Cytology versus histology in thyroid nodules: the Impact of Bethesda Categories III and IV

Original Article

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Abstract

Aim: To evaluate diagnostic performance of fine-needle aspiration cytology (FNAC) in thyroid nodules and identify predictors of malignancy in Bethesda III–IV nodules.
Study Design: Single-center retrospective study.
Materials and Methods: Adults undergoing surgery between 2016–2025 were included. Cytology was classified as benign, suspicious/malignant, or indeterminate (Bethesda II, V–VI, III–IV, respectively), and histology as benign or malignant. Cytology–histology concordance and FNAC accuracy were evaluated using different approaches to indeterminate cytology. Associations between malignancy and clinical and ultrasound features were analyzed in indeterminate nodules.
Results: Among 72 patients, 23 had benign cytology, 14 suspicious/malignant, and 35 indeterminate. Cytology–histology concordance was weak but became excellent after excluding indeterminate cases (κ 0.266 vs 0.830; p<0.001). FNAC accuracy ranged from 56.9% to 91.9%, depending on handling of indeterminate cytology. No variable was significantly associated with malignancy in Bethesda III–IV nodules.
Conclusions: Bethesda III–IV nodules reduce FNAC accuracy. Identifying predictors of malignancy will improve surgical selection.

Keywords: thyroid nodule; fine-needle aspiration cytology (FNAC); accuracy; indeterminate cytology.

Introduction

Nodular thyroid disease is very common, with an incidence of 50% to 60% in the general population [1]. The increasing use and improved sensitivity of imaging studies have contributed to the rising frequency of thyroid nodules through the incidental detection of small, asymptomatic lesions. The vast majority of thyroid nodules are benign and remain asymptomatic, requiring no treatment beyond appropriate, regular surveillance. The clinical

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challenge lies in accurately identifying malignant or high-risk cases while balancing the need for investigation and treatment against the risk of overtreatment and unpredictable natural history of these lesions. In this context, fine-needle aspiration cytology (FNAC) plays a key role in the initial evaluation of thyroid nodules and identification of such cases [1,2].

According to the international guidelines, FNAC is indicated when malignancy is suspected or the nodule is considered high risk based on size, clinical factors, and ultrasound characteristics [3,4]. The Bethesda system is routinely used to classify the results and guide management. Surgery is indicated for nodules with suspicious (*Bethesda* V) or malignant (*Bethesda* VI) cytology and for symptomatic nodules with benign cytology (*Bethesda* II). The management of other categories, however, remains controversial and varies among centers. For nodules with a nondiagnostic result (*Bethesda* I) or atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS, *Bethesda* III), a repeat FNAC may be considered, whereas for follicular neoplasms (*Bethesda* IV), early surgical referral is usually advocated for diagnostic clarification [2,3,4].

Histologic examination is considered the gold standard for the diagnosis of thyroid nodules, as it overcomes the limitations of cytology in indeterminate cases and when tissue architecture is crucial for a definitive diagnosis[5]. Obtaining a histologic diagnosis requires surgery, which carries substantial risks and complications; therefore, it is reserved for cases where less invasive methods, such as FNAC, fail to provide a reliable diagnosis [2].

The main objectives of this study were to evaluate the agreement between cytology and histology and to determine the diagnostic accuracy of FNAC in thyroid nodules, considering different clinical scenarios for the management of inconclusive cytology. Additionally, we aimed to identify the potential factors associated with malignancy in nodules with inconclusive cytology to improve the selection of surgical candidates and, thereby, reduce associated morbidity.

Materials and Methods

We conducted a retrospective longitudinal study in the Department of Otolaryngology of a tertiary care center in northern Portugal. We included patients aged ≥18 years who underwent surgery for nodular thyroid disease between January 1, 2016, and December 31, 2025. All preoperative cytology results were classified according to the Bethesda system and subsequently categorized into three groups: benign cytology (*Bethesda* II), suspicious/malignant cytology (*Bethesda* V–VI), and inconclusive cytology (*Bethesda* III–IV). Nodules with nondiagnostic cytology (*Bethesda* I) underwent a second FNAC and were reclassified into one of the other five categories. We excluded cases without a preoperative cytology result and cases with persistently nondiagnostic cytology (*Bethesda* I) despite a repeat FNAC. Histologic examination of the surgical specimen was considered the definitive diagnosis and was classified as either benign or malignant. When available, the thyroid ultrasound results were classified according to the Thyroid Imaging Reporting and Data System (TI-RADS).

