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# Association of patient characteristics, ultrasound features, and molecular testing with malignancy risk in Bethesda III–V thyroid nodules

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## Abstract

**Objective:** To evaluate the role of patient characteristics, ultrasound findings, and molecular testing in predicting risk of malignancy in Bethesda III, IV, and V thyroid nodules.

**Design:** Single institution retrospective review of 230 patients with Bethesda III, IV, and V cytopathology undergoing thyroidectomy between 2009 and 2018.

**Setting:** Private and public tertiary urban university hospitals at the same academic institution.

**Subjects and methods:** Patients who underwent thyroidectomy with Bethesda III, IV, and V nodules were included. Patient demographics, presence of underlying thyroid disease, nodule size, sonographic features, gene expression results, and surgical procedure were documented. Correlation between these variables and final histopathologic diagnosis of malignancy was analyzed.

**Results:** The 230 patients (103 Bethesda III, 64 Bethesda IV, and 63 Bethesda V) were included for analysis. Bethesda III nodules harbored malignancy in 26.2% of cases compared with 26.6% of Bethesda IV nodules and 82.5% of Bethesda V nodules. On multivariate analysis, age was inversely correlated with a diagnosis of malignancy (OR: 0.98, 95% confidence interval [CI]: 0.96–0.99, $p = .03$) Although the presence of microcalcifications was positively associated with cancer (OR: 2.31, CI: 1.24–4.29, $p = .008$) The co-occurrence of microcalcifications and irregular margins was associated with a higher odds of malignancy (OR: 4.42, 95% CI: 1.32–14.93, $p = .016$), whereas the combination of microcalcifications, irregular margins, and hypoechogenicity was associated with the greatest cancer risk (OR: 5.52, 95% CI: 1.12–27.78, $p = .036$).

**Conclusions:** The presence of microcalcifications in thyroid nodules categorized as Bethesda III–V is an independent risk factor for malignancy. The combination of microcalcifications, irregular margins, and hypoechogenicity is associated

Level of evidence: 3

with a greater malignancy risk in nodules indeterminate for thyroid cancer on cytopathology.

KEYWORDS
cytopathology, fine needle aspiration, thyroid cancer, thyroid nodule, ultrasound

## 1 | INTRODUCTION

Since its inception in 2009, the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) has served an important role in guiding the management of thyroid nodules.[1,2] The Bethesda system stratifies nodules according to their risk of representing malignancy, with values of III, IV, and V falling in a category that is indeterminate for thyroid cancer. As a result, the ideal treatment of these nodules remains a topic of ongoing debate.[3,4] According to management guidelines from the American Thyroid Association, Bethesda III lesions may be managed with repeat fine needle aspiration (FNA), molecular testing, and surveillance or diagnostic surgery.[2,5] Bethesda IV nodules may undergo molecular testing or diagnostic hemithyroidectomy, with options for more conservative or aggressive management in select cases.[2,5,6] The management of Bethesda V lesions is generally similar to that of a proven malignancy, with surgical management options including hemi-, near-total, and total thyroidectomy.[2,5] Still, active surveillance represents an accepted treatment for many patients with small and indolent nodules of any Bethesda category, including those with Bethesda V and VI cytopathology.[5] Given the multitude of treatment options for nodules in each of these Bethesda categories, decision-making is dependent upon patient and provider preference as well as supplementary information such as diagnostic imaging and molecular testing.

Several studies in the literature have sought to investigate potential predictors of malignancy in indeterminate thyroid nodules. Underlying thyroid disease, such as Hashimoto's thyroiditis and Grave's disease, has been suggested by multiple studies to influence risk of thyroid cancer.[7–9] Ultrasound evaluation is also frequently utilized in the evaluation of indeterminate thyroid nodules, with features including nodule size, presence of microcalcifications, and irregular margins having been associated with malignancy in previous studies.[4,10,11] More recently, gene expression classifiers (GEC) comparing mRNA expression in FNA samples with a panel of known oncogenes have been developed to help guide the management of indeterminate nodules.[12–14] Whereas many of these characteristics have been studied individually, the comparative risk of these variables in estimating malignancy risk in patients with nodules categorized as Bethesda III–V is still poorly defined.

