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ORIGINAL ARTICLE

Poorly differentiated thyroid carcinoma and poorly differentiated area in differentiated thyroid carcinoma: is there any difference?

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Abstract

Purpose Poorly differentiated thyroid carcinoma (PDTC) patients have worse outcomes than patients with differentiated thyroid carcinoma (DTC), but the implication of poorly differentiated areas (PDAs) noted in DTC is not very well understood. The aim of the present study was to compare the clinicopathologic profiles and outcomes of PDTC and DTC with PDA.

Methods A total of 142 patients, managed at out center between September 1989 and June 2016, were enrolled in this retrospective study. Histology was reviewed, and the patients were divided in the following three groups: poorly differentiated carcinoma [PDTC; group 1 ($n = 27$)]; papillary thyroid carcinoma with PDA [PTC with PDA; group 2 ($n = 27$)]; and follicular thyroid carcinoma with PDA [FTC with PDA; group 3 ($n = 88$)]. Clinico-pathologic profiles and outcomes were compared between the three groups. The Kaplan–Meier method was used for survival analysis. The log-rank test and Cox regression model were used to perform univariate and multivariate analyses of the factors affecting the overall survival (OS).

Results The clinical profiles of the three groups were comparable except for significantly less incidence of lymph node involvement ($p = 0.002$) and extra-thyroidal invasion ($p = 0.002$) and higher incidence of distant metastases ($p = 0.01$) in group 3. Median follow-up period was 47.5 months, and 5- and 10-year OS were 57 and 14%, respectively. There was no difference between OS of PDTC and DTC (group 2 + 3), but group 3 patients had significantly better OS than group 2 patients. Univariate analysis revealed that tumor size ($p = 0.04$), extra-thyroidal invasion ($p = 0.05$), lateral compartment lymphadenopathy ($p = 0.002$), distant metastases ($p = < 0.001$), absence of encapsulation ($p = 0.03$), and > 75% PDA ($p = 0.001$) were associated with worse OS. Multivariate analysis revealed tumor size ($p = 0.005$), distant metastases ($p = 0.012$), lymphadenopathy ($p = 0.017$), TNM staging ($p = < 0.001$), and PDA > 75% ($p = < 0.001$) to be significantly associated with OS.

Conclusion There is no difference in the outcomes of PDTC and DTC with PDA. However, PTC patients with PDA have worse outcomes than FTC patients with PDA. Irrespective of tumor type, the presence of more than 75% PDA in DTC is associated with adverse outcomes.

Keywords Differentiated thyroid carcinoma · Poorly differentiated area · Aggressive thyroid carcinoma

Introduction

Poorly differentiated thyroid cancer (PDTC) was first accepted as a distinct type of thyroid carcinoma of follicular origin when the World Health Organization (WHO) incorporated it in its classification of thyroid cancer in 2004. They defined PDTC as a "follicular cell neoplasm with limited evidence of structural follicular cell differentiation that occupies morphologically and behaviorally an intermediate position between differentiated and undifferentiated carcinoma" [1]. After the initial description of PDTC by Sakamoto and Carcangiu separately during the 1980s, various authors continued to use different criteria for its diagnosis [2, 3]. It was not until 2006 that the Turin consensus conference

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brought about uniformity in the diagnostic criteria for PDTC [4]. The reported incidence of PDTC varies from less than 1–3% in Japan and USA to 15% in Northern Italy, iodine sufficient (ISA) and deficient (IDA) areas, respectively [5, 6]. The difference in incidence of PDTC could partly be due to different diagnostic criteria used and unidentified environmental or genetic factors influencing its occurrence. PDTC can arise de novo or by de-differentiation of already existing differentiated thyroid carcinoma (DTC) [7].

PDTC patients have worse outcomes than patients with DTC, but the implication of poorly differentiated areas (PDA) in DTC is not very well understood. The thyroid cancers classified as DTC may contain various proportions of PDA. As per published reports, PDA components as low as 10% can confer aggressive behavior in a tumor [8, 9]. This observation forces one to wonder if all DTCs containing any degree of PDAs should be labeled as PDTC. Our institute is a tertiary referral center in Northern India and caters to thyroid cancer patients mostly from IDA. The proportion of PDTC in our patients is relatively high [10, 11]. The aim of the present study was to compare the clinico-pathologic profiles and outcomes of PDTC and DTC with PDA.

