PATHOLOGIC PROGNOSTIC FACTORS IN THYROID CARCINOMA: WHAT THE CLINICIAN SHOULD EXPECT FROM THE PATHOLOGIST

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THE FACTORS

- Tumor stage-extent
- Tumor subtype
- Vascular/lymphatic invasion
- Nodal status
- Molecular characteristics
- Important clues
TUMOR STAGE

- SIZE
- SPREAD—NODAL OR OTHER METS
- THE PROBLEM OF EXTRATHYROIDAL EXTENSION

![Graph](image1)

*Fig. 3. Papillary carcinoma: survivalship curves for occult, intrathyroid, and extrathyroid lesions also, curve (dotted line) for normal persons of comparable age and sex.*
CONCLUSIONS

Skeletal muscle
90% for ETE
96% for ENE

Adipose tissue
79% for ETE
80% for ENE

Nerve
62% for ETE
85% for ENE

Thick-walled vessels
29% for ETE
36% for ENE
THE PROBLEM IS THE THYROID CAPSULE

- Only part of the thyroid has a “capsule”—usually anterior and lateral gland.
- Importantly, isthmus and posterior aspects have no or incomplete capsules.
- Thus the thyroid and perithyroidal fat and wisps of skeletal muscle interdigitate. If a tumor arises or involves these areas, it may still be confined to the gland.

THE PROBLEM IS THE THYROID CAPSULE

- Thus staging these tumors as Stage T3 is not correct nor predictive of a tumor that is truly high stage (as compared with cancers of other sites).
- Often extrathyroidal extension is seen with microcarcinoma.
- So far there is little evidence in the literature as to how to resolve this issue.

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AGGRESSIVE THYROID CANCERS

- PAPILLARY CARCINOMA SUBTYPES
- POORLY DIFFERENTIATED CARCINOMA
- HIGH GRADE DIFFERENTIATED CARCINOMA
- HURTHLE CELL CARCINOMA
- ANAPLASTIC CARCINOMA
- MEDULLARY CARCINOMA

PAPILLARY THYROID CARCINOMA

- SUBTYPES
  - TALL CELL
  - COLUMNAR
  - DIFFUSE SCLEROSIS VARIANT
  - SOLID VARIANT
  - HOBNAIL CELL VARIANT
  - MICROPAPILLARY VARIANT
  - PROGNOSIS WORSE THAN USUAL PTC

PAPILLARY THYROID CARCINOMA

- TALL CELL VARIANT
  - Approximately 10-15% of PTC
  - Older patients
  - Large tumors
  - Extrathyroidal
  - Vascular invasion
  - 25% mortality at ten years
INTRANUCLEAR INCLUSION

TALL CELL VARIANT
- PARTIAL VS TOTAL
- MEANING OF RECOGNIZING SMALL AMOUNT TALL CELL VARIANT
- RECURRENCES AND NODAL METS
- DEDIFFERENTIATION

PEPILLARY THYROID CARCINOMA
PAPILLARY THYROID CARCINOMA

DEFINITION: TALL CELL VARIANT

Literature is replete with percentages needed to diagnose as tall cell carcinoma: 70%, 50%, 30%, 10%??

TALL CELL VARIANT

- Often underrecognized
- At least 40% of tall cell histology is not noted especially those tumors with focal tall cell features
- These cases in recurrences or nodal mets often have a larger percentage of tall cell histology.

Montone, K et al 2010 USCAP

TALL CELL PAPILLARY CARCINOMA

Tall cell PTC and PTC with tall cell features (30-50%) when compared to classic PTC, showed
- Older age
- Larger tumors
- More extensive ETE
- More positive resection margins
- Higher pathologic stage
- Lower disease free survival
- More nodal disease and ENE
- Risk of anaplastic transformation

CONCLUSION: TALL CELL DEFINED AS > 50% TALL CELL HISTOLOGY; PTC WITH TALL CELL FEATURES (30-50% TALL CELL HISTOLOGY). BOTH BEHAVE WORSE THAN CLASSIC PTC. SO SUGGEST 30% TALL CELL HISTOLOGY SHOULD BE CUTOFF.

