Diagnostic accuracy of ultrasound and fine-needle aspiration in the study of thyroid nodule and multinodular goitre

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Summary
Objective: Ultrasonography and cytology obtained by fine-needle aspiration are part of the basic study of the thyroid nodule. Although they are not diagnostic in every case, they are cost-effective methods that inform surgical treatment and its extent. The purpose of this study was to evaluate the accuracy of ultrasonography associated with fine-needle aspiration to predict malignancy in nodular thyroid pathology.

Design and patients: We collected prospective data from patients undergoing thyroidectomy by single nodule or multinodular goitre between 2006 and 2016. A total of 417 patients were included. Ultrasounds were classified as suspected of malignancy if they had 2 or more of the following characteristics: hypoechogenicity, microcalcifications, intranodular central hypervascularization, irregular margins and poorly defined edges.

Measurements: Ultrasound and fine-needle aspiration accuracy.

Results: In the postoperative study, 40% presented malignant pathology. 33% of patients with nonsuspicious ultrasound and 73% of those with suspicious ultrasound had malignant disease. Among patients with single nodule and suspicious ultrasound, the malignancy rate reached 80%. As for cytology, 100% of Bethesda VI patients, 88% of V, 63% of IV, 31% of III and 12% of II were found to have carcinoma. The combination of the 2 tests showed a high predictive value, particularly in cases of Bethesda IV cytology.

Conclusions: Thyroid cytology provides high predictive value of the presence of carcinoma. The predictive value of ultrasound is also high, mainly in the study of isolated nodules. The combination of the 2 tests results in increased diagnostic accuracy.

Keywords
fine-needle aspiration, multinodular goitre, thyroid cancer, thyroid nodule, ultrasound
1 | INTRODUCTION

The incidence of thyroid nodules is high, with a reported prevalence of 19%-68% in the unselected population. They are frequently asymptomatic, and their study is important because of the risk of associated malignancy in 7%-15% of cases.

Cervical ultrasound (US) is the first-line imaging study, recommended to determine the need for a cytological study. Its usefulness in thyroid pathology is widely accepted. Ultrasound-guided fine-needle aspiration (FNA) is a minimally invasive procedure that provides valuable clinical and pathological information for ordering specimens according to the Bethesda classification. The combination of both diagnostic tests represents the optimal diagnostic approach in most cases.

The main objective of this study was to ascertain the relationship between ultrasound features and cytopathology to predict malignancy of a thyroid nodule. A secondary objective was to study whether the accuracy of diagnostic tests is similar in patients with a single nodule and with multinodular goitre (MNG).

2 | MATERIALS AND METHODS

Data from patients who underwent thyroidectomy at a single tertiary hospital and who had been studied preoperatively through thyroid US and FNA was collected between March 2006 and January 2016. Demographic and clinical information was obtained through a retrospective review of medical records and a prospectively collected thyroid pathology database.

Surgical interventions were performed by a team of 2 general surgeons from the Endocrine Surgery Unit at Santa Creu i Sant Pau Hospital in Barcelona, Spain. The surgical indication was made by individually assessing the patient’s clinical, ultrasound and cytological data according to our centre’s protocol. Patients with at least 1 of the following criteria were referred for surgery: high suspicion of malignancy, rapid nodule growth, compressive symptomatology, nodules larger than 4 cm, repeatedly nondiagnostic FNA, as well as those who expressed desire of being intervened either for aesthetic reasons or for uneasiness with the diagnosis.

A thyroid ultrasound was performed preoperatively by 2 radiologists specialized in neck ultrasound to describe the presence or absence of the following parameters: echogenicity, microcalcifications, irregular borders, intranodular increase in central vascularization and presence of a halo. Echogenicity was determined as a function of the surrounding tissue and is classified as anechoic, hypoechoic, isoechoic, hyperechoic or heterogeneous echogenicity. The presence of micro- or macrocalcifications was determined. The shape of the nodule was classified as regular or irregular. Doppler echography was studied if there was an increase in vascularization at the intranodular level. A halo was defined as the presence of hypoechoogenicity surrounding the nodule. MNG was defined as an enlarged thyroid with 2 or more nodules.

According to ultrasound characteristics, patients were classified into 2 different groups. “Benign ultrasound” if they had 1 or no malignant features; “Suspicious ultrasound” when they had 2 or more malignant features.