From a clinical standpoint, it would be beneficial to determine which Bethesda III, IV, and V nodules are at higher risk of harboring a malignancy to better guide the decision-making process for management of these nodules, including the decision to undergo surgical excision versus pursuing more conservative options. Thus, the aim of this study is to determine the comparative effects of different demographic characteristics, underlying thyroid diseases, sonographic features, and GEC results on risk of malignancy in thyroid nodules categorized as Bethesda III, IV or V. These results may help guide the management of indeterminate thyroid nodules in clinical practice.

## 2 | MATERIALS AND METHODS

This study was approved by the University of Southern California (USC) Institutional Review Board. Patients undergoing thyroidectomy at the Keck Hospital of USC and LAC+USC Medical Center from 2009 to 2018 were identified and retrospectively analyzed through electronic medical records. Patients with nodules categorized as Bethesda III, IV or V on FNA were included in the study. In cases where FNA was performed prior to referral to our institution, cytology slides were re-read or the FNA was repeated at USC. It is standard practice at our institution to have our pathologists review all cytology slides that are received from an outside hospital to ensure the reliability and consistency of the cytology results. In cases where cytology slides from the referring provider were not available, the FNA was repeated. In both of these instances, the diagnosis made at our institution was considered the final diagnosis for this study. Nodules that were re-classified from an indeterminate category at the referring institution to a definitive category (Bethesda II or VI) by our cytopathologists were excluded from analysis. No patients underwent repeat FNA if the initial FNA was performed at our institution and showed Bethesda III–V cytology. If metastatic disease was present in the neck prior to thyroidectomy and diagnosed either clinically or through FNA, the patients were excluded. Patients diagnosed with undifferentiated thyroid cancers were also excluded, such that malignancies included in the study were papillary and follicular thyroid cancer. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features was not considered a malignancy for this study.[2,15]

The Afirma GEC molecular test was performed in some patients as part of the malignancy risk assessment process. This test measures mRNA transcripts in a thyroid nodule FNA and compares these with 167 known oncogenes to classify nodules as benign or suspicious.[12] The decision to undergo molecular testing was made on an individual basis factoring in patients' preferences, comorbidities, and surgical candidacy as part of the discussion between the surgeon and patient.[2]

Patient demographics, coexisting thyroid diseases, ultrasound features, Afirma GEC results, type of surgical procedure performed and histopathologic results after surgery were collected. Demographic characteristics included in the analysis were age, gender, and race.

Underlying thyroid diseases included Hashimoto's thyroiditis, multinodular goiter, Grave's disease, and hypothyroidism of any cause. The ultrasound features analyzed were nodule size, presence of microcalcifications, margin irregularity, vascularity, hypoechogenicity, and solid versus cystic appearance. When performed, results of the Afirma GEC were reported as benign, suspicious or unsatisfactory. The type of surgical procedure was recorded as either hemithyroidectomy or total thyroidectomy, and any past thyroid surgery was also noted. The final histologic diagnosis of the aspirated nodule was categorized as either benign or malignant. Of note, only the final histopathology of the thyroid nodule, which underwent FNA was considered when making a diagnosis of benign or malignant disease. In all cases, the thyroid lobe that was aspirated and the lobe containing the malignant nodule on final pathology were the same. Any incidentally discovered malignant nodules in the surgical specimen were not factored into the diagnoses reported in this study.

Chi-squared tests with Yates' continuity correction, Fisher's exact tests, and two-tailed unpaired *t*-tests were used for univariate statistical analysis. Multivariate logistic regression was performed to identify independent risk factors for malignancy. The regression included gender, age, race-ethnicity and presence of thyroid disease as well as the ultrasound characteristics investigated in this study. Afirma results were not included due to the large number of patients who did not have test results. All analyses were conducted using SPSS version 16.0 (IBM, Armonk, NY) software. The $\alpha$ level was set at <.05 for statistical significance.

