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# Clinicopathological Correlation in Comparision with Morphological Variants of Papillary Carcinoma of the Thyroid: A 3 Year Study in a Tertiary Care Center

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***Abstract:*** *Different histopathological patterns and variants of Papillary Carcinoma Thyroid have been reported to influence the prognosis of the patients. Fifty six cases of papillary carcinoma of the thyroid diagnosed at Govt .Stanley Medical college ,Department of pathology over a three year period were reviewed with the aim of identifying these variants. Forty three (76.8%) were classical papillary carcinoma. Five(8.9%) follicular variant, 4 (7.1%) micropapillary variant, 2 (3.6%) encapsulated variant, one case of oncocytic ,one case of warthin like variant were reported. The mean age at diagnosis was 37 years. Most common presentation was multinodular goiter followed by solitary nodule. In this study we reviewed the clinical presentation and the various histological patterns.*

***Keywords****: Histopathology, papillary carcinoma .*

## I. Introduction

Papillary thyroid carcinoma (PTC) is the most common type of malignant thyroid tumor constituting more than 70% of thyroid malignancies(1, 2).These common tumors tend to be biologically indolent and have an excellent prognosis. The annual incidence is about 3.7per 100,000 of the population (3).Most tumors were diagnosed in patients in the third and fifth decades (4,5). Women were affected more than men in a ratio of 2:1 to 4:1 (5).

Patients with PTC usually present with a palpable nodule in the thyroid which produce cold nodule on radioactive iodine scan(1,2). A few patients may present with cervical lymphadenopathy. Non-palpable nodules of PTC may be discovered incidentally after CT and MRI examination. The gross appearance of PTC can be quite variable most cases are solid, whitish, firm, and clearly invasive; fewer than 10% were encapsulated .Tumors were considered multifocal when two or more foci were found in one or both lobes. 10% of cases showed marked cystic changes. Sometimes the papillary formations were evident to the naked eye.

There were numerous histopathological variants of PTC of which classical PTC is the most common (80%).The conventional PTC shows a branching papillary architecture with central fibrovascular core (1,2) covered by cells with eosinophilic cytoplasm and enlarged oval nuclei with nuclear overlapping(10).The nuclei of papillary cancer have been described as clear, ground glass, empty, or Orphan Annie eyed(11,12).Clear nuclei are found in over 80% of such lesions, intranuclear inclusions in about 80–85%,and nuclear grooves are seen in almost all the cases.(13,14,15). Psammoma bodies that represent dystrophic calcifications, are usually present within the cores of papillae, stroma, or in lymphatic vessels, but not within the neoplastic follicles.As indicated in a recent investigation, new variants of PTC or other histological patterns may correlate with patient prognosis (9). In this study we have analyzed the clinicopathological features along with histopathological patterns in our tertiary care hospital.

## II. Materials And Methods

This retrospective study engaged every case of Papillary thyroid carcinoma which had been recorded in Department of pathology ,Govt Stanley Medical college for a period of three years from june 2011 to june 2014 .Fifty six cases of papillary carcinoma of the thyroid diagnosed based on histopathology were reviewed. Paraffin blocks along with Hematoxylin and eosin stained sections were available for review in all cases. Different histopathological patterns of papillary carcinoma along with additional histopathological features were analyzed. The patient's age and gender were noted along with the mode of clinical presentation and the presence or absence of lymph node metastases.

## III. Results

A retrospective analysis of 56 papillary thyroid carcinomas were made in order to sub classify them into their morphological variants(Table-1).

In all cases the gross appearance was solid, whitish, firm( Figure-1 &2).Two cases showed cystic degeneration & one case showed calcification (Figure-3). Of these 56 cases, the commonest histopathological variant were classical papillary carcinomas(76.8%)(Figure-4 &5), followed by follicular variant (8.9%) (Figure-6).

Papillary microcarcinomas were defined as tumors with less than 1.0 cm in diameter on histological examination. In our study 4 cases(7.1%) showed micropapillary pattern (Figure-7).In addition we also found 2 cases (3.6%) of encapsulated variant ,1 case (1.8%) of oncocytic and warthin like variant(Figure-8) in our study.

