

Diagnosis and Management of Thyroid Cancer: A Case-based Review and Opportunities for Translational Research

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Goals and Objectives

- Review current ATA recommendations for the following in a case-based manner:
- Diagnostic testing for thyroid cancer diagnosis.
- Initial treatments for patients diagnosed with thyroid cancer.
- Key concepts in monitoring thyroid cancer.

Thyroid Cancer Incidence is Rising in the United States

- 2008 Estimate for United States from NCI and American Cancer Society ^{1,2}
 - 37,340 New Cases
 - 1,590 Cause-related Mortalities
 - 388,386 patients with thyroid cancer
- Incidence rate is increasing in both men and women at fastest rate of all cancers
- Mortality has been stable since the early 1970s and remains very low, but dependent on stage at diagnosis.

¹ <http://SEER.cancer.gov>
² www.cancer.org

American Thyroid Association Guidelines Levels of Evidence

- Modified USPSTF categories
- Level A: Strongly Recommends: Based on strong evidence that a service or intervention improves health outcomes.
- Level B: Recommends: Based on fair evidence limited by the number, quality, or consistency of studies.
- Level C: Recommends based on expert opinion
- Level D: Recommends against based on expert opinion.
- Level E: Recommends against based in fair evidence.
- Level F: Recommends against based on strong evidence.
- Level I: Recommends neither for nor against based on insufficient, poor quality, or conflicting evidence.

1. Cooper DS, et al Thyroid 2006 16; 2006

2. US Preventive Services Task Force Ratings: Strengths of Recommendations and Quality of Evidence. Guide to Clinical Preventive Services, 3rd ed. Periodic Updates 2000-2003. Agency for Healthcare Research and Quality. Rockville, MD.

Illustrative Case

- A 42 year old woman is in the office for and annual physical.
- She has no specific complaints other than fatigue.
- She has no dry skin, constipation, or other signs/symptoms of hypothyroidism.
- She has no heart palpitations, heat intolerance or tremor.

Case

- On physical examination, BP is 112/72; HR: 72
- Neck exam reveals an ~2 cm rubbery thyroid nodule on the left that moves easily with swallowing. There are no palpable nodes. It is non-tender. No nodularity is noted in the right side.
- Remainder of the examination is normal.

Case

- What are the appropriate diagnostic tests for this presumed solitary thyroid nodule?

Case

R1: ATA guidelines

“Measure serum TSH in the initial evaluation of a thyroid nodule.” Level: C

R2: “Thyroid sonography should be performed in all patients with one or more selected nodules.” Level: B

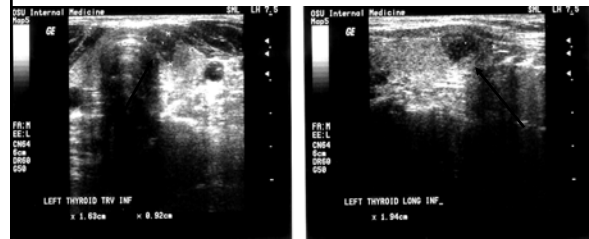
Note: Nuclear Imaging of thyroid nodules at this stage should be performed in individuals with low TSH levels to determine if a nodule is “hot.”

Cooper DS, et al. Thyroid 2006. 16:109-142

Case

- TSH is 1.2 m U/L (normal range 0.4-4.2 mU/L).
- Thyroid ultrasound confirms the presence of a 2.2x2.3x2.1 cm nodule on the left side. There is a smaller 0.8x0.6x0.4 cm nodule on the right. No abnormal lymph nodes are identified in the central or lateral neck regions.
- What is the appropriate next step?

Thyroid Ultrasound Example



Case

- R5: “Fine Needle Aspiration is the procedure of choice in the evaluation of thyroid nodules.” Level A
 - Only exception would be if the TSH is low, in which case a nuclear medicine (iodine) scan would be performed
- Ultrasound-guided is optimal.

