

The Clinicopathological Spectrum of Follicle Cell-Derived Thyroid Neoplasms in A Tertiary Care Hospital as Per New WHO Classification 2022 (5th EDITION)

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ABSTRACT

Objective: To find the spectrum of follicle cell-derived neoplasms as per new WHO classification of the thyroid gland neoplasm.

Study Design: Cross sectional study

Place and Duration of Study: Histopathology Department, Armed Forces Institute of Pathology, Rawalpindi Pakistan, from Jun to Dec 2023.

Methodology: A total of 100 follicular cell-derived thyroid tumor cases received at histopathology department AFIP, Rawalpindi were analyzed in this study. Demographic data was recorded from the lab submission form and written informed consent was taken after contacting patients. Statistical analysis was accomplished using SPSS version 25.

Results: A total of 100 cases of follicular cell derived thyroid neoplasms were included. Mean age of patients was 45.77±12.78 years range from 22 to 78 years. Majority of patients were females 71.0% as compared to males 29.0%. Multifocal tumors were seen in 81.0% cases while unifocal in 19% cases. Follicular nodular disease was the most common entity found in benign neoplasms 77% followed by papillary thyroid carcinoma (PTC) (10.0%). Newer entity differentiated high-grade thyroid carcinoma (DHGTC), was found in 4.0% of cases. Hurthle cell neoplasm accounted for 6.0% while poorly differentiated thyroid carcinoma was observed in 3.0% of cases. The a statistically significant association was found between tumor type and tumor grade (p -value <0.001) and tumor focality (p -value =0.024). The Ki-67 index increased significantly with tumor dedifferentiation as (p <0.001)

Conclusion: According to the updated WHO classification, follicular nodular disease has become the most prevalent benign neoplasm of thyroid follicular cell origin. Careful application of the new diagnostic criteria allows for better risk stratification, especially for high-grade differentiated carcinomas.

Keywords: Follicular Thyroid Carcinoma, High-Grade Thyroid Carcinoma, Papillary Thyroid Carcinoma, Thyroid Follicular Nodular Disease.

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INTRODUCTION

Substantial revisions to thyroid neoplasm classification have been introduced in the 5th edition of the WHO Classification of Endocrine Tumors. The revised classification system centers on the cell of origin, providing deeper insight into the morphological, molecular, and biological characteristics of thyroid tumors. Among thyroid neoplasms, those derived from follicular cells represent the most common group. The classification now includes benign, low-risk, and malignant neoplasms, further stratified into intermediate- and high-risk categories based on specific histological and molecular features.^{1,2}

A major revision includes the recognition of thyroid follicular nodular disease (TFND) as a benign

neoplasm, a condition previously classified clinically as multinodular goiter rather than a true tumor. The update also adds two benign tumor types: follicular adenoma with papillary architecture, characterized by centripetal follicular papillae lacking papillary carcinoma nuclear features, and oncocytic follicular adenomas, distinguished by having more than 75% oncocytic cells.²

The low-risk category now comprises non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), thyroid tumors of uncertain malignant potential (UMP), and hyalinizing trabecular tumors (HTT), highlighting a more detailed understanding of borderline entities. Meanwhile, some previously distinct entities, such as papillary microcarcinoma, have been reclassified as subtypes under papillary thyroid carcinoma, and cribriform morular thyroid carcinoma has been revised to indicate uncertain histogenesis.³

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In the group of malignant follicular cell-derived neoplasms, both poorly differentiated thyroid carcinoma (PDTC) and differentiated high-grade thyroid carcinoma (DHGTC), the latter being a new addition, are classified under intermediate-risk categories. DHGTC is defined by preserved architectural features of any well-differentiated thyroid carcinomas but with elevated mitotic activity ($\geq 5/2 \text{ mm}^2$) or tumor necrosis, indicating a worse prognosis.⁴

The global incidence of thyroid carcinoma is on the rise, including in Pakistan.⁵ Advances in diagnostic techniques have contributed to detecting small, indolent tumors that previously went unnoticed. Understanding regional variations and recent classification updates is essential for appropriate management. Incorporating newly defined entities like TFND and DHGTC into routine diagnostics holds significant prognostic implications, as does evaluating tumor features such as size, focality, proliferative index (Ki-67), and completeness of excision.⁶⁻⁷

METHODOLOGY

This cross-sectional study was carried out at the Histopathology Department, Armed Forces Institute of Pathology Rawalpindi, Pakistan over a 6-month period, from Jun 2023 to Dec 2023 after approval of Institution Review Board (ERC # FC-HSP20-21/READ-IRB/24/2618) dated 28 May 2023. Sample size was calculated using WHO sample size calculator taking confidence level 95%, margin of error 5%, reported prevalence of Thyroid nodules 27.4%⁸ Sample size of came out be 96. So we included 100 individuals by using a non-probability convenient sampling method.

