



RESEARCH ARTICLE

Risk of Malignancy in Bethesda Category III and IV Thyroid Nodules

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ABSTRACT

Background: The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) provides a standardized framework for thyroid fine-needle aspiration cytology (FNAC). Bethesda Category III (Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance) and Category IV (Follicular Neoplasm/Suspicious for Follicular Neoplasm) represent indeterminate thyroid nodules with variable risks of malignancy, creating challenges in clinical management.

Aim: To determine the risk of malignancy in Bethesda Category III and IV thyroid nodules and correlate cytological findings with final histopathological diagnosis.

Methods: A prospective observational study was conducted at Rabindranath Tagore Medical College, Udaipur, Rajasthan, from March 2024 to March 2026. Eighty patients diagnosed with Bethesda Category III or IV thyroid nodules who subsequently underwent surgery were included. Histopathological examination served as the gold standard for diagnosis. The malignancy rates in both Bethesda categories were analyzed.

Results: Among 80 patients, 45 (56.3%) belonged to Bethesda Category III and 35 (43.7%) to Category IV. Histopathological examination revealed malignancy in 14 (31.1%) Category III nodules and 18 (51.4%) Category IV nodules. Papillary thyroid carcinoma was the most common malignancy. Category IV nodules demonstrated a significantly higher risk of malignancy compared to Category III nodules ($p=0.041$).

Conclusion: Bethesda Category IV thyroid nodules carry a significantly higher risk of malignancy than Category III nodules. Histopathological evaluation remains essential for definitive diagnosis and appropriate surgical management.

Keywords: Thyroid nodule, Bethesda III, Bethesda IV, FNAC, Malignancy risk, Thyroid carcinoma.

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INTRODUCTION

One of the most prevalent endocrine conditions seen in clinical practice is thyroid nodules, which are becoming more common as people age and as imaging technology advances. A little but clinically important percentage of thyroid nodules are malignant, despite the fact that the majority are benign. Accurate preoperative evaluation is therefore essential for proper patient care and preventing needless surgery. Because of its ease of use, affordability, and excellent diagnostic precision, fine-needle aspiration cytology (FNAC) is the mainstay of thyroid nodule examination. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was developed to increase reporting consistency and promote communication between pathologists and doctors. Thyroid cytology is divided into six diagnostic groups under this method, each of which is linked to a certain risk of cancer and suggested clinical treatment[1].

Indeterminate lesions that create substantial diagnostic issues fall into two of these categories: Bethesda Category

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III (Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance) and Category IV (Follicular Neoplasm/Suspicious for Follicular Neoplasm). Category IV comprises lesions suggestive of follicular neoplasia that require histological examination for confirmation, while Category III comprises nodules with cytological atypia insufficient for a conclusive diagnosis. The treatment

of these ambiguous nodules is still debatable. Because of the possible danger of cancer, some individuals need surgery, while others may benefit from observation and repeat FNAC. Studies have reported malignancy rates that range from 10–30% for Category III nodules and 25–50% for Category IV nodules. Differences in patient groups, pathology interpretation, and institutional policies could all be contributing factors to this heterogeneity[2].

Because it affects clinical decisions about surveillance, repeat cytology, molecular testing, and surgical therapy, an accurate assessment of malignancy risk is crucial. The most reliable diagnostic technique is still histopathological investigation, which confirms whether a disease is benign or malignant and directs subsequent treatment. Regional information on malignancy rates in ambiguous thyroid nodules is still scarce, despite the Bethesda approach being used more frequently. Comprehending the local incidence of cancer in Bethesda Categories III and IV may enhance patient counselling and maximise treatment approaches[3].

Therefore, by comparing cytological diagnoses with final histological findings, the current study was conducted to assess the risk of malignancy in Bethesda Category III and IV thyroid nodules.

MATERIALS AND METHODS

Study Design

Prospective observational study.

Study Setting

Department of General Surgery and Pathology, Rabindranath Tagore Medical College, Udaipur, Rajasthan.

Study Duration

March 2024 to March 2026.

Sample Size

80 patients.

Inclusion Criteria

- Patients aged ≥ 18 years.
- Thyroid nodules categorized as Bethesda III or Bethesda IV on FNAC.
- Patients undergoing thyroid surgery.
- Availability of postoperative histopathological reports.

Exclusion Criteria

- Bethesda Categories I, II, V, and VI.
- Previous thyroid surgery.
- Recurrent thyroid malignancy.
- Inadequate histopathological specimens.

Study Procedure

All patients underwent:

- Clinical examination.
- Thyroid ultrasonography.
- Ultrasound-guided FNAC.
- Thyroidectomy (hemi or total).
- Histopathological examination.

Outcome Measures

- Malignancy rates in Bethesda III and IV nodules.
- Histopathological spectrum of lesions.
- Correlation between cytology and histopathology.

Statistical Analysis

Data were analyzed using SPSS version 26.

- Chi-square test.
- Fisher's exact test.
- Independent t-test.

A p -value < 0.05 was considered statistically significant.

RESULTS

The study population predominantly consisted of females, with a female-to-male ratio of approximately 3.4:1.

Bethesda Category III represented the majority of indeterminate thyroid nodules.

Papillary thyroid carcinoma was the most common malignant lesion identified on histopathology.