Cooper DS, et al. Thyroid 2006. 16:109-142

Diagnostic Capabilities of Thyroid FNA

- FNA can accurately diagnose papillary thyroid cancer.
- FNA **cannot** accurately distinguish between benign and malignant follicular thyroid lesions.
- FNA can accurately diagnose benign thyroid lesions
- An insufficiency rate of approximately 10% is common

Clinical Endpoints of FNA Results

- **Malignant Cells Present on the FNA has >99% accuracy; recommend surgery (total/near-total thyroidectomy).**
- **Suspicious for Malignancy: 50-75% chance of PTC, recommend surgery (total/near total thyroidectomy).**
- **Suspicious for Follicular Neoplasm: ~20-30% chance of malignancy, recommend surgery either hemithyroidectomy or total/near total thyroidectomy.**
- **No Malignant Cells Seen: <1% cancer of cancer, recommend monitoring with ultrasound periodically. Repeat FNA if nodule is large or is growing.**
- **Unsatisfactory: Repeat FNA in 3-6 months. If repeatedly non-diagnostic or grows, recommend surgery to obtain diagnosis.**

Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. Diagn Cytopathol. 2008 Jun;36(6):425-37.

Case

- FNA was performed under ultrasound guidance.
 - Results revealed cellular atypia, minimal colloid, evidence of nuclear grooves and intranuclear cytoplasmic inclusion bodies.
 - Felt to be consistent with papillary thyroid cancer.

Types of Treatment Utilized in Thyroid Cancer Patients

- Surgical Thyroidectomy
- Radioiodine Therapy
- TSH-suppressive doses of L-thyroxine
- External Beam Radiation Therapy
- Chemotherapy/Clinical Trials

Goals of Initial Therapy for Thyroid Cancer

- ATA Guidelines: "Remove the tumor, disease that has extended beyond the thyroid capsule, and involved cervical lymph nodes."
- "To minimize treatment- and disease- related morbidity."
- "To permit accurate staging of disease."
- "To facilitate postoperative treatment with radioactive iodine, where appropriate."
- "To permit accurate long-term surveillance for disease recurrence."
- "To minimize the risk of disease recurrence and metastatic spread."

Cooper DS, et al. Thyroid 2006. 16:109-142

Case

- You are asked by the patient if she should have her entire thyroid gland removed or if half can be removed.
- What are the recommendations for initial surgery for patients with diagnosed thyroid cancer?

Initial Surgery for Thyroid Cancer

- R. 26 "For most patients with thyroid cancer, the initial surgical procedure should be near-total or total thyroidectomy. Lobectomy alone may be sufficient for patients with small, low-risk, isolated intrathyroidal papillary thyroid carcinomas in the absence of cervical nodal metastases." Level: A
- R. 27&28. Routine lymph node dissection should be considered for patients with PTC or Hurthle Cell Thyroid Cancer; lateral compartment dissection is generally recommended only the presence of malignant lateral nodes. Levels: B

Cooper DS, et al. Thyroid 2006. 16:109-142

Case

- Ultrasound performed prior to FNA did not reveal lymphadenopathy.
- Total Thyroidectomy was recommended based on the pre-operative diagnosis of PTC.
- The risks of thyroidectomy, including recurrent laryngeal nerve damage and hypoparathyroidism, were discussed with the patient.

Case

- The patient underwent a near-total thyroidectomy and she recovered well with no hypocalcemia and with a normal voice.
- Pathology: 2.2x2.1x1.9 cm PTC. The nodule in the opposite lobe was benign. No metastases to nodes were identified.
- TNM: T2, N0, Mx PTC

Radioactive Iodine Therapy

- The first treatment also called remnant ablation, treats both residual normal, and potentially, if present, residual cancer.
- Some, but not all retrospective studies have demonstrated a reduced recurrence rate for patients treated with I-131. Some show a reduction in mortality, while others do not.
- The improvement in recurrence rates, when it has been demonstrated has been limited to patients with PTCs greater than 1.5 cm, with local invasion, multifocal disease, and in some cases nodal spread.

Recommendation Regarding I-131 Remnant Ablation

- R. 32. Radioiodine ablation is recommended for patients with stages III and IV disease (AJCC sixth edition), all patients with stage II disease < age 45 and most patients >45, and selected patients with stage 1 disease. Level B
- Our patient (assuming no distant disease) has stage 1 (T2N0M0) disease with a tumor size >2.0 cm with no lymph node spread.

