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## **FNA diagnosis of poorly differentiated thyroid carcinoma. A review of the recent literature.**

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## **Abstract**

Poorly differentiated thyroid carcinoma (PDTC) is a follicular cell-derived tumor which was recognized as a distinct entity by the WHO in 2004. The natural history and pathological features of PDTC are reported to be intermediate between those of well-differentiated and undifferentiated (anaplastic) thyroid carcinomas.

Preoperative identification of PDTC could facilitate better initial patient management in many cases, namely more extensive surgery, without any delay. However, according to some experts, a diagnosis of PDTC can only be rendered on histologic specimens based on criteria recommended in the "Turin proposal". Actually PDTC recognition on routine thyroid cytology presents a notable challenge. Although high-grade features (namely necrosis and mitoses) can be recognized in fine-needle aspiration material, other cytomorphological features have limited value for the preoperative diagnosis of PDTC and cytomorphologic features for a definitive diagnosis of PDTC have not yet been clearly defined. Here, we review the current status and future prospects for cytologic recognition of PDTC; we emphasize the features that should raise suspicion of this rare condition in fine-needle aspiration cytology and provide an update on molecular features and management of PDTC.

**Keywords:** thyroid; poorly differentiated thyroid carcinoma; fine-needle aspiration; cytological features; review.

## Introduction

Poorly differentiated thyroid carcinoma (PDTC) is a neoplasm with morphological features and biological behavior intermediate between well-differentiated thyroid carcinoma (WDTC) and undifferentiated (anaplastic) thyroid carcinoma (ATC).<sup>1</sup> According to current models, PDTC may either develop by dedifferentiation of WDTC, or *de novo* from benign thyroid follicular cells; it can also represent an intermediate step in the progression to ATC.<sup>2-4</sup> Currently, the histologic diagnosis of PDTC is based on the “Turin criteria”, which include the presence of solid, trabecular, or insular (STI) patterns and at least one of convoluted nuclei, mitoses ( $\geq 3$  per 10 HPF), or necrosis, in the absence of nuclear features of papillary thyroid carcinoma (PTC).<sup>5</sup>

The lack of consensus on the definition of PDTC before the definition of the “Turin criteria” in 2006 resulted in variable data regarding its epidemiology, as the term PDTC encompassed a heterogeneous group of tumors.<sup>6</sup> More recent studies reported its prevalence as less than 1% of all thyroid malignancies in Japan, 1.8% in the United States, and up to 6.7% in northern Italy.<sup>7, 8</sup> The mean age at presentation is between 55 and 63 years, with the youngest patient being 9 years old. A slight female preponderance has been described.<sup>4, 6, 8-10</sup>

The management of patients with PDTC overlaps with that of patients with WDTC, but the clinical response is less favorable due to the more aggressive nature of the disease; thus the overall 10-year survival rate is approximately only 50%.<sup>11, 12</sup> The presence of even a minor component of PDTC in an otherwise WDTC can potentially impact patient prognosis.<sup>13</sup> Molecular studies have demonstrated that PDTCs frequently carry *RAS* or *BRAF* mutations, also found in WDTC, as well as additional alterations such as *TERT* promoter and *TP53* mutations;

the latter two are thought to be involved in the progression of WDTCs towards the less differentiated PDTC and ATC.<sup>14</sup>

The recognition of PDTC as a distinct entity and the introduction of better defined histomorphologic criteria facilitated a uniform diagnostic approach for pathologists; however, the cytological diagnosis of PDTC remains problematic.<sup>5</sup> In various studies, approximately one fourth of all PDTC aspirations were reported as malignant but classified as WDTC, and one third were reported as follicular neoplasm/suspicious for a follicular neoplasm (FN/SFN); such may lead to a less extensive initial procedure (notably lobectomy instead of total thyroidectomy), necessitating additional surgery (i.e., completion thyroidectomy with or without lymph node dissection).<sup>15-18</sup>

The aim of this review is to assess the current literature to investigate the present and future roles of cytology and molecular analysis in the diagnosis of this uncommon but aggressive thyroid carcinoma.

### **Historical perspective**

In 1983, Sakamoto et al. proposed the term “poorly differentiated thyroid carcinoma” to designate a variant of papillary and follicular thyroid carcinomas that was less differentiated and had an aggressive behavior although it was lacking features of ATC. The histologic diagnosis relied on the presence of a solid, trabecular, or scirrhous growth pattern.<sup>9</sup> Shortly thereafter, Carcangiu et al. reported on the same entity, restricting the use of the term “PDTC” to “insular” patterned tumors in the presence of high-grade features, such as necrosis with the formation of “peritheliomatous” structures, capsular and vascular invasion, and mitotic activity.<sup>4</sup> Although

the 2004 WHO Classification of Tumors of Endocrine Organs classified PDTC as a distinct tumor type,<sup>1</sup> its diagnostic criteria were not well defined, and their evaluation in routine clinical practice was prone to subjectivity.

