The incidence of thyroid carcinoma in the nodules.

A retrospective study

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Fine-needle aspiration (22G) is the diagnostic procedure chosen to study the nature of suspicious thyroid nodules. In 2008 the SIAPEC-IAP work group issued the results of Italian Consensus about the clinical management of patients with thyroid nodular disease, and introduced diagnostic categories aimed to standardize the diagnostic and therapeutic process of patients affected by thyroid nodules. This retrospective study is aimed to assess the incidence of carcinoma at definitive histological examination after total thyroidectomy of nodules with TIR3 cytological diagnosis.

KEY WORDS: CEUS, FNAC, Surgery, Thyroid nodules

Introduction

Fine-needle aspiration (FNAC) is the easier and safer diagnostic procedure, as well as the one with the best cost-benefit ratio, to lead patients affected by thyroid nodules to a diagnosis, allowing to differentiate between the ones requiring surgery and the ones requiring medical therapy only and a clinical follow up [1,2]. The diagnostic accuracy of this method within not-functioning nodular pathology is 95%, with less than 2% of false negative and less than 3% of false positive [1,3]. The selection of patients undergoing to FNAC must be according to clinical criteria (female gender, previous neck radiotherapy, family history of thyroid carcinoma), physical (palpable nodule, hard, still, suspected laterocervical mass) and by ultrasound (nodules bigger than 1 cm Ø, hypo-echoic, with calcifications and irregular vascularization) [4,5].

The management of some of such lesions was often controversial because of the lack, for many years, of a real international terminology [1,6]. During the last decade many scientific societies proposed some guidelines, but in 2008, almost contemporarily, were issued the Bethesda System for reporting Thyroid Cytology (Table I) and the classification drawn up by the SIAPEC-IAP work group [2,3]. Such classifications are aimed to define a standard strategy for each patient in order to support both the clinician and the surgeon in defining the best therapeutic process [7]. In the Florence SIAPEC-IAP consensus were defined 5 different diagnostic categories (Table II): TIR1 (not diagnostic), TIR2 (negative for malignant cells), TIR3 (inconclusive/undefined – follicular proliferation), TIR4 (suspicious for malignancy), TIR5 (positive for malignant cells). Based on this classification, patients management with TIR2, TIR4 and 5 is quite easy; TIR3 category is the most complex, since it includes all follicular pathologies: adenomatoid hyperplasia, adenoma,

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TABLE I - *Bethesda Classification*

I	Non diagnostic / unsatisfactory	Cyst fluid only Virtually acellular specimen Other (sangue oscurante, artefatti di coagulazione, etc)
II	Benign	Consistent with a benign follicular nodule (includes adenomatoid nodules, colloid nodules etc.) Consistent with Hashimoto thyroiditis in a proper clinical context Consistent with granulomatous (subacute) thyroiditis Other
III	Atypia of undetermined significance or follicular lesion of undetermined significance	
IV	Follicular neoplasm for follicular neoplasm	Specify if *Hurthle cells*
V	Suspicious for malignacy	Suspicious for papillary carcinoma Suspicious for medullary carcinoma Suspicious for metastatic carcinoma Suspicious fot lymphoma Other
VI	Malignant	Papillary thyroid carcinoma, poorly differentiated carcinoma, medullary thyroid carcinoma, anaplastic carcinoma, squamous cell carcinoma, metastatic carcinomao, non-Hodgkin lymphoma, other

micro-invasive follicular carcinoma, oxiphil cells lesion and some rare case of follicular variant of papillary carcinoma. In such instances cytology is not able to provide a complete diagnosis which is possible only by a final histological examination: this category represents 20% of histological examinations, about 20% of which are malignant lesions at histology test [3,5]. Such category can be compared to AUS-FLUS (atypical follicular lesion of undetermined significance): surgical Thyroidectomy is advisable for both, possibly after a FNC repetition, but only in selected cases aimed to avoid not needed surgery [4,8,9]. In order to reduce surgery for benign nodules, some molecular genetics methods were developed, next to the cytological methods (BRAF mutations, RET/PTC, PAX8/PPRgamma, RET) and ultrasound ones (CEUS – contrast-enhanced ultrasound scan and elastosonography) that seem to be helpful in differential analysis of undetermined lesions before surgery [10,11].

