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Original Research Article

Multivariate analysis of histopathological features as prognostic factors in fifty cases of thyroid neoplasm: a retrospective study done at tertiary care centre

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ABSTRACT

Background: Number of prognostic factors for thyroid carcinoma have been identified including age, gender and tumor characteristics, such as histology and stage. The importance of these factors as independent predictors of survival for patients with differentiated thyroid carcinoma has been extensively studied but remains uncertain.
Methods: A retrospective analysis of 50 thyroid carcinomas was made to assess prognostic factors including histological variants from September 2019 to February 2022 at our centre. The surgical and histopathological data were studied.
Results: 72% patients had papillary thyroid cancer. Multivariate analysis was done and factors showing prognostic significance were tumour size, extrathyroid extension, extranodal extension, lymphovascular, perineural invasion, histological type, necrosis, focality, capsular invasion were found to have poor prognosis.
Conclusions: There are histopathological factors which can modify the course and influence the line of treatment of thyroid neoplasms.

Keywords: Thyroid carcinoma, Prognosis, Focality, Histological, Thyroidectomy

INTRODUCTION

Thyroid carcinomas (TCs) usually arise from follicular epithelial cells. Among them, less frequent are medullary TCs of neuroendocrine origin and least are thyroid tumors of mesenchymal origin.[1] Further classification considering the genetic profile is necessary.[2] TCs are divided into three main groups based on histopathological findings: well differentiated (DTCs), poorly differentiated (PDTCs), and undifferentiated or anaplastic TCs (ATCs). DTCs are most prevalent, with most common being papillary thyroid carcinoma (PTC), followed by follicular thyroid carcinoma (FTC). Great diversity exists within the PTC group, consisting of several subtypes based on distinct histopathological features, genetic molecular findings, aggressiveness, and prognosis.[1-6] The most frequent are typical and follicular variants, but the most adverse are tall cell and diffuse sclerosing variants of PTC.[5-8] FTC is the second most common TC, and according to the WHO classification is characterized by relatively well-differentiated cancer cells and absence of typical nuclear features of PTC.[9-11] Anaplastic thyroid

cancer (ATC) is a rare and aggressive form of TC, accounting for 1% to 2% of all TC. Although the incidence of DTC is increasing, due to increased diagnoses of microPTC, the incidence of AC appears stable over the last few decades. On the contrary, mortality from this cancer is proportionately high accounting for 20% to 50% of all TCs.[12,13] Clinical and constitutional findings are important for the initial risk stratification and prognosis, but dynamic risk stratification and re-evaluation of the prognostic factors are also important during the follow-up period.[14] The objective of our study was to evaluate the prognostic influence of histopathological parameters in a retrospective study done in a tertiary cancer care centre in 50 cases of thyroid neoplasm during September 2019 to February 2021.

METHODS

A retrospective analysis based on data retrieved from the pathology department at Bhagwan Mahaveer Cancer hospital and research centre, Jaipur, Rajasthan across a study period of 1.5 years was conducted. The histopathology reports of thyroid neoplasm patients were undertaken from September 2019 to February 2021.

Inclusion and exclusion criteria

The inclusion criteria of patients for this analysis were as follows: all lobectomies/hemithyroidectomy/subtotal thyroidectomy/near total thyroidectomy/total thyroidectomy specimens received at the pathology department, BMCHRC during study period. All age group and both genders are included. All thyroid lesions including benign as well as malignant. The exclusion criteria were: Incisional biopsies of thyroid lesions, Outside operated cases (where no details are available).