In 2006, a consensus conference for PDTC was held in Turin, Italy.<sup>5</sup> Pathologists from Italy, Japan, and the United States reviewed a cohort of 83 cases which had been selected according to the presence of solid, trabecular, insular (STI) growth patterns. The result was the proposition of a set of histologic criteria for the diagnosis of PTDC, which are in current use. Thus, a diagnosis of PDTC requires (i) the presence of an STI growth pattern; (ii) the absence of PTC nuclear features; and (iii) at least one of the following features: convoluted nuclei,  $\geq 3$  mitoses per 10 HPF, and/or necrosis.<sup>5</sup>

An alternative classification system to the Turin criteria has been proposed by Hiltzik et al. in 2006 and is based on the experience at the Memorial Sloan Kettering Cancer Center (MSKCC); they reported that PDTC defined on the basis of necrosis and mitoses ( $\geq 5$  per 10 HPF) constitutes a group of tumors that is more homogeneous than the group of PDTC defined by growth pattern and is more aggressive.<sup>19</sup> They also found that these patients with PDTC defined by their criteria have an outcome intermediate between that of well-differentiated PTC and FTC, and that of highly aggressive ATC, with an overall survival (OS) at 5 years of 60% compared with 98%, and 0%, for WDTC and ATC, respectively. The authors also compared the outcome of PDTC defined on the basis of necrosis and/or mitoses to that of PDTC classified according to the Turin criteria: the latter also showed an intermediate prognosis between WDTC and ATC, but when the two OS curves were compared, the OS rate of PDTC according to MSKCC criteria (60%

at 5 years) appeared to be worse than the OS rate of PDTC according to Turin criteria (83% at 5 years).<sup>5, 19</sup>

In the new WHO Classification of Tumors of Endocrine Organs, published in 2017, PDTC is still be considered as a distinct neoplastic entity.<sup>20</sup>

### **Cytological features of PDTC**

According to established practices, a definitive diagnosis of PDTC is primarily limited to histopathology specimens. Despite attempts by some groups, there are no universally accepted cytological criteria for the diagnosis of PDTC that can be applied to thyroid fine-needle aspiration (FNA) material. This is unfortunate because the preoperative identification of PDTC could lead in many cases to a more aggressive initial management of these patients:<sup>15-18</sup> in fact, in the frame of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), PDTC is often classified as a follicular lesion (diagnostic category IV, FN/SFN), which entails a surgical lobectomy.<sup>21</sup>

In 2009, Bongiovanni et al. studied a series of 40 histologically-proven PDTCs and compared their cytological features with a control group of 40 WDTCs. The combined presence on FNA of STI cytoarchitectural pattern, single cells, high nuclear/cytoplasmic (N/C) ratio, and severe crowding was highly predictive of PDTC.<sup>15</sup> In 2012, Barwad et al., conducted a study on insular-patterned PDTC lesions, and the most frequent findings were hypercellularity, monomorphic small cells arranged in solid clusters or single cells, scant to moderate cytoplasm, and the presence of mitotic activity.<sup>16</sup> Similarly, in 2015 Kane et al. analyzed a series of 44 PDTC cases and compared a subset of selected cytologic features with WDTC. According to their

findings, hypercellularity, insular pattern, small cell size, high N/C ratio, granular chromatin, severe nuclear overlapping, mild nuclear pleomorphism, abrupt nucleomegaly, apoptosis, necrosis, and mitosis were observed more commonly in PDTC. All of these features showed statistical significance in univariate analysis, whereas only small cell size remained significant using logistic regression analysis.<sup>17</sup> In 2016, Purkait et al. reported that the presence of cell nests and three-dimensional clusters, endothelial wrapping of cell groups, singly dispersed cells, and peripheral alignment of nuclei within nests were the most important cytological features for identifying PDTC in their series of 7 FNA cases.<sup>18</sup> Interestingly, this was the only series that also reported the presence of nuclear features of PTC. The latter may be the reason why some cases were classified as atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) and suspicious for malignancy (SM).

When these cytologic studies are considered together, insular or solid patterns and high cellularity emerge as the most common cytologic features as emphasized by all four studies.<sup>15-18</sup> Single cell pattern, high N/C ratio, granular chromatin and mitotic activity were described in different combinations by three of the four series. Endothelial wrapping of cell clusters, scant cytoplasm, nuclear pleomorphism, nuclear crowding/overlapping and apoptosis were less frequently reported (Table 1) (Figure 1).<sup>15-18</sup> A few recent case reports have contributed to the literature on the topic. One of them described cytological findings highly suggestive of PDTC, such as hypercellular smears composed of monomorphic small follicular cells with scant cytoplasm, arranged in cohesive clusters or singly dispersed;<sup>22</sup> others, instead, did not identify any features as characteristic of PDTC.<sup>23-25</sup>



Of the total 101 cases in the literature, only 27 (27%) were preoperatively recognized as PDTC.<sup>15-18</sup> The remaining 74 cases comprised the following diagnoses: poorly differentiated carcinoma, not otherwise specified (NOS) (n=7, 7%); carcinoma, NOS (n=4, 4%); papillary thyroid carcinoma (PTC) (n=10, 10%); medullary thyroid carcinoma (MTC) (n=3, 3%); follicular variant (FV)-PTC (n=13, 13%); suspicious for PTC (n=1, 1%); follicular neoplasm or suspicious for follicular neoplasm (FN/SFN) (n=34, 33%); and lastly, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) (n=2, 2%) (Figure 2).<sup>26</sup>

One third of the reported PDTC cases were initially diagnosed as FN/SFN, which is not surprising considering that PDTC lacks, by definition, the characteristic nuclear features of PTC and can have overlapping features with follicular adenoma/carcinoma with respect to hypercellularity, cellular monotony, and cytoarchitecture.<sup>5, 18</sup> However, because a report of FN/SFN commonly leads to hemithyroidectomy or molecular testing as opposed to direct total thyroidectomy with possible neck lymph node dissection, this misclassification can have important implications for clinical management (Figure 3).<sup>11</sup>

The specific diagnosis of PDTC or PDC, NOS was made in only 34% of cases. Overall, the lack of accepted criteria for diagnosing PDTC on FNA material reflects the difficulty in accurately transferring the histologic diagnostic criteria of PDTC onto cytologic criteria. The reason is that the histologic criteria of PDTC overlap in cytology with features of WDTC. Convoluted “raisinoid” nuclei can be found in a variety of conditions, mainly PTC, and are not specific for PDTC. In addition, the frequent coexistence of a WDTC component can easily confound the diagnosis of PDTC on FNA.<sup>26</sup> Moreover, an oncocytic variant of PDTC has been described at the histological level, raising the additional challenge of distinguishing between PDTC and FN/SFN,

oncocytic type (Figure 4).<sup>27, 28</sup> At best, the diagnosis of PDTC can be suggested in a subset of FNA cases, but consistent accurate diagnosis based upon cytomorphology has yet to be achieved.

