What’s an NIFTP?
Keeping Up To Date in Thyroid 2018

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AJCC staging 2018

AJCC stage I
• <55, Any T, Any N, MO
• 55+ T2 (2-4cm), N0/NX, MO

AJCC Stage II
• <55, Any T, Any N, **M1**
• 55+ T1 (<2cm), N1, M0
• 55+ T2 (2-4), N1, M0
• 55+ T3a (>4), Any N, M0
• 55+ T3b (growth to strap muscle), Any N, M0
• (IIA, IIB, large bulky LNM?)

AJCC stage III
• 55+ T4a (grows extensively beyond/ near thyroid), Any N, M0

AJCC Stage IVA
• 55+ T4b (extensive spread tissue, into blood vessels, toward spine), Any N, M0

AJCC Stage IVB
• 55+ Any T, Any N, **M1**
AJCC 8th Edition: New Staging System (stratify the risk of death)

**AJCC 8th EDITION: 1/1/2018**

- 80% stage 1, DSS 98-100%
- Stage II DSS 85-95%
- stage III DSS 60-70%
- stage IV DSS <50%

- 8th edition better separates patients based on projected survival
- Fewer patients dying with better pre-op assessments and earlier surgeries with advent of US training

**AJCC 7th EDITION:**

- 60% stage 1 DSS 97-100%
- stage II DSS 97-100%
- Stage III DSS 88-95%
- Stage IV DSS 50-75%

- ~23% patients now downstaged in 8th ed. SEER data and 24% National Cancer Database (NCDB)
- Stages more significantly associated with DSS and OS making 8th edition superior for predicting survival

AJCC: American Joint Committee on Cancer, DSS disease specific survival THYROID vol 27, no. 11, 2007, Thyroid volume 26, no 3, 2016 (9400+ patients)
TBSRTC: The Bethesda System for Reporting Thyroid Cytology: version 2 (2018)
Stratify the Risk of Malignancy (beyond US)

• Six cytology-based Dx categories stay same (2010)
• Associated malignancy risk % changed
• Molecular testing to further assess malignancy risk in nodules, NIFTP recognized by WHO
• Lobectomy as treatment option
• Orients patients towards more conservative management decisions (lobectomies vs totals)
Revised Thyroid Bethesda System

- Change in risk of malignancy
- AUS or FLUS changes from 5-15% to 10-30%
- Follicular Neoplasm (suspicious for follicular neoplasm) changes from 20-30% to 25-40%
- Suspicious of malignancy category changes from 60-75% to 50-75%
- Malignant category allows for lobectomy except those with metastatic disease.

AUS: atypia of undetermined significance, FLUS: follicular lesions of undetermined significance
Bethesda 2010 vs 2017

est. risk of malignancy

- Nondiagnostic/ unsatisfactory
- Benign
- Atypia of undetermined significance or follicular lesion of US (AUS/FLUS)
- Follicular neoplasm or suspicious for a follicular neoplasm
- Suspicious for malignancy
- Malignant: limited to classic features of PTC (papillae, psomoma bodies, numerous inclusions

- 1-4%, now 5-10%
- 0-3%
- 5-15% now 10-30% (6-18% with NIFTP, incorporate molecular testing over repeat FNA)
- 15-30% now 25-40% (10-40% WITH NEW NIFTP, may be FA, FTC, FVPTC or NIFTP)
- 60-75% now 50-75% (45-60% with NIFTP, molecular testing BRAF)
- 97-99% lobectomy? (94-96% due to NIFTP, option of lobectomy up to 4 cm ATA)

(NIFTP is surgical disease)
The Genetic Basis for Thyroid Cancer

Applying genetics to FVPTC

Follicular thyroid epithelial cell

• Papillary thyroid cancer
  – \textit{BRAFV600E}
  – \textit{RET/PTC fusions}

• Follicular thyroid cancer
  – \textit{RAS}
  – \textit{PAX8-PPARY}
AUS/FLUS

FVPTC = 85% of all follicular patterned thyroid cancer

Encapsulated

EFVPTC

(N, H, K) RAS, PAX8/PPAR

Encapsulated
Non-invasive

Follicular adenoma
NIFTP
Noninvasive Follicular tumor with papillary-like nuclear features
No Comp. T, no RAI

Minimally Invasive
Few vessels
Indolent
Less likely to have Nodes
(hemithyroidectomy)

Infiltrative (Invasive)

IFVPTC

BRAF, RET/PTC

More likely to have ETE +LN mets
Behave like classic PTC
(>1 cm total thyroidectomy)

Extensive invasion
Capsular or vascular Invasion (FTC)
(like angioinvasive FTC)
Cons. Total thyroidectomy
May have D.M.
consider RAI
Nomenclature revision for Encapsulated Follicular Variant of PTC: (Reduce overtreatment of indolent tumors)

• Encapsulated FVPTC without capsular or vascular invasion behave like follicular adenomas. Clonal process driven by distinct oncogene mutation [RAS]

