Poorly differentiated thyroid carcinoma: 5 years after the 2004 WHO classification of endocrine tumours.

POORLY DIFFERENTIATED THYROID CARCINOMA:

5 years after the 2004 WHO Classification of Endocrine Tumors.

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Short title: poorly differentiated thyroid carcinoma

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Abstract

Poorly differentiated thyroid carcinoma (PDTC) was originally described in 1983 but included in the WHO classification of thyroid tumors in the 2004 edition, only. The diagnostic problems encountered in these five years of application of the WHO criteria are here reviewed. A long debate is still going on the nature of PDTC, its morphological diagnostic features, its clinical significance and its optimal therapeutic approach. A consensus conference held in Turin in 2006 confirmed the geographical differences among claimed classical forms of PDTC and suggested a diagnostic algorithm based on the presence of a solid/trabecular/insular growth pattern and of high grade features, in line with the WHO definition of PDTC, capable to select tumors with a distinct aggressive clinical behaviour. This worked well for PDTC cases from mountain areas (e.g. Northern Italy), where most, if not all, thyroid carcinomas having high grade features also share a solid/trabecular/insular pattern of growth. However, this scheme might be less easily applicable for American and Japanese cases, possibly due to heterogeneous architectural and cytological features; indeed some Authors still prefer to base their diagnostic work up on the recognition of high grade features only, including mitotic index and necrosis, irrespective of the growth pattern.

Keywords: poorly differentiated carcinoma, thyroid, diagnosis

Foreword

Since the original description of poorly differentiated thyroid carcinoma (PDTC) in 1983 [1], a long debate has occurred on the very nature of this tumor, on its morphological diagnostic features, on its molecular profile and on its clinical significance [2-10]. PDTC was defined as a thyroglobulin-producing non-follicular non-papillary thyroid carcinoma, having an intermediate behaviour between well differentiated and anaplastic carcinomas. In the 2004 WHO Classification of Endocrine Tumors [11], PDTC was introduced as a separate entity, and its recognition was based on both architectural (non-follicular/non-papillary growth pattern) and high-grade features (invasive growth, high mitotic index and necrosis).

After five years, the above mentioned proposed criteria are still controversial and heterogeneously applied in the diagnostic practice. Therefore, some overlap exists with other tumor categories, including the solid variant and the tall cell variant of papillary carcinoma on the one side and follicular carcinomas with predominant solid/trabecular growth patterns on the other (**Figure 1**). As a result, the term PDTC encompasses a remarkably heterogeneous group of tumors only partially related, thus preventing a reproducible and well defined diagnostic approach (**Table 1**) and, perhaps, an appropriate clinical management. Such heterogeneity became dramatically evident at a consensus meeting held in Turin in 2006, in which allegedly clear cut examples of PDTC collected from different countries (indeed continents) were reviewed and discussed (see below).

Established facts

With regard to PDTC diagnosis, some issues seem relatively well-defined. These include:

1) PDTC displays predominant solid/trabecular/insular growth patterns which may coexist with more or less extensive differentiated components of the follicular or papillary type on the one side, and of the anaplastic carcinoma type on the other. While this latter event is extremely

rare, representing less than 1% of cases at least in our series from a mountain area of Northern Italy, the former is more common; however, such combination does not seem to affect PDTC prognosis, which is generally driven by the poorly differentiated component and is worse than that of the corresponding conventional follicular or papillary carcinomas.

2) PDTC having predominant oncocytic changes (oxyphilic, Hurthle cell) are not a separate entity, but a variant of PDTC. In fact, the current WHO classification of thyroid tumors [11] has incorporated oncocytic tumors as variants of the conventional follicular-derived neoplastic subtypes, including PDTC. The presence of mitochondrion-rich cells and/or oncocytic changes can be recorded in the pathology report, but is not a relevant diagnostic or prognostic feature requiring a different tumor categorisation [12, 13].

3) The immunohistochemical profile of PDTC is that of a follicular-derived tumor, including thyroglobulin production (generally, in intracellular paranuclear vacuoles) and TTF-1 expression. PDTC was labelled as "poorly differentiated" based on the assumption that lack of follicles was a synonym of loss of normal thyroid structure (indeed conventional papillary cancer also lacks follicles, but is nevertheless a well differentiated thyroid tumor). However, from a functional or endocrine point of view, the majority of PDTC maintain their capacity to produce hormones, and thyroglobulin is an important immunohistochemical marker for the differential diagnosis of PDTC from other trabecular lesions of the thyroid gland [14], as well as a useful post-operative serum marker in the patient's follow up. Markers of malignancy in follicular tumors (such as HBME-1, galectin-3, etc) may also be expressed in PDTC, but have no practical diagnostic application, since morphological signs of malignancy (i.e. vascular invasion) are unequivocally present in all cases.

Open questions

From the publication of the WHO classification of Tumors of Endocrine Organs [11] five years ago, a large debate was generated on PDTC morphological and clinical features, which is still ongoing worldwide. Some issues, among others, will be briefly commented on, with special reference to the most recently published studies on the matter.