Indeed, while different series have shown a variable distribution of cases according to TBSRTC, the overall percentage of PDTC cases, which are accurately recognized on FNA samples, has not improved over time (Figure 5).

### **Differential diagnosis and immunohistochemistry**

The differential diagnosis of PDTC includes WDTC (PTC and FC), ATC, as well as MTC and secondary thyroid neoplasms. In particular, a subset of PDTC can exhibit a predominantly single-cell pattern suggestive of MTC. Kane et al. described 3 such PDTC cases.<sup>17</sup> For the differential diagnosis of PDTC with MTC or secondary neoplasms, immunostaining on cytology slides or on cell block material can effectively discriminate between these possibilities: PDTC is immunoreactive for thyroglobulin and, unlike MTC, it is negative for calcitonin and carcinoembryonic antigen (CEA).<sup>26, 29</sup> However, immunohistochemistry is useless in differential diagnosis with other thyroid cancers of follicular derivation: PAX-8 and TTF-1 are used to prove thyroid origin in differential diagnosis with secondary thyroid neoplasms, but they are not specific for PDTC.

### **Molecular features**

Less differentiated thyroid carcinomas have been shown to harbor a higher mutation burden.<sup>14, 30-32</sup> In cases of PDTC, the median number of mutations was found to be two.<sup>30</sup> Recent

molecular studies using next-generation sequencing (NGS) on aggressive thyroid carcinomas analyzed a total number of 87 PDTCs, showing that mutually exclusive *BRAFV600E* and *RAS* mutations represent the main drivers in PDTC, being present in 33% and 45% of cases, respectively.<sup>14, 30, 31</sup> Landa et al. observed an interesting relationship between PDTC *BRAF/RAS* mutation status and histological features: among PDTC diagnosed according to the Turin criteria, 92% harbored *RAS* mutations, whereas among PDTC diagnosed as proposed by Hiltzik et al. (necrosis and/or  $\geq 5$  mitoses per 10 HPF), *BRAFV600E* mutations were found in 81%.<sup>30</sup> Similar to WDTC, the presence of *BRAFV600E* or *RAS* mutations correlated with the metastatic pattern, with *BRAF*-mutant PDTC preferentially metastasizing to regional lymph nodes and *RAS*-mutant PDTC having a higher rate of systemic metastases.<sup>30</sup>

In addition to mutations shared with PTC and FTC, other genetic alterations exist in PDTC that are frequently detected in less differentiated tumors. Notably, mutations in the promoter of telomerase reverse transcriptase (*TERT*) have been found in approximately 40% of PDTC, a prevalence intermediate between the more differentiated PTC (10%) and the undifferentiated ATC (73%). Mutations in *TERT* have been reported to correlate with aggressive clinical behavior, regional and distant metastases and disease-specific mortality.<sup>14, 32</sup> *TERT* mutations occur as a subclonal event in PTC, while they seem to be clonal in PDTC and ATC; therefore, they are considered a potential step in the development of aggressive thyroid cancer.<sup>14, 30</sup>

*TP53* mutations, which are extremely rare in PTC and FTC, are reported in 10-26% of PDTC; they seem to play an important role in the dedifferentiation of WDTCs, and they are regarded as late events in tumor evolution.<sup>30, 33</sup> Accordingly, in tumors presenting both papillary

and undifferentiated components, *TP53* mutations have been found only in the undifferentiated component.<sup>34</sup> Mutations in the eukaryotic translation initiation factor *EIF1AX* are present in 11% of PDTC: these mutations are reported in only 1% of PTC, where they occur in a mutually exclusive manner with *BRAFV600E* and *RAS* mutations;<sup>30</sup> in addition, using NGS, Landa et al. identified a number of novel genes that can be mutated in PDTC, at frequencies of 1-4%.<sup>30</sup> When microRNA (miRNA) expression profiles were investigated, miR-150, miR-183-3p, miR-221 and miR-222 were the most dysregulated miRNAs, with a promising role for distinction between WDTC and PDTCs.<sup>35</sup>

The available data on molecular features of PDTC are based on analyses of histologically-confirmed tumors. For the time being, the utility of molecular testing to identify PDTC cases in cytologic specimens has not been well documented. Given that a high percentage of PDTC are classified cytologically within the indeterminate FN/SFN Bethesda category (Figure 2), molecular testing could be useful, in a subset of cases, for their diagnosis. Or at the least, results of molecular testing could help triage cases for more aggressive initial management. Indeed, the 2015 American Thyroid Association guidelines stipulate that molecular screening may be used for indeterminate thyroid aspirations, though they do not make specific reference to the molecular diagnosis of PDTC (recommendation 15).<sup>36</sup> In-house or commercially available mutation panel tests could be useful to identify mutations (notably *TERT*, *TP53* and *EIF1AX*), which are more common in advanced, aggressive and/or dedifferentiated carcinomas, including PDTC.<sup>14, 30</sup>

