Oncocytic and high grade non-anaplastic thyroid carcinoma

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Director of Head and Neck Pathology
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Memorial Sloan-Kettering Cancer Center
New York, NY
- M.D. at 21 yrs old
- Description of 75 entities: Sinus Histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease), desmoplastic small round cell tumor, poorly differentiated thyroid carcinoma, papillary thyroid carcinoma follicular variant….
- Director of Pathology, Yale
- Chairman of Pathology, Memorial Sloan-Kettering Cancer Center
- Chairman of Pathology, National cancer institute (tumori), Milan
“No classification is more difficult to establish than that of thyroid carcinomas. Their pleomorphism is almost the rule; very few are adapted to a precise classification.

….. Of all cancers, they teach, perhaps, the greatest lessons of humility to histopathologists.”
ONCOCYTIC LESIONS OF
THE THYROID GLAND
Oncocytic Change

- Cellular enlargement characterized by an abundant eosinophilic granular cytoplasm (as a result of the accumulation of mitochondria in the vast majority of cases).
THE ONCOCYTE

Vesicular nucleus with large central nucleolus
ELECTRON MICROSCOPY OF HURTHLE CELL

Mitochondria
Terminology of Oncocytic Cells of the Thyroid

- “HURTHLE” (Most commonly used term and a misnomer). The cells Karl Hurthle described in dogs were probably C cells. 1894.
- “ASKENAZY” cells (Germany): Initial description by Askenazy in 1898.
- Oxyphilic cells.
- Oncocyte.
Classification of Oncocytic Lesions of the Thyroid Gland

TUMORS

• Oncocytic (ex-Hurthle cell) adenoma.

• Oncocytic (ex-Hurthle cell) carcinoma
Classification of Oncocytic Lesions of the Thyroid Gland

**TUMORS**

- Oncocytic (NIFTP)
- Papillary carcinoma, oncocytic variant.
- Poorly differentiated carcinoma with predominant oncocytic features.
- Medullary carcinoma, oncocytic variant.
Classification of Oncocytic Lesions of the Thyroid Gland

NON-NEOPLASTIC

- “Hyperplastic” nodule composed of Hurthle cells
**Oncocytic (ex-Hurthle cell) adenoma**

- **Definition:** A benign encapsulated thyroid tumor, composed predominantly (>75%) of follicular cells with oncocytic features.
- These cells **DO NOT** display the nuclear features of papillary thyroid carcinomas.
- **THERE IS NO CAPSULAR OR VASCULAR INVASION.**
Follicular adenoma growth patterns

Follicular pattern

Solid/trabecular pattern
(previously known as Unknown Malignant Behavior)
ONCOCYTIC (ex-HURTHLE CELL) ADENOMA

• THE LACK OF CAPSULAR INVASION AND VASCULAR INVASION DEFINE THE BENIGN PHENOTYPE.

but this definition did not come easily.
First Controversy: Criteria To Define Malignancy

- **1907:** Langhans: First description of Hurthle cell tumor: no microscopic evidence of malignancy in 5 cases, 2 of which died.
- **1926:** Wegelin: Majority of Hurthle cell tumors are benign
- **1941:** Harry: All Hurthle cell tumors are adenocarcinomas of moderate malignancy.
- **1941:** Warren: Hurthle cell tumors are “benign tumors with malignant potential”.
First Controversy: Criteria To Define Malignancy

- **1951: American Cancer Society:** “All Hurthle cell neoplasms should be treated aggressively during the initial operation because of their malignant potential”.

- **1951: Frazell and Duffy:** Vascular invasion crucial.

- **1954: Horn:** “The mere observation of tumor cells within vascular lumina may well be artifact and the source of diagnostic error...”
• 1974: Thompson NW, Dunn EL, Batsakis JG et al.: “any (Hurthle cell) lesion over 2 cm, regardless of what the pathologist says should be treated definitively at the time of original operation”.

