REVIEW

Poorly differentiated thyroid carcinoma: a clinician's perspective

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Abstract

Poorly differentiated thyroid carcinoma (PDTC) is a rare thyroid carcinoma originating from follicular epithelial cells. No explicit consensus can be achieved to date due to sparse clinical data, potentially compromising the outcomes of patients. In this comprehensive review from a clinician's perspective, the epidemiology and prognosis are described, diagnosis based on manifestations, pathology, and medical imaging are discussed, and both traditional and emerging therapeutics are addressed as well. Turin consensus remains the mainstay diagnostic criteria for PDTC, and individualized assessments are decisive for treatment option. The prognosis is optimal if complete resection is performed at early stage but dismal in nearly half of patients with locally advanced and/or distant metastatic diseases, in which adjuvant therapies such as ^{131}I therapy, external beam radiation therapy, and chemotherapy should be incorporated. Emerging therapeutics including molecular targeted therapy, differentiation therapy, and immunotherapy deserve further investigations to improve the prognosis of PDTC patients with advanced disease.

Key Words

▶ poorly differentiated thyroid carcinoma

▶ PDTC

Introduction

The incidence of thyroid cancer, the most common endocrine malignancy, has been increasing over the past decades. More than 87% of thyroid cancers are distinguished as differentiated thyroid carcinoma (DTC), including papillary thyroid cancer carcinoma (PTC), follicular thyroid carcinoma (FTC), and Hürthle cell cancer (1). Notwithstanding diverse biological features, most DTC patients are characterized with a favorable prognosis, as reflected by 10-year survival rates of about 90% (2). On the opposite, anaplastic thyroid carcinomas (ATCs), which are characterized by aggressive and rapidly fatal nature, typically confer a dismal outcome as reflected by 2-year survival rates of about 10–15% (3).

As an individual form of thyroid carcinoma derived from follicular epithelial cells, poorly differentiated thyroid carcinoma (PDTC) ranks between DTC and ATC regarding the degree of differentiation (4). PDTC was initially proposed as a separate entity by Sakamoto *et al.* in 1983 (5), immediately followed by Carcangiu *et al.* who deemed the histologic growth pattern as 'insular' carcinoma in 1984 (6). Twenty years later, PDTC was recognized as a distinct pathologic entity in the classification of thyroid tumors

by World Health Organization (WHO) Classification of Endocrine Tumors ([7]). In 2006, pathologists from Italy, Japan, and the United States refined the definition of PDTC in Turin by reviewing a cohort of 83 cases that had been selected according to the presence of solid/trabecular/insular (STI) growth patterns. Heretofore, a consensus of pathological diagnostic criteria of PDTC was initially developed based on the characteristics of morphological features ([8]). The latest 2017 WHO Classification of Tumors of Endocrine Organs adopted the Turin criteria for PDTC and indicated that any poorly differentiated component should be mentioned in the pathology report.

PDTC accounts for 3–5% of all thyroid carcinomas ([9], [10]), and the variation in incidence is commonly ascribed to environmental factors and differences in histopathological interpretation ([11]). A mean age between 55 and 63 years and a slight female preponderance can be found, which is similar to those of DTC and ATC ([12], [13]). The 5-, 10-, and 15-year survival rates of PDTC patients were 50–85%, 34–50%, and 0%, respectively ([14], [15], [16], [17]). Despite low constituent ratio in thyroid carcinoma, a relatively high number of deaths related to thyroid carcinoma are attributable to PDTC.

Currently, sparse clinical data, insufficient diagnosis, and no explicit management algorithm make the standard treatment of PDTC unclear. The clinical therapeutic options mainly extrapolated from the preformed experiences on DTC and ATC may prevent PDTC patients from getting maximum benefit. We performed a comprehensive PubMed search combined with hand search using the term 'poorly differentiated thyroid carcinoma', yielding 1568 articles prior to June 31, 2021. Hereby, the clinical diagnosis and treatment including surgery, ^{131}I therapy, external beam radiation therapy (EBRT), chemotherapy, and emerging therapeutics are addressed in detail in this dedicated review.