Material and methods

This retrospective study consisted of patients who were managed in our department between 1989 and 2016 and whose final histology was reported either as PDTC, papillary thyroid carcinoma (PTC), or follicular thyroid carcinoma (FTC) with PDA. A total of 1542 patients with all types of thyroid carcinoma were managed during the study period, and, after exclusion of various types, 152 patients with PDTC or DTC with PDA (PTC with PDA and FTC with PDA) were identified. Finally, 142 patients with evaluable histology material were included in the study. The case retrieval flow chart is shown in Fig. 1. The Institute's Ethics Committee (2016-84-MCH-EXP) approved the study. Patients with mixed medullary and follicular thyroid cancers and DTC with components of both PDA and de-differentiation were excluded from the study. Patients with insufficient data were also excluded from the analysis.

Histology review

All histology slides were meticulously reviewed by two independent experienced pathologists with a special interest in thyroid pathology. Archived hematoxylin and eosin slides sampled from the specimen received after surgical resection (thyroid and neck lymph nodes) were retrieved and assessed for quality. New slides were prepared from archival tissue blocks in cases where slides were of poor quality. PDTC was diagnosed as per the Turin criteria [4]. In addition, the percentage of PDA in PTC and FTC was

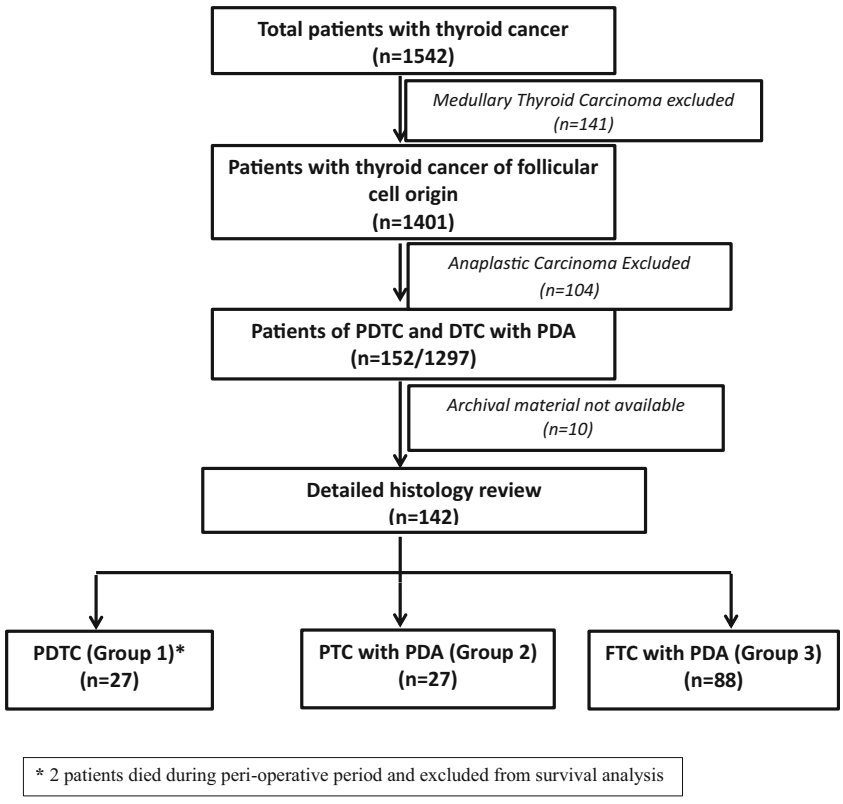

Fig. 1 Case retrieval flow chart. *Two patients died during the peri-operative period and were excluded from the survival analysis

ascertained, and histo-morphological features were noted. After histological review, the patients were classified into three groups, as follows:

Group 1. (PDTC)—defined as tumors where there was no evidence of any DTC component.
Group 2. (PTC with PDA)—defined as tumors composed of PTC with any proportion of PDA.
Group 3. (FTC with PDA)—defined as tumors composed of FTC with any proportion of PDA.

The location of tumor, tumor diameter, and presence or absence of multicentricity were recorded. The tumor was assessed for presence or absence of capsule. Presence and extent of capsular invasion and vascular invasion was defined in accordance with the Armed Forces Institute of Pathology Fascicle (AFIP) criteria [12]. Presence or absence of necrosis and calcification was also recorded. Mitotic rate was determined by counting 10 high-power fields in the areas of greatest concentration of mitotic figures. Details regarding resected lymph nodes were also reviewed, including the total number removed, number affected by metastases, and the presence of extranodal extension.

