# Risk of Malignancy in Bethesda Category III Thyroid Nodules with Nuclear Atypia: A Retrospective Study Based on Thyroidectomy Findings

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**Abstract:** *Background*: Thyroid nodules with cytological features of atypia of undetermined significance (AUS), particularly those with nuclear atypia, represent a diagnostic challenge due to their variable malignancy risk. The 2023 revision of the Bethesda System has refined AUS subcategories to improve malignancy risk stratification. The aim of this study was to evaluate the risk of malignancy in Bethesda Category III thyroid nodules with nuclear atypia by correlating cytological findings with post-thyroidectomy histopathological results.

*Material and Methods*: This retrospective observational study included 156 patients who underwent thyroid fine-needle aspiration cytology between 2020 and 2024 and were diagnosed with AUS featuring nuclear atypia. All patients subsequently underwent thyroidectomy. Malignancy rates were determined based on final histopathological diagnoses. Statistical analysis was performed using SPSS version 29.0, applying Chi-square and Fisher's exact tests, with a significance threshold set at $p < 0.05$.

*Results*: The overall malignancy rate was 34.6%, increasing to 39.7% when NIFTP cases were included Fifty papillary carcinomas were identified, 28 of which were <1 cm. In 23 patients who received repeated AUS diagnoses, the malignancy rate reached 73.9% ($p = 0.011$). No statistically significant differences were found between benign and malignant groups in terms of age ($p = 0.655$), gender ($p > 0.05$), or lymphocytic thyroiditis ($p = 0.3$). The reported malignancy rates were exclusively to the cohort of Bethesda Category III nodules with nuclear atypia, which constituted the entire study population.

*Conclusion*: Thyroid nodules classified as AUS with nuclear atypia are associated with a higher-than-expected risk of malignancy, especially in cases with repeated AUS diagnoses. These findings underscore the importance of subclassifying AUS cases to improve risk stratification and guide clinical decision-making.

**Keywords:** Thyroid nodule, Bethesda, nuclear atypia, risk of malignancy.

## INTRODUCTION

Thyroid nodules are commonly encountered lesions in the general population, and evaluating their malignancy risk plays a crucial role in clinical management. Fine-needle aspiration cytology (FNAC) is one of the primary diagnostic tools used for this purpose and is categorized according to the Bethesda System [1]. The Bethesda System was revised in 2023 and now includes the following diagnostic categories: Nondiagnostic, Benign, Atypia of Undetermined Significance (AUS), Follicular Neoplasm, Suspicious for Malignancy and Malignant. In the latest classification, the AUS category is subdivided into nuclear atypia and other types [1].

Bethesda Category III (AUS) encompasses thyroid nodules with heterogeneous cytological features and an indeterminate risk of malignancy. Since the introduction of the Bethesda System for Reporting Thyroid Cytopathology (BSRTC), numerous studies have focused on this category; however, estimating the risk of malignancy (ROM) remains a matter of debate [2-4]. Although AUS is generally considered to be associated with a low risk of malignancy, this risk is thought to be lower than that of the Suspicious for Malignancy (SFM) category, yet it may partially overlap with Follicular Neoplasm (FN) and related diagnostic groups [1, 5]. Furthermore, the introduction of the term "Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP)" in 2016 has also influenced the expected ROM for AUS. Including NIFTP in the benign category leads to a reduction in the calculated malignancy risk associated with AUS and AUS aspirates with nuclear atypia are reported to have approximately twice the ROM compared to cases with only architectural atypia [1].

Although the 2023 Bethesda update reports a ROM of 22% (range: 13–30%) for the AUS category, excluding NIFTP decreases this estimate to approximately 16% [1]. However, numerous studies have reported higher rates [6-8]. A meta-analysis by Crescenzi *et al*. found ROM values ranging from 15% to 44% among AUS subgroups [9]. Although previous meta-analyses, such as that by Crescenzi *et al*. [9], have demonstrated wide variability in malignancy risk among AUS subgroups, data focusing specifically on nuclear atypia remain limited. This study aims to

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address this gap by exclusively evaluating AUS cases with nuclear atypia.