Diagnosis

A lump neck with rapid volume growth is the most common symptom and sign of PDTC, along with hoarse voice, dyspnea, or dysphagia if laryngeal nerve, weasand, or esophagus is invaded. However, none of the clinical features can accurately diagnose PDTC. Minority of cases may be recognized by fine-needle aspiration biopsy (FNAB) ([18]). As is demonstrated in Fig. 1, the definitive diagnosis mainly relies on histopathology, while immunohistochemistry and molecular characteristics substantially increase the diagnostic accuracy ([19]). There is
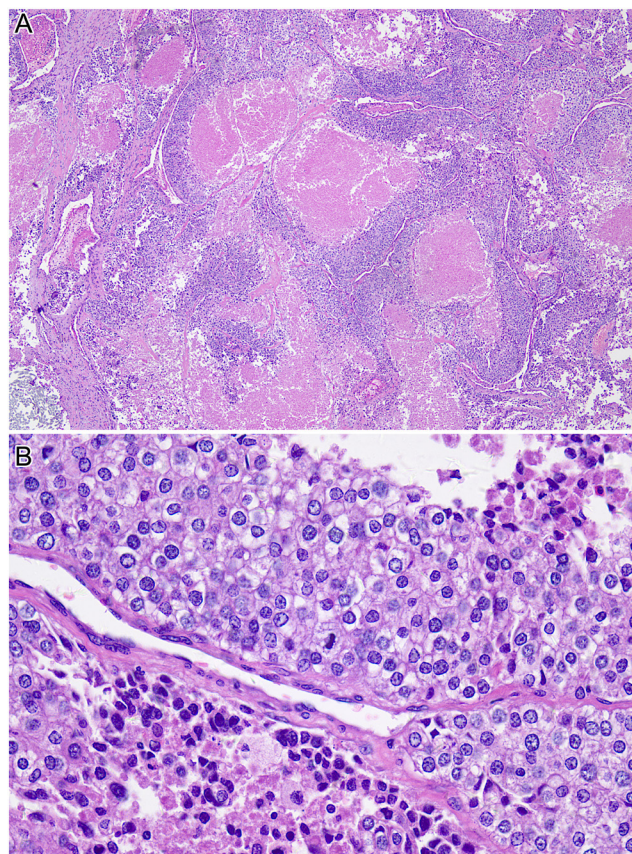
Figure 1
Poorly differentiated thyroid carcinoma in a 64-year-old male. Panel A shows marked tumor necrosis (×40). Panel B shows solid trabecular tumor without nuclear features of papillary thyroid carcinoma. Foci of necrosis are found in the upper and lower parts of the photo. Mitotic figure is presented in the center of the figure (×400). Hematoxylin and eosin staining. Somatic mutation of TERT promoter (C228T) was confirmed by next-generation sequencing.

a higher frequency of *TP53* and *TERT* promoter mutations in PDTC compared to DTCs ([19]). Besides, although 15% of PDTC patients are metastatic at presentation, it is of note that distant metastases occurred in up to 37–85%, and 60% died of distant disease over the course ([20], [21], [22]), which strengthen the significance of comprehensive assessments for patients as the basis of treatment strategy ([23]).

Pathology

PDTC is traditionally defined by a specific histopathology assisted with immunohistochemistry and molecular genetics, which is substantially compensated by the biological behaviors of tumor. The Turin standards based on the growth pattern of STI and the Memorial Sloan Kettering Cancer Center (MSKCC) standards

based on proliferative grading are mainly involved in the histopathological definition of PDTC.

Histopathology nature

According to the Turin consensus, the following requirements for diagnosis of PDTC should be met: I. STI microscopic growth pattern; II. lack of well-developed nuclear features of papillary carcinoma; III. presence of at least one of the following features: convoluted nuclei, mitotic activity ≥3/10 high power microscopic fields (HPF), and necrosis (24). The above 'Turin consensus criteria' was adopted as a uniform definition for histopathological diagnosis for PDTC in the WHO Classification of Endocrine Tumors (25). A representative histopathologic figure is presented (Fig. 1).

Nevertheless, the deficiencies of the above Turin consensus exist. First, features distinguishing PDTC from other follicular epithelial cell-derived tumors are unclear. For instance, some overlap exists in the differential diagnosis between PDTC and the solid variant of papillary carcinoma or DTCs with predominant solid or trabecular growth patterns (26). A recent study has demonstrated that PTC with high-grade features, which has a higher *BRAF^V600E* mutation rate, a trend toward more gene fusions compared with those with PDTC, and more aggressive behavior, should be considered a distinct group from PDTC (27). Secondly, there has not been a threshold of the minimum proportion of poorly differentiated (PD) area in DTC tissue to diagnose PDTC since the survival data in patients with PD area >50% did not differ from those with PD area >10%, and no difference was found in the outcomes of PDTC and DTC with PD area (28, 29), which makes us wonder the presence of any PD area should be enough to label a tumor as PDTC rather than the proportion. Finally, Hiltzik *et al.* showed that growth patterns did not correlate with overall survival using multivariate analysis, suggesting that the growth pattern may not be representative of tumor aggressiveness (30).

