Risk of malignancy in thyroid nodules Bethesda III sub classification into nuclear atypia and architectural atypia. *A retrospective study*

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ABSTRACT

Objectives: To identify the risk of malignancy in the Bethesda III category based on histopathological subclassification.

Methods: We retrospectively analyzed 193 patients with Bethesda III thyroid nodules who underwent surgical resection. The primary outcome was the malignancy risk associated with each histopathological sub-classification.

Results: Of 193 patients, final histopathology revealed malignant nodules in 96 (49.7%). The malignancy rates varied among the Bethesda III subcategories, with Hürthle cell atypia of undetermined significance 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). Papillary thyroid carcinoma was the most common malignant tumor in all Bethesda III subcategories.

Conclusion: Bethesda III nodules pose a clinical challenge. Our findings indicate a higher risk of malignancy in patients with cytologic atypia. Bethesda III subclassification may improve clinical decisions and interdisciplinary communication

Keywords: thyroid neoplasms, thyroid nodule, thyroid cancer, atypia of undetermined significance, follicular lesion of undetermined significance

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Thyroid cancer is the most prevalent endocrine malignancy and one of the most common malignancies worldwide. Over the past few decades, thyroid cancer has been increasing in incidence. However, the mortality rate has decreased recently.[1] In Saudi Arabia, thyroid cancer is common, mostly among females, accounting for 12.9% of all malignancies.[2] Fine-needle aspiration (FNA) of the thyroid remains an essential component of thyroid nodule management. The American Thyroid Association developed the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) in 2009 to improve the communication between pathologists and surgeons. The BSRTC 2023 update classifies all biopsied thyroid nodules into six categories: non-diagnostic (Bethesda I), benign (Bethesda II), atypia of undetermined significance (AUS; Bethesda III), follicular neoplasm (Bethesda IV), suspicious for malignancy (Bethesda V), and malignant nodules (Bethesda VI). [3,4]

The 2017 BSRTC advises hospital laboratories to use only one nomenclature in the Bethesda III category (AUS). The risk of malignancy in AUS is heavily influenced by the classification of noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP). When NIFTP is excluded, the reported malignancy rates range from 6–20%, whereas if NIFTP is included, the risk elevates to 13–30%. This distinction highlights the significant impact of NIFTP classification on risk assessment and underscores the importance of precise diagnostic categorization in guiding clinical management decisions for thyroid nodules.[3–5]

Atypia of undetermined significance/follicular lesions of undetermined significance (AUS/FLUS) has been subclassified into architectural, cytological with nuclear changes, and Hürthle cell subcategories. The ambiguity in the diagnosis of AUS/FLUS puts surgeons in a dilemma regarding whether to perform molecular testing, repeat FNA, or hemithyroidectomy.[6]

Several studies have evaluated the risk of malignancy of Bethesda III subcategories, classified based on histological appearance into cytological atypia (C), architectural atypia (A), both cytologic and architectural atypia (B), and Hürthle cells (H).[7–9] A Turkish study reported the malignancy rates of Bethesda III when subdivided into the cytological atypia subgroup as 28.8% and that into the architectural atypia subgroup as 7.1%.[5] In this study, we aimed to identify the risk of malignancy in the Bethesda III category based on histopathological subclassification.

Methods. This retrospective cohort study was conducted at King Abdulaziz Medical City (KAMC), Riyadh, Saudi Arabia, from January 2016 to March 2023. A total of 1097 patients were screened who underwent FNA for thyroid nodules, of which 197 were Bethesda type III. All patients with Bethesda

III thyroid nodules based on preoperative cytological examination who underwent hemithyroidectomy or total thyroidectomy for the purpose of reaching a diagnosis, symptomatic goiter, or cosmetic reasons were included in the study. Bethesda III patients who did not undergo thyroidectomy or those who underwent surgery outside our facility were excluded from the study. A total of 193 patients met the inclusion criteria and were included in this study.

The Bethesda System for Reporting Thyroid Cytopathology 2017 edition was followed in this study.

Data collection sheet. A standardized data extraction form was used to gather information from patients' medical records. A team of trained research assistants collected the data under the supervision of the principal investigator. The following data were extracted.

i) Demographics: Including age, gender, and history of malignancies. ii) Diagnostic information: Fine-needle aspiration (FNA) results and final surgical histopathological outcomes. iii) Treatment specifics: Details of surgical procedures, such as timing and type.

To minimize potential bias during data collection, the research assistants were blinded to the study objectives.

Ethical consideration. This study followed the ethical criteria of the Declaration of Helsinki. The approval of the study protocol was granted (NRC23R-249-04) by King Abdullah International Medical Research Center (KAIMRC, Riyadh, Saudi Arabia. Consent was taken from all patients, their data were anonymized.

Statistical analysis. IBM SPSS Statistics for MacBook, v. 25.0 (IBM Corp., Armonk, N.Y., USA)[10] was used to analyze the data. Categorical variables are presented as frequencies and percentages, while continuous variables are presented as means with standard deviations. The Chi squared test was used to compare categorical variables, specifically to evaluate differences in malignancy rates among the Bethesda III subcategories. Statistical significance was set at $p<0.05$.

Results. This study included 193 patients who underwent hemithyroidectomy or total thyroidectomy with preoperative Bethesda III category on FNA. The mean age of the patients was 46.21 (±13.57) years, and females represented most of our sample (82.4%). Final histopathology revealed malignant nodules in 96 patients (49.7%). Table 1 shows the demographic and clinical characteristics of the study participants.