The clinical case records of all the included patients were reviewed, and the following parameters were noted: demographic and clinical details, thyroid hormone reports, fine-needle aspiration cytology (FNAC) reports, findings of pre-operative laryngoscopy assessment of the vocal cords, details of surgical procedures, and intraoperative assessment of extra-thyroidal extension. Data on surgical morbidity and mortality was also collected. Follow-up data was obtained from the outpatient record registry or via postal, telephone, or email communication.

Adjuvant therapy and follow-up

Post-surgery, after stopping levothyroxine for a month, serum thyrotropin (TSH), thyroglobulin (Tg), and anti-Tg levels were measured followed by a radioiodine (RAI) scan. The Department of Nuclear Medicine at our institute follows a fixed-dose radioiodine therapy (RAIT) schedule. PDTC patients with even minimal extra-thyroidal invasion (R1 resection) and DTC patients with R2 resection are referred for adjuvant external beam radiotherapy (EBRT). It is usually administered after the first dose of RAIT. Patients are followed-up at 6 monthly intervals. Tg levels, RAI scan findings, details of RAIT, and EBRT were recorded. Any other therapy detail, including tyrosine kinase inhibitors (TKI) and chemotherapy, was also noted. Follow-up events and mortality were recorded and entered in a proforma.

Definitions and standards

1. TNM staging of the American Joint Committee on Cancer (AJCC) manual 8th edition was used to stage all cases [13]. Since all patients were operated on prior to 2017, all were reclassified.
2. Synchronous distant metastasis was defined as the metastases detected preoperatively or detected on first radioiodine scan obtained after surgery or within 6 months of surgery. Metastases detected 6 months after surgery are termed as metachronous metastases.
3. Overt metastasis was defined as the presence of symptomatic disease and/or radiologically evident disease and occult as that was apparent only on a whole-body RAI scan.
4. Recurrence was defined as elevated serum Tg or anti-Tg antibody levels with or without structural or RAI scan evidence of disease 6 months after primary treatment.
5. The day of surgery was taken as the reference point to calculate overall survival (OS) and disease-free survival (DFS).

Statistical analysis

Statistical analysis was performed with SPSS software (version 22.0). ANOVA test was used to compare means between groups, while Kruskal–Wallis test was used for non-parametric variables. Kaplan–Meier method was used for survival analysis. Log-rank test and Cox regression model were used to perform univariate and multivariate analyses of the factors affecting the OS. A p value of less than 0.05 was considered to be statistically significant.

Results

One hundred forty-two patients were included in the study. There were 27 (18.5%), 27 (18.5%), and 88 (63%) patients in the PDTC (group 1), PTC with PDA (group 2), and FTC with PDA (group 3) group, respectively (Fig. 2a–c). Two patients in group 2 died in the hospital during the post-operative period and were excluded from survival analysis.

A summary of the clinical profiles of the groups is provided in Table 1. The mean age of the entire cohort of patients was 50.9 $\pm$ 13.6 years with no significant difference between the 3 groups; 65% patients were younger than 55 years. In total, 91% of the patients presented with new-onset disease and 9% of the patients presented with recurrent disease. Median duration of thyroid swelling was 36 months. Compressive symptoms were present in 27.5% patients. Voice change, dyspnea, and dysphagia were noted in 16, 15, and 11% patients, respectively. There was no history of radiation exposure. Pre-operative laryngoscopy revealed unilateral vocal cord palsy in 17% of the patients.