Fine-needle aspiration was carried out according to our hospital protocol in patients with palpable nodules, nodules with 2 or more US malignancy features, hot nodules in PET scan, nodules >2 cm and in the predominant nodule in the context of a MNG. Cytology was classified according to the Bethesda system as I: nondiagnostic or unsatisfactory; II: Benign; III: Atypia of undetermined significance or follicular lesion of undetermined significance; IV: Follicular neoplasm or suspicious for a follicular neoplasm; V: Suspicious for malignancy; VI: Malignant.

In a subgroup of patients (375 cases), we studied the concordance of ultrasound and cytology analysis with the pathological study of the sample.

After the intervention, samples were analysed by 2 pathologists specialized in endocrine pathology. Micropapillary carcinoma was defined as papillary thyroid cancer smaller than 1 cm in size and nonmicropapillary carcinoma as thyroid papillary cancer equal to or larger than 1 cm in size.

In terms of statistical analysis, qualitative variables were expressed in absolute numbers and percentages. For each ultrasound criteria of malignancy studied, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were determined. The ability of each ultrasound characteristic to detect malignancy was determined.

The association between the presence or absence of ultrasound features and the result of the surgical specimen was evaluated through contingency tables using chi-square tests. An alpha risk of 5% and a 95% confidence interval were used as limit of statistical significance in all cases.

Concordance of ultrasound was evaluated through the kappa test, using anatomical pathology as a reference method and a confidence level of 95%. The concordance test was qualified under the assumptions of Landis and Koch: poor or weak if $k < 0.40$; Moderate if $0.41 - 0.60$; Good if $0.61 - 0.80$ and very good for $k > 1.13$.

3 | RESULTS

A total of 492 patients were evaluated. Of these, 75 were excluded from the analysis for the following reasons: preoperative study performed by CT scan without ultrasound ($n = 7$), patient undergoing reintervention ($n = 21$), lack of data related to FNA or US ($n = 40$) and cytology obtained from adenopathy ($n = 7$). A total of 417 patients met inclusion criteria, mainly women (82%), with a mean age of 53.8 years (SD = 15.8). The surgical technique used was hemithyroidectomy in 155 cases and total thyroidec- tomy in 262.

Anatomopathological studies of the thyroidectomy samples found a total of 165 (40%) malignant tumours and 252 (60%) with
benign pathology. Malignant tumours were classified as follows: 93 papillary carcinomas, 34 micropapillary carcinomas, 22 follicular carcinomas, 7 medullary carcinomas, 3 presented with 2 different tumours in the same specimen (papillary and follicular), 2 anaplastic carcinoma, 1 poorly differentiated thyroid carcinoma, 1 metastasis of clear cell carcinoma and 2 large B cell lymphoma.

In preoperative evaluation, 346 patients (83%) presented benign US, 113 (33%) of which presented carcinoma in the definitive study. Of the 71 patients (17%) who had suspicious US, 52 (73%) presented carcinoma in the definitive study. Overall, US had a sensitivity of 32%, specificity of 93%, PPV of 73% and NPV of 67%.

The majority of patients (n = 186, 45%) had Bethesda II cytology. The relationship between cytology, US and percentage of malignancy is shown in Table 1. The presence of suspicious US increased from 38.5% in Bethesda II to 100% in Bethesda VI. A greater diagnostic accuracy was observed for single nodules when compared to MNG.

Of the 207 patients (49.6%) with a single nodule, 165 (80%) were classified as low-risk ultrasound, yet 61 (37%) of them had carcinoma in the anatomopathological study. Of the 42 patients (20%) who had a suspicious ultrasound, 34 (80%) were diagnosed with carcinoma in the anatomopathological study (Table 2).

Of the 210 patients (50.4%) with MNG, 181 (87%) were classified as low-risk ultrasound, yet 52 (29%) of them were diagnosed with carcinoma in the definitive anatomopathological study. Of the 29

### Table 1
The relationship between cytology, US and percentage of malignancy

| Bethesda | Pathology | US (0-1) | US (2-3) | Total |
|----------|-----------|----------|----------|-------|
| I (n = 21) | Benign | 9 | 2 | 11 |
| | Malignant | 9 | 1 | 10 |
| | % Malignancy | 50% | 33.3 | 47.6 |
| II (n = 186) | Benign | 156 | 8 | 164 |
| | Malignant | 17 | 5 | 22 |
| | % Malignancy | 9.8 | 38.5 | 11.8 |
| III (n = 80) | Benign | 48 | 7 | 55 |
| | Malignant | 20 | 5 | 25 |
| | % Malignancy | 29.4 | 41.7 | 31.25 |
| IV (n = 40) | Benign | 14 | 1 | 15 |
| | Malignant | 22 | 3 | 25 |
| | % Malignancy | 61.1 | 75.0 | 62.5 |
| V (n = 56) | Benign | 6 | 1 | 7 |
| | Malignant | 28 | 21 | 49 |
| | % Malignancy | 82.4 | 95.5 | 87.5 |
| VI (n = 34) | Benign | 0 | 0 | 0 |
| | Malignant | 17 | 17 | 34 |
| | % Malignancy | 100.0 | 100.0 | 100.0 |
| Total | 113/346 | 52/71 | 165/417 |
| % Malignancy | 32.7 | 73.2 | 39.6 |

