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Systematic Review Article

Cytomorphological Features of Papillary Thyroid Carcinoma Variants: A Systematic Review

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Abstract
Papillary thyroid carcinoma (PTC) is the most common malignancy of the thyroid gland. It exhibits significant histological and cytological heterogeneity, with various recognized variants. This systematic review aims to provide a comprehensive analysis of cytological findings in different variants of PTC A systematic literature search was conducted in major databases, including PubMed, Embase, and Cochrane, using predefined inclusion and exclusion criteria. Relevant studies that reported cytological findings of PTC variants were included. Data extraction and quality assessment were performed for each selected study. The results highlighted the morphological features of various PTC variants, including classical, follicular, tall cell, oncocytic, diffuse sclerosing, cribriform etc. Cytological features unique to each variant were analyzed, including architectural patterns and specific nuclear characteristics. In conclusion, this systematic review provides a comprehensive analysis of cytological findings in different variants of PTC. The distinct cytological features can aid in the accurate diagnosis and classification of PTC variants, facilitating appropriate management and treatment decisions. Further research and validation of these findings are warranted to enhance the understanding and clinical utility of such cytological assessment.

Keywords: Cytology, carcinoma, papillary thyroid carcinoma, malignancy, thyroid, variants

INTRODUCTION
Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, accounting for about 80% of all thyroid cancers. PTC has several variants, each with unique clinico-pathological features. The aim of this systematic review is to summarize the cytological findings of PTC variants.

METHOD: The Preferred Reporting Items for Systematic Reviews (PRISMA) and Meta-analysis statement served as the instructions for conducting this systematic review. Since all the information was gathered from previously published studies, neither patient permission nor ethical clearance was required.

Search strategy: A systematic literature search was performed in PubMed, Embase, and Cochrane Library databases up to April 2023.

Inclusion criteria: Those studies which reported the cytological findings of PTC variants were included in the review. The following keywords were used: "papillary thyroid carcinoma," "cytology," "variant," "cytological features," "FNAC" and "fine-needle aspiration."

Exclusion criteria: Studies that met one of the following criteria were excluded: abstracts, conference abstracts, letter or comments to the editor, or studies on animals and articles with no free full text.

RESULTS:
A total of 3649 studies were recorded on various databases pertaining to papillary thyroid carcinoma. Of which, 1146 studies were found to be relevant as per our inclusion criteria after further refinement of the results. A total of 396 studies had free full text. Finally, 81 studies, fulfilling all the above mentioned relevant inclusion criteria, were included in the review, comprising a total of 1111 patients with PTC. The most common PTC variant was classical PTC, followed by follicular variant PTC, tall cell variant PTC, and oncocytic variant PTC. The cytological features of classical PTC included the presence of papillary structures, nuclear grooves, intranuclear inclusions, and

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psammoma bodies. Follicular variant PTC showed similar features to follicular adenoma, including microfollicular and trabecular arrangements with scant colloid. The tall cell variant PTC had elongated cells with clear cytoplasm and distinct cell borders, while the oncocytic variant PTC showed abundant eosinophilic cytoplasm and prominent nucleoli. A summary of the findings noted in various studies have been incorporated in Table 1.

Table 1: Cytological features of morphologic variants of papillary thyroid carcinoma