In the present study the mean age at diagnosis for papillary carcinoma was 37 years ranges from 16-70.There were 11 male and 45 female patients with the female to male ratio of 4:1.

The mode of clinical presentation varied. The patients with classical papillary carcinoma presented with multinodular goiter in 34 cases(60.7%), solitary cold nodule in 18 cases(32.1%), Thyroid involvement with cervical metastases in 3 cases(5.4%), and isolated lymphnode enlargement histologically presenting as PTC in 1 case(1.8%). Among 56 papillary carcinomas 8 cases (14.3%) showed hashimoto's thyroiditis in the background and 48 cases (85.7%) showed nodular colloid goitre.

## IV. Discussion

Papillary thyroid carcinoma is a major histological type of differentiated carcinoma of the thyroid . In the present study the mean age at diagnosis for papillary carcinoma was 37 years, ranges from 16-70 and the female to male ratio of 4:1.This correlate with the study conducted by Gauhar et al(16). Patients with PTC usually present with solitary or multiple nodules in the thyroid(17). Regional lymph node metastases are extremely common (≥50%) at initial presentation of usual papillary cancer.This feature does not adversely affect long-term prognosis (18). Hence, attempts at staging papillary carcinoma may have minimal clinical significance. Some patients will present with cervical node enlargement and will have no obvious thyroid tumor. Frequently the nodal metastasis will involve one node that may be cystic(19). In our study 52 cases (92.8%) presented as nodules in the thyroid. Only 3(5.4%) patients presented with thyroid enlargement with cervical lymphadenopathy. Isolated lymphnode enlargement histologically presenting as PTC was seen in only one case (1.8%). Papillary carcinoma can also arise in ectopic thyroid tissue such as struma ovary (including the follicular and microcarcinoma variants (20). The thyroid tissue present in thyroglossal cyst can undergo malignant transformation, usually in the form of papillary carcinoma(21,22).

The interrelationship between PTC and chronic lymphocytic thyroiditis or Hashimoto's thyroiditis disorders has been presented in several studies(23,24,25). After the first documentation by Dailey et al. in 1955, the reported rate of coexistence of these 2 diseases ranged from 0.3 to 38%.(26). In our study the incidence of PTC with hashimoto's thyroiditis was found to be 14.3%.The incidence of autoimmune thyroiditis was significantly higher in patients with PTC than in those with adenomatous goiters or follicular adenoma(27). Most studies have shown better clinical presentations, less frequent recurrences, and lower cancer mortality in PTC patients with coexisting chronic lymphocytic thyroiditis than in those without it (25) .A BRAF (V600E) mutation in PTC cells was revealed as a factor that facilitates tumor cell growth and progression. A study conducted by Kim et al. revealed that the BRAF (V600E) mutation was present in 27 (72.9%) patients with and 61 (95.3%) patients without chronic lymphocytic thyroiditis. The low mutation frequency partially explains the better prognosis in PTC patients with chronic lymphocytic thyroiditis(28).

There are numerous histopathologic variants of PTC(Table -2). Each variant shows combination of specific growth patterns, cell types and stromal changes. A major problem in classifying PTC into various subtypes is that the criteria used to define these subtypes are not rigorously defined. There is general agreement that the subtype classification that is used should constitute the predominant pattern of the neoplasm.

The most prevalent variant in our study ,was the Classical, followed by the Follicular variant.Together accounted for 85.7 % of the total. Similar percentages have been observed in other series (29).Follicular variant of PTC look like follicular neoplasm when examined grossly. It composed of follicles of variable sizes with hyper eosinophilic ''bubble gum''like colloid.The cytological features of PTC are important to establish the diagnosis in these tumors (1, 2).The prognosis of these tumors is similar to the typical PTC, except diffuse or multinodular follicular variant, and invasive variant which has a more aggressive clinical course (2). An extremely uncommon macrofollicular variant is composed largely of macrofollicles (>50% cross sectional area)and can be easily confused with a hyperplastic or colloid nodules from low power observation. The cytological features of PTC are seen at higher magnification (2).

