Ultrasound guided fine-needle aspiration biopsy of thyroid nodules: Guidelines and recommendations vs clinical practice; a 12-month study of 89 patients

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KEYWORDS

Thyroid nodules;
Ultrasound;
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Abstract *Introduction:* Given the high prevalence of thyroid nodules in the general population it is essential to develop a method for identifying those nodules which require fine-needle aspiration biopsy (FNAB) due to suspicion for malignancy in order to avoid over- or under treatment of this disease. The ultrasound (US) criteria identified by Kim et al. and the American Association of Clinical Endocrinologists appear to be the most sensitive and most specific. The purpose of this study was to analyze a sample of patients who underwent FNAB of the thyroid and to compare the obtained data with the international guidelines and the recommendations for management of thyroid nodules.

Materials and methods: This study analyzed the clinical, anamnestic and US reasons for which 97 nodules located in 89 patients underwent FNAB, and the data were compared with the criteria set by the guidelines and with the cytological results.

Results: Echogenicity was indication for FNAB in 99% of cases, appearance of the margins in 75.3%, presence of calcifications in 93.8% and presence of vascularity in 73.2%. In a total of 4.1% of cases, cytological outcome was positive for malignancy, 21.6% necessitated monitoring, 4.1% were referred to surgery and histological examination of the surgical specimen and 63.9% resulted negative for malignancy.

Discussion: The finding of hypoechoic nodules often leads to continued investigation; the presence of intranodular vascularization detected at Doppler US is perceived as suspicious and the presence of microcalcifications always leads to further investigation. On the request of the endocrinologist the dominant nodule in a goiter is in most cases subjected to FNAB even if the volume has not increased. Adequate US criteria can help identify potentially malignant nodules and guide implementation of FNAB. However, identification of malignant nodules using instrumental investigation cannot disregard medical records and clinical laboratory tests. According to the authors' experience, a close collaboration between endocrinologists, radiologists and pathologists is essential for a correct evaluation of patients with thyroid nodules in

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order to avoid over or under estimation of the risk of malignancy of a nodule and therefore of the necessity to perform further examinations.

Sommario *Introduzione:* Data l'elevata prevalenza di noduli tiroidei nella popolazione generale è indispensabile un metodo di individuazione dei noduli sospetti per neoplasia da sottoporre an FNAB per evitare un sovra o sotto trattamento della patologia. I criteri ecografici individuati da Dizionario - Visualizza dizionario dettaglKim et al e dall'American Association of Clinical Endocrinologists risultano essere rispettivamente i più sensibili e più specifici.

Lo scopo dello studio è di analizzare un campione di pazienti sottoposti a biopsia tiroidea con ago sottile (Fine-Needle Aspiration Biopsy - FNAB) e verificare quanto nella pratica clinica si faccia riferimento alle linee guida.

Materiali e metodi: Sono state analizzate le motivazioni clinico-anamnestiche e/o ecografiche per cui 97 (in 89 pazienti) noduli sono stati sottoposti FNAB; i dati sono stati confrontati con i criteri indicati dalle linee guida ed con i risultati citologici.

Risultati: L'ecogenicità era indicata nel 99% dei casi, l'aspetto dei margini nel 75.3%, la presenza di calcificazioni nel 93.8%, la presenza di vascolarizzazione nel 73.2%. Il 4.1% dei noduli punti è risultato positivo per neoplasia, il 21.6% da monitorare, il 4.1% da sottoporre ad esame istologico (su pezzo chirurgico) ed il 63.9% negativo.

Discussione: Il nodulo ipoecogeno induce spesso alla prosecuzione degli accertamenti; la presenza di vascolarizzazione al Doppler viene percepita come sospetta; la presenza di microcalcificazioni dà sempre seguito ad accertamenti ulteriori. Il nodulo prevalente in uno struma viene sottoposto an FNAB anche in molti casi in cui non ha subito crescita, in base a specifica richiesta endocrinologica.

I criteri ecografici consentono di identificare i noduli potenzialmente maligni e di orientare l'esecuzione di FNAB; l'identificazione di noduli maligni con esami strumentali non può prescindere dai dati anamnestici e clinico-laboratoristici. Quindi, anche in base alla nostra esperienza, è fondamentale la collaborazione tra endocrinologi, radiologi ed anatomo-patologi per una corretta valutazione del paziente con noduli tiroidei al fine di evitare sovra o sottostima del rischio di malignità di un nodulo e dunque della necessità o meno di eseguire esami di approfondimento.

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Introduction

Thyroid cancer (Table 1) accounts for only 1% of all malignancies [1,2]. About 3%–8% of nodules are palpable and 20%–70% are detected at US examination; the overall risk of malignancy is 5%–13% [3] so a consistent diagnostic approach to patients with thyroid nodules is essential to avoid the risk of over or under treatment. The most appropriate diagnostic procedures such as ultrasound (US) examination, cytological examination and scintigraphy are carried out on the basis of the patient's clinical history, physical examination and biochemical data (TSH, free thyroxine, calcitonin, antibodies, etc.)

