Papillary Microcarcinoma of Thyroid- A Clinicopathological Study in a Tertiary Care Hospital in South India

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ABSTRACT

BACKGROUND

The incidence of papillary carcinoma of thyroid has shown an increase in the last few decades. One contributing factor is the identification of Papillary Microcarcinoma of thyroid. Papillary Microcarcinoma is defined as a papillary carcinoma which is ≤ 10 mm in size in the greatest dimension. Though it is associated with excellent prognosis, controversies still exist regarding the treatment and follow up of these patients.

METHODS

This study is a retrospective study done in a tertiary care hospital in South India over a period of one year from July 2016 to June 2017. All surgically removed thyroid specimens submitted to the Pathology Department of the hospital were studied. The demographic details, clinical features, ultrasound and other imaging studies were obtained from the medical records. The FNAC findings, gross features of surgically removed thyroid and histopathological findings of these thyroid specimens were recorded and analysed. The records of the follow up of these patients were obtained from the corresponding clinical department.

RESULTS

Among the 486 thyroid samples received, 59 (12.13%) were malignant tumours of the thyroid, out of which Papillary carcinoma was seen in 50 cases (84.7%) including 11 cases of Papillary Microcarcinoma constituting 18.6% of all thyroid malignancies and 2.26% of thyroidectomies during the study period. Mean age of patients with PMC was 43.9 with a female: male ratio of 10:1. 10 cases were incidental PMC, while one was suspected to be papillary carcinoma on ultrasound examination and FNAC. Only one patient showed high risk features of multifocality, extrathyroidal extension and lymph node metastases. Hence she was given RAI. All patients were followed up. No recurrence has been noted in the two year period of follow up.

CONCLUSIONS

Papillary Microcarcinoma is being increasingly diagnosed, most of them being incidental. Hence thorough histopathological examination is mandatory to identify these lesions. Though PMC has an excellent prognosis, aggressive treatment may be required in patients with high risk features including nonincidental, lymph node metastasis, multifocality, and extra-thyroid extension.

KEY WORDS

Papillary Carcinoma Thyroid, Papillary Microcarcinoma, Incidental, Low Risk, High Risk

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BACKGROUND

Papillary carcinoma is the most common type of thyroid malignancy worldwide. It shows a female preponderance. The incidence of well differentiated thyroid carcinoma, particularly papillary cancer, has been increasing in the last 20-30 years. The WHO has published a revised classification of thyroid tumours in 2017. Many histologic variants of papillary carcinoma of thyroid have been identified. These variants assume importance because of their clinical behaviour and the type of management. Some variants like the tall cell variant, trabecular variant are associated with more aggressive behaviour. Some variants like encapsulated variant and papillary microcarcinoma have been shown to be less aggressive with a more favourable prognosis. WHO has recognised 15 variants of papillary carcinoma of thyroid which are based on the histologic features. It is pertinent to note that Papillary Microcarcinoma (PMC) is the only variant based on macroscopic dimensions and not on histologic features.

The term "occult thyroid carcinoma" was introduced in 1928 by Graham to describe thyroid tumours that are clinically hidden but present as metastatic cervical lymph nodes. Later the term "occult" was extended to cover all thyroid cancers less than 15 mm in diameter irrespective of their clinical presentation. The term "latent carcinoma" was used to describe those tumours which were discovered incidentally in thyroidectomy or lobectomy specimens or at autopsy. These latent or occult carcinomas may or may not be microcarcinoma and may show variable histologic patterns. The term incidental cancer was used to denote an unsuspected cancer identified incidentally on pathologic examination of thyroid tissue removed for benign disease. But studies have shown that though a majority of incidental thyroid carcinomas are papillary microcarcinomas, a small percentage of incidental carcinomas is comprised of follicular carcinoma, undifferentiated carcinoma and medullary carcinoma.

Hence to avoid confusion in the terminology and to assess the clinical behaviour and treatment modalities, the WHO has put forward strict criteria for the diagnosis of PMC.

PMC is defined as a papillary carcinoma of ≤ 10 mm in size in its greatest dimension.[1] Diagnosis of PMC comprises of 3 groups:

1. Patients with incidentally found PMC after surgery for benign disease or at autopsy which form the majority of cases.
2. Patients with incidentally detected PMC mainly on Ultrasound Examination and evaluated by Fine Needle Aspiration Cytology.
3. Patients with clinically apparent metastases of thyroid carcinoma where the primary tumour is not detectable before surgery and microcarcinoma is found in the histological specimen.

