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HISTOPATHOLOGICAL REVIEW AND RE-CATEGORIZATION OF THYROID MALIGNANCIES BASED ON WHO CLASSIFICATION OF ENDOCRINE TUMORS, 2022

Pathomorphology

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ABSTRACT

Thyroid cancer (TC) is the commonest endocrine malignant tumor whose incidence has been increasing steadily for decades in the world. This alarming rise in the incidence of thyroid malignancies, even in the face of low and stable and mortality rates is thought to be predominantly driven by overdiagnosis; notably evident in the case of papillary thyroid tumors. This has led to otherwise indolent tumors being aggressively managed causing potential harms to patients and levying unnecessary costs on an already overburdened healthcare system. The 5th edition of the World Health Organization (WHO) classification of endocrine tumors, released in 2022, has introduced several changes to the nomenclature, grading and prognostication of thyroid proliferations based on pathologic features and molecular profile that can help in improving risk stratification by categorizing tumors based on histological and molecular characteristics, thereby reducing the burden of diagnosis of incidental and indolent lesions, as well as de-escalate the treatment. The present study attempts to review the histopathological diagnosis of all previously reported thyroid neoplasms at our institution and reclassify them according to the recently updated criteria.

KEYWORDS

Thyroid cancer (TC), WHO Classification, PTC, FTC, MTC, NIFTP, FT-UMP, WD-UMPs, IEFV-PTC, PDTC, DHGTC, risk stratification, overdiagnosis

INTRODUCTION:

Thyroid cancer (TC) is the commonest endocrine malignant tumor whose incidence has been increasing steadily for decades in the world.[1] The incidence of thyroid cancer in India is 5.4 per lakh population, with papillary thyroid cancer being the most common variant.[2] The 5th edition of the World Health Organization (WHO) classification of endocrine tumors, released in 2022, has introduced several changes to the nomenclature, grading and prognostication of thyroid proliferations based on pathologic features and molecular profile that are essential for clinical risk stratification and prognosis.[3,4] It categorizes thyroid neoplasms originating from follicular cells, according to prognostic risk categories, into benign, low-risk and malignant neoplasms.[3,4,5] The new classification also emphasizes the need to classify papillary thyroid carcinoma based on histo morphological features rather than tumor size, so that small papillary microcarcinomas (<1cm in size) may not be erroneously treated as low-risk disease.[3,4,5] Additionally, it introduces a grading system to differentiate indolent from aggressive thyroid tumors.[3,4,5] The present study attempts to perform a histopathological review of all thyroid neoplasms previously diagnosed in our institute according the criteria outlined in 4th edition of the World Health Organization (WHO) classification of endocrine tumors, 2017[6] and attempt to reclassify them as per the recently updated criteria.

MATERIALS AND METHODS:

46 cases of thyroid carcinomas reported in the Department of Pathology, Chhattisgarh Institute of Medical Sciences (CIMS), Bilaspur were between 2016 to 2023 were reevaluated retrospectively. Tumors were initially classified based on the 2017 WHO classification of thyroid neoplasms (4ed). Subsequently, histopathology slides from each of the diagnosed cases were retrieved from the archives and subjected to a histopathological review based on the following criteria:

- Architectural pattern- papillary, follicular, cribriform, trabecular, insular, solid
- Predominant cell type- papillary, follicular, tall cell, hobnail cell, oncocytic, squamous, undifferentiated, anaplastic
- Nuclear features- Orphan Annie Eye (ground glass) appearance; nuclear grooving, folding, convolution; nuclear pleomorphism
- Mitotic Index[3]-
- <3/2mm^2(10HPF), >3/2mm^2(10HPF)- for poorly differentiated thyroid carcinoma (PDTC)
- >5/2mm^2(10HPF)- for differentiated high-grade thyroid carcinoma (DHGTC)
- Encapsulation- complete, partialInvasion[3]- minimally invasive, encapsulated angioinvasive, widely invasive
- Tumor necrosis- present, absent

After re-evaluating the slides based on the aforementioned histological features, the tumors were reclassified in accordance with the 2022 World Health Organization (WHO) classification of thyroid neoplasms (5ed) and prognosis reassessed.