A total of 14,507 patients visited the hospital for various ailments and 10,200 biopsies were sent to our department for histopathological examination, out of which 7200 were diagnosed as malignant cases. Of the 7200 malignant cases, 408 (5.6%) cases were thyroid malignancies. One hundred forty five (35.53%) out of 408 thyroid cancers underwent thyroid surgeries, Fifty consecutive cases who fulfilled the inclusion criteria were registered in our study. Relevant history, examination findings, age and clinical diagnosis were recorded from hospital registration form. Gross examination findings of specimens were recorded. All grossed, processed, stained sections of haematoxylin and eosin were reviewed and observed under microscope. All the cases were reported as per CAP protocol Thyroid. The slides were thoroughly examined and following points were considered regarding tumor prognostic factor like serum markers, location and size of tumor, appearance of the tumor (proliferative/infiltrative/ulcerative), Focality, distances from margins (Capsule/Surgical Resection margin/random margins), lymph node status, histological subtype, stage, lymphovascular invasion, perinural invasion, necrosis, margin, Extrathyroidal Extension, Extranodal Extension, pTNM staging, distant metastasis and Association with Hashimoto thyroiditis.

Data were described in terms of range; mean±standard deviation (SD), frequencies (number of cases) and relative frequencies(percentages) as appropriate. For comparing categorical data, Chi square ($\chi 2$) test was performed and exact test was used when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using (Statistical Package for the Social Science) SPSS 21 version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

RESULTS

Age range in this study varies from 22 to 77 years. Youngest case was of 22 years and oldest was 77 years of age. The median age for both male and female was 44.80 years and standard deviation was 15.04. 58% patients were female while remaining 42% were male, F:M ratio 1.38:1. Malignancy was found in right lobe (32%) followed by left lobe (26%) then bilateral lobe (20%) and bilateral lobe along with Isthmus (14%) and each 4% by isthmus and left lobe along with isthmus. 4% of patient had benign etiology where as 96% patients had malignant tumors. All benign cases 4% were trabecular sdenoma as shown in (Figure 1) whereas among malignant majority were papillary carcinoma, shown in (Figure 2) around 72% followed by lesser common follicular carcinoma 14%, shown in (Figure 3) and least among all follicular variant of papillary carcinoma 10%, shown in (Figure 4). (1/2) Benign case underwent lobectomy and other (1/2) underwent total thyroidectomy. Majority of the patients underwent lobectomy 58% followed by sub-total thyroidectomy 20%, total thyroidectomy 14% and 4% each cases undertook hemithyroidectomy and isthumectomy. Among benign cases (1/2) cases were each multifocal and unifocal. overall data shows majority tumors were unifocal (62%) whereas multifocal were 38%.

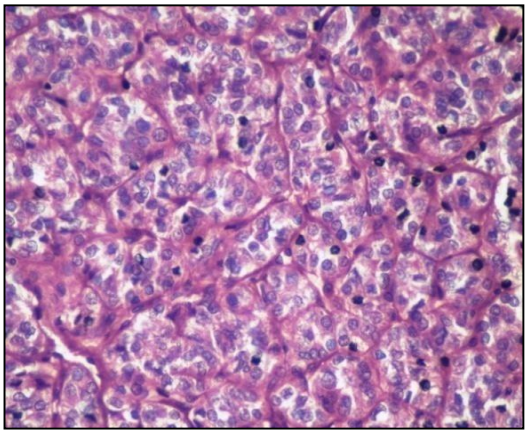

Figure 1: HandE 40X trabecular adenoma.

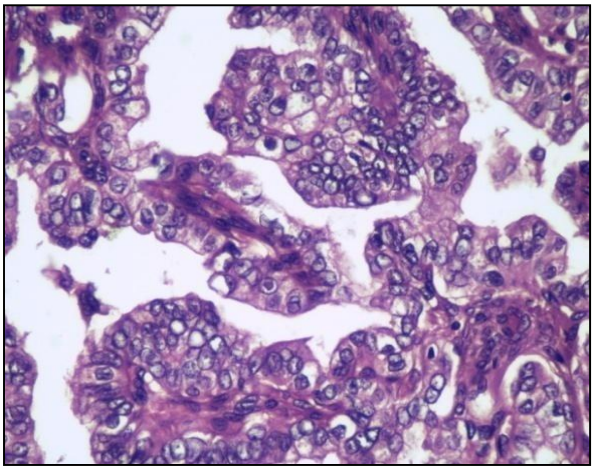

Figure 2: HandE 40X papillary carcinoma thyroid.

