MICROCARCINOMA OF THYROID

PAPILLARY; MEDULLARY
MICROCARCINOMA OF THYROID

DEFINITION BY SIZE

○ Most < 1 cm
○ (some up to 1.5 cm)

○ “OCCULT” carcinoma designation
MICROCARCINOMA OF THYROID

DIAGNOSIS BY CYTOLOGY
It is possible.
Both medullary and papillary microcancers can be diagnosed.
Some may be clinically significant—about 10%.

Yang et al (2002)
MICROCARCINOMA OF THYROID

DIAGNOSIS BY CYTOLOGY

Limits include:
Lesion size
Lesion location
Quality of ultrasound equipment
Ability and experience of “biopsier”
MICROCARCINOMA OF THYROID

PAPILLARY
MICROCARCINOMA OF THYROID

PAPILLARY

- AUTOPSY
- SURGERY
  - INCIDENTAL
  - PRIMARY
MICROCARCINOMA OF THYROID

PAPILLARY

AUTOPSY

- 3-36% of adults
- Not age dependent
- Care of examination
- Geography differences
MICROCARCINOMA OF THYROID

PAPILLARY-SURGICAL

INCIDENCE: 24-38%

NTNG, CLT, Benign nodule

Care with which gland examined

No relationship with age.
MICROCARCINOMA OF THYROID

PAPILLARY

○ INCIDENTAL

- IF SOLITARY, NO FURTHER THERAPY
MICROCARCINOMA OF THYROID

PAPILLARY

QUESTION:

WHAT IF MULTIPLE FOCl?

SIZE CRITERION-1 cm
MICROCARCINOMA OF THYROID

● PAPILLARY

○ QUESTION:

○ WHAT IF INVOLVES THYROID “CAPSULE”?
MICROCARCINOMA OF THYROID

PAPILLARY-SURGICAL PRIMARY TO METASTASIS

TREAT LIKE CLINICAL PAPILLARY CANCER
MICROCARCINOMA OF THYROID

PAPILLARY

QUESTION:
Will it grow up to be clinical cancer?
MICROCARCINOMA OF THYROID

PAPILLARY

Molecular analysis shows microcarcinomas have similar genetic changes as clinical cancers

Hunt et al 2002
MICROCARCINOMA OF THYROID

PAPILLARY

QUESTION:
Why do they remain micro in size?

HYPOTHESIS (Folkman): lack of angiogenesis.
MICROCARCINOMA OF THYROID

PAPILLARY

QUESTION:
WHY do some metastasize to lymph nodes?
Clinical presentation.
MICROCARCINOMA OF THYROID

PAPILLARY

ACCESS TO LYMPHATICS
EARLY ON.

German study 1995 difference of interaction of papillary versus follicular carcinoma and vascular endothelium.
MICROCARCINOMA OF THYROID

PAPILLARY

MICROCARCINOMA—METASTASIZE---REGRESSION?
MICROCARCINOMA OF THYROID

- A rare phenomenon is the presence of thyroid carcinoma, usually lowgrade and papillary with no primary identified in the gland.
- Series from MSKCC described 7 cases, of which five had fibrosis or scars in the gland.
- All cases with PTC were NED.
- So if find only psammoma bodies or only a scar, this may mean total involution of the primary.

Xu et al Human Pathol 2017.

MSKCC series 2017
MICROCARCINOMA OF THYROID

The PROBLEMATIC PSAMMOMA BODY

In gland, often in lymphatics. These are “ghosts of dead papillae” so this means viable tumor at some point was in lymphatics. On occasion may see viable tumor associated with psammoma bodies.
MICROCARCINOMA OF THYROID

The PROBLEMATIC PSAMMOMA BODY

In lymph nodes, this represents metastasis even if no viable tumor.

Rare to see nodal mets if no psammoma bodies in tumor or in thyroid lymphatics.
MICROCARCINOMA OF THYROID

PAPILLARY

LATERAL ABERRANT THYROID
  In lymph node
  Outside of lymph node
MICROCARCINOMA OF THYROID

MEDIAL THYROID IN NODES

IS it ALWAYS metastasis?