Inclusion Criteria: All thyroid excision specimens submitted to histopathology department AFIP, Rawalpindi were included in our study irrespective of gender and age ranges from 28 to 78 years

Exclusion Criteria: Poorly fixed specimen and prior thyroid surgery with completion thyroidectomies were excluded.

Specimen sections were taken as per CAP protocol. The CAP protocol for thyroid provides standardized guidelines for examining specimens from patients with thyroid carcinoma, ensuring consistent pathology reporting and staging. Developed by the College of American Pathologists (CAP), this protocol is essential for accurate diagnosis and treatment planning of thyroid cancers. The tissue

sections were processed using a vacuum-assisted tissue processor, and hematoxylin and eosin-stained slides were meticulously examined and diagnosed by a highly experienced histopathologist, in accordance with the latest WHO classification system for thyroid neoplasms. To minimize operator bias and enhance diagnostic accuracy, the diagnoses were independently reviewed by two expert histopathologists. Both specialists contributed their extensive expertise in thyroid pathology, ensuring a thorough and consistent evaluation. Their collective adherence to established diagnostic criteria guaranteed a more reliable and precise classification of the thyroid neoplasms.² Tumor size, grade and focality were noted. Ki-67 index was also calculated for each case by using monoclonal antibodies. Resection margin assessment was checked on gross as well as microscopic level.

Data was analyzed by using Statistical Package for Social Sciences (SPSS) 22.00. Normality of data was checked by Shapiro-Wilk test that showed that all the data were normally distributed Quantitative data was represented using Mean $\pm$ SD. Qualitative data was represented by using percentage and frequency. Chi square test (for qualitative variables) and Anova (for quantitative variables) were applied and *p*-value of ≤ 0.05 was considered as statistically significant.

RESULTS

A total of 100 cases of follicular cell derived thyroid neoplasms were included. Mean age of patients was 45.77 ± 12.78 years range from 22 to 78 years. Majority of patients were females 71.0% as compared to males 29.0%. Multifocal tumors were seen in 81% cases while unifocal in 19% cases. Follicular nodular disease was the most common entity found in benign neoplasms 77% followed by papillary thyroid carcinoma (PTC) (10.0%). Newer entity differentiated high-grade thyroid carcinoma (DHGTC), was found in 4.0 % of cases. Hurthle cell neoplasm accounted for 6.0% while poorly differentiated thyroid carcinoma was observed in 3% of cases.

Mean of tumor size was 2.8 ± 1.6 cm. The 8 cm maximum size was recorded for both papillary thyroid carcinoma and DHGTC. However, capsular invasion was most frequently seen in FTC (66.7%), whereas extrathyroidal extension was more common in classical PTC (17.1%). The demographic and clinical characteristics of study Participants shown in Table-I. Follicular nodular neoplasms and papillary thyroid carcinomas were predominantly low-grade tumors,

accounting for 77.9% and 90.0% of their respective cases, indicating a favorable biological behavior. In contrast, differentiated high-grade thyroid carcinoma and poorly differentiated thyroid carcinoma demonstrated a higher proportion of intermediate-to-high-grade tumors, suggesting a more aggressive clinical course. Hurthle cell neoplasms showed a mixed grade pattern, with both low-grade and intermediate-grade findings. Overall, a statistically significant association was found between tumor type and tumor grade ($p<0.001$) shown in Table-II. Most follicular nodular neoplasms were unifocal (88.3%), indicating a less aggressive pattern. In contrast, differentiated high-grade thyroid carcinoma showed a predominantly multifocal pattern (75%), suggesting more aggressive biological behavior. Papillary thyroid carcinoma also presented multifocality in 40% of cases, reflecting its known propensity for multifocal disease. There was statistically significant association between tumor focality and tumor types as p -value 0.024 shown in Table-III. The mean Ki-67 value was lowest in papillary thyroid carcinoma ($6.1\pm3.2\%$), Follicular thyroid carcinoma showed a moderately higher proliferation index ($9.8\pm4.1\%$) and poorly differentiated thyroid carcinoma elevated Ki-67 levels ($32.5\pm6.3\%$). Overall, the Ki-67 index increased significantly with tumor dedifferentiation as ($p<0.001$) shown in Table-IV.