To evaluate the association between cytologic and histologic results, we used the Pearson chi-square test and considered two scenarios: one including all cases and one excluding inconclusive cytology results. To evaluate the agreement between cytologic and histologic results, we calculated the kappa coefficient (κ) for the same two scenarios. To evaluate the diagnostic performance of FNAC, we determined the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of cytology relative to histology, which was considered the diagnostic gold standard. To analyze the impact of inconclusive cytology results on the diagnostic performance of FNAC, we considered three clinical scenarios for surgical decision-making: an exclusion approach (inconclusive cytology results excluded from the analysis), a conservative approach (inconclusive cytology results treated as benign), and an interventional approach (inconclusive cytology

results treated as suspicious/malignant). For *Bethesda* III and IV nodules, we evaluated the association between the histologic diagnosis and clinical and ultrasound characteristics of the nodule. Additionally, we assessed whether the time between FNAC and surgery (in months) was associated with the histologic diagnosis of these nodules. The clinical characteristics analyzed were sex (male/female); age at the time of FNAC (< 55 years/≥ 55 years); symptoms at initial presentation (asymptomatic/palpable mass/compressive symptoms or rapid growth); personal history of neck irradiation (no/yes); personal history of cancer (no/yes); personal history of thyroid disease (no/lymphocytic thyroiditis/Graves disease/nontoxic multinodular goiter/toxic multinodular goiter/solitary nodule); current or past smoking (no/yes); and history of at least one cardiovascular risk factor (no/yes), including overweight/obesity, dyslipidemia, hypertension, and diabetes mellitus. The ultrasound characteristics analyzed were multifocality (solitary nodule/multifocal nodular disease); maximum diameter (mm); size category (< 1 cm/1–4 cm/≥ 4 cm); and TI-RADS category (low, ≤3; high, >3). Associations between categorical variables were analyzed using the Pearson chi-square test. For continuous variables, we used the parametric Student *t*-test and one-way analysis of variance (ANOVA) for normally distributed data, and the nonparametric Mann–Whitney U and Kruskal–Wallis tests for non-normally distributed data.

Data were obtained from the *SClínico* electronic health record system. Statistical analysis was performed with IBM SPSS Statistics version 30.0.0.0 (IBM Corp, Armonk, NY). Statistical significance was set at $P < 0.05$.

Results

Among the initial sample of 79 patients, 7 patients were excluded because they had not undergone preoperative cytologic evaluation of the nodule or because they had persistently nondiagnostic cytology (*Bethesda* I) despite a repeat FNAC. The final sample included 72 patients with a mean age of 51.3 ± 14.3 years, of whom 58 patients (80.6%) were women. At initial presentation, 27 patients (37.5%) were asymptomatic, 11 patients (25.0%) had a palpable neck mass, and 27 patients (37.5%) reported compressive symptoms and/or rapid nodule growth. The demographic and clinical characteristics of the patients are summarized in Table 1.

Overall, 35 nodules (48.6%) were located in the right lobe, 34 (47.2%) in the left lobe, and 2 (2.8%) in the isthmus. The median nodule diameter at the time of FNAC was 32.0 mm (interquartile range [IQR], 21.0 mm). Most nodules were classified as TI-RADS 3 (40.3%) or TI-RADS 4 (44.4%). The ultrasound characteristics of the thyroid nodules are summarized in Table 2. Only one patient did not undergo a thyroid ultrasound before FNAC.