Table 2 illustrates the malignancy rates in Bethesda III subcategories. Hürthle cell AUS had the highest malignancy rate (55.6%), followed by cytological (55.4%), architectural (50.6%), and both cytological and architectural (33.3%) atypia. However, there was no significant difference in the malignancy rate among the Bethesda III subcategories ($p=0.240$). Among malignant tumors, papillary thyroid carcinoma was the most common pathology in all Bethesda III subcategories (Table 2).

Discussion. Thyroid cancer is the most common endocrine malignancy and one of the most widespread cancers globally.[1] Our current study findings revealed a Bethesda III rate of 17.9%, which is consistent with the rates reported in the existing literature regarding the prevalence of Bethesda III category (AUS) in thyroid nodules, with the rates ranging from 13.2–14.5%.[10,11] The variability in malignancy rates within this category underscores the importance of considering additional diagnostic steps, such as repeat FNA, molecular testing, diagnostic lobectomy, or surveillance, to guide appropriate management decisions for patients with thyroid nodules.

Our study showed a high malignancy rate in the Bethesda III category (49.7%), which is higher than what was reported in 2023 BSRTC (22%). Moreover, a study conducted by Zarif et al.[12] in Saudi Arabia, showed a similar malignancy rate in Bethesda III (50%).

While our results indicate a higher risk of malignancy in Hürthle cell AUS, it is crucial to note that this observation was based on a relatively small sample size, with only 9 cases involved. The limited number of cases

Table 1 - Demographic and clinical characteristics of all study participants.

Variables	Statistics (n=193)
Age (mean ± SD)	46.21 (±13.57)
Gender	
Male	34 (17.6%)
Female	159 (82.4%)
Final histopathology	
Benign	97 (50.3%)
Malignant	96 (49.7%)
Bethesda III subcategory	
Architectural atypia	89 (46.1%)
Cytologic atypia	65 (33.7%)
Cytologic and architectural atypia	30 (15.5%)
Hürthle cell AUS	9 (4.7%)

AUS: atypia of an undetermined significance, SD: standard deviation

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Table 2 - Malignancy rate in different Bethesda III subcategories.

Bethesda III Subcategory	Benign (n=97)	Malignant (n=96)	*P*-value	PTC (n=83)	FTC (n=13)
Architectural atypia	44 (49.4%)	45 (50.6%)	0.240	36 (80.0%)	9 (20.0%)
Cytologic and architectural atypia	20 (66.7%)	10 (33.3%)		7 (70.0%)	3 (30.0%)
Cytologic atypia	29 (44.6%)	36 (55.4%)		35 (97.2%)	1 (2.8%)
Hürthle cell AUS	4 (44.4%)	5 (55.6%)		5 (100.0%)	0 (0.0%)

PTC: papillary thyroid carcinoma, FTC: follicular thyroid carcinoma, AUS: Atypia of an undetermined significance

may enhance the significance of our findings. Hürthle cell AUS were followed by AUS with cytologic atypia (AUS-C), although the difference was not statistically significant. Multiple studies have shown similar results, but with statistical significance. Zhao et al[13] reported that AUS-C had the highest risk of malignancy (92.6%), whereas Kim et al[14] reported a lower rate of malignancy in patients with cytological atypia (65.8%). Johnson et al[7] has suggested the separation of Bethesda III while reporting FNA into cytologic atypia and architectural atypia based on their conclusion that AUS-C has a higher risk of malignancy. Our study reported a high malignancy rate in architectural atypia, similar to that in cytologic atypia, as opposed to previously published articles that reported a low malignancy rate of architectural atypia. Moreover, the notable differences in malignancy rates between our study and that by Durmus et al[5] prompted a critical examination of the atypical classification criteria. Our findings of 50.6% malignancy for architectural atypia and 55.4% for cytological atypia contrast with those reported by Durmus. Durmus' subdivision into cytological subgroup revealed a 28.8% malignancy, whereas that into architectural atypia subgroup revealed 7.1% malignancy. These disparities underscore the need for standardized diagnostic criteria to improve accuracy and inform management strategies in pathology. The higher risk of malignancy in cytologic atypia suggests that FNA Bethesda III should be reported in different subcategories to facilitate clinical decision-making. Based on these results, surgeons can explain the risks of malignant nodules to their patients without the dilemma of repeated FNA, molecular testing, or diagnostic lobectomy.

Regarding risk factors, Liu et al[11] highlighted that over half of the AUS/FLUS nodules were malignant. They also identified the male gender, aspect ratio >1, microcalcification, and the BRAFV600E mutation as independent predictors of malignancy. Surgical treatment is recommended for AUS/FLUS nodules if any of these features are present. Sonographic features are also important predictors of AUS/FLUS findings. Huang et al[15] retrospectively analyzed 272 patients with surgically treated Bethesda category III nodules, and demonstrated that both microcalcification and shape were independent risk factors for malignancy.

The main limitation of this study was its design, which limited the study participants to those who underwent surgical resection based on other clinical and radiological indications. The strength of this study was that all FNA and final histopathological slides were read by the same consultant pathologist. Further prospective studies with larger sample sizes are warranted to draw stronger conclusions.

In conclusion, Bethesda III thyroid nodules presents with challenging clinical decisions. Our study and similar other studies show a higher risk of cytologic atypia; therefore, sub-classification should be taken into consideration to ease clinical decisions and communication between different specialties.

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