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RESEARCH ARTICLE

CHANGING TRENDS IN PAPILLARY CARCINOMA THYROID –A STUDY OF LOCAL RECURRENCE AND INCIDENCE IN AGGRESSIVE VARIANTS OF PAPILLARY CARCINOMA, A SINGLE INSTITUTIONAL STUDY

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Abstract

Background: The incidence of papillary carcinoma thyroids have undoubtedlyincreased in India especially in the largely due to various high quality imaging studies obtained. Theclassical papillary carcinoma thyroid (PTC) is highly curable in 85% of the cases due to its slow biological behaviour but the aggressive variants of papillary carcinoma does not have the same biological behaviour.The clinical treatment of these aggressive PTC variants should be tailored to the disease stage, with an understanding that these variants are often associated with higher-risk features.

Methods: A prospective and retrospective observational study, where patients who underwent total thyroidectomy for papillary carcinoma thyroid from 2016 November to September 2022 are analysed. The incidence of aggressive variants, local recurrence rate and recurrence site and probable ethological and risk factors are collected.

Result: The overall trend among the aggressive variants of papillary carcinoma thyroid is on a steady raise in the past 5 years with female predominance n=105(60%). Out of 175 cases n= 54 (38.3%) showed local recurrence with highest recurrence for clear cell variant n= 4 (80%). The association of Long standing thyroiditis Out of 175 patients n=60 (34.3%) patients have thyroiditis at the time of diagnosis of papillary carcinoma and Warthin's variant showed strongest association 85% and it was stasistically significant (p =0.005) while other habituations like alcohol, smoking and life style diseases like DM and HTN have no association with aggressive variants of PTC

Conclusion: It has been observed that there is consistent yearly increase in the incidence of aggressive variants of papillary carcinoma over the past 5 years with maximum number reported in the year 2021 - 2022. The aggressive variants of PTC have been found to have more chance of Local recurrence and the most common site for local recurrence is Lymphnodes.Thyroiditis has been identified as an independent risk factor for developing aggressive variants of PTC, with statistical significance ($p < 0.005$).

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Introduction:-

Thyroid carcinomas have demonstrated changing patterns over the last 30 years. Studies like Marcadis AR et al Changes in trends in thyroid cancer incidence in the United States, 1992 to 2016. [1] have shown that incidence of papillary carcinomas have significantly increased over the past decade. The most common thyroid cancer in the state of Kerala is Papillary carcinoma of thyroid. Indu Elizabeth et al Rising Thyroid Cancer Incidence in Southern India: An Epidemic of Overdiagnosis? 2017 suggest that the number of Papillary Carcinoma has increased steadily and the aggressive variants of papillary carcinomas are more common . The clinical and pathological high risk profile of these variant make it difficult to diagnose and is challenging for both pathologist and clinician to arrive at a conclusion and to start a treatment protocol. Our purpose of this study was to analyse incidence, 5 year recurrence rate of aggressive variant of thyroid cancer and to determine the probable aetiology and risks factors of the cancer. No study has done so far to find the aetiology of aggressive variants of papillary carcinoma. Aggressive variants requires aggressive methods of treatment such as resection of the strap and Central neck dissection. Identification of the clinical features and risk factors that may point to aggressive variants of papillary carcinoma which helps us to change the approach of our treatment such as deciding to go for CND and strap muscle resection while planning for a total thyroidectomy.

Methods:-

(a) **Study design**- Retrospective and prospective cohort study
(b) **Study setting** - General Surgery department, Amrita Institute of Medical Sciences
(c) **Selection process** - We intend to recruit patients presenting to our department with thyroid swelling and who underwent total thyroidectomy.
(d) **Study duration** - Patients presenting in the Department of General Surgery , who is diagnosed with aggressive variant of PTC from November 2017 - September 2022.
(e) **Sample size** -Based on the incidence of aggressive variants of Papillary carcinoma (10.4%) was observed in an earlier publication (Tall cell papillary cancer incidence and prognosis published in AMERICAN JOURNAL OF SURGERY VOL 168) and with 95% confidence and 5% absolute error ,the minimum sample size comes to 143.