Cooper DS, et al. *Thyroid* 2006. 16:109-142

Who Does Not Appear to Benefit from Radioiodine?

- Patients with PTC <1.0 cm that is intrathyroidal without nodal spread have an excellent prognosis that has not been shown to improve with I-131 therapy.
- Patients with intrathyroidal PTCs 1.0-1.5 cm also have an excellent prognosis and may not benefit from I-131 therapy.

Benefits of Radioiodine Therapy

- Depending on the study and stage of disease: may reduce recurrence rates and/or improve mortality.
- Improve sensitivity of follow-up
 - Ablation of all normal tissue creates a "clean slate" for monitoring biochemically and radiographically.
- Allow for diagnosis and characterization of distant metastases if present.
- May treat residual cancer.

Risks of Radioiodine Therapy

- Sialoadenitis
 - Can be painful, especially with repeated doses.
 - Can cause tooth decay and altered taste sensation.
- Lacrimal Duct Stenosis:
 - More common with high doses; can be surgically corrected.
- Secondary Malignancies:
 - Rare, occurs more commonly with repeated high doses. Leukemia, salivary cancers are most common. Others (colorectal, bone/soft tissue, breast) have been described but the results have been inconsistent.
- Early Menopause: ~12 months in one study.
- Delay in pregnancy: Recommended to wait 12 months to become pregnant.
- Marrow and Lung Toxicity: Occasionally seen in patients who have received multiple high doses of I-131.
- Reduce Sperm Count: Rarely seen with high doses.

Cooper DS, et al. *Thyroid* 2006. 16:109-142

Case

- After discussion of the Risks and Benefits of Radioiodine, the patient is scheduled to receive therapy.
- What special preparations needed for patients scheduled to receive radioiodine therapy?

Preparation for Radioiodine Therapy

- High Levels of TSH are needed to facilitate radioiodine therapy.
 - Withdrawal from Thyroid hormone
 - Effective
 - Causes often-time severe, transient symptoms
 - Inexpensive
 - Recombinant human TSH administration
 - IM injections
 - Well-tolerated
 - Studied for a shorter period of time
 - Expensive
 - Approved for Remnant Ablation only
 - Low Iodine Diet

RhTSH versus Thyroxine Withdrawal for I-131 Therapy

- rhTSH was approved in 2007 for remnant ablation.
 - Pacini et al. Randomized, controlled multicenter study
 - 63 patients randomized to thyroxine withdrawal vs rhTSH preparation for remnant ablative therapy with 100 mCi I-131.
 - Rate of remnant ablation defined as uptake <0.1% on scan 8 months later. Tg levels were a secondary endpoint.

Pacini F, et al. *J Clin Endocrinol Metab.* 2006; 91:926-932.

RhTSH versus Thyroxine Withdrawal for I-131 Therapy

- 100% of patients in both groups had successful ablation of iodine uptake.
- The rates of patients with stimulated Tg levels <1 ng/ml or <2 ng/ml were the same between the two groups.
- Quality of life scores (Billewicz and SF36 scales) was better in patients treated with rhTSH
- The authors concluded that rhTSH preparation for remnant ablative I-131 therapy was as effective and hypothyroid preparation at achieving ablation with fewer hypothyroid symptoms.

Pacini F, et al. *J Clin Endocrinol Metab.* 2006; 91:926-932.

Recommendations for Radioiodine Preparation

- R33. "Patients undergoing radioiodine therapy or diagnostic testing can be prepared by LT4 withdrawal...with measurement of serum TSH to determine timing of testing (TSH>30 mU/L)." Level B.
- R37. "Remnant ablation can be performed following thyroxine withdrawal or rhTSH stimulation." Level B.
- R38. "A low iodine diet for 1-2 weeks is recommended for patients undergoing radioiodine remnant ablation, particularly for those patients with high iodine intake." Level B.

