ENCAPSULATED CARCINOMA OF FOLLICULAR CELL ORIGIN

by

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Encapsulated carcinoma of follicular cell origin

- Papillary thyroid carcinoma, follicular variant
- Papillary thyroid carcinoma, classical type
- Follicular and Hurthle cell (oncocytic) carcinoma
- Poorly differentiated thyroid carcinoma
- Anaplastic carcinomas
Our focus today

- Encapsulated papillary thyroid carcinoma, follicular variant.

- Encapsulated follicular carcinoma and Hurthle cell (oncocytic) carcinoma
SOME IMPORTANT LIMITATIONS OF THE CURRENT CLASSIFICATIONS OF THYROID CARCINOMAS

• Encapsulated follicular variant of papillary carcinoma: controversial at the diagnostic and prognostic level.

• The concept of minimally invasive Follicular/Hurthle cell carcinoma still poorly defined, vague.
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

• A PROBLEMATIC AND CONTROVERSIAL ENTITY.
Papillary Carcinoma
Follicular variant (Modern definition)

- Subset of papillary carcinoma entirely or almost completely composed of follicles lined by cells having the nuclear features of papillary carcinoma.
“NUCLEAR FEATURES ARE EVERYTHING”

- Clear nuclei, grooves, pseudoinclusions

- NUCLEAR FEATURES ALONE DIAGNOSTIC OF PAPILLARY CARCINOMA FOLLICULAR VARIANT EVEN IN THE TOTAL ABSENCE OF INVASION
Spectrum of nuclear changes in follicular lesions

Follicular adenoma

Follicular variant
INTEROBSERVER VARIABILITY
(Lloyd et al. Am J Surg Path)

87 cases from Mayo clinic were reviewed by 8 pathologists with > 10 years experience in endocrine pathology.

- Cases diagnosed as follicular variant ranged from 57.5 to 100%
- ONLY 50.6% were diagnosed as follicular variant by ALL pathologists.
- Of 21 patients with follicular variant and metastatic disease, a BENIGN diagnosis was made in 3 cases.
## INTRAOBSERVER AGREEMENT AMONG EXPERTS

<table>
<thead>
<tr>
<th>EXPERT</th>
<th>Agreement Follicular variant Dx:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4/7 (57%)</td>
</tr>
<tr>
<td>2</td>
<td>6/7 (86%)</td>
</tr>
<tr>
<td>3</td>
<td>11/12 (92%)</td>
</tr>
<tr>
<td>4</td>
<td>1/6 (17%)</td>
</tr>
<tr>
<td>5</td>
<td>14/14 (100%)</td>
</tr>
<tr>
<td>6</td>
<td>1/2 (50%)</td>
</tr>
</tbody>
</table>

IMMUNOHISTOCHEMISTRY

Aimed at differentiating it from follicular adenoma

- Cytokeratin 19
- Galectin 3, 7.
- Leu 7
- Thyroid peroxidase
- CD 10 promising according to 1 report
- HBME-1
**Helpful:** Marker of papillary carcinoma, follicular variant but not follicular adenoma in some studies.

(Cheung CC et al. *Mod Pathol* 14:338342, 2001)

**Not helpful:** Found in follicular adenomas and papillary carcinoma, follicular variant.

Galectin-3

- Lectin involved in cell-cell and cell-matrix interactions

- **HELPFUL:** Differentiate between minimally invasive follicular carcinomas (94%) and adenomas (8%) on FNA.


- **NOT HELPFUL:** stains only 47% of encapsulated papillary carcinoma follicular variant.

Follicular adenoma

Hurthle cell adenoma

Follicular carcinoma

Galectin-3 immunostaining
HBME-1

- Mesothelioma marker

- **Helpful:** Highly specific (90%) with low sensitivity in the diagnosis of follicular patterned carcinomas (61%).
  Prasad ML et al. *Mod Pathol* 18:48-57, 2005

- **Not that helpful:** 84% of follicular variant and 55% of follicular adenoma.
  de Matos PS et al. *Histopathology* 47:391-401, 2005
Hyperplastic follicular lesion

Relatively small round nuclei
FALSE POSITIVE HBME-1 STAIN OF HYPERPLASTIC FOLLICLE

Membranous staining supposedly specific
Combination of immunohistochemical markers in FNA

- **Helpful**: Galectin 3 and HBME-1 have a positive predictive value of 100% and a negative predictive value of 94%.
  
