Thyroid Cancer: When to Treat?

MEGAN R. HAYMART, MD
ASSOCIATE PROFESSOR OF MEDICINE
UNIVERSITY OF MICHIGAN
MICHIGAN AACE 2018 ANNUAL MEETING
Thyroid Cancer: When Not to Treat?

FOCUS WILL BE ON LOW-RISK THYROID CANCER
Agenda

Define low-risk thyroid cancer
Discuss benefits and risks of management options
Tailor the treatment to the patient
What is low-risk thyroid cancer?

Table 1. Defining Low-Risk Based on Survival versus Recurrence

<table>
<thead>
<tr>
<th>Survival Focus</th>
<th>Recurrence Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AJCC TNM 7th ed.</strong></td>
<td><strong>AJCC TNM 8th ed.</strong></td>
</tr>
<tr>
<td><strong>&lt; 45 years and Stage I</strong></td>
<td><strong>&lt; 55 years and Stage I</strong></td>
</tr>
<tr>
<td>Any T, Any N, M0</td>
<td>Any T, Any N, M0</td>
</tr>
<tr>
<td><strong>&lt; 45 years and Stage II</strong></td>
<td><strong>&lt; 55 years and Stage II</strong></td>
</tr>
<tr>
<td>Any T, Any N, M1</td>
<td>Any T, Any N, M1</td>
</tr>
<tr>
<td><strong>≥ 45 years and Stage I</strong></td>
<td><strong>≥ 55 years and Stage I</strong></td>
</tr>
<tr>
<td>T ≤ 2 cm, N0, M0</td>
<td>T &gt; 2 cm but ≤ 4 cm, N0/NX, M0</td>
</tr>
<tr>
<td><strong>≥ 45 years and Stage II</strong></td>
<td><strong>≥ 55 years and Stage II</strong></td>
</tr>
<tr>
<td>T &gt; 2 cm but ≤ 4 cm, N0, M0</td>
<td>T &gt; 2 cm but ≤ 4 cm, N1, M0</td>
</tr>
<tr>
<td></td>
<td>T &gt; 4 cm or any T and gross extrathyroidal extension invading only strap muscle, Any N, M0</td>
</tr>
<tr>
<td></td>
<td>Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (&lt;4 foci) vascular invasion</td>
</tr>
<tr>
<td></td>
<td>Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including BRAFV600E mutated (if known)</td>
</tr>
</tbody>
</table>

Low-risk thyroid cancer

No LN mets, and ≤ 4 cm

≤ 2 cm

≤ 1 cm
Definition of Papillary Thyroid Microcarcinoma

• Clinical studies vary with some defining papillary thyroid microcarcinoma as ≤ 1 cm and others as < 1 cm.

• According to the World Health Organization, papillary thyroid microcarcinoma is a papillary thyroid cancer ≤ 1 cm.

• For AJCC TNM staging, T1a is ≤ 1 cm.
Rise in Incidence of Papillary Thyroid Microcarcinomas

PTMC especially common in patients > 45 years

Hughes DT et al. Thyroid 21(3):231-6.
Tumors ≤ 1 cm are the Most Common Tumor Size

Proportion of Differentiated Thyroid Cancers

- > 4 cm
- 2-4 cm
- 1-2 cm
- ≤ 1 cm

Legend:
- ≤ 1 cm
- 1-2 cm
- 2-4 cm
- > 4 cm
Papillary Thyroid Microcarcinomas are Common

Up to 36% of patients who die from another cause will have incidental discovery of a small thyroid cancer on thorough autopsy.

Thyroid Cancer: How to Treat?

Disease severity is on a continuum

Treatment intensity is on a continuum

Treatment intensity should fit disease severity
No active treatment ≠ No management of disease

Active surveillance is still disease management

Active surveillance consists of close monitoring of the cancer without initial surgery or other more intensive therapies

Active surveillance involves medical decision making, surveillance strategy, and patient education
Why consider less intensive treatment?

It is important to balance benefits - risks
Balancing benefits-risks

Benefit of Less Intensive Treatment:
- Less risk for harm from treatment

Benefit of More Intensive Treatment:
- Easier long-term follow-up
  - More certainty that cancer is gone

Risks of Less Intensive Treatment:
- More difficult long-term follow-up
  - Less certainty that cancer is gone

Risks of More Intensive Treatment:
- More risk for harm from treatment
Survival is similar with lobectomy and total thyroidectomy

![Cumulative Risk of Death Due to Thyroid Cancer](image)

Surgical risks are greater with more intensive surgery

A prior study using the Nationwide Inpatient Sample from 2003 to 2009 found that out of 62,722 thyroid procedures performed for both benign and malignant conditions, there was a significantly increased risk of complications after total thyroidectomy compared to lobectomy (20.4 versus 10.8%; p<0.0001).