Materials and Methods

In order to assess the occurrence of carcinoma in patients with undetermined cytological diagnosis and, therefore, better define the therapy process for such patients, in our retrospective study we have assessed 153 patients with a TIR3 pre-surgery diagnosis, who underwent to total Thyroidectomy, from January 2009 to December 2012, at A.O.U. "Federico II". Were excluded all patients with positive FNC for TIR 4 and 5, with a positive anamnesis for a previous neck irradiation, patients who had already thyroid surgery before, and the ones who had a conservative therapeutic approach (lobe-isthmectomy, lobectomy). Cytology diagnosis on slides was performed by expert pathologists, also from various institutes, but were all based on SIAPEC-IAP classification. FNAC was performed in all cases by using a 22 G needle, aided by an ultrasound scan guidance except for those cases of superficial and palpable nodules. Total thyroidectomy was the treatment chosen as well for those patients to whom needle aspiration was carried out in a <2cm nodule (122); 72 were subjects showing either single micronodule formation or a multiple bilateral one as detected by echography, 21 patients showed gland simple hyperplasia with increased volumes index, even in the absence of micronodules to counterlateral lobe. In the remaining subjects (29), the possibility of total thyroidectomy, if definitive hystology was positive for carcinoma, implied a refusal to undergo to a second surgery, therefore in these patients, we performed total thyroidectomy. Moreover, since 2010 at the Department of Diagnostic Imaging of A.O.U. "Federico II" of Naples, 27 out of 153 patients had contrast-enhanced ultrasound scan (CEUS), using contrast medium Sonovue, imaging method integrated to the traditional ultrasound scan with color and power Doppler. For all patients we took into account some variables, searching for a possible correlation: age, gender, nodule size, final histological diagno-

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TABLE II - *Clinical – cytological classification by needle aspiration as by SIAPEC-IAP (October 2007)*

Class	Diagnosis Category	Recommended Treatment	Hystology Correspondence
TIR-1	Not diagnostic/ not representative	Not diagnostic: repetition after 1 month. Cyst/hemorrhage: check and/or repetition	Cyst
TIR-2	Negative for malignant cells	Clinical check, as by opinion of clinician or cytopathologist it can be repeated to minimize FN	Nodular goiter; micro follicular adenomatous nodule in goiter; thyroiditis.
TIR-3	Unconclusive/undetermined (follicular proliferation)	Surgical removal of lesion and histology test. Not extemporary test. Some useful markers (GAL-3, HBME-1, CK19)	Follicular ad; neoplasm to oxhiphil cells; follicular ca minim. invasive; papillary ca follicular var.
TIR-4	Suspicious for Malignancy	Possible repetition of FNC as by opinion of clinician or under suggestion of cytopathologist. Surgical removal of lesion with possible extemporary test.	Mainly follicular variant of papillary carcinoma
TIR-5	Positive for malignant cells	Surgery for differentated carcinoma. Proceding diagnosis process in case of anaplastic ca., metastasis or lymphoma	Malignant neoplasia

sis; the possible influence of gender, age and nodule size on a diagnosis of malignancy at histological test was studied by means of the $\chi 2$ statistical test, considering statistically significant any value of $p<0.05$.