Besides, Volante found that PDTC patients with a low numerical score demonstrated a survival curve similar to DTC group, while necrosis and high mitotic rate represented the worst and most relevant prognostic factors (31). Innovatively, the head and neck pathologists at MSKCC diagnose this tumor using high mitotic rate (≥5 mitosis/10 HPF) and/or fresh tumor necrosis (30, 32). Meanwhile, high-grade pathological parameters, including a mitotic index of >3/HPF, necrosis, predominant presence of an insular component, have been found to be associated with a poor prognosis in terms of ongoing disease or death (33, 34).

Immunohistochemical features

Immunohistochemistry has been widely considered to increase the accuracy of diagnosis by narrowing the differential diagnoses and reflecting the progression of tumor. Moreover, the results of immunohistochemistry confirm the theory of a continuum from DTC to ATC through PDTC. However, no specific immunohistochemical marker has been established for the detection of PDTC yet (14, 18).

Majority of DTCs express high levels of thyroglobulin (Tg); however, the expression of Tg was absent or weakly positive in more than half of PDTCs (35). Although the role of Tg expression as a diagnosis criterion of PDTC remains undetermined, a study has shown that Tg expression in PDTC may predict the iodine avidity of lesions (36). PDTC is immunoreactive for thyroid transcription factor 1 (TTF1), PAX-8, and cytokeratin, confirming that PDTC originates from follicular epithelial cells in another perspective. Contrarily, ATC, rarely expressing Tg or TTF1, is diagnostically supported by strong positive immunoreaction with cytokeratin, and 85% of ATC was reported to be positive for PAX-8 (18, 37). The absence of membranous expression of E-cadherin, which relates to the differentiation level of thyroid carcinomas, helps distinguishing PDTC from DTC (38).

In addition, the negative expression of calcitonin, chromogranin, and carcinoembryonic antigen in PDTC can exclude neuroendocrine tumors, that is, medullary thyroid carcinoma (39). Likewise, PDTC is not immunoreactive with hematopoietic cellular markers, such as B-lymphocyte antigen (CD19 and CD20) and plasma cell marker (CD138), which helps ruling out lymphoproliferative disorders (14). In addition, high expression of IMP3, which is associated with tumor-associated death, lymph node metastasis, and distant metastasis, is useful for predicting poor prognosis (11).

Molecular characteristics

From the perspective of molecular characteristics, increasing evidence prove that PDTC is derived from DTC and is the intermediate state between DTC and ATC (40). The genetic alterations, including *RAS* (including *HRAS*, *NRAS*, and *KRAS*) mutation, *BRAF* mutation (predominantly V600E), *TERT* promoter mutations (*C228T* and *C250T*) activating telomerase and contributing to tumorigenesis, inactivating *TP53* mutations, and *ATM* mutations, have been found in PDTC. The understanding of tumor's molecular characteristics becomes more detailed and comprehensive given the next-generation sequencing. The heterogeneity of genetic characteristics

may be reflected by different response to a certain targeted treatment, providing implication for treatment options and their clinical outcomes (40). To date, however, the role of molecular profiling in directing therapy for PDTC remains indeterminate due to insufficient data (31).

High frequencies of mutually exclusive mutations of *RAS* and *BRAF* have been found in PDTCs. *RAS* activates both the MAP kinase pathway and the PI3K/AKT pathway, and the presence of *RAS* gene alterations could be found in 25–35% of PDTCs (41, 42, 43). BRAF is specific to the activation of the MAP kinase pathway and the *BRAF* mutation is present in 15–27% of patients with PDTC (41, 42). The strong association of PDTC-Turin tumors with RAS mutations had been found, whereas PDTC-MSK tumors were strongly associated with BRAF (44). Moreover, PDTCs derived from papillary thyroid cancer with mutant *BRAF* possess a higher probability of regional nodal metastases, and distant metastases occur more frequently in patients with follicular thyroid cancer-derived *RAS*-mutant PDTC (1, 44).

As another kind of common alteration in PDTC, *TERT* promoter mutation has been identified with a frequency of 40%, ranking in the middle of PTC (9%) and ATC (65–73%) (44). *TERT* encodes the reverse transcriptase component of the telomerase complex and is highly expressed in most human cancer cells (45). Mutations of *TERT* promoter gene in PDTC usually indicate an aggressive phenotype and a dismal prognosis. In PDTC and ATC, a significant co-occurring association between *TERT* promoter mutation and *BRAF* or *RAS* mutation has been identified (44). This is most likely due to the *de novo* binding elements on the mutant *TERT* promoter for MAPK signaling-activated E-26 family of transcription factors (46), causing *TERT* over-expression and induction of an immortalized phenotype.