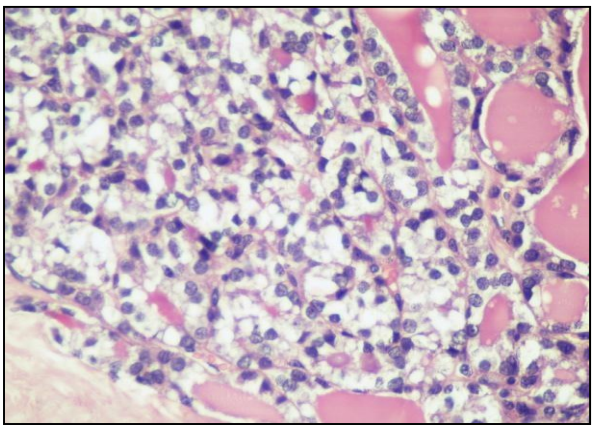

Figure 3: H and E 40X follicular carcinoma thyroid.

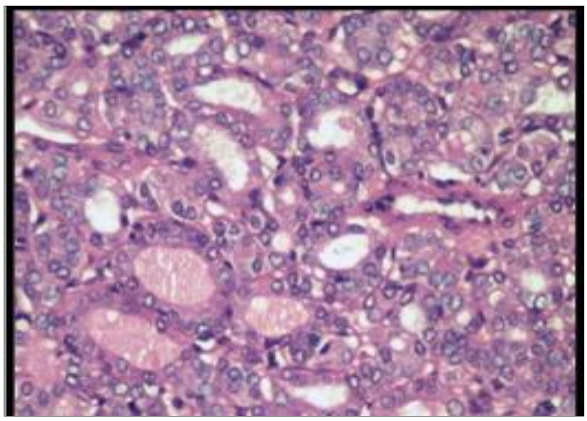

Figure 4: H and E 40X follicular variant of papillary carcinoma thyroid.

In the present study, among malignant cases 52% cases had Intact Capsule, 38% showed invasion, focal Invasion was seen in 65% cases and 4% cases had distance of 1mm (<5 mm). Majority of tumor 50% did not show lymphovascular invasion (LVI) whereas it was seen in 46% cases. 92% malignant cases did not show perineural invasion (PNI). 4% cases showed PNI. 30% cases did not show necrosis followed by 28% cases having 5-10% necrosis, 26% cases having ≤5% necrosis, 8% cases had 10-15% necrosis whereas 6% and 2% cases having >20% and 15-20% necrosis seen. 76% cases did not show extrathyroidal extension (ETE), whereas it was seen in 20% cases. 48% cases did not show extranodal extension (ENE), 22% cases showed ENE whereas in 26% cases Nodes were not assessed. Out of 50 cases, 94% cases did not show distant metastasis whereas 2% cases showed metastasis.

Table 1: Correlation of prognostic factors in thyroid malignancies with statistically significant p values.

Parameters						
Capsule	**N0**	**N1**	**N0**	**N1**	**N0**	**N1**
FCT	0	0	0	0	4	0
FVPCT	1	0	0	0	0	2
PCT	0	1	4	9	4	9
Total	1	1	4	9	8	11
P value	0.157		-		0.022	
LVI	**S**		**NS**			
	N0	**N1**	**N0**	**N1**		
FCT	4	0	0	0		
FVPCT	0	2	1	0		
PCT	2	10	6	9		
Total	6	12	7	9		
P value	0.005		0.242			
PNI	**S**		**NS**			
	N0	**N1**	**N0**	**N1**		
FCT	0	0	4	0		
FVPCT	0	0	8	2		
PCT	0	2	1	7		
Total	0	2	13	19		
P value	-		0.035			

Continued.

