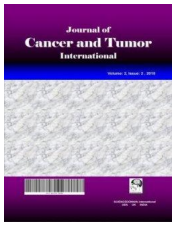

Journal of Cancer and Tumor International

7(3): 1-7, 2018; Article no.JCTI.40857
ISSN: 2454-7360

Clinicopathological Features and Prognostic Outcome of Poorly Differentiated Thyroid Carcinoma: 10 -Year Experience in a Tertiary Care Institute at South India

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Authors' contributions

This work was carried out in collaboration between both authors. Author SZH designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author KRC managed the analyses of the study and the literature searches. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JCTI/2018/40857
Editor(s):
(1) Bing Yan, Department of Oncology, Hainan Branch of PLA General Hospital, China.
Reviewers:
(1) Tariq Namad, Military Hospital Mohamed V. Rabat, Morocco.
(2) Eleonore Fröhlich, Medical University of Graz, Austria.
Complete Peer review History: http://www.sciencedomain.org/review-history/24001

Original Research Article

Received 25th January 2018
Accepted 1st April 2018
Published 5th April 2018

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

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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%.

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

Keywords: Poorly differentiated thyroid carcinoma; Turin; insular; thyroid carcinoma.

1. INTRODUCTION

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

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

The prevalence of poorly differentiated carcinoma based on the Turin proposal varies among regions. The reported prevalence rate was 0.3% in Japan, 2–4% in Europe, 1.8% in the USA and 6.7% in Italy (a series from a single Institution, the University of Turin) [4,5]. This wide geographical variation may be due to environmental and ethnic factors. The prevalence was higher in the mountainous region of Italy, in agreement with higher prevalence in areas with iodine deficiency [6].

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

2. 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 using SPSS software (version 23.0). Kaplan Meir survival analysis was performed.

3. RESULTS

Among 626 thyroid malignancies, only 19 cases of PDTC were treated during the study period. The median age of presentation was 54 years (ranges from 40 to 65 years), of which 17 were females and 2 were males. All patients had presented with goiter with a median duration of 6 years. All patients were clinically and biochemically euthyroid. Only 2 cases (10.5%)

were reported as PDTC on fine needle aspiration cytology. Total thyroidectomy was performed in all cases and three patients had neck dissection along with total thyroidectomy. The mean tumor size was 6 cm (6 to 13 cm). The predominant histological subtype was the insular pattern in 12 cases (63.2%) followed by trabecular in 6 cases (31.6%) and solid in one case (5.3%). The extrathyroidal extension was documented in 16 cases (84.2%) and lymphovascular invasion in 13 cases (68.4%). Tumor necrosis was present in 79% of cases. 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%). Tumor recurrence was seen in 3 patients (15.8%). The 5-year survival rate was 36%. Table 1 summarizes the clinicopathological characteristics and treatment given.

Table 1. Clinicopathological characteristics of poorly differentiated thyroid carcinoma cases (n=19)

	n	%
Age, in years	45 to 65 (range)	54 (median)
Sex Males	2	10.5
Females	17	89.5
Clinical presentation		
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
FNAC		
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
Type of surgery		
Total thyroidectomy only	16	84.2
Total thyroidectomy with neck dissection	3	15.8
Adjuvant therapy		
Radio iodine	2	10.5
EBRT	17	89.5
Histopathology		
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

4. DISCUSSION

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

PDTC are usually under diagnosed with fine needle aspiration cytology. It closely resembles that of medullary carcinoma thyroid. In our study, only 2 out of 19 (10.5%) cases were reported as poorly differentiated thyroid carcinoma. Bongiovanni et al. reported a series of 40 cases of PDTC of which only 11(27.5%) cases were diagnosed preoperatively as PDTC on FNAC [10]. Kane and Sharma in their study group of 44 cases, only 9 (20.5%) cases were diagnosed on cytology as PDTC [11].

PDTC frequently metastasize to regional lymph nodes in 50 to 85% of cases [12,13]. The lymph node metastasis rate in our study group was very low about 15.8%. But the rate of distant metastasis was higher (68.4%), of which 9 patients had lung metastasis and 4 had bone metastasis, which corresponds to the most common sites reported in other studies [13].

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

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

There is only limited literature regarding post-surgical treatment for PDTC. Because of the rarity of the disease, no randomized control trials on adjuvant therapy and only few retrospective studies are available. There is limited evidence to show whether I^{131} therapy is beneficial in PDTC. There are studies which demonstrated a lower expression of sodium iodide symporter in PDTC [18]. But adjuvant radioiodine therapy can be considered in all patients because of its potential benefit and relative safety [12]. The dose of radioiodine required is higher (>100 mCi) than that is used in differentiated thyroid carcinoma. Even then the response to therapy might be lower than DTC.

Radiation therapy has an advantage of preventing local relapse but whether it improves the survival outcome is not known. So the role of adjuvant external beam radiotherapy is not well 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 (Fig. 1). On the test of

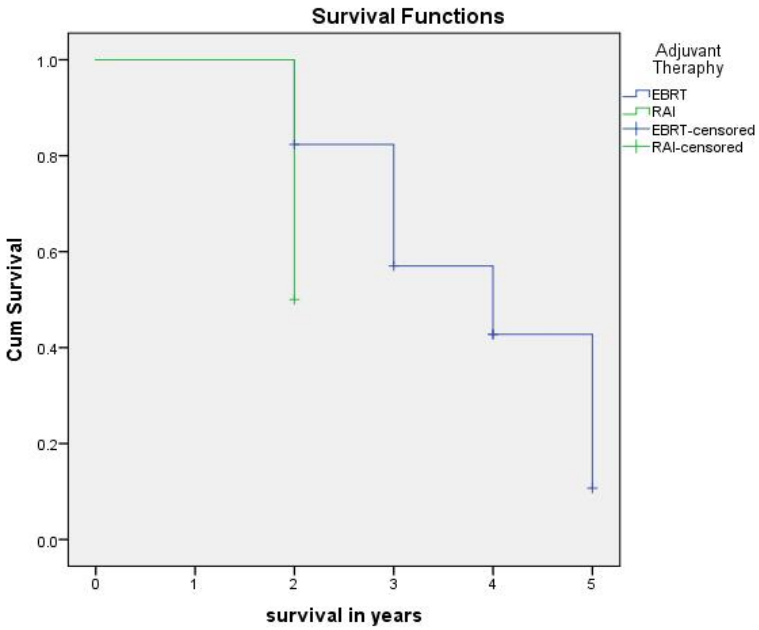

Fig. 1. Kaplan Meir survival analysis for adjuvant therapies

equality of survival distributions (P > .01), this was statistically insignificant (Table 2).

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

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

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

5. CONCLUSION

Poorly differentiated thyroid cancer is an aggressive and rare thyroid cancer. The prevalence rate in our study population was 3% and the overall 5-yr survival rate was 36%. The tumor behavior in our study population was more aggressive than that of other regions. Surgery remains the mainstay of 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.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history/24001