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Poorly differentiated thyroid carcinoma

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ABSTRACT

Poorly differentiated thyroid carcinoma (PDTC) is an aggressive form of follicular cell derived thyroid carcinoma with a prognosis intermediate between the indolent well differentiated thyroid carcinomas and the rapidly growing often fatal anaplastic carcinoma. While all investigators agree on the presence of this entity, there is disagreement in regard to its definition. In 2006, a set of criteria based solely on mitotic index ≥5/10 high power fields and/or tumor necrosis was proposed by a group of researchers from Memorial Sloan Kettering Cancer Center (MSKCC criteria) in New York. A year later, alternative diagnostic criteria of PDTC, so called the Turin proposal, were advocated by an international consensus group. The Turin proposal requires three criteria: 1) solid/trabecular/insular growth pattern; 2) absence of nuclear features of papillary carcinoma; and 3) at least one of the following three features: mitotic index ≥3/10 high power fields (HPFs), necrosis, or convoluted nuclei. In this review, we summarize the histology, diagnostic criteria (Turin proposal and MSKCC criteria) with their pros and cons, the prognostic factors, and molecular profile of PDTC, aiming to provide a practical and compreshensive review of this challenging entity.

Introduction

Poorly differentiated thyroid carcinoma (PDTC) is an uncommon type of thyroid follicular cell-derived carcinoma, accounting for 1-3% of all thyroid carcinomas diagnosed.[1] It carries an intermediate prognosis in between well-differentiated carcinoma (e.g. papillary carcinoma, follicular carcinoma and Hurthle cell carcinoma) and anaplastic carcinoma with a reported mortality of 38-57%.[2–5] Clinically, PDTC typically affects patients in their late 50s (median 59) and shows a higher male: female ratio of 1:1.6 compared with the 1:3 ratio of well-differentiated thyroid carcinoma.[6,7]

In the past three decades, several key studies have been published aiming to establish the diagnostic criteria, prognostic factors and molecular signatures of PDTC. In the current review, we aim to summarize the evolution of PDTC, focusing specifically on the pathologic diagnostic aspect and genomics of this entity.

PDTC: History and diagnostic criteria

In 1907, Theodor Langhans was the first to describe a thyroid carcinoma with insular growth pattern, and he labeled the tumor "wuchernde Struma"[8] in German or "proliferating goiter" in English . The term "poorly differentiated carcinoma of thyroid gland" was introduced into the English literature by Granner and Buckwalter in 1963.[9] However, their histologic description of predominant small cell, giant cell, and spindle cell morphology is more akin to the contemporary description of anaplastic thyroid carcinoma rather than PDTC. In the early 1980's, two separate groups reported on a thyroid tumor having a prognosis in between well differentiated thyroid carcinomas and anaplastic thyroid carcinomas. Both groups named this tumor poorly differentiated thyroid carcinoma (PDTC). Both articles defined it mainly on the basis of a solid/trabecular/insular growth pattern and a degree of "atypia" lower than the one seen in anaplastic tumors.[10,11]

In 2004, PDTC was included in the World Health Organization (WHO) classification (3rd edition) as a "follicular-cell neoplasm that show limited evidence of structural follicular cell differentiation and occupy both morphologically and behaviorally an intermediate position between differentiated and undifferentiated carcinomas".[12] However, such definition is rather vague, and the only well-described histologic feature included in the 2004 WHO classification was insular/trabecular/solid growth pattern.[12]

In 2006, a group of researchers from Memorial Sloan Kettering Cancer Center (MSKCC) in New York proposed a definition of PDTC based on the presence of a mitotic index ≥5/10 high power fields (HPFs) and/or tumor necrosis in a carcinoma showing histological and/or immunohistochemical evidence of follicular cell differentiation independently of growth pattern.[4] Tumors defined on the basis of these MSKCC criteria showed an overall survival of 60% at 5 years