In our study papillary microcarcinoma was found in 4 cases(7.1%) .whereas study by Girardi et al revealed that the microcarcinoma variant was the most prevalent, with 42.1% of cases, followed by the classical and follicular variants(30). These tumors were usually found incidentally and measure less than 1 cm in diameter. patients may occasionally present with cervical lymph node metastases.Nonencapsulated tumours are more aggressive than encapsulated tumors.

We encountered one case of ‘‘Warthin-like’’ variant of PTC which showed Tumor cells with abundant eosinophilic cytoplasm line the papillae, and the papillary cores contain a brisk lymphoplasmacytic infiltrate. The diagnosis is usually based on the nuclear features of PTC. It follow a clinical course similar to conventional PTC (31).

Certain subtypes of papillary carcinoma are associated with more aggressive clinical behavior that include tall cell variant, columnar cell variant,diffuse sclerosis variant and solid variant .In our study we have not encountered any of these variants. Among this the tall cell variant is composed of cells with height at least 2–3 times as tall as they are wide and nuclear features similar to conventional PTC. Tall cells should represent 50% or more of the papillary carcinoma cells.Nuclear pseudoinclusions may be more prominent. Most patients are older and present with large bulky tumors and they usually have a more aggressive course than the usual PTC (32).The columnar cell variant is a rare variant of PTC that is made up of pseudo stratified columnar cells with supranucleur and subnuclear cytoplasmic vacuoles. some tumors may resemble endometrial or colonic adenocarcinomas (33). The nuclear features of conventional PTC are not well represented in these tumors, so if the patient presents with metastatic lesions, they may be mistaken for metastatic adenocarcinoma from lung, colon or endometrium(1,2).

The diffuse sclerosing variant are more common in younger patients (34) characterized by diffuse involvement of the thyroid. Papillary structures in dilated lymphovascular spaces are often present. These tumors show extensive squamous metaplasia, abundant psamomma bodies, stromal fibrosis and prominent lymphocytic infiltration . A significant number of patients may have lymph node and lung metastasis (1,2).The solid cell variant consist of sheets of tumor cells, which have cytological features of typical PTC.Vascular invasion and extrathyroidal extension are present in about a third of cases(2). They are more common in children with a history of radiation exposure.Cribriform-morular variant is usually associated with familial adenomatous polyposis and Gardner Syndrome. The tumor has a prominent cribriform pattern with solid and spindle cell areas as well as squamous morules. Focal papillary architecture is usually present(2). The tumor is positive for thyroglobulin focally and shows positive nuclear staining for beta catenin.

Rarely PTC may show fasciitis like stroma, prominent hobnailing of lining epithelial cells(35), focal insular component. Clinical significance of these lesions are unknown. The composite tumor consists of separate areas or cells with PTC constitute< 25% and medullary thyroid carcinoma (2). Immunostaining for thyroglobulin and calcitonin helps to make the distinction of the two components. PTC can also undergo dedifferentiation or transformation to anaplastic carcinoma (1,2). In a study of 109 anaplastic carcinomas, Albores Saavedra et al. found that 46.8% PTC coexisted with anaplastic carcinoma (34 conventional type 14 tall cell variant and 3 follicular variant )supporting the concept of dedifferenation of PTC leading to anaplastic carcinoma.

Immunohistochemical markers such as TTF-1 and thyroglobulin are very helpful in confirming the thyroid origin of PTC, especially when the tumor is present outside of the thyroid gland(1,2).TTF-1 is also expressed in lung carcinomas and small cell carcinomas in many sites,
so it is most useful when combined with thyroglobulin. Because of difficulties in distinguishing some follicular variants of PTC from adenomas and adenomatoid nodules, markers such as HBME-1 and CITED-1 have been used with increasing frequency(36).