As a tumor suppressor gene, however, *p53* gene plays vital role in hindering or reversing carcinogenic effects. Mutant *TP53*, which is more prevalent in ATC (65–73%), is highly prevalent in patients with PDTC (16–28%) but rarely associated with DTC (15, 47, 48). On the other side, alterations in *p53* gene were circumscribed in the less differentiated part of tumor histological samples containing both DTC and PDTC components. Therefore, *p53* mutations may predict that tumor will be triggered by dedifferentiation and evolution to PDTC and ATC (15). *ATM*, another tumor suppressor gene controlling the cell-cycle checkpoint and repair DNA, mutates in 7% of PDTC and 9% of ATC. This finding suggests that PDTC carrying *ATM* mutation may possess an aggressive behavior before progression to ATC (44). Lastly, *RET/PTC* rearrangement and *PAX8:PPARγ* rearrangement which occur in other

thyroid carcinomas are almost never found in PDTC (42, 47). PDTC in children and adolescents were strongly associated with *DICER1* mutations, which are distinct from adult-onset PDTC (49).

Medical imaging

Local recurrence and distant metastasis have been revealed as independent predictors for worse disease-specific survival (50). Meanwhile, the extent of invasion appears to be an important parameter that affects the clinical outcome for patients with PDTC (51). Therefore, the individual assessment becomes indispensable not only for diagnosis but also for management. Anatomic imaging assessments have been strongly compensated by molecular imaging in the last decade, which has been recently updated by our group (52).

High-resolution sonography and FNAB are sensitive and convenient diagnostic tools for thyroid carcinoma. PDTC commonly presents as relatively low echo or heterogeneous echo mass with a circumscribed margin and an oval-to-round shape on sonography (23). As vocal cord and laryngeal nerve are frequently affected in patients with extrathyroidal extension, the preoperative evaluation is critical. Esophagography, esophagoscopy, bronchoscopy, and the evaluation of vocal cord function may lay an important foundation for therapeutic decision-making via assessing neighboring structures possibly involved (47). If extrathyroidal extension or extensive local invasion is suspected, the use of enhanced CT and MRI helps to clarify the anatomic relationship between the lesion and surrounding structures (47).

Nuclear medicine imaging, such as ^{131}I whole-body scan and ^{18}F-FDG PET scan, offers detailed information on disease at molecular and cellular levels based on metabolism and biochemical processes (51). Of note, the dedifferentiation of tumor with consequent deficiency of the sodium/iodine symporter trafficking to membrane may result in negative ^{131}I scans, while ^{18}F-FDG PET/CT is able to detect distant metastases in 71% of patients with a history of PDTC, increased thyroglobulin levels, and negative ^{131}I imaging ('flip-flop' theory) (Fig. 2). Besides, ^{18}F-FDG PET/CT is also useful in planning EBRT and assessing response to treatment since the total volume of FDG-avid disease has been recognized as a single risk factor predicting survival (53, 54). As a demonstration of tumor heterogeneity, different patterns of tumoral uptakes were detected on ^{18}F-FDG, ^{68}Ga-DOTATATE, and ^{68}Ga-PSMA PET/CT (55).
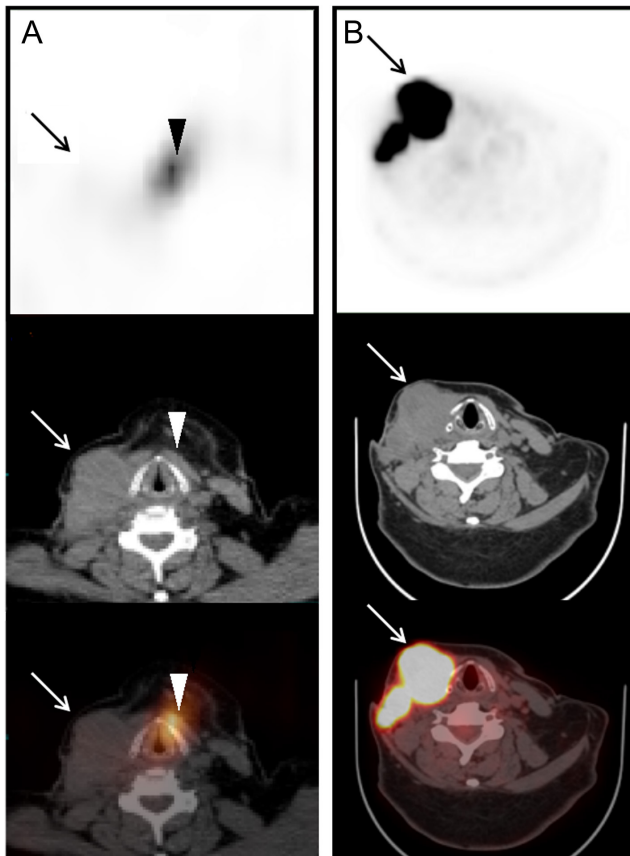
Figure 2