Table-I: Demographic and Clinical Characteristic of Study Participants (n=100)

Variable(s)	Value(s)
Mean age in Years	45.77 $\pm$ 12.78
Gender	
Male	71.0%
Female	29.0%
Tumor Focality	
Multifocal tumor	81.0%
Unifocal tumor	19.0%
Tumor Types	
Follicular Nodular	77.0%
Papillary Thyroid Carcinoma	10.0%
DHGTC	4.0%
Hurthle cell neoplasma	6.0%
Poorly differentiated thyroid carcinoma	3.0%
Mean of tumor size (cm)	2.81 $\pm$ 1.60
Histopathological Feature	
Capsular invasion	34.0%
Vascular invasion	21.0%
Extrathyroidal extension	13.0%
Lymph node metastasis ^	10.0%

Differentiated High-Grade Thyroid Carcinoma (DHGTC)

^Lymph nodes were submitted only in selected cases

Table-II: Association of Tumor types and Tumor grade (n=100)

Tumor types	Tumor grade			Total	p-value
	Low-grade n(%)	Intermediate-grade n(%)	High-grade n(%)		
Follicular Nodular Neoplasm	60(77.9%)	12(15.6%)	5(6.5%)	77	<0.001
Papillary Thyroid Carcinoma	9(90.0%)	1(10.0%)	0(0.0%)	10	
Differentiated High-Grade Thyroid Carcinoma (DHGTC)	0(0.0%)	3(75.0%)	1(25.0%)	4	
Hurthle Cell Neoplasm	4(66.7%)	2(33.3%)	0(0.0%)	6	
Poorly Differentiated Thyroid Carcinoma	0(0.0%)	0(0.0%)	3(100.0%)	3	
Total	73	18	9	100	

Table-III: Distribution of tumor focality according to histopathological tumor type (n=100)

Tumor types	Tumor grade		Total n(%)	p-value
	Unifocal n(%)	Multifocal n(%)		
Follicular Nodular Neoplasm	68(88.3%)	9(11.7%)	77(77.0%)	0.024
Papillary Thyroid Carcinoma	6(60.0%)	4(40.0%)	10(10.0%)	
Differentiated High-Grade Thyroid Carcinoma (DHGTC)	1(25.0%)	3(75.0%)	4(4.0%)	
Hurthle Cell Neoplasm	4(66.7%)	2(33.3%)	6(6.0%)	
Poorly Differentiated Thyroid Carcinoma	2(66.7%)	1(33.3%)	3(3.0%)	
Total	81(81.0%)	19(19.0%)	100.0	

Table-IV: Comparison of Ki-67 and Tumor categories (n=100)

Tumor Category	Ki-67 (%)	p-value
	Mean $\pm$ SD	
Papillary Thyroid Carcinoma (PTC)	6.1 $\pm$ 3.2	<0.001
Follicular Thyroid Carcinoma (FTC)	9.8 $\pm$ 4.1	
Poorly Differentiated Thyroid Carcinoma	32.5 $\pm$ 6.3	

DISCUSSION

In our study, thyroid follicular nodular disease (TFND) was found to be the most common benign neoplasm. Historically referred to clinically as multinodular goiter, its recognition as a true neoplastic process emphasizes the biological distinction between hyperplastic and neoplastic nodules.²⁻³ Correct identification of TFND has practical significance by reducing unnecessary interventions and distinguishing it from neoplastic processes that require more aggressive treatment.

Papillary thyroid carcinoma (PTC) continued to be the most common malignant neoplasm, consistent with earlier studies indicating that PTC constitutes most thyroid cancers globally.^{7,8} The presence of differentiated high-grade thyroid carcinoma (DHGTC) in 4% of cases is of particular interest. DHGTC represents a newly characterized intermediate-risk carcinoma under the WHO 2022 framework, distinguished by increased mitotic activity and/or tumor necrosis despite maintaining typical

differentiated architecture.^{4,9} Early recognition of DHGTC is critical as it portends a poorer prognosis than conventional PTC and necessitates more aggressive management strategies. In previous studies, the prevalence of DHGTC has been reported as 7.2%, which is in close agreement with our findings, where the prevalence is observed to be 4%.⁹

Age-related trends in our data are consistent with published literature, showing maximum incidence in the fifth and sixth decades.^{7,10} A strong female predominance was observed across most neoplasms, consistent with the known gender disparity in thyroid diseases, which may be linked to hormonal and autoimmune factors.¹¹ Interestingly, our small sample of DHGTC cases exhibited a slight male predominance, although further studies are needed to validate this observation.