Factors such as iodination programmes in low iodine intake areas, detailed histopathological examination of excised thyroid tissue, increase in the number of total thyroidectomy procedures and improved imaging techniques, ultrasonography and FNAC have resulted in increased identification of papillary carcinoma of thyroid, both large (> 10 mm) and PMC.

It is to be noted that histologically PMC could be encapsulated or non-encapsulated, and could show any of the histologic patterns of papillary carcinoma, namely conventional, follicular or mixed papillary and follicular pattern or even any one of the rarer variants like tall cell, hobnail etc…

The clinical significance and recommendations for management of PMCs is still evolving. In general, PMC is considered low risk cancer type with greater than 90% disease free survival after long term follow-up. But certain high-risk factors like multifocality, histologic features, extra-thyroid extension, lymph node metastases have been identified and require more aggressive treatment. Thus though they are small and may be discovered incidentally, the pathology reporting protocol has to be followed similar to the other thyroid cancers.

Objectives

i) to identify the incidence of Papillary Microcarcinoma of Thyroid diagnosed during a period of one year in our hospital, which is a tertiary care centre in South India.
ii) to analyse the clinical and pathological characteristics of Papillary Microcarcinoma of Thyroid and to compare them with that of conventional and other variants of Papillary Carcinoma of Thyroid.
iii) to review the findings of similar studies documented in literature and present our experience.

METHODS

This was a retrospective study done during the period of one year from July 2016 to June 2017 in the Pathology Department of our hospital, which is a tertiary care centre in South India. This study includes all surgically removed thyroid specimens which were submitted to the Pathology Department for histopathological examination during the study period. The demographic details, clinical features, ultrasound and other imaging studies were obtained from the medical records. The Fine needle aspiration cytology findings, gross features of surgically removed thyroid and histopathological findings of these thyroid specimens were recorded and analysed. The records of the follow up of these patients were obtained from the corresponding clinical department.

Statistical Analysis

Categorical Variables were presented as group percentage; total numbers and continuous variables were presented as average, mean, ratio.

RESULTS

During the study period, out of 11,771 surgical specimens received in the Pathology Department, 486 were of thyroid (4.12%). Among the thyroid specimens received, 59 (12.13%) were malignant tumours of thyroid, out of which

Papillary carcinoma formed the bulk, (50 cases) constituting 84.7% of all thyroid malignancies diagnosed in that period, including 11 cases of Papillary Microcarcinoma of thyroid. (PMC). (Table 1)

Sl. No.	Type of Malignancy	Number of Cases	Males	Females
1	Papillary Carcinoma	50 (84.7%)	9 (18%)	41 (82%)
	i) Conventional type	34	7	27
	ii) Follicular variant	4	1	3
	iii) Diffuse Sclerosing variant	1	0	1
	iv) Papillary Microcarcinoma	11 (18.6%)	1 (9.1%)	10 (90.9%)
2	Medullary Carcinoma	2 (3.39%)	1	1
3	Insular Carcinoma	2 (3.39%)	0	2
4	Anaplastic Carcinoma	2 (3.39%)	1	1
5	Non-Hodgkin Lymphoma	2 (3.39%)	0	2
6	Metastatic carcinoma	1 (1.69%)	1	0
	Total	**59**	**12 (20.34%)**	**47 (79.66%)**

Table 1. Thyroid Malignancies Diagnosed during the Study Period

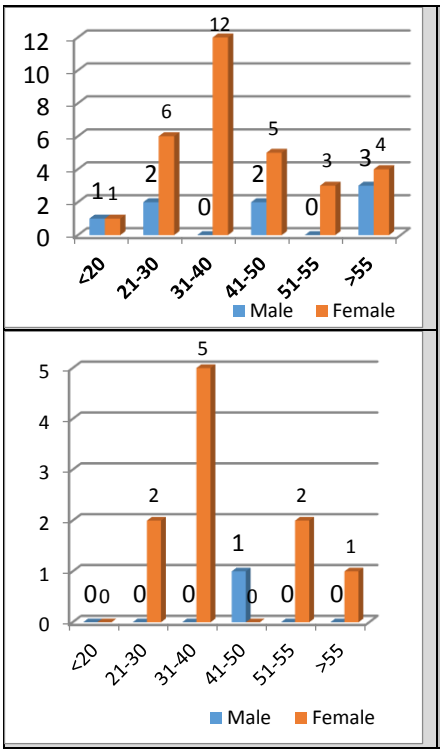

Figure 1. Age of the Patients Diagnosed with Papillary Carcinoma Other Than PMC and Those with PMC

