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HEAD AND NECK

Core-needle biopsy in thyroid nodules: performance, accuracy, and complications

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Abstract

Objective To evaluate the performance of core-needle biopsy (CNB) in thyroid using a cohort of patients in which it was used as first choice.

Methods Our institutional review board approved this retrospective study. We reviewed all CNB performed in our center over a period of 11 years. Ultrasound-guided CNBs were performed using a spring-loaded 18-gauge biopsy needle. We used a classification with four diagnostic categories for CNB results: insufficient, benign, follicular lesion (indeterminate), and malignant. Final diagnosis was based on surgical diagnosis or follow-up of at least 2 years in non-operated patients.

Results The study included 4412 CNB in 4112 nodules of 3768 patients, 300 of them repeated biopsies. Results were 148 insufficient (3.4%), 3706 benign (84%), 278 follicular lesions (6.3%), and 280 malignant (6.3%). Considering follicular lesion and malignancy CNB results as positive (both lead to the recommendation of surgery) sensitivity was 96% (CI 93.2–97.8) and specificity 93.7% (CI 92.9–94.5). Predictive positive value for a follicular lesion diagnosis was 12.2% and for a malignancy diagnosis, 98.6%. CNB likelihood ratio for malignancy of a malignant diagnosis was 841.9 (CI 315.8–2313.3), of a malignant/follicular lesion diagnosis was 23.4 (CI 20.1–27.3), and of a benign diagnosis was 0.04 (CI 0.02–0.07). Repeated CNB in 53 insufficient biopsies obtained 50 diagnostic results. Minor complications occurred in 2.2% of CNB, and major in four procedures (0.09%).

Conclusions CNB in thyroid nodules is accurate and has few complications and a low rate of non-diagnostic and indeterminate diagnoses. It can be an alternative method when FNAC has poor performance. Repeating biopsy is useful after non-diagnostic biopsies.

Key Points

• *Core-needle biopsy of thyroid has a low ratio non-diagnostic and indeterminate results.*
• *Core-needle biopsy results are highly reliable, especially benign results.*
• *Complication rate of core-needle biopsy of thyroid is low.*

Keywords Core-needle biopsy · Thyroid nodule · Thyroid carcinoma · Ultrasound · Fine-needle aspiration

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Abbreviations

BSRTC	Bethesda System for Reporting Thyroid Cytopathology
CNB	Core-needle biopsy
FNAC	Fine-needle aspiration cytology
PTC	Papillary thyroid carcinoma

Introduction

Increasing incidence of thyroid nodules has made it necessary a precise diagnostic tool to identify potential malignancies. Although sensitivity of ultrasound is high, its specificity is relatively low and fine-needle aspiration cytology (FNAC) is frequently required. This technique has two major limitations: non-diagnostic samples and indeterminate results, non-definitive for malignancy, usually included in categories III and IV of Bethesda System for Reporting Thyroid Cytopathology (BSRTC) [1]. Both groups can reach up to 30% of all FNAC in published series [2, 3]. The most accepted answer to non-diagnostic and Bethesda III results is to repeat FNAC, although the result will be non-diagnostic again in almost half of the cases. A partial thyroidectomy is usually warranted in Bethesda IV, although, in most of these cases, the final diagnosis will be a benign lesion [3].

US-guided core-needle biopsy (CNB) has demonstrated good diagnostic results [4] when used after non-diagnostic [5–7] and Bethesda III results on FNAC [5, 8, 9]. Some authors have also reported an excellent performance of CNB in selected thyroid nodules with suspicious US features and even as a first biopsy technique [10–18].

Although US-guided FNAC is recommended as a first-choice method in diagnosis of thyroid nodules, CNB has been suggested as an alternative to repeating FNAC for thyroid nodules with non-diagnostic cytology or atypia of undetermined significance in previous FNAC [19, 20].

In our faculty, and due to the poor performance of FNAC, we choose CNB as an alternative, giving us the unique opportunity to evaluate the performance of CNB in a large cohort of patients in which it was used as first biopsy technique of choice.

Our objective is to describe the performance of CNB in thyroid, including also the ratio of non-diagnostic or indeterminate results, the diagnostic performance of repeated biopsies, and the complications.

