# Poorly Differentiated Thyroid Carcinoma

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**KEYWORDS**

• Thyroid • Carcinoma • Poorly differentiated • Insular

## ABSTRACT

Poorly differentiated thyroid carcinoma (PDTC) has been recognized for the past 30 years as an entity showing intermediate differentiation and clinical behavior between well-differentiated thyroid carcinomas (ie, papillary thyroid carcinoma and follicular thyroid carcinoma) and anaplastic thyroid carcinoma; however, there has been considerable controversy around the definition of PDTC. In this review, the evolution in the definition of PDTC, current diagnostic criteria, differential diagnoses, potentially helpful immunohistochemical studies, and molecular alterations are discussed with the aim of highlighting where the diagnosis of PDTC currently stands.

## OVERVIEW

Poorly differentiated thyroid carcinoma (PDTC) is a rare follicular cell–derived thyroid tumor accounting for approximately 0.5% to 7% of thyroid malignancies,[1,2] with the higher end of this range seen in iodine-deficient areas, such as Northern Italy. The average patient age is 55 to 70 years, and there is a slight female predominance (approximately 1.3–2.0 to 1).[1,3–5] The prognosis is significantly worse than that of papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC).[1,3–6] Distant metastases are common,[1,3,6] with lung and bone the most frequent sites.[7,8] Because PDTC has been variously defined, the prognosis has not been entirely established; however, the 5- and 10-year survival rates of patients with PDTC as defined by the Turin criteria (discussed later) are approximately 70% and 50%, respectively.[1]

### *Key Histologic Features* of Poorly Differentiated Thyroid Carcinoma

- Areas of solid/trabecular/insular growth
- Lack of nuclear features of papillary thyroid carcinoma in the poorly differentiated component
- Convoluted nuclei
- Increased mitotic activity (greater than or equal to 3 mitoses per 10 high power fields)
- Coagulative tumor necrosis

Histologically, PDTCs are invasive tumors that demonstrate areas of solid/trabecular/insular growth, a lack of nuclear features of PTC in these areas, and increased mitotic activity and/or necrosis.[5] Although immunohistochemistry may be used in the evaluation of cases in which a diagnosis of PDTC is considered, it is not required because the diagnosis of PDTC rests on histologic features.

## EVOLUTION IN THE DEFINITION OF POORLY DIFFERENTIATED THYROID CARCINOMA

The term *poorly differentiated thyroid carcinoma*, was loosely used in older literature to describe undifferentiated thyroid carcinoma.[9] The diagnosis of PDTC as it is now known, however, was initially put forth in 2 seminal articles published in the early 1980s. At that time, follicular cell–derived thyroid carcinomas were considered histologically and prognostically as either well-differentiated (ie, PTC

The authors have no conflicts of interest to disclose.
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Surgical Pathology 7 (2014) 475–489
http://dx.doi.org/10.1016/j.path.2014.08.001
1875-9181/14/$ – see front matter Published by Elsevier Inc.

or FTC) or undifferentiated/anaplastic thyroid carcinoma (ATC).[10] In 1983, Sakamoto and colleagues[11] identified a subset of thyroid carcinomas using architecture alone that had a poor clinical outcome in the absence of transformation to ATC. Histologically, these tumors were defined as having a nonglandular component as demonstrated by a solid, trabecular, or scirrhous (single cells or cords of cells within a fibrous stroma) architecture. Clinically, they demonstrated a behavior that was situated between that of indolent well-differentiated tumors and rapidly fatal ATC. The following year, Carcangiu and colleagues[12] described a histologic subset of thyroid carcinomas with a similar prognosis as described by Sakamoto and colleagues (ie, intermediate between well-differentiated carcinomas and ATC) that they referred to as poorly differentiated, or insular, thyroid carcinoma. Insular referred to the nests of tumor cells that were sharply demarcated from the adjacent stroma secondary to artifactual clefting, imparting an appearance similar to that of carcinoid tumors with an insular growth pattern. Although architecture was also a key component of the tumors in their cohort, in addition they described unique cytologic features (uniform small cells with a small amount of cytoplasm and small nuclei lacking prominent nucleoli), increased proliferative activity, and associated necrosis. The investigators emphasized that the tumor that they were describing was not a new entity but one that had likely been recognized in 1907 by Langerhans as *wuchernde Struma*[13] and subsequently regarded as a subset of various other diagnostic groups, including FTC, PTC, medullary thyroid carcinoma (MTC), and ATC.[10] Thus, PDTC as defined by Carcangiu and colleagues was a considerably more exclusive category compared with that of Sakamoto and colleagues, requiring high-grade features (mitotic activity and necrosis) in addition to a particular growth pattern.

Over the subsequent years, there was significant controversy in the thyroid pathology community about PDTC as a diagnostic entity.[14,15] In addition to the question of whether PDTC could be defined by growth pattern alone or required high-grade features as well, some groups were characterizing variants of PTC, such as tall cell and columnar cell variants, as PDTC on the basis of their more aggressive clinical behavior compared with conventional PTC.[16–18] Additionally, some studies were reporting a lack of prognostic significance of solid growth or an insular architecture alone.[19–21] Volante and colleagues[22] aimed to investigate the importance of high-grade features in tumors with a solid/trabecular/insular growth pattern. Examining a cohort of 183 cases with these growth patterns (comprising at least 10% of the tumor), the investigators found that patient age, mitotic count greater than 3 per 10 high-power fields (HPFs), and tumor necrosis were all independent prognostic variables in multivariate analysis. Hiltzik and colleagues[7] further emphasized the importance of high-grade features. These investigators defined PDTC as a follicular cell–derived tumor that had tumor necrosis and/or greater than or equal to 5 mitoses per 10 HPFs, regardless of the tumor growth pattern. Of their cohort that included 58 patients, 66% patients had or developed distant metastases (predominantly lung and bone, with rare liver, spleen, and kidney metastases), 74% developed disease recurrence or disease progression, and 38% of patients died of disease, with a 5-year overall survival rate of 60%. Necrosis was present in 83% of cases and the mean mitotic rate was 6 mitoses per 10 HPFs. Although they reported that growth pattern did not seem to influence outcome, it should be noted that there was a predominant solid/trabecular/insular growth pattern in 79% of their cases.

It was not until 2004 that PDTC was recognized as a separate tumor entity in the World Health Organization (WHO) Tumors of Endocrine Organs.[23] In the 2004 WHO classification, PDTC was defined as a tumor with a predominantly solid/trabecular/insular architecture together with an infiltrative growth pattern, necrosis, and obvious vascular invasion. Additionally, the tumor cells of PDTC were described as generally small and uniform with hyperchromatic to vesicular nuclei and indistinct nucleoli. Importantly, tall cell and columnar cell variants of PTC were excluded from the category of PDTC. Although the 2004 WHO classification identified the main diagnostic features of PDTC, there was still uncertainty about how to apply the criteria and variability in application between pathologists in different countries. Hence, in 2006, an international consensus conference of 12 thyroid pathologists from Japan, Europe, and the United States was held in Turin, Italy; 83 cases from these countries that had areas of solid/trabecular/insular growth were reviewed.[5] Based on the review of these cases, an algorithmic approach was proposed for the diagnosis of PDTC. According to the Turin proposal, the diagnosis of PDTC requires the presence of a solid/trabecular/insular architecture, a lack of nuclear features of PTC, and the presence of one of the following: convoluted nuclei, necrosis, and/or a mitotic count of 3 or more per 10 HPFs. This approach was based on the finding that necrosis was strongly correlated with a shorter survival (regardless of extent), as was a mitotic count of 3