Results

Initially we divided our 153 patients according to gender, 16 men and 137 women; age, 67 over 50 years of age and 86 younger; nodule size (based on AJCC classification for staging), 122 with nodules <2cm and 31 with nodules ≥2cm. The results are reported in (Tab. III). Disease prevalence is higher in women, but there is no increase in the risk of malignancy which is statistically significant in this group (p=0.653). From age perspective, undetermined nodular disease seems quite evenly distributed, the stratification by age does not seem connected to an increase of carcinoma at the final histology (p=0.374). Finally, nodule size as well as the other two variables taken into account in our study, are not significantly connected to an increase of malignancy (p=0.515). Final histology test, run after total thyroidectomy resulted as follows: 65 cases of follicular Adenoma (42.4%), 60 cases of follicular hyperplasia (39.2%), 13 cases of follicular carcinoma (8,49%), 8 cases of follicular variant of papillary carcinoma (5.2%), 2 cases of classical variant of papillary carcinoma (1.3%), 5 cases of lesions to oxiphil cells (3,2%); to a total of 23 cases of carcinoma (15%). We must point out that in 4 out of these 23 cases there was a diagnosis of ipsilateral incidental micro-carcinoma (3 cases of papillary carcinoma and one case of follicular carcinoma); while in 2 occasions we found a carcinoma in the contra-lateral lobe (in both cases a follicular variant of papillary carcinoma); this suggested the possibility of a multifocal malignancy, whose only therapy approach requires a total thyroidectomy. In 2 cases there was also a diagnosis of carcinoma in a nodule which was different from the one that underwent to pre-surgery biopsy. The percentage of unnecessary thyroidectomy, in our retrospective study, is in line with what reported in literature [1,2,12], in order to reduce as much as possible such occurrence it is desirable the introduction of contrast-enhanced ultrasound scan (CEUS), an imaging method which integrates traditional ecocolor doppler. Out of the 27 patients who in pre surgery had contrast-enhanced ultrasound scan (CEUS), 21 had a final diagnosis of benignity, in 6 cases there was a malignant neoplasm (5 papillary carcinoma and 1 follicular carcinoma): all these patients at CEUS showed a inhomogeneous enhancement pattern. The results about the assessment of the various contrast-

TABLE III - *Results*

	Malignant Nodules	Benign Nodules	P (test χ^2)
Gender			p 0.653
Male	4	12	
Female	19	118	
Age			p 0.374
>50	11	56	
<50	12	74	
Nodule size			p 0.515
<2 cm	12	110	
>2 cm	7	24	

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ultrasound-graphic patterns related to contrast media distribution into thyroid lesions (homogeneous, not-homogeneous, with peripheral shroud, etc.) showed, however, a poor diagnostic accuracy in malignant nodules identification. Actually, in our case studies as well, although small by number, we found a low specificity. Contrast media wash in and wash out of lesions seem to be a more reliable parameter; but further evidence, with increasing number of patients, is necessary to confirm this hypothesis [12]. Recently the elastosonography makes it possible to identify the properties of elasticity or hardness of thyroid nodules, in the characterization of these nodules, this technique has shown, regardless of size, that nodules "hard" are associated with a higher risk of malignancy; it is, in fact, possible to identify different score, that depending on the different elasticity of the various portions of the nodule allow to characterize [13]. Moreover, still in order to reduce unnecessary thyroidectomies, molecular genetics studies could be used to identify a subpopulation of patients showing indeterminate cytology with low carcinoma probability; some markers (GAL 3, HBME1, CK 19) can increase diagnosis accuracy: conservative approach will be therefore addressed to those TIR3 patients showing negative result (benign) to the classification test of gene expression [14].

Discussion

Needle aspiration in Thyroid diagnostics is aimed to stratify the risk of malignancy in patients having nodules [4]; in spite of the high significance of the method in detecting the presence of carcinoma (89-100%), the specific detection has instead a more variable range, between 69 and 96% [12,15]. Such difference is due to the presence of intermediate groups, which means undetermined diagnosis categories both in Bethesda classification and in the Consensus SIAPEC-IAP one [3,11]: in fact there is a wide variability and subjectivity in interpreting undetermined cytology tests (AUS-FLUS e TIR3); they are cases where cytology features are not absolutely benign, so as the cellular atypia or cyto-architectural atypia rate is not such to allow a neoplasm diagnosis [15, 16]. The use of a standard classification certainly led to similar results in literature regarding the malignancy risk of undetermined lesions : 15% of our study is in line with the results of Yassa et al (24%) [17], Jo et al (17%) [1], Yang et al (19%) [18] issues. The management of such patients is quite debated, in most of case studies less than 20-30% of undetermined cases is malignant at histology [19,20], but in the absence of valid criteria to distinguish lesions, these are treated with surgery: detecting a carcinoma is an event to be taken into account, and even more the event of multifocal carcinoma, even if not very frequent, must suggest surgery approach implying total thyroidectomy; performing conservative surgery (lobectomy, lobeistmectomy) must be reserved for limited cases: young patients, without any nodular pathology at counter-lateral lobe, in absence of risk factors (familiarity, previous neck irradiation) [21]. According to this we can say that in such cases, where nodule clinic and ultrasound features are fundamental, it is advisable to perform another FNAC after 3-6 months. Some case studies put into evidence that some factors like age, gender and nodule size, would outline a group of TIR3 patients at risk for malignancy [4,5,15]; but according to our results there is no statistically significant connection between such factors and neoplasm occurrence. We also found some carcinoma cases in a nodule different from the one submitted to biopsy; they are occasional samples connected to TIR3 that have not a specific collocation in literature. Our retrospective survey has also taken into account patients undergoing to contrast-enhanced ultrasound scan (CEUS) in pre surgery; this method could play an integration role to FNAC into the diagnosis algorithm for thyroid nodules: the introduction of contrast medium in ultrasound scan as echo amplifier in the assessment of tissue micro circulation in order to increase ultrasound scan diagnosis potential can offer the chance distinguish benign nodules from malignant ones by identifying some specific enhancement patterns in the various focal lesions [10]; the effectiveness and predictive value of this diagnosis method, even if promising according to literature [10,22,23] should be assessed by a wider and perspective case study. In fact this kind of work, retrospective, as well as the small number of patients undergoing CEUS did not allow statistically significant results.

