUVmax and MTV after stratification of serum TSH levels [38]. Even the relief on CT scan of calcifications and focal uptake with high SUVmax correlates with a high likelihood of thyroid cancer [39].

Otherwise some authors have reported that FDG accumulation may be normal in the thyroid, such as a moderate to severe, diffuse or focal, FDG activity [40].

Therefore, further studies are needed to state if 18F-FDG PET or PET/CT may be used in daily practice to identify malignancies in the context of benign thyroid diseases.

A further major clinical problem in the management of thyroid nodules is the need of detecting the few malignant lesions in the

context of a multinodular benign thyroid disease, so that the first may be initiated to adequate treatment and the latter may avoid unnecessary surgery or take advantage of a “tailored” operation.

The cyto-fine needle aspiration is the most accurate procedure to determine whether a thyroid nodule shows elements of risk that would justify surgical excision or if the probability of benignity is so high to advise the simple clinical observation [41]. The surgical pre-selection based on FNA reduces the need of surgery to less than 20% of the nodular lesions, and over 50% of these prove to be malignant at histology [42].

The only palpable thyroid nodules that do not require FNA are those that shows an increased radioiodine uptake compared with the surrounding parenchyma. These lesions are autonomously functioning adenomas or hyperplastic functioning nodules, and present an extremely low risk of malignancy.

The probability of finding a neoplastic outbreak in a multinodular goiter does not substantially change compared to individual solid nodules. Since ultrasound does not provide information about the discriminatory nature of the nodule, these lesions should be subjected to FNA [43–46].

The cytological diagnosis of malignancy is extremely accurate when performed by an experienced thyroid cytopathologist (2–5% false positives), his judgment of benignity is likewise reliable and justifies a conservative approach.

However, there are particular conditions in which surgical excision may be indicated despite a negative cytology such as, for example, in the case of scintigraphic uptake of 99 m Tc pertechnetate or radioiodine at the level of the cervical lymph nodes or family history of medullary thyroid carcinoma [47].

The cytological diagnosis of suspected malignancy is less specific, indicating a likelihood of malignancy ranging between 25% and 75%.

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 [48].

Thus, an aspect that emerges from our study is the complete lack of data – medical history, ultrasound, scintigraphy – that could reveal the presence of a tumor in the surgical specimen. In all patients with incidental carcinoma, 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. All these conditions were attributable to non-neoplastic diseases that in some cases, being the contralateral thyroid lobe intact, we treated with lobectomy and that we had to totalize in a second time on the basis of the histological response.

Even in the presence of intraoperative dubious conditions – such as a hard lump on palpation – we are used to perform the lobectomy anyway, after achieving the patient informed consent prior to surgery, since, according to the international literature, extemporaneous histological examination is not indicated on the thyroid.

In the management of thyroid nodular lesions the only reliable test seems to be the fine needle aspiration cytology, which, at least, can put in doubt the supposed benignity. Our confidence in the method is strengthened by the fact that, to date, we have found only two cases of false negative FNA.

Almost all authors agree on the indication to submit to FNA each uninodular goiter, regardless of toxicity, ultrasound appearance, vascularization, iodine uptake. Otherwise the same uniqueness of views is not shared regarding the multinodular goiter, which, in our experience too, is not free of risk for cancer.

If we consider our 165 patients operated for benign disease, only a small part was subjected to FNA, precisely, only 2 of the 30 patients with incidental carcinoma, however unsuccessfully. This confirms 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. Moreover this points out the major and persisting limit of ultrasound investigation, that remains an operator-dependent procedure, so that different sonographers may sometimes express a diverging evaluation of the same patient.

Therefore, we hope a closer collaboration between surgeon, endocrinologist, radiologist, pathologist and nuclear medicine specialist, to improve diagnostic accuracy, that could permit a better definition of multinodular thyroid diseases, steer to the most proper treatment – medical or surgical – and, in the latter case, support the choice of the most suitable procedure for the patient.

A further debated question is the timing of surgery in patients in progress of medical therapy for benign thyroid diseases.

Several considerations may oppose to delayed surgery. First of all the frequency of incidental carcinomas.

Then the fact that modern surgery is safe in expert hands: thyroidectomy is a poorly demolitive procedure, well standardized (identification of the recurrent nerves, preservation of the parathyroid glands), and possibly, in selected cases, may be performed a mini-invasive video assisted approach.

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 reasonably acceptable a close follow-up performed by surgeons and endocrinologists in patients with toxic multinodular goiter, aimed to the early detection of malignancies.

#### 4. Conclusions

Despite technical improvements of preoperative diagnostic, the incidental thyroid carcinoma is still a common occurrence, and no clinical or instrumental assessment has proved, till now, adequate accuracy to identify malignancy, especially in the context of a benign thyreopathy.

Ultrasound scan and FNA at present are the best diagnostic means to study thyroid nodules and to select the indication and the options to surgical treatment. Our experience demonstrates that a slight margin of improvement is still possible, even working on these two proven methods. Further enhancements are desirable, and several proposals seem promising.

More sophisticated tools – elastosonography and 18F-FDG PET or PET/CT – are still under evaluation. Finally recent studies are trying to identify and develop new thyroid tumor markers aimed to diagnostic and prognostic use.

In conclusion we recommend and once again emphasize the need for a multispecialistic team to approach thyroid diseases, and the need for establishing a relationship of trust with the patient, which must be duly informed and reassured about his condition.

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None.

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None.

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#### Author contribution

**Angela Pezzolla:** Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

**Rinaldo Marzaioli:** Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

**Serafina Lattarulo:** Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

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**Giovanni Conzo:** Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

**Anna Ciampolillo:** Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

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**Ferdinando Massimiliano Anelli:** Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

**Andrea Madaro:** Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

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