There is no standardized approach to determine the surgical necessity in Bethesda Category III nodules. While repeat FNAC, molecular testing, and ultrasonographic risk stratification are useful, definitive histopathological diagnosis following thyroidectomy remains the most reliable method, particularly in cases of repeated AUS [1].

This study aims to determine the risk of malignancy in thyroid nodules classified as AUS with nuclear atypia by comparing cytological findings with post-thyroidectomy histopathological results.

## MATERIAL AND METHODS

### *Study Design and Patient Selection*

This retrospective observational study included patients who underwent thyroid FNAC between 2020 and 2024 at Giresun University Training and Research Hospital and were subsequently treated with thyroidectomy. All fine-needle aspiration cytology procedures were performed under ultrasound guidance by experienced clinicians. Indications for thyroidectomy included repeated AUS diagnosis, suspicious ultrasonographic features, clinical risk factors, or clinician judgment based on multidisciplinary evaluation.

Inclusion criteria were as follows: • Patients diagnosed with Bethesda Category III based on FNAC, • Patients with confirmed histopathological diagnosis and adequate clinical follow-up data.

### *Data Collection and Classification*

Demographic data, FNAC reports, and histopathological results were retrospectively collected from the hospital archives. Cytological results were updated according to the 2023 Bethesda System. Histopathological diagnoses were classified according to the World Health Organization (WHO) and College of American Pathologists (CAP) guidelines. The incidence of malignancy in Category III nodules with nuclear atypia was statistically analyzed by comparing cytological and histopathological findings.

### *Statistical Analysis*

Data were analyzed using SPSS version 29.0. Chi-square and Fisher's exact tests were used to evaluate differences between groups. A p-value $< 0.05$ was considered statistically significant.

## RESULTS

A total of 156 patients diagnosed with AUS due to nuclear atypia and who underwent thyroidectomy were included in the study. Thirteen patients diagnosed with AUS based on architectural atypia or other features were excluded.

The mean age of the patients was 52.9 ± 11.94 years. In terms of gender, 82.7% were female and 17.3% were male.

The distribution of final histopathological diagnoses among patients with Bethesda Category III thyroid nodules with nuclear atypia is shown below and depicted in 1.

- Multinodular Goiter (MNG): 65 cases (41.7%)
- Papillary Carcinoma (PC): 50 cases (32%)
- Follicular Adenoma: 19 cases (12.2%)
- Hürthle Cell Adenoma: 9 cases (5.8%)
- NIFTP: 8 cases (5.1%)
- Hürthle Cell Carcinoma: 2 cases (1.3%)
- Follicular Carcinoma : 1 case (0.6%)
- Medullary Carcinoma: 1 case (0.6%)
- Follicular Tumor of Uncertain Malignant Potential: 1 case (0.6%)

According to the post-thyroidectomy histopathological findings, malignancy was detected in 54 cases (34.6%). When 8 cases (5.1%) of NIFTP were included in the malignant group, the total malignancy rate increased to 39.7%. Fifty cases were diagnosed as PC, 28 of which were smaller than 1 cm.

A total of 23 cases received a repeated AUS diagnosis. The malignancy rate in this group was 73.9%. Statistical analysis revealed a significant difference in malignancy risk between patients with a single AUS diagnosis and those with two AUS diagnoses ($p = 0.011$). Table **1** presents a summary of the key findings.