(f) **Statistical Analysis** -
· Incidence aggressive variants of Papillary carcinoma will be estimated in percentage with 95% confidence interval.
· To test the statistical significant association between risk factors and aggressive variants, chi square test will be applied.
· To find the independent risk factors of aggressive variants will be assessed by multiple logistic regressions.
Inclusion criteria -
1. Retrospective data of all the patients with proven histopathology of papillary carcinoma, who underwent total Thyroidectomy from 2016 January to 2020 December.
2. Prospective data of all patients diagnosed with papillary carcinoma undergoing Total Thyroidectomy from December 2020 to December 2021 with suspicious or proven carcinoma under general surgery department
Exclusion criteria -
1. Carcinomas other than papillary carcinoma of thyroid like medullary/ follicular / anaplastic carcinoma of thyroid.
2. Any other thyroid swellings like MNG, Benign goiter

Result:-

There has been a consistent yearly increase in the incidence of aggressive variants of papillary carcinoma over the past 5 years (Table 1). Among the aggressive variants, **the most common type is the tall cell variant n=141 (80%)** (Table 2).

The overall recurrence rate among the aggressive variants of PTC is 39.4% (Table 3) with highest recurrence rate for clear cell variant n=4 (80%). The most common site of recurrence is in the Lymph nodes n=35 (50.7%) followed by post thyroidectomy thyroid bed n=28 (40.7%) (Table 4**).** The Geographical distribution of aggressive variant of PTC is toward the southern and central districts of Kerala which includes Ernakulum, Alappuzha, Kollam, Trivanthupuram etc.

Females are more predominant n=105(60%) compared to males in the aggressive variants of papillary carcinoma (Table 5) and the mean age group is 54 years. Exception is seen in case of Wartinstumor, where younger age groups are predominantly involved 38+/- 14.

36% of patients had history of diabeties mellitus among the aggressive variants of PTC while 42.3% of patients had hypertension but both were not statistically significant. **Long standing Thyroiditis was seen in 34.2% of patients who were diagnosed with aggressive variants of PTC and it was spastically significant with p value of 0.001(Table 5).** Analysing the other known risk factors like alcohol and smoking was not found to be significant risk factors for aggressive variants of PTC.

Discussion:-

Incidence And Trends

The incidence of Classical papillary cancer has increased from 4.8 per 100,000 in 1975 to 14.9 per 100,000 in a report based on the Surveillance, Epidemiology, and End Results (SEER) database. The current study data among the aggressive variants of PTC has also showed that there is a significant increase in the incidence over the 5 year study period. Among the rare variants, tall variant has the highest incidence rate. The highest incidence 26.8% (n=47) of rare variant was in the year 2021 -2022. Sekkath Veedu J, Wang K, et al [1] - Trends in thyroid cancer incidence in India. In their study an increase from 2.4 to 3.9 in women and in men there has been a raise from 0.9 to 1.3 with a relative increase of 62% and 48%. Studies have concluded that the rising incidence rate of differentiated thyroid cancer (DTC) is largely due to overdiagnosis. Most data indicating a thyroid cancer "epidemic" come from high-income countries, leading to the perception that this issue primarily affects the developed world.