1) *Mitoses and necrosis vs growth pattern*. Several studies based on large case series identified high mitotic index and presence of necrosis as relevant parameters associated to adverse prognosis in thyroid cancer, and therefore considered them a distinctive hallmark of PDTC [13, 15]. Indeed, such high grade features were considered by some of these Authors the only relevant ones for PDTC definition [15], irrespective of the growth pattern. As a consequence, in the PDTC group, aggressive variants of well differentiated carcinomas were also included, such as the tall cell variant of papillary carcinoma (indeed having distinct pathological features and clinical behaviour, compared to PDTC) [16, 17]. On the other side, the presence of a predominant insular component was demonstrated to be associated *per se* to a more aggressive behaviour, even in recent papers [18]. Recently, the "Turin proposal" summarized the results of a consensus conference that involved 12 pathologists from Japan, United States and Europe, and suggested a diagnostic algorithm for PDTC diagnosis [19, 20]. According to such algorithm, a PDTC is defined by the following diagnostic criteria: i) presence of a solid/trabecular/insular pattern of growth in an otherwise malignant thyroid lesion (to an extent not clearly settled: "the majority of the tumor" is mentioned as a requirement in the WHO book); ii) absence of the conventional nuclear features of papillary carcinoma, to distinguish PDTC from the solid variant of papillary carcinoma, which is characterized by a solid/trabecular growth pattern, but bears a significantly better prognosis than PDTC in the adult population [21]; iii) presence of convoluted nuclei or mitotic activity >3x10 HPF or tumor necrosis (at least one feature). Convoluted nuclei are smaller and darker than papillary carcinoma nuclei, and are round, hyperchromatic with convolutions of the nuclear membrane ("raisin-like" contours). A recent Japanese study [22] aimed

at investigating the prevalence and clinical significance of "three types of poorly differentiated carcinoma" - as defined by Sakamoto [1], WHO classification [11] and the Turin proposal [19] - as well as of the tall cell variant of papillary carcinoma; this study confirmed that different tumor groups are identified by the different inclusion criteria and showed that significant differences among the groups were also present in terms of survival, being cases identified according to the Turin proposal those associated to the worst survival rates.

2) *Prognostic factors in PDTC.* It is widely shared that PDTCs have a distinct and intermediate prognosis within the spectrum of follicular-derived thyroid cancers [16]. However, prognostic stratification of PDTC patients is largely biased by the extensive overlap existing between "diagnostic" and "prognostic" parameters. As an example, the presence of a high mitotic index and/or necrosis has been alternatively considered a diagnostic hallmark of PDTC or a negative prognostic indicator. As a consequence, several parameters have variably been proposed to be associated to a worse prognosis in PDTC, but very few have been confirmed in additional studies and by means of appropriate statistical (multivariate) analysis. Running through the most recent studies applying the WHO classification, age 45 or higher, high TNM stage, extrathyroidal extension, presence of distant metastases and no post-operative radioiodine therapy administration (indeed the most relevant parameter at multivariate analysis) have been associated to a more aggressive clinical course in PDTC [17, 23].

3) *Radioiodine uptake*. From a clinical perspective, the immunohistochemical profile of thyroglobulin production is reflected by the ability of radioiodine uptake displayed by the majority of PDTC (up to 80% of cases), both in the primary tumors and in distant metastases [8, 13, 15, 23, 24]. In our and other Authors' experience, radioiodine uptake by the tumor is associated to successful ^{131}I radiotherapy [8, 17, 23], although this view is not shared by other Authors [25, 26], possibly reflecting geographical differences in terms of different tumor stages at the time of radioiodine treatment and/or different timing and dosage of radioactive iodine administration. However, standard postoperative dosages of ^{131}I do not differ from those of well

differentiated thyroid cancer [17, 23]. It is worth noticing that recently a high prevalence of PDTC histotype was found in a series of radioiodine refractory metastatic thyroid cancers, and that, in this specific subgroup of patients, the presence of necrosis and extrathyroidal extension were associated to shorter disease-specific survival [27].

4) *PDTC-specific molecular signatures?* Several molecular alterations have been investigated to define PDTC histogenesis, but the molecular genetic data so far reported in the literature reflect the heterogeneity of the case series analyzed, as the result of the discrepancies in PDTC diagnosis and classification. Generally, irrespective of the selection criteria applied, RAS point mutations appear to be a common molecular alteration in these tumors, although they were found with highly variable frequency and wide variation in specific types of RAS mutations [4, 28, 29]. Likewise, BRAF mutations were detected in poorly differentiated carcinomas having residual papillary carcinoma foci [30, 31], but not in cases lacking the morphologic evidence of transition from well differentiated papillary to poorly differentiated carcinoma [32]. Interestingly, in a recent study, BRAF mutations have been associated to FDG-PET–positive radioiodine refractory thyroid cancers [33]. RET/PTC1 rearrangements were found in a fraction of poorly differentiated carcinomas having the nuclear features of papillary carcinoma and/or some (residual) foci of papillary carcinoma [34]. The occurrence of β-catenin mutations in PDTC is controversial, ranging from 0% [35] to 32% [36] of tumors in two different studies. Finally, TP53 mutations were described in a subset of PDTC by different authors [37, 38], and proposed as a molecular marker of thyroid tumor de-differentiation and progression.