## 3 | RESULTS

A total of 1387 patients undergoing thyroidectomy were identified and examined through electronic medical records, with 230 meeting

**TABLE 1** Demographic and clinical characteristics of included patients according to final histologic diagnosis

| | All patients, *n* | Benign, *n* (%) | Cancer, *n* (%) | *p* values |
|---|---|---|---|---|
| Total | 230 | 134 (58.3%) | 96 (41.7%) | |
| Age | 54.3 (95% CI: 52.3–56.3) | 56.0 (95% CI: 53.2–58.7) | 51.9 (95% CI: 49.0–54.9) | .045[a] |
| Gender | | | | |
| Male | 62 | 34 (54.8%) | 28 (45.2%) | .625 |
| Female | 168 | 100 (59.5%) | 68 (40.5%) | |
| Race-ethnicity | | | | |
| African American | 10 | 6 (60.0%) | 4 (40.0%) | .828 |
| Asian | 24 | 16 (66.7%) | 8 (33.3%) | |
| Hispanic | 65 | 38 (58.5%) | 27 (41.5%) | |
| White | 116 | 67 (57.8%) | 49 (42.2%) | |
| Other | 15 | 7 (46.7%) | 8 (53.3%) | |
| Bethesda category | | | | |
| III | 103 | 76 (73.8%) | 27 (26.2%) | <.001[a] |
| IV | 64 | 47 (73.4%) | 17 (26.6%) | |
| V | 63 | 11 (17.5%) | 52 (82.5%) | |
| Presence of thyroid disease | | | | |
| Yes | 84 | 51 (60.7%) | 33 (39.3%) | .665 |
| No | 146 | 83 (56.8%) | 63 (43.2%) | |
| Hashimoto's thyroiditis | | | | |
| Yes | 25 | 15 (60.0%) | 10 (40.0%) | 1.000 |
| No | 205 | 119 (58.0%) | 86 (42.0%) | |
| Multinodular goiter | | | | |
| Yes | 52 | 33 (63.5%) | 19 (36.5%) | .481 |
| No | 178 | 101 (56.7%) | 77 (43.3%) | |
| Grave's disease | | | | |
| Yes | 5 | 2 (40.0%) | 3 (60.0%) | .652 |
| No | 225 | 132 (58.7%) | 93 (41.3%) | |
| Prior thyroid surgery | | | | |
| Yes | 10 | 6 (60.0%) | 4 (40.0%) | 1.000 |
| No | 220 | 128 (58.2%) | 92 (41.8%) | |

[a]Indicates statistical significance.

**TABLE 2** Ultrasound findings and molecular test results in Bethesda III–V nodules according to final histologic diagnosis

| | All patients, *n* | Benign, *n* (%) | Cancer, *n* (%) | *p* values | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|---|
| Total | 230 | 134 (58.3%) | 96 (41.7%) | | | |
| Nodule diameter on ultrasound (cm) | 2.62 (95% CI: 2.38–2.85) | 2.76 (95% CI: 2.45–3.07) | 2.43 (95% CI: 2.06–2.80) | .180 | | |
| Microcalcifications | | | | | | |
| Yes | 79 | 34 (43.0%) | 45 (57.0%) | .001[a] | 47.4% | 74.4% |
| No | 149 | 99 (66.4%) | 50 (33.6%) | | | |
| Not reported | 2 | 1 (50.0%) | 1 (50.0%) | | | |
| Irregular margins | | | | | | |
| Yes | 21 | 7 (33.3%) | 14 (66.7%) | .038[a] | 14.9% | 94.4% |
| No | 198 | 118 (59.6%) | 80 (40.4%) | | | |
| Not reported | 11 | 9 (81.8%) | 2 (18.2%) | | | |
| Hypoechogenicity | | | | | | |
| Yes | 86 | 46 (53.5%) | 40 (46.5%) | .393 | 43.5% | 63.2% |
| No | 131 | 79 (60.3%) | 52 (39.7%) | | | |
| Not reported | 13 | 9 (69.2%) | 4 (30.8%) | | | |
| Vascularity | | | | | | |
| Yes | 74 | 46 (62.2%) | 28 (37.8%) | .405 | 30.4% | 63.2% |
| No | 143 | 79 (55.2%) | 64 (44.8%) | | | |
| Not reported | 13 | 9 (69.2%) | 4 (30.8%) | | | |
| Solid appearance | | | | | | |
| Yes | 121 | 72 (59.5%) | 49 (40.5%) | .651 | 52.7% | 43.3% |
| No | 99 | 55 (55.6%) | 44 (44.4%) | | | |
| Not reported | 10 | 7 (70.0%) | 3 (30.0%) | | | |
| Microcalcifications + irregular margins | | | | | | |
| Yes | 16 | 4 (25.0%) | 12 (75.0%) | .015[a] | 12.8% | 96.8% |
| No | 203 | 121 (59.6%) | 82 (40.4%) | | | |
| Not reported | 11 | 9 (81.8%) | 2 (18.2%) | | | |
| Microcalcifications + hypoechogenicity | | | | | | |
| Yes | 33 | 14 (42.4%) | 19 (57.6%) | .055 | 20.7% | 88.8% |
| No | 184 | 111 (60.3%) | 73 (39.7%) | | | |
| Not reported | 13 | 9 (69.2%) | 4 (30.8%) | | | |
| Irregular margins + hypoechogenicity | | | | | | |
| Yes | 13 | 5 (38.5%) | 8 (61.5%) | .177 | 8.8% | 95.8% |
| No | 196 | 113 (57.7%) | 83 (42.3%) | | | |