Methods

Our Institutional Review Board approved the study. We have retrospectively reviewed all the patients who underwent US-guided CNB of a thyroid nodule from October 1, 2005, to December 1, 2015, in our institution. As the period of study is so long, indications for biopsy changed due to the changes in the guidelines during this time. Indications included suspicious features on US or clinical exam or high-risk history. All patients referred to the radiology department for biopsy underwent US-guided CNB.

All the patients signed an informed consent for the biopsy. Demographics, US features, localization and size of the nodules, biopsy results, final diagnosis, and complications of the biopsy were recorded in all the cases. A major complication was defined as an event that required additional intervention or originated a permanent disability.

Surgery was indicated after a CNB result of malignancy or follicular lesion and, in nodules with benign CNB, because of the size, growth, local compressive symptoms, or patient's choice.

CNB technique

CNB was performed using real-time free-hand US guidance with 10–12 MHz linear probes. One of the following US platforms was used: ATL 5000, IU22 and Epiq (Philips HC), and RS80 (Samsung). Three radiologists with at least 1, 4, and 15 years of experience in US-guided biopsies or residents under the supervision of these radiologists performed all procedures. Informed consent was obtained from all patients.

CNB was performed using a spring-loaded 18-gauge full-core Biopince biopsy needle (Argon MD). This needle has a variable stroke length of 13, 23, and 33 mm, thus allowing different sample sizes according to the volume and position of nodule.

Each patient was placed supine with the neck extended. After an initial US evaluation to identify the thyroid nodules of interest, 1% lidocaine was injected in the path. The biopsy needle was advanced to the edge of the nodule and then triggered (Fig. 1). At least two CNB specimens of each thyroid nodule were obtained. Mixed solid-cystic nodules were emptied using a 22-G needle before obtaining a CNB from the residual solid portion, and this fluid was sent for cytological exam. Patients were discharged after a firm local compression of the puncture site.

Specimen analysis

CNB samples were placed in cooled saline solution and immediately transported to the pathology laboratory. Refrigeration of the transport medium prevented tissue autolysis and contributed to maintain the samples in optimal conditions. Upon arrival in the laboratory, biopsy core samples were fixed in formalin processed and included in paraffin following routine methods. In the last 2 years, specimens were directly fixed in formalin immediately after the biopsy and sent to pathology laboratory. Four-micron histologic slices were obtained and stained with hematoxylin and eosin. Some unstained slides were stored for immunohistochemical studies, when needed. A certified pathologist analyzed each biopsy sample.

Due to the lack of a standard classification for thyroid CNB, we used a classification made of four diagnostic categories: insufficient, benign, follicular lesion, and malignant. Diagnostic criteria for every category have been described elsewhere [21, 22]. This was used as CNB diagnosis.

As some of the pathologists of the Department did not use initially the same criteria to assign the cases to each category, all the reports of the biopsies were reviewed by one of two certified pathologists without knowledge of the final diagnosis, to check for the correct assignation of every CNB to one of the diagnostic categories. When they found inconsistencies with the assignation, they reviewed the case in a multi-head microscope and made a definitive classification.

