Original Article

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Comparison of Histopathological Features of 'Incidental' and 'Non-Incidental' Papillary Thyroid Microcarcinomas

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ABSTRACT

Background: Papillary thyroid microcarcinoma (Pm) is defined as a papillary carcinoma with size ≤ 10mm. On clinical and histological grounds, there are two presentations-'incidental' and 'non-incidental'. Histopathological parameters like intratumoral/peritumoral fibrosis, multifocality, infiltrative borders, subcapsular location, lymphovascular emboli and histological type have been introduced in the reporting of Pm, besides the size which is considered an important prognostic/risk factor.

Methods: The present study is a 5-year retrospective comparative study between the Pm which were incidentally detected, and those which had been previously diagnosed on fine needle aspiration/radiology or clinically suspicious of Pm.

Result: The number of cases in both incidental (111) and non-incidental (110) Pm have been found to be comparable in the present study, which is attributable to meticulous grossing and extensive sampling of all thyroidectomy specimen. Size and multifocality has been significantly different between incidental and non-incidental Pm (p-value <0.05). The parameters like intratumoral/peritumoral fibrosis, infiltrative border and subcapsular location were significantly higher in larger sizes (>5mm) of non-incidental Pm (p-value <0.05). These parameters, however, were not found to be significant when analysed individually or with one another, between the two groups (p-value >0.05). In the incidental Pm of size ≤ 5mm, a good proportion of cases show these parameters, implicating their importance for further follow-up.

Conclusion: Size and focality has been found to differ between incidental and non-incidental Pm. The histological parameters defined for Pm need to be followed up for a longer period to identify the prognostic significance, and their role in the different manifestation of incidental and non-incidental Pm.

Keywords: *Thyroid Microcarcinoma, Peritumoral Fibrosis, Subcapsular Location, Infiltrative Borders.*

Introduction

Papillary thyroid microcarcinoma (Pm) is defined by World Health Organisation (WHO) as a Papillary thyroid carcinoma of 10 mm or less in greatest dimension.[1,2] On clinical and histological grounds, there are two different presentations of Pm – a) 'incidental' which is identified post-operatively at histological examination of thyroid specimens following thyroid surgery for benign disease, b) 'non-incidental' which is diagnosed before surgery by Fine needle aspiration of small thyroid nodules detected at neck ultrasound or at other diagnostic procedures, or for presence of nodal metastasis.[3]

The incidental Pm group is said to have excellent prognosis and there is no risk of recurrence or death.[3,4] The non-incidental group show more aggressive behaviour, associated with lymph node metastasis at presentation, loco-regional recurrences and multifocality of tumor.[3,5,6]

The studies previously conducted on papillary thyroid microcarcinoma focussed on the size of lesion in predicting the outcome of the disease. Recent studies have put forwarded other histopathological parameters which could contribute to the risk stratification in Pm. These include intratumoral/peritumoral fibrosis/sclerosis, location of tumor close to capsule (subcapsular location), multifocality/intraglandular tumor spread, infiltrative border, lymphovascular emboli/nodal metastasis and aggressive histological variant like tall cell morphology.[1,7,8,9]

The present study compares the histopathological parameters recently described for thyroid Pm, between the 'incidental' and 'non-incidental' groups, and determines their role, if any, in the manifestation of the disease.

Materials and Methods

The present study is a 5-year retrospective comparative study between 'incidental' and 'non-incidental' Pm. The data has been collected from January 2013 to December 2017. Patients diagnosed with Papillary thyroid microcarcinoma (Pm) and on follow-up with ultrasound of the neck and Iodine radioisotope uptake scan for detection of residual thyroid carcinoma were included in the present study. In case of tumor multifocality, size of the largest foci was considered in deciding to include it in Pm subgroup.

The Pm which were detected on examination of histopathology sections, without any prior suspicion on investigations like Fine needle aspiration or ultrasound neck, were considered as 'Incidental' Pm and those which had suspicion on clinical, ultrasound and fine needle aspiration were considered as 'Non-incidental'. All thyroid specimen received in our laboratory were serially sliced into thin slices, and extensive sampling of the suspicious areas are done to rule out Pm.