Cooper DS, et al. *Thyroid* 2006. 16:109-142

Dosing Recommendations

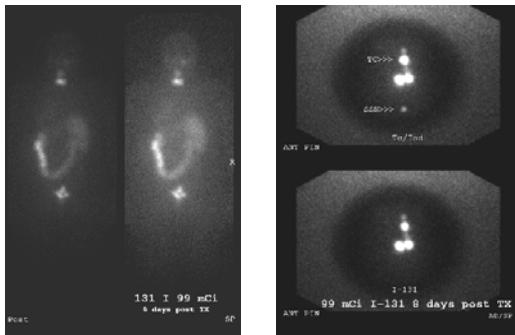
- R35. "The minimum activity (30-100 mCi) necessary to achieve successful remnant ablation, particularly for low-risk patients." Level B
- R36. "If residual microscopic disease is suspected or documented, or if there is a more aggressive tumor histology, then higher activities (100-200 mCi) may be appropriate." Level C

Cooper DS, et al. *Thyroid* 2006. 16:109-142

Case

- Because the tumor was staged as a T2 I-131 remnant ablation was recommended.
- She received with 50 mCi of I-131 following thyroxine withdrawal.
- Pre- and post-therapy diagnostic scans revealed uptake in the thyroid bed with no lateral uptake or iodine-avid distant metastases.
- She is then placed on thyroid hormone

Example of I-131 scan of bed uptake



TSH Suppression Therapy

- All patients with thyroid cancer require treatment with L-thyroxine.
- R40. "Initial thyrotropin suppression to below 0.1 mU/L is recommended for high-risk patients with thyroid cancer, while maintenance of the TSH at or slightly below the lower limit of normal (0.1 to 0.5 mU/L) is appropriate for low risk patients." Level B

Cooper DS, et al. *Thyroid* 2006. 16:109-142

Case

- The patient is initially placed on 125 mcg of L-thyroxine daily (weighs 135 lbs) and the dose is increase to 150 mcg to achieve a TSH level of 0.1 mU/L.
- She is tolerating this well with no heart palpitations or anxiety.
- How and when should she be monitored for her thyroid cancer?

Methods of Monitoring Patients with Thyroid Cancer

- Biochemical:
 - Measurement of serum thyroglobulin
- Radiographic
 - Neck Imaging with US or if not available, CT or MRI
 - Imaging for distant metastases in selected cases
 - I-131 whole body scanning

Serum Thyroglobulin (Tg) Measurement

- Highly specific and sensitive for thyroid tissue.
- Becomes specific for thyroid cancer after thyroidectomy and I-131 ablation therapy.
- Must be measured with simultaneous anti-Tg antibodies as these can interfere and cause false abnormal (often undetectable) results.
- Must be measured with TSH as this can stimulate Tg levels.
- Tg levels are the cornerstone of monitoring, especially in patients who do not have anti-Tg antibodies (~85% of patients).

Neck Imaging

- A neck ultrasound to examine nodes bilaterally by a skilled operator is highly sensitive for detecting recurrent or residual PTC. FNA can also be performed if indicated.
- FTC rarely spreads to neck nodes and may be less sensitive in these patients.
- Other neck imaging such as CT or MRI may be ordered in selected cases or based on preferences at individual practice sites.

Chest Imaging

- Chest CT scans are generally performed in the following situations:
 - high risk of distant metastases
 - high Tg levels
 - elevated Tg levels with negative neck imaging or FTC
 - positive iodine scans in the lung
 - some patients with persistently elevated anti-Tg antibody levels with negative neck imaging.
- Chest radiographs are insensitive for thyroid cancer as many metastases are small.

Nuclear Imaging

- Whole body radioiodine scanning
 - Less sensitive than Tg levels, particularly for detecting neck disease.
 - May still be performed in selected PTC cases, particularly those patients who have anti-Tg antibodies.
 - Perhaps greater utility for FTC
- FDG PET or PET/CT imaging
 - PET imaging is most helpful in patients with poorly differentiated tumors or with high Tg levels and negative neck and chest imaging.
 - May Provide prognostic information in patients with distant metastases¹.
 - TSH stimulation may improve sensitivity².

¹ Robbins RJ, et al. J Clin Endocrinol Metab. 2006;91: 498-505
² Chin BB, et al. J Clin Endocrinol Metab. 2004;89:91-95.

Case

- Three months after I-131 therapy; the patient had a TSH level of 0.15 mU/L and a serum Tg level <0.2 ng/ml with undetectable anti-Tg antibodies.
- Nine months after I-131 therapy; TSH was 0.08 mU/L; Tg was <0.2 ng/ml with undetectable anti-Tg antibodies.
- What is recommended at this point?