• A ‘benign” condition: reduces the incidence of malignancy in the Indeterminate FNA Categories. Non-invasive, follicular pattern, nuclear features of PTC (must examine entire capsule)

• High favorability outcome, <1% risk recurrence 15y. Rare cases of encapsulated FVPTC (and even tumors called benign follicular adenomas) that subsequently present with metastatic disease, estimated incidence 0.6% of encapsulated noninvasive FVPTC

• New recommended terminology NIFTP: Noninvasive follicular tumor with papillary-like nuclear features: distinct class thyroid tumor, NOT CANCER

Gilbert H. Daniels, (Thyroid Unit Harvard Medical School), Follicular Variant of Papillary Thyroid Carcinoma: Hybrid or Mixture? Thyroid June 2016. ATA guidelines 2017.
2016 Paradigm Shift FVPTC

• Reclassification reduces the risk of malignancy (pre-test probability) across Bethesda categories (AUS/FLUS, FN/SFN, SM)

• Total thyroidectomy for a *BRAFV600E* or *RET/PTC* positive FNA specimen from nodules >1.5cm

• Hemi-thyroidectomy reasonable for many *RAS*-mutant nodules. A majority of these prove to be encapsulated FVPTCs.
# NIFTP: Benign or Malignant (intermediate stage)

<table>
<thead>
<tr>
<th>Growth Pattern</th>
<th>Nuclear Features PTC</th>
<th>Main oncogene</th>
<th>Tumor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>Yes</td>
<td>BRAF</td>
<td>Papillary Microcarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Classic PTC</td>
</tr>
<tr>
<td>Follicular</td>
<td>Yes</td>
<td>RAS</td>
<td>NIFTP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Invasive EVPTC</td>
</tr>
<tr>
<td>Follicular</td>
<td>No</td>
<td>RAS</td>
<td>Follicular adenoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Follicular Thyroid Carcinoma</td>
</tr>
</tbody>
</table>
ACR TI-RADS
American College of Radiology Thyroid imaging, Reporting and Data System

• Goal was to decrease number of biopsies performed
• Even in the mildly suspicious category, no FNA recommended until nodule >2.5cm (ignoring the low-risk cancers.
• No FU nodules <15mm
• Instead of general pattern recognition, it is a scoring and applying risk categories.
• Composition, echogenicity, shape, margins, echogenic foci
• Standardizes score to travel (your score like BI-RADS)
• Score 0 benign, 1: not suspicious, 3: mildly suspicious, 4-6 moderately suspicious, 7 highly suspicious
• ****no mention neck assessment LN****
Risk Stratification

• 2009 ATA: Tumor type, size, margins, LN involvement, distant metastasis

• 2015 ATA: ALL THE ABOVE, PLUS:
  – Histologic variants of Thyroid cancer
  – Vascular invasion with number of invaded vessels
  – Multifocality
  – Number of LN examined and involved
  – Size of largest metastatic focus to the LN
  – Extranodal extension
  – Consideration of genetic markers

Eric Alexander, Endo ATA 6/20/14, Cooper et al, ATA guidelines 2015
Problem

• Most community based practices continue use of RAI in low risk patients despite an abundance of data showing minimal benefit and significant associated side effects and risks of RAI use.

• Why: (5 most commonly sited reasons)
  – Lack of confidence patient will return for follow up
  – Pt might be the 2% that won’t do well
  – RAI makes Tg undetectable, easier to follow
  – Will “cure” remaining disease
  – “This is not MD Anderson, Mayo, Sloan Kettering CC”
Birth of I 131 for DTC 1960-1980

- Thought to “complete a thyroidectomy”
- All DTC treated same: high risk, low risk, PTC, HCC
- Data was observational (based on suboptimal surgeries)
- High complication rate for TT (13%)
- Studies showing benefit largely with +nodes/lung mets (not low risk)
- Poor pre-op assessment
- No histology assessment, all tx same

*Antonio Sitges-Serra, Low-risk papillary thyroid cancer: times are changing
Expert Rev. Endocrinol. Metab. 9(1), 9–18 (2014)
1990s Decline of I 131

- Low risk: multiple studies unable to show recurrence or mortality benefit (10,11)
- Cause specific mortality in MACIS <6 (low risk) 1%/20y
- Developed sensitive Tg assays (2014 ultra sensitive Tg!)
- Sensitive US for the Dx of disease extension/recurrences
- Expert surgeries: Endocrine thyroid surgical fellowships
- Improved risk prediction

- HOWEVER: Made minimal impact on the management protocols built on the earlier observational studies.
National Thyroid Cancer Treatment Cooperative Study Group 2001, 2936 patients, 2 decades of data the concluded that “no treatment modality, including radioactive iodine, was associated with altered survival in stage I patients.