Parameters								
ETE	**NS**		**S**					
	N0	**N1**	**N0**	**N1**				
FCT	3	0	1	0				
FVPCT	1	1	0	1				
PCT	8	12	0	7				
Total	12	13	1	8				
P value	0.152		0.011					
ENE	**NS**		**S**		**NA**			
	T1-2	**T3-4**	**T1-2**	**T3-4**	**T1-2**	**T3-4**		
FCT	3	0	0	4	0	0		
FVPCT	2	0	1	0	1	1		
PCT	6	2	15	4	4	5		
Total	11	2	16	8	5	6		
P value	0.677		0.007		0.887			
Focality	**T1-2**		**T3-4**					
Unifocal	24		6					
Multifocal	8		10					
Total	32		16					
P value	0.025							
ENE	**PNI**							
	S		**NS**					
S	2		9					
NS	0		24					
NA		13						
P value	0.0327							
ETE stage								
ENE		**S**		**NS**				
	I	36		6				
	II	2		3				
	IVB	0		1				
P value	0.008							
ETE-ENE		**S**		**NS**				
	S	7		4				
	NS	2		22				
	NA	1		12				
P value	0.0005							
Necrosis								
Stage		**<5%**	**5-15%**	**15-20%**	**>20%**	**NS**		
	I	12	15	1	1	13		
	II	1	3	0	1	0		
	IVB	0	0	0	1	0		
P value	0.010							
Distant metastasis								
Stage		**NS**		**S**				
	I	42		0				
	II	5		0				
	IVB	0		1				
P value	0.0001							
Multifocal pct with capsular invasion		**N0**	**N1**	**Nx**				
		1	11	2				
		14						
P value		0.0031						
Laterality		**Isthmus**		**Rt lobe**		**Lt lobe**		**Rt, Lt lobe with isthmus**
		N0	**N1**	**N0**	**N1**	**N0**	**N1**	**N0**	**N1**
FCT		-	-	1	0	1	0	1	0
FVPCT		-	-	1	0	0	1	0	1
PCT		1	1	4	3	2	4	0	5
P value		-		0.526		0.315		0.030	

FTC: follicular thyroid carcinoma; FVPCT: follicular variant of papillary thyroid carcinoma; PCT: papillary thyroid carcinoma; LV: lymph vascular invasion; PNI: Perineural invasion; ETE: Extrathyroidal extension; ENE: Extranodal extension.

Table 2: Correlation of prognostic factors in thyroid malignancies with statistically insignificant p values.

Parameters Age (years)	<30		31-40		41-50		>50	
H. sub type	T1-2	T3-4	T1-2	T3-4	T1-2	T3-4	T1-2	T3-4
FCT	0	1	0	1	1	0	2	2
FVPCT	0	0	2	0	1	0	1	1
PCT	4	3	6	3	7	2	8	3
P value	0.285		0.223		0.543		0.878	
H. sub type	N0	N1	N0	N1	N0	N1	N0	N1
FCT	1	0	1	0	0	0	2	0
FVPCT	0	0	0	0	0	1	1	1
PCT	1	6	3	4	1	3	3	6
P value	0.250		0.285		0.576		0.230	
Sex	**F**		**M**					
H. sub type	T1-2	T3-4	T1-2	T3-4	-			
FCT	2	2	1	2	-			
FVPCT	3	0	1	1	-			
PCT	13	7	12	4	-			
P value	0.363		0.325					
H. sub type	N0	N1	N0	N1	-			
FCT	2	0	2	0	-			
FVPCT	0	1	1	1	-			
PCT	4	10	4	9	-			
P value	0.106		0.174		-			
ETE	**NS**		**S**					
H. sub type	T1-2	T3-4	T1-2	T3-4	-			
FCT	3	3	0	1	-			
FVPCT	2	1	2	0	-			
PCT	23	6	2	5	-			
P value	0.319		0.132		-			

FTC: Follicular thyroid carcinoma; FVPCT: Follicular variant of papillary thyroid carcinoma; PCT: Papillary thyroid carcinoma; ETE: Extrathyroidal extension.

In present study, 40% cases were in T1 category, 30% cases belonged to T3 category. 24% cases were in T2 and only 2% cases were in T4. Out of 50 cases, Majority 42% cases had N1 stage whereas 26% cases showed N0 and in 28% cases Nx category is found. Only 8% cases showed association with hashimoto thyroiditis (HT) whereas 92% did not show association with HT. Statistically significant correlations relation between histological features are shown in (Table 1).

