What really is an indeterminate FNA thyroid nodule?

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What really is an undetdetermiate FNA thyroid nodule?

BACKGROUND: *Thyroid nodules are usually benign; however, 5 to 15% prove to be malignant. Fine-needle aspiration (FNA) has become the gold standard in the evaluation of thyroid nodules, especially in single nodule more than a centimeter and / or in smaller nodule with ultrasound characters of malignancy.*
METHODS: *We evaluated retrospectively 179 patients with "undetermined" thyroid fine needle aspiration, undergoing surgery. We compared cytology and histology and we evaluated sex, age, the presence of thyroiditis and dimension of the indeterminate nodule as predictors of malignancy.*
RESULTS: *In 48 patients (26.8%) histological examination confirmed the indeterminate cytological diagnosis and this means that the nodule underwent FNA was diagnosed in effects such as cancer. In 29 patients, on histological examination, the nodule underwent FNA was not diagnosed as cancer, but one or more carcinomas were diagnosed in the same lobe of indeterminate nodule, but in different location and / or in the contralateral lobe. In 102 patients, the definitive histological examination did not confirm the suspected diagnosis and we found a significant positive association only between male sex and histological malignancy.*
CONCLUSIONS: *The indeterminate FNA still remains a challenge for the surgeon because it is not yet possible to discriminate patients who really need surgery from those that can be followed in follow-up. The potential of molecular diagnostics for thyroid nodules with indeterminate cytology is promising, but many of these markers are too complex or expensive for routine clinical use or are still poorly standardized.*

KEY WORDS: Indeterminate FNA, Thyroid, Thyroid fine needle aspiration

Introduction

Thyroid follicles remodel continuously, responding to stimuli, such as thyrotropin, growth factors, cytokines and iodine. Nodules develop when growth signals drive hyperplasia or when a follicular cell acquires a genetic mutation that confers autonomous growth and are commonly seen in clinical practice, especially in elderly patients and females.

When a patient presents a thyroid nodule, the primary concern is whether it is benign or malignant [1].

Thyroid nodule are usually benign; however, 5 to 15% prove to be malignant [2,3]. 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 % [4]. Unfortunately, the preoperative characterization of some thyroid nodules is still a challenge and many lesions, which diagnosis remain *indeterminate* after fine-needle aspiration cytology, are referred to surgery. About 80% of these thyroid nodules are classified as benign at final histology.

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The objective of this study was examine the malignancy rate in nodules classified as "indeterminate" on cytology.

Materials and Methods

We evaluated retrospectively 179 patients with "undetermined" thyroid fine needle aspiration, undergoing surgery. The patients, 138 men and 41 men, had a mean age of 52.13 years (range 20-79) and had thyroid fine-needle aspiration due to the presence of a *single* nodule larger than 1 cm or due to the presence of a *single* nodule smaller than 1 cm but with suspicious ultrasonographic features or due to the presence of a suspicious nodule within a goitre. Cytology was evaluated and classified as undetermined - TIR 3 - according to the Italian SIAPEC classification. This classification includes 5 categories: unsatisfactory (Tir1/Thy1), benign (Tir2/Thy2), indeterminate (Tir3/Thy3), suspicious for malignancy (Tir4/Thy 4) and positive for malignancy (Tir5/Thy 5).

Some patients had been previously subjected to fine needle aspiration on the same nodule with non-diagnostic (TIR 1) or negative (TIR 2) result. In most cases, the patients had a positive family history for thyroid disease, without a particular exposure to ionizing radiation. At the time of surgery the patients had normal values of thyroid hormones because the thyroid function had never been compromised or because was improved with medical therapy and in all the patients we evaluated the presence of thyroiditis with autoantibody dosage. Only 5 patients chose to undergo lobectomy, by the data of ultrasound single nodule and integrity of contralateral lobe, and in the awareness of the need to complete the surgery after histological examination. The other 174 patients underwent total thyroidectomy due to the presence of multiple nodules or chronic thyroiditis or by express wish of the patients. In all patients was evaluated histology and has been compared with the previous cytology.