### Table 2
The relationship between cytology, US and percentage of malignancy in patients with a single thyroid nodule

| Bethesda | Pathology | US (0-1) | US (2-3) | Total |
|----------|-----------|----------|----------|-------|
| I (n = 13) | Benign | 6 | 1 | 7 |
| | Malignant | 5 | 1 | 6 |
| | % Malignancy | 45.5 | 50.0 | 46.2 |
| II (n = 63) | Benign | 53 | 3 | 56 |
| | Malignant | 4 | 3 | 7 |
| | % Malignancy | 7 | 50 | 11.1 |
| III (n = 53) | Benign | 33 | 4 | 37 |
| | Malignant | 13 | 3 | 16 |
| | % Malignancy | 28.3 | 42.9 | 30.2 |
| IV (n = 25) | Benign | 10 | 0 | 10 |
| | Malignant | 12 | 3 | 15 |
| | % Malignancy | 54.5 | 100.0 | 60 |
| V (n = 29) | Benign | 2 | 0 | 2 |
| | Malignant | 15 | 12 | 27 |
| | % Malignancy | 88.2 | 100.0 | 93.1 |
| VI (n = 24) | Benign | 0 | 0 | 0 |
| | Malignant | 12 | 12 | 24 |
| | % Malignancy | 100.0 | 100.0 | 100.0 |
| Total | 61/165 | 34/42 | 95/207 |
| % Malignancy | 37 | 80.1 | 45.9 |

### Table 3
The relationship between cytology, US and percentage of malignancy in patients with multinodular goitre

| Bethesda | Pathology | US (0-1) | US (2-3) | Total |
|----------|-----------|----------|----------|-------|
| I (n = 8) | Benign | 3 | 1 | 4 |
| | Malignant | 4 | 0 | 4 |
| | % Malignancy | 57.1 | 0.0 | 50.0 |
| II (n = 123) | Benign | 103 | 5 | 108 |
| | Malignant | 13 | 2 | 15 |
| | % Malignancy | 11.2 | 28.6 | 12.2 |
| III (n = 27) | Benign | 15 | 3 | 18 |
| | Malignant | 7 | 2 | 9 |
| | % Malignancy | 31.8 | 40 | 33.3 |
| IV (n = 15) | Benign | 4 | 1 | 5 |
| | Malignant | 10 | 0 | 10 |
| | % Malignancy | 71.4 | 0.0 | 66.7 |
| V (n = 27) | Benign | 4 | 1 | 5 |
| | Malignant | 13 | 9 | 22 |
| | % Malignancy | 76.5 | 90.0 | 81.5 |
| VI (n = 10) | Benign | 0 | 0 | 0 |
| | Malignant | 5 | 5 | 10 |
| | % Malignancy | 100.0 | 100.0 | 100.0 |
| Total | 52/181 | 18/29 | 70/210 |
| % Malignancy | 28.7 | 62.1 | 33.3 |
patients (14%) who had suspicious ultrasound, 18 (62%) were diagnosed with carcinoma in the pathology study (Table 3).

The sensitivity of the US study in patients with single nodule was 10% higher than in patients with MNG (36% vs 26%), with a specificity of 92% in both cases. The positive and negative predictive values for single nodule cases were of 81% and 63%, respectively, compared to 62% and 71% in MNG. There was a statistically significant difference ($P = .001$) between the percentage of malignancy in single nodule and MNG patients (46% vs 33%).

As for the detailed study of the US characteristics, hypoechogenicity was present in 31.5% of cases, 57% of which were malignant. The presence of hypoechogenicity showed high sensitivity (89%) but a low specificity (46%) to detect malignant thyroid nodules.

Microcalcifications were present in 26% of the studied cases, 57% of which were malignant. This was a highly specific US feature (82%) that showed poor sensitivity (39%).

Increased thyroid nodule central vascularity was present in 13% of cases, 56% of which were malignant. This feature had moderate sensitivity (65%) and specificity (56%).