Study	Variant	Cytological Findings
Kini et al.[1] (1980)	Classical	Papillary structures with or without central fibrovascular core, fine powdery to granular chromatin, nuclear grooves, intranuclear inclusions, and psammoma bodies
Kim et al.[2] (1997)	Oxyphilic	Papillary clusters with or without core, round to polygonal cells, abundant granular cytoplasm, fine powdery chromatin
Ohori et al.[3] (2010)	Classical	Nuclear grooves, intranuclear inclusions, psammoma bodies, and nuclear enlargement
Ibrahim AA et al.[4] (2016)	Follicular	Microfollicular and trabecular arrangements with scant colloid, occasional microfollicles, and macrophages
Olson et al.[5] (2013)	Follicular	Round to cuboidal cells, microfollicular pattern, scant colloid, and thickened nuclear membranes
Yoon et al.[6] (2014)	Follicular	Microfollicular pattern, scanty pale cytoplasm, scant colloid, and nuclear enlargement
Wu et al.[7] (2018)	Tall Cell	Papillary without central cores, elongated cells with clear cytoplasm, distinct cell borders, and psammoma bodies
Kakudo et al.[8] (2015)	Tall Cell	Large polygonal, squamoid or hurthleiod cells, abundant dense cytoplasm, tall cells with nuclear enlargement and fine powdery to granular chromatin
Hirokawa et al.[9] (2016)	Tall Cell	Elongated cells with clear cytoplasm, nuclear atypia, and psammoma bodies
Lang et al.[10] (2016)	Oncocytic	Round to polygonal cells, abundant granular eosinophilic cytoplasm
Kakudo et al.[11] (2011)	Oncocytic	Round to polygonal cells, abundant eosinophilic cytoplasm
Moon et al. [12] (2012)	Warthin's-like	Papillae lined by large oncocytic cells with cores of dense lymphoplasmacytic infiltrate, cells with abundant eosinophilic cytolasm resembling hurthle cells.
Takagi et al.[13] (2014)	Diffuse Sclerosing	Solid cell balls and/or hollow balls containing lymphocytes; hobnail cells; septate cytoplasmic vacuoles; large unilocular vacuoles; squamous differentiation; abundant psammoma bodies; lymphocytic background; absence/ relative lack of characteristic nuclear features of papillary carcinoma.
Boonyaarunnate T et al.[14] (2013)	Cribriform-Morular	Cribriform pattern, dense cellular morules. papillary with or without central cores, monolayered sheets absent
Ohashi R. et al.[15] (2020)	Solid	Cohesive, syncytial or trabecular clusters accompanied by some discohesiveness in the absence of necrosis
Bongiovanni M et al.[16] (2017)	Columnar	Papillary structures lined by cells with pseudostratified nuclei. Paucity of nuclear pseudoinclusions& grooves
Lee et al.[17] (2017)	Cribriform	Papillary structures with prominent cribriform architecture, nuclear grooves and powdery to finely granular chromatin
Tabaqchali et al.[18] (2000)	Diffuse Sclerosing	Papillae uncommon, monolayered sheets, medium-sized round cells, diffuse sclerosing cytology

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DISCUSSION

The hallmark clinical signs of PTC include thyroid swelling with or without lymph node enlargement. However, it is not uncommon that PTC is diagnosed incidentally and patient may not have typical presentation. [1] In children also, the clinical presentation is generally similar to those in adults, although there are some differences. Children with PTC are more likely to have multifocal tumours and lymph node metastases than adults with PTC. The tumours in children are also more likely to be smaller and less aggressive than those in adults. There are several variants of PTC with different cytomorphological features as mentioned in above studies (Table 1). The prognostic significance of various variants of papillary thyroid carcinoma (PTC)has been summarized here:

1. Classical Variant: The most common variant of PTC with a good prognosis, with a 10-year survival rate exceeding95%. [1], [3]
2. Follicular Variant: This variant also generally has a good prognosis, with a 10-year survival rate exceeding 95%. [4], [5], [6]
3. Tall Cell Variant: This variant has a slightly worse prognosis than classical PTC, with a 10-year survival rate of around 85%. [7], [8], [9]
4. Oncocytic Variant: The prognosis for this variant is similar to that of classical PTC, with a 10-year survival rate exceeding95%. [2], [10], [11]
5. Warthin-like Variant: This variant may have a worse prognosis than classical PTC, with a 10-year survival rate of around 80%. [12]
6. Diffuse Sclerosing Variant: This variant may have a worse prognosis than classical PTC, with a 10-year survival rate of around 70-80%. [13], [18]
7. Cribriform-Morular Variant: This variant is rare, and the prognosis may depend on whether it is associated with familial adenomatous polyposis (FAP). In patients with FAP, the prognosis may be worse, with a higher risk of recurrence and metastasis. [14]
8. Solid Variant: This variant may have a worse prognosis than classical PTC, with a higher risk of recurrence and metastasis. [15]
9. Columnar Variant: This variant is rare, and the prognosis is not well established. [16]
10. Cribriform Variant: This variant is also rare, &the prognosis hasn't been well established. [17]

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer in children, accounting for approximately 50-60% of all paediatric thyroid cancers. PTC in children is on the rise, although the exact reasons for this are unclear.[1] The prognosis for PTC in adults and children are generally good, especially in children a 10-year survival rate exceeding 95% is recorded. However, there is a higher risk of recurrence in children than in adults, and long-term follow-up is necessary to monitor for recurrence. [1] Treatment of PTC in children is similar to that in adults and typically involves surgical removal of the thyroid gland (total thyroidectomy) followed by radioactive iodine therapy. However, the optimal management of PTC in children is still the subject of ongoing research, and there is debate about the use of radioactive iodine therapy in children.

CONCLUSION

The cytological findings of PTC variants differ from each other, and a correct diagnosis is important for appropriate management. One should be aware of these differences to optimize the diagnostic accuracy of fine-needle aspiration cytology in the evaluation of thyroid nodules suspicious for PTC. The final crux is that it is essential to recognise the distinctive cytological characteristics of each form of PTC in order to assess the prognosis and determine the best course of treatment. More studies are needed worldwide, so as to establish a dedicated classification system of papillary thyroid carcinoma variants as per the refined cytological criteria for the better and timely diagnosis of such a prevalent malignancy.

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