Criteria for those who believe it is benign:

- Only in capsule of node
- Totally follicular pattern
- No nuclear change
- No psammoma bodies
MICROCARCINOMA OF THYROID

PAPILLARY

QUESTIONS REMAINING:

- Multifocality—intraglandular lymphatic spread—
- In macro cancer: YES/ ? Independent
- In microcancer: independent primaries (Asa et al 1999 *ret/ptc*)
MICROCARCINOMA OF THYROID

PAPILLARY

QUESTIONS REMAINING:

MICROCARCINOMA IN CHILDREN—SIZE CRITERION
(Williams, ED. for Chernobyl panel 2001)
MICROCARCINOMA OF THYROID

- PAPILLARY
  - QUESTIONS REMAINING

- WHAT ABOUT MOLECULAR TESTING

- CAN THIS PREDICT AGGRESSIVE BEHAVIOR IN mPTC?
MICROCARCINOMA OF THYROID

- BRAF mutation
- Some claim that those microcarcinomas that will behave “badly” will have mutation (>70% v. 32%) (Pitt)
- Others claim that only mptc that do badly are those that have aggressive histology or large nodal metastases.
MICROCARCINOMA OF THYROID

Combined MOLECULAR- PATHOLOGIC SCORE to predict tumor aggressiveness in mptc (Nemeier et al Cancer 2012)

HISTOLOGIC FEATURES:
Superficial location
Intraglandular spread;
Tumor fibrosis

AND Braf mutation
MICROCARCINOMA OF THYROID

SCORING SYSTEM
MP SCORE  Low, intermediate and high risk---

0%, 20% and 60% for regional node mets and/or recurrence.
THE CONCEPT OF ACTIVE SURVEILLANCE
Asian endocrinologists began the concept of watchful waiting for mptc discovered incidentally on US and undergoing FNA for diagnosis. With patient consent, they were and are followed with yearly US. The great majority do not change and surgery is avoided.
MICROCARCINOMA OF THYROID

ACTIVE SURVEILLANCE

In US, some institutions are following this approach with full patient consent and cooperation. It seems that these tiny lesions either do not grow or grow so slowly that they appear clinically and prognostically irrelevant.

In large Japanese study only 7% of patients had progression.
MICROCARCINOMA OF THYROID

FROZEN SECTION
Dr. LiVolsi,

I am an endocrinologist practicing in ______ and I have an 18 year old female patient who had a thyroid lobectomy for a “follicular adenoma”. The surgeon sent the lobe for frozen section and the pathologist saw a 4 mm subcapsular white nodule. He froze this; the diagnosis was deferred; now there is nothing
mPTC and FROZEN SECTION

left of the lesion for permanent sections.

Although I have never heard of you, my colleague thought you might look at the available slides and help my young patient with a definitive diagnosis.

Can I send you the slides?
mPTC and FROZEN SECTION

This is one of three cases I have seen in the past three years wherein subcentimeter nodules have been identified on intraoperative examination by the pathologist and subjected to frozen section. In all three, an definite diagnosis was never made.
WARNING!!!

- Lesional tissue may *disappear* on permanent sections and if tissue remains, *artifact* of freezing destroys nuclear morphology and you may never reach a definitive diagnosis. **Do not freeze subcentimeter nodules**
mPTC and FROZEN SECTION

If you deal with insistent surgeons, and you feel comfortable with cytology specimens, intraop cytology could be a diagnostic modality and will preserve the tissue for good permanent sections without artifacts.

In addition, making a diagnosis of an incidental mPTC intraoperatively may lead to **OVERTREATMENT** (ie, completion thyroidectomy) which is not needed.
mPTC and FROZEN SECTION

The AAES is preparing a “white paper” of guidelines for thyroidectomy in all types of thyroid lesions and they are recommending against frozen section for any intrathyroidal nodule.
MICROCARCINOMA OF THYROID

MEDULLARY
MICROCARCINOMA OF THYROID

DIAGNOSIS BY CYTOLOGY

It is possible.

Both medullary and papillary microcancers can be diagnosed.

Take care when making cytology diagnosis of MTC. Unless known familial or known germline mutation, ask for serum calcitonin before definite diagnosis.
MICROMEDULLARY CARCINOMA

Can occur in

Familial setting

Sporadic setting
MICROMEDULLARY CARCINOMA

Can occur in

Familial setting

Sporadic setting
MICROMEDULLARY CARCINOMA

Defined as 1 cm or less.

Often found in prophylactic thyroidectomies for family members with known germline mutations in ret protoncogene.