'Flip-flop' phenomenon in a 60-year-old woman with PDTC. Panel A shows ^{131}I-nonavid lymph node metastases by SPECT/CT scan (upper, SPECT image; middle, CT image; lower, SPECT/CT fusion image). Panel B shows lymph node metastases uptaking fluorodeoxyglucose by ^{18}F-FDG PET/CT imaging with maximum standardized uptake value of 33.6 (upper, PET image; middle, CT image; lower, PET/CT fusion image). Arrow, lymph node metastases; Aarrow head, thyroid remnant.

Management

Currently, it is difficult to draw conclusions about the uniform recommendations from the literatures available concerning the therapeutic procedures for PDTC. Surgery remains the mainstay of treatment among the traditional therapeutic modalities. Multimodal therapy may prolong 5-year-survival rate, varying between 47% and 89% (Table 1).

Surgery

Total thyroidectomy with lymph node dissection is the first-line management for PDTC ideally. Esophageal submucosal resection, unilateral recurrent nerve resection, or palliative surgery would be chosen if tumor invades surrounding structures, such as esophagus, trachea, larynx, and recurrent nerve (20). The policy in the management of

patients with PDTC and gross extrathyroidal extension is to achieve removal of all gross diseases in order to control the central compartment of the neck, minimize the risk of locoregional recurrence, and hence prevent life-threatening airway obstruction or hemorrhage. Nevertheless, data on the impact of operative approaches on clinical outcomes are insufficient to draw any conclusion (56). Satisfactory locoregional control with excellent 5-year locoregional control rate of 81% can be achieved by total thyroidectomy and clearance of all gross diseases (50, 57). One-third of PDTCs can be cured by lesion resection followed by ^{131}I therapy (10). Besides, particular attention must be paid to non-cured patients or those with metastases, especially during follow-up.

[131]I therapy

Compared to DTC, PDTC does not usually respond to ^{131}I therapy despite iodine avidity in some foci. To date, the majority of studies did not confirm the impact of ^{131}I therapy on prolonging disease-specific survival or overall survival (47, 58, 59, 60). It was considered reasonable to utilize ^{131}I therapy to control distant metastases which concentrate iodine well (50, 56, 61). The ^{131}I-avidity, which is found in 70–80% of patients with PDTC, provides the basis for ^{131}I therapy (22, 39, 50). Sanders *et al.* advocated that ^{131}I therapy ought to be considered in every patient with PDTC after complete surgery, in light of the potential for ^{131}I uptake and the lack of major side effects (62). Furthermore, the American Thyroid Association encourages that the patients with aggressive tumor histology should receive high dose (100–200 mCi) of ^{131}I, including the insular variants (63, 64).

Nevertheless, there are also cases where the lesions show potential ability of uptaking ^{131}I, but the therapeutic effect is not ideal. This may be ascribed to an impaired thyroid hormone synthesis system, yielding shortened ^{131}I retention time and reduced radiation dose, which might be reflected by the discrepancy between pre-therapeutic [99mTc]-pertechnetate scan and post-therapeutic ^{131}I scintigraphy (Fig. 3). Favorable therapeutic effect may be achieved in patients with lesions retaining ^{131}I for a sufficient period of time, which can be reflected by post-therapeutic whole body scan 3–7 days after ^{131}I administration (Fig. 4). Recently, our group has demonstrated that the combined use of the maximum target/background ratio of 8.1 on the whole body scan and change rate of thyroid stimulating hormone-suppressed thyroglobulin level of 25.4% may efficiently identify biochemical responders/non-responders to next course

Table 1 The characteristics and outcomes of patients with PDTC in cohort studies classified by therapeutic regimen.