Molecular studies have shown that BRAF mutation (V600E) has proven to be relatively restricted to PTC and anaplastic thyroid carcinomas. BRAF mutations have been reported to be predictive of several factors including tumor behavior and response to radioactive iodine , but more studies are needed in this area.RET/PTC rearrangement is found mainly in PTC with a highly variable frequency (5–80%) (37).

Recent studies have shown that normal thyroid tissues and follicular adenomas express low levels of HMGA2 and IMP3 mRNA compared to papillary and follicular carcinomas. So measurements of the levels of expression these markers by quantitative RT–PCR helps to separate benign from low grade malignant thyroid neoplasms in most cases (38).

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## V. Conclusion

Papillary carcinoma thyroid are the most common thyroid malignancies. The age and sex distribution with papillary carcinoma in our setup is very much similar to other parts of the world. Histopathology is the gold standard method in diagnosing papillary carcinoma thyroid. In view of the prognostic implications, it is important for pathologists to specify the variant of papillary carcinoma in their histopathology diagnosis. Recent studies on various biomarkers and Molecular markers can be useful in separating follicular variant of PTC from follicular adenomas These approaches should allow the pathologist to use these new techniques in solving difficult diagnostic problems in thyroid pathology.

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**Tables**

| Variants | Number of cases (n=56) | % |
|---|---|---|
| **Classical papillary carcinoma** | 43 | 76.8% |
| **Follicular variant** | 5 | 8.9% |
| **Micropapillary variant** | 4 | 7.1% |
| **Encapsulated variant** | 2 | 3.6% |
| **Oncocytic variant** | 1 | 1.8% |
| **Warthin like variant** | 1 | 1.8% |

**Table 1 Distribution Of Tumor Patterns**

**Table 2 Histopathological Variants Of Papillary Carcinoma**

| |
|---|
| Classical variant |
| Follicular variant |
| Macrofollicular variant |
| Micropapillary variant |
| Encapsulated variant |
| Oncocytic variant |
| Warthin like variant |
| Tall cell variant |
| Columnar cell variant |
| Solid variant |
| Diffuse sclerosing variant |
| Cribriform morular variant |
| Clear cell variant |
| Papillary carcinoma with fascitis like stroma |
| Papillary carcinoma with prominent hobnailing |
| Papillary carcinoma with focal insular pattern |
| Papillary carcinoma with squamous or mucoepidermoid carcinoma |
| Papillary carcinoma with spindle and giant cell carcinoma |
| Papillary carcinoma with medullary carcinoma |
| Papillary carcinoma with anaplastic differentiation |

WHO Classification Of Tumors ,Pathology & Genetic,Endocrine Pathology,IARC 2004.

