

Factors Determining Risk Categories in Differentiated Thyroid Carcinoma: Study of an Indian Cohort

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Abstract

Introduction: Differentiated thyroid carcinoma/cancer (DTC) burden in developing countries could be different from that of the developed nations. **Aims and Objectives:** To describe the clinicopathological characteristics in a cohort of DTC patients in a south Indian state of Kerala and to compare with the data from other centres. **Materials and Methods:** A retrospective analysis of the data collected on DTC patients, from January 2010 to August 2018, attending thyroid cancer clinic at a tertiary care centre. **Results:** Among the 944 patients (male 262; female 682; mean age 43.8 years; standard deviation, SD 13.8), types of tumour were as follows: classical papillary thyroid carcinoma (cPTC) 48.3%, follicular variants of PTC (FVPTC) 28.8%, follicular and hurthle cell carcinoma (FTC&HCC) 10.1%. Mean size of the tumour was 2.7 cm (SD 1.8) papillary thyroid micro carcinomas (PTMC) were seen in 113 patients (12%), which were detected incidentally. Metastases were present at diagnosis in 40.2% cases, most common site being cervical lymph nodes. Distant metastases were seen in 113 patients (14.5%) and commonest site was bone. The American Thyroid Association (ATA) risk stratification was possible only in 684 subjects and showed 31.3% low risk, 41.8% intermediate risk and 26.9% at high-risk category. Lymph node metastasis and distant metastasis were the commonest determining factors for intermediate and high-risk category, respectively. High-risk category was significantly higher in patients >55 years, tumour size >4 cm, FTC/HCC tumour type and extranodal extension (ENE) of lymph node metastasis. Radio active iodine ablation was given to 85.2% subjects. **Conclusion:** In our DTC population, FVPTC formed the second most common type and PTMC were all incidentalomas. Metastasis at diagnosis was higher suggesting delayed presentation. Old age, FTC/HCC, large size of the tumour, ENE were significantly higher in high-risk patients. Rest of the features of these cohort was comparable with the United States cohort of DTC patients.

Keywords: American Thyroid Association risk stratification, clinicopathological characteristics, differentiated thyroid cancer/carcinoma, Indian population

INTRODUCTION

Differentiated thyroid cancer/carcinoma (DTC) accounts for >90% of thyroid cancers and comprises of two major histological types: papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). Hurthle Cell Carcinoma (HCC), which also belongs to DTC, is uncommon. Despite the rising incidence, prognosis of DTC remains excellent, with a 10-year cancer-specific survival of up to 90%.^[1] As per the National Cancer Registry Program of the Indian Council of Medical Research 2012–2014, thyroid cancer is among the top 10 cancers in women after breast cancer in the districts of Thiruvananthapuram and Kollam, southern state of Kerala. The age adjusted incidence rates were 13.3/100000 women at Thiruvananthapuram and 12/100000 at Kollam. The presentation and outcome of DTC in developing countries

could be different from that of the developed nations. Data of the disease burden and clinicopathological characteristics from this part of the world are limited.

The primary objective of the present study was to describe the clinicopathological characteristics of a cohort of DTC patients managed at the Thyroid Cancer Clinic of Amrita Institute of

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Medical Sciences (AIMS), a tertiary care centre in Kochi, Kerala over a period of 10 years. The secondary objective was to examine the relationship between patient and tumour-related factors and the American Thyroid Association (ATA) 2009 risk categories.

