

**CLINICOPATHOLOGICAL FEATURES AND PROGNOSTIC
OUTCOME OF POORLY DIFFERENTIATED THYROID CARCINOMA:
10 -YEAR EXPERIENCE IN A TERTIARY CARE INSTITUTE AT
SOUTH INDIA**

ABSTRACT

Introduction: Poorly differentiated thyroid carcinoma (PDTC) is a rare malignancy which accounts for only 1 to 15% of all thyroid cancers. There is only limited literature on PDTC regarding its clinical behavior and treatment consensus, and there was no published data from south Indian population.

Aim: To study the clinicopathological characteristics, treatment and prognostic outcome of PDTC cases treated in our institute.

Materials and Methods: This is a retrospective study over a period of 10 years from 2005 to 2014 at Department of Endocrine surgery, Madras medical college, a tertiary referral center in South India. The following data were collected from medical records: demographics, clinical presentation, treatment given, histopathological characteristics and the clinical outcome of all PDTC cases diagnosed based on Turin's criteria. The data were analyzed, and statistical analysis was performed.

Results: Among 626 thyroid malignancies, only 19 cases of PDTC were treated during the study period. The median age of presentation was 54 years, of which 17 were females, and 2 were males. All patients have presented with goiter with a median duration of 6 years. Total thyroidectomy was performed in all cases, and three patients had neck dissection along with total thyroidectomy. The predominant histological subtype was the insular pattern. The cervical lymph node metastasis was seen in 3 cases (15.8%). The distant metastatic rate was 68.4% of which 9 cases had lung and 4 had bone metastasis. Adjuvant radioiodine therapy was given only in 2 patients (10.5%) and the majority received external beam radiotherapy (89.5%). The overall 5-year survival rate was 36%.

26 **Conclusion:** Poorly differentiated thyroid cancer is aggressive and rare thyroid cancer. The
27 prevalence rate in our study population was 3%. The tumor behavior in our study population was
28 more aggressive than that of other regions. Surgery remains the mainstay of treatment in the control
29 of loco regional disease. EBRT was the primary form of adjuvant therapy in our study population
30 which showed a better survival advantage than RAI. More extensive studies are required regarding
31 consensus for adjuvant therapy and optimal management of PDTC.

32 **KEYWORDS:** *Poorly differentiated thyroid carcinoma, Turin, insular, thyroid carcinoma*

33 INTRODUCTION

34 Thyroid cancers are the most common among endocrine malignancies. The majority of
35 thyroid tumors comprise well-differentiated (papillary and follicular) thyroid carcinomas. Poorly
36 differentiated thyroid carcinomas (PDTC) are those which have a biological behavior intermediate
37 between well-differentiated carcinomas and aggressive anaplastic thyroid carcinomas. It is postulated
38 that the poorly differentiated component represents dedifferentiation of papillary or follicular thyroid
39 carcinoma but most of the PDTC develop de novo.

40 The entity poorly differentiated thyroid carcinoma was first described by Sakamoto et al in
41 1983.^[1] But in his classification, aggressive variants of papillary thyroid carcinoma and hurthle cell
42 carcinoma were included. In 1984 Carcangiu et al described a series of 25 cases and termed as
43 poorly differentiated insular thyroid carcinoma.^[2] In 2004 WHO has adopted this as a separate
44 histopathological entity independent from follicular and papillary carcinoma. But there was an
45 inconsistency in diagnostic criteria for PDTC. Hence an International consensus meeting was held in
46 Turin, in March 2006 to establish diagnostic criteria for PDTC.^[3] According to Turin's criteria, PDTC is
47 defined by the presence of solid/trabecular/insular growth pattern, absence of conventional nuclear
48 features of papillary carcinoma and least one of the following features: convoluted nuclei, mitotic
49 activity $\geq 3/10$ HPF or tumor necrosis should be noted.