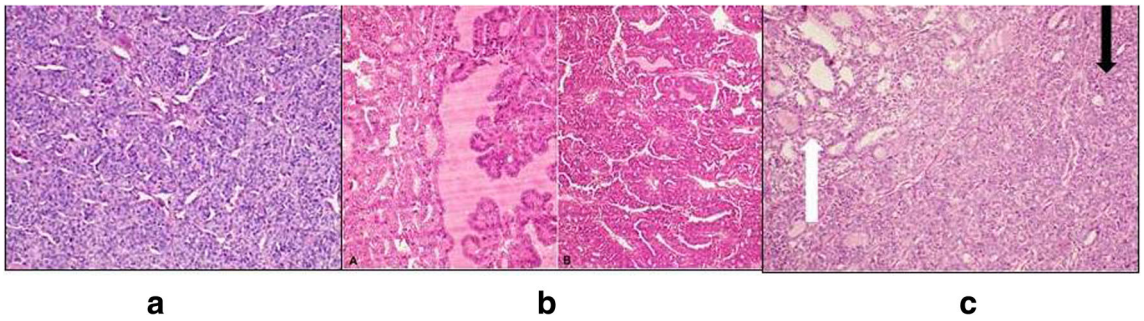

Fig. 2 **a** Photomicrograph of solid variant of PDTC. **b** Composite photomicrograph depicting PTC on the right side (A) with PDA on the left side (B). **c** Photomicrograph depicting FTC in the upper left part (white arrow) with PDA in the lower right part (black arrow)

Incidence of extra-thyroidal invasion, lymph node metastases, and distant metastases was significantly high in group 1 ($p = 0.002$), group 2 ($p = 0.002$), and group 3 ($p = 0.01$), respectively. Overall prevalence of distant metastases was 53%. Overt metastases were noted in 59% and scan detected in 41% of the patients. The skeletal system was the most commonly involved system (70%), either alone or in combination with other systems. There was no significant difference in overall stage distribution between the groups (Table 1).

Details of surgery and adjuvant therapy are summarized in Table 2. Group 1 patients had higher incidence of incomplete resection or debulking surgery in comparison to others, although the difference was not significant. Central compartment lymph node dissection (CCLND), lateral neck node dissection (LND), and mediastinal lymph node dissection (MLND) were performed in 30, 23.8, and 0.8% patients, respectively. Group 3 patients were least likely to require lymph node dissection ($p = < 0.001$). There was no significant difference in the incidence of transient and permanent hypoparathyroidism and post-operative recurrent laryngeal nerve (RLN) palsy between the 3 groups. Overall, 78% of the patients received RAIT and 21% received EBRT. The first post-RAIT scan was negative in 36% of the patients. The remaining patients had an average of 4 (2–9) RAIT sessions and received a median cumulative dose 460 mCi of RAI. Mean dose per session was 115.4 ± 36 mCi. Three patients received the tyrosine kinase inhibitor (TKI) Sorafenib (400 mg tablet twice a day) for slightly more than 3 months for progressive symptomatic disease. All patients had to discontinue Sorafenib use because of the development of severe hand–foot syndrome despite 50% dose reduction. Five patients received zoledronic acid infusions, and re-differentiation therapy (retinoic acid) was administered in 2 patients. One patient received Samarium therapy for palliation of severe bone pain.

The mean tumor size of the entire cohort was 6.2 ± 2.7 cm, and there was no significant difference between the groups (Table 3). Mixed tumor morphology pattern was the most prevalent pattern, and the highest incidence was noted in group 1 ($p = < 0.001$). Incidence of encapsulation, capsular invasion, and vascular invasion was significantly high in group 3 ($p = <0.001$). No difference was observed in any other histological parameters between the groups.

Median follow-up of the entire cohort was 47.5 months (1–208). Post-operative serum Tg values of 62% ($n = 88$) of the patients were available. The median level of post-operative Tg was 74.3 ng/ml (0.2–500), and 9% ($n = 8$) of the patients had elevated anti-Tg levels. Whole-body RAI scanning was performed in 82.4% ($n = 117$) of the patients. Five- and 10-year OS of the entire cohort was 57 and 14%, respectively. Median survival was 63 months. Sixty-four percent of the patients in group 1, 85% in group 2, and 62% in group 3 died. All except one patient died of the thyroid cancer. Among surviving patients, 66, 50, and 39% of the patients in groups 1, 2, and 3, respectively, were living with the disease. There was no difference in OS of PDTC vs DTC (group 2 + 3), but group 3 patients had significantly better OS than group 2 (Fig. 3a, b). Figure 3b, c depicts OS in patients with tumors containing less and more than 75% PDA. Univariate analysis revealed that tumor size > 4 cm ($p = 0.04$), extra-thyroidal invasion ($p = 0.05$), lateral compartment lymphadenopathy ($p = 0.002$), distant metastases ($p = < 0.001$), absence of encapsulation ($p = 0.03$), and presence of > 75% PDA in tumor ($p = 0.001$) were associated with worse survival. Multivariate analysis revealed that tumor size ($p = 0.005$), distant metastases ($p = 0.012$), lymph node involvement ($p = 0.017$), PDA ($p = < 0.001$), and TNM stage ($p = < 0.001$) were found to be significantly associated with survival whereas other factors were not (Table 4).

