Diabetes and thyroid diseases: clinical features and management
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Thyroid cancer: pre and post-operative management according to the new guidelines

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Haugen BR et al.
2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 26: 1-133, 2016.

http://www.thyroid.org/professionals/ata-professional-guidelines/
Objectives

- Highlight new developments in the 2015 American Thyroid Association Guidelines for the Management of Thyroid nodules and Thyroid Cancer.
- Discuss ultrasound-based evaluation of nodules.
- Emphasize need for dynamic staging.
- Discuss selective use of radioiodine therapy: less is more.
- Illustrate the use of tyrosine-kinase inhibitor therapy in advanced thyroid cancer.
Patient C. A-R., ♀, 59 y

- From an iodine-deficient region in Mexico
- TSH 2.8 mU/l
- Otherwise healthy
What is your next step?

1. $^{123}$Iodine uptake and scan?

1. Fine-needle aspiration biopsy?
What is the risk of malignancy?

1. Low

2. High
Ultrasound for the indication of FNA

ATA Nodule Sonographic Pattern Risk of Malignancy

- **High Suspicion** (70-90%)
  - microcalcifications
  - hypoechoic, irregular margins
  - hypoechoic, taller than wide
  - hypoechoic, irregular margins, extrathyroidal extension
- **Intermediate Suspicion** (10-20%)
  - hypoechoic solid regular margin
  - hypoechoic solid regular margin
- **Low Suspicion** (5-10%)
  - hyperechoic solid regular margin
  - isoechoic solid regular margin
  - partially cystic with eccentric solid area
- **Very low Suspicion** (<3%)
  - spongiform
  - partially cystic no suspicious features
  - partially cystic no suspicious features
- **Benign** (<1%)
  - cyst
Recommendation

Thyroid nodule diagnostic FNA is recommended for:
A) Nodules ≥ 1 cm with high suspicion sonographic pattern
B) Nodules ≥ 1 cm with intermediate suspicion sonographic pattern
C) Nodules ≥ 1.5 cm with low suspicion sonographic pattern
D) Nodules ≥ 2 cm with very low suspicion sonographic pattern (e.g. spongiform)

Thyroid nodule diagnostic FNA is not required for:
E) Nodules that do not meet the above criteria
F) Nodules that are purely cystic
Patient C. A-R., ♀, 59 y

- Papillary thyroid cancer (classic type)
- Multifocal tumor
- 4.5 x 2.1 x 3.0 cm in right lobe, 1.9 cm in left lobe, 6 mm in left lobe.
- Positive margin with extension of tumor tissue into the strap muscle on the right.
- 2/7 positive lymph nodes.
- T4aN1aMx
What is the initial risk level for this patient?

1. Intermediate risk

1. High risk
Why perform cancer staging?

To provide **prognostic/predictive** information, which informs **therapeutic or surveillance** strategies.

- **AJCC/UICC TNM staging** Predicts Mortality
- **ATA Initial Risk Stratification** Predicts Risk of Recurrence Updated in 2015 Guidelines
- **ATA Response to Therapy Assessment** Dynamic Risk New in 2015 Guidelines Acknowledges that Risk Changes over time
ATA Initial Risk Stratification

2009 Guidelines
• Primary tumor size
• Resection margin
• Lymph node involvement
• Distant metastasis

2015 Guidelines
All of the above +
• Histologic variants
• Vascular invasion and number of invaded vessels
• Multifocality
• Number of lymph nodes examined and involved
• Site of the largest metastatic lymph node focus
• Extranodal extension
### ATA Low Risk

- **Papillary Thyroid Cancer** (with all of the following):
  - No local or distant metastases
  - All macroscopic tumor has been resected
  - No tumor invasion of loco-regional tissues or structures
  - The tumor does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma)
  - If $^{131}$I is given, there are no RAI avid metastatic foci outside the thyroid bed on the first post-treatment whole-body RAI scan

- No vascular invasion
- Clinical N0 or $\leq$ 5 pathologic N1 micrometastases ($<0.2$ cm in largest dimension)
- Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer
- Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal ($<4$ foci) vascular invasion
- Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including BRAF V600E mutated (if known)
### ATA Initial Risk Stratification

#### ATA Intermediate Risk
- Microscopic invasion of tumor into the perithyroidal soft tissues
- RAI avid metastatic foci in the neck on the first post-treatment whole-body RAI scan
- Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma)
- Papillary thyroid cancer with vascular invasion
- Clinical N1 or >5 pathologic N1 with all involved lymph nodes < 3 cm in largest dimension
- Multifocal papillary microcarcinoma with extrathyroidal extension and V600E BRAF mutated (if known)

#### ATA High Risk
- Macroscopic invasion of tumor into the perithyroidal soft tissues (gross extrathyroidal extension)
- Incomplete tumor resection
- Distant metastases
- Post-operative serum thyroglobulin suggestive of distant metastases
Risk of Structural Disease Recurrence
(In patients without structurally identifiable disease after initial therapy)