Observation:

Table 1. Thyroid Malignancy Categorization based on the 2017 WHO Classification of Thyroid Neoplasms (4ed)

Sl. No.	Type	Male	Female	Total
1.	Papillary Carcinoma	02	38	40
	• Classical Variant			14
	• Follicular Variant			23
	• Solid Variant			02
	• Cribriform-Morular Variant			01
2.	Follicular Carcinoma	00	01	01
3.	Medullary Carcinoma	00	02	02
4.	Poorly Differentiated Carcinoma	01	02	03
Total		03	43	46

Table 2. Categorization of cytoarchitectural features

Sl. No.	Architectural Pattern	With papillary nuclear features	Without papillary nuclear features	No. of cases
1.	Follicular	23	02*	25*
2.	Papillary	14	00	14
3.	Insular/trabecular/solid	02	03	05
4.	Cribriform-Morular	01	00	01
5.	Medullary	00	02*	02*
	Total	40	06	46

*1 case with mixed follicular- medullary features

Table 3. Categorization of encapsulation

Sl. No.	Histomorphology (as per 2017 Classif.)	Encapsulation		Total cases
		Complete	Incomplete	
1.	Papillary	25	15	40
2.	Follicular	00	01	01
3.	Medullary	00	02	02
4.	Poorly Differentiated	00	03	03
	Total	25	21	46

Table 4. Categorization of invasiveness

Sl. No.	Histomorphology (as per 2017 Classif.)	Non invasive	Minimally Invasive	Encapsulated Angio-invasive	Widely Invasive	Total cases
1.	Papillary	25	03	00	12	40
2.	Follicular	00	00	01	00	01
3.	Medullary	00	01	01	00	02
4.	Poorly Differentiated	00	00	00	03	03
	Total	25	04	02	15	46

Table 5. Categorization of mitotic index

Sl. No.	Histomorphology (as per 2017 Classif.)	Mitotic Index			Total cases
		<3/2mm2 (10HPF)	>3/2mm2 (10HPF)	>5/2m2 (10HPF)	
1.	Papillary	34	02	04	40
2.	Follicular	00	01	00	01
3.	Medullary	00	01	01	02
4.	Poorly Differentiated	00	01	02	03
	Total				46

Table 6. Thyroid malignancy recategorization based on the 2022 WHO Classification of Thyroid Neoplasms (5ed)

CATEGORIES	Classification	No. of cases
Low-risk Follicular Cell-Derived Thyroid Neoplasms	Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP)	25
	Follicular Thyroid Tumors of Uncertain Malignant Potential (FT-UMPs)	02
	Well-Differentiated Tumors of Uncertain Malignant Potential (WD-UMPs)	01
Follicular Cell-Derived Malignant Neoplasms	Follicular Thyroid Carcinoma (FTC)	01
	Invasive Encapsulated Follicular Variant Papillary Thyroid Carcinoma (IEFV-PTC)	00
	Papillary Thyroid Carcinoma (PTC)	11
	• Classic subtype	03
	• Follicular subtype	06
	• Solid subtype	02
High-grade Follicular-derived Carcinomas	Poorly differentiated thyroid carcinoma (PDTC)	02
	Differentiated high-grade thyroid carcinoma (DHGTC)	01
Thyroid C-Cell-Derived Carcinoma	Medullary Thyroid Carcinoma (MTC)	01
	Mixed Medullary and Follicular Cell-Derived Carcinomas	01
Tumors of Uncertain Histogenesis	Cribriform-Morular Carcinoma	01
Total		46