• 1988: McLeod et al: The therapy of Hurthle cell tumors is controversial because of the “unreliable correlation between their histopathologic features and clinical behavior.”
After 80 long years ........
Traditional Microscopic Criteria of Capsular and Vascular Invasion Define Malignancy


Assessment of capsular invasion in thyroid tumors
CAPSULAR INVASION
Vascular invasion

Follicular neoplasm

Capsule

No (A)
Yes (B)
Yes (C)
Yes (D)
Yes (E)
No (F)

Chan JK
Extracapsular vascular invasion

Intra-capsular vascular invasion
VASCULAR INVASION

- Hurthle cell in tumor thrombus
- Endothelial cell of vessel
- Endothelial cell on tumor thrombus
Pitfalls in the Diagnosis of Hurthle Cell Adenoma

1. FNA induced necrosis

2. Misplaced follicles through the capsule along the FNA track. (Mistaken for capsular invasion).

3. Incomplete capsular invasion (old criteria)

4. Artifactual dislodgment of tumor cells in vessels due to sectioning.

5. Psammoma body-like structures within follicular lumen.
HURTHLE CELL ADENOMA TOTALLY INFARCTED BY FNA
FNA ARTEFACT SIMULATING INVASION
FNA ARTEFACT SIMULATING INVASION

Hurthle cells

lymphocyte

Reactive fibroblast
FNA induced capsule rupture simulating invasion

Capsule

Hemosiderin due to FNA
CAPSULAR IRREGULARITY MIMICKING CAPSULAR INVASION (OLD CRITERIA FOR INVASION)
ARTIFACTUAL DISLODGEMENT OF TUMOR CELLS IN VESSELS SIMULATING VASCULAR INVASION

- Lumen
- Hurthle cell fragment
- Endothelial cells
PSEUDOPSAMMOMA BODY IN HURTHLE CELL ADENOMA
SECOND CONTROVERSY:
STRATIFICATION OF PATIENTS
WITH HURTHLE CELL
CARCINOMA.
FOLLICULAR and HURTHLE CELL CARCINOMA.

- Diagnosis of follicular carcinoma depends on capsular and vascular invasion.

- Criteria for capsular and lymphovascular invasion controversial.

- Definition of minimally invasive carcinoma controversial.
FOLLICULAR and HURTHLE CELL CARCINOMA.

• Diagnosis of follicular carcinoma depends on capsular and vascular invasion.

• Criteria for capsular and lymphovascular invasion controversial.

• Definition of minimally invasive carcinoma controversial.
Why is it clinically important?

- Not all surgeons treat minimally invasive carcinoma with total thyroidectomy and RAI.

- Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion do not routinely require adjuvant RAI.

*American Thyroid Association Guidelines Task Force 2015 update*
Why is it clinically important?

National Comprehensive Cancer Network guidelines 2021 follicular/Hurthle cell ca

- Lobectomy
  - Widely invasive/extensive angioinvasion (>4 foci) → Completion Thyroidectomy/RAI
  - Minimally invasive (microcapsular) < 4 foci vascular invasion → Completion Thyroidectomy/RAI
    Or Observe (preferred)
WIDELY INVASIVE FOLLICULAR/HURTHLE CELL CARCINOMA

- Grossly apparent invasion of thyroid and/or soft tissue.

- Poor prognosis: 25-50% mortality at 10 years.

- Unanimous agreement.

Remnant of tumor capsule
Widely invasive Hurthle cell carcinoma

Multinodular invasive growth pattern

Extra-thyroid vascular invasion
Metastatic Hurthle cell carcinoma to Lymph node
MINIMALLY INVASIVE FOLLICULAR/HURTHLE CELL CARCINOMA

VARIOUS DEFINITIONS
All Well defined grossly encapsulated follicular/Hurthle cell carcinomas = Minimally Invasive

- Grossly well defined and encapsulated tumor with capsular and/or vascular invasion that is usually microscopic. (Overall low risk)

Alternative terminology for encapsulated follicular/Hurthle carcinoma (Dr Livolsi)

• **Encapsulated follicular carcinoma with capsular invasion only**: Minimally invasive (Extremely low risk)