## Prognosis and management

PDTC is associated with an intermediate prognosis between WDTC and ATC. A high rate of local recurrence, frequent distant metastases, and extrathyroidal invasion characterize the clinical course of PDTC; regional lymph node metastases are present at the time of diagnosis in more than 50% of patients. The latter are subject to detection by FNA. The European Society of Medical Oncology (ESMO) clinical guidelines recommend central compartment and/or lateral neck lymph node dissection be considered in addition to total thyroidectomy in the initial surgical management of PDTC. Suppression of TSH with levothyroxine should be started immediately after surgery.<sup>11</sup> Being less differentiated compared to WDTC, PDTC cells are even less able to take up and organify iodine and to secrete thyroglobulin under the stimulus of thyroid-stimulating hormone (TSH). Nevertheless, the initial management is similar to that of WDTC, and it normally includes radioactive iodine (<sup>131</sup>I) therapy after surgery, especially since in many cases there is an admixture of PDTC and WDTC components in the same tumor.<sup>37</sup> However, the treating clinician must be aware of two important caveats: (i) The tumor may be or may become radioiodine-refractory; thus, it is prudent to perform imaging by <sup>18</sup>F-DG-PET, whether or not there is radioiodine uptake of the post-treatment scan. (ii) The level of thyroglobulin (if it is even detectable) may underestimate the volume of disease present, complicating the follow-up; thus, periodic imaging by <sup>18</sup>F-DG-PET or another cross-sectional modality should be considered during follow-up. Overall, the management of PDTC should follow the principles of radioiodine-refractory WDTC. External beam radiation therapy (EBRT) may be used for unresectable disease or persistent locoregional disease after surgery; chemotherapy achieves only transient and incomplete responses.<sup>11, 37</sup> Recently, systemic

therapies using tyrosine kinase inhibitors (sorafenib and lenvatinib) have been approved for radioiodine-refractory WDTC;<sup>38, 39</sup> these drugs should then be considered for use in progressive cases of PDTC that are radioiodine-refractory.

## **Conclusions**

Despite increased awareness of PDTC after its recognition as a distinct entity by the WHO in 2004 and the development of defined histological criteria in 2006 (“Turin Criteria”) and in 2006 (“MSKCC definition”), the cytologic diagnosis of PDTC has remained a challenge for cytopathologists. Insular or solid architecture, hypercellularity, high N/C ratio, and mitotic activity are features that may suggest a diagnosis of PDTC in a thyroid FNA. Still, accurate FNA diagnosis of PDTC remains an elusive goal. The cytologic accuracy for PDTC may be improved via molecular testing for cases in the indeterminate categories of TBSRTC to identify PDTC-related genetic alterations frequently associated with an aggressive biologic behavior.

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## Figure legends

**Figure 1.** Cytomorphological features of poorly differentiated thyroid carcinoma. (A) Smears are usually hypercellular, often with a background of cellular or necrotic debris and devoid of colloid. A minor follicular architecture is frequently present (smear, May-Grunwald Giemsa [MGG] stain, x100). (B) In clear-cut cases an insular arrangement of follicular cells can be seen (smear, Papanicolaou stain, x400). (C) A predominant single-cell pattern with high nuclear/cytoplasmic ratio can also be observed and may be the only architectural pattern present (smear, Papanicolaou stain, x400). (D) In the same case, by MGG staining, a mitotic figure was also present (arrow). The differential diagnosis with medullary thyroid carcinoma and anaplastic carcinoma can be addressed with the help of immunocytochemistry and clinicopathological correlation (smear, MGG stain, x400). (E) A cluster of follicular cells with microfollicular and vague insular architecture. Note the granular chromatin and conspicuous nucleoli. Not surprisingly this case was diagnosed as follicular neoplasm/suspicious for a follicular neoplasm (smear, Papanicolaou stain, x400). (F) Another example of a loosely cohesive cluster of follicular cells with delicate cytoplasm and diagnosed as follicular neoplasm/suspicious for a follicular neoplasm (smear, Papanicolaou stain, x400).

**Figure 2.** Preoperative fine-needle aspiration diagnosis of poorly differentiated thyroid carcinoma as reported in literature series and subdivided according to The Bethesda System for Reporting Thyroid Cytopathology.

**Figure 3.** A 72 year old man was diagnosed with a FN/SFN on cytology. (A) The smear shows hypercellularity and some microfollicular structures (arrows) next to oval (“insular”) aggregates of thyrocytes (smear, Papanicolaou stain, x400). (B) At higher power, many round to oval aggregates were observed and could have raised the suspicion of a PDTC component as well (smear, MGG stain, x40).

**Figure 4.** Main cytomorphological features of oncocytic (Hürthle cell) poorly differentiated thyroid carcinoma in a 68 year old female. Clinically, the nodule appeared over several months and was limited to the thyroid gland. (A) The smear shows isolated-cell architecture with follicular cells having abundant, granular and eosinophilic cytoplasm and low to intermediate N/C ratio. Some nuclei were apoptotic and the background contained necrosis (smear, Papanicolaou stain, x100). (B) The same features were present in the cell block, with isolated oncocytic cells and necrotic debris. The cytological diagnosis was suspicious for malignancy (cell block, Haematoxylin and eosin stain, x100). (C) Grossly, the mass was 6.5 x 5 x 5 cm in dimension, well circumscribed, limited to the thyroid gland, and showed a mahogany brown appearance. (D) On histology, insular structures with punctate foci of necrosis were easily identified. Cells had a oncocytic cytoplasm and a dyshesive pattern. Extensive capsular and vascular invasion were identified (Haematoxylin and eosin stain, x100).