Surgical risks are greater with more intensive surgery

Our prior work evaluating 27,912 SEER-Medicare patients who underwent surgery for thyroid cancer found that 8% of patients with localized disease have hypoparathyroidism and 2.4% have vocal fold paralysis.

In multivariable analysis, total thyroidectomy was associated with a significantly higher rate of complications (odds ratio 1.59; 95% confidence interval, 1.41-1.80) as compared to lobectomy.

Surgical risks:

Total thyroidectomy > lobectomy > active surveillance
Thyroid hormone replacement is more commonly needed with more intensive treatment.

All patients need life-long thyroid hormone replacement after total thyroidectomy as compared to ~20% after lobectomy and 0% secondary to active surveillance.
Radioactive iodine treatment does not impact survival in patients with PTMC

Radioactive iodine does not impact recurrence free-survival for PTMC

Kaplan–Meier estimate of recurrence-free survival in intermediate-risk patients with papillary thyroid microcarcinoma stratified according to radioactive iodine (P = 0.52).

Risks secondary to RAI are dose-dependent but even the lowest risk thyroid cancer patients have risks.

For low-risk patients use of RAI was associated with a significantly increased risk of leukemia and salivary gland cancer.

Clinical Guidelines know Best

THE DO’S AND DON’TS OF PTMC MANAGEMENT
Case 1:

- A 65 yo male patient has a carotid duplex. An incidental thyroid nodule is noted. Follow-up ultrasound reveals a 0.9 cm left sided thyroid nodule. No worrisome lymph nodes are noted on bedside US. Do you recommend FNA?

a) No
b) Yes
How to Manage?
Don’t FNA

• Don’t biopsy nodules < 1 cm

Haugen BR et al. 2015 ATA Guidelines Thyroid. 2016; (1): 1-133.
If you operate, Do less

• If the patient has a biopsy prior to seeing you in clinic and it is PTMC, lobectomy is adequate surgery if surgery is pursued (assuming no extrathyroidal extension and no lymph node involvement)

• Radioactive iodine is not necessary

Haugen BR et al. 2015 ATA Guidelines Thyroid. 2016; (1): 1-133.
But perhaps...don’t operate

• Active surveillance can be considered in patients with papillary thyroid microcarcinomas without clinically evident metastases or local invasion and no cytologic evidence of aggressive disease

Haugen BR et al. 2015 ATA Guidelines Thyroid. 2016; (1): 1-133.
Do follow?
Older patients with low-risk PTMC may be candidates for active surveillance

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>&lt; 40 (N=169)</th>
<th>40-59 (N=570)</th>
<th>≥ 60 (N=496)</th>
<th>Total (N=1,235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size increase</td>
<td>14 (5.9%)</td>
<td>33 (5.7%)</td>
<td>11 (2.2%)</td>
<td>58 (p=0.0014)</td>
</tr>
<tr>
<td>New LN mets</td>
<td>9 (5.3%)</td>
<td>8 (1.4%)</td>
<td>2 (0.4%)</td>
<td>19 (p&lt;0.0001)</td>
</tr>
<tr>
<td>New clinical disease</td>
<td>15 (8.9%)</td>
<td>20 (3.5%)</td>
<td>8 (1.6%)</td>
<td>43 (p&lt;0.0001)</td>
</tr>
</tbody>
</table>

An increase in tumor size was defined as an increase in size by 3mm or more, 1-2 times/year US was used to detect suspicious lymph nodes and then patients underwent FNA with measurement of thyroglobulin in needle washout, new clinical disease was classified as the tumor size reaching 12 mm or larger OR the appearance of new lymph node metastasis.