• **Encapsulated follicular carcinoma with vascular invasion**: Angioinvasive follicular carcinoma. (High risk)

Vascular invasion ≠ Capsular invasion
Another terminology based on the number of invasive foci (Memorial Sloan-Kettering)

- **capsular invasion**: Minimally invasive (extremely low risk)
- **> 4 foci of vascular invasion**: Encapsulated follicular carcinoma with extensive vascular invasion (High risk)
- **In between (<4 foci of vascular)**: Encapsulated follicular carcinoma with focal vascular invasion (lower risk)

![Diagram showing 1 VI and 6 VI with ≠ symbol]
Relapse free survival (RFS) according to number of foci of vascular invasion in encapsulated follicular carcinoma, oncocytic variant

Median FU: 35.9 months

In 1986, Dr Lang stated that $\geq 5$ foci of vascular invasion defines widely invasive follicular carcinoma but his article was dismissed (arbitrary).

50 yr old with grossly encapsulated Hurthle cell carcinoma with extensive microscopic angioinvasion

Bone metastases 10 years later
Impact of vascular invasion on nomenclature of follicular/Hurthle cell carcinomas (WHO 2017-2022)

• Minimally invasive: Capsular invasion only

• Angioinvasive: Any vascular invasion (VI) in encapsulated tumors. Focal (<4 foci of VI). Extensive (≥ 4 foci of VI)

• Widely invasive: Gross and extensive invasion of thyroid gland.
Integrated Genomic Analysis of Hürthle Cell Cancer


Cancer Cell 2018
Widespread chromosomal losses and mitochondrial DNA alterations as genetic drivers in Hürthle cell Carcinoma


Cancer Cell 2018
Genetic profile of oncocytic (Hurthle cell) carcinomas different from other thyroid carcinoma

<table>
<thead>
<tr>
<th>Gene</th>
<th>Prevalence stratified by thyroid histology</th>
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<tbody>
<tr>
<td></td>
<td>PTC</td>
</tr>
<tr>
<td>RET point mutation RET rearrangements</td>
<td>0%</td>
</tr>
<tr>
<td>BRAF mutations</td>
<td>30-70%</td>
</tr>
<tr>
<td>RAS mutations</td>
<td>10%</td>
</tr>
<tr>
<td>PIK3CA point mutation or amplification</td>
<td>10-30%</td>
</tr>
<tr>
<td>PPARG rearrangement</td>
<td>25-60%</td>
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</tbody>
</table>

PTC-papillary thyroid cancer
FTC-follicular thyroid cancer
PDTC-poorly differentiated thyroid cancer
ATC-anaplastic thyroid cancer

Lower follicular carcinoma type canonical mutations
Genetic profile of Hurthle cell carcinomas different from other thyroid carcinoma

- Widespread chromosomal loss leading to haploidy or uniparental disomy: 54%
- Frequent mitochondrial DNA mutations: 67%

Gopal et al. Cancer Cell 2018
Ganly et al Cancer Cell 2018
RTK/PIK3/RAS Pathway altered in 55% tumors

Good response to Everolimus

Ganly et al Cancer Cell 2018
Tumor type and recurrence free survival in encapsulated PTC, follicular carcinomas and Hurthle cell carcinoma (N=267). Median follow up: 6 years

Xu B et al. *Hum Pathol.* 2015
RAI(+) distant metastases by histology

- All patients
- Confirmed Hx

Oncocytic (Hurthle cell) carcinoma
Third controversy: Is Oncocytic (Hurthle cell) carcinoma a subtype of follicular carcinoma?

