Poorly differentiated thyroid cancer

“Die wuchernde Struma”
Historical View

• original observation by Langhans in 1907
  – “Über die epithelialen Formen der malignen Struma.”
• During the following decades recognition of these tumors as a distinct entity was neglected

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Virchows Arch (A). 1907;189:69–188.
Historical View

• International Workshop on Thyroid Tumor Pathology in San Miniato, 1984
  – existence and recognition of a class of thyroid neoplasms with a microscopic appearance and natural history intermediate between WDTC and undifferentiated (anaplastic) carcinoma was proposed

• Little uniformity of applied defining criteria

Historical View

• Sakamoto (*architectural criteria*)
  – pattern of growth (solid, trabecular, “scirrhous”)
  – nuclei, mitotic rate, necrosis no role

• Carcangiu (*architectural and high grade features*)
  – insular pattern of growth
  – necrosis with formation
  – small round hyperchromatic nuclei
  – mitotic activity

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Malignant thyroid tumor of follicular cells

- Follicular carcinoma
  - Papillary carcinoma (etc)
    - NO
      - STI pattern
    - YES
      - Typical PTC nuclei throughout
  - Solid variant of papillary carcinoma
    - YES
      - Presence of at least one of the following: convoluted nuclei or necrosis or mitoses
    - NO
      - Follicular carcinoma (solid growth pattern)
        - NO
          - PD CARCINOMA
            - pure
            - with coexistent papillary carcinoma
            - other type of carcinoma
        - YES
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- solid, trabecular, insular
- “majority of tumor should have an insular, solid, trabecular pattern” (WHO)
- only a small percentage of this architecture (<20% of the tumors) needed for some
- more than 50% of these architectures is needed for others

Poorly Differentiated Thyroid Carcinomas: How Much Poorly Differentiated is Needed?

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Malignant thyroid tumor of follicular cells

Follicular carcinoma
Papillary carcinoma (etc)

NO

YES

STI pattern

Solid variant of papillary carcinoma

YES

NO

Typical PTC nuclei throughout

Presence of at least one of the following: convoluted nuclei or necrosis or mitoses

Follicular carcinoma (solid growth pattern)

NO

YES

PD CARCINOMA

- pure
- with coexistent papillary carcinoma
- other type of carcinoma
- with round nuclei
- with convoluted nuclei

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Malignant thyroid tumor of follicular cells

- STI pattern

Follicular carcinoma
  - Papillary carcinoma (etc)
  - YES
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  - NO
  - Presence of at least one of the following: convoluted nuclei or necrosis or mitoses

Solid variant of papillary carcinoma
  - YES
  - NO
  - PD CARCINOMA

Follicular carcinoma (solid growth pattern)
  - NO
  - YES

>3 mitosis/10hpf

- pure
- with coexistent papillary carcinoma
- other type of carcinoma
- with round nuclei
- with convoluted nuclei

Macroscopy

- often >5 cm
- firm and solid
- gray-white cut surface
- focal soft areas of necrosis
Microscopy
Cytology

• “A definite diagnosis of PDTC can be made only at the histological level” (WHO)

• majority diagnosed “suspicious for a follicular neoplasm” or “suspicious for PTC”
Cytology

• highly cellular with a bloody background, scant colloid, and rare necrosis
• cells are arranged in loosely cohesive solid or trabecular clusters or in insular
• cell population: isolated small to medium-size cells with scant cytoplasm, round nuclei, inconspicuous nucleoli, and high N/C ratio.
Cytology
IHC

Positive:
• TTF-1, Tg (often focal)
• HBME-1, galectin-3
• Ki-67 usually 10-30%

Negative:
• Calcitonin, CEA, neuroendocrine markers
• E-cadherin

• no specific markers
• role in distinguishing PDTC from other entities (e.g. medullary carcinoma or metastatic)
Histogenesis

• De novo
• Pre-existing WT-TC
  – Follicular
  – Papillary

• Genetic alterations:
  – Variable results
  – Depending on inclusion and exclusion criteria!
Table 1
Thyroid tumors with their characteristics and mutational profiles.

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Prevalence (% of thyroid cancers)</th>
<th>10-Year survival (%)</th>
<th>Mutations observed and their prevalence</th>
<th>Effects of these mutations on tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary carcinoma</td>
<td>80–85</td>
<td>95–98%</td>
<td>BRAF (V600E) 45% RET/PTC 20% RAS 10% TRK &lt;5%</td>
<td>Promoting tumorigenesis, invasion, metastasis, recurrence and mortality</td>
</tr>
<tr>
<td>Follicular carcinoma</td>
<td>10–15</td>
<td>90–95</td>
<td>RAS 45% PAX8-PPARY 35% PIK3CA &lt;10% PTEN &lt;10% BRAF (V600E) &lt;10%</td>
<td>Promoting tumorigenesis, invasion, metastasis, recurrence and mortality</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>3–5</td>
<td>60–80</td>
<td>Familial forms of RET &gt;95% Sporadic RET 50%</td>
<td></td>
</tr>
<tr>
<td>Poorly differentiated carcinoma</td>
<td>&lt;2</td>
<td>50</td>
<td>RAS35% BETA CATENIN 20% TP53 20% BRAF 15% PIK3CA 10% AKT 10%</td>
<td>Promoting tumorigenesis and tumor progression, invasion, metastasis, recurrence and mortality</td>
</tr>
<tr>
<td>Anaplastic carcinoma</td>
<td>1–2</td>
<td>&lt;10</td>
<td>TP53 70% BETA CATENIN 65% RAS 55% BRAF 20% PIK3CA 20% PTEN &lt;10 AKT 10%</td>
<td>Promoting tumorigenesis and tumor progression, invasion, metastasis, recurrence and mortality</td>
</tr>
</tbody>
</table>
Treatment

• total thyroidectomy (or completion thyroidectomy)
• LN dissection
• followed by $^{131}$I administration
• thyroxin suppression

• external beam radiation
  – unresectable, incompletely excised tumors or loco-regional recurrences
• chemotherapy not established yet
Prognosis

- intermediate between WDTC and anaplastic thyroid carcinoma
- usually related to regional and distant metastases
- majority of patients dies within first 3y *(WHO)*
“PDTC was defined by histological and/or immunohistochemical evidence of follicular cell differentiation and the presence of tumor necrosis and/or ≥ five mitoses per 10 high-power fields”
References

• **Adv Anat Pathol** 2009;16:283–289
• *Virchows Arch (A).* 1907;189:69–188.
• *Cancer.* 1983;52:1849–1855