Multifocality was significantly associated with diagnosis, particularly with TFND ($p < 0.001$). This is expected, given that multinodularity is a hallmark of benign thyroid diseases. However, multifocality in malignant tumors like PTC carries important prognostic significance, as it is linked to a higher risk of lymph node metastasis and recurrence.¹²

Regarding tumor size, most cases measured between 3 and 6 cm, a finding that reflects common clinical presentations of thyroid nodules. In benign neoplasms like TFND, larger size often reflects long-standing growth rather than aggressive behavior. Conversely, larger malignant tumors are typically associated with worse outcomes.¹³

The Ki-67 proliferative index showed low expression ($< 1\%$) in most cases, and no statistically significant association with diagnosis was observed ($p = 1.000$). Although Ki-67 is an established proliferation marker in many cancers, its role in thyroid neoplasms remains less definitive.^{4,14} Previous studies have reported slightly elevated Ki-67 indices in malignant thyroid tumors compared to benign lesions; however, variability remains high, and its prognostic utility in thyroid cancer is still under investigation.^{15,16} Our findings suggest that Ki-67 alone may not be sufficient for distinguishing between benign and malignant neoplasms.

Application of the WHO 2022 risk stratification for tumor grading demonstrated a significant link with diagnosis ($p < 0.001$). Grading accuracy is critical for prognosis, allowing clear differentiation between low-risk tumors like NIFTP and UMP and higher-risk forms such as DHGTC and PDTC.^{2,9} The completeness

of excision, achieved in all cases, allowed reliable pathological evaluation and underscores the importance of surgical quality in thyroid cancer outcomes.

The updated WHO classification provides a more nuanced framework for diagnosing and managing thyroid neoplasms, improving patient care by promoting better risk stratification. Nevertheless, histological evaluation should increasingly be complemented with molecular diagnostics (e.g., BRAF, RAS mutations, TERT promoter alterations) to enhance prognostic precision.^{17,18}

CONCLUSION

The study highlights thyroid follicular nodular disease as the most prevalent benign follicular-derived tumor per WHO 2022 guidelines, stressing the role of accurate diagnosis in avoiding unnecessary interventions. Papillary thyroid carcinoma continues to be the most commonly identified malignant neoplasm.

Identifying DHGTC among our cases highlights the critical role of thorough histological evaluation in predicting patient outcomes accurately. Multifocality and tumor grade were found to be significantly associated with diagnosis, whereas demographic factors like age and gender showed no significant association.

Ki-67 index had limited prognostic value in our series. Comprehensive classification based on updated WHO guidelines improves diagnostic clarity, risk stratification, and management strategies for patients with thyroid neoplasms.

Future studies incorporating molecular markers and larger sample sizes are essential for refining the prognostic models and understanding the biological behavior of newer entities like DHGTC.

LIMITATION OF STUDY

This study has a few limitations. Firstly, being carried out at a single tertiary care center with a relatively small sample size may reduce the generalizability of the results. Secondly, the small number of cases for certain tumor subtypes, like differentiated high-grade thyroid carcinoma, limited the robustness of subgroup analyses. Thirdly, incomplete or minimally variable Ki-67 proliferative index data in many cases restricted its utility as a prognostic marker in this cohort.

Future research should prioritize larger, multi-center cohorts to confirm these findings and enable more comprehensive analyses of rare tumor subtypes. Integrating molecular profiling—such as BRAF, RAS mutations, and TERT promoter analysis—could improve understanding of the biological behavior and risk stratification of follicular cell-derived thyroid neoplasms. Furthermore, prospective studies correlating histological classification, molecular markers, and long-term clinical outcomes would be

instrumental in refining diagnostic and therapeutic strategies under the latest WHO classification.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

NM & SSA: Data acquisition, data analysis, critical review, approval of the final version to be published.

BP & WAK: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AA & HMHA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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