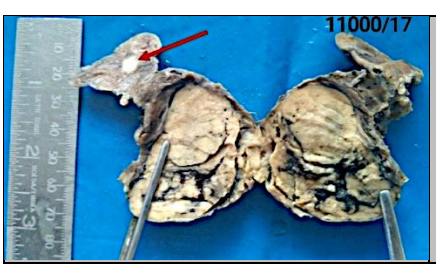

Figure 2. Arrow Shows the Focus of PMC in a Total Thyroidectomy Specimen

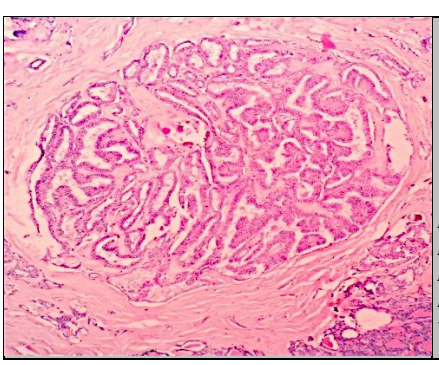

Figure 3. H & E 10X Magnification. A Focus of PMC with Sclerosis

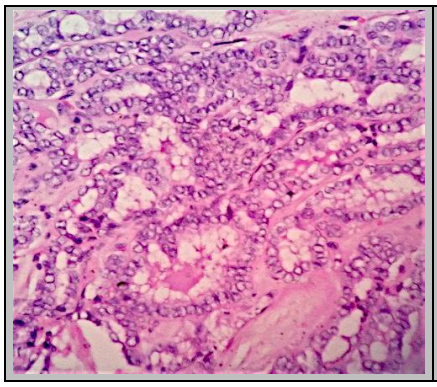

Figure 4. H&E 40X Magnification. Predominantly Follicular Pattern

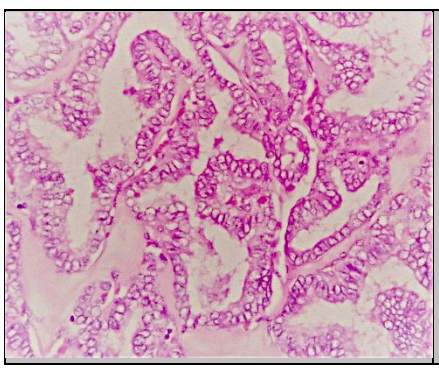

Figure 5. H & E 40 X Magnification. Typical Nuclear Features of Papillary Carcinoma

When comparing the sex ratio, females had a higher incidence of all malignancies, all variants of papillary carcinoma put together and also when papillary microcarcinoma alone was considered. (Figure 1) The following table gives the comparison of various parameters, both clinical and histopathological between PMC and other variants of papillary carcinoma put together.

Sl. No.	Clinicopathologic Characteristic	Papillary Carcinoma Other Than PMC	PMC (Papillary Microcarcinoma)
1	Total no: of cases	39	11
2	Female: Male ratio	4.56: 1	10: 1
3	Age Range	16 - 65	29 - 72
4	Average Age	38.4 Yrs	43.9 Yrs.
5	Unifocal	27 (69.23%)	10 (90.91%)
6	Multifocal	12 (30.77%)	1 (9.09%)
7	Size Range	1.2 – 8.0 cm	0.2 – 0.8 cm
8	Average Size	2.75 cm	0.46 cm
9	**Clinical Diagnosis**		
	i) Papillary Carcinoma	23	Suspicious for Papillary Carcinoma on USG & FNAC 1
	ii) Multinodular Goitre	14	MNG 8 SNT 1
	iii) Solitary Nodule Thyroid	2	Toxic Goitre 1
10	**Microscopic Pattern**		
	i) Conventional	34	Conventional 5
	ii) Follicular variant	4	Follicular pattern 2
	iii) Diffuse Sclerosing variant	1	Mixed pattern 4
11	Encapsulation	16	7
12	Associated findings	Nodular Colloid Goitre 24 Lymphocytic Thyroiditis 15	Nodular Colloid Goitre 9 Follicular Adenoma 1 Lymphocytic Thyroiditis 1
13	Extrathyroidal Extension	14	1
14	Nodal metastases	21	1
15	Distant metastases	1	NIL
16	Recurrence	2	NIL

Table 2. Comparison of Clinicopathologic Characteristics of PMC and Other Types of Papillary Carcinoma

Papillary Microcarcinoma (PMC) was detected in 2.26% of thyroidectomies received in our Institute. Out of the 11 cases of PMC, 10 were incidentally detected constituting 2.05% of the surgically removed thyroid gland. One case was identified as suspicious for papillary carcinoma both on USG examination and FNAC; the patient being a 72-year-old woman. Among the other 10 patients, 8 were diagnosed as MNG on FNAC, USG and clinically. One patient had Goitre with Toxic symptoms and one was diagnosed as Solitary Nodule Left lobe of Thyroid. This patient had follicular adenoma in left lobe and right lobe showed a focus of PMC.

