Original Article

Comparison of Clinical and Ultrasonographic Features of Poorly Differentiated Thyroid Carcinoma and Papillary Thyroid Carcinoma

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Abstract

Background: The clinical behavior and management of poorly differentiated thyroid carcinoma (PDTC) are very different from papillary thyroid carcinoma (PTC). By comparing the clinical and ultrasonographic features between the two tumors, we proposed to provide more possibilities for recognizing PDTC before treatment.

Methods: The data of 13 PDTCs and 39 age- and gender-matched PTCs in Peking Union Medical College Hospital between December 2003 and September 2013 were retrospectively reviewed. The clinical and ultrasonic features between the two groups were compared.

Results: The frequencies of family history of carcinoma, complication with other thyroid lesions, lymph node metastases, recurrent laryngeal nerve injuries, and distant metastases were higher in PDTCs (30.8%, 61.6%, 69.2%, 23.1%, and 46.2%, respectively) than those in PTCs (2.6%, 23.1%, 25.6%, 2.6%, and 2.6%, respectively) ($P < 0.05$). The mortality rate of PDTCs was greatly higher than PTCs ($P < 0.01$). Conventional ultrasound showed that the size of PDTCs was larger than that of PTCs (3.1 ± 1.9 cm vs. 1.7 ± 1.0 cm). Clear margins and rich and/or irregular blood flow were found in 92.3% of PDTCs, which differed substantially from PTCs (51.7% and 53.8%, respectively) ($P < 0.05$).

Conclusions: PDTC is more aggressive and its mortality rate is higher than PTCs. Accordingly, more attention should be given to suspicious thyroid cancer nodules that show large size, regular shape, and rich blood flow signals on ultrasound to exclude the possibility of PDTCs.

Key words: Diagnosis; Papillary Thyroid Carcinoma; Poorly Differentiated Thyroid Carcinoma; Ultrasound; Well-differentiated Thyroid Carcinoma

Introduction

Malignant tumors of thyroid follicular cell origin are categorized as well-differentiated thyroid carcinoma (WDTC), consisting the majority of papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma, poorly differentiated thyroid carcinoma (PDTC), and undifferentiated/anaplastic thyroid carcinoma (ATC). WDTC especially PTC confers a favorable prognosis. ATC is uniformly aggressive and often fatal.[1] PDTC occupies an intermediate area between WDTC and ATC. It is more aggressive than WDTC but less aggressive than ATC.[2] The 5-year, 10-year and 15-year survival rates are considerably lower in patients with PDTC (50%, 34%, and 0, respectively) than those in patients

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with WDTC (95%, 86%, and 81%, respectively).[3-5] PDTC often has a high incidence of recurrence despite appropriate treatment. For clinicians, it is important to recognize this entity.[6]

At present, ultrasound is the most important imaging method used for the preoperative evaluation of thyroid nodules, which focuses on the differentiation of benign and malignant lesions. As most thyroid carcinomas are PTCs,[7] PDTC accounts for only about 1% of all thyroid cancers,[8] and the malignant ultrasonographic features reported in the literature have mainly been based on PTC. However, there may be differences in the ultrasonographic features of PTC and PDTC. Nonetheless, no study has reported on the diagnosis of suspicious PDTC based on integrating clinical and ultrasonographic features. Herein, we retrospectively analyzed our hospital database to study the differences between PDTC and PTC with the aim to provide more possibilities for recognizing PDTC earlier.