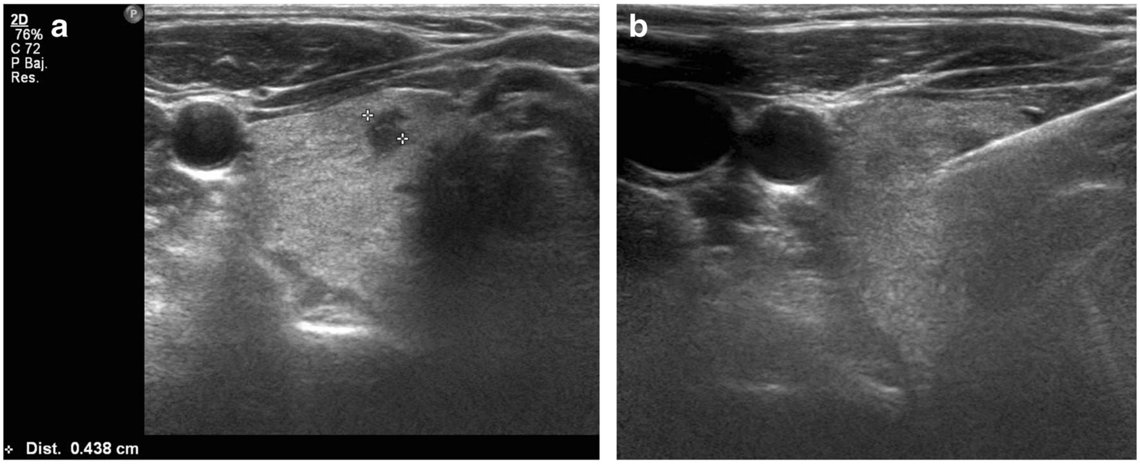

Fig. 1 Core-needle biopsy of a small papillary thyroid carcinoma. (**a**) Suspicious 5-mm nodule in right thyroid lobe. **b** Biopsy of the lesion with transisthmic access

When thyroidectomy was performed, surgery specimens were usually evaluated by the same pathologist who performed the CNB analysis. Surgical pathology diagnosis was based on classical histopathological criteria. Indeterminate lesions interpreted as follicular or Hürthle cell neoplasms could only be deemed malignant if histological evidence of capsular, lymphatic, or vascular invasion was identified.

Statistical analysis

Final diagnosis was based on surgical diagnosis in resected lesions, and on CNB and clinical evolution in the rest. All non-resected lesions were followed for at least 2 years after the biopsy. For lesions non-diagnostic on CNB that were followed up during at least 2 years without significant changes, final diagnosis was benign.

ANOVA was used to test age and size of the nodules. Chi-square test or Fisher's exact test was used to compare frequencies for categorical variables such as nodular content, lobe, solitary or multinodular goiter, and size.

A two-tailed p value less than 5% was considered significant. Confidence interval was calculated at a confidence level of 95%. Statistical analysis was performed with the SPSS software, version 24.

Results

We included 4412 CNB in 4112 nodules of 3768 patients, 579 (15.4%) of them male and 3189 (84.6%) female, with an age range of 3–93 years old (mean 56.7; SD 14.2). In 320 patients, two nodules were biopsied, and three different lesions in 12 patients. These biopsies include the cases presented in a previous study [21]. This previous study included only resected nodules to test the correlation between biopsy and surgical results.

Size of nodules ranged from 3 to 90 mm (mean 25.1 mm, SD 14.2). In 27.1%, CNB was performed on solitary nodules and the rest in multinodular goiters. Nodules were isthmic in 300 cases (7.3%). Nodules were completely solid in 73.5% and had some cystic component in 26.5%.

In 253 cases, CNB was repeated once, 22 twice, and one was biopsied four times (all four with benign result). Reasons for repeating CNB included insufficient result in previous CNB, suspicious features on US with a benign CNB result, increase in size, morphological change, and clinic suspicion.

The review of the pathological reports changed the category of the CNB diagnosis with respect to the category described in the initial pathological report in 109 cases. In 102 CNB from predominately cystic lesions initially regarded as insufficient, the review considered them as valid, all benign. Similarly, seven nodules initially labeled as follicular lesions which described follicles of different sizes containing colloid and no evidence of capsule in the initial report were reclassified as benign after review.

The 4412 CNB results were 148 insufficient (3.4%), 3706 benign (84%), 278 follicular lesions (6.3%), and 280 malignant (6.3%). This number includes repeated biopsies performed on nodules with previous CNB diagnosis of insufficient (53), benign (224), and follicular lesion (23). Follicular lesions were classified on CNB as pure follicular in 188 cases and as oncocytic neoplasms in 90.

Final diagnosis was based on surgical resection in 1167 cases (303 malignant, 697 benign and 167 adenomas) and on follow-up in 3245 cases (22 malignant and 3223 benign). Comparison between CNB diagnosis and final diagnosis can be seen in Table 1. Malignant final diagnosis included 313 thyroid carcinomas (279 papillary, 19 follicular, 7 medullary, 5 anaplastic, 2 poorly differentiated, 1 mucoepidermoid), 6 lymphomas, 5 metastatic carcinomas, and 1 parathyroid carcinoma.