PMC was seen in Right lobe in 5 patients, Left lobe in 4 patients and in Isthmus in 2 patients. Only one thyroid exhibited multifocality. Bilaterality was not detected in any case. Total thyroidectomy was the most favoured surgical procedure in our Institute, for both benign and malignant thyroid disorders. Hence, among the 11 cases of PMC diagnosed, 10 patients had undergone total thyroidectomy and hemithyroidectomy was done in only one patient.

The mean size of PMC in this study was 4.6 mm with a range of 2.0 - 8.0 mm. (Figure 2). The lesion was <5 mm in 4 patients and ≥ 5 mm in 7 patients. On comparing the microscopic pattern observed, 45.5% of PMC showed conventional pattern, while 18.2% showed follicular pattern and the rest showed mixed pattern (36.3%). (Figures 3, 4, 5,) Encapsulation of the tumour was identified in 7 cases (63.6%). The associated findings in the rest of the thyroid was nodular colloid goitre in 9 patients (81.8%). One patient had Lymphocytic Thyroiditis and one had Follicular Adenoma involving the other lobe.

In our study only one patient showed histologic evidence of extrathyroidal extension, lymphatic invasion and lymph node metastases. In this thyroid, the lesion was located in the isthmus close to the thyroid capsule. Since all these features are associated with high risk of recurrence, this patient was further treated with radioactive I 131 ablation. The staging which was done using the latest guidelines, revealed that 10 patients were in Stage I and only one in Stage II because of age >55 years. All patients are on follow up and no recurrence has been observed over a period of 2 years.

DISCUSSION

In the last four decades, in several epidemiological studies around the world, the incidence of PMC is found to be on the rise.[2] Papillary microcarcinoma has been reported to show high variable prevalence rates in different countries, the highest rates have been reported in Finland (35.6%) and Japan (18-24%); lowest is reported in Switzerland (1.2%).[3,4] Majority of them are incidental findings. The prevalence of PMC in autopsy series ranges from 1.7-35.6%.[5] In clinical series, the incidence of PMC in patients operated for benign thyroid disease is much lower and ranges from 3-17%.[6] Therefore it appears that the vast majority of these latent tumours remain dormant and do not grow to clinically apparent disease.[7] Hay et al studied 900 cases of PMC from Mayo Clinic from 1954 – 2004 and observed that only 0.3% of cases died due to causes related to PMC.[8] Despite its high incidence and prevalence, PMC rarely causes death. Hence, they are designated as Low risk thyroid cancers. In view of the excellent prognosis and to avoid overtreatment, the Porto proposal suggests renaming the entity as papillary microtumour to take away the connotation of malignancy.[9]

Review of several studies revealed the clinical and histopathological characteristics of PMC. 28% had multifocal tumours, 18% bilateral tumours, 12.5% extrathyroidal extension, 10.7% lymph node metastasis, 4.2% tumour recurrence and 0.2% mortality related to PMC.[10] The table 2 given below compares the clinicopathological aspects of PMC in various studies undertaken in different geographic locations as compared to this present study.

Characteristics	This Study	Domingnez J et al[11]	Elena ZA et al[12]	Gurleyik E et al[13]	Noguchi S et al[14]	Dideban S et al[15]	Hay ID et al[8]	Baudin E et al[16]
Age	43.9	44.5	55.1	44.1	45.2	47.2	46	41.9
F:M	10:1	9:1	9.7:1	6.4:1	9:1	4.6:1	1.7:1	2.7:1
Mean tumour size in mm	4.6	6.2	5.4	4.9	4.6	5.9	7.0	5.9
Multifocality in %	9.09	38.8	22.8	18	85.8	28	23.8	40
Ete in %	9.09	16.7	8	-	2.4	24	2	15
Ln mets in %	9.09	16.7	1.8	-	14.2	26	30	43
Dist mets in %	nil	-	-	-	-	-	0.3	-
Recurrence	nil	-	-	-	3.5	-	8	3.9