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intermediate between well differentiated and anaplastic thyroid carcinomas. Shortly afterwards, a uniform set of diagnostic criteria for PDTC, namely the Turin proposal, was put forward by a group of international thyroid experts.[5] The Turin proposal requires for a diagnosis of PDTC the following: 1) solid/trabecular/insular growth pattern; 2) the absence of nuclear features of papillary thyroid carcinoma; and 3) one or more of the following three features: convoluted nuclei, mitotic index of 3 or more per 10 HPF, and tumor necrosis.[5] As is the case for the MSKCC criteria, the Turin proposal is able to capture tumors with intermediate prognosis in between well differentiated thyroid and anaplastic carcinomas.[4,5] However, when the non-anaplastic tumors in their series were stratified using tumor necrosis, those without tumor necrosis behaved like indolent papillary thyroid carcinomas (PTC).[5] Similar results were reported in 2004 by Volante et al, where a numerical scoring system based mainly on tumor necrosis was able to stratify patients with PDTC defined on the basis of solid/trabecular/insular architecture only. Their tumors with a low numerical scoring system (i.e. without tumor necrosis) behaved even better than their PTC cases.[13] Hiltzik et al. have shown that growth patterns (solid vs. follicular/papillary) as well as cell type (Hurthle, papillary) did not influence overall survival in PDTC defined by MSKCC criteria. Of note, both Turin proposal and MSKCC criteria allow PDTC to show oncocytic (Hurthle cell) changes. Based on the above studies (including Turin proposal and MSKCC criteria),[4,5,13] it is the presence of elevated mitotic activity and/or tumor necrosis rather than growth pattern or cell type that drives outcome in PDTC. A comparison of these two sets of diagnostic criteria is provided in Table 1, Figs. 1 and 2.

Several studies have assessed the MSKCC criteria of PDTC. Gnemmi et al found that the Turin proposal and the MSKCC criteria to be almost equivalent in stratifying patients into an intermediate prognostic category with a concordance rate of 75%. In their series, the MSKCC criteria were reliable and simple allowing detection of tumors with high-grade features, notably some papillary carcinomas that displayed an intermediate prognosis. In their opinion, MSKCC criteria are not helpful in encapsulated carcinomas while the criterion of convoluted nuclei present in the Turin proposal has no prognostic value.[14] The latter term is defined as “small round hyperchromatic nuclei with convolution of the nuclear membranes”.[5] In view of its lack of prognostic value, many pathologists do not use convoluted nuclei to diagnose PDTC and thus deviate from the Turin proposal.[15] The study of Skansing et al analyzed 225 non-anaplastic follicular cell derived thyroid carcinoma with a median follow up of 28 years for the patients who were alive (range 20-43 years).[16] These authors found that tumor necrosis and mitosis (as used in the MSKCC definition) identify a group of patients with an intermediate prognosis. In their opinion, a simplification of the actually used criteria for poorly differentiated carcinomas (i.e. the Turin proposal) based on mitotic rate and tumor necrosis may be justified.[16]

Recently, it has been shown that the MSKCC criteria are superior to the Turin proposal in identifying differentiated thyroid carcinoma that result in disease specific death.[17] Indeed, PDTC diagnosed solely on the basis of high mitotic count and/or tumor necrosis using MSKCC criteria is the main cause of disease specific death in non-anaplastic thyroid carcinoma[17] while the Turin proposal PDTC are not. PDTC defined by MSKCC criteria are also the major contributor of radioactive iodine refractory disease.[18]

This could be due to the fact the MSKCC criteria capture more intermediate prognosis thyroid carcinomas than the Turin proposal. Indeed, several studies utilizing both MSKCC criteria and Turin proposal have shown that in general PDTC fulfilling the Turin proposal also meet the MSKCC criteria, whereas a subset (37-65%) of PDTC defined using MSKCC criteria shows non-solid growth pattern and/or nuclear features of papillary thyroid carcinoma, and therefore does not fulfill the Turin definition of PDTC.[17,19,20]

In 2017, the 4th edition of WHO classification adopted the Turin proposal as the definition of PDTC.[1] However, the authors of the WHO acknowledge that the Turin proposal does not capture all intermediate prognosis thyroid carcinomas. They state that grading (based on mitosis and tumor necrosis) can also capture intermediate prognosis thyroid carcinomas and reference the MSKCC criteria article published in 2006.[1] Whatever PDTC definition is used, it is paramount for pathologists to report on mitotic rate and the presence of tumor necrosis in thyroid carcinoma in view of their very important prognostic values. This has significant practical implications. We have encountered cases of PTC with high mitotic activity and/or tumor necrosis that have been reported as “classical PTC” or “follicular variant PTC” with the patients developing RAI refractory incurable disease. Such a terminology can misguide clinicians and patient into thinking they are dealing with one of the most indolent malignant tumors in the human body. One can just imagine the disappointment and shock of both patient and treating physician when the tumor recurs in a few years and is refractory to RAI with the need for targeted or experimental therapies. The importance of reporting mitotic activity and tumor necrosis in thyroid carcinomas is progressively gaining its deserved attention. While mitotic activity is a reporting optional item in the current College of American Pathologists (CAP) checklist,[21] both mitotic activity and tumor necrosis are mandatory reporting elements in the International Collaboration on Cancer Reporting (ICCR) dataset[22] on thyroid carcinoma.