- Follicular carcinoma *seems very different* from Hurthle cell carcinoma at molecular level, and in regard to RAI avidity and recurrence rates
WHO 2017-2022

• Hurthle cell tumors *not subtypes* of follicular carcinomas
HURTHLE CELL TUMOR

- Traditional Microscopic Criteria of Capsular and Vascular Invasion Define Malignancy.
- Extent of vascular invasion Stratify Patients into Prognostic Categories…as long as distant metastases are excluded at presentation.
Papillary Carcinoma, Oncocytic Variant Definition

- An oncocytic tumor with the nuclear features of papillary carcinoma but the cell are not tall (papillary or follicular growth pattern)
PAPILLARY CARCINOMA, CLASSICAL WITH ONCOCYTIC FEATURES

papillae
PAPILLARY CARCINOMA, CLASSICAL
WITH ONCOCYTIC FEATURES

Rarefaction of cytoplasm

Papillary nuclei
PAPILLARY CARCINOMA, FOLLICULAR VARIANT WITH ONCOCYTIC FEATURES
“Old clinicians used to say that the classification of thyroid cancer was very simple. There was a group of well differentiated, slow growing tumors that never killed anybody, and a group of rapidly growing tumors that killed everybody”

L. Woolner
Dept. of Pathology
Mayo Clinic
Poorly Differentiated Thyroid Carcinomas

- Tumors of follicular cell origin showing histologic and prognostic features intermediate between Well Differentiated Thyroid Carcinomas and Anaplastic Carcinoma.
“Wuchernde struma”
T. Langhans
1907

Insular carcinoma
Carcangiu, Zampi, Rosai
1984
HISTOLOGIC FEATURES OF POORLY DIFFERENTIATED THYROID CARCINOMAS

- Solid/trabecular/insular growth
- Necrosis
- Capsular invasion
- Vascular invasion

*If all the above are present, everybody agrees on the Poorly differentiated diagnosis*
THE BIG QUESTION

• WHAT DEFINES POORLY DIFFERENTIATED THYROID CARCINOMAS?

- SOLID GROWTH PATTERN ALONE
OR
- MITOSIS/NECROSIS ALONE
Trabecular/solid/insular poorly differentiated thyroid carcinomas irrespective of mitosis/necrosis

83% at 5 years

Scoring of poorly differentiated thyroid carcinomas (Volante et al)

- Necrosis: 3 points
- Mitosis > 3 per 10 HPF, age >45: 1 point each

- **Group 1**: 0-1 (NO NECROSIS)
- **Group 2**: 2-3 (Necrosis or mitosis/age>45)
- **Group 3**: 4-5 (Necrosis and mitosis/age>45)
Trabecular/solid/insular poorly differentiated thyroid carcinomas

- No necrosis
- Necrosis

Cumulative proportion surviving vs Time (mos)

Histologic diagnosis:
- Group 1
- Group 2
- Group 3

Scoring system:
- Group 1: score 0-1
- Group 2: score 2-3
- Group 3: score 4-5

American Cancer Society
“POORLY DIFFERENTIATED THYROID CARCINOMAS: DEFINED ON THE BASIS OF MITOSIS AND NECROSIS. A clinico-pathologic study of 58 cases.

Poorly differentiated thyroid carcinomas defined on the basis of mitosis (≥ 5/10 HPF) and/or necrosis (MSKCC)

Fulfill also Turin

Overall survival
Poorly differentiated thyroid ca defined on the basis of mitosis and necrosis

Predictors of survival within PDC
- Tumor > 4cm  p=0.02
- Absence of a capsule  p=0.001
- Extra-thyroid extension p=0.001
- Margins  p=0.001

Factor with no influence on survival
Growth pattern (solid vs foll/pap)  p=1
Poorly Differentiated Carcinoma

Turin proposal
Solid/nested/insular growth pattern, and
Absence of nuclear features of PTC, and
At least one of the following features:
• Convoluted nuclei
• Mitotic index of ≥ 3/10 HPFs
• Tumor necrosis


Adopted by previous WHO 4th ed
TURIN PROPOSAL

Overall survival distribution: diagnosis

- PTC
- PD
- ANA
- FTC

No necrosis

Overall survival distribution: necrosis

- Necrosis present
- Necrosis absent

Overall survival distribution: mitoses

- $m_t < 3$
- $m_t \geq 3$

Overall survival distribution: PD carcinoma types

- PD NOS
- PD PTC type

Percent survival

p=0.001

p<0.001

p=0.011

p=0.475
POORLY DIFFERENTIATED THYROID CARCINOMA DEFINED ON THE BASIS OF MITOSIS/NECROSIS

- Main cause of radioactive iodine (RAI) refractory disease (46%).