Table 3. Comparison of Different Studies on PMC

The mean age of patients with PMC was 43.9 years in this study, which compares with that of many other studies. (Hay et al, Baudin et al, Noguchi et al).[8,14,16] There was no patient <20 years of age and between 40–50 years in this study. 63.67% (7 cases) were below 40 years of age and only one was above 55 years, which is the cut off age as per the AJCC 8th edition. The lone male patient was 48 years old. Females were more commonly affected than males with a F: M ratio of 10:1, 90.9% being females. This corresponds with a study conducted in Romania by Elena ZA et al.[12] who reported a ratio of 9.7:1. Other studies have reported varying M: F ratios, but most studies have shown a female preponderance varying from 55–90%. Very few studies have documented a male preponderance.[17] Autopsy studies, decades apart show that gender is not a risk factor for PMC.[4,5]

On comparing with the studies documented in literature, it was found that they have reported a mean size variation from 4.1 -8.0 mm,[18] while the mean size was 4.6 mm in this study. Multifocality was observed only in one patient in this study constituting 9.1%. Other studies have reported varying proportions of multifocality in PMC ranging from 7.1% - 85.8%.[8,14,16] Extrathyroid soft tissue involvement by the tumour was recognised in only one patient (9.09%). The rates reported in literature varies from 2-18%. Similarly the occurrence of lymph node metastasis varies from 1.2 – 43%

Therefore, it appears that PMC has varied clinicopathological presentations, though associated with excellent prognosis. Hence, many studies have been undertaken to identify and establish the high risk clinical and histopathological features which determine the outcome of patients with PMC. Factors such as age at diagnosis, gender, tumour size, incidental or non-incidental, multifocality, lymph node metastases and molecular characteristics such as BRAF mutations have been studied.[19,20-22]

The tumour size and aggressiveness has been studied by several authors. Tumour size ≥5 mm is likely to have aggressive behaviour and is an independent risk factor for metastasis and recurrence.[23] Most of the recurrences occur during the first 10 years of follow up. The reason for aggressive tumour behaviour and recurrence in PMC may be attributed to molecular characteristics like BRAF mutations present in 17-52% as reported in different studies cited above.

The presence of incidental thyroid cancer is an important issue in patients with benign thyroid diseases who underwent thyroid surgery. Postoperatively, PMC was identified approximately in 1 out of 10 cases (9.4%) as reported by Gurleyik et al.[13] Other studies have reported the prevalence of I-PMC to be between 7.1-16.3% [24,25]. In this study I-PMC was the most common with an incidence of 2.04% among surgically removed thyroid specimens. Incidental tumours are associated with very good prognosis. According to American thyroid association guidelines, completion thyroidectomy is not recommended for I-PMC that were diagnosed postoperatively No additional therapy is required if it represents an incidental finding in surgical specimens, be it a lobectomy or thyroidectomy.

Some studies recommend that the designation of papillary thyroid microcarcinoma should not be applied to children and adolescents under 19 years old, as a significant number of these subcentimeter papillary carcinomas occurring in the paediatric population display extrathyroid extension and distant metastases.[9] The factors which have been found to be associated with high risk of recurrence and metastasis include children, size greater than 5 mm, non-incidental tumours, histological and microscopic pattern (similar to that of the larger counterpart), multifocality, extrathyroid extension, lymph node and distant metastases, genetic alterations.[26] Therefore, patients with high risk features like multifocality, lymphatic invasion, extrathyroidal extension, aggressive morphology and non- incidental tumours may require full blown treatment including total thyroidectomy and RAI. The others are followed up for 10 years.

It is of interest to note that studies in Japan have been conducted in low risk PMC patients who have been managed with active surveillance trials.[27,28] They have concluded that in carefully identified adult patients with low risk PMC, active surveillance is the first line of management. None of the patients who were on active surveillance for 10 years developed life threatening distant metastases or died of papillary carcinoma thyroid. Further, efforts are underway to arrive at a combined scoring system for PMC incorporating clinicopathological, histological and molecular features to identify the high-risk patients who may require aggressive therapy.

CONCLUSIONS

PMC is increasingly being diagnosed following surgery for benign thyroid diseases. Hence thorough histopathological examination is mandatory to identify these occult micro-carcinomas in thyroidectomies performed for indications other than malignancies. The overall prognosis of PMC is excellent. Incidental PMC has a very good disease free outcome. Tumours with multifocality, extra thyroid extension and lymph node involvement have more chance of recurrence. PMC in general has a benign course. Aggressive treatment may be reserved only for those with high risk features. A regular follow up may be sufficient for the other patients.

Improvements in the stratification of PMC patients should allow clinicians to better adjust the intensity of therapy and avoid overtreatment in most patients with PMC, which has been associated with side effects and deterioration of quality of life. In properly selected patients, active surveillance has been shown to be feasible with low risk of progression of disease and lower rates of side effects related to therapy.

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