Poorly differentiated and anaplastic carcinoma

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Manuel Sobrinho-Simões
Emeritus Professor of Pathology, University of Porto
Director, Ipatimup/i3S
THYROID CARCINOMAS

Follicular carcinoma
Papillary carcinoma
Hürthle cell carcinoma*
Medullary carcinoma
Poorly differentiated ca*
Undifferentiated carcinoma

WHO book on Endocrine Tumours, 3rd edition, 2004
Diagnostic, prognostic and predictive information in folicular-cell carcinomas

Precancerous &
Well circumscri/encapsulated ca without angioinvasion

Advanced carcinomas *
- Staging
- Poorly diff ** /RAI resp
- Therapy selection

Classification (Name)

* Excluding undifferentiated/anaplastic carcinoma
** High grade carcinoma, not adequate in my opinion
Follicular ca

Poorly diff ca

Papillary ca

Poorly diff ca

Undifferentiated/anaplastic ca

Soares et al, Virchow's Arch 444:572, 2004
Poorly differentiated carcinoma
TG + dot-like
TTF1 +

Undifferentiated carcinoma
TG –
TTF1 –/+ 
PAX8 +/- 
Keratins +/-

WHO book, 2017
The differential diagnosis between PDTC and anaplastic (undifferentiated) carcinoma will depend mainly from TG and TTF1 positivity
Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers

Compared to PDTCs, ATCs had a greater mutation burden, including a higher frequency of mutations in TP53, TERT promoter, PI3K/AKT/mTOR pathway effectors, SWI/SNF subunits, and histone methyltransferases.

<table>
<thead>
<tr>
<th>Type</th>
<th>Mutation Rate</th>
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<tbody>
<tr>
<td>Papillary &amp; Follicular ca</td>
<td>0-11%</td>
</tr>
<tr>
<td>Poorly differentiated ca</td>
<td>17-38%</td>
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<tr>
<td>Undifferentiated (anaplastic) ca</td>
<td>56-86%</td>
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Preto et al. Oncogene 23:1316, 2004
Undifferentiated/anaplastic carcinoma
Targeting CD47 in Anaplastic Thyroid Carcinoma Enhances Tumor Phagocytosis by Macrophages and Is a Promising Therapeutic Strategy

...Immunotherapy... is urgently needed. CD47 is a "don't eat me" signal, which prevents cancer cells from phagocytosis by binding to signal regulatory protein alpha on macrophages

Schürch CM et al. Thyroid 29:979-992, 2019

Some cases of ATC carry a good prognosis – all of us are trying to figure out: why and how?
Poorly differentiated thyroid carcinoma (PDTC) is a follicular cell neoplasm that shows limited evidence of follicular cell differentiation and is morphologically and behaviorally intermediate between differentiated (follicular and papillary) carcinomas and anaplastic carcinoma. It is not easy to apply objective criteria to separate differentiated from undifferentiated carcinoma. PDTC, WHO book, 2017
San Miniato Meeting, 1984

Official creation of insular/poorly differentiated thyroid carcinoma

Multi-continental study on poorly differentiated thyroid carcinoma (PDCa)

Turin, March 3-4  2006
Insular/Poorly differentiated thyroid carcinoma

Courtesy of Mauro Papotti
Typical dot-like positivity for thyroglobulin in poorly differentiated ca
Follicular ca

Poorly diff ca

Undifferentiated / anaplastic ca

Poorly diff ca

Papillary ca

RASmut

BRAFmut

Distant metastases

Lymph node metastases

Soares et al, Virchows Arch, 2004

Turin consensus criteria for the histopathological diagnosis of “Poorly differentiated thyroid carcinoma” with or without predominant insular pattern

PDTC, WHO book, 2017
Two major problems
Identification of convoluted nuclei &
Assume the PTC nuclei are present throughout the tumour

Fig. 4537 Algorithm for the diagnosis of poorly differentiated (PD) thyroid carcinoma using the Turin consensus criteria.
Aggressive forms of papillary or follicular carcinomas should not be included in the poorly differentiated category if they retain distinct features of differentiation (papillary carcinoma nuclei, papillae or follicles) throughout the tumour.

PDTC, WHO book, 2017
Widely invasive FTC

Sometimes difficult to separate from Poorly differentiated carcinoma
Trabecular/solid variant of PTC

Widely invasive follicular ca

Poorly diff ca

Namely in (very) young patients


PDTC, WHO book, 2017
Turin versus Memorial Sloan Kettering (MSK)

Turin consensus criteria for the histopathological diagnosis of “Poorly differentiated thyroid carcinoma” with or without predominant insular pattern


The group of R Ghossein classifies as poorly differentiated carcinoma every follicular cell-derived carcinoma that does not fit into the category of well differentiated carcinoma nor in the category of undifferentiated, anaplastic carcinoma (foci of necrosis, high mitotic index)

Hiltzik et al, Cancer, 2006
Solid/trabecular variant of PTC regardless of mitoses and foci of necrosis (WHO, 2017)

Provided the PTC nuclei are throughout – if not, one may diagnose a PDTC due to necrosis and mitoses
The issue of “focal” PDTC...

PDTC can coexist with other thyroid cancer histotypes including classic PTC,... and tall cell and hobnail variants of PTC

Some studies have shown that the focal presence of PDTC (even accounting for as little as 10% of an otherwise well-differentiated tumour) may be associated with aggressive features and/or may unfavourably affect prognosis.

PDTC, WHO book, 2017
Staging/completeness of surgery
Responsiveness to radioactive iodine

PDTC, WHO book, 2017
Other prognostic factors in PDTC

Age & Tumour necrosis
RAS mutations
Down regulation of miR-150

TERTp mutations?
Other mutations?

PDTC, WHO book, 2017
TERT promoter mutations in thyroid tumours (n=469)

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Papillary carcinoma</td>
<td>7.5%</td>
</tr>
<tr>
<td>Follicular carcinoma</td>
<td>17.1%</td>
</tr>
<tr>
<td>Poorly differentiated ca</td>
<td>29.0%</td>
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<tr>
<td>Undifferentiated (anaplastic) ca</td>
<td>33.3%</td>
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Melo et al, J Clin Endocrinol Metab, 2014
Melo et al, J Clin Endocrinol Metab, 2017

TERT promoter mutations are significantly associated with distant metastases and mortality in PTC, FTC and PDTC.
A last point

Like many colleagues I do not know if there is evidence enough to separate the so-called "high-grade carcinoma" of the thyroid from poorly differentiated thyroid carcinoma.

High-grade carcinoma (usually PTC + "high grade" features).

Poorly differentiated thyroid carcinoma.

Baloch ZW, LiVolsi VA, Special types of thyroid carcinoma. Histopathology, 72:40, 2018