50 The prevalence of poorly differentiated carcinoma based on the Turin proposal varies among
51 regions. The reported prevalence rate was 0.3% in Japan, 2–4% in Europe, 1.8% in the USA and
52 6.7% in Italy (a series from a single Institution, the University of Turin).^[4, 5] This wide geographical

53 variation may be due to environmental and ethnic factors. The prevalence was higher in the
54 mountainous region of Italy, in agreement with higher prevalence in areas with iodine deficiency.^[6]

55 Because of the rarity of PDTC, there are only a few published data in the literature. Since
56 there is no published data from south Indian population and being a tertiary care center, we indent to
57 report our experience in poorly differentiated thyroid carcinoma over a 10 year period.

58 MATERIAL AND METHODS

59 This is a retrospective study over a period of 10 years from 2005 to 2014 at Department of Endocrine
60 surgery, Madras medical college, a tertiary referral center in South India. The following data were
61 collected from medical records: demographics, clinical presentation, treatment given,
62 histopathological characteristics and the clinical outcome of all PDTC cases diagnosed based on
63 Turin's criteria. The data were analyzed and statistical analysis was performed using SPSS software
64 (version 23.0). Kaplan Meir survival analysis was performed.

65 RESULTS

66 Among 626 thyroid malignancies, only 19 cases of PDTC were treated during the study
67 period. The median age of presentation was 54 years (ranges from 40 to 65 years), of which 17 were
68 females and 2 were males. All patients had presented with goiter with a median duration of 6 years.
69 All patients were clinically and biochemically euthyroid. Only 2 cases (10.5%) were reported as PDTC
70 on fine needle aspiration cytology. Total thyroidectomy was performed in all cases and three patients
71 had neck dissection along with total thyroidectomy. The mean tumor size was 3.3 cm (6 to 13 cm).
72 The predominant histological subtype was the insular pattern in 12 cases (63.2%) followed by
73 trabecular in 6 cases (31.6%) and solid in one case (5.3%). The extrathyroidal extension was
74 documented in 16 cases (84.2%) and lymphovascular invasion in 13 cases (68.4%). Tumor necrosis
75 was present in 79% of cases. The cervical lymph node metastasis was seen in 3 cases (15.8%). The
76 distant metastatic rate was 68.4% of which 9 cases had lung and 4 had bone metastasis. Adjuvant
77 radioiodine therapy was given only in 2 patients (10.5%) and the majority received external beam
78 radiotherapy (89.5%). Tumor recurrence was seen in 3 patients (15.8%). The 5-year survival rate was
79 36%. Table 1 summarizes the clinicopathological characteristics and treatment given.

80 **Table 1: Clinicopathological characteristics of poorly differentiated thyroid carcinoma cases**
81 **(n=19)**

	n	%
Age, in years	45 to 65 (range)	54 (median)
Sex Males	2	10.5
Females	17	89.5
<u>Clinical presentation</u>		
Goitre	19	100
Size on presentation	9.5±3.5	
Median duration, in years	6	
Dyspnoea	6	31.6
Dysphagia	2	10.5
Hoarseness of voice	2	10.5
Neck pain	10	52.6
Cervical lymph nodes	3	15.8
Distant metastasis	13	68.4
Lung	9	47.4
Bone	4	21.1
TFT		
Euthyroid	19	100
<u>FNAC</u>		
PDTC	2	10.5
Follicular neoplasm	5	26.3
Suspicious of malignancy	4	21.1
Papillary carcinoma	2	10.5
Medullary carcinoma	2	10.5
Hashimotos thyroiditis	4	21.1
<u>Type of surgery</u>		
Total thyroidectomy only	16	84.2

Total thyroidectomy with neck dissection	3	15.8
<u>Adjuvant therapy</u>		
Radio iodine	2	10.5
EBRT	17	89.5
<u>Histopathology</u>		
Pattern		
Insular	12	63.2
Trabecular	6	31.6
Solid	1	5.3
Extrathyroidal extension	16	84.2
Lymphovascular invasion	13	68.4
Presence of necrosis	15	79
Mitosis > 3/10 HPF	18	94.7