Discussion

Our study shows that the clinical profile of PDTC and subsets of DTC with PDA are comparable except for significantly high incidence of extra-thyroidal invasion, lymph node metastases, and distant metastases in pure PDTC, PTC with PDA, and FTC with PDA groups, respectively. All the groups had advanced disease presentation with large tumors, high incidence of extra-thyroidal invasion, and distant metastases. There was no significant difference in OS of pure PDTC and DTC with PDA groups, but PTC with PDA had worse

Table 1 Clinico-pathologic profile

S.N.	Variable	Whole cohort $N = 142$	Group 1[a] $n = 27$	Group 2[b] $n = 27$	Group 3[c] $n = 88$	p value
1.	Mean age ± SD in years	50.9 ± 13.6	50.1 ± 12.0	53.2 ± 15.8	50.4 ± 13.4	0.620
2.	Male:female	1:2.1	1:4.4	1.3:1	1:2.4	0.090
3.	Presentation, *n* (%)					0.855
	➢ Primary	130 (91)	25 (92)	24 (89)	81 (92)	
	➢ Recurrent	12 (9)	2 (8)	3 (12)	7 (8)	
4.	Retrosternal extension, *n* (%)	27 (19)	7 (26)	3 (11)	17 (19)	0.400
5.	Extra-thyroidal extension, *n* (%)	51 (36)	16 (59)	13 (48)	32 (25)	0.002
6.	Structures involved, *n* (%)					
	➢ Strap muscles	46 (32)	14 (52)	14 (52)	18 (20)	< 0.001
	➢ Trachea	31 (22)	10 (37)	9 (33)	12 (14)	0.010
	➢ Recurrent laryngeal nerve	15 (11)	7 (26)	04 (15)	4 (4)	0.005
	➢ Esophagus	9 (6)	6 (22)	–	3 (3)	0.001
	➢ Common carotid artery	4 (3)	1 (4)	–	3 (3)	0.800
	➢ Pre-vertebral fascia	4 (3)	–	2 (7)	2 (2)	
7.	Metastasis, *n* (%)					
	➢ Synchronous	59 (42)	10 (37)	7 (26)	42 (48)	0.010
	➢ Metachronous	16 (19)	5 (29)	7 (35)	4 (9)	
8.	Tumor (T), *n* (%)					
	➢ T1	02 (01)	00	00	02 (02)	0.020
	➢ T2	26 (18)	03 (11)	03 (11)	20 (23)	
	➢ T3a	49 (35)	04 (15)	07 (26)	38 (43)	
	➢ T3b	16 (11)	05 (19)	04 (15)	07 (08)	
	➢ T4a	44 (31)	14 (52)	11 (41)	19 (22)	
	➢ T4b	05 (04)	01 (04)	02 (08)	02 (02)	
9.	Node (N), *n* (%)					
	➢ N0	99 (70)	12 (44)	15 (56)	72 (82)	0.002
	➢ N1a	14 (10)	05 (19)	03 (11)	06 (07)	
	➢ N1b	29 (20)	10 (37)	09 (33)	10 (11)	
10.	Stage, *n* (%)[d]					
	➢ Stage I	53 (37)	11 (41)	10 (37)	32 (36)	0.400
	➢ Stage II	57 (40)	10 (37)	8 (30)	39 (44)	
	➢ Stage III	16 (11)	4 (15)	7 (26)	5 (6)	
	➢ Stage IVa	1 (0.7)	–	–	1 (1.5)	
	➢ Stage IVb	15 (10.5)	2 (7)	2 (7)	11 (12.5)	

[a] Group 1 (PDTC) is defined as tumor where there was no evidence of any DTC component

[b] Group 2 (PTC with PDA) is defined as tumors composed of PTC with any proportion of PDA

[c] Group 3 (FTC with PDA) is defined as tumors composed of FTC with any proportion of PDA

[d] Staging as per American Joint Committee on Cancer (AJCC) manual 8th edition

On comparing PDTC (group 1) vs DTC with PDA (group 2 + 3), the former had significantly high incidence of extra-thyroidal invasion ($p = 0.007$), T4 tumors ($p = 0.033$), and lymph nodal involvement ($p = 0.006$)

survival than FTC with PDA. Presence of more than 75% PDA in DTC, irrespective of tumor type, had an adverse influence on survival. Furthermore, well-described prognostic factors, such as presence of lymphadenopathy and tumor encapsulation, were found to have a significant influence on OS.