Advancements in diagnostic modalities and the increased sensitivity of ultrasonography have enabled early detection of suspicious thyroid nodules. Consequently, the incidence of rare variants of papillary thyroid carcinoma is on the rise, likely due to earlier diagnosis. This trend is expected to continue in the coming years and warrants close attention

Distribution Of Histological Variants

In our research, out of 175 aggressive variants of papillary carcinoma thyroid 80% of the aggressive variants were Tall cell variant . Diffuse sclerosing type formed 5.7% , hobnail and Warthin variant formed 4% while clear cell variant , and oncocytic variant contributed to 2.9 and 2.3% respectively. Donaldson et al [2] reported in their systematic review and meta-analysis prevalence of hobnail cell variant was 1.08% out of all papillary thyroid carcinoma cases. Karkuzhali etl al [3] in their study reported clear cell accounting to 0.3%, diffuse sclerosing 0.5%, oncocytic 1.1%, tall cell carcinoma 0.3%. Comparing to other studies our research shows that the most common rare variant is Tall cell variant and other variants forms less than 5%. Ronald Ghossein et al. [4] reported that the tall cell variant (TCV) is the most common rare variant of papillary thyroid carcinoma (PTC) and concluded that TCV is a biologically and clinically aggressive form of PTC that remains underdiagnosed. TCV is frequently found in patients with radioactive iodine (RAI)-refractory disease and shows a high prevalence of BRAF mutations, making these mutations a promising target in cases unresponsive to RAI therapy.

Age

The mean age of classical papillary carcinoma thyroid is around 40 years. Karkuzhali et al [3] Of the total 377 cases, 278 (or 73.7% of the total) occurred in people younger than 45, while 99 (or 26.3% of the total) occurred in people older than 45. Diagnosis occurred on average at the ages of 37.26 [95% confidence interval: 35.82, 38.71] in females and 45.74 [95% confidence interval: 41.95, 49.54] in males. There are no studies that has looked into age distribution of aggressive variants of papillary carcinoma thyroid. In our study the average age group was above 50 years predominantly in 50-60 years of age. The mean age of tall cell variant of papillary carcinoma was 54.01 years (SD 16.50). An exception to this was seen in Warthin variant which had the mean age of 38 years (SD 14.49).

All though classical papillary carcinoma of thyroid was seen in the early 3rd and 4th decade of life, it has been observed that the aggressive variants is seen in the later 5th to 6th decade of life.

Recurrence Rate

The total recurrence rate in our study among the rare variants of papillary carcinoma thyroid in 5 year follow-up is 39%. The highest recurrence rate among the rare variants is seen with clear cell 80% (n=4). Tall cell variant has a recurrence rate of 38% (n= 54). The lowest recurrence is seen in hobnail (25%). Tumor recurrences are observed in eight to twenty eight percent of patients with classical Papillary thyroid carcinoma. Zhang, X. et al- Clinic pathological features of recurrent papillary thyroid cancer report have shown tall cell, columnar cell, diffuse sclerosing and oncocytic variants had higher risk of recurrences and metastases [5]. There are no studies currently undertaken that reported the 5 year recurrence among the rare variants of papillary carcinoma thyroid. In our study

the recurrence rate among the rare variants is high (39%) with the highest recurrence for clear cell variant although data is not statically significant (p= 0.3).

Recurrence Site

According to research, lymph nodes and thyroid tissue are the most typical locations of recurrence. Tumour recurrences are observed in eight to twenty eight percent of patients with Papillary thyroid carcinoma. In our study 50 % (n= 35) of the recurrence is in the lymphnodes while 40% (n=28) of recurrence were in the thyroid bed. The rest 4% of the recurrence were in the perithyroidal tissue like strap muscles and another 4% distant recurrences which involves brain and skeletal tissue. Ywata et al [6] reported recurrence in 4.3% patients in their study and mostly lymph nodes were involved in recurrence. Their study reported distant metastasis in 0.4% patients and showed that tumour size (more than 10 mm), multifocal lesions, extrathyroidal extension of tumour and lymph node metastasis were independent risk factors for recurrence. Various studies have shown tall cell, columnar cell, diffuse sclerosing and oncocytic variants had higher risk of recurrences and metastases. Our study observation shows that most of the recurrences are in the Lymphnode and thyroid bed even after all the patient underwent radioiodine ablation therapy. Hence the chance for a recurrence is high in a patient diagnosed with rare variants of papillary carcinoma and the need for a prophylactic central compartment dissection has to be considered in such patients.