Conclusions

PDTC still represent a challenging issue for both pathologists and clinicians. Their classification into a separate group by the WHO is justified by their biological and clinical

behaviour - intermediate between well differentiated and anaplastic thyroid cancers, but they are affected by a still equivocal diagnostic approach and by an incompletely standardized therapy. A certain degree of confusion depends on the overlap between diagnostic and prognostic parameters in PDTC (e.g. vascular invasion, growth pattern, mitotic index, necrosis, and others), thus making a strict prognostic stratification of PDTC patients difficult, and subsequently a well-defined therapeutic approach poorly achievable. Molecular data are controversial and limited by the heterogeneous case series analyzed, and should be re-defined in strictly re-classified PDTC and devoted to both understanding the histogenesis of PDTC and identifying novel prognostic and predictive markers in this type of aggressive thyroid tumors.

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Table 1. Established facts and controversial issues onto poorly differentiated thyroid carcinoma.

Established fact	Comment	Controversy
Solid/trabecular/ insular growth pattern should be predominant	Growth pattern recognition is a keystone for PDTC recognition, although it is not unique of this tumor entity [11]	
Follicular, papillary and anaplastic carcinoma components may be associated	The presence of an associated component defines a subset of PDTC (i.e. so called "papillary type" [19]) but, except for the association with anaplastic carcinoma, bears no clinical implication	
The presence of predominant oncocytic features defines the oncocytic variant of PDTC	PDTC with predominant oncocytic features behave as the "conventional" type [12]; they share with other oncocytic thyroid tumors common morphological features but their immunophenotypical and molecular profile is yet unexploited	
Follicular derivation is proven by thyroglobulin and TTF-1 positive IHC	The role of immunohistochemistry in PDTC diagnosis is limited to exclusion of other thyroid lesions not derived from the follicular epithelium (i.e. medullary carcinoma, parathyroid tumors, metastases) [14]	
	The presence of necrosis and/or high mitotic count are considered diagnostic of PDTC when associated to a predominant solid/trabecular/insular growth pattern [19]; however, they are considered exclusive hallmarks of PDTC by some Authors, irrespective of the growth pattern [15]	High grade features are diagnostic of PDTC
	"Convoluted" nuclei have been introduced in the	Convoluted nuclei

	Turin proposal as a distinctive feature of a subset of PDTC [19]. However their exact histopathogenetic meaning and diagnostic reproducibility are poorly defined.	are diagnostic of PDTC
	At multivariate survival analysis age ≥45 yrs, high pTNM stage, extrathyroidal extension, presence of distant metastases and no radioiodine therapy administration have been associated to worse prognosis [17, 23]. The presence of necrosis and high mitotic count are known relevant prognostic parameters in thyroid tumors, but, since they are diagnostic parameters in PDTC, their prognostic role is equivocal in this tumor type and prognostic cut off threshold (i.e. for mitoses) are to be settled	Relevant prognostic parameters in PD carcinoma
	Up to 80% of PDTC uptake radioiodine, but data on the responsiveness rate to radioiodine therapy are controversial in the literature [8, 17, 23, 25, 26], and a high prevalence of PDTC histotype has been found in radioiodine refractory metastatic thyroid cancers [27]	Is radioiodine therapy useful in PDTC?
	RAS gene, namely NRAS, demonstrates the highest rate of mutations in PDTC, occurring in 20 to 60% of cases [4, 28], whereas BRAF and RET/PTC alterations are variably reported in the literature in PDTC, according to the different selection criteria used	PDTC molecular pathogenesis

Legend. PDTC: poorly differentiated thyroid carcinoma. IHC: immunohistochemistry.

Figure legend

Figure 1. Comparative illustration of typical features of PDTC and some of its mimics.

"PDTC" column of figures: PDTC is a malignat thyroid tumor with wide vascular invasion (top left) and common peritheliomatous necrosis (top right); residual microfollicular architecture may be admixed with predominant solid/trabecular/insular areas (middle left) and a subset of cases shows the so-called "convoluted" nuclei (middle right; mitotic figure in the inset); predominant oncocytic features in an otherwise PDTC define the oncocytic variant (bottom left; necrotic focus at the top of figure); nuclear pleomorphism may be encountered particularly in oncocytic areas (bottom right) but does not necessarily imply anaplastic transformation

"PDTC mimics" column of figures: malignant thyroid tumors that enter in the differential diagnosis with PDTC include follicular carcinoma with solid growth (top) that may show extensive vascular invasione (top inset) but lacks necrosis or increased mitotic activity, solid variant of papillary carcinoma (middle right) that shows the typical papillary carcinoma nuclei (middle left) and medullary carcinoma with predominant solid growth (bottom right) lacking amyloid stroma (bottom left); in this latter case, thyroglobulin and/or calcitonin immunohistochemistry is essential for a correct diagnosis.

PDTC
PDTC mimics
PDTC with necrosis
PDTC with convoluted nuclei
PDTC with oncocytic features
solid FTC
solid PTC
solid MTC amyloid-free