High Risk
Gross extrathyroidal extension, incomplete tumor resection, distant metastases, or lymph node >3 cm

Intermediate Risk
Aggressive histology, minor extrathyroidal extension, vascular invasion, or > 5 involved lymph nodes (0.2-3 cm)

Low Risk
Intrathyroidal DTC ≤ 5 LN micrometastases (< 0.2 cm)

FTC, extensive vascular invasion (≈ 30-55%)
pT4a gross ETE (≈ 30-40%)
pN1 with extranodal extension, >3 LN involved (≈ 40%)
PTC, > 1 cm, TERT mutated ± BRAF mutated* (>40%)
pN1, any LN > 3 cm (≈ 30%)
PTC, extrathyroidal, BRAF mutated* (≈ 10-40%)
PTC, vascular invasion (≈ 15-30%)
Clinical N1 (≈20%)
pN1, > 5 LN involved (≈20%)
Intrathyroidal PTC, < 4 cm, BRAF mutated* (≈10%)
pT3 minor ETE (≈ 3-8%)
pN1, all LN < 0.2 cm (≈5%)
pN1, ≤ 5 LN involved (≈5%)
Intrathyroidal PTC, 2-4 cm (≈ 5%)
Multifocal PMC (≈ 4-6%)
pN1 without extranodal extension, ≤ 3 LN involved (2%)
Minimally invasive FTC (≈ 2-3%)
Intrathyroidal, < 4 cm, BRAF wild type* (≈ 1-2%)
Intrathyroidal unifocal PMC, BRAF mutated*, (≈ 1-2%)
Intrathyroidal, encapsulated, FV-PTC (≈ 1-2%)
Unifocal PMC (≈ 1-2%)
Do you recommend radioiodine therapy?

1. No

1. I will only decide after a diagnostic scan
Differentiated use of radioiodine

Initial Therapy

Evaluation of post-operative disease status (Thyroglobulin, ultrasound, RAI scanning)

Differentiated approach to radioiodine therapy
Differentiated use of radioiodine

- Remnant ablation
- Destruction of residual thyroid tissue to facilitate surveillance
- Adjuvant radioiodine therapy
- RAI therapy of presumed residual or metastatic disease
- Radioiodine therapy
- RAI therapy for known residual or metastatic disease
### Differentiated use of radioiodine

| ATA Low Risk | RAI not typically recommended (if all present) | - Classic papillary thyroid carcinoma  
- Intrathyroidal lesion  
- Unifocal or multifocal  
- Postoperative Tg <1 ng/ml  
- No Tg-antibodies |
| ATA Intermediate Risk | RAI selectively recommended | - Primary tumor 1 – 4 cm  
- High risk histology  
- Lymphovascular invasion  
- Cervical lymph node metastases  
- Macroscopic multifocality (one focus > 1 cm)  
- Postoperative Tg <5-10 ng/ml  
- Presence of Tg-Abs |
| ATA High Risk | RAI typically recommended (if any present) | - Gross extrathyroidal extension  
- Primary tumor > 4 cm  
- Postoperative Tg >5-10 ng/ml  
- Known or suspected distant metastases |
Do you recommend radioiodine therapy?

- Diagnostic scan: Uptake in several neck lesions and diffuse uptake in both lungs
  
  - Therapy with 175 mCi $^{131}$iodine
TSH suppressive therapy

- Normalize TSH
  - Prevent Symptoms of Hypothyroidism
- Suppress TSH
  - Decreased Risk of Recurrence of Thyroid Cancer

No or small amount of functional thyroid tissue
What is your TSH goal?

1. Undetectable
2. 0.1 to 0.4 mU/l
## Targets for TSH suppression

<table>
<thead>
<tr>
<th>Increasing risk of TSH suppression</th>
<th>Excellent</th>
<th>Indeterminate</th>
<th>Biochemical Incomplete**</th>
<th>Structural incomplete</th>
</tr>
</thead>
<tbody>
<tr>
<td>No known risk</td>
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<tr>
<td>Menopause</td>
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<td>Tachycardia</td>
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<td>Osteopenia</td>
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<tr>
<td>Age &gt; 60</td>
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<tr>
<td>Osteoporosis</td>
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<tr>
<td>Atrial fibrillation</td>
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* - 0.5 mU/L represents the lower limit of the reference range for the TSH assay which can be 0.3-0.5 mU/L depending on the specific assay

** - TSH target for patients with a biochemical incomplete response can be quite different based on original ATA risk, Tg level, Tg trend over time and risk of TSH suppression
TSH suppressive therapy

Normal range for TSH: 0.4 - 4.0 mU/L

Low risk: TSH 0.1 – 0.5 mU/L
High risk: TSH <0.1 mU/L

With increasing suppression of TSH:

- Increased risk of atrial fibrillation
- Aggravation of postmenopausal osteoporosis
- Increased risk of signs/symptoms of thyrotoxicosis
Less is more

Less is More

Kim B et al.
Less is More: Comparing the 2015 and 2009 American Thyroid Association Guidelines for Thyroid Nodules and Cancer. Thyroid. 2016 May 3. [Epub ahead of print]
Summary and Perspectives

- Worldwide, we are faced with an increasing incidence of thyroid cancer.
- Detailed guidelines provide an evidence-based framework for the diagnosis and management of thyroid cancer.
- FNA should be recommended based on ultrasound risk stratification model.
- Cytological results should be reported according to the Bethesda cytology system.
- Molecular markers start to complement cytology in the diagnosis of indeterminate results.
Summary and Perspectives

- Lobectomy may be considered as the initial surgical approach for follicular-cell derived thyroid cancers from 1-4 cm in size.