Methods

Patients

This study was approved by the Ethics Committee of Peking Union Medical College Hospital, and written informed consents were obtained from all patients to use their data in this study. A total of 29 patients with primary PDTC were treated at Peking Union Medical College Hospital from November 2003 to December 2013. Six cases with incomplete clinical data, 2 cases without surgical treatment, 3 cases with initial surgery at another hospital, and 3 cases with no ultrasound reports were excluded. Finally, 13 patients (10 women and 3 men) with 16 nodules (three patients had two nodules each) were included in this study. The age of all 13 patients of PDTC ranged from 30 to 77 years, with a mean age of 48.1 ± 14.8 years. The maximum diameter of the nodules ranged from 0.5 to 6.9 cm. Five patients underwent fine needle biopsy (FNA), of whom 3 were suggested PTC, 1 was suggested finding carcinoma cells, and only one was suggested PDTC. In the database during the corresponding period, 39 gender- and age-matched cases pathologically diagnosed with PTC were randomly selected. The age of the patients with PTC is ranged from 29 to 73 years, with a mean age of 47.0 ± 12.6 years. There were 30 women and 9 men with a total of 51 nodules (12 patients had two nodules each). The maximum diameter of the nodules ranged from 0.3 to 3.8 cm. Twenty PTC patients underwent FNA, 14 were suggested PTC, 2 were found suspicious tumor cell, 3 were suggested follicular lesion, and 1 was suggested not finding enough cells to make a diagnosis.

Ultrasound evaluation

Age, gender, family history of carcinoma, complication with other thyroid lesions, single/multiple nodules, single/multi focal carcinoma, lymph node metastases, recurrent laryngeal nerve injury, distant metastases, tumor, node, metastasis stage, and survival rate were recorded.

All patients underwent routine thyroid ultrasound examinations with GELogic7, GELogic9, or PhilipsIU22 before surgery with transducer frequencies of 8–15 MHz and 5–12 MHz. Preoperative ultrasound images of the largest nodule were retrospectively reviewed. In particular, standard ultrasound features were analyzed, including shape (regular or irregular: regular shapes refer to all round and oval shapes while irregular shapes refer to all other shapes, such as large lobular, small lobular, and nodular), margin (clear or unclear), anteroposterior to transverse diameter ratio (<1 or ≥1), echogenicity (isoechoic or hypoechoic), echotexture (homogeneous or heterogeneous), cystic features (solid-cystic or solid), calcification (absence/other calcification or micro-calcification: micro-calcification refers to calcifications with a diameter ≤0.1 cm while absence/other calcification refers to other types of calcifications, such as curved calcifications, strip calcifications, and conglomerate calcifications), and the presence of capsular infiltration. Blood flow was divided into three types such as[9] (a) no blood flow signal of any type within or around nodules, (b) blood flow signals around nodules, (c) rich and irregular blood flow signals within nodules. For statistical convenience, the first and the second types were grouped together as absence/not rich blood flow, and the latter was referred to as rich/irregular blood flow.

Statistical analysis

Statistical package for social analysis (SPSS for Windows, IBM Corp., USA) version 19.0 was used for data analysis. Data are presented as mean ± standard deviation (SD). A Student's *t*-test was used for comparison of patient ages and the size of nodules. Fisher's exact test was used for comparison of clinical and ultrasonic features and mortality rate. Survival analysis was calculated by the Kaplan–Meier method. A $P < 0.05$ was considered statistically significant.

Results

Clinical features

Patients with PDTC had a significantly higher frequency of family history of carcinoma than those with PTC (30.8% vs. 2.6%, respectively) and also had a higher proportion of multiple thyroid lesions including nodular goiter and Hashimoto's thyroiditis (61.6% vs. 23.1%, respectively). Nine cases of PDTC (69.2%) had lymph node metastases, which was significantly higher than PTC (25.6%, $P = 0.007$). A statistically significant difference was also seen between the number of patients with hoarseness and recurrent laryngeal nerve injury between PTDC ($n = 3$; 23.1%) and PTC ($n = 1$; 2.6%) ($P = 0.044$). Six patients with PDTC had distant metastases involving soft tissues of the neck, internal jugular vein, esophagus, superior mediastinum, liver, and lung. The proportion of stage III–IV tumors in patients with PDTC (9/13, 69.2%) was higher than those with PTC (16/39, 41.0%) ($P = 0.025$). However, there was no difference in the occurrence of single or multiple nodules ($P = 0.503$, $P = 0.373$) [Table 1].