In view of the above discussion, the pathologist is bound to perform an accurate mitotic count and especially identify tumor necrosis correctly. Mitotic count should be performed in the area of highest mitotic activity in 10 consecutive HPFs (approximately 2 mm^2).[22] Tumor necrosis is defined as coagulative or comedo-necrosis containing nuclear debris and should be differentiated from infarct-like necrosis related to previous fine needle aspiration (FNA) or ischemic changes within the tumor. Reactive changes seen in the latter two situations such as fibrovascular proliferation, hemorrhage and hemosiderin laden macrophages, should help exclude tumor necrosis.[22] Since high mitotic rate and tumor necrosis are such important prognostic factors in thyroid carcinomas, what are the clues on low power that should prompt the pathologist to carefully look for these parameters. In our experience, a solid growth and/or a mixture of phenotype (e,g. areas of tall cells admixed with others composed of Hurthle and follicular cells) are not unusually found in PDTC. Their presence should elicit a meticulous search for mitosis and tumor necrosis.

Differential diagnosis

Because of the presence of solid growth pattern in many cases, PDTC can be confused with medullary thyroid carcinomas. The presence of colloid in some areas of the tumor should easily exclude medullary carcinoma. In difficult cases, immunostaining can reliably resolve the issue since PDTC are positive for thyroglobulin and PAX8 and negative

Table 1
Diagnostic criteria of poorly differentiated thyroid carcinoma: a comparison of Turin proposal and MSKCC criteria

	Turin proposal[5]	MSKCC criteria[4]
Architectural pattern	solid/trabecular/insular growth required	Any
Nuclear features	Lack of nuclear features of papillary thyroid carcinoma required	Any
Necrosis, mitosis and convoluted nuclei	At least one of the following three features:Mitotic index ≥3/10 HPFs, Tumor necrosis, Convoluted nuclei,	At least one of the following two features:Mitotic index ≥5/10 HPFs, Tumor necrosis

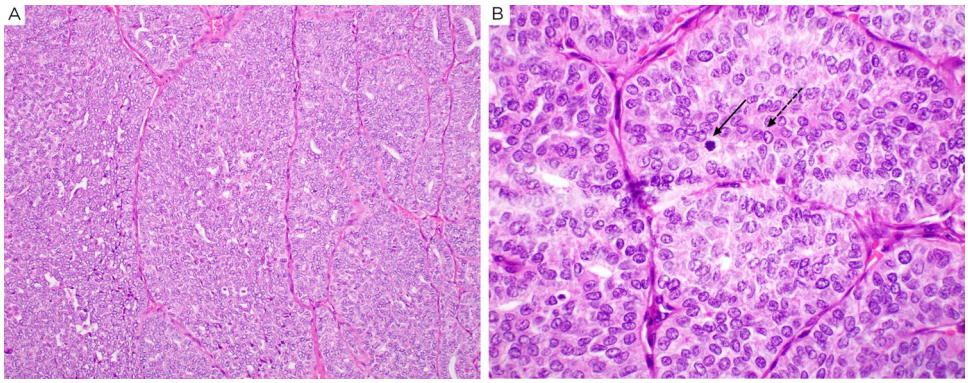

Fig. 1. Histologic features of poorly differentiated thyroid carcinoma (PDTC) meeting MSKCC criteria but not fulfilling the Turin proposal. The patient was a 72 year old man with a 5.5 cm thyroid mass and bone metastases. He died of disease 4 years after diagnosis. A: Medium power view showing a solid nested growth pattern. B: The tumor cells have the nuclear features of papillary thyroid carcinoma such as clearing, overlapping and grooves (dashed arrow). Mitotic rate was ≥ 5/10 high power fields, 400x (solid arrow indicating mitosis).

for calcitonin, chromogranin and synaptophysin. In contrast, medullary carcinomas are positive for calcitonin and other neuroendocrine markers, rarely express PAX8 (when positive in a patchy manner only) and are negative for thyroglobulin. Pathologists should be aware that PDTC can display a dot like pattern of thyroglobulin immunostaining that can be missed upon rapid examination at low power. The solid variant of PTC has to be distinguished from PDTC because of the much better prognosis of the former (1). Solid variant PTC lacks the high mitotic rate and tumor necrosis required for the diagnosis of PDTC. An important distinction is to separate PDTC from anaplastic thyroid carcinoma. Poorly differentiated thyroid carcinomas lack the prominent nuclear pleomorphism of anaplastic tumors. The PDTC almost always label with thyroglobulin and display diffuse TTF-1 positivity while anaplastic carcinomas extremely rarely stain for thyroglobulin. TTF-1 positivity can occur in a small subset of anaplastic carcinoma but it is usually focal.