MATERIALS AND METHODS

This was a retrospective analysis of data on DTC collected from January 2010 to August 2018 at AIMS. Consecutive cases were taken from the prospectively maintained thyroid carcinoma database, set up in 2010. Present study consisted of 944 DTC patients who were followed and managed under the supervision of a single senior Endocrinologist at the Thyroid Cancer Clinic of our institute from 2010. Medullary, poorly differentiated and anaplastic carcinomas were excluded from the study. This cohort was heterogenous as it included patients who underwent initial therapy for DTC at a peripheral centre and came to AIMS for follow-up, patients who received initial therapy for DTC from AIMS and continued follow-up, as well as those who underwent initial surgery elsewhere and completion surgery at AIMS. Since 2010, the ATA 2009 risk stratification system was implemented in the clinic. The 2015 risk stratification could not be applied because of lack of details in the outside histopathology reports (HPR). The follow-up used the response to therapy categories outlined and validated by Tuttle *et al.*^[2] Since 2009 guidelines had not specified which risk category follicular and hurthle cell carcinomas belonged, we included our small numbers of these two types as intermediate category.

The study was approved by the institutional review board.

The ethics committee is obtained and also provide the date of the approval on 11 March 2019.

Statistical analysis

Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) software. For descriptive statistics, categorical variables were expressed as numbers and percentages. Continuous variables were summarized using mean and standard deviation (SD) in case of normal distribution of data. To test the statistical significance of patient and tumour-related factors with ATA risk categories, the Chi-square test was applied. A *P* value <0.05 was considered statistically significant.

Laboratory assays

Thyroglobulin (Tg) level was determined by the electrochemiluminescence immunoassay (Elecsys 2010-Cobas). Anti thyroglobulin antibody (Tg-Ab) was assessed using the ARCHITECT anti-Tg assay (Abbott, USA) from 2010 to mid-2017 (Upper limit 4.11 IU/mL). From July 2017, Tg-Ab was determined by Elecsys 2010-(Cobas) (measuring range: 10–4000 IU/mL upper limit being 115 IU/mL). TSH was assayed using the ARCHITECT TSH assay from 2010 to mid-2017. From

then on, the testing used the Elecsys 2010-(Cobas). The reference range is 0.005–100 µIU/mL with a functional sensitivity of 0.014 µIU/mL.

RESULTS

A total of 944 DTC patients were included in our study, the clinical profile of this cohort is given in Table 1. There were 262 males and 682 females (male to female ratio: 0.4:1). The mean age at presentation was 43.3 years (SD 13.9) (range: 8–81 years).

Nearly half of the subjects received initial surgical treatment at our centre whereas, the rest were treated initially at a peripheral centre and then referred to our centre. After initial evaluation at our centre, 57 of these outside patients (6%) underwent further surgical treatment.

Initial presentation

The most common clinical presentation was neck swelling in 816 patients (86.4%), which included solitary nodule, multinodular goiter and cervical adenopathy. However, in 40 patients, distant metastasis was the first manifestation of DTC. There was one lingual thyroid carcinoma and one fluoro deoxy glucose positron emission tomography/computed tomography (FDG PET/CT) detected thyroid nodule that turned out to be DTC.

Pattern of initial thyroid surgery

Among this cohort, 515 subjects (55.5%) had total thyroidectomy (TT) alone while 196 subjects (21.4%) had some form of lymph node dissection (LND). Completion thyroidectomy was necessary for 128 (13.5%) subjects.

Histopathological characteristics

The most common tumour type was classical cPTC followed by follicular variants of PTC (FVPTC) [Table 2]. There were 113 (12%) papillary thyroid micro carcinomas (PTMC) which were found incidentally post thyroidectomy for other thyroid disorders such as multinodular goiter, Graves disease, etc.

Table 1: Clinical profile of the study population (n=944)

Variables	Number (%)
Mean age	43.8 years (SD 13.8)
Age category	
<20 years	34 (3.6)
20-40 years	352 (37.3)
40-60 years	428 (45.3)
>60 years	130 (13.8)
Gender distribution	Females 682 (72.8) Males 262 (27.2) M:F 0.4:1
Institution of initial therapy	
Surgery done at institution:	469 (49.7)
Surgery done at peripheral center:	418 (44.3)
Both	57 (6)

Metastasis at diagnosis

Metastasis was present in 113 (41.5%) subjects most commonly to lymph nodes (n 231 34%). The distant metastases at diagnosis was seen in 14.5% and locations were as given in Figure 1.