Geographical Distribution

28% of patients in our research study are residents of Ernakulum and this might be due to referral bias as the hospital is a tertiary referral center for the residence in and around the district of Ernakulum. Alappuzha n=29 (16.6) and Trissur n=29 (16.6) are the second highest followed by Kollam (9.7%), Pathanamthitta (6.7%), and Thiruvanthupuram (5.5%) . According to the study Indu Elizabeth Mathew and Aju Mathew [7] - Rising Thyroid Cancer Incidence in Southern India: An Epidemic of Over diagnosis? Trivandrum has the highest incidence recorded 6.9 per 100,000, rising to 10 in 2009 and 13.3 in 2012. There was a 93% increase in incidence rates over less than a decade. Even though our research is a single institutional study, what can be concluded is that there has be a raising trend in the aggressive variants of papillary carcinoma and the south India especially the northern districts of Kerala have high burden of aggressive variants of papillary carcinoma thyroid.

Risk Factors And Ethiology

In this study we have looked into the multiple risk factors and ethology for aggressive variants of papillary carcinoma of which most of them have been proven risk factors for classical papillary carcinoma thyroid. The risk factors we have analyzed include Smoking , Alcohol , Diabetes mellitus , Hypertension , Thyroiditis. According to the results in the current study, 26.3 % of the participants with diabetes mellitus and 25.1% of participants with hypertension showed association. Highest association with smoking was for diffuse sclerosing (50%) and clear cell (42%). But the is no statistical significant (p=0.4).

Hong et al [8] in their meta-analysis on alcohol intake and risk of thyroid cancer concluded that alcohol intake increased the risk of thyroid cancer. Controversies are reported in association of smoking and thyroid cancer. Smoking, however, is linked to a lower risk of thyroid cancer, according to a recent meta-analysis of 31 observational studies . There is still inconsistency in those results, though. A meta-analysis of 14 case-control studies published in 2003 found a significant trend toward lower risk of thyroid cancer, but this was not seen after adjustment for smoking [9].

Ionising Radiation exposure, especially in childhood, is the only established risk factor for developing thyroid cancer , hence it has been not looked into in this study. History of benign thyroid nodules/adenomas or goitre, iodine intake, obesity, and alcohol consumption may all increase the risk of developing thyroid cancer. Papillary thyroid cancer stood out from other histological types in terms of the strength of these associations.

A large sample single center study by Ling et al [10] reported Papillary thyroid carcinoma patients with hypertension , mostly males above 40 years of age were found to have invasive carcinoma. In the present study 43% of patients had association with Hypertension even though it is not statistically significant (p=0.3).

Asssociation Of Thyroiditis With Diagnosis

Out of 175 patients 34.3% (n=60) patients have thyroiditis at the time of diagnosis of papillary carcinoma. The Warthin's variation has the strongest associated (85%) among the aggressive variants of Papillary carcinoma. This

was followed by the tall cell (33%) and diffuse sclerosing (40%) subtypes. Yeo et al [11] was found that WLPTCs were associated with Hashimoto's thyroiditis at a higher rate than classic PTCs (93% vs. 36%, respectively; P 0.001) and that they had a lower rate of BRAF mutation than classic PTCs (65% vs. 84%, respectively; P = 0.007).

Autoimmunity and chronic lymphocytic thyroiditis have shown a concomitant rise along with PTC over the years. The possibility of autoimmune thyroiditis (AIT) as a predisposing factor for papillary thyroid carcinoma has been suggested. Therefore the lymphocytic infiltration in PTC could either be a risk factor for papillary carcinoma or it could be a reaction to the tumour. This leaves the possibility that papillary carcinoma tends to develop in thyroids having lymphocytic thyroiditis.