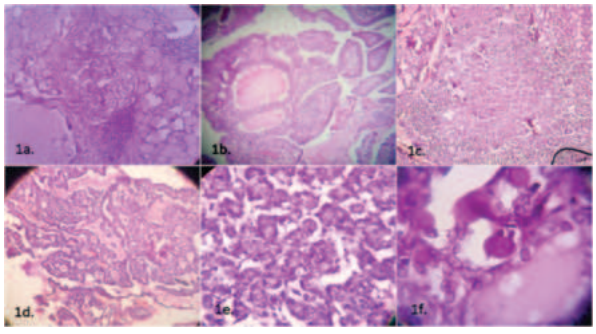

Fig.1. a. Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP); b. Papillary Thyroid Carcinoma (PTC)- classic subtype; c. d. PTC- follicular subtype; e. PTC – 'Orphan Annie Eye' nuclei, f. PTC- Psammoma Body

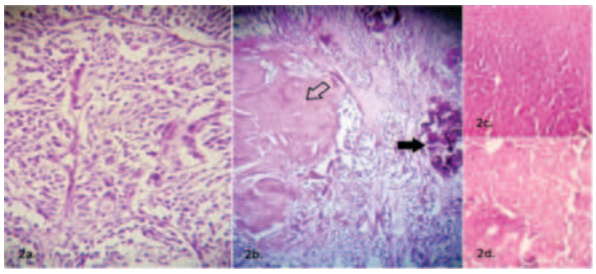

Fig.2. a. Medullary Thyroid Carcinoma(MTC) - spindle cells, nested growth pattern; b. MTC- amyloid deposits (open arrow), calcification (black arrow); c. Poorly Differentiated Thyroid Carcinoma (PDTC); d. Cribriform-Morular Carcinoma

DISCUSSION:

Thyroid cancer is the most common malignancy of the endocrine system[7] and has been showing a rising incidence in developing countries like India.[8] Thyroid malignancies show a strong female preponderance, with most populations having a significantly higher incidence in women than in men.[9] Highest incidences are seen in the 31-40, followed by 41–50-year age groups.[10,12] Both the aforementioned patterns were reflected in our study as well; with 43 (93.4%) out of 46 patients being female, and 67.5% (n=31) of them presenting at 21-40 years, followed by 19.5% (n=9) at 41-60 years; whereas only 6.5%.

Conventionally, thyroid malignancies have been classified on the basis of cell of origin. Differentiated thyroid neoplasms (DTC) arise from the thyroid follicular cells and comprise papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), and Hurthle cell cancers which account for 90-95% of all thyroid malignancies.[13] PTC is the most common endocrine cancer, responsible for 96% of all new and 66.8% of endocrine cancer deaths.[14] Medullary thyroid carcinoma (MTC) accounts for around 1 to 2%, and anaplastic thyroid carcinoma accounts for less than 1% of all thyroid cancers.[13]

In concordance with this, PTC was the commonest thyroid malignancy diagnosed at our institution (n=40). However, upon applying the WHO 2022 diagnostic criteria and reviewing the cases again, 28 cases could be reclassified as Low-risk Follicular Cell-Derived Thyroid Neoplasms with 25 cases satisfying the diagnostic criteria for Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) due to complete encapsulation, low mitotic activity (<3/2mm^2) and lack of any evidence of capsular or vascular invasion.[3,4,5,15] 2 cases showed partial-to-complete encapsulation with evidence of capsular invasion and even the formation of a second capsule beyond the infiltrating tumor seen in 1 case. However, equivocal papillary nuclear features were not evident in either, causing them to be reclassified as Follicular Thyroid Tumors of Uncertain Malignant Potential (FT-UMPs).[5,15,16] A single case showing definitive features of PTC, but with complete encapsulation and invasion only through the partial thickness of the capsule was reclassified as Well-Differentiated Tumor of Uncertain Malignant Potential (WD-UMP).[5,15,16,17]