ATA 2009 risk stratification

ATA risk stratification at 6 months was possible only in 684/944 (72.5%) patients. Of these, 214 (31.3%) were at low risk, 286 (41.8%) were at intermediate risk and 184 (26.9%) were at high risk.

Factors determining high risk category

The features that made patients high risk are demonstrated in Figure 2. Among the 184 patients with high-risk category, 113 patients (61.4%) had distant metastasis. Among the rest, gross extrathyroidal extension alone was the reason for high risk in 46 subjects, high Tg value >100 ng/mL alone was the cause of high risk in 18 patients and remaining 7 subjects had both gross ETE and high TG value.

Intermediate-risk category

Among the 286 patients belonging to intermediate-risk category group, 167 (58.4%) patients had lymph nodal metastasis whereas histopathological features alone was the cause of intermediate risk in 73 patients, iodine uptake outside thyroid bed in the post iodine therapy scan alone contributed to intermediate risk in 27 subjects. Remaining subjects had combination of these features [Figure 3].

Comparison of ATA risk categories

When the distribution of tumour-related factors and age as well as gender were compared in three risk categories [Table 3]: older age, FTC and larger tumours were more common in high-risk group compared to low- and intermediate-risk categories. On the one hand, gender and tumour focality were comparable in all risk categories. On the other hand, both capsular invasion and ENE were higher in high risk compared with the intermediate category. Presence of lymphocytic thyroiditis (LT) was significantly lower in high-risk patients compared to other two categories.

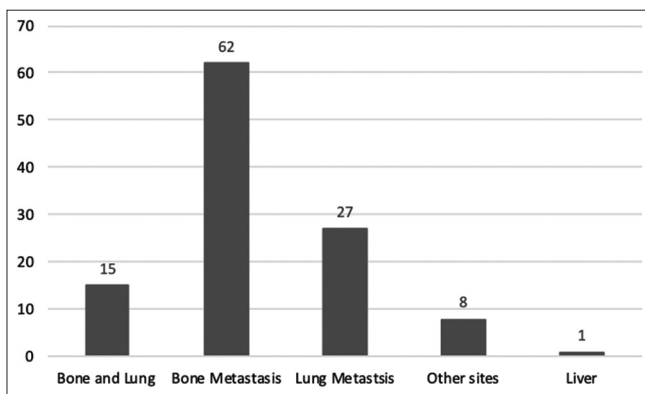


Figure 1: Distribution of the location of distant metastases at diagnosis (n 113/776)

Table 2: Baseline Histopathological Characteristics of the cohort (n=717)

Characteristics (number of subjects)	n (%)
Tumour type (n 944)	
Classical papillary thyroid carcinoma	455 (48.3)
Papillary thyroid micro carcinoma	113 (12.0)
PTC with poorly differentiated areas	8 (0.8)
Variants of papillary thyroid carcinoma	272 (28.8)
Follicular variant (FVPTC)	212
Tall cell variant	49
Columnar variant	2
Diffuse sclerosing variant	1
Oncocytic variant	7
Warthin Variant	1
Follicular thyroid carcinoma (FTC)	78 (8.3)
Hurthle cell carcinoma (HCC)	18 (1.9)
Tumour size (n 717) (mean)	2.7 cm (SD1.8 cm)
<2 cm	292 (40.7)
2-4 cm	315 (43.9)
>4 cm	110 (15.3)
Tumour location (n=762)	
Unifocal	483 (63.4)
Multifocal	279 (36.6)
Capsular invasion (n=651)	Present: 300 (46.1)
Vascular Invasion (n=587)	Present: 191 (32.5)
Extrathyroidal extension (n 567)	
Present	171 (30)
Microscopic	107
Gross and microscopic	64
Lymphocytic Thyroiditis (n 605)	
Present	344 (56.9%)
Metastasis at presentation (n 776)	322 (41.5)
Lymph nodal mets alone	209
Distant mets alone	91
Both lymphnode and distant mets	22
Lymphnode metastasis (n 678)	
Present	231 (34%)
Number of nodes <5	138
>5	93
Extranodal extension present	88 (35.5)