Extrathyroid Extension / Fixity

Postoperative HPE reported extra thyroid extension commonly seen in tall cell, clear cell, diffuse sclerosis, Warthin variant with highest association in clear cell variant (80%). [12] Cherearu et al reported Diffuse sclerosis type had 77% extrathyroidal extension while in this study 100% of patients with diffuse sclerosing had fixity and it is statistically significant (p=0.001) . Extrathyroidal extension is reported in 23.5% of papillary thyroid carcinomas and it is considered as adverse prognostic factor associated with increased risk of recurrence and mortality.

Limitations of this study:

- As the study was a single institutional study, the trends around the other districts of kerala couldn't be accessed
- The sample size is limited as aggressive variants of papillary carcinoma is rare and patients visit was affected with COVID pandemic

Conclusion:-

1. Over the past five years, the incidence of aggressive variants of papillary thyroid carcinoma (PTC) has consistently increased, with the highest number of cases reported in 2021-2022. Among these aggressive variants, the tall cell variant is the most common, comprising 141 cases (80%).
2. Aggressive PTC variants have a high rate of local recurrence.
3. The most common site of recurrence noted in our study is in the lymphnodes n=35(50.7%) and second most common site is the thyroid bed n=28(40.7%) with is similar to the recurrence site for classical PTC
4. Similar to classical PTC , our study also observed females predominance n=105(60%) in the aggressive variants of papillary carcinoma, However the mean age group was slightly higher in aggressive variants. Exception is seen in case of Wartins tumor, where younger age groups are predominantly involved 38+/- 14.
5. Thyroiditis was identified as an independent risk factor for developing aggressive PTC variants, with statistical significance ($p < 0.005$).
6. Hypothyroidism was also found to a risk factor associated with aggressive variants
7. No other risk factors analyzed in our study was found to be statistically significant
8. Early diagnosis along with meticulous surgical resection and close follow-up is critical in deciding disease free survival, as aggressive variants of PTC has been found to have more chance of Local recurrence.
9. In view of the exponential increase in the number of thyroid cancers as reported by Surveillance, Epidemiology, and End Results (SEER) database in 2018 [1,2], it wound be worthwhile to initiate a large population based study, to ascertain the pattern of thyroid cancers across the states.

Tables

Table 1:- Incidence of aggressive variants of PTC from 2017 -2022.

	DIAGNOSIS					
YEAR	TALL CELL (%)	CLEAR CELL (%)	DIFFUSE SCLEROSIS (%)	HOBN AIL (%)	WARTHIN VARIENT (%)	ONCOCYTIC VARIANT (%)
2017 – 2018 n=22	17 (77.5)	0 (0)	2 (9)	0	1(4.5)	2 (9)
2018-2019 n=25	22 (88)	0	1 (4)	0	1 (4)	1 (4)
2019-2020 n=36	34 (94)	0	1 (2.7)	1 (2.7)	0	0
2020-2021 n=45	31 (68)	4 (8.8)	4 (8.8)	2 (4.4)	4 (8.8)	0
2021-2022 n=47	38(80.8)	1 (2)	3 (6.3)	3 (6.3)	2 (4.2)	0

Table 2:- Distributionofhistologicalvariants.

DIAGNOSIS	FREQUENCY n=175	PERCENTAGE (%)
TALLCELL	141	80.6
CLEAR CELL	5	2.9
DIFFUSESCLEROSIS	10	5.7
HOBNAIL	8	4.6
WARTHINVARIENT	7	4.0
ONCOCYTICVARIANT	4	2.3

Table 3:- Recurrence Rate among the aggressive variants of PTC.

RECCURENCE	DIAGNOSIS					
	TALLCELL (%)	CLEAR CELL (%)	DIFFUSESCLEROSIS (%)	HOBNAIL (%)	WARTHIN VARIENT (%)	ONCOCYTICVARIANT (%)
Yes n= 69	54 (38.3)	4 (80)	5 (50)	2 (25)	2 (28.6)	2 (50)
No n=106	87 (61.7)	1 (20)	5 (50)	6 (75)	5 (71.4)	2 (50)

Table 4:- Site of recurrence in the aggressive variants of PTC.