Pathologic prognostic factors in PDTC

Using insular growth pattern or MSKCC parameters of high mitotic rate and/or tumor necrosis as the diagnostic criteria for PDTC, several groups have shown that the percentage of PDTC within a thyroid mass has no significant impact on overall survival[4,13,23] and that any PDTC component in a well-differentiated thyroid carcinoma (e.g. papillary thyroid carcinoma and follicular thyroid carcinoma) independently incurs a worse prognosis.[24] Similarly, using Turin proposal, recent studies have shown that as little as 10% of PDTC within a thyroid mass is associated with a poor prognosis which does not differ significantly from the prognosis of a tumor with >50% of PDTC. Additionally, Bichoo et al. have shown that pure PDTC and PDTC with well-differentiated thyroid carcinoma areas have similar 5-year and 10-year overall survival [25]. Taken together, the evidence suggests that it is the diagnosis of PDTC rather than the amount of PDTC within a thyroid mass that dictates outcome. Therefore, it is crucial for pathologists to recognize a poorly differentiated component in an otherwise well-differentiated thyroid carcinoma. On the other hand, the amount of PDTC does not appear to be prognostically relevant and is excluded as a reporting element from the CAP checklist[21] and the ICCR dataset[22] of thyroid carcinoma reporting.

Using MSKCC criteria, two studies have shown that encapsulated PDTC, especially those without capsular or vascular invasion following adequate sampling, is associated with a more favorable outcome compared with unencapsulated PDTC.[4,26] Recently, using the Turin proposal, Wong et al.[27] have shown that the extent of invasion has prognostic significance in PDTC. While encapsulated PDTC with capsular or focal vascular invasion has an excellent outcome with a 5-year disease free survival (DFS) of 100%, the 5-year DFS of PDTC with extensive angioinvasion or widely-invasive PDTC decreases to 73% and 17% respectively.[27]

Other pathologic factors that have been identified as independent prognostic factors in PDTC include tumor size,[4,14] extrathyroidal extension into perithyroidal soft tissue,[4,28] and pT4a disease.[6] Although very rare, thyroid carcinomas fulfilling the MSKCC and Turin proposal criteria of PDTC do occur in the pediatric population (≤ 21 year old).[29,30] While some have been reported to be aggressive and interestingly associated with *DICER1* somatic and germline mutations,[29] other series have not shown an independent prognostic value for PDTC in children.[30,31] Clearly additional studies are needed to assess the clinical significance of PDTC in children and young adults.

Based on the above data, pathologists should report on encapsulation, extent of vascular invasion, presence of extrathyroidal extension in addition to pathologic TNM staging in PDTC; whereas the percentage of PDTC within a thyroid tumor does not seem to be prognostically relevant.

Genomics of PDTC

In the past decade, several studies have reported on the genetic profile of over 200 cases of PDTC using targeted next generation sequencing techniques[19,20,32–35] and their results are summarized in