Comparison of age between groups revealed a mean age of 50.3 ± 12.2 years in the malignant group and 54.8 ± 11.5 years in the benign group, with no statistically significant difference ($p = 0.655$, independent t-test). Lymphocytic thyroiditis was

**Table 1: Summary of Key Findings and Malignancy Rates in AUS Cases with Nuclear Atypia**

| | Case number | Mean age | ROM |
|---|---|---|---|
| Total AUS (nuclear atypia) cases included | 156 | 52.9 ± 11.94 | 34.6%<br>39.4%(including NIFTP) |
| Female (%) | 82.7% | 52.45 ± 10.48 | 34.9% |
| Male (%) | 17.3% | 55.5 ± 12.2 | 33.3 % |
| Malignancy rate in repeated AUS cases (%) | 14.7% | | 73.9% |

Footnote: The comparison of malignancy risk between female and male patients was performed using the chi-square test, and no statistically significant difference was observed (p = 0.87).

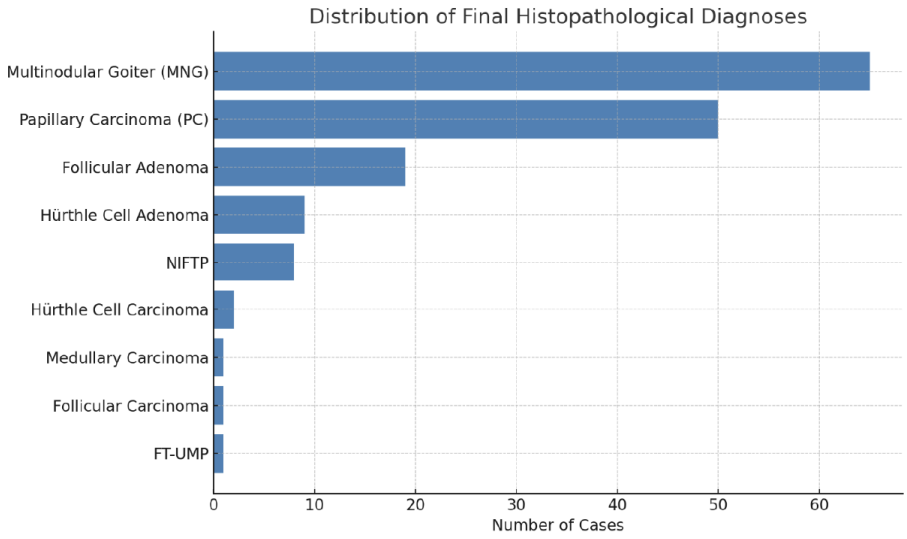


**Figure 1:** Distribution of final histopathological diagnoses in patients with Bethesda Category III thyroid nodules showing nuclear atypia. Multinodular goiter was the most common diagnosis, followed by papillary carcinoma. Less frequent diagnoses included follicular adenoma, Hürthle cell adenoma, NIFTP, and various malignant neoplasms such as Hürthle cell carcinoma, follicular carcinoma, medullary carcinoma, and follicular tumor of uncertain malignant potential (FT-UMP).

observed in 42.3% of all cases: 37% in malignant and 43% in benign cases. No statistically significant association was found between lymphocytic thyroiditis and malignancy (p = 0.3).

## DISCUSSION

Although atypia was previously categorized as nuclear and architectural in earlier versions of the Bethesda system, the 2023 revision defined these subgroups more explicitly. In this study, malignancy was identified in 34.6% of the 156 patients with nuclear atypia diagnosed as AUS. This rate exceeds the 22% ROM suggested in the 2023 Bethesda update for the entire AUS category and supports the expectation of higher risk in nuclear atypia.

Previous studies addressing the AUS/FLUS category in general have reported varying ROM rates. For example, Hassan *et al*. reported malignancy in 33.5% of 170 AUS cases [10]. The same study reported no significant difference in malignancy rates between genders, although women tended to have more favorable tumor types [10]. Similarly, Ho *et al*. found an overall malignancy rate of 37.8% in those who underwent surgery [3]. Fewer studies have specifically focused on the nuclear atypia subgroup. In a study by Alwadi *et al*., of 193 patients, final histopathology revealed malignant nodules in 96 cases (49.7%). The malignancy rates varied among the Bethesda III subcategories, with Hürthle cell atypia demonstrating the highest rate (55.6%), followed by cytological atypia (55.4%), architectural atypia (50.6%), and combined cytological and architectural atypia (33.3%). However, no significant difference in malignancy rates was observed among the Bethesda III subcategories (p = 0.240) [11]. Differences between our findings and those reported by Alwadi *et al*. may be attributed to variations in cohort size, inclusion criteria, and the exclusive focus on nuclear atypia in our study, which is known to confer