Recurrence	Frequency n=69	Percentage
LN	35	50.7
Thyroid bed	28	40.7
PeriThyroidal Tissue	3	4.3
Distant recurrence	3	4.3

Table 5:- Association of Thyroiditiswith Aggressive variants of PTC.

THYRODITIS	DIAGNOSIS						P Value
	TALLCELL (%)	CLEAR CELL (%)	DIFFUSESCLEROSIS (%)	HOBNAIL (%)	WARTHIN VARIENT (%)	ONCOCYTICVARIANT (%)	**0.05**
Yes n=60	47 (33.3)	1 (20)	4 (40)	1 (12.5)	6 (85.7)	1 (25)	
No n=115	94 (66.7)	4 (80)	6 (60)	7 (87.5)	1 (14.3)	3 (75)	

References:-

1. Janeesh Sekkath Veedu, Kevin Wang, Feitong Lei, Quan Chen, Bin Huang, Aju Mathew: Trends in thyroid cancer incidence in India. 10.1200/JCO.2018.36.15_suppl.e18095
2. Lane B. Donaldson, Flora Yan, Patrick F. Morgan : Hobnail variant of papillary thyroid carcinoma: a systematic review and meta-analysis.. 10.1007/s12020-020-02505-z
3. Karkuzhali P, Yogambal M, Kumar M: An Indian Tertiary Care Hospital Scenario of Papillary Carcinoma of Thyroid. J Clin Diagn Res. 2017, 11:26-29. 10.7860/JCDR/2017/27673.10095
4. Ronald A Ghossein 1, Rebecca Leboeuf, Kepal N Patel, et al.: Tall cell variant of papillary thyroid carcinoma without extrathyroid extension: Biologic behaviour and clinical implications. Thyroid. 2007, 17:655-61. 10.1089/thy.2007.0061

5. Jian Zhu, Xinli Wang, Xiaoxuan Zhang, et al.: Clinicopathological features of recurrent papillary thyroid cancer. DiagnPathol 10. 96
6. Ywata de Carvalho A, Kohler HF, Gomes CC, Vartanian JG, Kowalski LP: Predictive factors for recurrence of papillary thyroid carcinoma: analysis of 4,085 patients. 2021, 41:236-242. 10.14639/0392-100X-N1412
7. Indu Elizabeth Mathew, Aju Mathew: Rising Thyroid Cancer Incidence in Southern India: An Epidemic of Overdiagnosis?. 10.1210/js.2017-00097
8. Seung-Hee Hong, Seung-Kwon Myung, Hyeon Suk Kim: Alcohol Intake and Risk of Thyroid Cancer: A Meta-Analysis of Observational Studies. 10.4143/crt.2016.161
9. Cho YA, Kim J: Thyroid cancer risk and smoking status: a meta-analysis. 2014, 25:1187-95. 10.1007/s10552-014-0422-2
10. Ling-Rui Li, Jun-Long Song, Han-Qing Liu, et al.: Hypertension Was Associated with Higher Tumor Stages in Papillary Thyroid Cancer: A Large Sample Single-Center Study. 10.1089/met.2022.0033
11. Yeo, Lee, Kim, et al.: The Warthin-Like Variant of Papillary Thyroid Carcinoma: A Comparison with Classic Type in the Patients with Coexisting Hashimoto's Thyroiditis. 2015, 10:1155/2015
12. Nathalie Chereau, Xavier Giudicelli, Francois Pattou: Diffuse Sclerosing Variant of Papillary Thyroid Carcinoma Is Associated With Aggressive Histopathological Features and a Poor Outcome: Results of a Large Multicentric Study. 10.1210/jc.2016-2341.