False positive diagnosis included three hyperplasic lesions with partial nuclear changes that had been identified as

Table 1 Comparison between CNB diagnosis and final diagnosis

Core biopsy (*n*, 4412)	Final diagnosis			PPV (%)
	Benign (3920)	Adenoma (167)	Malignant (325)	
Insufficient (*n*, 148)	144 (97.3%)	2 (1.3%)	2 (1.3%)	1.3
Benign (*n*, 3706)	3673 (99.1%)	20 (0.5%)	13 (0.4%)	0.4
Follicular lesion (*n*, 278)	99 (35.6%)	145 (52.2%)	34 (12.2%)	12.2
Follicular neoplasm (*n*, 188)	69 (36.7%)	96 (51.1%)	23 (12.2%)	12.2
Oncocytic neoplasm (*n*, 90)	30 (33.3%)	49 (54.4%)	11 (12.2%)	12.2
Malignant (*n*, 280)	4 (1.4%)	0	276 (98.6%)	98.6

PPV positive predictive value for malignancy of each CNB result

suspicious of PTC in CNB, and one hyperplasic nodule with squamous metaplasia classified as squamous carcinoma in CNB [21].

Results in repeated CNB can be seen in Table 2. Final diagnosis in all the lesions with repeated CNB was benign except in the case with insufficient first CNB and malignant second biopsy, which was a papillary thyroid carcinoma (PTC).

Regarding the causes of insufficient result, in 63 of 148 cases, there was no tissue in the specimen, while in the other 85 cases, the specimen contained scarce thyroid tissue, insufficient for diagnosis. Fibrotic tissue was present in 83 of them, usually with serological evidence of thyroid autoimmunity. Fibromuscular content, suggesting that the target was not reached, appeared in 82 cases.

Comparison of patient and nodule characteristics of CNB with valid and insufficient results showed that nodules with an insufficient result were significantly more frequent smaller, cystic, and located in the isthmus (Table 3). The pathological report of CNB labeled as follicular lesion detailed some degree of nuclear atypia in 44% of cases finally diagnosed as malignant, and in 14% of benign ones.

If we consider follicular lesion and malignancy results on CNB as positive, which is more appropriate as both lead to the recommendation of resection, CNB had a sensitivity of 96% (CI 93.2–97.8) and specificity of 93.7% (CI 92.9–94.5). Considering follicular lesion diagnosis on CNB as benign, sensitivity was 84.9% (CI 80.6–88.6%) and specificity 99.9% (CI 99.8–100%).

Predictive positive values of every diagnostic category are shown in Table 1. Likelihood ratio for malignancy of a malignant CNB diagnosis was 841.9 (CI 315.8–2313.3), for a malignant/follicular lesion CNB diagnosis (both lead to surgery) was 23.4 (CI 20.1–27.3), and for a benign CNB diagnosis was 0.04 (CI 0.02–0.07).

Nodules < 1 cm in diameter were 311 (7%). CNB malignancy ratio in nodules < 1 cm was 14.8%, significantly higher than in larger lesions (5.7%).

Minor complications occurred in 98 procedures (2.2%). The most frequent was local hematoma non-requiring additional measures. Less common was vasovagal syncope after puncture. Major complications appeared in four procedures (0.09%) and were two significant hematomas, that required monitoring, a pseudoaneurysm, that was successfully treated by US-guided percutaneous thrombin injection, and an injury of the recurrent laryngeal nerve which caused permanent vocal cord palsy in a solid posterior paratracheal nodule of

Table 2 Results of repeated core-needle biopsies and final diagnosis

First CNB diagnosis	Repeated CNB diagnosis	Final diagnosis
Insufficient 53	Insufficient 3	Benign 3
	Benign 47	Benign 47
	Follicular lesion 2	Adenoma 2
	Malignant 1	Malignant 1
Follicular lesion 23	Insufficient 1	Benign 1
	Benign 12	Benign 12
	Follicular lesion 10	Adenoma 4, benign 6
Benign 224	Insufficient 6	Benign 6
	Benign 215	Benign 215
	Follicular lesion 3	Adenoma 2, benign 1

Table 3 Comparison of patient and nodule characteristics of CNB with valid and insufficient results

	Core biopsy		
	Insufficient	Valid	*p*
Number (*n*, 4412)	148	4264	
Mean age (SD), year	54.3 (15.4)	56.8 (14.1)	.3
Sex (M/F)	20/128	532/3088	.47
Mean size (SD), mm	20.8 (10.4)	25.2 (14)	< .001
Single lesion (%)	37.2	27.4	.11
Isthmic (%)	19	7.4	< .0001
Solid (%)*	52	74.3	< .0001
Cystic (%)*	23	4.1	< .0001
< 10 mm (%)	8.8	7	.52
< 15 mm (%)	29.7	23.5	.08

*More than 75% of solid or cystic content respectively

20 mm. All two major hemorrhages and pseudoaneurysm occurred in mixed-solid-and-cystic lesions, bigger than 4 cm, vascularized, and benign.