Therapeutics	Reference	Sample size	Age (mean)	Diagnosis criteria for PDTC	Tumor size (cm, mean)	ETI (%)	LM (%)	DM (%)	5-year survival rate (%)
TT	Tanaka 2011 (13)	29	57	TIS pattern	3.1	55.2	72.4	13.8	89.3
	Wong 2019 (51)	47	57	2017 Endocrine WHO criteria	4.3	100	38	19	67
TT/thyroidectomy and RT	Volante 2004 (17)	183	56.3	TIS pattern	5.3	54	NR	NR	85
	Hiltzik 2006 (30)	58	56.5	Follicular cell differentiation + necrosis or mitotic index >5/10 HPF	5.6	64	12	66	60
	Cherkaoui 2015 (61)	7	60	Turin criteria	4	NR	51.7	NR	85
	Yu 2017 (57)	18	62	Turin criteria	5.8	44	28	28	83
TT and RT and EBRT	Jung 2007 (32)	49	49.3	TIS pattern + necrosis	4.7	59	29	33	68
	Lin 2007 (56)	67	50.3	TIS pattern	4.2	NR	NR	49.3	67
	Ibrahimpasic 2013 (20)	27	70	Follicular cell differentiation + necrosis or mitotic index >5/10 HPF	NR	30	80	37	47
	Ibrahimpasic 2014 (50)	91	59	Follicular cell differentiation + necrosis or mitotic index >5/10 HPF	NR	30	40.7	26	62
TT and RT and EBRT and CH	Siironen 2010 (60)	8	66	Turin criteria	5.6	63	37.5	37.5	50
TT and RT and EBRT and TKI	de la Fouchardière 2018 (10)	104	62	Turin criteria	NR	40	21.2	35.8	72.8
RT and EBRT	Zhang 2021 (66)	522	NR	NR	NR	NR	51.7	NR	73.7

CH, chemotherapy; DM, distant metastasis; ETI, extrathyroidal invasion; LM, lymph node metastasis; NR, not reported; RT, radioiodine therapy; TKI, tyrosine kinase inhibitors; TT, total thyroidectomy.
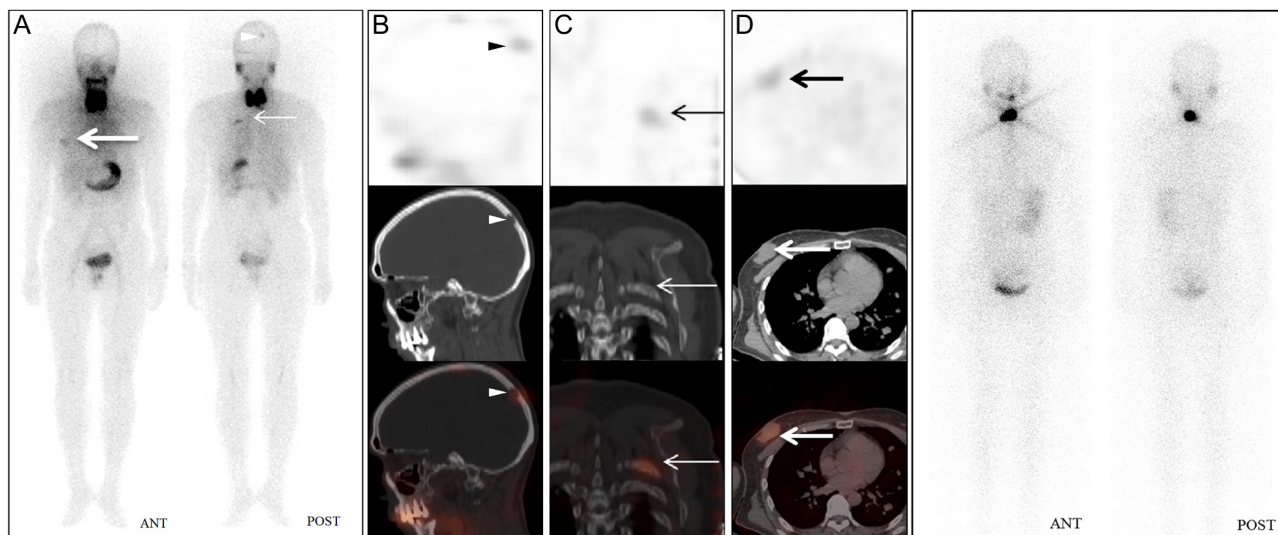
Figure 3