A RISK-STRATIFIED APPROACH TO DECISION MAKING IN PROBABLE OR PROVEN PAPILLARY MICROCARCINOMA

<table>
<thead>
<tr>
<th>Candidates for observation</th>
<th>Tumor/neck US characteristics</th>
<th>Patient characteristics</th>
<th>Medical team characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ideal</td>
<td>• Solitary thyroid nodule</td>
<td>• Older patients (&gt;60 years)</td>
<td>• Experienced multidisciplinary management team</td>
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<tr>
<td></td>
<td>• Well-defined margins</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• Surrounded by ≥2 mm normal thyroid parenchyma</td>
<td>• Willing to accept an active surveillance approach</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No evidence of extrathyroidal extension</td>
<td>• Understands that a surgical intervention may be necessary in the future</td>
<td></td>
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<tr>
<td></td>
<td>• Previous US documenting stability</td>
<td>• Expected to be compliant with follow-up plans</td>
<td></td>
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<tr>
<td></td>
<td>cN0</td>
<td>• Supportive significant others (including other members of their healthcare team)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cM0</td>
<td>• Life-threatening comorbidities</td>
<td></td>
</tr>
<tr>
<td>Appropriate</td>
<td>• Multifocal papillary microcarcinomas</td>
<td>• Middle-aged patients (18–59 years)</td>
<td>• Experienced endocrinologist or thyroid surgeon</td>
</tr>
<tr>
<td></td>
<td>• Subcapsular locations not adjacent to RLN without evidence of extrathyroidal extension</td>
<td>• Strong family history of papillary thyroid cancer</td>
<td>• Neck ultrasonography routinely available</td>
</tr>
<tr>
<td></td>
<td>• Ill-defined margins</td>
<td>• Child bearing potential</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Background ultrasonographic findings that will make follow-up difficult (thyroiditis, nonspecific lymphadenopathy, multiple other benign-appearing thyroid nodules)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• FDG-avid papillary microcarcinomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inappropriate</td>
<td>• Evidence of aggressive cytology on FNA (rare)</td>
<td>• Young patients (&lt;18 years)</td>
<td>• Reliable neck ultrasonography not available</td>
</tr>
<tr>
<td></td>
<td>• Subcapsular locations adjacent to RLN</td>
<td>• Unlikely to be compliant with follow-up plans</td>
<td>• Little experience with thyroid cancer management</td>
</tr>
<tr>
<td></td>
<td>• Evidence of extrathyroidal extension</td>
<td>• Not willing to accept an observation approach</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Clinical evidence of invasion of RLN or trachea (rare)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• M1 disease at initial evaluation or identified during follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• M1 disease (rare)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• Documented increase in size of ≥3 mm in a confirmed papillary thyroid cancer tumor</td>
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</tr>
</tbody>
</table>

US, ultrasound; RLN, recurrent laryngeal nerve; FDG, fluorodeoxyglucose; FNA, fine-needle aspiration.

How to follow PTMC?

• Ultrasound

• Thyroglobulin (?)
<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Median Age at Diagnosis (yr)</th>
<th>Sex of Affected Patients</th>
<th>Intensive Treatment Option</th>
<th>Risks Associated with Intensive Treatment</th>
<th>Active Surveillance Option</th>
<th>Physician in Charge</th>
<th>Stage of Adoption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>66</td>
<td>100% male</td>
<td>Radical prostatectomy or radiation</td>
<td>Impotence and incontinence</td>
<td>Prostate exam; prostate-specific antigen testing; biopsy</td>
<td>Urologist</td>
<td>In practice</td>
</tr>
<tr>
<td>Thyroid</td>
<td>51</td>
<td>75% female, 25% male</td>
<td>Total thyroidectomy, with or without lymph-node resection and radioactive iodine</td>
<td>Permanent change in voice and permanent low calcium levels</td>
<td>Neck ultrasound and testing of serum thyroglobulin</td>
<td>Endocrinologist</td>
<td>In trials</td>
</tr>
<tr>
<td>Breast (DCIS)</td>
<td>62</td>
<td>Nearly 100% female</td>
<td>Mastectomy or lumpectomy with radiation</td>
<td>Surgical complications and lymphedema</td>
<td>Mammography</td>
<td>Unclear</td>
<td>In discussion</td>
</tr>
</tbody>
</table>
Is there a role for shared decision making?

Q: What is shared decision making?

A: When health care providers and patients work together to decide the best way to treat their health problem.
14 recorded conversations about lung cancer screening between PCPs or pulmonologists and patients.

OPTION (Observing Patient Involvement in Decision Making) was the validated scale the reviewers used to determine extent to which physicians involved patients in decisions.

Mean OPTION score was 6 on a scale of 0-100 (range, 0-17). Mean time spent discussing lung cancer screening was 0:59 minutes (range, 0:16-2:19 minute).

Brenner AT et al. JAMA Int Med 2018; Aug 13 [Epub ahead of print]
Shared decision making for low-risk thyroid cancer

- Clinician lists options, including “no action” if reasonable
- Clinician explains pros and cons of options
- Clinician checks the patients preferred information format (words/numbers/visual display)
- Clinician explores patients expectations and fears
- Clinician checks to see that the patient understood the information
- Clinician provides opportunities for questions
- Clinician asks patients preferred level of involvement in decision making
- An option for deferring a decision is provided

Since there is a spectrum of disease severity, in the future active surveillance (“no active treatment”) may be an option for more patients.
Age and comorbidity should factor into decision making

1129 patients ≥ 70 years with 2527 nodules ≥ 1 cm were evaluated

67.3% benign FNA

Of patients who went to surgery: 44.7% benign histology

Only 17 (1.5%) had high-risk cancers defined as anaplastic, medullary, poorly differentiated carcinoma, or presence of distant metastases

10 of these patients with high-risk cancers died from their thyroid cancer

Among all other patients (n=1112), 14.4% died from other causes

A history of non-thyroidal malignancy and CAD were associated with increased likelihood of death from other causes

Tailor treatment to the patient
Thyroid Cancer: How to Manage?

FOCUS ON LOW-RISK THYROID CANCER
Thank-you