In 48 patients (26.8%) histological examination confirmed the *indeterminate* cytological diagnosis and this means that the nodule underwent FNA was diagnosed in effects such as cancer. This is important because in 29 patients, however, on histological examination, the nodule underwent FNA was not diagnosed as cancer, but one or more carcinomas (in 5 patients) were diagnosed in the same lobe of indeterminate nodule, but in different location and / or in the contralateral lobe. In 102 patients, the definitive histological examination did not confirm the suspected diagnosis: the indeterminate nodule was benign and has not been diagnosed any "incidental" cancer.

Ultimately, in 131 patients, 73.2% of cases, there was no correspondence between indeterminate (TIR 3) cytology and histological examination.

In our series of 48 carcinomas, we had 30 follicular variant of papillary thyroid carcinomas, 7 follicular carcinomas, 4 follicular - Hurtle cell carcinomas, 3 papillary carcinomas, 3 follicular variant of papillary - Hurtle cell carcinomas, 1 papillary - Hurtle cell carcinoma. In the TNM classification, we rated the "T" with the following results: 6 T1a, 13T1b, 15 T2, 14 T3 (including 1 T3N1). In 13 cases the histological examination, in addition to confirming the presence of a carcinoma in correspondence of the nodule subjected to FNA, has diagnosed the presence of one or more other neoplastic foci. Two of the five patients undergoing lobectomy in which was confirmed the diagnosis of carcinoma on nodule subjected to FNA, have completed the surgery and in one of them was also found a small incidental carcinoma on the controlateral lobe.

After surgery, all patients were followed by endocrinologist who advised the possible radioiodine. In our experience we have no permanent voice disorders and / or hypocalcemia and all the patients, currently, are in good health.

In the 48 patients with cancer on indeterminate FNA nodule and in the 102 patients without cancer, we have also considered any predictors of malignancy. In particular, we considered sex, age (> or < of 65 years), the presence of thyroiditis and dimension (> or < 1 cm) of the indeterminate nodule.

We found a significant positive association between male sex and histological malignancy with an odds ratio male/female of 3,28. Patients older than 65 years didn't show an increased risk of malignancy compared to younger patients (OR <65 years / >65 years: 1,66). There wasn't a relationship between presence or absence of thyroiditis at the histological examination with presence of a thyroid carcinoma in the nodule underwent FNA (OR thyroiditic / not thyroiditic: 1.03). Even nodules dimension wasn't found to be discriminant using a cut off of 1 cm (OR > 1 cm / < 1 cm: 1.50).

Discussion

When a nodule is found, the most important clinical problem is to exclude malignancy, which accounts for approximately 5%-15% of all thyroid nodules. A combination of clinical factors (age, sex, exposure to radiation, familial traits) and ultrasonographic (US) features (echogenicity, solid nodule, vascularization, calcifications and margins) determines whether or not the clinician should proceed with further tests or observation. Individual US features are not now considered accurate predictors of thyroid cancer, despite four or five US suspicious features, taken together, may indicate malignancy [2]. US is helpful to the initial decision-making process, but cannot be considered the diagnostic investigation that allows us the diagnosis between benign and malignant nodules, then combination with other evaluations is needed. Ultrasonographically guided thyroid fine needle aspiration (US-FNA) is regarded as the first-line screen-