- Low volume lymph nodal metastases are now considered low risk.

- Radioiodine remnant ablation and therapy should follow a risk-based indication. Low risk patients do not benefit from radioiodine therapy.
Summary and Perspectives

- Surveillance needs to be individualized and the response to therapy needs to be stratified.
- For patients with advanced thyroid cancer, new systemic therapies have shown efficacy in terms of increasing the progression-free survival (PFS); the impact on long-term survival awaits further characterization.
- Redifferentiation therapies may be able to reinduce radiiodine uptake in selected patients in the future.
Surveillance for differentiated thyroid cancer

Questions

- Residual disease?
- Recurrent disease?

If yes, where?

Therapy
Surveillance for differentiated thyroid cancer

- Needs to be individualized!

- Measurement of Thyroglobulin (Tg), Tg-Abs
- Ultrasound of the neck
- Whole body scan with radioiodine
  - After withdrawal of thyroid hormone
  - After stimulation with recombinant human TSH
- CT chest, neck
- PET-Scan (Tg-positive, scan-negative patients)
Therapy for residual/recurrent thyroid cancer

- Needs to be individualized!
- Surgery
- Radioiodine
- Ethanol injection into locoregional lymph nodes
- External beam radiation
- Systemic therapy (Tyrosine kinase inhibitors)
Metastatic poorly differentiated thyroid carcinoma with predominant insular pattern. T3N\textsuperscript{x}M1, STAGE IVC.

- 5/16/2012 thyroidectomy at OSH.
- 5.2 cm lesion, capsular invasion present, extensive lymphatic and vascular invasion, minimal focal extension into perithyroidal tissue.
- Summer 2012 \textsuperscript{131}iodine therapy. Dose and scan findings not known.
- 7/1/2013 PET scan no abnormal FDG uptake.
- 7/8/2013 diagnostic withdrawal \textsuperscript{131}iodine scan without uptake.
Patient L.B., ♀, 59 y

- 4/15/14 TSH 0.04, FT4 1.1, TG 275.10, TG-Ab <0.9.
- 9/22/14 WBS: questionable prominence of activity diffusely in the lung fields, which could relate to the multiple pulmonary metastases. However, the activity is not intense or focal.
- 9/25/14 200.0 mCi $^{131}$iodine therapy.
- 10/2/14 post-therapy scan: no definite functioning thyroid tissue within the neck; very mild diffuse activity in both lungs, but this is not focal or intense.
- 12/5/2014 CT: Progression of multiple metastatic lesions.
Patient L.B., ♀, 59 y
Patient L.B., ♀, 59 y

- 1/2015 ER admission with acute pulmonary distress. Discharge on home oxygen.
- Started on Sorafenib on 2/16/2015. The dose had to be reduced from 400 to 200 mg because of hand-foot syndrome.

4/15/15: CT scan showed decrease lung nodule size and mediastinal lymphadenopathy.
Response to Lenvatinib

Patient L.B., CT 12/5/2014

Patient L.B., CT 8/25/2015
Lenvatinib in radioiodine-refractory thyroid cancer

## Tyrosine kinase inhibitors for thyroid cancer

<table>
<thead>
<tr>
<th>Cancer subtype</th>
<th>Drug</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Papillary, Follicular, Hürthle</td>
<td>Sorafenib, Lenvatinib, Pazopanib, Vemurafenib, Dabrafenib, Trametinib, Sunitinib, Cediranib, Fostamatinib, Vandetanib, Cabozantinib</td>
<td>FDA approved, FDA approved</td>
</tr>
<tr>
<td>Medullary</td>
<td>Vandetanib, Cabozantinib, Sunitinib, Motesanib</td>
<td>FDA approved, FDA approved</td>
</tr>
</tbody>
</table>
Patient L.B., ♀, 59 y
Patient L.B., ♀, 59 y

- **6/20/15:** CT scan showed decrease lung nodule size and stable mediastinal lymphadenopathy but progression of disease in the liver, peritoneum, abdominal wall and a gluteal soft tissue lesion.

- **6/22/15:** started on Lenvatinib 24 mg PO daily. cfDNA genomic profiling showed no actionable mutation.

- **8/25/2015 CT** The lung nodules are smaller. Some are cavitating suggesting a positive response to therapy. The subcutaneous nodules have almost resolved. Resolved hepatic lesions.