Conclusions

Our case study, in accordance to international literature, confirms the need to provide a surgical approach to patients having a TIR3 pre surgical cytology diagnosis, taking into account the malignancy risk for such nodules and because of the finding, although rare, of incidental neoplasm in counter lateral lobe. The conservative approach (lobectomy or lobeistmectomy) can be proposed in selected cases: the decision is based essentially on clinical – anamnestic and ultrasound scan criteria, since other parameters like age, gender and nodule size seem to have not a statistically significant connection to the occurrence of carcinoma.

Riassunto

L'ago aspirato con ago sottile (22G) rappresenta la procedura diagnostica di scelta per lo studio della natura dei noduli tiroidei sospetti. Nel 2008 il gruppo di lavoro SIAPEC-IAP ha pubblicato i risultati della Consensus italiana sulla gestione clinica del paziente con patologia nodulare tiroidea, introducendo categorie diagnostiche

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che possano standardizzare l'iter diagnostico e terapeutico dei pazienti affetti da noduli tiroidei. Questo studio retrospettivo valuta l'incidenza di carcinoma all'esame istologico definitivo dopo tiroidectomia totale nei noduli con diagnosi citologica di TIR 3.

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Commento e Commentary

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La patologia nodulare della tiroide rappresenta l'endocrinopatia più frequente e lo scopo primario della diagnostica è quello di differenziare i noduli benigni da quelli maligni o sospetti per una adeguata soluzione chirugica. L'esame citologico mediante agoaspirazione rappresenta, al momento attuale, l'indagine di maggior accuratezza diagnostica con una sensibilità di oltre il 90% nei centri di riferimento. Infatti, mentre, per alcune neoplasie, quali il carcinoma papillifero, il carcinoma anaplastico ed il carcinoma midollare la risposta citologica ha una affidabilità del 100% per le neoplasie follicolari non è possibile ottenere una diagnosi citologica definitiva.
Questo gruppo di lesioni è rappresentato citologicamente dalla categoria Thy3 o lesione indeterminata che nell'80% dei casi all'esame definitivo postoperatorio risulta di natura benigna, adenoma follicolare o iperplasia adenomatosa, e, solo nel 20-25% dei casi la diagnosi è di neoplasia maligna, ovvero di un carcinoma follicolare,di un carcinoma a cellule di Hurthle o un di un carcinoma papillifero variante follicolare. Nel 2008 Baloch ZW et al. (Bethesda/classificazione) ritennero opportuno suddividere le lesioni follicolari in due sottogruppi, un primo costituito dalle lesioni follicolari di tipo indeterminato da sottoporre al solo controllo clinico ed ad una nuova valutazione citologica ed un secondo gruppo cui appartengono le neoplasie follicolari e a cellule di Hurthle sospette per carcinoma con indicazione chirurgica per controllo istologico. Liggio ed i suoi collaboratori, nel loro interessante lavoro, confermano le difficoltà diagnostiche delle lesioni citologicamente definite Thy 3 ed infatti anche nel loro studio, come confermato in letteratura, si è registrato un elevato numero di interventi con diagnosi definitiva di lesione benigna (85%). Gli A.A. ritengono che una diagnostica strumentale più sensibile (ecografia con contrasto ed elastografia) possa consentire una maggiore definizione delle lesioni follicolari e sia in grado di acquisire ulteriori elementi di sospetto per suggerire la conferma chirurgica. In un recente studio [1] abbiamo adottato una nostra classificazione citologica, in accordo con le linee guida della British Thyroid Association, con l'intento di meglio definire le lesioni della categoria Thy 3 e ridurre il numero degli interventi associati ad una patologia benigna.
A questo scopo abbiamo studiato tutti i nostri pazienti con la diagnosi citologica Thy3 oltre che con la citologia convenzionale anche con la citologia in fase liquida che ha il vantaggio di poter associare sia lo studio immunoistochimico che la biologia molecolare. Basandoci su questa subclassificazione siamo riusciti a ridurre il numero delle tiroidectomie "non necessarie" dal 58 al 42%. Concordiamo con gli A.A. sulla indicazione alla tiroidectomia totale, quale intervento di elezione nei pazienti con diagnosi citologica preoperatoria di carcinoma papillifero ed associamo la linfectomia del compartimento centrale nei casi con positività linfonodale o con fattori clinici di rischio. Riteniamo che l'intervento di lobectomia possa essere indicato nei pazienti con nodulo singolo ed in assenza di fattori prognostici di rischio per neoplasia.