**Figures**

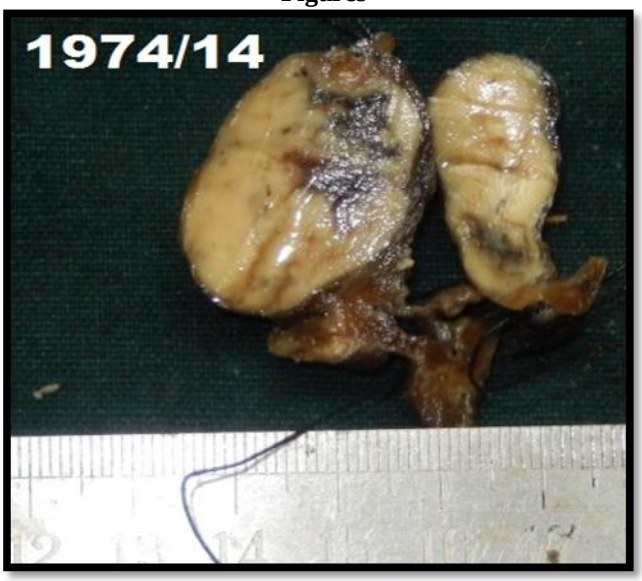


**Figure-1:** Gross picture of classical papillary Carcinoma-solid, gray white firm

**Figure-2:** Gross picture of micro papillary carcinoma

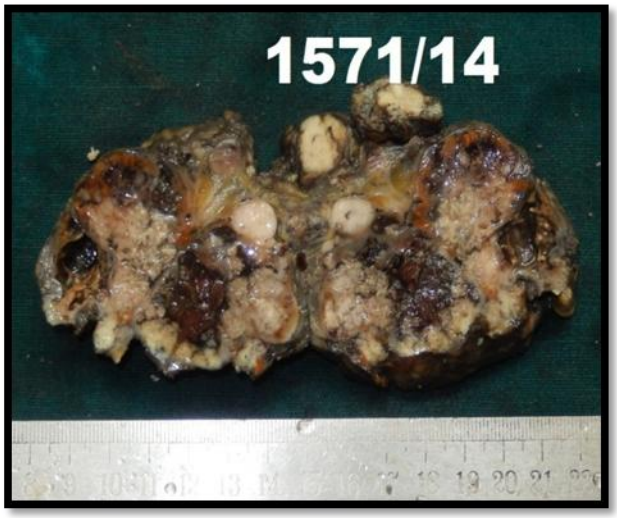


**Figure-3:** Gross picture of papillary carcinoma-solid,gray white firm With areas of calcification

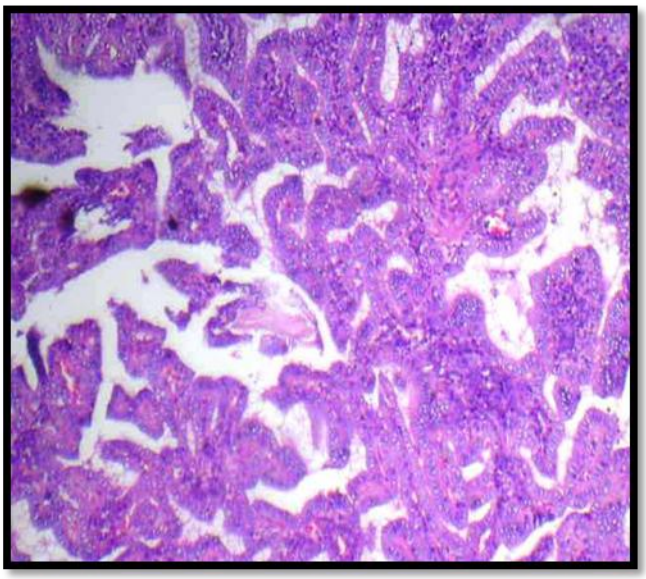

**Figure-4:** Classical papillary carcinoma (H&E 10X)

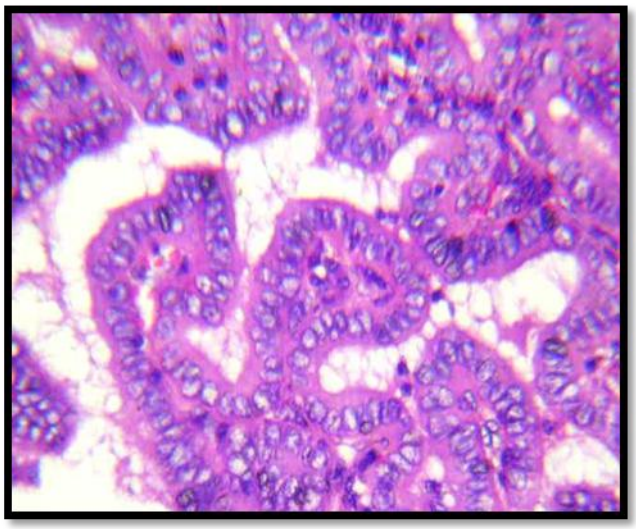

**Figure-5:** Classical papillary carcinoma-nuclear features(H&E 40X)

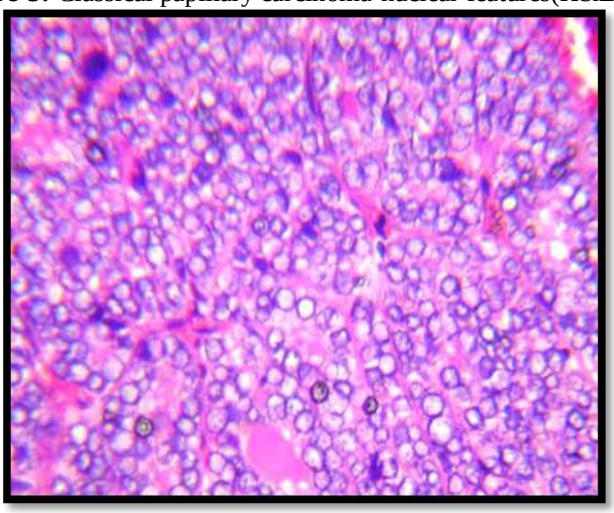

**Figure-6 :** Follicular variant of papillary carcinoma(H&E 10X)

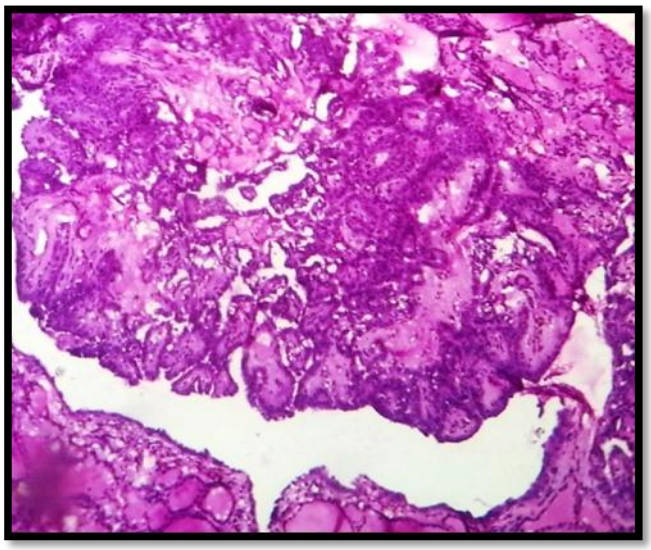