- Many of these RAI-refractory PDCs (68%) initially diagnosed as classical PTC, Hurthle cell ca, and follicular ca.

- Main cause of death from non-anaplastic thyroid carcinoma (55%).

72 year old man with 5.5 cm mass

Solid nested growth

High mitotic rate and clear nuclei
72 year old man with 5.5 cm mass

Turin proposal: Papillary carcinoma (clear nuclei)

MSKCC: Poorly diff carcinoma
Outcome

• Vertebral and lung metastasis
• D.O.D 4 years after diagnosis
WHO 2022
High grade follicular cell derived non-anaplastic thyroid carcinomas

• Invasive carcinoma of thyroid follicular cells

• High grade features as defined by mitotic count and tumour necrosis

• No anaplastic histology.
WHO 2022
High grade follicular cell derived non-anaplastic thyroid carcinomas

• Poorly Differentiated Thyroid Carcinoma (PDTC)

• High grade differentiated thyroid carcinomas (HGDTC)
**WHO 2022 high grade follicular cell derived non-anaplastic thyroid carcinoma**

<table>
<thead>
<tr>
<th></th>
<th>PDTC (Turin criteria)</th>
<th>High grade differentiated thyroid carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Growth Pattern</strong></td>
<td>Solid/trabecular/insular required</td>
<td>Papillary, follicular, solid*</td>
</tr>
<tr>
<td><strong>Nuclear Cytology</strong></td>
<td>No features of PTC required</td>
<td>Any</td>
</tr>
<tr>
<td><strong>Tumor Necrosis, Mitosis and Convoluted Nuclei</strong></td>
<td>one of the following three features: Mitotic count ≥3/2 mm² Tumor necrosis Convoluted nuclei</td>
<td>one of the following two features: Mitotic count ≥5/2 mm² Tumor necrosis</td>
</tr>
<tr>
<td><strong>Anaplastic features</strong></td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>
# High grade follicular cell derived non-anaplastic thyroid carcinoma

## Molecular profile

<table>
<thead>
<tr>
<th>Subtype</th>
<th>BRAF V600E</th>
<th>RAS(^a)</th>
<th>TERT</th>
<th>TP53</th>
<th>EIF1AX</th>
<th>PTEN</th>
<th>PIK3CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly differentiated thyroid carcinoma (PDTC)</td>
<td>6%</td>
<td>44%</td>
<td>44%</td>
<td>15%</td>
<td>15%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>High grade differentiated thyroid carcinoma (HGDTC)</td>
<td>81%</td>
<td>6%</td>
<td>39%</td>
<td>3%</td>
<td>3%</td>
<td>0%</td>
<td>3%</td>
</tr>
</tbody>
</table>
High grade (HG) thyroid carcinomas (n=364)
- TERT and TP53 mutation: 55% and 11%
- Adverse independent prognostic factors are: older age, male sex, extensive necrosis, infiltration, vascular invasion, positive margin, lymph node metastasis, PTEN, TP53, and TERT mutations.

Similar overall and disease specific survival

Poorly differentiated carcinoma
- RAS-predominant
- RAI avid
- Higher frequency of distant metastasis
- Lower rate of nodal metastasis

HG differentiated carcinoma (n=164)
- BRAF V600E-predominant
- RAI non-avid
- Lower frequency of distant metastasis
- Higher rate of nodal metastasis

Toward a New nomenclature in tumours that better reflects behavior

• For staging:
  - From anatomic grouping (6, 7th AJCC edition) to Anatomic/prognostic grouping (8th AJCC edition)

• For pathologic entities:
  - Based on *prognostically relevant histologic features* rather than clinically irrelevant histopathology. (Pathologist = Clinician with a microscope)
The wisdom of Julian Huxley

‘Cancer (malignancy) must be defined operatively in terms of what the tumor cells do, not what they look like; otherwise the term ceases to have biological meaning’

THE END