ing test in triaging patients with thyroid nodules. Its usefulness has increased significantly in recent years, especially for the possibilities it offers, to aspire smaller and deep-seated nodules [4] whose management is based on data correlating a specific cytological reading with the probability of malignancy. A US-FNA must be performed for thyroid nodules greater than 1 cm, but, as nodule size is not a useful means of distinguishing malignant from benign nodules, a US-FNA must be performed in nodules smaller than 1 cm with suspicious US features, too. The features as the marked hypoechogenicity, the microlobulated or irregular margins, the microcalcifications [5], the anteroposterior diameter greater than the transverse diameter, the intra-nodular vascularization more than to be predictors of malignancy, may indicate which nodules undergo FNA. In preoperative time, US-FNA has been shown to classify 62 to 85% of thyroid nodules as benign thereby avoiding diagnostic surgery, [3] then the main role of thyroid FNA is to triage patients for either surgery or conservative management. FNA diagnoses that suggest malignancy or the presence of neoplasia are managed surgically, whereas patients with FNA diagnoses that show a benign lesion can be followed clinically [4]. Diagnoses and diagnostic categories are defined differently among institution and even between in the same institution. The Papanicolaou Society of Cytopatololy proposed 6 diagnostic categories (the Bethesda System) for the classification of thyroid fine-needle aspiration cytology. Cytological diagnoses were classified as (1) unsatisfactory, (2) benign, (3) atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), (4) follicular neoplasm/suspicious for a follicular neoplasm (FN/SFN) and Hurtle cell neoplasm (HN), (5) suspicious for malignancy and (6) positive for malignancy [6]. This classification has many similarities with the Italian Society of Anatomic Pathology and Cytology classification (SIAPEC) and British Thyroid Association classification that include 5 categories: unsatisfactory (Tir1/Thy1), benign (Tir2/Thy2), indeterminate (Tir3/Thy3), suspicious for malignancy (Tir4/Thy 4) and positive for malignancy (Tir5/Thy 5).

The diagnosis of AUS/FLUS (third category of Bethesda System), is a controversial category in thyroid fine-needle aspiration, not only for its questioned clinical utility, but for its very existence as an expression of uncertainty. A variety of names have been used for such cases, including atypical follicular lesion, atypical cellular lesion and atypical epithelial cells. According to recent guidelines for thyroid FNA, third category of Bethesda System is an heterogeneous category that includes cases with ambiguous cytological findings that appear to be greater than would be expected of a non-neoplastic process, yet the degree of cellular or architectural atypia is insufficient for an interpretation of "follicular neoplasm" or "suspicious for malignancy".

A variety of factors can induce atypia, including inflammation and repair, which may be difficult to distinguish these cells from malignant cells. In these cases, pathologist favored a benign nodule, however, follicular neoplasm or papillary carcinoma of the thyroid (PTC), could not be ruled out completely. Another cytology by FNA can be able to provide a more definitive diagnosis. The malignant rate is from 5% to 15%, [7] higher that than observed in patients with nodules in the benign category (7.3%) [4].

In the FN/SFN/HN category (fourth category) cells have scant or absent colloid and follicular cells or Hurthle cells form syncytial or thick, 3-dimensional clusters, loosely cohesive microfollicles and there are isolated, intact, individual cells too. FN nuclei generally are overlapping, enlarged, round and lacked typical nuclear features of PCT. The differential diagnosis for this category is among follicular/Hurthle cell adenoma (FA/HA), follicular/Hurthle cell carcinoma (FC/HC) and the follicular variant of papillary carcinoma (FVPCT). In these cases, only formal histological assessment can differentiate between benign and malignant lesion, for the histologic evidence of capsular and/or vascular invasion. The prevalence of malignancy varies from 15% to 30% [7] and most of these carcinoma are FVPCT. Hurtle cell neoplasm does not predict more malignancy than follicular neoplasm, but only a higher risk of Hurtle cell carcinoma [4]. The third and fourth category of Bethesda System are united in the category of the Tir3/Thy3 in the Italian and British systems for classification. The British Thyroid Association, Royal College of Physicians and Royal College of Pathologists have recently upgraded the five-tiered cytological classification of thyroid FNA, dividing the previous Thy3 category (indeterminate for malignancy) into two new subcategories [7]: Thy3a (atypia) and Thy3f (follicular). In the Thy 3a, FNA shows cytological atypia or other features which suggest the possibility of neoplasia, but which aren't sufficient to put it into any other category. Thy 3a are only a small minority of Thy3 cases. Thy3f, ("f" for follicular) is the classification for FNA in which samples suggesting follicular neoplasms. These are likely to form the majority of the Thy3 category. The histological possibilities therefore include hyperplastic or other cellular but non-neoplastic nodules including follicular adenomas, follicular carcinomas and follicular variants of papillary thyroid carcinoma. These nodules cannot be reliably distinguished on cytology alone. Samples consisting almost exclusively/exclusively of Hürthle cells are also included here [8].