**Figure-7:** Micropapillary carcinoma thyroid(H&E 10X)

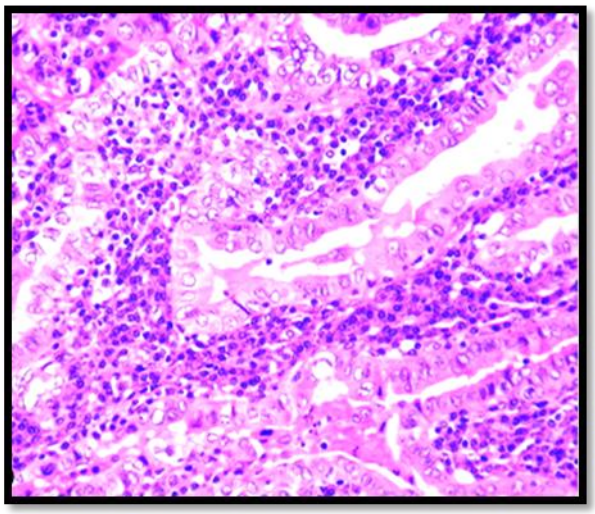

**Figure-8:** Warthin like variant of papillary carcinoma (H&E 10X)

**Figure captions & legends:**
**Figure-1:** Gross Picture Of Classical Papillary Carcinoma-Solid,Gray White Firm
**Figure-2:** Gross Picture Of Micro Papillary Carcinoma
**Figure-3**: Gross Picture Of Papillary Carcinoma-Solid,Gray White Firm With Areas Of Calcification
**Figure-4:** Classical Papillary Carcinoma (H&E 10x)
**Figure-5:** Classical Papillary Carcinoma-Nuclear Features(H&E 40x)
**Figure-6 :** Follicular Variant Of Papillary Carcinoma(H&E 10x)
**Figure-7:** Micropapillary Carcinoma Thyroid(H&E 10x)
**Figure-8:** Warthin Like Variant Of Papillary Carcinoma(H&E 10x)