**TABLE 2** (Continued)

| | All patients, *n* | Benign, *n* (%) | Cancer, *n* (%) | *p* values | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|---|
| Not reported | 21 | 16 (76.2%) | 5 (23.8%) | | | |
| Microcalcifications + irregular margins + hypoechogenicity | | | | | | |
| Yes | 10 | 2 (20.0%) | 8 (80.0%) | .040[a] | 8.8% | 98.3% |
| No | 199 | 116 (58.3%) | 83 (41.7%) | | | |
| Not reported | 21 | 16 (76.2%) | 5 (23.8%) | | | |
| Afirma GEC result | | | | | | |
| Suspicious | 30 | 15 (50.0%) | 15 (50.0%) | .113 | 93.8% | 28.6% |
| Benign | 7 | 6 (85.7%) | 1 (14.3%) | | | |
| Unsatisfactory | 0 | 0 (0.0%) | 0 (0.0%) | | | |
| Not reported | 193 | 113 (58.5%) | 80 (41.5%) | | | |

Abbreviations: CI, confidence interval; GEC, gene expression classifier.
[a]Indicates statistical significance.

criteria for inclusion. Table 1 summarizes the demographic and clinical characteristics of patients included in the study. The mean patient age was 54.3 (range: 19–97) years and 73.0% were female. Of included patients, 36.5% had underlying thyroid disease, including 22.6% with multinodular goiter, 10.9% with Hashimoto's thyroiditis and 2.2% with Grave's disease. Based on cytopathologic reports, 103 nodules were classified as Bethesda III (44.8%), 64 were categorized as Bethesda IV (27.8%) and 63 were Bethesda V (27.4%). In 14 patients (6.1%), the Bethesda category was changed from the initial category assigned at the referring hospital after cytology slide review or repeat FNA was performed at our institution. A total of 81 patients were treated with hemithyroidectomy (35.2%) whereas 149 were treated with total thyroidectomy (64.8%). On final histologic evaluation, 134 nodules were benign (58.3%) and 96 were malignant (41.7%).

When comparing patients with benign and malignant disease on univariate analysis, the average age of patients with benign nodules was 56.0 (95% confidence interval [CI]: 53.2–58.7) years compared with 51.9 (95% CI: 49.0–54.9) years for patients with malignancy ($p = .045$) (Table 1). Bethesda III nodules had a malignancy rate of 26.2%, compared with a rate of 26.6% in Bethesda IV nodules and 82.5% in nodules categorized as Bethesda V ($p < .001$).

Table 2 displays the ultrasound findings and molecular test results for included patients compared by final histologic diagnosis. Among nodules with microcalcifications, 57.0% were malignant compared with 33.6% of nodules without microcalcifications ($p = .001$). Nodules with irregular margins were also more likely to be malignant than those with regular margins (66.7% vs. 40.4%, $p = .038$). Nodules with hypoechogenicity had a higher rate of malignancy than those without this feature, although this difference was not statistically significant (46.5% vs. 39.7%, $p = .393$). GEC results were sensitive (93.8%) but not specific (28.6%) for a final histologic diagnosis of cancer, and a suspicious result was not significantly predictive of malignancy on univariate analysis ($p = .113$). All other individual demographic, clinical and ultrasound characteristics did not significantly differ in their risk of malignancy.