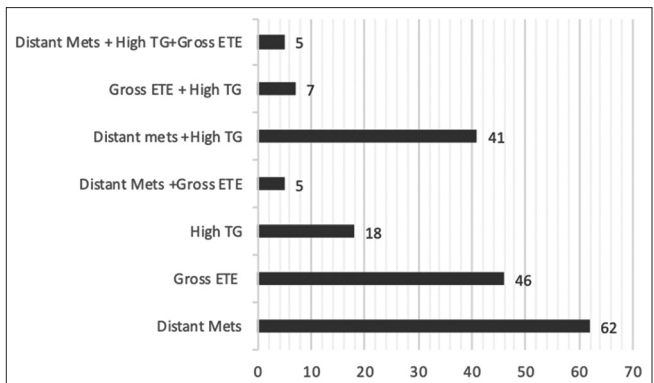


Figure 2: Distribution of features contributing to high-risk category (n 184). Distant mets – distant metastasis detected at the time of diagnosis by any mode of imaging, Gross ETE – gross extrathyroidal extension of the tumour, high Tg – postoperative preablation thyroglobulin level > 100

Table 3: Distribution of tumour and patient related factors in ATA risk categories

Patient and Tumour-Related Factors	ATA risk category			P
	Low n 214 (31.2%)	Intermediate n 286 (41.8%)	High n 184 (27%)	
Age category (n 684)				<0.001
<55 years	174 (33.3)	239 (45.8)	109 (20.9)	
>55 years	40 (24.7)	47 (29.0)	71 (46.3)	
Gender				NS
Male (n 196)	50 (25.5)	95 (48.4)	51 (26)	
Female (n 488)	164 (33.6)	191 (39.1)	133 (27.3)	
Tumour type				<0.001
PTC and variants (n 622)	208 (33.4)	267 (42.9)	147 (23.6)	
FTC and HCC (n 62)	6 (9.7)	19 (30.6)	37 (59.7)	
Size (n 589)				<0.001
<2 cm	121 (49.6)	96 (39.3)	27 (11.1)	
2-4 cm	59 (23.6)	123 (49.2)	68 (27.2)	
>4 cm	21 (22.1)	34 (35.8)	40 (42.1)	
Tumour foci (n 610)				NS
Unifocal	141 (37.2)	153 (40.4)	85 (22.4)	
Multifocal	69 (29.9)	106 (45.9)	56 (24.2)	
Capsular invasion (n 576)				<0.001
Present	20 (8.2)	120 (48.2)	110 (43.7)	
Absent	181 (55.5)	118 (36.2)	27 (8.3)	
Lymphocytic thyroiditis (n 525)				<0.001
Yes	100 (36.6)	134 (49.1)	39 (14.3)	
No	87 (34.5)	90 (35.7)	75 (29.8)	
Presence of ENE in LN mets (n 559)	-	51 (30.5)	37 (57.8)	<0.001

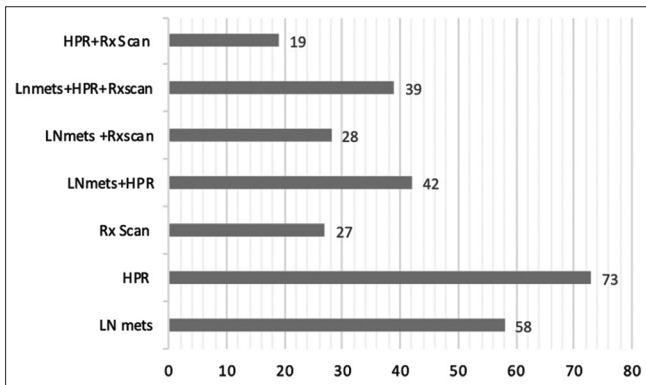


Figure 3: Distribution of factors determining intermediate risk category (n 286). LN mets – Lymph Node metastasis, HPR - histopathological features (Vascular invasion, microscopic extra thyroidal Invasion, Aggressive histology of tumour) Rx scan - Post RAI therapy scan showing Uptake in neck outside Thyroid Bed