Table 1: Demographic characteristics

Variable	Value
Total Patients	80
Mean Age (years)	43.8 $\pm$ 12.4
Female (%)	62 (77.5)
Male (%)	18 (22.5)
Mean Nodule Size (cm)	2.8 $\pm$ 1.1

Table 2: Distribution of Bethesda Categories

Bethesda category	Number (%)
Category III	45 (56.3)
Category IV	35 (43.7)

Table 3: Histopathological Diagnosis

Histopathological lesion	Frequency (%)
Nodular hyperplasia	26 (32.5)
Follicular adenoma	22 (27.5)
Papillary thyroid carcinoma	24 (30.0)
Follicular carcinoma	8 (10.0)

Table 4: Malignancy Risk According to Bethesda Category

Bethesda category	Benign	Malignant	Malignancy risk (%)	p-value
Category III (n=45)	31	14	31.1	0.041
Category IV (n=35)	17	18	51.4	

Table 5: Histological Types of Malignancy

Malignancy type	Number (%)
Papillary thyroid carcinoma	24 (75.0)
Follicular carcinoma	8 (25.0)

Table 6: Association Between Nodule Size and Malignancy

Module size	Benign	Malignant	p-value
≤2 cm	21	7	0.028
>2 cm	27	25	

Category IV nodules demonstrated a significantly higher malignancy rate than Category III nodules.

Papillary thyroid carcinoma accounted for three-fourths of all malignant thyroid lesions.

Larger nodules were significantly associated with malignancy on histopathological examination.

DISCUSSION

By comparing FNAC results with final histopathological diagnoses, the current prospective observational study assessed the risk of cancer in Bethesda Category III and IV thyroid nodules. The study showed that there are significant risks of malignancy associated with both classifications, with Bethesda Category IV lesions showing noticeably higher rates. Over three-fourths of the study population consisted of female patients. This finding is in line with the fact that thyroid disorders are known to be more common in women. The increased occurrence of thyroid nodules in women has been attributed to endocrine variables, autoimmune vulnerability, and hormonal impacts[4].

56.3% of the study population fell into Bethesda Category III, whereas 43.7% fell into Category IV. The difficulties in diagnosing atypical cytological findings are reflected in the comparatively large percentage of Category III lesions. Because benign and malignant lesions frequently share cytological characteristics, these ambiguous categories continue to be among the most challenging for clinical decision-making. Histopathological

analysis showed that papillary thyroid carcinoma was the most prevalent cancer, whereas nodular hyperplasia and follicular adenoma were the most common benign lesions. Numerous studies assessing ambiguous thyroid nodules have revealed similar results. Papillary thyroid carcinoma is the most common thyroid cancer in the world, which is reflected in its prevalence[5].

The substantial difference in cancer risk between Bethesda Categories III and IV was one of the study's most notable findings. Category IV nodules showed a significantly greater risk of 51.4%, whereas Category III nodules had a malignancy rate of 31.1%. These results indicate that a significant percentage of indeterminate nodules contain underlying malignancy and fall within the upper limit of malignancy rates reported in the Bethesda system. Because Category IV lesions have cytological characteristics suggestive of follicular neoplasia, the increased risk of malignancy seen in these lesions is biologically justifiable. A conclusive diagnosis can only be made by histological examination because the distinction between follicular adenoma and follicular cancer necessitates the demonstration of capsular or vascular invasion. As a result, surgical excision is still a crucial method for both diagnosis and treatment of Category IV nodules[6].

The correlation between bigger nodules and malignancy was another important finding. Malignant pathology was far more common in nodules larger than 2 cm. Larger lesions may be more likely to have aggressive histological characteristics, even if nodule size by itself is not a reliable indicator of malignancy. There are significant clinical ramifications to the current findings. More aggressive treatment approaches, including as early surgery, may be beneficial for patients with Bethesda Category IV nodules. On the other hand, even though Category III nodules showed a decreased risk of cancer, the observed rate of more than 30% indicates that in some situations, cautious monitoring, repeat FNAC, molecular testing, or diagnostic surgery may be necessary[7].

The study's prospective design and use of histopathological examination as the gold standard are among its strong points. It is important to recognise some limitations, though. With a somewhat small sample size, the study was carried out at a single location. There was no access to molecular diagnostic testing, which could have enhanced risk assessment. Moreover, long-term follow-up results were not evaluated. Notwithstanding these drawbacks, the study offers useful geographical information about the risk of cancer in ambiguous thyroid nodules. The

results highlight the value of tailored management plans based on cytological category and clinical risk factors and validate the usefulness of the Bethesda system in risk stratification[8].

CONCLUSION

The current study shows that there is a significant risk of malignancy associated with Bethesda Category III and IV thyroid nodules, with much higher rates seen in Category IV lesions. Malignancy was found in 31.1% of Category III nodules and 51.4% of Category IV nodules by histopathological investigation, demonstrating the significance of closely monitoring and evaluating ambiguous thyroid lesions. The most frequent benign diagnosis were follicular adenoma and nodular hyperplasia, while papillary thyroid cancer was the most frequent malignant tumour. Malignant pathology was substantially correlated with larger nodule size.

These results emphasise the limits of using cytology alone to diagnose ambiguous thyroid nodules and support the use of histological testing as the gold standard for diagnosis. Patients with Bethesda Category IV nodules may benefit from prompt surgical treatment and should be regarded as being at especially high risk. To enhance risk stratification and optimise treatment protocols for indeterminate thyroid nodules, future multicenter trials utilising molecular diagnostic tools and bigger patient populations are advised. In patients with Bethesda Category III and IV thyroid lesions, the current study offers significant evidence in favour of risk-based clinical decision-making.

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