PDTC are relatively aggressive types of thyroid follicular cell tumors that occupy a position in between the indolent DTC and the most lethal undifferentiated thyroid cancer [1]. In this study, we used the Turin criteria for diagnosis of PDTC. This system takes into consideration both histomorphology and high-grade cytological features to diagnose PDTC and has been validated by other researchers [14]. Some centers use only high-grade features to diagnose PDTC and have reported comparable diagnostic sensitivity as the Turin criteria [15, 16]. However, what proportion of PDA within a DTC imparts its PDTC character is not clear. Only a few studies have shown that the presence of even a minor component of PDTC can impart aggressive behavior to DTC [8]. In our study, 97% of the tumors had more than 10% PDA. PDTC and DTC with PDA constituted 11% of all thyroid cancers of

Table 2 Overview of surgery and adjuvant therapy

S.N.	Variable	Whole cohort	Group 1 $n = 27$	Group 2 $n = 27$	Group 3 $n = 88$	p value
1.	Thyroid surgery, n (%)					
	➢ Total thyroidectomy	136 (96)	24 (88)	25 (93)	87 (99)	0.100
	➢ Near total thyroidectomy	1 (1)	1 (4)	–	–	
	➢ Hemi thyroidectomy	1 (1)	1 (4)	–	–	
	➢ Tumor de-bulking	4 (3)	1 (4)	2 (7)	1 (1)	
2.	Lymph node surgery, n (%)[d]					
	➢ CCLND	18 (13)	8 (30)	4 (15)	6 (7)	< 0.001
	➢ U/L SLND	8 (6)	4 (15)	1 (4)	3 (3)	
	➢ B/L SLND	1 (0.8)	–	1 (4)	–	
	➢ CCLND + U/L SLND	19 (13)	5 (18)	7 (26)	6 (7)	
	➢ CCLND + B/L SLND	6 (4)	2 (7.5)	2 (7)	2 (2)	
	➢ Mediastinal LND	1 (0.8)	–	–	1 (1)	
3.	Other procedures, n (%)					
	➢ Laryngotracheal resection	4 (3)	–	3 (11)	1 (1)	0.600
	➢ Shave resection	27 (19)	10 (37)	6 (22)	11 (12)	
	➢ Thrombectomy	16 (11)	7 (26)	1 (4)	8 (9)	
	➢ Tracheostomy	15 (11)	4 (15)	3 (11)	8 (9)	
4.	Resection of metastasis, n (%)	20 (38)	03 (38)	03 (50)	14 (36)	
5.	Radioiodine therapy					
	➢ Received, n (%)	110 (78)	20 (74)	19 (70)	71 (81)	0.500
	➢ Median cumulative dose mCi	460	378	310	635	
6.	EBRT, n (%)	30 (21)	5 (18)	4 (15)	21 (24)	
	➢ Loco-regional	13 (43)	3 (60)	3 (75)	7 (33)	0.500
	➢ Distant[e]	17 (57)	2 (40)	1 (25)	14 (67)	0.200

[a] Group 1 (PDTC) is defined as tumor where there was no evidence of any DTC component

[b] Group 2 (PTC with PDA) is defined as tumors composed of PTC with any proportion of PDA

[c] Group 3 (FTC with PDA) is defined as tumors composed of FTC with any proportion of PDA

[d] CCLND, central compartment lymph node dissection; U/L SLND, unilateral selective neck dissection; B/L SLND, bilateral selective neck dissection

[e] For palliation of metastatic disease

On comparing PDTC (group 1) vs DTC with PDA (group 2 + 3), the former had significantly high incidence of other procedures, i.e., shave resection and thrombectomy ($p = 0.027$)

follicular cell origin (152/1297). This figure is comparable to that reported from other IDA [5, 6].

The mean age at presentation was not different between pure PDTC and DTC with PDA groups; this finding is also comparable to those of previous studies [15, 16]. It is also true that there was an overall female preponderance, but, surprisingly, men outnumbered women in PTC with PDA group [15, 17].