The H&E stained slides were retrieved and the histopathological parameters (intratumoral/peritumoral fibrosis, subcapsular location, multifocality/intraglandular tumor spread, infiltrative borders, histological variants like tall cell/oncocytic/solid/poorly differentiated/hobnail/anaplastic) were looked for, as described in Figure 1-4. With respect to histological variant, the Pm were divided into favourable (classical, follicular or mixed classical and follicular) and unfavourable (tall cell, solid, oncocytic, hobnail, anaplastic, poorly differentiated) groups. The clinical details with previous investigations like ultrasound neck and fine needle aspiration were collected from the patient information system in the software. The details of patient follow-up were also collected in a similar way.

The comparison of the histopathological parameters between the two groups were done and assessed in terms of its presentation.

Statistical Analysis

Chi-square test was used to compare the data in the two groups, using 95% level of significance. Two sample t-test was used for comparing the mean.

Result

A total of 2100 thyroidectomies/hemithyroidectomies were received in the Department of Pathology, Amrita Institute of Medical Sciences during the period of January 2013 to December 2017. Out of these, 221 were papillary thyroid microcarcinoma (111 incidental Pm, 110 non-incidental Pm). Table 1 shows the findings between the incidental and non-incidental thyroid papillary microcarcinoma, with respect to clinico-histopathological features.

Amongst the features studied in Table 1, size of the Pm, foci and nodal metastasis at the time of presentation were significantly different between the incidental and non-incidental group. Considering 5mm as the cut-off for size difference, the incidental Pm was found to have significantly larger number of cases with size ≤ 5mm, whereas non-incidental Pm had larger number of cases with size > 5mm (p value = 0.000781, result significant at p <0.05). Similarly, single foci was significantly higher in incidental Pm and multiple foci higher in non-incidental Pm (p value = 0.00383, result significant at p <0.05). Nodal metastasis at the time of presentation of disease was found only in non-incidental Pm. Lymphovascular emboli were observed in 2 patients in incidental Pm, which was, however, not significantly different from non-incidental Pm (p value = 0.224, result not significant at p <0.05).

There was no significant difference between the age at presentation (p value >0.05) and sex (p value = 0.830, result not significant at p <0.05) of the individuals, between the incidental and non-incidental Pm groups. However, presentation in females was more than in males in both the groups.

Significant difference in histopathological features-fibrosis (p value = 0.140, result not significant at p <0.05), infiltrative borders (p value = 0.830, result not significant at p <0.05), subcapsular location (p value = 0.119, result not significant at p <0.05) and histological type (favourable/unfavourable) (p value = 0.986, result not significant at p <0.05) were also not observed between the two groups.

The incidental and non -incidental were then further analysed (Table 2) based on co-presentation of at least two of the histopathological features and with respect to size of the Pm, taking 5mm as the cut-off for size difference. Histological subtype and lymph node metastasis/lymphovascular emboli were not considered here due to its low number, which is not suitable for statistical calculations.

Considering 5mm as a cut-off size, single foci (p value = 0.045, result significant at p <0.05) was found to be significantly higher in incidental group than in non-incidental Pm, with size ≤ 5mm. However, there as no significant difference in focality between incidental and non-incidental Pm, with size > 5mm (p value = 0.271, result not significant at p <0.05).

In Pm of size > 5mm, intratumoral/peritumoral fibrosis (p value = 0.000025, result significant at p <0.05), subcapsular location (p value = 0.000764, result significant at p <0.05) and infiltrative border (p value = 0.0046, result significant at p <0.05) were significantly higher in non-incidental Pm than in incidental Pm.

Again, considering Pm of ≤ 5mm, intratumoral/peritumoral fibrosis (p value = 0.687, result not significant at p < 0.05), subcapsular location (p value = 0.880, result not significant at p < 0.05) and infiltrative border (p value = 0.324, result not significant at p < 0.05) were not significantly different between incidental and non -incidental. However, it was seen that a good number of cases in this group show intratumoral/peritumoral fibrosis (18.3%), subcapsular location (10.3%) and infiltrative border (14.9%).

Infiltrative borders with intratumoral/peritumoral fibrosis (p value = 0.052, result not significant at $p < 0.05$), subcapsular location with intratumoral/peritumoral fibrosis (p value = 0.338, result not significant at $p < 0.05$) and subcapsular location with infiltrative borders (p value = 0.843, result not significant at $p < 0.05$) were also not found to be significant between the incidental and non-incidental Pm.