The discrepancy between 99mTc-pertechnetate and 131I scintigraphy in a 52-year-old woman with PDTC. Panel A shows multiple lesions accumulating 99mTc-pertechnetate in the skull and chest by 99mTc-pertechnetate WBS before thyroidectomy. SPECT/CT reveals 99mTc-pertechnetate-avid lesions in parietal bone (B, upper, SPECT image; middle, CT image; lower, SPECT/CT fusion image), left posterior rib (C, upper, SPECT image; middle, CT image; lower, SPECT/CT fusion image), and the right breast (D, upper, SPECT image; middle, CT image; lower, SPECT/CT fusion image). Histological analysis of punctured tissues from the right breast lump and the resected thyroid lobe demonstrates metastatic PDTC and PDTC, respectively. Panel E displays no 131I uptake in the above 99mTc-pertechnetate-avid lesions by post therapeutic 131I WBS on day 3 after the administration of 7.4 GBq of 131I. Arrow head, parietal bone metastasis; thin arrow, left posterior rib metastasis; thick arrow, right breast metastasis.
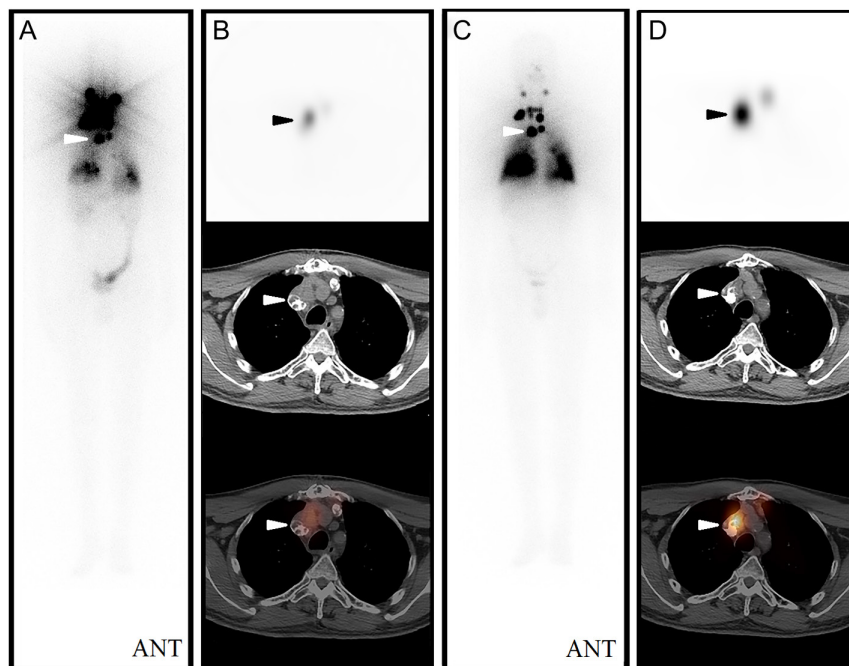
Figure 4
Response to radioiodine therapy in a 62-year-old man with PDTC. Panel A shows several 'hot spots' in neck and chest, diffuse distribution of ^{131}I in both lungs by post-therapeutic whole-body scan on day 3 after the initial administration of 7.4 GBq of [131]I. SPECT/CT scan shows ^{131}I-avid mediastinal lymph node measuring 34 mm × 28 mm (B, upper, SPECT image; middle, CT image; lower, SPECT/CT fusion image). Panel C shows similar findings to the initial post-therapeutic ^{131}I whole body scan on day 3 after the second administration of 7.4 GBq. Panel D shows the shrinkage of the mediastinal lymph node measuring 29 mm × 25 mm (upper, SPECT image; middle, CT image; lower, SPECT/CT fusion image). Arrow head, mediastinal lymph node.

of ^{131}I therapy, warranting management optimization of patients with ^{131}I-avid lesions (65).

External beam radiation therapy

EBRT has been confirmed as an option for controlling local disease for patients with PDTC, which is based on extrapolation from studies about poor-prognosis DTC where substantial data exist regarding treatment benefit (47, 62). Sanders *et al.* suggested that EBRT should be considered in patients with tumors larger than 4 cm, extrathyroidal extension, lymph node metastasis or irradical surgery, unresectable disease. Therefore, EBRT may be selected as a palliative treatment for PDTC if ^{131}I treatment fails in localized tumors, like local bone metastasis (62). According to the latest research, only the PDTC patients in high-risk cohort based on individualized nomogram were found eligible to benefit from postoperative radiotherapy (66). Intensity-modulated radiotherapy may be considered for adequately planning target volume coverage and minimizing dose to spinal cord (22, 67). During the course of radiation therapy, moderate skin erythema, dry or moist desquamation, and the mucositis of the esophagus, trachea, and larynx rarely occurred and are acceptable (68) but may make the subsequent surgery more difficult (69).

Chemotherapy

At present, there are no effective chemotherapy drugs or regimens dedicated for PDTC. Early studies of *in vitro* cell culture and chemosensitivity testing may prevent the administration of ineffective chemotherapeutic drugs, including adriamycin, cisplatin, cyclophosphamide, etoposide, and carboplatin (70). Several dosage regimens, such as adriamycin (68), a combination of methotrexate, adriamycin, bleomycin, and vinblastine (71), adriamycin-cisplatin combination, and paclitaxel-carboplatin regimen (72), have been explored for the chemotherapy of PDTC. Despite efforts to find a chemotherapeutic agent or a combination of agents to modulate PDTC progression, systemic chemotherapy has not yet produced clinically promising results.