  Rossi ED et al. *Histopathology* 006;48:795-800.

- **Not helpful**: Galectin 3 and HBME-1 have no practical value in the diagnosis of borderline follicular tumors (tissue sections).

The case *FOR* immunohistochemical markers

- *Helpful* if multiple markers used.

- *Helpful* if interpretation performed in the context of tumor’s morphology.
The case AGAINST immunohistochemical markers

- Very good for classical papillary carcinoma (but we do not need them) Do not stratify patients.

- Add very little to follicular patterned lesions

- Can be dangerous IN FNA AND EVEN IN TISSUE SECTIONS SINCE THEY STAIN THYROIDITIS, REACTIVE CELLS IN FNA SITES
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

• A CONTROVERSIAL ENTITY AS TO ITS BEHAVIOR
Papillary Carcinoma Follicular Variant

**SUBVARIANTS**

- Encapsulated
- Infiltrative
- Multinodular

Problematic, most common

Original description, 1977
• DO ALL THESE FOLLICULAR VARIANT SUBTYPES BELONG TO THE PAPILLARY THYROID CARCINOMA CLASS OF TUMORS?
Mitogen-activated protein kinase (MAPK) pathway is activated in thyroid carcinoma.
Mitogen-activated protein kinase (MAPK) pathway is **activated** in thyroid carcinoma.
1) Correlate with histiotype
2) little overlap

RET/PTC

Y905 → Grb7/10

Y1015 → PLC_ → PKC

Grb2

SOS

RAL-GDS

BRAF

MEK

ERK

PI3-K

Papillary carcinoma

Papillary carcinoma

Foll adenoma/ca
<table>
<thead>
<tr>
<th></th>
<th>Foll Variant</th>
<th>Follicular Adenoma/ Ca</th>
<th>Classical Pap</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET/PTC</td>
<td>3%</td>
<td>0%</td>
<td>28%</td>
</tr>
<tr>
<td>RAS</td>
<td>40%</td>
<td>24-50%</td>
<td>0%</td>
</tr>
<tr>
<td>BRAF</td>
<td>3%</td>
<td>0%</td>
<td>53%</td>
</tr>
</tbody>
</table>

*Nikiforov group*
The Cancer Genome Atlas
mRNA clusters in papillary ca correlate with histo subtype

mRNA seq subtype 1  mRNA seq subtype 2  mRNA seq subtype 3  mRNA seq subtype 4

Follicular variant  Classical  Tall
The Cancer Genome Atlas

Methylated genes clusters in papillary ca correlate with histo subtype

- Methylation subtype 1
- Methylation subtype 2
- Methylation subtype 3

**Diagram:**
*HISTOLOGICAL.TYPE*

- Follicular variant
- Classical
- Tall

Chi-square test P = 9.77e-10
The Cancer Genome Atlas
microRNA clusters in papillary ca correlate with histo subtype

miR seq subtype 1

miR seq subtype 2

miR seq subtype 3

Follicular variant

Classical

Tall

Chi-square test $P = 1.05e-14$
Molecular Findings

• Molecular profile of Follicular Variant much closer to Follicular Adenoma and Carcinoma than to Classical papillary Carcinoma.
Follicular variant of papillary thyroid carcinomas: a clinicopathologic study of a problematic entity.

Jeffrey Liu MD, Bhuvanesh Singh MD, PhD
Giovanni Tallini MD, Diane L. Carlson MD, Nora Katabi MD, Ashok Shaha MD, R. Michael Tuttle MD, Ronald A. Ghossein MD.

Cancer. 2006, 107:1255-64.
MSKCC STUDY

• Detailed microscopic review of all cases between 1980-1995 labeled:
  - Follicular variant papillary carcinoma
  - Follicular adenoma
  - Follicular carcinoma
MSKCC STUDY
INCLUSION CRITERIA

• Follicular variant of papillary carcinoma as defined by AFIP fascicle.