Table 1: Clinico-histopathological features of Incidental and Non-incidental Papillary thyroid microcarcinoma.

		Incidental Pm	Non-incidental Pm
Total number of cases		**111**	**110**
Age at presentation (Mean ± SD)		49.71 ± 11.14	47.20 ± 12.34
Sex	Male	17	18
	Female	94	92
Size of micro-carcinoma	≤5mm	87	63
	>5mm	24	47
Foci	Single	94	75
	Multiple	17	35
Infiltrative borders		17	18
Intratumoral/ peritumoral fibrosis		21	30
Location	Subcapsular	12	20
	Intrathyroidal	99	90
Histological type	Favourable *	104	103
	Unfavourable (Or mixed with unfavourable morphology) **	07	07
Lymphovascular emboli		02	05
Nodal metastasis at the time of presentation		0	9

** Favourable-classical, follicular or mixed classical and follicular*

*** Unfavourable (or mixed with unfavourable)-tall cell, solid, oncocytic, hobnail, anaplastic, poorly differentiated*

Table 2: Analysis of histological parameters between incidental and non-incidental Pm.

			Incidental	Non-incidental
Infiltrative borders with fibrosis			09	15
Subcapsular location with fibrosis			02	07
Subcapsular location with infiltrative borders			04	06
Fibrosis	Size	≤5mm	16	10
		>5mm	05	20
Subcapsular Location	Size	≤5mm	09	07
		>5mm	03	13
Infiltrative borders	Size	≤5mm	13	06
		>5mm	04	12
Foci	≤5mm	single	77	48
		multiple	10	15
	>5mm	single	17	27
		multiple	07	20

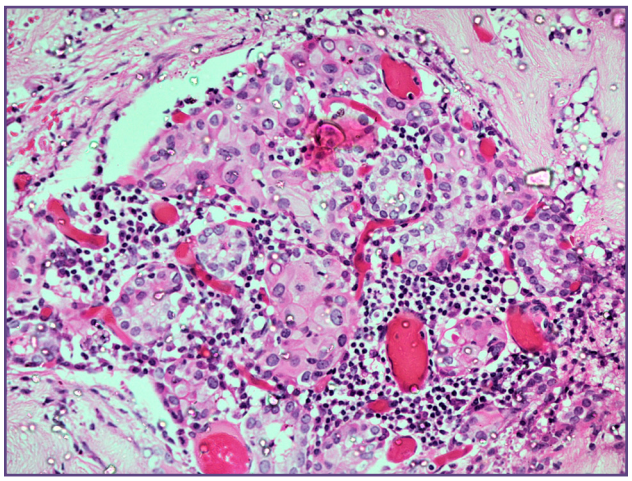

Fig. 1; Papillary thyroid microcarcinoma with oncocytic cells.

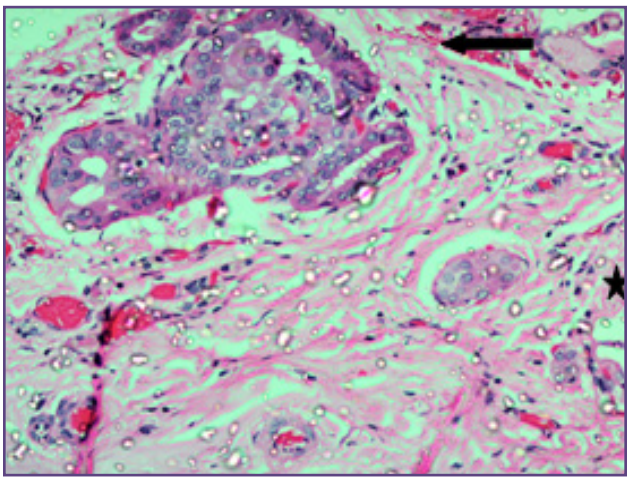

Fig. 2: Papillary thyroid microcarcinoma with oncocytic cells (star) and tall cells (arrow).