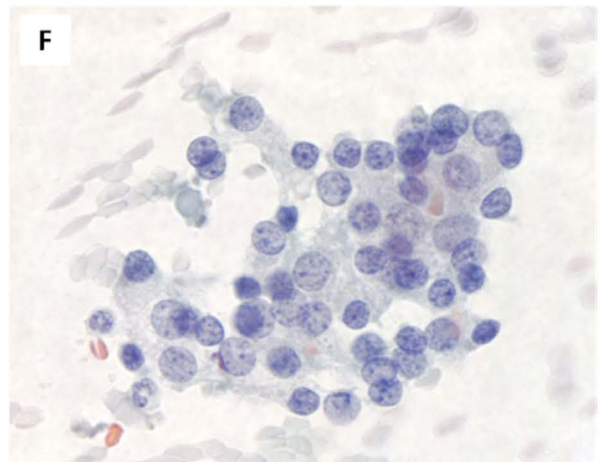
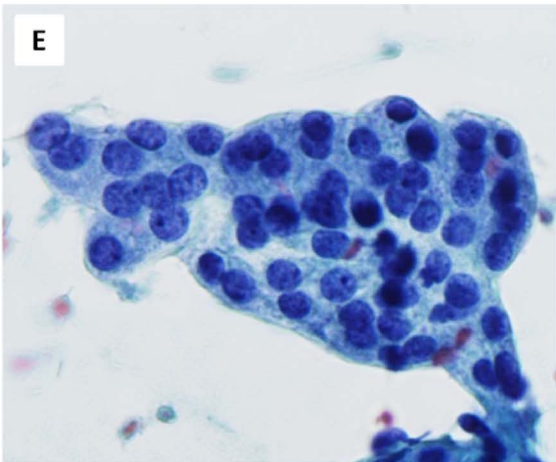
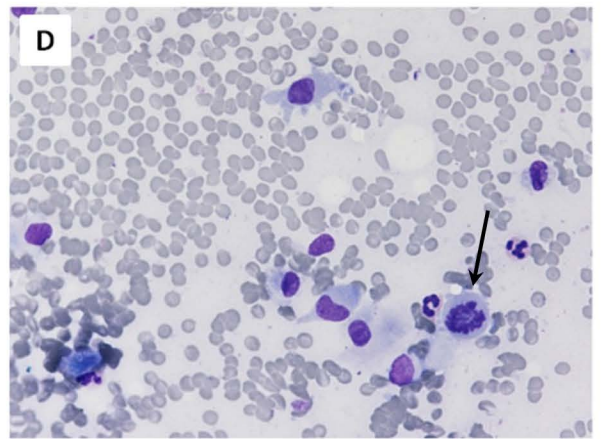
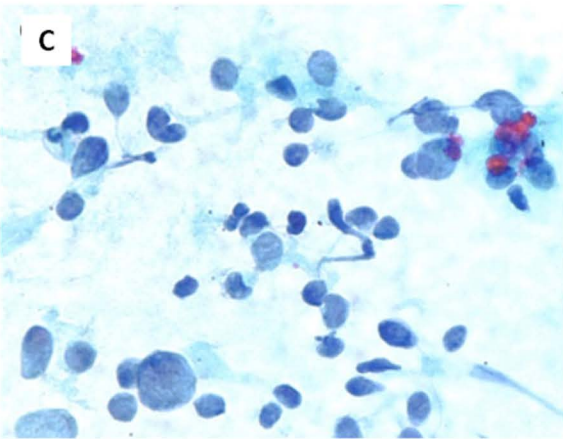
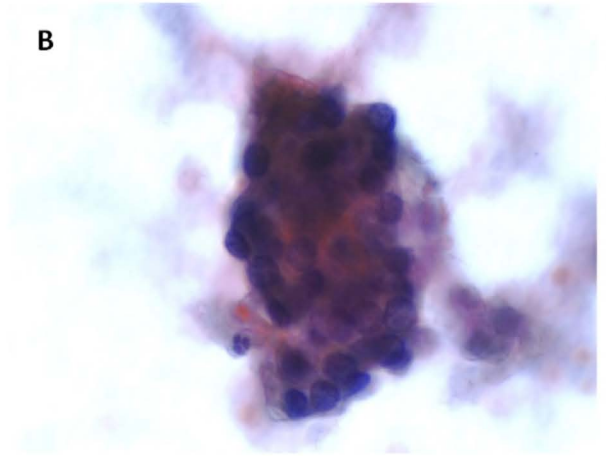
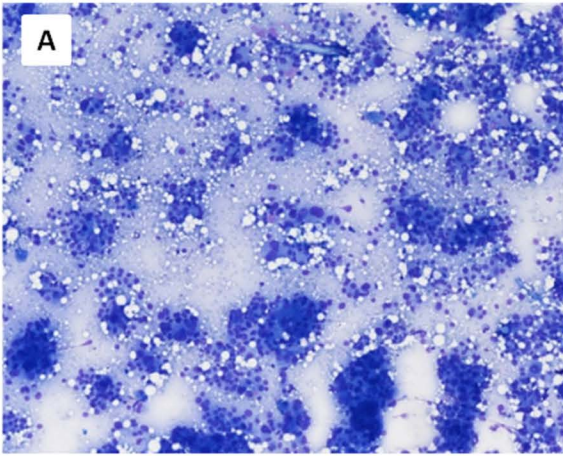
**Figure 5.** Preoperative fine-needle aspiration diagnoses of reported series of poorly differentiated thyroid carcinoma grouped into diagnostic categories according to the Bethesda System for Reporting Thyroid Cytopathology.