• >= 1 CM

• No more than 2 additional foci of microcarcinomas
ENCAPSULATED FOLLICULAR VARIANT
INFILTRATIVE FOLLICULAR VARIANT
Infiltrative follicular variant
78 cases fulfilling MSKCC study criteria

- ENCAPSULATED follicular variant: 61
  - Without invasion: 43
  - Invasive: 18

- Diffuse/infiltrative: 17 *

- Total: 78

* Incidence similar to Rosai 1977 paper.
## Follicular Variant MSKCC Study All cases

<table>
<thead>
<tr>
<th></th>
<th>Encapsulated</th>
<th>Non-encapsulated</th>
<th><em>p</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median size:</strong></td>
<td>2.5 cm</td>
<td>2.3 cm</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Female:</strong></td>
<td>80%</td>
<td>59%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Median age:</strong></td>
<td>40.7 yrs</td>
<td>43.0 yrs</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Encapsulated</td>
<td>Non-encapsulated</td>
<td>( p )</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------</td>
<td>------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Marked fibrosis:</td>
<td>18%</td>
<td>88%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LN met:</td>
<td>5%</td>
<td>65%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Extra-thyroid extension:</td>
<td>5%</td>
<td>65%</td>
<td>&lt;0.0001</td>
</tr>
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</table>
69 cases with adequate FU  
MSKCC study 1980-1995  
(Median follow up 10.8 years)

<table>
<thead>
<tr>
<th>SUBTYPE</th>
<th>(n)</th>
<th>REC/AWD/DOD (%)</th>
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<tbody>
<tr>
<td><strong>Encapsulated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>without invasion:</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>with invasion:</td>
<td>13</td>
<td>1REC (8%)</td>
</tr>
<tr>
<td><strong>Infiltrative/Diffuse</strong></td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>
ENCAPSULATED FOLLICULAR VARIANT WITHOUT INVASION TREATED BY LOBECTOMY ALONE

- 31 treated by LOBECTOMY and no RAI

- No Recurrence and No lymph node metastasis.

- Median FU: 11.1 years

- Median size: 2.3 cm

- Median age: 43.4
Encapsulated Follicular variant (n=83) vs Follicular adenoma (n=52) vs follicular carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Encapsulated follicular variant non-invasive (n=57)</th>
<th>Follicular adenoma (n=52)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients %</td>
<td>No of patients %</td>
<td></td>
</tr>
<tr>
<td>Nodal/distant Metastasis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>0 0</td>
<td>0 0</td>
<td>1</td>
</tr>
<tr>
<td>Absent</td>
<td>57 100</td>
<td>52 100</td>
<td></td>
</tr>
<tr>
<td>Thyroidectomy</td>
<td></td>
<td></td>
<td>0.0003</td>
</tr>
<tr>
<td>&lt;total</td>
<td>39 68</td>
<td>49 94</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>18 32</td>
<td>3 6</td>
<td></td>
</tr>
<tr>
<td>RAI therapy:</td>
<td></td>
<td></td>
<td>0.0002</td>
</tr>
<tr>
<td>Administered</td>
<td>13 23</td>
<td>0 0</td>
<td></td>
</tr>
<tr>
<td>Not given</td>
<td>44 77</td>
<td>52 100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Encapsulated follicular variant non-invasive (n=57)</td>
<td>Follicular adenoma (n=52)</td>
<td>P value</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------------------------------------</td>
<td>---------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>No of patients</td>
<td>%</td>
<td>No of patients</td>
<td>%</td>
</tr>
<tr>
<td><strong>Recurrence:</strong></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Present</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>56</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td><strong>Status at last follow up:</strong></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>AWD/DOD</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>NED</td>
<td>56</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td><strong>Follow up (years):</strong></td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>9.5</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.2-27</td>
<td>0.25-18.6</td>
<td></td>
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</table>
ENCAPSULATED NON-INVASIVE FOLLICULAR VARIANT WITHOUT ADJUVANT RADIOACTIVE IODINE THERAPY (n=39)