Most of Italian pathologists employ the five-tiered Italian Society of Anatomic Pathology and Cytology (SIAPEC) reporting system, including 'indeterminate for malignancy – Tir3', which is still treated as only one group, [7] and this is the classification used in our study. In follicular or Hürthle cell neoplasms, cytology cannot distinguish a malignant tumor from a benign one and confirmation of malignancy is possible only with histologi-

cal examination of the tumor, but also the patients with atypia of undetermined significance or follicular lesion of undetermined significance may have a follicular neoplasm or a papillary carcinoma.

These two categories, together, (indeterminate lesions) are associated with an approximately 25% risk of malignancy [2,9]. Despite a low risk of malignancy, diagnostic surgery is often necessary in determining a final pathology, then surgery and histological examination is still required by the current guidelines of thyroid societies and also in Italian practice, a Tir3 diagnosis usually leads to surgical treatment, although clinical (age, performance status of the patient) and personal variables may change the final therapeutic option [7].

According to the guidelines of Papanicolau Society of Cytopathology [6] and the American Association of Clinical Endocrinologist thyroid nodules with atypical cellular lesions, follicular neoplasm and Hurtle cell neoplasm should be managed by surgical removal as malignant nodules. Total thyroidectomy is preferable in patients who have bilateral nodular disease, who have large tumors (>4 cm), when marked atypia is seen on the biopsy, or who prefer to undergo bilateral thyroidectomy to avoid the possibility of requiring future surgery on the contralateral lobectomy. For isolated nodules indeterminate on cytology, a surgical procedure such as thyroid lobectomy may be proposed. Postoperative diagnosis of malignant would lead to a completion thyroidecytomy in some case, but two stage thyroid surgery has higher morbidity and increase cost if compared with initial total thyroidectomy [10]. The patient should be properly informed of these possibilities and our experience shows that patients choose in most cases total thyroidectomy, "ab initio".

The possibility of more exhaustive pre-surgical evaluation might reduce unnecessary (about 70% of cases) surgery; then, there is a need for alternative or adjunctive diagnostic tools that can provide an more accurate preoperative diagnosis. 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 [11]. In these patients the metabolic tumor volume measured by F-FDG PET/CT seems able to predict malignancies. 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 [12]. 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 contest of benign or indeterminate thyroid diseases.

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 [13-15].

Some authors proposed repeat FNA in indeterminate cytology nodules but by other, once the cytological diagnosis "indeterminate" is made, both patients and surgeons ultimately will decide for surgery and on the other hand, the second cytological diagnosis does not necessarily cancel the validity of the first. Core-needle biopsy seems more useful than FNAB repetition in reducing non-diagnostic cytology but its utility in cases of indeterminate cytology after FNAB is still debated [16].

Hee Jung Moon, Jin Young Kwak [17] have studied the role of intra operative frozen section (FS) analysis in the surgical management of thyroid nodules diagnosed as suspicious or indeterminate on fine needle aspiration biopsy. By their experience, when a thyroid nodule, not classified as carcinoma on US-FNAB has suspicious malignant US features, FS may be unnecessary due to a very high risk of malignancy (94.9%). In contrast, when a thyroid nodule read as suspicious or indeterminate on US-FNAB has no suspicious malignant US features, FS can help surgeons determine the extent of surgery.

A smaller nodule does not correlate with a benign lesion then, the nodule size is not a useful means of distinguishing malignant from benign nodules, as already reported by several other authors [18,19]. Sex, age, laboratory data (thyroglobulin, TSH, thyroid hormone, the presence or absence of autoantibodies) were taken into account by the various authors, but to date are not considered sure predictors of malignancy. By our experience and by others authors, the risk of carcinoma is higher in men than in women [20] and patients with carcinoma are older than those with a benign disease but in other experiences the median age of patients with carcinoma is not statistically different from the median age of those with a benign disease [19].