DISCUSSION

This study represents a single-institution experience with DTC patients from a tertiary care centre of a developing nation. We described the clinicopathological characteristics and factors that contribute to ATA risk categories in this cohort of DTC and compared this with the data from other countries. Female predominance was seen in our cohort as in other series. Nearly 34 patients, in this cohort, were <20 years.

The commonest form of initial surgical treatment was total thyroidectomy followed by thyroidectomy with LND but about 13.6% needed completion thyroidectomy due to inadequate initial surgery.

Nearly half of the patients had initial surgical treatment outside, which has resulted in lack of HPR details and risk stratification in almost one third of the study. In our cohort, the most common type of tumour was cPTC followed by FVPTC, the two together making up the bulk of cases. Small number of PTMC in this cohort were found incidentally. FTC and HCC formed 10% of our cohort. Compared to other studies, tumour size was higher in this cohort, with almost 60% presenting with >2 cm tumours.^[3,4] This may be due to late presentation or delay in seeking treatment. In this cohort, capsular invasion was reported more common than vascular and extrathyroidal extension.

Though neck swelling was the commonest mode of presentation of DTC, in 4.2% (40/944) of our cohort, the first manifestation of DTC was as distant metastasis. Almost 40% of our population had metastasis at presentation and as in other studies, lymph nodes were the most common metastatic site. Bone was the commonest sites of distant metastasis followed by lung. Bone metastasis is typically associated with an overall worse prognosis than lung metastasis.^[5] The incidence of bone metastasis is reported in the literature to be between 1% and 20%.^[3] A study from China^[1] where data for

nearly 25 years from a single institution was available, 4.2% of patients had distant metastasis at diagnosis, not significantly different from our data. However, a similar study from the United States^[6] reported only 2.9%. It is possible that the low rate in the United States study was from difference in patient selection. Although both these studies showed more lung than bone metastases, poor prognosis was associated with extrapulmonary metastases.

As ATA risk stratification 2015 could not be applied to our cohort due to the lack of some HPR details, ATA 2009 system was used for risk stratification after initial therapy. Most patients belonged to intermediate risk and one fourth, to high risk. This pattern was comparable to the data from the United States.^[2] Lymph nodal and distant metastasis, respectively, were the commonest determining factors for the intermediate and high-risk category in our cohort. However, a significant number of patients were assigned to high-risk category because of gross extrathyroidal extension. Similarly, many patients without lymph nodal metastasis were classified as intermediate-risk category because of the vascular invasion, microscopic extrathyroidal extension and lymphnode uptake in the post therapy iodine scan. Follow-up of this cohort should tell us whether the different criteria that defined risk categories singly or in combination made a significant difference in response to therapy and outcome.

Among the tumour-related factors, larger size, capsular invasion, and presence of ENE were significantly more common in high-risk group in our cohort. It is important to note that neither 2009 ATA guidelines nor the more recent 2015 recommendations did not incorporate ENE or size of the tumour in the risk categorization. The presence of ENE, which is a well-known adverse prognostic factor for various other cancer types, has emerged as an additional important risk factor not only for persistence/recurrence of DTC but also for long-term outcome.^[7] Presence of ENE might be changing

the risk category from intermediate to high and may confer the need for more aggressive therapy such as RAI.^[8] In our cohort, 52 tumours showed ENE and among them, 60% were in the high risk and 40% in the intermediate risk. Follow-up and outcome study of these patients might suggest the need to incorporate ENE as a variable for risk stratification.