Delay in seeking medical advice may partly explain the high number of patients presenting with advanced stages of the disease in the current study; however, advanced presentation is common in PDTC. The percentage of tumors measuring ≥ 4 cm was 43–62% in previous studies [15, 16]. Incidence of extra-thyroidal invasion ranges between 30 and 44%, and about a quarter to one-third of the patients present with distant metastases [15, 16, 18, 19]. In the current study, 80% of the patients had tumors measuring ≥ 4 cm, 36% had extra-thyroidal spread, and 42% had distant metastases at the time of presentation.

Five-year OS was reported to be in the range of 60–85%, and it was 57% in our study [15–17, 20]. The main reason for the lower survival could be the high incidence of distant metastases in our study. The finding that patients with FTC and PDA had better OS than those with PTC and PDA is surprising, as FTC are considered to be more aggressive tumors than PTC; this may be attributed to a cumulative effect of advanced age, male gender, and high incidence of extra-thyroidal invasion and metachronous metastases in the PTC with PDA group. All these factors are associated with adverse outcomes [15–18, 21]. As reported in previous studies, we found that tumor size, metastases, and tumor stage were significant factors affecting OS [15, 16]. On the contrary, age was not a significant factor for survival. The explanation for this could be that the mean age of the cohort was lower than that in previous studies and there were limited elderly patients in our study for meaningful statistical analysis. As far as histological features are concerned, unlike previously published reports, multicentricity, presence of necrosis, and a mitotic index > 3 per 10 HPF were not associated with worse outcomes [22, 23].

Previous reports have suggested that presence of even a minor component of PDA in DTC is associated with worse outcomes [8, 9]. In the current study, presence of even 10%

Table 3 Summary of histology features

S.N.	Feature	Whole cohort	Group 1 $n = 27$	Group 2 $n = 27$	Group 3 $n = 88$	p value
1.	Mean tumor size ± SD (cm)	6.2 ± 2.7	7.1 ± 2.7	5.4 ± 2.1	6.1 ± 2.8	0.700
	Tumor group, *n* (%)					0.400
	➢ < 4 cm	29 (20)	3 (11)	7 (26)	19 (22)	
	➢ >/= 4 cm	113 (80)	24 (89)	20 (74)	69 (78)	
2.	Tumor morphology, *n* (%)					< 0.001
	➢ Insular	27 (19)	1 (4)	10 (37)	16 (18)	
	➢ Solid	40 (28)	4 (15)	10 (37)	26 (30)	
	➢ Trabecular	11 (08)	1 (4)	3 (11)	7 (8)	
	➢ Mixed	64 (45)	21 (76)	4 (15)	39 (44)	
3.	Area of PDTC, *n* (%)					< 0.001
	➢ < 10%	5 (3)	–	5 (19)	–	
	➢ 10–25%	35 (24.5)	–	4 (15)	31 (35)	
	➢ 25–50%	36 (25.5)	–	9 (33)	27 (31)	
	➢ 50–75%	15 (11)	–	3 (11)	12 (14)	
	➢ > 75%	51 (36)	27 (100)	6 (22)	18 (20)	
4.	Necrosis, *n* (%)	89 (63)	21 (76)	18 (67)	50 (57)	0.100
5.	Presence of mitosis, *n* (%)	89 (63)	19 (70)	17 (63)	53 (60)	0.600
6.	Encapsulation, *n* (%)	80 (56)	9 (33)	12 (44)	59 (67)	0.003
7.	Multicentricity, *n* (%)	59 (41)	9 (33)	12 (44)	38 (43)	0.620
8.	Capsular invasion, *n* (%)	112 (80)	23 (85)	5 (19)	85 (96)	< 0.001
9.	Vascular invasion, *n* (%)	100 (70)	19 (70)	7 (26)	74 (84)	< 0.001

[a] Group 1 (PDTC) is defined as tumor where there was no evidence of any DTC component

[b] Group 2 (PTC with PDA) is defined as tumors composed of PTC with any proportion of PDA

[c] Group 3 (FTC with PDA) is defined as tumors composed of FTC with any proportion of PDA

On comparing PDTC (group 1) vs DTC with PDA (group 2 + 3), the former had significantly high incidence of mixed pattern tumor morphology ($p = 0.002$) and less encapsulation ($p = 0.007$)