Until the end of follow-up, all patients with PTC were alive, 5 patients died of PDTC, 1 died of cardiac stoke,

Table 1: Clinicopathological characteristics of PDTC and PTC

Parameter	PDTC (n = 13)	PTC (n = 39)	P
Age (mean ± SD, years)	48.1 ± 14.8	47.0 ± 12.6	0.920*
Male/female	3/10	9/30	1.000
Family history of tumor, n (%)	4 (30.8)	1 (2.6)	0.011
Other thyroid lesions, n (%)	8 (61.6)	9 (23.1)	0.017
Nodular goiter	3 (37.5)	0 (0.0)	
Chronic lymphocytic thyroiditis	5 (62.5)	9 (100)	
Nodule, n (%)			
Single	5 (38.5)	17 (43.6)	1.000
Multiple	8 (61.5)	22 (56.4)	
Carcinoma, n (%)			
Unifocal	10 (76.9)	26 (66.7)	0.730
Multifocal	3 (23.1)	13 (33.3)	
Positive lymph nodes, n (%)			
Yes	9 (69.2)	10 (25.6)	0.007
No	4 (30.8)	29 (74.4)	
Recurrent laryngeal nerve injury, n (%)			
Presence	3 (23.1)	1 (2.6)	0.044
Absence	10 (76.9)	38 (97.4)	
Metastases, n (%)			
Presence	6 (46.2)	1 (2.6)	0.001
Absence	7 (53.8)	38 (97.4)	
TNM stage, n (%)			
I	4 (30.8)	23 (59.0)	0.025†
II	0 (0.0)	0 (0.0)	
III	3 (23.1)	10 (26.5)	
IV	6 (46.2)	6 (15.4)	

*t = 0.098, †χ^2 = 5.130. PDTC: Poorly differentiated thyroid carcinoma; PTC: Papillary thyroid carcinoma; TNM: Tumor, node, metastasis.

and 1 died from accident. The survival time of PTC group was 19–109 months while that of PDTC group was 10–74 months. The mortality rate of PDTC was greatly higher than PTC (P < 0.001) [Figure 1].

Ultrasonographic features

The size of PDTC was larger than that of PTC (P = 0.003). Compared with PTC, the margins of PDTC tended to be clear, and the blood flow was rich/irregular (P < 0.05) [Figure 2]. However, there were no significant differences in shape, anteroposterior to transverse ratio, cystic features, echogenicity, homogeneity, calcification, or presence of capsular infiltration [Table 2].

Discussion

In 2004, PDTC was officially listed as a distinct entity in the classification of thyroid carcinoma by the World Health Organization. Later, in 2006, the pathologic diagnostic criteria for PDTC were further detailed at a conference held in Turin.[10] According to the consensus reached that conference, PDTC is a malignant tumor that originates from thyroid follicular cells, and trabecular, island, and/or solid growth patterns are necessary for diagnosis. Tumor cells do not have the classic features of PTC nuclei and have at least

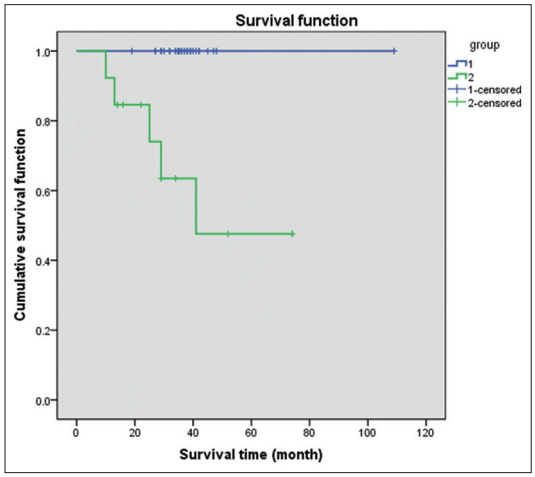

Figure 1: The survival curve between papillary thyroid carcinoma and poorly differentiated thyroid carcinoma. There is statistical difference of the survival curve between papillary thyroid carcinoma and poorly differentiated thyroid carcinoma, P < 0.001.

one of the following characteristics: (1) a solid/trabecular/insular pattern of growth, (2) absence of conventional nuclear features of papillary carcinoma, and (3) presence of at least one of the following features: Convoluted nuclei, mitotic activity (≥3 × 10 HPF), necrosis.