Out of the Follicular Cell-Derived Malignant Neoplasms, 11 cases were diagnosed as Papillary Thyroid Carcinoma (PTC) based on the presence of the characteristic nuclear features like finely granular chromatin ("Orphan Annie-eyed" nuclei), nuclear grooving and intranuclear inclusion bodies along with varied degrees of unequivocal capsular and/or vascular invasion.[13,18] For the purpose of subclassification of PTCs, the term *"variant"* was eschewed in favor of *"subtype"* as per the recommendation of the 2022 WHO Classification of Thyroid Neoplasms (5ed).[4,5,19] Accordingly, 6 cases previously reported as "follicular variant of papillary carcinoma" were redesignated as Papillary Carcinoma Thyroid (PTC), Follicular Subtype. 3 were categorized as the Classic Subtype because of the diagnostic papillary architecture with fibrovascular cores and presence of psammoma bodies.[18] 2 cases containing >50% insular and solid growth patterns were designated as PTC, Solid subtype. 1 case previously diagnosed as Cribriform-Morular Variant of PTC, was now put into the separate category of Cribriform-Morular Carcinoma as these tumors do not arise from follicular cells and are presumed to be of

unknown histogenesis.[3,4,5] However, none of the cases satisfied the diagnostic criteria for Invasive Encapsulated Follicular Variant Papillary Thyroid Carcinoma (IEFV-PTC).[5]

In a stark deviation from most studies, we found only a single case of Follicular Thyroid Carcinoma (FTC) in our series. Even though most studies from India and abroad have found FTC to be the next commonest thyroid malignancy after PTC, [10,13,20,21] our findings may still be in concordance with the opinion of Sobrinho-Simões et al[22] that regardless of the differences from series to series, *bona fide* FTC has become relatively rarer nowadays in contrast to its high frequency in the first half of last century.[22,23]

The 3 High-grade Follicular-derived Carcinoma cases previously diagnosed as Poorly Differentiated Carcinoma were reevaluated as per Turin criteria, also adopted by the WHO Committee (absence of PTC-like nuclear features, tumor having a solid/ trabecular/insular morphology, invasive growth pattern, along with at least one of the following characteristics: convoluted nuclei, ≥3 mitosis/2mm^2 or 10 HPF, and tumor necrosis).[3,4,5,19] Upon review, only 2 out of 3 cases satisfied the aforementioned criteria, while the 3rd was redesignated as Differentiated High Grade Thyroid Carcinoma (DHGTC) due to parts of tumor showing mixed papillary, solid and oncocytic morphology, but with high grade of pleomorphism, brisk mitotic activity (>5 MF/2mm^2- previously 10HPF) and tumor necrosis at the same time.[3,4,5,19] This case also happened to be the only male patient having a high-grade thyroid carcinoma, giving credence to the fact that DHGTCs show a higher predominance in males.[24]

Finally, the 2 cases of Medullary Thyroid Carcinoma were reviewed and graded as per the recommendation of the 2022 WHO Classification system. Both the Thyroid C-Cell-Derived Carcinomas were categorized as Low grade owing to <5MF/10HPF and absence of necrosis.[3,4,5] Only 1 tumor was designated as Classical Medullary Carcinoma Thyroid (MTC) due presence of diagnostic histomorphological features; namely, the characteristic "salt-and-pepper" chromatin of neuroendocrine tumors, a nesting growth pattern, deposition of amyloid and stromal calcification.[25,26] However, the 2nd tumor showed significant areas of follicular differentiation with non-neuroendocrine chromatin morphology along with classical MTC-like areas. This case was therefore reindexed as Mixed Medullary and Follicular Cell-Derived Carcinoma.[3,4,5]

CONCLUSION:

The alarming rise in the incidence of thyroid malignancies, even in the face of low and stable and mortality rates is thought to be predominantly driven by overdiagnosis, notably evident in the case of papillary thyroid tumors; where overdiagnosis has spuriously pushed up the incidence by 60-90% in some countries.[9,10,11,27] causing potential harms to patients and levying unnecessary costs on an already overburdened healthcare system.[10] The 2022 WHO Classification, therefore, can help in improving risk stratification by categorizing tumors based on histological and molecular characteristics[3,4,19] and can reduce the burden of diagnosis of incidental and indolent lesions, as well as de-escalate the treatment.[27]

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