The absence of a halo was observed in <1% of patients and was not described in 96% of the cases. Irregular margins were present in 6% of cases, 54% of which were malignant and were not described in 88% of cases. Due to the high rate of thyroid nodules for which the absence or absence of a halo and irregular margins were not described, its diagnostic accuracy can hardly be assessed. Most US reports described the dimensions of the nodules without clearly specifying what each measurement represented. Thus, the “taller than wider” US characteristic was excluded from the study.

The general concordance level of malignant nodules was weak for the following criteria: hypoechogenicity ($K = 0.33, P < .001$), presence of microcalcifications ($K = 0.22, P < .001$) and increased vascularityization ($K = 0.20, P = .04$). Concordance results were not statistically significant with respect to other features (Table 4).

Hypoechogenicity, microcalcifications and irregular margins are more frequently observed in thyroid nodules classified as Bethesda V and VI, as shown in Figure 1.

4 | DISCUSSION

The incidence of thyroid nodules is high. In Spain, approximately 4% of the general population will present with a thyroid nodule and it has been reported that 7% to 15% of cases may be malignant. Thyroid carcinoma diagnoses have been increasing over the past few years, probably due to the ease of access and extensive use of cervical US. In our series, we found about 40% of carcinomas, likely influenced by our centre’s policy to prioritize patients with more malignancy criteria and refer the rest of cases to other centres. The challenge lies in the determination of true malignancy. When examining a thyroid nodule, US features that indicate malignancy, especially when 2 or more are present, increase the likelihood of finding carcinoma. However, US features alone are rarely diagnostic.

We found that the presence of 2 or more US malignancy features significantly increases the likelihood of cancer, from 33% to 73%. The Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer, published by the American Thyroid Association, indicates that patients with 2 or more criteria of ultrasound malignancy, always including hypoechogenicity, have an estimated rate of malignancy >70%-90%. The increase was more marked in patients diagnosed with single thyroid nodules, where suspicious ultrasound detected up to 81% of malignancy, compared to patients with MNG, where the percentage of malignancy was of 62%. This suggests that the positive predictive value of preoperative ultrasonography is greater in patients with a single thyroid nodule. Nevertheless, only 17% of the patients had “suspicious US”, with a sensitivity of 32%. Other publications have proposed similar classifications based on diverse ultrasound characteristics. These have high sensitivities and accuracies and aim to rationalize the use of ultrasound and FNA. The TI-RADS system has high sensitivity and precision values (88% and 94%, respectively), the American Association of Clinical Endocrinologist criteria has a higher specificity but lower sensitivity (94% and 74%, respectively), and the Kim criteria provides greater sensitivity (93%) with a specificity of 81%. Nevertheless, the criteria used by Society of Radiologist in Ultrasound is based on the size of the nodules and is less precise in the detection of malignancy. In conclusion, ultrasound-based reporting systems provide better management of patients while being cost-effective and reducing unnecessary FNA.

It should be noted that, when reviewing radiology reports, certain US characteristics of malignancy were not mentioned. This raises the question of whether these were present and not mentioned or if they were not directly observed. Thus, it is important to call for more comprehensive reports on the characteristics of thyroid nodules.

Regarding FNA results, certain differences are observed as compared to data published by other authors. Specifically, in the Bethesda

| TABLE 4 | Statistic parameters in the detection of malignancy for US features studied |
|----------|---------------------------------|---------------------------------|------------------|------------------|-------------------|-------------------|-------------------|
| US Criteria | Sensitivity | Specificity | PPV | NPV | Accuracy (CI 95%) | Chi-squarea | Concordance with pathology |
| Hypoechogenicity | 89.3 | 46.3 | 56.8 | 84.6 | 65.3 (57.8-72.7) | 30.4 | $K = 0.33 (P = .000)$ |
| Microcalcifications | 38.9 | 81.8 | 57.1 | 68.2 | 65.3 (60.3-70.3) | 19.7 | $K = 0.22 (P = .000)$ |
| Absence of a halo | 33.3 | 84.6 | 33.3 | 84.6 | 75.0 (50.7-99.3) | 4.00 | $K = 0.17 (P = .47)$ |
| Irregular margins | 61.9 | 56 | 54.2 | 63.6 | 58.7 (43.4-74.0) | 2.7 | $K = 0.17 (P = .22)$ |
| Increased vascularity | 65.1 | 56 | 56 | 65.1 | 60.2 (49.7-70.7) | 7.6 | $K = 0.20 (P = .04)$ |

aChi-square 5.9915 (alfa: 0.05).
Tumors with MNG and single nodule. Other studies report a similar incidence of malignant disease in patients with thyroid cancer in a nodule decreases as the number of nodules increases.