PDA in DTC was associated with a worse 5-year OS (65%) compared to our historic control (PTC = 87% and FTC = 80%) [11]. This finding makes us wonder whether the presence of even a small area of PDA should be enough to label a tumor as PDTC, as it is the current practice to label a DTC as an anaplastic carcinoma if any area of anaplasia is noted within the tumor [1]. The FTC proportion among DTC was relatively high at our center. This fact prompted us to analyze PTC with PDA and FTC with PDA separately. This subset analysis of DTC with PDA is not available in the literature, and this is one of the main strengths of this study. The main limitation of the study is its retrospective nature and its

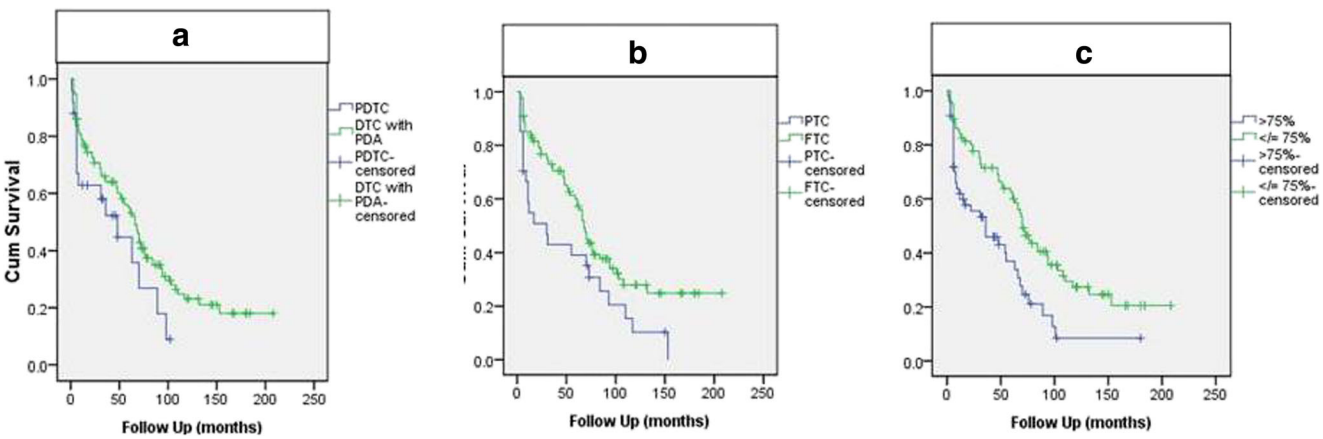

Fig. 3 **a** OS-PDTC (group 1) vs DTC with PDA (groups 2 and 3 combined). **b** OS-PTC with PDA (group 2) vs FTC with PDA (group 3). **c** OS-based on percentage of PDA in DTC

Table 4 Results of multivariate analysis for survival

S. N.	Variable	*n*	Median survival	*p* value
1.	Group			0.001
	➢ 1	25	48	
	➢ 2	27	30	
	➢ 3	88	68	
2.	Tumor size			0.005
	➢ < 4 cm	29	77	
	➢ ≥ 4 cm	111	63	
3.	Extra-thyroidal invasion			0.270
	➢ Present	49	36	
	➢ Absent	91	68	
4.	Lymph node involvement			0.019
	➢ No	99	68	
	➢ Central compartment	13	69	
	➢ Lateral neck nodes	28	15	
5.	Metastasis			0.012
	➢ Present	58	48	
	➢ Absent	82	89	
6.	AMES category			0.880
	➢ High risk	111	54	
	➢ Low risk	29	132	
7.	TNM stage			0.029
	➢ I	53	110	
	➢ II	57	48	
	➢ III	16	70	
	➢ IVA	1	16	
	➢ IVB	15	63	
8.	Encapsulation			0.770
	➢ Present	79	68	
	➢ Absent	61	47	
9.	Tumor area			< 0.001
	➢ < 10%	05	55	
	➢ 11–20%	35	73	
	➢ 21–50%	36	70	
	➢ 51–75%	15	70	
	➢ > 75%	49	36	

On comparing PDTC (group 1) vs DTC with PDA (group 2 + 3), there was no significant difference in survival ($p = 0.078$)

associated inherent weaknesses. Thus, some cases had to be excluded at the beginning of the study and subsequently from survival analysis.

Conclusion

Presence of even a small area of PDA within DTC imparts its aggressive behavior. There is no difference in the outcomes of PDTC and DTC with PDA. Within the DTC group, PTC with PDA patients have worse outcomes than the FTC with PDA group. Further studies are required to validate this unique finding.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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