Fine-Needle Aspiration Biopsy (FNAB) has proved to be an accurate procedure in the diagnosis of thyroid neoplasm [1] with the exception of follicular thyroid lesions where diagnosis requires evaluation of vascular and capsular invasion to be performed on a histological specimen [2]. The most recent guidelines were published by *The American Thyroid Association* (ATA) in 2009 [4] and by the *American Association of Clinical Endocrinologists* (AACE), the *Italian Association of Medical Endocrinologists* (AME) and the *European Thyroid Association* (ETA) in 2010 [5] including a revision published in 2011 [6].

The ATA guidelines [4] recommend US examination in all patients with palpable nodules and with nodules detected incidentally in the course of other investigations and FNAB in all suspicious nodules measuring > 5 mm (grade A recommendation). The AACE/AME/ETA guidelines recommend US examination in all patients with palpable nodules or patients at risk and FNAB also of nodules <10 mm if the clinical and/or US appearance arouse suspicion.

Comparative studies have suggested that the most useful US criteria are those proposed by Kim et al. [7], the AACE [5] and the *Society of Radiologists in Ultrasound* [8]. Comparison of the three sets of guidelines showed that the criteria proposed by Kim et al reached the highest sensitivity, that those proposed by AACE presented the highest specificity (Table 2) and that these two sets of criteria were more accurate than the criteria published by the *Society of Radiologists in Ultrasound* [9]. Comparison of US findings can guide the differential diagnosis (Table 3). The purpose of this paper was to analyze a sample of patients who underwent FNAB, evaluate the characteristics of the nodules and, if possible, the clinical motivation for the performance of FNAB, comparing the data obtained in our daily practice with the guidelines and the recommendations of the leading associations of endocrinology.

Table 1 Classification of thyroid lesions.

Follicular epithelium	<i>Malignant</i>
	Differentiated/poorly differentiated: <ul style="list-style-type: none"> ■ Papillary ■ Follicular (insular and Hürthle cells) ■ Mixed papillary-follicular carcinoma Undifferentiated carcinoma: <ul style="list-style-type: none"> ■ Anaplastic carcinoma
Nonepithelial	<i>Benign</i>
	Adenoma: <ul style="list-style-type: none"> ■ Macrofollicular ■ Microfollicular ■ Hürthle cells
Parafollicular C cells	Lymphoma Sarcoma Teratoma
Metastasis	Medullary carcinoma
	Kidney, breast, lung, melanoma, colon, stomach, pancreas, head and neck

Materials and methods

The patients were recruited from October 2009 to October 2010; in this period, 89 consecutive patients referred to the US section of the San Carlo Borromeo Hospital in Milan underwent US-guided FNAB for the evaluation of thyroid nodules. All the patients agreed to participate in the study, and informed written consent was obtained from all patients. Overall mean age was 59 years (range 16–85 years), 24 were males (mean age 57 years; range 18–79 years) and 65 were females (mean age 60 years; range 16–85 years). FNAB was requested by an endocrinologist or a radiologist. The procedures were carried out alternately by two experienced radiologists. The adequacy of the sample was assessed in real-time alternately by two equally experienced pathologists, the same pathologists who subsequently performed the final reading of the microscope slide.

Sampling was carried out using a fine needle (caliber 22 Gauge), manual aspiration and a 5–10 ml syringe. The material smeared on a microscope slide was fixed and permeabilized using Citofix and stained with hematoxylin and eosin using the Papanicolaou technique. Immunohistochemical analysis was not performed. Cytological

Table 2 US characteristics.

Kim et al. criteria	AACE criteria
Microcalcifications	Irregular margins
Irregular or microlobulated margins	Intralesional vascular spots
Marked hypoechogenicity	Thickness greater than the length
Thickness greater than the length	Microcalcifications

outcome was classified in 5 subgroups according to the criteria proposed by AACE-AME in 2010 [5]. For sample evaluation, both the extended diagnosis and the presence or absence of malignant cells were considered.

Patients with nodules which were negative for malignancy were referred to an endocrinologist for evaluation of the most adequate follow-up. The pathologist recommended US follow-up in patients with nodules presenting cellular alteration of equivocal interpretation which were negative for malignancy. Monitoring or submission to histological analysis was recommended as appropriate in indeterminate nodules if the suspicious lesion was a follicular variant or non-specific neoplasm or in the presence of Hürthle cells. Patients with lesions positive for malignancy were referred directly to surgery. In the presence of artefacts due to poor quality of the diagnostic samples and/or low cellularity, repeated FNAB was recommended.