Bejarano *et al*.[11] reported a male:female ratio of 1:2.4 of PDTC, patient age from 6 to 69 years, and a peak incidence in patients older than 45 years. Our report is consistent with previous reports.[11-14] Regarding clinical symptoms, a significantly higher proportion of patients had a family history of carcinoma in the PDTC group (30.6%; 1 case of thyroid carcinoma, 1 case of liver carcinoma, 1 case of lung carcinoma, and 1 case of brain tumor) than those in the PTC group (2.6%). Family history of carcinoma is a major risk factor for thyroid carcinomas.[15-17] In this study, the proportion of patients with a family history of carcinoma in PDTC group was higher than that of PTC group, suggesting that a family history of other tumors can also increase the risk of thyroid carcinoma. However, due to the limited sample size in this study, this will require validation in a larger patient cohort.

The results of this study suggest that patients with nodular goiter or Hashimoto thyroiditis have a higher risk of PDTC than PTC; thus, close clinical observation and follow-up are recommended. The proliferation of follicular cells in the nodular goiter may be associated with a greater possibility of atypical hyperplasia and vascular proliferation. In addition, proliferation may favor progression to carcinoma.[18] Indeed, many studies[19-22] have confirmed that Hashimoto thyroiditis is correlated with thyroid carcinoma. The reason may be that Hashimoto thyroiditis increases the patient's immune response, leading to hyperplasia of thyroid follicular epithelial cells through stimulation of lymphocytes and results in the occurrence of atypical hyperplasia at the focus transitional zone.[23]

Owing to the low incidence but high malignant potential, PDTC is not well recognized and is often discovered

incidentally during treatment when it has metastasized to lymph nodes or distant organs. As it is reported in the literature, most patients with PDTC in our study had multiple distant metastases at diagnosis.[2] PDTC is characterized by rapid, invasive growth, and higher mortality rate than PTC and is prone to lymphatic and other remote metastases. Accurate preoperative diagnosis, clinical staging, and risk assessment are very important to help make the treatment protocol and establish prognosis.

Table 2: Ultrasonographic features of PDTC and PTC

Features	PDTC (n = 13)	PTC (n = 39)	P
Size (mean ± SD, cm)	3.1 ± 2.0	1.7 ± 1.0	0.003*
Shape, n (%)			
Regular	2 (15.4)	5 (12.8)	1.000
Irregular	11 (84.6)	34 (87.2)	
Margins, n (%)			
Clear	12 (92.3)	20 (51.3)	0.008
Indistinct	1 (7.7)	19 (48.7)	
Anteroposterior to transverse diameter ratio, n (%)			
<1	6 (46.2)	26 (66.7)	0.162
≥1	7 (53.8)	13 (33.3)	
Echogenicity, n (%)			
Isoechoic	1 (7.7)	6 (15.4)	0.432
Hypoechoic	12 (92.3)	33 (84.6)	
Echotexture, n (%)			
Homogeneous	6 (46.2)	8 (20.5)	0.077
Heterogeneous	7 (5.38)	31 (79.5)	
Cystic features, n (%)			
Solid-cystic	1 (7.7)	3 (7.7)	0.743
Solid	12 (92.3)	36 (92.3)	
Calcification, n (%)			
Absence/other calcification	6 (46.2)	16 (41.0)	0.497
Micro-calcification	7 (53.8)	23 (59.0)	
Vascularity, n (%)			
Irregular, rich blood flow	12 (92.3)	21 (53.8)	0.012
Absence/no rich blood flow	1 (7.7)	18 (46.2)	
Capsular invasion, n (%)			
Yes	2 (15.4)	15 (38.5)	0.114
No	11 (84.6)	24 (61.5)	

*t = 3.103. PDTC: Poorly differentiated thyroid carcinoma; PTC: Papillary thyroid carcinoma; SD: Standard deviation.