Emerging therapeutics

Emerging therapeutics, including molecular targeted therapy, differentiation therapy, and immunotherapy are primarily used for thyroid carcinomas poorly controlled by traditional treatment, although most of the relevant researches remain ongoing.

Molecular targeted therapy

Inhibiting angiogenesis and tumor cell proliferation are the two mechanisms involved in molecular targeted therapy for advanced or progressive ^{131}I-refractory thyroid carcinoma (63). Sorafenib and lenvatinib have been approved by the US Food and Drug Administration after seminal multicenter phase 3 studies for follicular cell-derived thyroid cancer in cases of progressive, recurrent, or metastatic disease not responsive to ^{131}I therapy.

In addition, several drugs listed in the Clinical Trials.gov database are being evaluated in ongoing trials, including cediranib, dabrafenib, cabozantinib, etc. (73). These agents selectively target multiple kinases, improving progression-free survival in patients with advanced DTC (74). When PDTC becomes ^{131}I-refractory, kinase inhibitor therapy should not be ignored in patients with rapidly progressive disease and those with tumor-relevant symptoms (64).

A significant reduction in tumor size in PDTC patients and enhancement in proapoptotic activity in PDTC cells *in vitro* have been reported by treatment with sunitinib (75) and erlotinib (76), respectively. The enhancement of doxorubicin-induced proapoptotic activity by erlotinib provided a preliminary experimental basis of the combined application of targeted therapy and chemotherapy (76). Lenvatinib can be used to obtain hemodynamic stability with a neoadjuvant intent before thyroidectomy and radioiodine therapy (77) and has been demonstrated to be safe and effective in PDTC patients including complete and long-term remission when combined with pembrolizumab (78). Thus, the application of targeted therapy in advanced or ^{131}I-refractory thyroid carcinoma may provide a new option for PDTC, and the exploration of relationship between PDTC and radioiodine-refractory differentiated thyroid carcinoma may be helpful to discover the pathological basis of radioiodine-refractory differentiated thyroid carcinoma. What we should not ignore is that most multikinase inhibitors do not bring significant overall survival benefit but induce a number of adverse effects in different grades, sometimes significantly impair quality of life, including fatigue, weight loss, indigestion, etc. (72). Our real-world study indicates that targeted therapy should be individualized to maximize survival benefit (79).

Differentiation therapy

Differentiation therapy has been deemed as a promising strategy that facilitates PDTC to recover the ability of ^{131}I uptake and leads to prolonged survival. Several treatment strategies, such as retinoic acid (80), peroxisome proliferator-activated receptor gamma agonists (81), tyrosine kinase inhibitors (82, 83, 84), and neuro trophin receptor kinase inhibitors (85) have been explored for the differentiation therapy. Moreover, miRNA, DNA, and histones modifications may also lead to profound gene expression changes to facilitate differentiation of thyroid cancer (86, 87, 88).

Unfortunately, accumulating evidences have shown that their clinical effectiveness remains insufficient (89). For instance, it was revealed that tyrosine kinase inhibitors induced visible ^{131}I uptake in only nearly 60% of subjects, and objective response was achieved in approximately one-third of patients who subsequently received therapeutic dose of [131]I. Besides, the preparation of thyrogen prior to ^{131}I therapy and sustained administration of tyrosine kinase inhibitor during ^{131}I therapy are questionable.

Immunotherapy

Immune checkpoint inhibitors are a promising treatment option in a number of malignancies (90). Combination strategies that target multiple aspects of the tumor microenvironment could provide a more durable benefit for PDTC patients. There is only one recent study which discovered that 25% were positive for PD-L1 among the 28 PDTC patients, and 29% co-expressed IDO1, making immune checkpoint inhibitors as monotherapy or in combination with an IDO1 inhibitor become a novel treatment modality for selected patients with PDTC (91).

Conclusions

PDTC has been recognized as a rare entity with poor overall prognosis and challenging management. The intermediate state of differentiation between DTC and ATC correlates both molecular characteristics and clinical manifestations. Comprehensive assessments based on pathological diagnosis and medical imaging are critical for therapeutic decision-making and follow-up. Surgery, ^{131}I therapy, and EBRT constitute the mainstay of traditional treatment for patients with advanced disease, while emerging therapies based on molecular alterations are promising, deserving further investigation to improve the prognosis of patients.

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