Ganly et al Thyroid (2014) MSKCC 453 cases
TALL CELL PAPILLA LiY CARCINOMA

Tall cell variant (TCV) is widely believed to be a more aggressive subtype of papillary thyroid carcinoma (PTC).

Design:
39 cases of PTC; 13 “endocrine” pathologists

TALL CELL PTC: DEFINITIONS VARY

<table>
<thead>
<tr>
<th>Definition</th>
<th>H:W</th>
<th>Tumor percent</th>
<th>Number of pathologist using the definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2:1</td>
<td>≥30%</td>
<td>1/13</td>
</tr>
<tr>
<td>B</td>
<td>2:1</td>
<td>≥50%</td>
<td>2/13</td>
</tr>
<tr>
<td>C</td>
<td>3:1</td>
<td>≥30%</td>
<td>5/13</td>
</tr>
<tr>
<td>D</td>
<td>3:1</td>
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</tr>
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RESULTS

• Overall strength of agreement was fair
  When definition of TALL CELL was >50% and cells 3 times as tall as wide, Kappa was moderate (0.49).
**CONCLUSIONS**

There is lack of unanimous diagnostic criteria for TALL CELL PTC. There is both over- and under diagnosis.


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**COLUMNAR CELL VARIANT**

- Less than 5% of PTC
- Men
- Extrathyroidal **
- Secretory look
- Stratified nuclei
- Bad prognosis if extrathyroidal

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**COLUMNAR CELL VARIANT**

- 54% of our series of 11 cases had positive immunostaining for CDX2 a GI marker.
- All other varieties of PTC were negative for this marker
- Rare case report of cribriform morular variant with focal positivity (this is tumor associated with FAP)
- Enriquez et al. (AJCP 2012)
**CDX 2 IMMUNOSTAIN**

**PAPILLARY THYROID CARCINOMA**

- **HOBNAIL SUBTYPE**
  - Original eight cases, predominantly women (subsequently up to 24 cases)
  - Average age 57
  - Average size 2.5 cm
  - ETE (50%) cervical nodes (75%)
  - Braf mutated (51%)
  - DOD (50%) at 3.5 yrs
  - Additional 2 patients AWD.

  (Acioli et al AJSP 2010)

- **HOBNAIL VARIANT**
  - 63% stage III or IV at diagnosis
  - Large size (3.7 +/- 2 cm)
  - ETE  58%
  - NODES  75%
  - 40% had tall cell features too
  - MOLECULAR: 80% Braf +; 20% ret/PTC

  Lubitz et al THYROID 2014.
MICROPAPILLARY TYPE
VERY RARE
Similar to this histology in other organs—breast, ovary, bladder
Do very poorly
Over 50% mortality at 5 years
Early access to lymphatics
Then disseminate widely.
IS FOLLICULAR VARIANT AN AGGRESSIVE SUBTYPE?

- DIFFICULT TO KNOW.
- DEFINITIONS VARY
- IF VASCULAR INVASION, MAY BEHAVE IN CLINICALLY AGGRESSIVE FASHION
AGGRESSIVE THYROID CARCINOMA

● AGGRESSIVE FEATURES DESPITE TYPE
  - Necrosis
  - Mitotic activity
  - Abnormal mitoses
  - CYTOLOGIC Pleomorphism (must be distinguished from random nuclear atypia which is equivalent to “ancient change” in Schwannomas ((often seen in Hurthle cell nodules)))

POORLY DIFFERENTIATED THYROID CARCINOMA

- There are two major subtypes
- Tumors can be poorly differentiated by:
  - HISTOLOGIC PATTERN Turin 2007
  - GRADING (Åkslen 2000; Tallini 2011)
POORLY DIFFERENTIATED THYROID CARCINOMA

HISTOLOGIC PATTERN Turin 2007

- Solid, trabecular or insular
- Mitoses easily found
- Abnormal mitoses
- Necrosis