Discussion

Our results show that CNB has good results for thyroid nodules even used as a primary diagnostic tool. We obtained, in the largest series published up to date to our knowledge, low proportions of non-diagnostic (3.4%) and inconclusive (6.3%) results. Moreover, repeated CNB in 53 insufficient biopsies obtained 50 diagnostic results. Considering follicular lesion and malignancy CNB results as positive (both lead to the recommendation of surgery) sensitivity was 96% (CI 93.2–97.8) and specificity 93.7% (CI 92.9–94.5). Finally, there were only 4 (0.09%) major complications among 4412 CNB. These results suggest that CNB can be used as a primary diagnostic tool for thyroid nodules, especially when FNAC has poor performance, as well as after previous non-diagnostic FNAC.

US-guided CNB is not considered in the guidelines as a first-choice method in diagnosis of thyroid nodules [19, 20]. However, a growing body of evidence suggests a role for this technique in the management of thyroid nodules. Several studies have found CNB as more accurate than repeated FNAC in thyroid nodules with an insufficient or indeterminate previous FNAC [5–9, 23, 24]. In a recent review, the relative risk of a non-diagnostic result for CNB over repeated FNAC was 0.27 [25].

Some studies have also reported good results for performing CNB on selected nodules with suspicious US features [11–14, 24]. However, other found higher rates of follicular neoplasm diagnosis on CNB group especially in intermediate and low suspicious nodules, suggesting that CNB do not decrease the inconclusive results in these nodules [26].

Comparison of CNB and FNAC as the initial biopsy technique has been addressed in a few studies. Some of them found that CNB was more accurate and sensitive and has less false negative and inconclusive results [27–29]. Other study found more complications for CNB without significant improvement in accuracy [30]. A recent review demonstrated for CNB a significantly lower non-diagnostic and inconclusive result than FNAC [31].

Despite this, a recent guideline stated that CNB utility as first-line diagnostic tool for initially detected thyroid nodules remains uncertain based on the scarce current evidence [19]. Our study which includes the analysis of 4412 consecutive CNB (the largest series to our knowledge) obtained a sensitivity of 96% and a specificity of 93.7%, thus adding to the evidence published up to date [16, 31–33].

One of the main assets of CNB in our series has been a low non-diagnostic sample rate (3.4%) confirming the findings of a recent meta-analysis [32]. It is clearly lower than rates previously published for FNAC [3, 34, 35]. A recent meta-analysis analyzing 25,445 FNAC found a non-diagnostic result rate of 12.9% [2]. As for FNAC [36], nodule size was lower and cystic content was more frequent in cases with insufficient samples than in cases with valid biopsy. The higher incidence of insufficient samples found in isthmic nodules has not been previously described, to our knowledge. This might be due to the specific technical difficulty for CNB in this area.

CNB ratio of indeterminate follicular lesions was also low. The Bethesda III diagnosis in FNAC is about 9.6% and the Bethesda IV is about 10.1% [2], above the 6.3% of the CNB in this series. This lower indeterminate result ratio may be due to the histological sample that allows diagnosing follicular variants of the PTC that FNAC includes frequently in the category of atypia/follicular lesion of undetermined significance [9, 37].

We have found no studies on the diagnostic accuracy of a second CNB after an initial insufficient one. This repetition obtains a diagnostic result in the case of FNAC of 63% [38] and 79.5% [36], clearly below the 94% of our series. However, it must be pointed out that the ratio of malignancy in insufficient CNB is very low (1.3%) raising the discussion of whether an insufficient CNB result could be managed as a benign result instead of repeating the biopsy.

Repeating biopsy in follicular lesions appears as a good option. In half of the cases in which this was done, diagnosis changed to benignity, further reducing the rate of indeterminate diagnosis and the need of surgery with no false negatives. These lesions were probably adenomatous hyperplasia, and in the second biopsy were sampled other parts of the nodule, with a more hyperplastic appearance.