**Table 1.** Cytological features associated with poorly differentiated thyroid carcinoma.

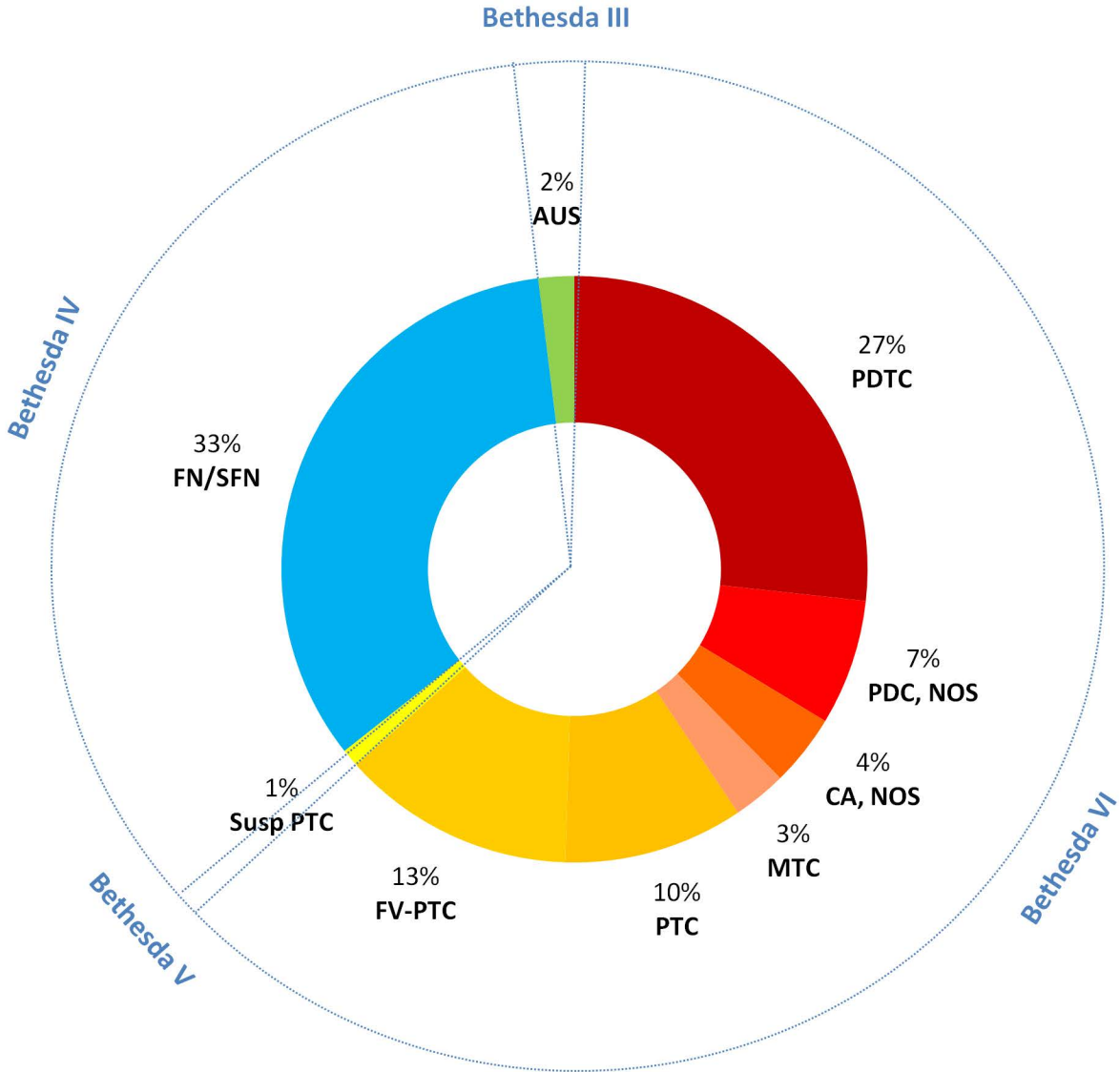
|   | <i>Frequency</i> | <i>p value</i> | <i>Reference</i>               |
|---|------------------|----------------|--------------------------------|
| <b>General features</b>                                     |                  |                |                                |
| <b>Pattern</b>  |                  |                |                                |
| <i>Insular, solid, trabecular</i>                           | 92.5% (37/40)    | <0.001         | Bongiovanni <i>et al.</i> (15) |
| <i>Insular</i>  | 79.5% (35/44)    | <0.001         | Kane <i>et al.</i> (17)        |
| <i>Solid</i>  | 100% (7/7)       | N/A            | Purkait <i>et al.</i> (18)     |
|   | 100% (10/10)     | N/A            | Barwad <i>et al.</i> (16)      |
| <i>Single cells</i>   | 75% (30/40)      | <0.0001        | Bongiovanni <i>et al.</i> (15) |
|   | 100% (10/10)     | N/A            | Barwad <i>et al.</i> (16)      |
| <i>Singly dispersed, loosely cohesive cells</i>             | 100% (7/7)       | N/A            | Purkait <i>et al.</i> (18)     |
| <i>Three-dimensional groups</i>                             | 100% (7/7)       | N/A            | Purkait <i>et al.</i> (18)     |
| <b>High cellularity</b>                                     | 60% (24/40)      | 0.007          | Bongiovanni <i>et al.</i> (15) |
|   | 71.4% (5/7)      | N/A            | Purkait <i>et al.</i> (18)     |
|   | 100% (10/10)     | N/A            | Barwad <i>et al.</i> (16)      |
|   | 84.1% (37/44)    | 0.001          | Kane <i>et al.</i> (17)        |
| <b>Necrosis</b>   | 15% (6/40)       | 0.025          | Bongiovanni <i>et al.</i> (15) |
|   | 34.1% (15/44)    | 0.001          | Kane <i>et al.</i> (17)        |
| <b>Background debris</b>                                    | 15% (6/40)       | <0.025         | Bongiovanni <i>et al.</i> (15) |
| <b>Transgressing endothelial cells within cell clusters</b> | 85.7% (6/7)      | N/A            | Purkait <i>et al.</i> (18)     |
| <b>Endothelial wrapping</b>                                 | 20% (8/40)       | 0.0053         | Bongiovanni <i>et al.</i> (15) |
|   | 71.4% (5/7)      | N/A            | Purkait <i>et al.</i> (18)     |
| <b>Peripheral orientation of nuclei in cell clusters</b>    | 71.4% (5/7)      | N/A            | Purkait <i>et al.</i> (18)     |
| <b>Cellular features</b>                                    |                  |                |                                |
| <b>High N/C ratio</b>                                       | 67.5% (27/40)    | <0.0001        | Bongiovanni <i>et al.</i> (15) |
|   | 100% (10/10)     | N/A            | Barwad <i>et al.</i> (16)      |
|   | 93.2% (41/44)    | <0.001         | Kane <i>et al.</i> (17)        |
| <b>Small cell size</b>                                      | 93.2% (41/44)    | <0.001         | Kane <i>et al.</i> (17)        |
| <b>Plasmacytoid appearance</b>                              | 25% (10/40)      | 0.0007         | Bongiovanni <i>et al.</i> (15) |
| <b>Cytoplasm</b>  |                  |                |                                |
| <i>Scant</i>  | 87.5% (35/40)    | 0.03           | Bongiovanni <i>et al.</i> (15) |
|   | 30% (3/10)       | N/A            | Barwad <i>et al.</i> (16)      |
| <i>Moderate</i>   | 60% (6/10)       | N/A            | Barwad <i>et al.</i> (16)      |
| <b>Nuclear features</b>                                     |                  |                |                                |
| <i>Atypia</i>   | 55% (22/40)      | <0.0001        | Bongiovanni <i>et al.</i> (15) |
| <i>Pleomorphism</i>   | 40% (16/40)      | 0.0052         | Bongiovanni <i>et al.</i> (15) |
|   | 86.4 (38/44)     | <0.0001        | Kane <i>et al.</i> (17)        |
| <i>Anisokaryosis</i>  | 50% (20/40)      | <0.0001        | Bongiovanni <i>et al.</i> (15) |
| <i>Crowding/nuclear overlapping</i>                         | 85.7% (6/7)      | N/A            | Purkait <i>et al.</i> (18)     |
|   | 70% (28/40)      | <0.0001        | Bongiovanni <i>et al.</i> (15) |
|   | 88.6% (39/44)    | <0.001         | Kane <i>et al.</i> (17)        |
| <i>Granular/coarse chromatin</i>                            | 40% (16/40)      | 0.026          | Bongiovanni <i>et al.</i> (15) |
|   | 80% (8/10)       | N/A            | Barwad <i>et al.</i> (16)      |
|   | 95.5% (42/44)    | <0.001         | Kane <i>et al.</i> (17)        |
| <b>Naked nuclei</b>   | 77.5% (31/40)    | 0.01           | Bongiovanni <i>et al.</i> (15) |
| <b>Mitotic activity</b>                                     | 42.5% (17/40)    | 0.0001         | Bongiovanni <i>et al.</i> (15) |
|   | 9/10 (90%)       | N/A            | Barwad <i>et al.</i> (16)      |
|   | 25% (11/44)      | <0.001         | Kane <i>et al.</i> (17)        |
| <b>Apoptosis</b>  | 45% (18/40)      | <0.0001        | Bongiovanni <i>et al.</i> (15) |
|   | 45% (20/44)      | <0.001         | Kane <i>et al.</i> (17)        |