- Median follow up (range): 10.5 yrs (0.2-27)
- Median tumor size (range): 2.9 cm (1.1-5.6)
- Median age (range): 48 yrs (26-78)
- Node/distant metastasis: None
- Recurrence: None
<table>
<thead>
<tr>
<th></th>
<th>Encapsulated follicular variant invasive (n=26)</th>
<th>Follicular carcinoma (n=14)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant Metastasis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>4 (at presentation)</td>
<td>0</td>
<td>0.28</td>
</tr>
<tr>
<td>Absent</td>
<td>22</td>
<td>14</td>
<td>100</td>
</tr>
<tr>
<td>Thyroidectomy</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>&lt;total</td>
<td>14</td>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>RAI therapy:</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Administered</td>
<td>8</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>Not given</td>
<td>18</td>
<td>10</td>
<td>71</td>
</tr>
</tbody>
</table>
Encapsulated follicular variant metastatic to rib without nodal metastasis

Vascular invasion

Rib met
# Encapsulated follicular variant PTC and outcome

<table>
<thead>
<tr>
<th>Reference</th>
<th>Invasion (No of pts)</th>
<th>Nodal met (No pts)</th>
<th>Follow up (yrs)</th>
<th>End point</th>
<th>Outcome (No of pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baloch, Livolsi (2000)</td>
<td>- Invasive (n=4)</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>Bone met (n=4)</td>
</tr>
<tr>
<td></td>
<td>- non-invasive, n=1 (? entirely examined)</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>Bone met (n=1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>NA</td>
<td>DOD</td>
<td>0/45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>NA</td>
<td>DOD</td>
<td>0/21</td>
</tr>
<tr>
<td>Piana (2010)</td>
<td>Non-invasive (n=45)</td>
<td>NA</td>
<td>NA</td>
<td>DOD</td>
<td>0/45</td>
</tr>
<tr>
<td></td>
<td>Invasive (n=21)</td>
<td>NA</td>
<td>NA</td>
<td>DOD</td>
<td>0/21</td>
</tr>
<tr>
<td>Barletta (2013)</td>
<td>Invasive (n=10)</td>
<td>0</td>
<td>median: 9.5</td>
<td>Rec (clinical)</td>
<td>0/10 1*/43 (2%)</td>
</tr>
<tr>
<td></td>
<td>Non-invasive (n=43)</td>
<td>0</td>
<td>Median: 5.8</td>
<td>Rec (clin/bioc hemical)</td>
<td>0/57 (No RAI)</td>
</tr>
<tr>
<td>Rosario (2013)</td>
<td>Non-invasive (n=57)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Tumor bed recurrence, positive margin
Molecular genotyping of Follicular variant according to its subtypes (Memorial Hospital).

- 28 encapsulated
- 19 infiltrative

MOLECULAR GENOTYPING OF FOLLICULAR VARIANT ACCORDING TO ITS SUBTYPES (paraffin tissue)

- Multiplexed Sequenom mass spectrometry-based mutation assay for 111 mutations.


- RT PCR screening for **RET/PTC** and **PAX8-PPAR gamma**
## Follicular Variant Molecular genotyping study

<table>
<thead>
<tr>
<th></th>
<th>Encapsulated (n=28)</th>
<th>Infiltrative (n=19)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF V600E:</strong></td>
<td>0</td>
<td>5 (26%)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>RAS</strong></td>
<td>10 (36%)</td>
<td>2 (10%)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>RET/PTC</strong></td>
<td>0</td>
<td>2 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>PAX8-PPARg</strong></td>
<td>1 (4%)</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>
Follicular variant of papillary carcinoma

- Encapsulated Non-invasive cases have an extremely low recurrence rate.

- Metastatic nodal pattern:
  - Encapsulated follicular variant close to follicular carcinoma
  - Infiltrative /diffuse close to classical papillary

- Molecular profile:
  - Encapsulated follicular variant similar to follicular adenoma/ carcinoma.
  - Infiltrative follicular variant close to classical papillary.
Relationship between papillary carcinoma (PTC), follicular variant of papillary carcinoma (FVPTC), follicular adenoma/carcinoma (FA/FTC)

Old concept:
- PTC
- FVPTC

New concept:
- Classical PTC
- FVPTC
- FA/FTC

Infiltrative/diffuse FVPTC
Encapsulated FVPTC
Reclassification of the encapsulated follicular variant as a close entity to the Follicular adenoma/carcinoma group