Often large tumors
Extraglandular extension
Vascular invasion
Mortality 50% or >> at 5 yrs

Often have well differentiated tumor at edge
- Papillary
- Follicular variant
- Follicular
- Hurthle cell
POORLY DIFFERENTIATED CARCINOMA

- **Patterns**
  - Solid
  - Trabecular
  - Insular
HIGH GRADE THYROID CARCINOMA

- **GRADING**
- Less well known or studied
- These tumors are recognizable by pattern as papillary, follicular, Hurthle
- Have “bad” features—necrosis, mitoses, much vascular invasion
- **HIGH GRADE**
- Tallini *Endo Pathol* 2011

**GRADING**

- No longterm followup studies with multivariate analysis to determine prognostic importance of **GRADING** in papillary carcinoma.
- Data so far anecdotal.
POORLY DIFFERENTIATED THYROID CARCINOMA

- MOLECULAR FINDINGS ARE AS CONFUSING AS THE DEFINITIONS OF PD THYROID CARCINOMA!!
  1. If residual papillary ca or follicular variant, may see ret/PTC translocations or Braf mutations
  2. If no PTC then most common molecular change is mutation in N-Ras (about 23%)

Volante, Nikiforov, Tallini (multiple references)

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VASCULAR/LYMPHATIC INVASION

- College of American Pathologists (CAP) synoptic reporting for cancers of various organs: ANGIOLYMPHATIC INVASION or LVI
- At least in the thyroid, does not make sense.
WHY SHOULD WE NOT DISTINGUISH?

Meaning of vascular invasion

Meaning of lymphatic invasion

MEANING OF VASCULAR INVASION:
- Hematogenous spread outside of neck—lungs, bone etc

MEANING OF LYMPHATIC INVASION:
- Local/regional nodes at risk; may have lymphangitic spread to lungs
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THE FACTORS
- Tumor stage-extent
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- **Nodal status**
- Molecular characteristics
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NODAL STATUS
- Location of nodes
- Size of metastases (Micrometastasis)
- Number of nodes involved
- Extranodal extension
- Psammoma body only
- Changing tumor subtype
NODAL STATUS

Central compartment—Is this always the first line of involvement?
Lateral compartments—what levels are at risk?
Value of ultrasound

SIZE OF METASTASIS
Review of literature which substantiates that all N1 disease is not the same in terms of prognostic import.
Suggests that microscopic N1 disease be approached differently and not be over treated

WHAT IS A MICROMETASTASIS IN LYMPH NODE IN THYROID CANCER?
If in other systems (breast, melanoma) micromet is defined as 2 mm or less, in Tiny (esp. central compartment nodes) node size may be 2 mm so a 1.5 or 1.8 mm metastasis makes little sense since it involves almost all of node.
FOLLOWUP DATA ON MICROMETASTASES IN THYROID CANCER—NOT AVAILABLE.

WILL TAKE YEARS!

NUMBER OF NODES INVOLVED

The risk of recurrent papillary carcinoma in the neck is also related to number of positive nodes: < 5 nodes (4%); >5 nodes (24%)

Randolph et al THYROID 2012.
The Isolated Psammoma Body in Node

Different from ovary where can have psammoma bodies without epithelium in nodes and does not mean metastasis. Indeed can have this in pelvic inflammatory disease.

Isolated Psammoma Body in Node

In the neck it means there is thyroid papillary carcinoma in that patient and it has spread to the node.

Hunt and Barnes AJCP 2003

The Problem of Extranodal Extension of Tumor
Fig. 2. Recurrence-free survival according to lymph node status at the time of diagnosis (n = 161) (where \( P = 0.0000 \approx P < 0.00005 \)).

Significant assoc. between 10-yr RFS & extranodal tumor growth

RESULTS

Overall intraclass correlation coefficient (ICC)

ETE: 20%
ENE: 39%

NODAL STATUS

THE CHANGING PERCENTAGE OF TUMOR SUBTYPE
In some types of papillary carcinoma, the percentage of histologic type in the node is different from that in the gland.