Figure 1 illustrates the distribution of cytologic results according to the Bethesda classification. The 7 nodules initially classified as *Bethesda* I were reclassified according to the result of the second FNAC: 1 as *Bethesda* II (11.1%), 3 as *Bethesda* IV (33.3%), 1 as *Bethesda* V (11.1%), and 2 as *Bethesda* VI (22.2%). Based on our study categories, 23 cytology results were classified as benign (31.9%), 14 as suspicious/malignant (19.4%), and 35 as inconclusive (48.6%). Histology was benign in 21 (91.3%), 1 (7.1%), and 28 (80%) of those cases, respectively (Table 3). The median time between FNAC and surgery was 4 months (IQR, 4.8).

In the overall cohort, there was a significant association between the cytologic and histologic diagnoses ($\chi^2 = 32.627$, $P < 0.001$), with fair agreement between cytology and histology ($\kappa = 0.266 \pm 0.058$, $P < 0.001$). When nodules with inconclusive cytology were excluded, the association remained significant ($\chi^2 = 25.572$, $P < 0.001$), and the agreement was almost perfect and substantially higher ($\kappa = 0.830 \pm 0.094$, $P < 0.001$). The diagnostic performance of FNAC varied substantially according to the clinical approach adopted for nodules with inconclusive cytology. Table 4 presents the agreement between cytologic and histologic results according to the different approaches

Table 1
Demographic and clinical characteristics of the study population (n = 72).

	Total n (%)
Sex	
Male	14 (19,4)
Female	58 (80,6)
Age	
< 55 years	36 (50,0)
≥ 55 years	36 (50,0)
Age (years), mean ± SD	51,3 ± 14,3
Initial symptoms	
Asymptomatic	27 (37,5)
Palpable mass	11 (25,0)
Compressive symptoms / rapid growth	27 (37,5)
Prior neck irradiation	
No	70 (97,2)
Yes	2 (2,8)
History of cancer	
No	64 (88,9)
Yes	8 (11,1)
Prior thyroid disease	
No	41 (56,9)
Lymphocytic thyroiditis	2 (2,8)
Graves disease	1 (1,4)
Nontoxic MNG	22 (30,6)
Toxic MNG	3 (4,2)
Solitary nodule	3 (4,2)
Current/past smoking	
No	61 (84,7)
Yes	11 (15,3)
CVRF (≥ 1)	
No	41 (56,9)
Yes	31 (43,1)

CVRF – Cardiovascular risk factors (including overweight/obesity, dyslipidemia, hypertension, and diabetes mellitus); MNG – multinodular goiter; SD – standard deviation

Table 2
Ultrasound characteristics of the thyroid nodules (n = 71).

	Total n (%)
Location	
Right lobe	35 (48,6)
Left lobe	34 (47,2)
Isthmus	2 (2,8)
Multifocality	
Solitary nodule	30 (41,7)
Multifocal nodular disease	41 (56,9)
Maximum diameter (mm), median (IQR)	32,0 (21,0)
Size category	
< 1 cm	3 (4,2)
1-4 cm	49 (68,1)
≥ 4 cm	19 (26,4)
Composition	
Solid	49 (68,1)
Cystic	1 (1,4)
Mixed	21 (29,2)
Echogenicity	
Isoechoic	30 (41,7)
Hypoechoic	25 (34,7)
Heterogeneous	14 (19,4)
Anechoic	2 (2,8)
Calcifications	
None	54 (75,0)
Microcalcifications	10 (13,9)
Coarse calcifications	7 (9,7)
TI-RADS classification	
TI-RADS 1	1 (1,4)
TI-RADS 2	7 (9,7)
TI-RADS 3	29 (40,3)
TI-RADS 4	32 (44,4)
TI-RADS 5	2 (2,8)

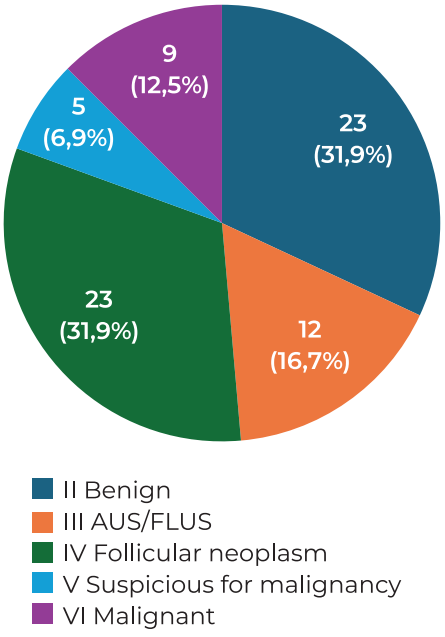
IQR – interquartile range; TI-RADS – Thyroid Imaging Reporting and Data System

Table 3
Agreement between cytologic and histologic results (n = 72).