The preoperative measurement of thyroglobulin alone fails to discriminate thyroid cancers from benign lesions. However, in some experience, thyroglobulin is an independent predictor of malignancy; as a consequence, its pre surgical determination should be considered in patients with thyroid nodules, especially when cytology is indeterminate; in particular, it seems that serum thyroglobulin concentration is higher in follicular and Hürthle cell carcinomas than in benign follicular or Hürthle cell nodules. [19, 21]

If thyroid hormones are not modified by the presence of a carcinoma, preoperative thyrotropin serum concentrations has more predictive value for malignancy [22] because TSH levels are higher in patients with a final diagnosis of carcinoma and moreover, it appears that there exists an increment in tumor size as a function of increment in the TSH level.

The presence of thyroiditis has been evaluated in different ways by the various authors but to date it did

not imply whether if this relation is causal or merely incidental. In particular, it is unclear whether thyroiditis is secondarily induced by cancer or if it is the thyroiditis that predisposes patients to the development of cancer. The recent concept that oncogenes responsible for thyroid neoplastic transformation are able to elicit an inflammatory protumorigenic response confirms the tight relationships among oncogenes, thyroiditis, and thyroid cancer. The specificity of RET/PTC, that is one of the most common rearrangement types for the thyroid cancer, was revised by several observations that reported its detection in some not neoplastic conditions such as thyroiditis [23].

On the basis of the above, there are no prognostic factors for malignancy in nodules with indeterminate cytology; therefore, current studies are trying the possible additional introduction of a genetic panel or other biomarkers which can determine a more accurate risk of malignancy in the indeterminate lesions and more precise preoperative selection of thyroid nodules for surgery or for follow-up.

Unfortunately many of these molecular markers are too complex or expensive for routine clinical use or are still poorly standardized [24].

Galectin-3, telomerase, thyroid peroxidase, RET-PTC, and p53) showed relatively high accuracy for detecting malignancy in thyroid nodules with indeterminate FNAB findings [25].

Galectin-3, the only submitted to wide multicenter studies [26,27], 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 [28,29]. Therefore, the use of LNA and galectin-3 detection on the aspirate specimen, represents a promising way to optimize the preoperative selection of thyroid nodular lesions [24].

Recent reports focused on the diagnostic value of panel of microRNAs (miR-222, miR-328, miR-197, and miR-21) or single microRNAs in indeterminate FNA biopsies of thyroid nodules, then FNA miRNA analysis could be a useful adjunct in these patients [30-32].

By an other experience, miRNAs may serve as a novel diagnostic tool in distinguishing malignant thyroid nodules from benign ones on FNAB specimens, but subgroup analysis suggests that a panel of miRNAs may have a higher sensitivity but a relatively lower specificity than that of single miRNA in distinguishing thyroid nodules [33].

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. In fact, although the $BRAF^{V600E}$ mutation is a useful molecular marker for the preoperative diagnosis of carcinoma because of the high prevalence of papillary carcinoma and the $BRAF^{V600E}$ mutation, the absence of the mutation is not suggestive of a benign condition. When thyroid nodules with cytological results suspicious for carcinoma don't have the $BRAF^{V600E}$ mutation, the presence of suspicious malignant features on US might help the surgeon plan the extent of thyroid surgery [34]. Tomei et al. [35] propose the use of BRAF test (after uncertain cytological diagnosis) to assess the malignancy of thyroid nodules at first, then the use of the c-KIT expression to ultimately assess the diagnosis of the nodules that otherwise would remain suspicious. The c-KIT expression-based classification is highly accurate and may provide a tool to overcome the difficulties in today's preoperative diagnosis of thyroid suspicious malignancies.