Ultrasound is a valid method for diagnosis and follow-up of thyroid carcinoma. With the help of ultrasound-guided FNA biopsy, thyroid carcinoma at an early stage can be accurately diagnosed. However, there are many reports of the misdiagnosis of PDTC; FNA may reveal a follicular tumor, follicular variant of PTC, adenomatous nodule, or PTC.[24] This may be related to the larger size, rapid invasive growth, limited amount of sample, and necrosis of the interested area of PDTC. If we do not take positive and effective intervention for the above cases, we may miss the best time for treatment and improving the prognosis. Our study showed that PDTC and PTC have a variety of ultrasound features in common, such as irregular shape, taller-than-wide, hypoechoic, heterogeneous, solid mass, and micro-calcification, and these characters are the indicators of suspicious malignant tumor.[25] In addition, three following features suggest that the lesion may be PDTC: Size larger than 3 cm, clear margin, and irregular/rich blood signals.

In this study, 92.3% of PDTC had clear margins (12/13) by ultrasonography, which was significantly higher than that of PTC ($P < 0.05$). In general, a tumor having margin echoes with a smooth and complete appearance can be considered have an intact capsule. Most nodules without margin echoes or with an indistinct and irregular shape are noncapsulated malignant lesions. As the foci of tumor cells in PTC is not clearly separated from the surrounding thyroid tissues, with common interstitial infiltration in the surrounding thyroid parenchyma,[26] the margin is unclear, and the edge shows spiculated infiltration by ultrasonography. However, the classical pathological feature of PDTC is an island structure, which is a distinct nest of tumor cells surrounded by a thin layer of fibrovascular stroma. The area between tumor foci and the fibrovascular core often forms an artificial fracture lacking either typical papilla or a follicular structure.[10] This may help explain why the ultrasonic margin is clear. About half of PTC showed sparse blood flow or no blood flow signal while 92.3% of PDTC displayed rich and prominent blood flow probably because of the higher malignant potential of PDTC, which is accompanied by stimulation of angiogenesis by tumor cells. In this regard, most blood vessels consist of arteries with irregular distribution.

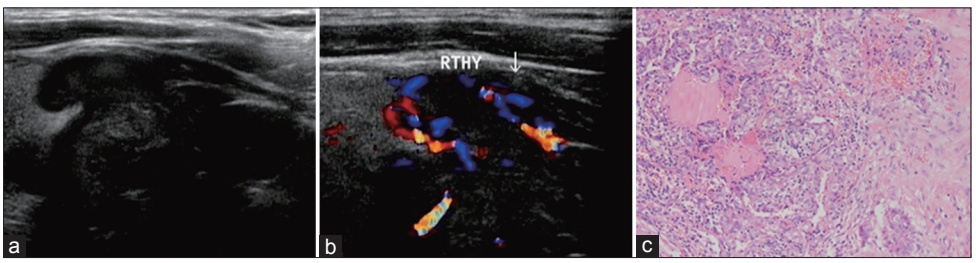

Figure 2: The ultrasonic and histological image of a poorly differentiated thyroid carcinoma case. A 56-year-old male patient with hoarseness for 1 month. (a) The longitudinal sonogram of a 6.5 cm × 4.4 cm irregular hypoechoic mass in the right thyroid and the capsule echo was not continuous. (b) Rich blood flow signals at the marginal and inner part of the mass. (c) The histological image of poorly differentiated thyroid carcinoma with large areas of necrosis and peripheral fibrosis. Tumor cells were relatively uniform in size, with round nuclei, vacuolar-shaped, and small nucleoli (H and E staining, Original magnification ×10).

In summary, PDTC is more aggressive, and its mortality rate is higher than PTC. Accordingly, more attention should be given to thyroid cancer nodules that show large size, regular shape, and rich blood flow signals on ultrasound to exclude the possibility of PDTC. Relatively smaller sample size is the main limitation of this study. More researches should be done to get more information in this field.

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Conflicts of interest

There are no conflicts of interest.

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