	Benign histology n (%)	Malignant histology n (%)	Total n (%)
Benign cytology (Bethesda II)	21 (42,0)	2 (9,1)	23 (31,9)
Suspicious/malignant cytology (Bethesda V–VI)	1 (2,0)	13 (59,1)	14 (19,4)
Inconclusive cytology (Bethesda III–IV)	28 (56,0)	7 (31,8)	35 (48,6)
Total	50	22	72

to nodules with inconclusive cytology, and Table 5 shows the main diagnostic metrics of FNAC (sensitivity, specificity, PPV, NPV, and accuracy) calculated for each scenario. When cases with inconclusive cytology were excluded, FNAC demonstrated high sensitivity

Figure 1
Distribution of cytologic results according to the Bethesda classification (n = 72).



AUS/FLUS – Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance

(86.7%) and specificity (95.5%) for the diagnosis of thyroid nodules, with the predictive values above 90% and diagnostic accuracy of 91.9%. When inconclusive cytology results were treated as benign (conservative approach), specificity remained high (98.0%); however, sensitivity decreased to 59.1% and NPV to 84.4%, resulting in a diagnostic accuracy of 86.1%. Conversely, when inconclusive cytology results were treated as suspicious/malignant (interventional approach), the sensitivity remained high (95.5%); however, specificity (42.0%), PPV (40.8%), and diagnostic accuracy (56.9%) decreased markedly.

The analysis of the clinical and ultrasound characteristics of nodules with inconclusive cytology is summarized in Table 6. Most of these nodules occurred in female patients (80.0%), in patients aged ≥55 years (71.4%), and in patients without a known history of thyroid disease (62.9%). They were

Table 4
Agreement between cytologic and histologic results according to the clinical approach to inconclusive cytology results (n = 72).

	Benign histology n (%)	Malignant histology n (%)	Total n (%)
Exclusion approach (n = 37)			
Benign cytology (Bethesda II)	21 (95,5%)	2 (13,3)	23 (62,2)
Suspicious/malignant cytology (Bethesda V–VI)	1 (4,5%)	13 (86,7)	14 (37,8)
Conservative approach			
Benign or inconclusive cytology (Bethesda II–IV)	49 (98,0)	9 (40,9)	58 (80,6)
Suspicious/malignant cytology (Bethesda V–VI)	1 (2,0)	13 (59,1)	14 (19,4)
Interventional approach			
Benign cytology (Bethesda II)	21 (42,0)	2 (9,1)	23 (31,9)
Suspicious/malignant or inconclusive cytology (Bethesda III–VI)	29 (58,0)	20 (90,9)	49 (68,1)
Total	50	22	72

Table 5
Diagnostic performance of fine-needle aspiration cytology according to the clinical approach to inconclusive cytology results (n = 72).

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Exclusion approach (n = 37)	86,7	95,5	92,9	91,3	91,9
Conservative approach	59,1	98,0	92,9	84,4	86,1
Interventional approach	95,5	42,0	40,8	91,3	56,9

NPV – negative predictive value; PPV – positive predictive value

Table 6
Clinical and ultrasound characteristics of cases with inconclusive cytology (n = 35).