Clusterin is a protein almost ubiquitously involved in neoplastic transformation and progression. 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. The analysis of RNA expression of CLU showed an increase in specific sCLU in patients TIR 3 with thyroid cancer confirmed at histology, suggesting a possible diagnostic and prognostic use of the sCLU, thus optimizing the management of these patients. Although preliminary, our results show a specific alteration of the relationship sCLU: nCLU during the progression from normal to malignant cell providing evidence for the potential use of isoforms of CLU as effective biomarkers for indeterminate thyroid nodule.

Ultimately, the thyroid nodule with indeterminate cytology still remains a challenge for the surgeon, because for nearly 70% of patients with post operative benign disease, this surgery would be unnecessary if the diagnosis were established preoperatively. Rago et al. [18] report an overall good prognosis in Thy 3 lesions with malignant histology, which suggests the possibility that more exhaustive pre-surgical evaluation might reduce unnecessary surgery. Do not forget that, although rare, complications from thyroid surgery - recurrent laryngeal nerve injury, postoperative bleeding, hypoparathyroidism and infection - can be serious or even life-threatening.

As for the majority of the authors, also in our opinion, surgery it is necessary in all TIR 3 cases because, at the moment, we have no other parameters to select malignant from benign nodule and in this we are comforted by the lack of long-term complications in our patients.

Thyroid lobectomy can be an the adequate treatment for indeterminate nodules only in some patients [36,37]. Surgeons' experience is an important factor which can influence the onset of these complications; the use of of ultrasonic dissector can only help surgical action but cannot replace the experience of the surgeon [38]. On the other hand, we do not consider acceptable the risk of leaving a tumor disease that certainly has low aggressive behavior, [39,40] but that often presents as "T3" for the infiltration of capsule, and not for the size. (29,2 % of the patients in our series). The potential of molecular diagnostics for thyroid nodules with indeterminate cytology is promising, but they should be used judiciously until further data guide us as to their precise value as well as their limitations. We point up the importance of clinical trials to determine the most cost effective protocol to utilize these diagnostic tools. Pending these new possibilities, we stress once again the importance of the role of the cytopathologist and clinical performing thyroid fine-needle aspiration. The 29 patients with carcinoma "incidental" show that one has overestimated the cytological analysis, the other did not point the nodule that on ultrasound examination was really suspicious.

Riassunto

BACKGROUND: I noduli tiroidei sono solitamente benigni; tuttavia, dal 5 al 15% possono rivelarsi maligni. L'agoaspirato tiroideo (FNA) è diventato il gold standard nella valutazione dei noduli tiroidei, in particolare nel singolo nodulo di dimensioni maggiori al centimetro e / o in noduli più piccoli, ma con caratteri ecografici di malignità.
METODI: Abbiamo valutato retrospettivamente 179 pazienti con FNA "indeterminato", sottoposti a intervento chirurgico sulla tiroide. Abbiamo confrontato esame citologico e istologico e abbiamo valutato il sesso, l'età, la presenza di tiroidite e la dimensione del nodulo indeterminato come fattori predittivi di malignità.
RISULTATI: In 48 pazienti (26,8%) l'esame istologico ha confermato la diagnosi citologica *indeterminata* e questo significa che il nodulo sottoposto a FNA è stato diagnosticato in effetti come un carcinoma. In 29 pazienti, all'esame istologico, il nodulo sottoposto a FNA è risultato essere benigno, ma uno o più carcinomi sono stati diagnosticati nello stesso lobo del nodulo indeterminato, ma in posizione diversa e/o nel lobo controlaterale. In 102 pazienti, l'esame istologico definitivo non ha confermato il sospetto diagnostico e abbiamo trovato una significativa correlazione positiva solo tra sesso maschile e malignità all'esame istologico definitivo.
CONCLUSIONI: Un FNA *indeterminato* rimane una sfida per il chirurgo, perché non è ancora possibile discriminare con certezza i pazienti che hanno realmente bisogno dell'intervento chirurgico, da quelli che possono essere seguiti in follow-up. Il potenziale della diagnostica molecolare per i noduli tiroidei con citologia indeterminata è promettente, ma l'utilizzo di molti di questi marcatori è ancora troppo complesso o costoso per un uso clinico routinario, proprio perché ancora poco standardizzato.

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