N/C, Nuclear/cytoplasmic; N/A, Not available

Figure 1



**Figure 2**



Abbreviations: AUS, atypia of undetermined significance; PDC, poorly differentiated thyroid carcinoma; PDC, poorly differentiated carcinoma; NOS, not otherwise specified; CA, carcinoma; MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma; FV-PTC, follicular variant of papillary thyroid carcinoma; Susp PTC, suspicious for papillary thyroid carcinoma; FN/SFN follicular neoplasm/suspicious for follicular neoplasm; AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; M, malignant; SM, suspicious for malignancy.

Figure 3

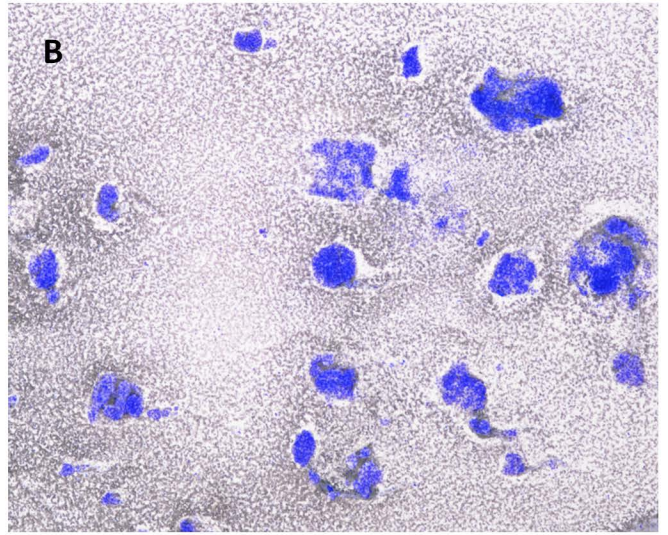
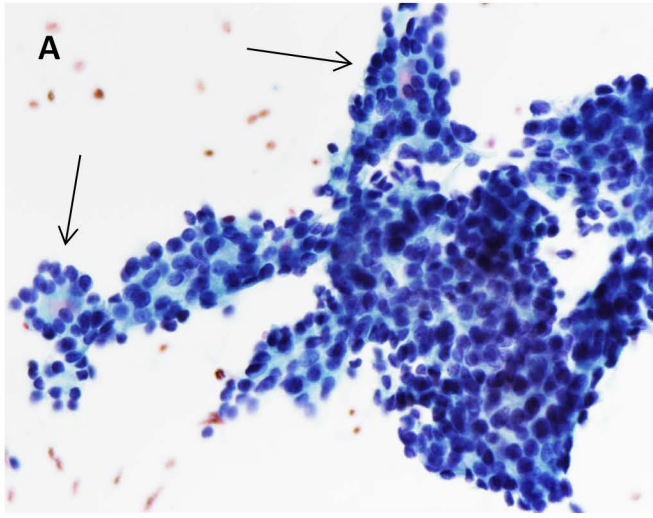