- *Semantics aside*, encapsulated follicular variant without invasion will be treated by lobectomy alone (like adenomas) even in the presence of adverse prognostic factors (>45 yrs, >4 cm).
Reclassification of the encapsulated follicular variant as a close entity to the Follicular adenoma/carcinoma group

Countless number of patients with non-invasive follicular variant will be spared unnecessary therapy with its attached morbidity, financial costs and the psychological impact of “a clinical cancer” diagnosis.
April 13, 2006
Second Opinion
Memorial Sloan Kettering
Department of Pathology
1275 York Avenue
New York, New York 10021

Dear Second Opinion:

Enclosed are the pathology report(s) you have requested as well as the following:

Patient Name:

RS06-4098 1 Slide

ZD:ks > > > > > Fed Ex

Please return these slides/blocks. It is original material and as such is the permanent record of this patient.

HOPEFULLY, MUCH LESS OF THAT STUFF...
• HOW CAN WE SPREAD THIS CONCEPT?
OBSTACLES FROM

- Endocrinologists who think RAI is “water”.
- Surgeons who overtreat microcarcinomas
- Expert pathologists who fail to communicate the extremely indolent nature of the non-invasive encapsulated follicular variant.
In practice

- We still have to call these lesions encapsulated follicular variant of papillary carcinoma but stress their extremely indolent behavior if non-invasive...

- Until we reclassify the follicular variant (March 2015) ..
STRATIFICATION OF PATIENTS WITH FOLLICULAR AND HURTHLE CELL CARCINOMA.
FOLLICULAR CARCINOMA AND ITS VARIANTS.

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

• Criteria for capsular and lymphovascular invasion controversial.

• Definition of minimally invasive carcinoma controversial.
Capsular invasion

Follicular neoplasm

Fibrous capsule

Not yet (B)

Yes (C)

No (A)

Yes (H)

Not yet (I)

Yes (D)

No (J)

Yes (E)

Not yet (F)

No (G)

Chan JKC
Vascular invasion

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

Follicular neoplasm
Capsule

Chan JK
WIDELY INVASIVE FOLLICULAR 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 follicular carcinoma, oncocytic variant

Multinodular invasive growth pattern

Extra-thyroid vascular invasion
THE PROBLEM

• VARIOUS DEFINITIONS USED FOR MINIMALLY INVASIVE FOLLICULAR CARCINOMA.
Why is it clinically important?

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

- “Small” encapsulated follicular carcinoma with capsular invasion only or focal vascular invasion may not require RAI.

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

National Comprehensive Cancer Network guidelines 2012

- Lobectomy
  - Invasive follicular cancer (extensive angioinvasion)
    - Completion Thyroidectomy/RAI
  - Minimally invasive follicular cancer (micro capsular and/or a few foci of vascular invasion)
    - Completion Thyroidectomy/RAI
    - Or
    - Observe
All Well defined grossly encapsulated follicular 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 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)

- 1-2 foci of capsular invasion: Minimally invasive (Low risk)
- > 4 foci of vascular invasion: Encapsulated follicular carcinoma with extensive vascular invasion (High risk)
- In between (e.g. 3 capsular, 1 vascular): Encapsulated follicular carcinoma with xx foci of capsular/vascular invasion (no recurrence but small number of cases)
Relapse free survival (RFS) according to number of foci of vascular invasion in encapsulated follicular carcinoma, oncocytic variant

Follow-up Interval (Months)

Proportion Surviving Free of Relapse

<4 foci
5-year RFS = 100%

>=4 foci
5-year RFS = 20%

p<0.0001

Extent of vascular invasion (VI) and recurrence free survival in encapsulated PTC, follicular carcinoma, Hurthle cell carcinoma (N=267) 
Median follow up: 6 years
In 1986, Dr Lang stated that \( \geq 5 \) foci of vascular invasion defines widely invasive follicular carcinoma but his article was dismissed (arbitrary).