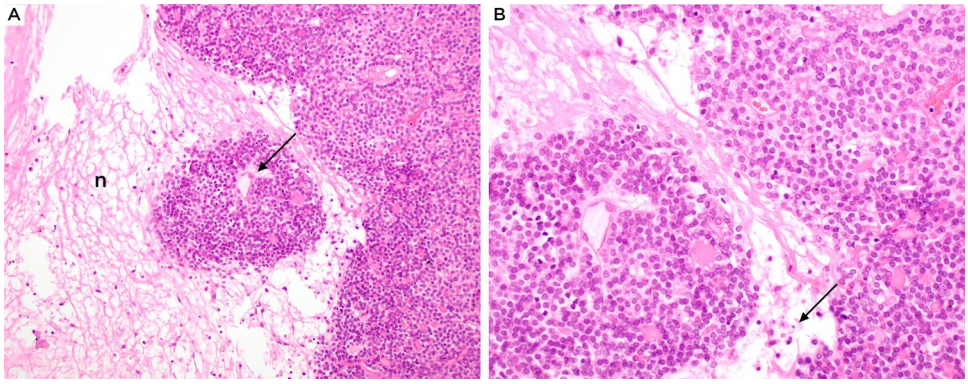

Fig. 2. Histologic features of poorly differentiated thyroid carcinoma (PDTC) fulfilling both MSKCC and Turin proposal criteria. The patient was a 56 year old male with a 4.5 cm thyroid mass and bone metastases. He died of disease 10 years after diagnosis. A: Medium power view showing a predominantly solid growing tumor. There is extensive tumor necrosis (n) associated with viable tumor surrounding a vessel (arrow) giving the so-called peritheliomatous appearance. B: The tumor nuclei are small and round lacking the full blown nuclear features of papillary carcinoma. Nuclear debris (arrow) are seen in areas of tumor necrosis.

Table 2
Molecular signature of poorly differentiated thyroid carcinoma: a summary of recent next generation sequencing studies.

	PDTC tested	PDTC criteria	BRAF	RAS	TERT	TP53	EIF1AX	PTEN	PIK3CA
Landa[19]	84	MSKCC	28 (33%)	24 (29%)	34 (40%)	7 (8%)	9 (11%)	3 (4%)	2 (2%)
Gerber[20]	23	MSKCC	4 (17%)	3 (13%)	NA	10 (43%)	NA	0 (0%)	0 (0%)
Duan[32]	41	Turin	9 (22%)	4 (10%)	NA	11 (27%)	9 (22%)	NA	8 (20%)
Yoo[33]	15	Turin	4 (27%)	4 (27%)	8 (53%)	3 (20%)	1 (7%)	1 (7%)	1 (7%)
Chen[34]	39	NA	6 (15%)	15 (38%)	NA	4 (10%)	NA	NA	1 (3%)
Nikiforov[35]	10	WHO 2004	1 (10%)	2 (20%)	NA	0 (0%)	NA	NA	1 (10%)
Total	212		52/212 (25%)	52/212 (25%)	42/99 (42%)	35/212 (17%)	19/140 (14%)	4/122 (3%)	13/212 (6%)

Table 2. Although these studies differ in term of the definition of PDTC, the genes included in next generation sequencing platforms, and the depth of coverage, several conclusions can be drawn from these studies.

First, similar to well-differentiated[36] and anaplastic thyroid carcinoma,[19,37,38] *BRAF* V600E and *RAS* mutations remain the mutually exclusive main driver mutations in PDTC, each being detected in 25% of PDTC.

Second, compared with well-differentiated thyroid carcinoma which carries a low number of mutation and anaplastic thyroid carcinoma which has a high mutation count,[19,37,38] the PDTC mutational load is intermediate between these two extremes. The median mutation burden detected in PTC, PDTC and ATC is 1, 2 and 6 per tumor respectively using MSK-IMPACT next generation sequencing panel.[19,36]

Third, PDTC harbors *TERT* promoter mutations in 42% of cases, *TP53* in 17%, *E1F1AX* in 14%, *PIK3CA* in 6%, *PTEN* mutations in 3%, alteration of histone methyltransferases in 7% and mismatch repair pathway in 2% of cases.[19,20,32–35] The mutation rate of these genes in PDTC is higher than what is seen in papillary thyroid carcinomas.[19,36] The persistence of driver mutations of *BRAF* and *RAS* and the increasing frequencies of additional alterations (e.g. *TERT* promoter mutation, *TP53* mutation, and alteration in PIK3CA-AKT-mTOR pathway) reveal a stepwise molecular pathogenesis of thyroid carcinoma from well-differentiated PTC, to PTDC, to anaplastic thyroid carcinoma. Alterations in RAS-RAF-MAPK pathway are early oncogenic driver mutations resulting in development of well-differentiated thyroid carcinoma (e.g. papillary carcinoma, follicular carcinoma and Hurthle cell carcinoma). Accumulation of additional mutations affecting *TERT, TP53*, PIK3CA-AKT-mTOR pathway, SWI/SNF nucleosome remodeling complex, mismatch repair genes and histone methyltransferase leads to tumor progression and dedifferentiation to PDTC and anaplastic carcinoma. Further supporting this stepwise progression model is the finding that *TERT* promoter mutations are subclonal in PTC while clonal in PDTC[19] suggesting that *TERT* promoter mutation may be a key transitional event.