	Bethesda III cytology (n = 12)			Bethesda IV cytology (n = 23)		
	Benign histology n (%)	Malignant histology n (%)	p	Benign histology n (%)	Malignant histology n (%)	p
Clinical characteristics						
Sex						
Male	3 (33,3)	1 (33,3)	0,745	3 (15,8)	0	0,547
Female	6 (66,7)	2 (66,7)		16 (84,2)	4 (100,0)	
Age						
< 55 years	5 (55,6)	0	0,205	4 (21,1)	1 (25,0)	0,654
≥ 55 years	4 (44,4)	3 (100,0)		15 (78,9)	3 (75,0)	
Initial symptoms						
Asymptomatic	5 (55,6)	2 (66,7)	0,643	10 (52,6)	3 (75,0)	0,776
Palpable mass	1 (11,1)	0		4 (21,1)	1 (25,0)	
Compressive symptoms/ rapid growth	3 (33,3)	1 (33,3)		5 (26,3)	0	
Prior neck irradiation						
No	9 (100,0)	3 (100,0)	ND	17 (89,5)	4 (100,0)	0,676
Yes	0	0		2 (10,5)	0	
History of cancer						
No	8 (88,9)	3 (100,0)	0,750	13 (68,4)	4 (100,0)	0,539
Yes	1 (11,1)	0		6 (31,6)	0	
Prior thyroid disease						
No	6 (66,7)	1 (33,3)	0,362	13 (68,4)	2 (50,0)	0,586
Lymphocytic thyroiditis	0	1 (33,3)		1 (5,3)	0	
Graves disease	0	0		0	0	
Nontoxic MNG	1 (11,1)	1 (33,3)		3 (15,8)	2 (50,0)	
Toxic MNG	1 (11,1)	0		1 (5,3)	0	
Solitary nodule	1 (11,1)	0		1 (5,3)	0	
Current/past smoking						
No	7 (77,8)	1 (33,3)	0,236	17 (89,5)	3 (75,0)	0,453
Yes	2 (22,2)	2 (66,7)		2 (10,5)	1 (25,0)	
CVRF (≥ 1)						
No	4 (44,4)	1 (33,3)	0,636	8 (42,1)	2 (50,0)	0,596
Yes	5 (55,6)	2 (66,7)		11 (57,9)	2 (50,0)	
Ultrasound characteristics						
Multifocality						
Solitary nodule	4 (44,4)	1 (33,3)	0,636	10 (52,6)	1 (25,0)	0,590
Multifocal nodular disease	5 (55,6)	2 (66,7)		9 (47,4)	3 (75,0)	
Maximum diameter (mm), median (IQR)	36,0 (23,5)	31,0 (7,0)	0,517	25,0 (25,0)	19,5 (4,8)	0,208
Size category						
< 1 cm	0	0	0,509	0	0	0,539
1–4 cm	6 (66,7)	3 (100,0)		14 (73,7)	4 (100,0)	
≥ 4 cm	3 (33,3)	0		5 (26,3)	0	
TI-RADS category						
Low (≤ 3)	6 (66,7)	2 (66,7)	0,764	8 (42,1)	1 (25,0)	0,483
High (> 3)	3 (33,3)	1 (33,3)		11 (57,9)	3 (75,0)	
Time between FNAC and surgery (months), median (IQR)	4,0 (4,5)	4,0 (2,0)	0,707	4,0 (3,0)	2,0 (4,3)	0,187

mostly asymptomatic (57.1%) and had been detected incidentally on imaging studies. On ultrasound, most nodules with inconclusive cytology occurred in patients with multifocal nodular disease (54.3%) and measured 1–4 cm (77.1%), with a median maximum diameter of 25.0 mm (IQR, 18.0). Bethesda III nodules were mostly classified as TI-RADS ≤ 3 (66.7%), whereas Bethesda IV nodules were more frequently classified as TI-RADS 4 or 5 (60.9%). The median time between FNAC and surgery was 4.0 months (IQR, 3.0). Among Bethesda III and IV nodules, no statistically significant differences were found between those with benign and those with malignant histology ($P > 0.05$ for all analyzed variables; Table 6).