* * *

Thyroid nodules are a common finding and most of them surgically removed are demonstrated to have a benign nature at histology. Therefore, it is important to reduce the number of unnecessary surgical procedures, and to acheive this goal, an accurate preoperative diagnosis should be done. The fine-needle aspiration cytology (FNAC) is the best diagnostic test available today, with an accuracy and sensitivity exceeding 95% in many series.
But, while the FNAC diagnostic accuracy approaches 100% for most thyroid neoplasms (e.g.PC, MTC and anaplastic carcinoma), it declines for follicular-patterned lesions, where the rate of indeterminate diagnosis is high and difficulties arise in discriminating benign from malignant histotypes. Up to 80% of cases diagnosed as follicular-patterned lesion are benign on histologic examination (hyperplasytic nodule or adenoma)while 20-30% of them present risk of malignancy. Classification schemes have been proposed to reduce the number of FP candidates submitted to surgery and at the same time to avoid any increase of false negative cases. Majority of thyroid associations guidelines agree that follicular patterned lesions should be divided into two categories: 1) follicular lesion (atypia) of undetermined significance- managed by repeat FNAC; 2) Follicular or Hurthle cell neoplasm (suspicious for follicular or Hurthle cell neoplasm)- most likely to be managed by surgical excision.In their interesting study, based on SIAPEC-IAP consensus, Liggio et al. report the data of 153 surgically treated patients for follicular-patterned lesions and confim the difficulties in distinguish patients requiring appropriate surgical procedure(at definitive histologic diagnosis: 130(85%) benign and 23 (15%) malignant).High data, but in line with literature.
In order to reduce unnecessary thyroidectomies the A.A. suggest to take in account contrast-enhanced ultrasound scan, which they performed in 27 patients with not statistically significant results.In our recent study[1] we have adopted a cytological subclassification, according to the British Thyroid Association, in the attempt to reduce the number of Thy3 who undergo surgery. We have studied all our patients with conventional smear (CS)associated with liquid-based cytology (LBC)wich allows to perform immunocytochemical studies, required in some cases to reach a definitive diagnosis (2).Based on our morphological categories we have obtained a reduction of unnecessary thyroidectomies fro 58% to 42%, with a poorly significant increase of the false-negative rate (from 1.9 to 2.4%). We agree with the A.A. in con-

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sidering total thyroidectomy the elective surgical treatment in all patients positive for papillary carcinoma and perform central neck dissection in those patients with clinically positive lymph nodes or with poor prognostic factors. But we take, also, in consideration dia gnostic lobectomy if the nodule is single and in absence of risk factors for malignancy.

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