Most common is percent of follicular pattern:
- May be follicular in node and papillary or mixed in primary
- May be papillary or mixed in node and overwhelmingly follicular in primary

**MAKES NO PROGNOSTIC DIFFERENCE**

In some types of papillary carcinoma, the percentage of histologic type in the node is different from that in the gland.

- In tall cell histology, often find small percent in primary and larger percentage of tall cell pattern in nodal mets.
- This portends that in some cases, the tall cell clone will take over as additional mets become evident and the tumor then will behave as tall cell variant.

**SO MAKES PROGNOSTIC DIFFERENCE**

**THE FACTORS**

- Tumor stage—extent
- Tumor subtype
- Vascular/lymphatic invasion
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- **Molecular characteristics**
- Important clues
MOLECULAR BIOLOGY

- Braf, Nras, Pax8/PPAR gamma, Ret/PTC

- DO ANY OF THEM MATTER?

- IN EARLY STAGE LESIONS?

MOLECULAR FEATURES

- **IMPORTANCE DIAGNOSTICALLY**
  
  - **Braf** mutation in an FNA sample if positive means with almost if not always 100% of cases THIS IS **PAPILLARY CARCINOMA**.
  
  - Similarly ret/PTC rearrangement (although some small percentage may not be cancer (thyroiditis)
  
  - For Pax8/PPAR gamma translocation not absolute since can see in benign nodules.

MOLECULAR FEATURES

- **IMPORTANCE DIAGNOSTICALLY**
  
  - Ras mutations can be found in histologically benign nodules.

  DOES THIS EQUATE WITH NONINVASIVE CARCINOMA—CARCINOMA IN SITU???
MOLECULAR FEATURES

IMPORTANCE PROGNOSTICALLY
• Braf mutation in a thyroid papillary carcinoma.
  1. Should this influence the initial surgery done?
  2. Should this influence postop treatment?
  3. Does this predict the prognosis.

IMPORTANCE PROGNOSTICALLY
• Braf mutation
  Literature debate: Some claim Braf positivity is an independent poor prognostic indicator.
  Others deny it.
  Xing M et al JAMA 2013

Braf mutation
• Xing et al support an important biological role for BRAF V600E in promoting aggressive tumor behavior.
• BUT
  • When extrathyroidal invasion, lymph node metastases, and distant metastases are taken into account, BRAF V600E status was no longer independently associated with mortality.
  
  Cappella and Mandel JAMA 2013.
In early stage (I and II) PTC
If adequate pathology evaluation, probably not.
What do you do if pathology features aggressive, but Braf negative??

Newer data suggests Braf mutation alone not enough to adversely influence prognosis, but if also TERT or p53 mutations –significantly affect outlook.

Tumor stage—extent
Tumor subtype
Vascular/lymphatic invasion
Nodal status
Molecular characteristics
Important clues to genetic/familial disease
CRIBRIFORM MORULAR VARIANT

- Needs to be recognized because of association with **FAMILIAL ADENOMATOUS POLYPOSIS**
- Therefore risk of GI adenocarcinoma.
MULTIPLE ONCOCYTIC NODULES (SOME NEOPLASTIC—BENIGN OR MALIGNANT)

COWDEN SYNDROME
- Risk of breast, endometrial and other cancers
- Germline mutations in PTEN

HOWEVER, HISTOLOGY NOT SPECIFIC

MEDULLARY CARCINOMA
- IF YOUNG PATIENT, IF MULTIFOCAL, IF CELL HYPERPLASIA

THINK FAMILIAL MEDULLARY CARCINOMA, and MEN 2.
AMYLOID Pro-calcitonin

CCH

CLUES TO GENETIC DISEASE
- Young patients, some pediatric age group
- Positive family history
- Multifocal lesions
- Bilateral lesions
- Often precursor pathologic lesion
- May have evidence of other syndrome lesions.
THE FACTORS

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QUESTIONS??