a higher malignancy risk. In another study, the overall ROM for AUS was found to be 44.3%, with a ROM of 50% in the AUS-nuclear atypia subgroup and 43.2% in the AUS-other subgroup [12]. Compared with previously published data reporting lower malignancy rates in AUS cases with architectural atypia, the higher rate observed in this study further supports the notion that nuclear atypia represents a higher-risk subgroup.

In this study, the malignancy rate increased to 39.7% when NIFTP cases were included. All AUS cases in this cohort had nuclear atypia, and consistent with previous findings that this subgroup carries a higher malignancy risk, this study demonstrated a markedly elevated rate. Although it was a smaller subset, in patients with two consecutive AUS diagnoses, the malignancy rate was as high as 73.9%. Statistical analysis revealed a significant difference in malignancy risk between patients with a single AUS diagnosis and those with two AUS diagnoses ($p = 0.011$). The consistency of repeated FNAC and the accuracy of this approach should also be emphasized. In the study by Hathi *et al*., the overall ROM was reported between 13.2% and 25.3%, while approximately 45.5% of nodules underwent diagnostic clarification after repeat FNAC [13]. The higher malignancy rate in this study may be attributed to the fact that all cases had nuclear atypia. This highlights the importance of subclassification within the AUS category and the close follow-up of nodules with nuclear atypia.

Although the mean age was lower in the malignant group (50.4 years) than in the benign group (54.8 years), this difference was not statistically significant. This finding is in contrast with some previous studies [7] that identified younger age as an independent risk factor for malignancy in Bethesda Category III nodules. Regarding gender distribution, this study did not reveal a statistically significant association between male gender and malignancy. While certain earlier studies reported higher malignancy rates among men, others have shown that, despite women tending to have more favorable tumor types, the overall malignancy rate did not significantly differ between genders [10].

In summary, the malignancy rate observed in this study was 34.7%, increasing to 39.7% when NIFTP cases were included—both exceeding the risk estimates provided in the 2023 Bethesda update. Furthermore, the broad range of malignancy rates recently reported in the literature further confirms the heterogeneous nature of Category III thyroid nodules. The inclusion or exclusion of NIFTP and minimally invasive lesions significantly affects the interpretation of ROM (risk of malignancy). A comprehensive evaluation incorporating clinical, radiological, and molecular features remains crucial for guiding appropriate management strategies. Additionally, because all cases in this study exhibited nuclear atypia, this data specifically pertain to the subgroup known to carry a higher risk and should be interpreted accordingly.

## LIMITATIONS

This study has several limitations. First, its retrospective and single-center design may limit the generalizability of the findings. Second, only patients who underwent thyroidectomy were included, potentially introducing selection bias and overestimating the risk of malignancy. Third, the focus on AUS cases with nuclear atypia, while important for risk stratification, may not reflect the overall AUS population. Additionally, histopathological evaluations were performed in a single institution without interobserver variability analysis, which may affect diagnostic consistency. Future multi-institutional studies with larger cohorts are warranted to validate these findings and improve their generalizability.

## CONCLUSION

This study supports the notion that nuclear atypia in AUS cases may be associated with an increased risk of malignancy and highlights the importance of evaluating this subgroup separately in clinical decision-making. Cytological subclassification of thyroid nodules may play a decisive role in guiding both surgical intervention and follow-up strategies. This approach can be considered an important step toward more effective communication and decision-making in the management of thyroid nodules. In clinical practice, thyroid nodules with nuclear atypia may benefit from closer surveillance, repeat FNAC, and consideration of molecular testing to guide optimal management decisions.

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