82

83 DISCUSSION

84 The prevalence of PDTC in our population was 3% which is lower than that of Italy (6.7%)^[6]
85 and higher than the reported rate from Japan (0.3%).^[7] These variations in prevalence rate among
86 geographical regions are probably because of genetic and environmental risk factors such as iodine
87 deficiency.^[8] Majority of our patients were in the older age group with a median age of 54 years
88 (ranges from 40 to 65 years), which corresponds to the age group of 55 to 65 years in the western
89 literature.^[9] Likewise, the majority of our patients were females (89%) which correspond to the female
90 predominance seen in PDTC.^[9]

91 PDTC are usually under diagnosed with fine needle aspiration cytology. It closely resembles
92 that of medullary carcinoma thyroid. In our study, only 2 out of 19 (10.5%) cases were reported as
93 poorly differentiated thyroid carcinoma. Bongiovanni et al reported a series of 40 cases of PDTC of
94 which only 11(27.5%) cases were diagnosed preoperatively as PDTC on FNAC [10]. Kane and

95 Sharma in their study group of 44 cases, only 9 (20.5%) cases were diagnosed on cytology as
96 PDTC.^[11]

97 PDTC frequently metastasize to regional lymph nodes in 50 to 85% of cases.^[12, 13] The lymph
98 node metastasis rate in our study group was very low about 15.8%. But the rate of distant metastasis
99 was higher (68.4%), of which 9 patients had lung metastasis and four had bone metastasis, which
100 corresponds to the most common sites reported in other studies.^[13]

101 Surgery remains the mainstay of treatment in PDTC and the most important factor for
102 improved survival is the complete resectability of the tumor. In our study, all patients had undergone
103 complete surgical resection either total thyroidectomy or total thyroidectomy with selective neck
104 dissection in patients with neck node involvement. Appropriate surgery with adjuvant therapy provides
105 excellent locoregional control in patients with PDTC.^[14]

106 The mean tumor size in our study population is 6 cm which was similar to the study from the
107 Philippines^[15] and higher than other series.^[7,16] The predominant histological pattern in our population
108 is the insular pattern which is the most common pattern observed in the literature.^[6,15,17] Extrathyroidal
109 extension and lymphovascular invasion were observed in 84.2% and 68.4% respectively which is
110 higher than that of other studies.^[5,6,7,15] Tumor necrosis (79%) and higher mitotic rate (94.7%) were
111 also observed to be greater than other studies. All of these features suggest the more aggressive
112 biological nature of the disease in our study population.

113 There is only limited literature regarding post-surgical treatment for PDTC. Because of the
114 rarity of the disease, no randomized control trials on adjuvant therapy and only few retrospective
115 studies are available. There is limited evidence to show whether I¹³¹ therapy is beneficial in PDTC.
116 There are studies which demonstrated a lower expression of sodium iodide symporter in PDTC.^[18] But
117 adjuvant radioiodine therapy can be considered in all patients because of its potential benefit and
118 relative safety.^[12] The dose of radioiodine required is higher (>100 mCi) than that is used in
119 differentiated thyroid carcinoma. Even then the response to therapy might be lower than DTC.

120 Radiation therapy has an advantage of preventing local relapse but whether it improves the
121 survival outcome is not known. So the role of adjuvant external beam radiotherapy is not well
122 established. There are some retrospective studies which have shown increased survival in patients

with PDTC versus anaplastic thyroid carcinoma (ATC), who received adjuvant EBRT.^[12] EBRT can be considered in patients with T3 tumors without distant metastasis, all T4 tumors and those with regional lymph node metastasis.^[12] In case of distant metastasis, there is no advantage in the use of EBRT to neck rather than for palliation.