Since the presence of microcalcifications, irregular margins and hypoechogenicity were associated with increased malignancy rates, all combinations of these ultrasound features were assessed for their correlations with cancer risk. The coexistence of two or three of these ultrasound features generally increased specificity but decreased sensitivity for malignancy (Table 2). Among nodules with evidence of both microcalcifications and irregular margins, 75.0% were diagnosed as malignant compared with 40.4% of nodules without these characteristics ($p = .015$). Nodules with all three ultrasound features had a malignancy rate of 80.0% compared with 41.7% in nodules without this combination of features ($p = .04$).

Table 3 summarizes risk factors associated with significantly increased odds of thyroid malignancy based on multivariate logistic regression. Patient age was inversely correlated with cancer risk, such that increasing age was associated with lower odds of malignancy (OR: 0.98, 95% CI: 0.96–0.99, $p = .028$). The presence of microcalcifications was positively correlated with a diagnosis of thyroid cancer (OR: 2.31, 95% CI: 1.24–4.29, $p = .008$), whereas irregular margins were not significantly predictive of malignancy (OR: 2.28, 95% CI:

**TABLE 3** Statistically significant risk factors for malignancy in Bethesda III–V nodules on multivariate logistic regression

| Variable | Odds ratio | *p* values |
|---|---|---|
| Age | 0.98 (95% CI: 0.96–0.99) | .028 |
| Microcalcifications | 2.31 (95% CI: 1.24–4.29) | .008 |
| Microcalcifications and irregular margins | 4.42 (95% CI: 1.32–14.93) | .016 |
| Microcalcifications, irregular margins, and hypoechogenicity | 5.52 (95% CI: 1.12–27.78) | .036 |

Abbreviation: CI, confidence interval.

0.79–6.58, $p = .126$). The copresence of microcalcifications and irregular margins was associated with higher odds of malignancy (OR: 4.42, 95% CI: 1.32–14.93, $p = .016$), and the combination of microcalcifications, irregular margins and hypoechogenicity resulted in the greatest cancer risk (OR: 5.52, 95% CI: 1.12–27.78, $p = .036$).

## 4 | DISCUSSION

This study investigated the demographic, clinical, and diagnostic characteristics associated with malignancy in patients with thyroid nodules categorized as Bethesda III–V on cytopathology. We identified that ultrasound evidence of microcalcifications was an independent risk factor for malignancy, which was diagnosed in 41.7% of patients overall. The combination of microcalcifications, irregular margins and hypoechogenicity was associated with a greater malignancy risk and had a high specificity but low sensitivity for thyroid cancer in patients with indeterminate nodules.

Our results were notable for an increased rate of malignancy (26.2%) among Bethesda III nodules compared to the rate of 6%–18% reported by the 2017 BSRTC.[2] A recent meta-analysis of cancer risk in Bethesda III nodules also found a higher malignancy rate than originally reported by the BSRTC.[16] Moreover, Ho et al. identified an elevated malignancy rate for Bethesda III nodules in their comprehensive cancer center, postulating that tertiary referral centers may diagnose higher rates of thyroid malignancy than those reported in other studies due to referral bias, in which patients admitted to these hospitals have a higher likelihood of being diagnosed with more advanced disease.[17] Additionally, all patients in our study underwent thyroidectomy, and since resection was performed due to unfavorable clinical or radiographic features, this form of selection bias may further artificially raise the malignancy rate in these patients. Whereas the cancer rate for Bethesda IV nodules in this study was similar to rates reported by the 2017 BSRTC, the 82.5% incidence of malignancy among Bethesda V nodules was higher than previously reported.[1,2] However, this elevated incidence is consistent with the range of malignancy rates for Bethesda V nodules identified in a meta-analysis by Krauss et al. and may also be the result of referral and selection bias at the tertiary hospitals in our study.[18]

We found that patient age was minimally and inversely correlated with malignancy, indicating that younger patients with indeterminate nodules were at a slightly higher risk of being diagnosed with thyroid cancer. Rago et al. identified that younger age was an independent risk factor for thyroid cancer in indeterminate nodules, and a study by Bessey et al. similarly reported an inverse correlation between patient age and malignancy risk for nodules undergoing FNA.[11,19] However, the authors of that study also noted female gender to be a significant risk factor for malignancy, contrasting with our finding that gender, as well as race-ethnicity and underlying thyroid disease, were not significant predictors of thyroid cancer.[19] Additionally, we did not identify increased nodule size to be significantly associated with malignancy, a finding consistent with the results of studies by both Kiernan et al and Rago et al but differing from several others in the literature.[4,11,20,21] Therefore, our results and others in the literature suggest that whereas younger age may lead to increased risk of malignancy in indeterminate thyroid nodules, other demographic characteristics, patient comorbidities and nodule size and may be inconsistent risk factors for generalizing malignancy risk on a population level.