44 yrs old male with a 4 cm encapsulated Hurthle cell carcinoma
Vascular invasion (7 foci)
Vascular invasion (7 foci)

Endothelial cells covering tumor thrombus
Outcome

• Recurred in cervical and mediastinal nodes 3 years after diagnosis

• Developed lung and bone metastasis

• Alive with disease 8.4 years after diagnosis
Molecular characterization of Hurthle cell carcinoma (MSKCC)

- Ian Ganly, Julio Ricarte Filho, Stephanie Eng, Rony Ghossein, Luc G.T. Morris, Yupu Liang, Nicholas Socci, Kasthuri Kannan, Qianxing Mo, James Fagin, Timothy A. Chan.

Histlogic stratification of Hurthle cell tumors for MSKCC molecular study

- **Hurthle cell adenoma**: No capsular invasion (CI) or vascular invasion (VI)
- **Minimally invasive Hurthle cell ca**: Encapsulated tumor with <4 foci of VI, no gross invasion, no extra-thyroid VI
- **Widely invasive Hurthle cell ca**: Encapsulated tumor with >=4 foci of VI, gross invasion, or extra-thyroid VI
Genetic alterations of Hurthle cell carcinomas vs other thyroid cancers

<table>
<thead>
<tr>
<th>Gene</th>
<th>Prevalence stratified by thyroid histology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PTC</td>
</tr>
<tr>
<td>RET point mutation</td>
<td>0%</td>
</tr>
<tr>
<td>RET rearrangements</td>
<td></td>
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<td></td>
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<tr>
<td></td>
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</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>
</tr>
</tbody>
</table>

PTC-papillary thyroid cancer
FTC-follicular thyroid cancer
PDTC-poorly differentiated thyroid cancer
ATC-anaplastic thyroid cancer
Chromosomal regions of gain and loss in papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) and Hurthle cell carcinoma (HCC)

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>PTC*</th>
<th>FTC**</th>
<th>HCC</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td>1p33-36</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2q21-24</td>
<td>1q</td>
<td>1p</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>4p16</td>
<td>4q24</td>
</tr>
<tr>
<td>4</td>
<td>4q11-26</td>
<td>5q15-5q35</td>
<td>6p23,6q26</td>
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<tr>
<td>5</td>
<td>5q14-21</td>
<td>5p16</td>
<td>6p23,6q26</td>
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<tr>
<td>6</td>
<td>6q11-22</td>
<td>6q12</td>
<td>6p23,6q26</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>7p15-7q36</td>
<td>7p15</td>
</tr>
<tr>
<td>8</td>
<td>8q21-23</td>
<td>7p15-7q36</td>
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<td>9</td>
<td>9q34</td>
<td>9q13-q21.3</td>
<td>9q33</td>
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<td>12</td>
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<tr>
<td>13</td>
<td>13q21-31</td>
<td>13q</td>
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<td>16</td>
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References


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**Frisk T et al. Low frequency of numerical chromosomal aberrations in follicular thyroid tumors detected by comparative genomic hybridization. Genes Chromosomes Cancer
Gene expression profiling of Hurthle cell tumors

Adenoma/Minimally invasive carcinoma ≠ Widely/extensively Angioinvasive carcinoma
Tumor type and recurrence free survival in encapsulated PTC, follicular carcinomas and Hurthle cell carcinoma (N=267).

Median follow up: 6 years
RAI(+) Distant Mets BY HISTOLOGY (Tala, Tuttle, et al)

- All patients
- Confirmed Histology
Follicular/Hurthle cell carcinoma

- Encapsulated follicular/Hurthle cell carcinoma with extensive angioinvasion should **NOT** be labeled minimally invasive.

- The extent of capsular and especially vascular invasion should be mentioned (focal, extensive).
Follicular/Hurthle cell carcinoma

**Extensive vascular invasion:** Worse outcome.
Aggressive Therapy.

**Focal vascular invasion:** probably minimal risk?
Therapy?
Is 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.
• Molecular findings can help us indirectly re-classify histologically tumors into **clinically relevant entities**

• A detailed histopathologic report (proliferative grading, microstaging) is a must and **clinically useful**.
THE END
Minimally invasive Hurthle cell carcinoma: <4 foci of VI

Widely Invasive/extensively angioinvasive HCC: >4 foci of VI, gross invasion, extra-thyroid VI