A study by Arora et al showed there was a significant increase in the survival rate for patients with PDTC who received radioiodine therapy compared to EBRT.^[19] Being a general public hospital and because of the financial constraints of our patients, a majority of our patients (89.5%) received adjuvant EBRT rather than radioiodine therapy. We have compared both forms of adjuvant therapy in terms of overall survival of our cases. The estimated mean survival time (in years) of 19 patients who have received EBRT is 3.21 ± 0.302 and their 95% Confidence Interval for the mean Estimate is (3.230, 4.413) and who have received RAI is (2.000 ± 0.000) and their 95% Confidence Interval for the mean Estimate is (2.000, 2.000). It concludes that the patients received EBRT therapy having longer survival when compared to patients who received RAI (Figure 1). On the test of equality of survival distributions ($P > .01$), this was statistically insignificant (Table 2).

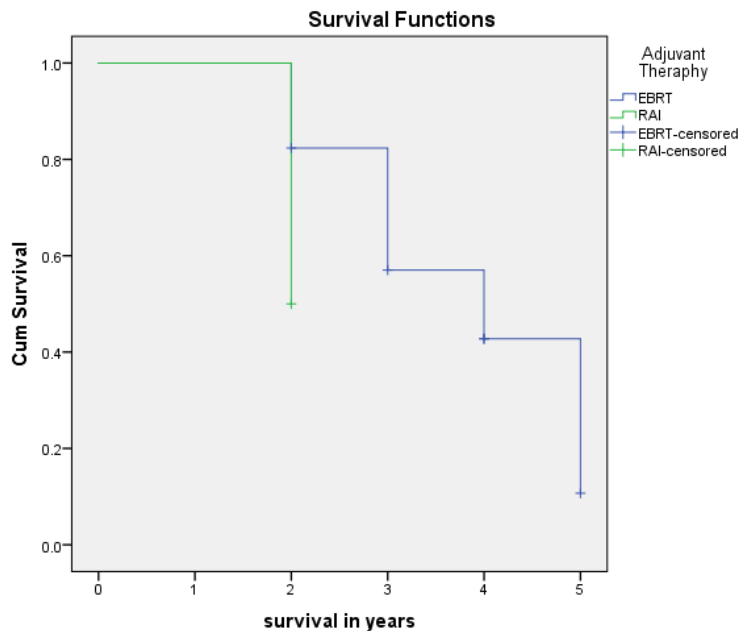


Figure 1: Kaplan Meir survival analysis for adjuvant therapies

Table 2: Test of equality of survival distributions

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	1.068	1	.301
Breslow (Generalized Wilcoxon)	1.068	1	.301
Tarone-Ware	1.068	1	.301

139

140 Sakamoto et al reported a 5-year survival rate of 65% in his study group of 258 patients with
141 PDTC.^[1] The prognosis falls in between that of well-differentiated and anaplastic thyroid
142 carcinomas.^[20] The 5-year overall survival rates range from 62% to 85% among various institutional
143 studies.^[6,16,21,22] Our study has a lower 5-year survival rate of 36% which might be due to the
144 biological aggressiveness of the tumor in our study population and majority of our patients (68.4%)
145 had distant metastasis at the time of presentation.

146 There are no previous reported studies from south Indian population. The prevalence rate in
147 our population is 3%. We offered a complete surgical cure in almost all patients. EBRT is the main
148 modality of adjuvant treatment in our study which showed a better survival advantage than radioiodine
149 therapy but was statistically insignificant. Our study has several limitations being retrospective study
150 and small sample size because of the rarity of the disease. Majority of our cases have shown an
151 aggressive biological behavior but we are unable to do any genetic testing because of limited
152 resources.

153 **CONCLUSION**

154 Poorly differentiated thyroid cancer is an aggressive and rare thyroid cancer. The prevalence
155 rate in our study population was 3% and the overall 5-yr survival rate was 36%. The tumor behavior in
156 our study population was more aggressive than that of other regions. Surgery remains the mainstay of
157 treatment in the control of loco regional disease. EBRT was the major form of adjuvant therapy in our

study population which showed a better survival advantage than RAI. Larger studies are required regarding consensus for adjuvant therapy and optimal management of PDTC.

Ethical approval and consent: NA

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