Among all malignant cases encountered, 87.5% cases had stage I, 10.41% cases had stage II and 2.08% cases had stage IVB. Only 8.33% of tumor were associated with hypothroidism belonging to stage I and 2.08% cases belonged to stage II whereas 79.166%, 8.33% and 2.08% belonging to stage I, II, IVB were not associated. 10.41% cases were found associated with hyperthyroidism and belonged to stage I 77.08%, 10.41% and 2.08% cases belonging to stage I, II, IVB were not associated with hyperthyroidism. No statistical significance was found between hypothyroidism, hyperthyroidism with stage of tumor. The (Table 2) shows histopathological cofactors that showed insignificant p value, FVPCT stands for follicular variant of papillary thyroid carcinoma in (Table 1-2).

DISCUSSION

The present study was carried out in department of pathology at centre from September 2019 to February 2021. Fifty consecutive cases who fulfilled the inclusion criteria were registered in our study. The assessment of prognostic factors in TC are relevant for planning the treatment.[15,16] There is handful of literature available regarding the value of the histopathological prognostic factors in TC.[17] Age has been categorized as an independent prognostic factor, a detailed correlation study of age has been done with increasing T, N stage. No statistically significant value was deduced in relating age with T3-4 with age 41-50 years and >50 years with p value 0.76 and 0.64 subsequently similarly lymphnode metastasis was compared with age groups, p value 0.576 and 0.230 were noted for 41-50 years and >50 years age group. Al-quahtani et al studied 252 thyroid specimens with age categorization of above and below 60 years. He deduced DTC in ≥60 years is more aggressive and associated with worse prognosis. Patients >60 years

experienced more locoregional recurrences, lymphnode metastasis (11.0%, p=0.025); similarly, more distant metastasis were observed (15.3%, p value 0.003).[18]

Tubiana et al conducted study on 542 thyroid specimens, he found age group >45 years showed higher relapse rate and distant metastasis with statistically significant p value 0.001 and higher rate of disease progression as compared to younger age group.[19] Studies report a poorer prognosis in men but others find no differences in sex.[20] It was correlated with advancing T, N. In regards to increasing N stage. Among females 22% patients showed positive lymphnodal metastasis whereas among males 20% of the patients showed positive lymphnodal metastasis. However, no statistical correlation could be established between sex of the patient and N stage with p value 0.106 and p value 0.174 for females and males. Similar findings found in comparing T stage with p value 0.363 and 0.325.

Rageh et al conducted study on 50 cases each for unifocal and multifocal PTC cases and stated capsular invasion with multifocality has higher rate of locoregional recurrence, is a predictor of both poor prognosis in TC and risk factors for central lymph node metastasis. The study stated statistically significant correlation to lymphnodal metastasis (p value 0.01) and recurrence rate (p value 0.01).[21] The recurrence was noted in 2% cases which showed multifocal PCT with capsular invasion. The multifocal PCT cases showing capsular invasion were analysed and found that 78.57% cases showed positive lymphnodal metastasis, 7.14% cases showed lymphnodal metastasis and 14.28% cases nodes were not addressed. Statistically significant correlation was established between multifocal papillary thyroid carcinoma (PCT) with capsular invasion and showing positive lymphnodal metastasis with p value 0.0031. The findings were consistent with above study. Among N stage, 22.91% cases showed positive lymphnodal metastasis and 16.66% cases showed lymphnodal metastasis in all cases of TC. Statistically significant correlation was established between N stage and capsular invasion with p value 0.022, which is consistent with above study. Akslen et al conducted study on 173 thyroidectomy specimens of TC and stated vascular invasion was identified as an independent prognostic factor. Although found in only 14% of the cases, its presence identifies a high-risk group with respect to TC deaths. Significant correlation was found between tumor infiltration and vascular invasion (p value 0.003).[22] In present study, among N stage of tumor 25% cases showed positive lymphnodal metastasis and 12.5% cases showed lymphnodal metastasis. Statistically significant correlation was found between N stage and LVI with p value 0.005. All 4% cases showing PNI were found to show LVI. The findings were consistent with above study.