Results

Of the 89 patients 27 had solitary nodules (30.3%) and 62 had multiple nodules (69.7%); 25 had multinodular goiter and 7 had nodules which had developed in a context of chronic inflammation. A total of 97 nodules were analyzed.

Motivation for FNAB requested by the endocrinologist was reported in 25 cases (Table 4).

Echogenicity pattern was indicated in 99% of cases, appearance of the margins in 75.3%, presence of calcifications in 93.8% and presence of vascularity in 73.2% (Table 5). Of the 97 nodules, 80.4% had at least one US feature suspicious for malignancy and 52.6% of the remaining 19.6% underwent FNAB for other reasons such as a solitary nodule, a nodule of recent appearance, etc.

In 49 cases (50.5%) the radiologist suggested a possible diagnosis based on US features (Table 3); in 32 cases (65.3%) this hypothetical diagnosis was in agreement with the subsequent cytological diagnosis.

Of the 18 nodules which were defined as indeterminate or with cytological outcome positive for malignancy 15 were hypoechoic (83.3%), 2 were isoechoic (11.1%) and 1 was hyperechoic (5.6%); 8 nodules presented intralesional vascularization (44.4%), 3 had irregular or blurred margins (16.7%) and 2 presented microcalcifications (11.1%).

Mean dimension of the analyzed nodules was 2.07 cm (range 0.7–7.2 cm); 12.4% of the nodules were <1 cm and 75.3% were ≥1 cm, 12.3% were not available.

Of the nodules <1 cm, one was suspected to be a follicular lesion of undetermined significance (to be histologically confirmed) and 2 samples were of poor quality and had to be repeated. Of the nodules ≥1 cm, 4 were positive for malignancy (75% were ≤3 cm) and 9 were of undetermined cytology (all > 3 cm).

FNAB outcome was: 73 nodules were negative for malignant cells (of which 11 required monitoring due to cellular alterations of equivocal interpretation), 14 were of undetermined cytology (of which 10 required monitoring due to suspected follicular variant or neoplasm of undetermined significance and 4 were suspected to contain Hürthle cells to be confirmed at histological analysis), 4 were positive for papillary carcinoma. In 3 cases FNAB had to be repeated due to artefacts/low cellularity and 3 were not available.

Table 3 Differential diagnosis based on US findings.

Diagnosis	Ecogenicity	Margins	Calcifications	Vascularity	Lymph nodes
Hyperplasia	Iso/anechoic Hyperechoic Hypoechoic with wall enhancement	Regular	Eggshell	Perilesional Intralesional	
Follicular adenomas	Iso (50%) Hyper (25%) Hypo (25%)	Regular	No	Perilesional Intralesional	
Non-follicular adenomas	Iso Hyper	Regular	No	Perilesional Intralesional	
Follicular carcinoma	Iso Hypo Hyper	Blurred irregular	Micro (rare)	Perilesional Intralesional	Rare
Papillary carcinoma	Hypo (90%) Iso/mixed (10%)	Irregular	Micro (frequent)	Perilesional Intralesional	Laterocervical
Cystic papillary carcinoma	Hypoechoic with cystic areas	Irregular Regular	Micro (in the solid parts)	In septa and solid spots	Laterocervical
Undifferentiated carcinoma	Hypo	Irregular	Micro/Macro	Perilesional Intralesional	Local invasion of the tissues and the vessels of the neck
Medullary carcinoma	Iso (70%) Hypo (30%)	Irregular	Micro (frequent)	Perilesional Intralesional	Laterocervical, with microcalcifications
Lymphoma	Hypoechoic	Irregular			

According to cytological examination 4.1% of the nodules were positive for malignancy, 21.6% required monitoring, 4.1% required histological examination and 63.9% were negative for malignancy. Based on the clinical, anamnestic and US features, dubious cases were submitted to close clinical and US monitoring or repeated FNAB within 3 months. Decision was made in collaboration with the endocrinologist.

Of the solitary nodules, 6 presented undetermined cytology (2 required monitoring, 4 required histological examination), 1 was negative for malignancy at cytological analysis but the presence of intranodular vascularity and increase in nodular size led to thyroidectomy and subsequent histological examination which showed follicular

carcinoma with trabecular areas of not otherwise specified neoplasm. The remaining nodules were negative for malignancy (2 required monitoring).

Table 4 Indications for FNAB.

Description	n.	%
Recently appeared	2	2.3%
Different from the other nodules	3	3.4%
The largest nodule	13	14.6%
Increased size	1	1.1%
Cystic nodule with solid spot	3	3.4%
Previous subtotal thyroidectomy	1	1.1%
Solitary nodule	1	1.1%
Suspicious vascularity	1	1.1%
Not specified	64	71.9%
Total	89	100%

Table 5 Frequency of reported US findings.