Figure 4

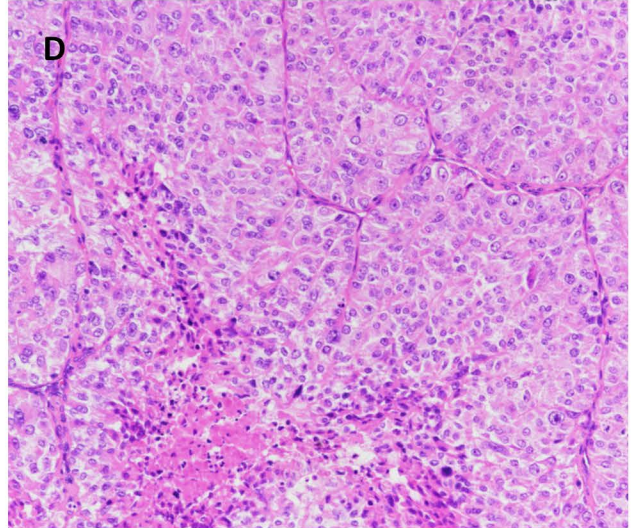
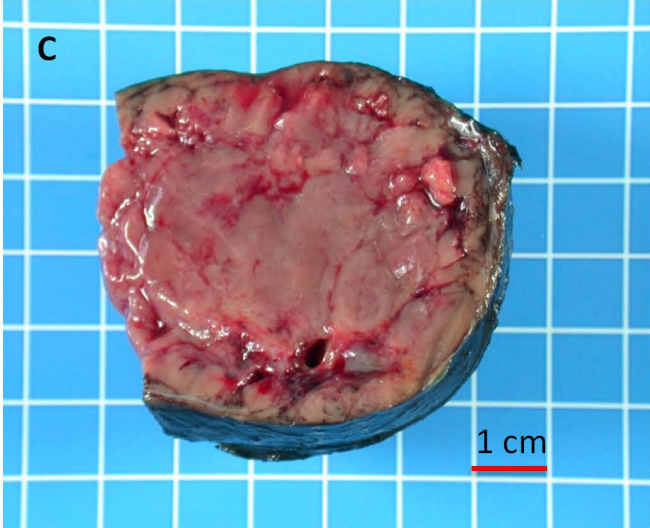
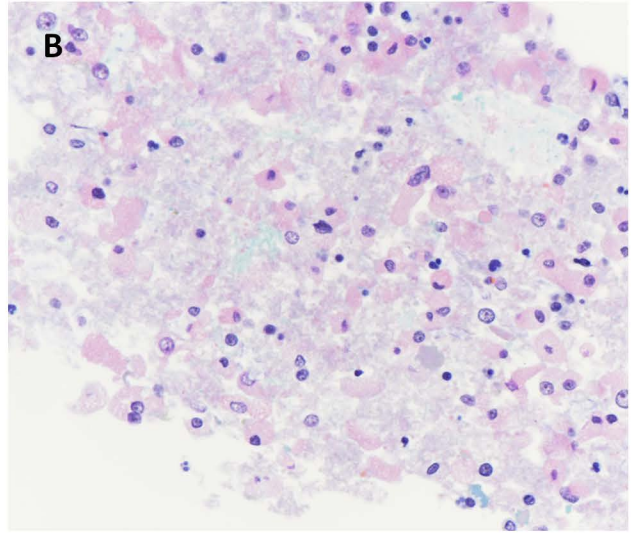
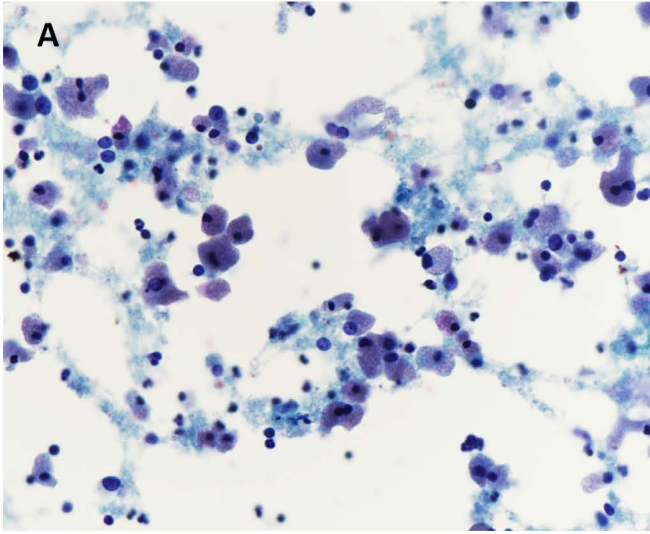




Figure 5