Fourth, several genetic events are adverse prognostic molecular markers in PDTC, including high mutation count, *EIF1AX* mutation, *TERT* promoter mutations and chromosome 1q gain.[19] For example, high (above median) number of somatic mutation is associated with a larger tumor size of > 4 cm, a higher frequency of distant metastasis, and a shorter overall survival.[19] However, these markers found to be predictive on univariate analysis have not been subjected to multivariate analysis. We therefore do not know if they have independent prognostic value.

Lastly, Landa et al. have utilized both Turin proposal and MSKCC criteria in their study, allowing correlation between genotype and PDTC diagnostic criteria[19] (Table 3). PDTC fulfilling both Turin and MSKCC criteria has high frequency of *RAS* (overall 44%, with *NRAS* 33%, *HRAS* 8% and *KRAS* 4%) and low frequency of *BRAF* V600E mutations (6%), whereas PDTC meeting MSKCC criteria but not Turin proposal is enriched with *BRAF* V600E mutations (81%) and shows some *RAS* (overall 6%, all being *NRAS*). Additionally, *EIF1AX* mutation, an event that often co-exists with *RAS* mutation and is associated with tumor aggressiveness,[19,39] is often seen in Turin-PDTC. The rate of *TERT* promoter mutation is comparable between the two groups, being 44% for PDTC fulfilling both criteria and 39% for PDTC meeting only the MSKCC criteria. In PDTC defined using MSKCC criteria, the presence of *RAS* or *BRAF* mutations also designate metastasis tropism. PDTCs with *RAS* mutation travel to distant sites rather than harbor nodal metastasis akin to *RAS*-mutated follicular carcinomas. In contrast, *BRAF*-mutated PDTCs tend to metastasize to regional lymph nodes rather than systemically resembling PTC which frequently harbors *BRAF* mutation.[19] Taken together, it is clear that Turin proposal captures *RAS*-mutated PDTC akin to follicular carcinoma and Hurthle cell carcinoma which tend to spread distantly, whereas MSKCC criteria additionally select a subgroup of *BRAF* V600E-mutated PDTC akin to papillary carcinoma with preferential tropism to regional lymph nodes.

Treatment and follow up

Poorly differentiated thyroid carcinoma are considered aggressive forms of differentiated thyroid carcinomas and therefore categorized as at least intermediate risk by the latest American Thyroid Association (ATA) guidelines.[40] The initial management consists of total thyroidectomy followed by RAI therapy in the vast majority of cases.[40] Consideration should be given to use ^{18}FDG-PET as part of the initial staging since a significant proportion of PDTC may not concentrate RAI[13,40] and are ^{18}FDG-PET avid. When PDTC becomes RAI refractory, kinase inhibitor therapy should be considered in patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise amenable to local control using other approaches.[40]

Conclusions

The modern pathologic diagnostic criteria of PDTC are the Turin proposal and the MSKCC PDTC definition. PDTC diagnosed by the MSKCC criteria can be divided into two subgroups: The first set of tumors concord with the Turin criteria is enriched with *RAS* and *EIF1AX* mutations and had a metastatic tropism to distant sites; the second does not fullfill the Turin proposal, shows non-solid growth and/or nuclear features of papillary carcinoma, contains a high frequency of *BRAF* V600E mutation, and has a propensity to lymph node metastsis. Although both defintions define a group of tumor whose prognosis is in between well differentiated thyroid and anaplastic carcinomas, the MSKCC criteria (mitotic rate/ tumor necrosis) capture additional intermediate prognosis carcinomas of follicular cell origin. It is therefore crucial to report on mitotic activity and tumor necrosis in any thyroid carcinomas as mandated by the ICCR[22] reporting guide on thyroid carcinomas. It is also important for pathologist to recognize a small amount of poorly differentiated component in a thyroid mass and to comment on tumor size, encapsulation, extent of vascular invasion and extrathyroidal extension in PDTC since these parametres help substratify patients in regard to their outcome. Some molecular markers such as *TERT* promoter mutations, *EIF1AX* and mutational load are promising prognostic factors but their additive independent predictive value has not yet been proven in PDTC. Future studies correlating molecular markers, morphologic features and outcome are needed to better stratify and treat PDTC patients..

Table 3
Molecular profile of PDTC according to PDTC definition.[19]

PDTC criteria	Number tested	BRAF V600E	RAS	TERT	TP53	EIF1AX	PTEN	PIK3CA
Both Turin and MSKCC criteria	52	6%	44%	44%	15%	15%	6%	2%
MSKCC criteria only	31	81%	6%	39%	3%	3%	0%	3%

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