Surveillance for Thyroid Cancer

- R45. "In low risk patients who have had remnant ablation and negative cervical ultrasound and TSH-suppressed Tg 6 months after treatment, serum Tg should be measured after thyroxine withdrawal or rhTSH stimulation approximately 12 months after the ablation to very absence of disease. The timing or necessity of subsequent stimulation is uncertain for those found to be free of disease." Level A

Cooper DS, et al. Thyroid 2006. 16:109-142

Surveillance for Thyroid Cancer

- R46. After the first whole body scan performed at the time of remnant ablation, low-risk patients with negative TSH-stimulated thyroglobulin and cervical ultrasound do not require routine diagnostic whole body scan during follow-up. Level A

Cooper DS, et al. *Thyroid* 2006. 16:109-142

Case

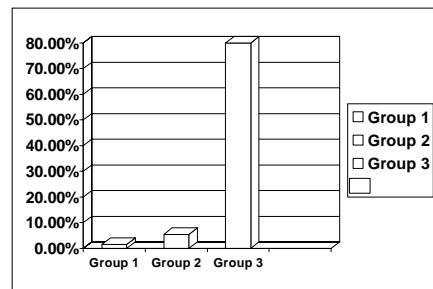
- 12 months after treatment a TSH-stimulated Tg level is obtained after rhTSH administration. The stimulated Tg level 72 hours after the second dose is <0.2 ng/ml with undetectable anti-Tg antibodies. Following this, a neck ultrasound is performed that does not reveal obvious evidence of thyroid cancer.
- This is consistent with a complete remission!
- How reliable is this assessment?

TSH-stimulated Tg predicts tumor recurrence

- Kloos and Mazzaferri examined 107 patients with thyroid cancer for recurrence as a function of prior stimulated Tg level. Patients were stratified to three groups based on initial TSH-stimulated Tg levels
 - Group 1: TSH-stimulated Tg <0.5 ng/ml (n=68)
 - Group 2: TSH-stimulated Tg 0.6 to 2.0 ng/ml (n=19)
 - Group 3: TSH-stimulated Tg >2.0 ng/ml (n=20)
- Pts were re-evaluated for recurrence based on Tg levels and imaging, including neck ultrasound at a mean of 3.3 yrs later

Kloos, RT et al. *J Clin Endocrinol Metab.* 90:5047-5057, 2005

Stimulated Tg levels Predict Recurrent/residual Thyroid Cancer



Kloos, RT et al. *J Clin Endocrinol Metab.* 90:5047-5057, 2005

Does a negative TSH-stimulated Tg predict a lack of tumor recurrence?

- Castagna, et al reported on a cohort of patients with undetectable stimulated Tg one year after I-131 therapy (n=68)
- 67 patients underwent repeat stimulated Tg and neck ultrasound 2.5 yrs later
- 1 patient (1.5%) developed a recurrence at follow up detected both by stimulated Tg and the neck ultrasound, but not basal Tg did not.

Castagna MG. *J Clin Endocrinol Metab* 2008; 93: 76-81.

Long-term Recurrence Risk

- Overall survival of patients with stage 1 thyroid cancer is similar to the general population
- The risk of residual or recurrent disease is ~15% with some being diagnosed decades later.
- For this reason, some form of long-term monitoring is recommended...usually based on Tg levels unless antibodies are positive along with periodic neck ultrasound.

Case

- The excellent prognosis was discussed in detail with the patient.
- Due to her young age, overall good health, and the relatively short duration of follow up of the studies, a repeat stimulated Tg and neck ultrasound are planned to be done about 3-5 years after her diagnosis. Tg levels will be measured on L-thyroxine every 6 months for the second year, then yearly thereafter if they remain undetectable.

Summary

- Thyroid Cancer is increasingly prevalent. In most cases it is early stage at diagnosis.
- When diagnosed early, it has an excellent long-term prognosis.
- Residual or recurrent disease in the neck is common and may require additional treatments with surgery and/or I-131.
- Recurrences can occur late, so long-term monitoring is recommended.
- Mortality from thyroid cancer is uncommon and is predicted by tumor stage at diagnosis.