ATA guidelines recommend judicial use of I131 in low-risk patients: (most low-risk patients continue to receive I131 -Guidelines do not translate into outpatient practices due to lack of confidence, fear, need to rid Tg)

Mayo Clinic Rochester: post/op recurrences were in regional nodes, especially in those who presented with metastatic neck nodes. 636 node-neg vs 527 node-positive cases: no statistically significant differences in 20-year outcomes (cause-specific mortality and tumor recurrence) observed between those having surgery alone vs those given postoperative RRA*

European consensus report 2005 (12 European countries) advised that “remnant ablation should be restricted to patients with incomplete surgical excision or poor prognostic factors for recurrence or death.”

*Hay ID. Selective use of radioactive iodine in the postoperative management of patients
AJCC 8\textsuperscript{th} Edition

- Cut point separating younger from older from 45 to 55yo.
- Stage one tumors may be up to 4 cm. vs 2cm
- Stage II reserved for tumors >4cm vs 2-4 cm
- **Stage II includes patients with nodal mets N1 or gross extrathyroidal extension (no longer stage III)**
- Stage III must have gross ETE into larynx, trachea, esophagus or RLN.
- Stage IV spread must extend into prevertebral fascia or encase major vessels foe stage IVA, or involve distant met for stage IVB (no longer IV subgroup A, B, or C as in 7\textsuperscript{th} edition)
BE A THOUGHTFUL ENDOCRINOLOGIST
Golden Rules for Managing PTC: right team

• Carefully choose your pathologist (+/- Local)
• Expert US scanning; pre op assessment vital.
• Know skills/limitations of your thyroid surgeon
• Use TNM stages and apply prognostic scoring (risk assessment)
• Permit tolerance of ‘detectable’ Tg levels
• Use I-131 therapy “selectively” reserve for high risk patients.
### RAI use 2015 ATA Guidelines

<table>
<thead>
<tr>
<th>ATA recurrence risk TNM staging</th>
<th>Description</th>
<th>Post surgical RAI recommendation (ROR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (no aggressive histo)</td>
<td>T&lt;1cm unifocal or multifocal</td>
<td>NO (~2%)</td>
</tr>
<tr>
<td>T1a/N0,Nx/M0, MX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk T1b, T2/N0,Nx/M0, MX</td>
<td>T1b 1-2cm</td>
<td>NO, not routine (~2%) (multifocal PTMC 4-6%)</td>
</tr>
<tr>
<td>T2 2-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low- indeterminate risk T3/N0,Nx/M0,MX</td>
<td>T&gt;4 cm or microscopic invasion</td>
<td>NO, not routine (p/o Tg?) unless adverse features</td>
</tr>
<tr>
<td>Low- indeterminate risk T1-3/N1a/M0,MX</td>
<td>CLN mets present</td>
<td>NO, if ≤ 5, (&lt;0.2cm) (~5%) Consider size and number</td>
</tr>
<tr>
<td>Indeterminate risk</td>
<td>Lateral nodes present</td>
<td>Consider size and number NO unless large, &gt;5LN (~20%)</td>
</tr>
<tr>
<td>Any T1-3/N1b/M0,MX</td>
<td>pT3 minor ETE (3-8%)</td>
<td></td>
</tr>
<tr>
<td>High risk T4/and N/any M</td>
<td>Gross ETE (BRAF 10%)</td>
<td>YES (10-40%) (VE 15-30%, ETE BRAF 10-40%)</td>
</tr>
<tr>
<td>High risk M1 (any T, any N)</td>
<td>Distant mets, ENE extranodal extension 40%</td>
<td>YES (30-55%) TERT &gt;40%</td>
</tr>
</tbody>
</table>
2015 ATA Recommendation

• In addition to the basic tumor features for AJCC/UICC thyroid cancer staging, pathology reports should include information helpful for risk assessment.
  – Presence of **vascular invasion/number of vessels invaded**
  – Number of LN examined and involved with tumor
  – Size of the largest metastatic foci to the LN
  – Presence of **extranodal extension** of the metastatic tumor. *(strong recommendation, moderate quality evidence)*
2015 ATA and NCCN guideline recommendations

• DO NOT recommend RAI ablation for all patients with locoregional lymph node metastases.

• ATA surgical affairs committee:
  – risk of recurrence in N1 disease is related to the number and size of involved lymph nodes
  – ≤5 microscopic LN metastases in the clinical N0 neck carries a risk of recurrence <5% (similar to multifocal papillary microcarcinoma).
Conclusions

• Learn to perform/or refer for pre-op neck surveillance US to recommend appropriate initial surgery for complete resection.

• Know the skills and/or limitations of your thyroid surgeon (should never take pt to OR without appropriate pre-op neck US).

• Define risk assessment: minimal disease, requires minimal treatment. MACIS <6, 20 year survival 99% without RAI.

• In a community based setting, low and intermediate risk stage I and II DTC can be managed safely, effectively and confidently without RAI using a 2wPONSTg <2ng/ml.

• A low, detectable and stable Tg is an easy tool to follow patients without RAI.

• Neck ultrasound and careful observation for any rising TREND of serum Tg concentrations, will routinely detect structural disease amenable to surgery.