Perineural invasion (PNI) has rarely been described and appears to occur in only 2% of TC. Rowe et al studied PTC (N=75), FTC (N=13), and benign thyroid tissues (N=26). PNI was associated with aggressive tumours and were associated with ETE. According to statistical analysis, it was present in 35% of PTC whereas no significant data retrieved for FTC and was independently associated with ETE (p=0.008).[23] Among the cases, all 4% cases showing PNI also showed ETE. Statistically significant correlation was found between ETE and PNI with p value 0.0327 and odds ratio 0.0654. All 4% cases showed positive lymphnodal metastasis which was consistent with bad prognosis. The incidence of gross ETE in DTC ranges from 5% to 34%, with relapse rate occurrence of 25-40%. Simpson et al conduted study 1074 patients with PTC and 504 with FTC followed for 4 to 24 years and stated ETE is also a potent prognostic factor, for PCT and FCT, had much poorer survival rates than those whose cancers did not (p<0.0001). Association of ENE along with ETE carried worse prognosis then any of the entity alone.[24] In present study, nodes were not accessed in 2% cases showing ETE. Remaining 80% cases showed positive lymphnodal metastasis,10% cases did not show lymphnode metastasis. Statistically significant correlation was found between N stage and ETE with p value 0.011. Among ETE case, 30% cases and 10% cases elonged to stage II, IVB along with majority 60% belonged to stage I. Statistically significant correlation was found between stage of tumor and ETE with p value 0.008. The findings were consistent with above study. Wu et al reported 240 patients with PTC stated frequent ENE coexists with lymph node status1b (95%) and ETE. The disease specific survival and recurrence free survival curve between patients with and without ENE differ significantly (p<0.0001). Of the 43 older patients without ENE none died from PTC, this is in contrast to 12 deaths from PTC among 27 patients who had ENE.[25] 64% cases showed ENE along with ETE whereas 36.36% cases did not show ETE. Statistically significant correlation was found between ETE and ENE with p value 0.0005. Absence of ENE was seen in maximum cases and no prognostic relevance could be gathered with its absence in cases showing p value 0.007 while comparing T stage. The findings were consistent with above study.

Alksen et al conducted study on 173 patients who were surgically treated for TC and stated 58.5% survival for 10 years in the patients with necrosis with tumor size less than 30 mm, compared with 93.4% in the other group (p<0.00005) with large tumor size.[22] Among stage of tumor, 2.08% cases EAC were found in stage I, II, IVB. Statistically significant correlation was found between increasing Necrosis and stage of tumor with p value 0.010. The above findings were found consistent with the study. Simpson et al conducted study on 1074 PTC cases and 504 FTC cases, stated that distant metastasis did not prove to be significant for cause-specific survival among patients with papillary cancer which was reflected in infrequent distant metastasis, the younger patients live with them for years.[23] Correlation of distant metastasis with stage of tumor was analysed. 2.08% cases that showed distant metastasis belonged to stage IVB and

statistically significant correlation was found. In our study following limitations were encountered the histopathological examination is the gold standard for the diagnosis of thyroid neoplasms. However, the morphological overlap is oftenly found in various cases and analysis is difficult. Numerous studies have found statistically significant inter and intra-observer variation in categorizing benign and malignant cases. Categorizing tumors as benign and malignant is important because of differences in line to surgery correlating to poor prognosis of malignancies, high recurrence rate and radio ablation therapy, in order to improve the disease-free survival rate of the patient. Our study was conducted at a Tertiary Cancer Care Hospital in a semi-urban setting so the frequency of malignant cases was higher than benign.

CONCLUSION

PTC is a common malignant neoplasm with excellent clinical behaviour even with lymph node metastases; however, there are histological factors, which can modify the course of these neoplasms. Therefore, we consider in this paper histological factors that influence line of treatment in TC. In conclusion, the prognosis of TC is strongly associated with variables as follows capsular invasion, LVI, PNI, ETE, ENE, Necrosis, Distant metastasis, increased tumor size.

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