Discussion

The results of this study indicate that FNAC has high diagnostic accuracy for thyroid nodules, but its performance decreases substantially when cytology results are inconclusive (*Bethesda* III–IV). Although a statistically significant association was found between cytologic and histologic diagnoses, cytology–histology agreement was only fair when all nodules were analyzed and increased substantially after nodules with inconclusive cytology were excluded, highlighting the negative impact of the *Bethesda* III and IV categories on the diagnostic accuracy of FNAC. Furthermore, no clinical or ultrasound factors associated with malignancy were identified in *Bethesda* III and IV nodules, which therefore remain a challenge in clinical practice, given the difficulty of stratifying risk and optimizing treatment decisions. FNAC has come to play a key role in the initial evaluation of thyroid nodules. It is a simple, rapid, minimally invasive procedure with few associated complications[6]. It has demonstrated high diagnostic performance [2,7]; however, its utility is limited in *Bethesda* III and IV nodules. These nodules constitute a heterogeneous group in which the distinction between benign and malignant lesions frequently depends on the evaluation of tissue architecture, which cannot be assessed via aspiration cytology. Consequently, the clinical management of these cases remains controversial and may involve repeat aspiration, ultrasound surveillance, or diagnostic surgery [3,4]. The diagnostic performance of FNAC depends substantially on the management strategy chosen in these cases. A conservative approach favors specificity and reduces the risk of unnecessary surgery at the cost of lower sensitivity. Conversely, an interventional approach increases sensitivity but markedly reduces specificity, thereby increasing the risk of overtreatment. Our results indicate that nodules with inconclusive cytology are mostly benign, which favors a conservative approach. Considering the low malignancy rate observed among inconclusive cytology results, a conservative strategy may avoid surgical morbidity and mortality without meaningfully affecting prognosis, even in the event of a delayed diagnosis. However, the literature indicates that the malignancy rate of these nodules varies substantially among centers [8,9]. Based on our findings, the use of clinical and ultrasound criteria alone appears insufficient for adequate risk stratification of *Bethesda* III and IV nodules, reflecting the heterogeneity of these lesions and reinforcing the potential contribution of complementary approaches, such as molecular testing and multivariable predictive models, which have been increasingly explored in recent literature[10,11]. This study strengthens the importance of FNAC as a reliable method in the initial diagnostic workup of thyroid nodules; however, it has some limitations. First, its retrospective design precluded the collection of complete clinical data regarding potential determinants of the initial decision to perform cytology and subsequent surgical management, such as a family history of thyroid cancer, nodule shape, vascular pattern, and margin irregularity. Second, because only patients who underwent surgery were included, the sample may overrepresent nodules with higher clinical or ultrasound suspicion and may therefore not reflect the general population of patients with nodular thyroid disease. Third, cytologic and ultrasound

interpretations are inherently observer-dependent, which may have influenced the results. Finally, this was a single-center study with a relatively small sample size, which may have limited the statistical power to identify significant associations, particularly in the analysis of *Bethesda* III and IV nodules. The high proportion of inconclusive cytology results (48.6%) and the low malignancy rate of these nodules (20.0%) reflect the case mix at our center and may not apply to the general population; consequently, the impact of *Bethesda* III and IV cytology results on the diagnostic performance of FNAC may have been overestimated. Future prospective studies should include larger, multicenter samples and use multivariable predictive models that combine clinical, imaging, and molecular data to improve the risk stratification of nodules with inconclusive cytology. Despite these limitations, this study has several strengths. The extended study period allowed us to include a representative sample, increasing the external validity of the results. The analysis of different clinical scenarios for the management of nodules with inconclusive cytology is a valuable contribution to clinical practice, as it clarifies the impact of treatment decisions on the diagnostic performance metrics of FNAC. Additionally, the inclusion of multiple clinical and ultrasound variables enabled a comprehensive evaluation of potential predictors of malignancy in nodules with inconclusive cytology, contributing to our understanding of how these risk factors interact.

Conclusion

Bethesda III and IV nodules account for most cases of cytology–histology disagreement and substantially decrease the accuracy of FNAC in diagnosing thyroid nodules. The development of multivariable predictive models that combine clinical, imaging, and molecular data will be essential for improving the risk stratification of these nodules and optimizing the selection of cases for surgery, thereby reducing the risk of overtreatment.

Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Data Confidentiality

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

Protection of humans and animals

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

Privacy policy, informed consent and Ethics Committee Authorization

The authors declare that they have written consent for the use of photographs of patients in this article.

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Availability of scientific data

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