The presence of microcalcifications on ultrasound evaluation was identified as an independent risk factor for thyroid cancer in our study, whereas other sonographic features in isolation were not significantly associated with malignancy. Microcalcifications, irregular margins, hypoechogenicity, vascularity and solid versus cystic appearance have all been previously suggested as sonographic features predictive of malignancy in indeterminate thyroid nodules.[5,10,22] However, reports in the literature regarding the utility of these ultrasound features vary in their findings, with some studies suggesting their potential utility and others reporting that specific sonographic characteristics are poorly predictive of thyroid cancer when taken singularly.[23–25] Our results indicated that the co-presentation of microcalcifications, irregular margins, and hypoechogenicity was associated with a greater odds of cancer than any of these features in isolation, and had higher specificity but lower sensitivity for a diagnosis of malignancy. This finding is consistent with the results of Rago et al, who similarly identified that this combination of features was significantly predictive and highly specific, although not sensitive, for malignancy in nodules at indeterminate risk of cancer.[11] Based on these results and findings from a recent meta-analysis, it appears that the identification of multiple suspicious features on ultrasound may be useful in identifying indeterminate nodules which are at higher risk of malignancy, although their absence should not be used to rule out the possibility of cancer.[11,26]

Our study showed that a suspicious Afirma GEC result was sensitive but nonspecific for a final histologic diagnosis of cancer. This finding is supported in the literature and indicates that the most validated utility of GECs for indeterminate thyroid nodules may be in an exclusionary role, with a benign test result suggesting a true lack of malignancy and pointing toward conservative management.[13,27–30] However, it is important to note that our institution does not routinely utilize the Afirma GEC test for indeterminate thyroid nodules and the decision to perform this test is individualized based on patient preferences and comorbidities, resulting in a reduced sample size that

underpowered our analysis for the association of this test with thyroid cancer. Whereas a benign result on this test has repeatedly shown to have a high-negative predictive value for ruling out thyroid malignancies, the utility of a suspicious result in guiding management is still unclear and requires additional investigation.[31]

This study has several limitations. Since our findings are based on retrospective data from electronic medical records, it is possible that misdocumentation of patient demographics, clinical variables, and ultrasound features may have led to inaccurate reporting of this information. Additionally, the reliability of ultrasound findings depends on operator experience, and multiple different operators may have performed the thyroid ultrasound evaluations for patients included in this study. Better standardization of ultrasound performance and reporting may have resulted in stronger associations between suspicious ultrasound characteristics and an eventual diagnosis of thyroid cancer. Moreover, since our institution is a tertiary referral center and all patients underwent thyroidectomy, there was likely referral and selection bias with regards to the patients included in the study. Such bias may have affected the malignancy rates observed among Bethesda III–V nodules, which were generally higher than averages reported in the literature. Furthermore, our results are based on data from a single academic institution, limiting the applicability of our findings to different patient populations. However, our study is unique in that it reports information collected from patients managed in both private and public hospitals, making our results more generalizable to the general population than others in the literature. Finally, we did not collect information on histopathologic characteristics associated with more aggressive disease among thyroid malignancies, such as extrathyroidal extension, lymph node involvement, lymphovascular invasion and perineural invasion. Future studies correlating these aggressive histologic characteristics with ultrasound findings and molecular test results may provide useful information for guiding the management of Bethesda III–V thyroid nodules.

## 5 | CONCLUSION

Evidence of microcalcifications on ultrasound evaluation of Bethesda III–V nodules may be an independent risk factor for malignancy. The copresence of microcalcifications, irregular margins and hypoechogenicity is associated with a greater malignancy risk in nodules with indeterminate cytopathology.

### FUNDING INFORMATION

None.

### CONFLICT OF INTEREST

The authors declare there is no potential conflict of interest.

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