Another finding was the lower prevalence of lymphocytic thyroiditis (LT) in high-risk patients. This might emphasize probable association of LT with low-risk tumour and better outcome in DTC.^[9] However, numbers are not large enough to make any further interpretation of this finding and follow-up studies are needed to evaluate this further.

When we compared our data with that from Mumbai-India,^[10] China^[11] and the United States^[2] it appears that gender distribution, age at presentation and dominant histology were comparable in these groups [Table 4]. Multifocality and extrathyroidal extension was more in the Mumbai cohort. Vascular and capsular invasions, however, were more common in our patients. Whereas risk for recurrence was evenly distributed in our patients, the North India group had more high-risk patients. However, our cohort had more distant metastasis at presentation. These differences between our data and the North Indian data can possibly be explained by the data source. Ours was an endocrine database where patients were entered from the time of diagnosis whereas the North India data came from a surgical database. It is possible that advanced cases enter into a surgical database. The Chinese data showed more low-risk patients while in the United States study, most patients fell in the intermediate risk. These differences may be due to the difference in the patient population studied.

The strength of this study is the large cohort, from a thyroid cancer care team of a single centre, under the supervision of a senior endocrinologist with the use of international guidelines in the evaluation and management with necessary

Table 4: Comparison of study cohort with DTC data from other centres

Parameter	Present Study (Kerala) n-944	Deshmukh <i>et al.</i> ^[10] (Mumbai-India 2017) n-221	Shen <i>et al.</i> ^[11] (China 2017) n-356	Tuttle <i>et al.</i> ^[2] (New York 2010) n-588
Female	682 (72.2%)	140 (63.3%)	284 (80%)	400 (68%)
Mean age at diagnosis	43.8 years; SD 13.8 years	41 (13-84 years)	41.5±12.7 years	46±15 years
Histology				
Classical PTC	456 (48.3%)	125 (55%)	331 (93%)	500 (85%)
FTC	76 (8.1%)	6 (2.6%)	25 (7%)	24 (4%)
HCC	18 (1.9%)	NA	NA	29 (5%)
Multifocality	279 (36.6%)	192 (86.8%)	65 (18.3%)	NA
Capsular invasion	300 (46.9%)	23 (10.4%)	Local invasion:	NA
Vascular invasion	191 (32.5%)	5 (2.3%)	45 (12.6%)	
Extrathyroidal extension	171 (30%)	80 (36%)	NA	NA
Distant metastasis at Diagnosis	113 (14.5%)	23/221 (10%)	21 (5.9%)	NA
ATA 2009 risk stratification				
Low	214 (31.1%)	25 (11.3%)	182 (51.2%)	135 (23%)
Intermediate	285 (41.8%)	60 (27%)	61 (17.1%)	294 (50%)
High	171 (26.9%)	126 (57%)	113 (31.7%)	159 (27%)

modifications to suit our population. However, there are a few limitations. Most patients who underwent initial surgery in peripheral hospitals lacked complete HPR, documents of paramount importance to initial management. This resulted in some missing data and the inability to do the risk categorization. Investigations were lacking in a few cases that could possibly be from financial constraints as very few of the cohort had health insurance.

CONCLUSION

The clinical features of this DTC cohort were not very different from the other published studies worldwide. FVPTC formed the second most common type after cPTC and 12.7% were PTMC. Nearly 40% of the patients presented with metastasis and it was the major determinant of high- and intermediate-risk categorization. Prevalence of distant metastases at disease presentation (14.5%) is higher than the other published data. Moreover, a preponderance of bone involvement over extraosseous sites was an unexpected finding. Older age, larger tumour size, FTC and ENE were significantly more common in high risk, suggesting that in our patient population, these variables may have to be factored into risk stratification, if indeed, long-term follow-up shows unfavourable outcome with these variables.

The study protocol has been approved by the Research Institute's Committee on Human Research.

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Conflicts of interest

There are no conflicts of interest.

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