40% observed) or in those suspicious for malignancy (Bethesda I and IV groups, our results show, respectively, 48% and 63% of malignancy, whereas a meta-analysis of 8 studies by Bongiovanni et al reported a range of malignancy of between 9% and 32% for Bethesda I and between 14% and 34% for Bethesda IV. This difference in outcomes was attributed to the higher prevalence of malignancy in our series, likely caused by the greater complexity of our patient population and higher rate of offsite referral for low risk of malignancy cases.

However, it is important to highlight the Bethesda II group, theoretically benign, where 38% of cases with suspicious US were found to have cancer, compared to 10% of those with nonsuspect US. Moreover, in patients with undetermined Bethesda (III), suspicious US resulted in 12% more malignancies detected. The combination of US characteristics and FNA findings results in an increase in diagnostic accuracy.

We decided to separately analyse patients with a single thyroid nodule and patients with MNG to establish possible differences in the diagnostic accuracy of US and FNA. Both diagnoses add up to approximately 50% of the sample size.

We observed a significant difference (P = .001) in the malignancy rate in patients with MNG (33%) as compared to those with a single nodule (46%). It has traditionally been considered that thyroid nodules found in the context of MNG are less likely to present carcinoma, but recent studies report conflicting results. In a meta-analysis by Brito et al patients with MNG were found to be less likely to present cancer when compared to patients who had single thyroid nodules. Frates et al described that the probability of cancer is independent of the number of nodules, but the probability of cancer in a nodule decreases as the number of nodules increases. Other studies report a similar incidence of malignant disease in patients with MNG and single nodule.

Hypoechochogenicity has been described as 1 of the most important ultrasound criteria associated with thyroid cancer. In this study, it was observed predominantly in malignant nodules (Bethesda VI, 44% observed) or in those suspicious for malignancy (Bethesda V, 33% observed). It was also observed in 50% of follicular neoplasms (Bethesda IV), 30% AUS/FLUS (Bethesda III) and 25% of benign cytologies (Bethesda II). Both the sensitivity (89%) and the specificity (46%) of hypoechochogenicity are comparable with those of previous studies (27%-87% and 43%-94%, respectively). Hypoechochogenicity has a weak (K = 0.33, P < .001) concordance with malignant neoplasia, but is not by itself diagnostic for malignant thyroid nodule.

The presence of microcalcifications is similar in the different nodule groups: malignant (Bethesda VI, 44% presence), suspicious (Bethesda V, 40% presence) and undetermined (Bethesda I, 37% presence). They are also present in 20% of benign nodules (Bethesda II). The sensitivity (39%) and specificity (82%) of this criterion are lower compared with previous studies (S 60% and E 98%). Unlike the findings in other studies, microcalcifications show statistically significant differences and a slight (K = 0.22, P < 0.001) concordance with malignant neoplasia.

Increased nodule vascularity was greater in malignant (Bethesda VI, 22% presence), suspicious (Bethesda V, 21% presence) and undetermined (Bethesda I, 21% presence) nodules and less frequent in benign (Bethesda II, 10%) nodules. This US characteristic showed a sensitivity similar to that of previous studies (S 65% vs 54%-74%), but a lower specificity (E 56% vs 79%-81%). This feature alone has a weak (K = 0.20, P = .04) concordance with malignancy.

In a recent meta-analysis by Brito et al. that studies US characteristics of malignancy, it was determined that intranodular calcifications had a sensitivity of 54% and a specificity of 81%; Hypoechochogenicity had a sensitivity of 73% and a specificity of 56%; And increased intranodular flow had a sensitivity of 48% and a specificity of 56%.

In general, all US malignancy characteristics are shown to increase as the grade of the Bethesda classification increases, disregarding Bethesda I (nondiagnostic cytologies) (Figure 1). This study has some limitations. It is retrospective cohort study, carried out in a single oncological tertiary centre and over an extended period of time (10 years).

In conclusion, thyroid cytology is highly predictive of thyroid carcinoma. The predictive value of US is also high, mainly in the study of single nodules. In our series, patients with a single nodule are more likely to present with carcinoma. The combination of 2 or more US features, observed in 17% of patients, increases the likelihood of carcinoma by 40%. Combining the 2 tests allows increased diagnostic accuracy and establishment of adequate treatment in most of the cases.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.
AUTHOR CONTRIBUTIONS

AM and PJ performed the operations; EL performed the pathology review; EM performed the ultrasound; AR wrote the manuscript; Eugenia M and AL reviewed the article; AM designed the research.

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