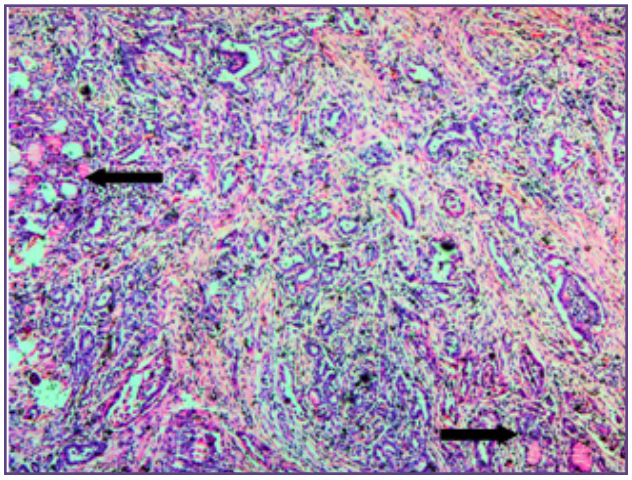

Fig. 3; Papillary thyroid microcarcinoma with infiltrative borders. Arrows show adjacent thyroid follicles infiltrated by tumor cells.

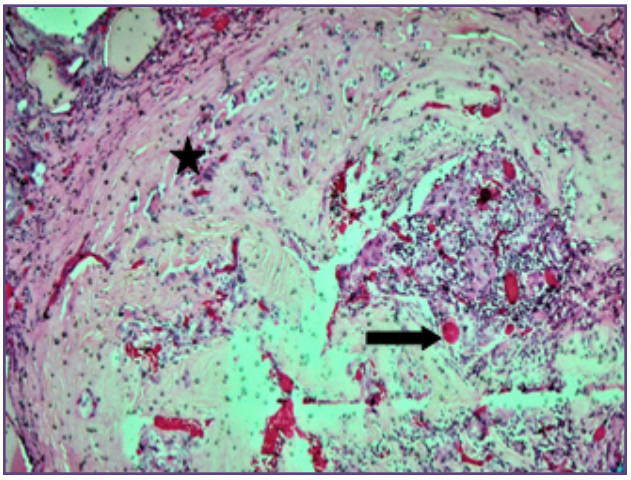

Fig. 4: Papillary thyroid microcarcinoma with intratumoral (arrow) and peritumoral (star) fibrosis.

Discussion

The prevalence of incidental and non-incidental Pm have been found to vary in different studies. Incidental Pm has been associated with Multinodular/ endemic goitre, and increased levels of Thyroid Stimulating Hormone. [3,10,11,12,13,14] Many researchers correlate the incidental Pm with the variable use of ultrasonography and ultrasound guided needle aspiration. Regardless of the pre -operative diagnostic method, cases of Pm are detected incidentally post-operatively in many instances. Cappelli C *et al* [15] noted that the prevalence of incidental Pm in patients who underwent ultrasound guided needle aspiration with negative results for the detection of carcinoma was 1.24 %.

In the present study, the number of cases in incidental and non-incidental Pm is comparable (Table 1). Examination of the entire specimen with slicing into very thin slices and extensive sampling have helped identify the smallest of incidental Pm (smallest size in the current study being < 1mm). Six cases were identified with size < 1mm, 4 being in the incidental and 2 being in the non-incidental group. The two cases in the non-incidental Pm had strong clinical suspicion of malignancy due to the female sex and higher age group (> 60 years). Although definitive radiological evidence was not present suspecting malignancy, there were features like altered vascularity and suspicious specks of calcification for which the patients were operated. The studies of Kim DW *et al* [16] and Zhang X *et al* [17] have put forward that Pm of size < 3mm and < 2mm respectively, are likely to be missed on radiology. For such cases, clinico-radiological correlation is recommended for further management of the patients.

Female preponderance is seen in both incidental and non-incidental Pm.[3,14,18] However, no difference is noted in the incidental and non-incidental group. This is in comparison with study of Provenzale *et al*.[3]

The mean age at presentation for incidental and non-incidental Pm (Table 1) is comparable and is not significantly different. The mean age of both the groups is again comparable with that observed in the study of Gurleyik E *et al* [14], Wada N *et al* [19], Pelizzo MR *at al* [20], Barbaro D*et al* [21] and many others. However, Provenzale *et al* [3] found that incidental Pm presented at a significant older age group (mean age ± s.d., 53.3 ± 13.2) than non-incidental (mean age ± s.d., 44.9 ± 14.8 years).