Predictive negative value of a benign CNB was 99.6%. Therefore, a sole CNB is sufficient to confirm benignity making it unnecessary a confirmatory biopsy [39], or even follow-up. False negative ratio for malignancy was very low (0.4%). False negatives were follicular or cystic variants of PTC in most cases [22].

Of PTC, 74% were pure or mixed follicular variants. This variant of papillary carcinomas is the most common cause of false negatives in FNAC [40]. In these lesions, however, CNB can obtain a reliable diagnosis [37]. False positive ratio was similar to the ratio published for FNAC [41] and probably is due, in both techniques, to pathologist's misjudgment when interpreting nuclear atypia.

In follicular lesions, the malignancy rate increased markedly in the presence of mild nuclear atypia, as already previously suggested for FNAC [42, 43]. The greatest difficulty persists, however, for the preoperative diagnosis of follicular carcinoma [22].

One of the challenges CNB faces is the current lack of a consensus on pathological report similar to the BSRTC for FNAC. Our classification is simpler than the cytologic classifications mainly because it does not differentiate follicular lesions of uncertain significance (Bethesda III) and follicular neoplasia (Bethesda IV) [1], including both categories in the same group as tumors characterized by their cell density. It also eliminates the suspicious of malignancy category (Bethesda V). A similar system in four categories has been proposed previously for FNAC [44, 45]. Recently, a Korean group has proposed a pathological classification for thyroid CNB that follows the cytological BSRTC, but we think that the system we have used is more straightforward and better adapted to the specific characteristics of CNB [46].

Another problem was that in some cases the biopsies have been misclassified in the initial report, as we have seen in the review. This happened especially in the cystic lesions, sometimes classified as insufficient despite having enough material to be considered as benign. A consensus is necessary to clearly define thyroid CNB's classification.

Regarding the size, we think that significantly higher malignancy ratio in nodules < 1 cm was probably related to the indication for biopsy, which in these nodules was usually the presence of suspicious US findings.

CNB complication rate is one of the concerns limiting the use of this technique. However, it is very low, and similar to that published for FNAC [15, 16, 27, 28, 31–33, 47]. It has been reported a more intense and lasting pain after CNB with respect to FNAC [48–50]. The biggest series published that specifically analyzes the complication rate of CNB in 6169 patients [49], found four major complications (0.06%): two hematomas requiring admission, a pseudoaneurysm treated with radiofrequency ablation, a persistent voice change, and a ratio of minor complications of 0.79%, most of them self-limiting hematomas. A recent meta-analysis obtained similar rates with a pooled proportion of 0.06% major complications and 1.08% minor complications [50]. These figures and the type of complications are similar to ours. In our case, the pseudoaneurysm was treated differently, but also successfully, by direct injection of thrombin. A recent guideline recommends manual compression of biopsy site after procedure for 20 to 30 min [19]. However, in our experience, a short compression is enough.

This study has several limitations. It is not a comparative study with FNAC, but we have enough published series for FNAC to know the performance of this technique without perform a new procedure on the patient. The study is retrospective, and protocols and guidelines changed during the study. However, this is not important as the final objective was just to assess the general accuracy of CNB in thyroid. Most of final diagnoses were obviously based in clinical follow-up instead in the pathological diagnosis of surgical specimens; however, we have demonstrated before the excellent correlation between CNB and surgery [21]. We used a specific spring-loaded device and the results might be different with other devices and equipment [25, 33]. Finally, the categories for CNB histopathologic diagnosis are not international standards as BRSTC is, but we managed this problem performing a review to make them homogeneously evaluated.

In conclusion, CNB in thyroid nodules is highly accurate and has a low rate of non-diagnostic and indeterminate diagnoses with few complications. It can be an alternative method when FNAC has poor performance. A repeated biopsy is useful in non-diagnostic previous biopsies.

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Compliance with ethical standards

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Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study, to perform the procedures described in it.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Some study subjects or cohorts have been previously reported in Paja M, del Cura JL, Zabala R, et al (2016) Ultrasound-guided core-needle biopsy in thyroid nodules. A study of 676 consecutive cases with surgical correlation. Eur Radiol 26:1–8.

Methodology
• retrospective
• observational
• performed at one institution

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