Usually multifocal, bilateral and associated with CCH.
MICROMEDULLARY CARCINOMA

In these cases, CCH is obvious even on H&E stains, often showing atypia.
THYROID TUMORS IN FAMILIAL SYNDROMES

Familial adenomatous polyposis (Gardner syndrome): cribriform morular variant of PTC, colonic, duodenal adenomas/carcinomas, fundic gland polyps with dysplasia, abdominal fibromatosis. (Gene: APC, Wnt pathway)

Multiple endocrine neoplasia, Type 1 (Wermer syndrome): follicular adenomas, pituitary tumors, parathyroid hyperplasia, pancreatic neuroendocrine tumors adrenal cortical lesions. Gene: Menin
THYROID TUMORS IN FAMILIAL SYNDROMES

Multiple endocrine neoplasia, Type 2A (Sipple syndrome): medullary thyroid carcinoma and CCH, parathyroid lesions, pheochromocytomas and AMH. Gene: Ret (various codons)

Multiple endocrine neoplasia, Type 2B (or 3): medullary thyroid carcinoma and CCH, pheochromocytomas and AMH, neuromas of oral areas and GI tract, skeletal and eye lens abnormalities. Gene: Ret (codon 918-(95%))
MICROMEDULLARY CARCINOMA

Can occur in

Familial setting

Sporadic setting
MICROMEDULLARY CARCINOMA

In Sporadic cases,

Usually unifocal

No CCH

Probably prognostically equivalent to mPTC.
MICROMEDULLARY CARCINOMA

1 cm or less
Obscures follicles
Irregular outline
Sclerosis
+/- amyloid
Neuroendocrine nuclei
MICROMEDULLARY CARCINOMA
THYROID

Remember:

In both familial and sporadic cases, once you have a mmtc it can metastasize to nodes.

A family anecdote----
Some endocrinologists believe that any diagnosis of MTC (even solitary and microscopic) requires genetic testing.

Some pathologists believe immunostaining for calcitonin to define C cell mass is needed.
Problem is that many apparently sporadic mmtc occur in older individuals (over 55) and without a family history of endocrine disorders. So genetic testing may be overkill.
MICROMEDULLARY CARCINOMA

In Sporadic cases,

However, many endocrinologists will suggest genetic testing of patients with mMTC. In our experience, patients who acquiesce to testing have always been negative.
MICROMEDULLARY CARCINOMA

For pathologic immunostains to assess C cell mass, the definition of C cell hyperplasia remains problematic. So this too may be overkill in terms of cost and resources expended.
MICROMEDULLARY CARCINOMA

Literature data suggests that MMTC of 0.5 cm or less is not associated with any clinical consequence.
However 22% of patients with tumors of size 5-10 mm may be associated with micrometastases to nodes.
C Cell Hyperplasia

Classified as

**primary** (associated with MEN2 syndromes);

**secondary** (associated with hypercalcemia, hypergastrinemia, Hashimoto)
C Cell Hyperplasia

“Neoplastic CCH” (MEN2 associated C-cell proliferative disease)

“Physiologic CCH” (secondary forms of CCH).

“Neoplastic” CCH consists of mildly to moderately atypical C-cells that can be recognized by H&E stains.
C Cell Hyperplasia

Physiologic CCH cannot be recognized with certainty with conventional stains and requires immunohistochemistry for diagnosis.
C Cell Hyperplasia

Molecular studies demonstrated that the “hyperplastic” C-cells in MEN2 syndromes represented clonal proliferations.
SUGGESTION:

“Neoplastic” CCH be replaced either by MTC in situ or by “thyroid intraepithelial neoplasia of C-cells” / “THINC”.

This CCH shows ret germline mutations.

NOT ACCEPTED BY 2017 WHO.
MICROCARCINOMA OF THYROID

ONE FINAL NOTE
MICROCARCINOMA OF THYROID

Some families with MEN 2 have germline ret mutations (most in codon 634) in which the thyroids contain C cell lesions (bilateral and multifocal) and follicular lesions (usually papillary microcarcinomas-multifocal). These are probably separate genetic events.

The medullary carcinoma is the more serious.
MICROCARCINOMA OF THYROID

In these patients, both types of tumor may metastasize to regional nodes. In most cases the metastatic lesions are separate. These are not Mixed Tumors!
MICROCARCINOMA OF THYROID

PAPILLARY; MEDULLARY
QUESTIONS?
Where is my thyroid gland?
THERE ARE THREE CHOICES

• UP A.

• MIDDLE B.

• LOW NECK C.
Where is my thyroid gland?
The thyroid gland is at the top!