The size of microcarcinoma has been a matter of debate with respect to its prognostic significance/high risk factor. Studies of Malandrino P *et al* [22] and Lombardi C *et al* [23] suggested that size of microcarcinoma, in combination with other clinico-pathological parameters, is associated with high risk features. A size of 5mm as a cut-off for distinguishing low-risk and high risk groups has been suggested. On the other hand, studies of Bradley NL *et al* [24], Chow SM *et al* [25] and Pellizzo MR *et al* [7] found no significant association of size with outcome of disease. The present study shows a significant difference in size of microcarcinoma between incidental and non-incidental Pm. Incidental Pm were significantly smaller (≤5mm) and non-incidental Pm were found to be significantly larger in size (> 5mm). This is in comparison with findings of Provenzale *et al* [3] and Mehanna H *et al*.[5]

Multifocality has been correlated with lymph node metastasis and loco-regional recurrences.[22] Multifocality appears to be a very early process of the spread and confirms itself to be a poor prognostic factor. With increase in size of tumour, multifocality has been found to correlate with extracapsular extension and lymph-node metastasis. [18] The present study shows multifocality to be significantly associated with non-incidental Pm than with incidental Pm. This is in comparison with the study of Pellegriti G *et al* [8] but contrasts the finding of Provenzale *et al*.[3]

Tumor subcapsular location and significant intratumor/peritumoral fibrosis have been associated with aggressive behavior of Pm.[7,8,9,25] It has been seen that microcarcinoma located at the surface of the thyroid gland also showed strong correlation with risk of tumor spread to regional lymph nodes and/or recurrence. Tumor location at the thyroid surface predisposes to extrathyroidal extension, making subcapsular location an important factor in the description of thyroid microcarcinoma.[24] In the present study, there has not been significant difference between incidental and non-incidental group with respect to subcapsular location.

Intratumoral/peritumoral fibrosis has been associated with lymph node and distant metastasis. This is proposed to be due to propensity for matrix fomation and angiogenesis. However, further investigations are required for the biological correlation.[26] In the present study, intratumoral/peritumoral fibrosis does not significantly differ between incidental and non-incidental Pm.

Along with above mentioned parameters, infiltrative border of microcarcinoma had also been studied and compared between the two groups, which, however, does not show significant difference. Infiltrative border may be similar to intraglandular spread/multifocality described by Niemeier LA *et al* [26], and need to be followed up to study its relevance as a prognostic/risk factor.

In the present study, no significant difference has been observed between incidental and non-incidental Pm with respect to the favourable/unfavourable histology variants of Pm. This is in contrast with the finding of Provenzale *et al* [3] who found that aggressive histology was significantly associated with non-incidental Pm.

Lymph node metastasis at the time of presentation has been associated only with non-incidental Pm, in the present study. This is in comparison with the study of Provenzale MA *et al*.[3]

In the present study, histological parameters have further been analysed with respect to one another and with respect to size (Table 2). When studied with respect to size, the parameters (intratumoral/peritumoral fibrosis, infiltrative border, subcapsular location) showed significant association with larger sizes (> 5mm) in non-incidental group. However, a good proportion of cases in incidental pm with size ≤ 5 mm also shows similar features. Therefore, it is important to look for these parameters in the smallest of microcarcinoma. Further, multifocality has been significantly associated with smaller (≤ 5mm) Pm in the non-incidental group than in incidental Pm. Therefore, it is important to submit multiple sections to rule out multifocality even in small Pm.

In the present 5-year retrospective study, follow-up of patients did not show any recurrence, nodal or distal metastasis during the study period. Pm is known to have recurrence/nodal or distal metastais after several years of its initial presentation. It is therefore necessary to follow-up patients for a longer period of time to assess the prognostic significance of these histological parameters.

Conclusion

Tumor size and focality has been found to differ significantly between incidental and non-incidental Pm. Size of Pm is also associated with intratumoral/ peritumioral fibrosis, infiltrative border and subcapsular location, which have been found more in larger tumors (> 5mm) in non-incidental group, with a good proportion of cases in incidental Pm with size ≤ 5mm. This focusses the need to put up the histopathological parameters even in the smallest of Pm, which would help to identify their prognostic significance.

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