		Number	%
Echogenicity	Anechoic with solid spots	5	5.15%
	Hypoechoic	61	62.89%
	Hypo-isoechoic	1	1.03%
	Isoechoic	13	13.40%
	Iso-Hyperechoic	1	1.03%
	Hyperechoic	12	12.37%
	Mixed	3	3.09%
	Not available	1	1.03%
Margins	Regular	60	61.86%
	Blurred/wavy	8	8.25%
	Irregular/lobulated	12	12.37%
	Other	17	17.53%
Calcifications	Absent	69	71.13%
	Microcalcifications	6	6.19%
	Rough	16	16.49%
	Not available	6	6.19%
Vascularity	Absent	21	21.65%
	Perinodular	10	10.31%
	Peri-intranodular	13	13.40%
	Intranodular	25	25.77%
	In the solid spot	2	2.06%
	Not available	26	26.80%

Figure 1 Markedly hypoechoic nodule with blurred margins (with magnification on the right side). Cytology outcome: specimen suspicious for papillary carcinoma.

In the 25 patients with multinodular goiter, 1 nodule was positive for papillary carcinoma, 4 presented undetermined cytology (3 required monitoring, 1 required histological examination) and 3 were negative for malignancy but required monitoring. A total of 20% presented increase in nodular size (2 of these were negative for malignancy, but required monitoring, 1 case of undetermined cytology was referred to histological examination and 2 were negative for malignancy).

Based on cytological examination, 5 patients were treated surgically in order to perform histological analysis of the surgical specimen or for removal of a malignant lesion diagnosed by FNAB: in 3 cases histological diagnosis showed cancer (2 papillary lesions and 1 follicular lesion), 1 Hürtle's adenoma and 1 Hashimoto's thyroiditis.

Discussion

Thyroid nodules are frequently evaluated by the radiologist, whose opinion contributes to the decision to perform FNAB or continue US monitoring. The presence of microcalcifications, whose specificity is approx. 98% although

sensitivity is low, always induces the radiologist to recommend FNAB [9,10]. Hypoechoic nodules always lead to continued investigation although specificity is 98% only when the US image shows a "marked hypoechoic pattern" [9] (Fig. 1). This cautious behavior explains the percentage of negative outcome of FNAT (42.3%) despite compliance with the guidelines on detection of suspicious nodules (Fig. 2).

The presence of a rich intralesional vascularity is perceived as suspicious, although some studies have concluded that color Doppler US does not increase the ability to identify malignant nodules [11] and that this technique only moderately increases sensitivity at the expense of specificity [12] (Fig. 3). Hypoechogenicity, vascularization and calcifications are generally considered more significant than appearance of nodule margins. Even if the margins are regular and well defined (in the presence also of only one of the above characteristics) this does not change the decision to perform FNAB (Table 5).

Multinodular goiter is known to be at a very low risk of developing cancer; however the growth of one of the nodules indicates an increased risk for malignancy [1]. This knowledge associated with the suspicious US findings mentioned above should always be considered as a sign of possible malignant

Figure 2 Hypoechoic nodules with blurred margins and microcalcifications. Cytology outcome: A) chronic thyroiditis; B) papillary carcinoma.

Figure 3 Nodules with intra- and perinodular vascularization. Cytology outcome: A) hyperplasia; B) papillary carcinoma.

transformation. The present study confirmed the data available in literature but it also pointed out that in many cases (48%) FNAB is carried out to evaluate the predominant nodule, regardless of the previously mentioned criteria.

In the present study the size of most of the malignant nodules was <3 cm; this is in line with the results reported by Moon et al. [13] who stated that malignant nodules are smaller than benign nodules. US monitoring is preferred to FNAB in nodules measuring less than 5–6 mm because of the difficulty to reach the target and the risk of obtaining inadequate samples.

In the authors' experience, FNAB may be appropriate in 8–10 mm nodules with malignant US characteristics in order to diagnose malignant nodules at a very early stage, thus preventing extracapsular growth and development of lymph node metastases, as already illustrated by Papini et al related to nodules sized between 8 and 15 mm [14].

The recommended US criteria permit efficient identification of potentially malignant nodules and can lead to appropriate decisions regarding the performance of FNAB; however identification of malignant nodules using diagnostic imaging requires also an accurate clinical history and reliable clinical laboratory data.

In the authors' experience, collaboration between endocrinologists, radiologists and pathologists is essential for a proper evaluation of patients with thyroid nodules in order to avoid over or under estimation of the risk of malignancy and of the need to perform further diagnostic investigations.

Conflict of interests

The authors have no conflict of interest to disclose.

Appendix. Supplementary material

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jus.2011.12.004](https://doi.org/10.1016/j.jus.2011.12.004).

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