Postoperative Management of Thyroid Cancer

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Faculty/Presenter Disclosure

• **Faculty:** Sebastiano Filetti

• **Relationships with commercial interests:**
  – Speakers Bureau/Advisory Board: AstraZeneca, Exelixis
Management of DTC: old paradigms

AXIOMS: All patients need
- Total thyroidectomy
- RAI therapy
- L-T4 suppressive therapy
- Life-long surveillance

Mazzaferri E & Kloos R, JCEM, 2001
Management of DTC: Today

Challenges in clinical practice

- Do all patients require total thyroidectomy?
- Do all patients require RAI remnant ablation therapy?
- Do all patients require TSH suppressive therapy?
- Do all patients require life-long surveillance?
Today

New paradigms

We are moving from a population-wide versus individual-based approach

Not all patients are the same

Low risk  Intermediate risk  High risk
### Changing paradigms: why?

#### 1. Changing population we see today

#### Stage at diagnosis & survival (SEER 2001-2008)

<table>
<thead>
<tr>
<th>Stage at diagnosis</th>
<th>5-year Relative Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrathyroidal</td>
<td>99.8</td>
</tr>
<tr>
<td>Regional metastases</td>
<td>96.8</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>55.4</td>
</tr>
<tr>
<td>Unknown</td>
<td>87.6</td>
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</tbody>
</table>

- **Intrathyroidal**: 68%
- **Regional metastases**: 25%
- **Distant metastases**: 5%
- **Unknown**: 2%
Changing paradigms: why?

1. Changing population we see today
2. Changing tools
Post-surgery follow-up: **aims**

1. To tailor management strategies to individual risk
2. To identify patients who are disease-free
3. To *early* identify patients with persistent disease
4. To *early* identify patients with recurrent disease
5. To monitor serum TSH levels throughout life

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**Early follow-up**

- 0 months
- 2-3 months

**Late follow-up**

- 12 months
Post-surgery follow-up: steps

What is the risk of persistent disease?

Do they need ^131I therapy?

Are they disease-free or do they still have persistent disease?

Early follow-up
Definition of the “risk”

How to assess the risk?

1. At diagnosis

- Surgery

- 0 months
- 2-3 months
- 12 months

months
Definition of the “risk”

Assessing the risk: staging systems

- AJCC/UICC
- AGES
- AMES
- EORTC
- MACIS
- OSU
- SKMNC

All these staging systems assess the mortality risk
Definition of the “risk”

Assessing the risk of recurrence: ATA score

Low
- pT1-2
- Nx/N0
- M0
- no aggressive histology

Intermediate
- pT3
- N1
- M0
- aggressive histology

High
- pT4
- M1

Intrathyroidal disease
Loco-regional disease
Metastatic disease

ATA guidelines, 2009
Definition of the “risk”

How to assess the risk?

- Surgery \( \pm I^{131} \)

Why?
- clinical course of the disease
- response to initial therapy and any subsequent treatment

2. Changes in risk category

“Appropriate management requires an ongoing reassessment of the risk... as new data are obtained during follow-up”

ATA guidelines, 2009
Post-surgery follow-up: steps

What is the risk of persistent disease?

Do they need $^{131}$I therapy?

Early follow-up

months

0 2-3 12
# $^{131}$I therapy: rationales

<table>
<thead>
<tr>
<th></th>
<th>Target</th>
<th>Goal</th>
<th>Expected benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Thyroid remnant ablation</td>
<td>Normal cells</td>
<td>Simplifying subsequent detection of residual/recurrent tumor tissue (DxWBS, Tg measurement)</td>
<td>Early detection of residual/recurrent tumor tissue</td>
</tr>
<tr>
<td>2. Adjuvant therapy</td>
<td>Neoplastic cells</td>
<td>Destruction of occult foci of neoplastic cells (if any)</td>
<td>To improve disease-free survival and overall survival</td>
</tr>
<tr>
<td>3. Therapy</td>
<td>Neoplastic cells</td>
<td>Destrucions of documented residual neoplastic cells</td>
<td>To improve overall survival</td>
</tr>
</tbody>
</table>
Clinical case #1

- **Total thyroidectomy** (multinodular goiter; right lobe growing nodule; neck discomfort)
- **Histology**: left side, papillary thyroid cancer, classic variant, 7 mm
  - pT1a, Nx – Stage I

Does he need $^{131}$I ablation/adjuvant therapy?
**Micro-PTC (PTMC): recurrences**

**Metanalysis**

What is the reason for this discrepancy?

Size cannot be used as the *only* criterion for determining the risk of recurrence.

Roti E et al., Eur J Endocrinol, 2008
PTMC: size not the only criterion!

Need for risk stratification

- Not family history of thyroid cancer
- No history of head and neck irradiation
- Tumor staging: Nx, N0, M0
- No extension beyond thyroid capsule
- Unifocal
- Not aggressive histologic subtype (e.g., tall cell subtype)
- Not locally invasive (angiolympathic invasion)

Very low risk patients

Durante et al., JCEM, 2010
ETA Consensus, 2006
PTMC: $^{131}$I therapy yes or no?

**Patients**

The majority!

Micro-PTC patients

n=946

- Very Low risk*
  n=710 (75%)

- Low/intermediate/high risk
  n=236 (25%)

Study population

n= 312 (44%)

≥ 5 years of follow-up

* Inclusion criteria

- Not family history of thyroid cancer
- No history of head and neck irradiation
- Tumor staging: $T1 \leq 1cm$, $N0$, $M0$
- No extension beyond thyroid capsule
- Unifocal
- Not aggressive histologic subtype (e.g., tall cell subtype)
- Not locally invasive (angiolympathic invasion)

Durante et al., JCEM, 2010
1. A set of clinical criteria can reliably identify those patients with micro-PTC who are most likely to experience complete cures with **total thyroidectomy**.

2. In these patients at **very low risk** (~75% of all micro-PTC cases), postoperative **131I therapy** is not necessary.
Clinical cases #2 & 3

- 51 yrs
  - Long standing multinodular goiter
  - Total thyroidectomy because of neck discomfort
  - **Histology**: PTC, classic variant, 12 mm
  - **pT1b, Nx** – Stage I
  - **Risk**: low

- 63 yrs
  - Cytologically suspicious thyroid nodule; suspicious lymph nodes
  - Total thyroidectomy + central neck dissection
  - **Histology**: PTC, follicular variant, 18 mm, minimal extrathyroidal extension, 2 out of 21 metastatic lymph nodes
  - **pT3, N1a** – Stage III
  - **Risk**: intermediate

**Do they need \(^{131}\text{I} \text{ablation/adjuvant therapy?**}**
131I therapy: yes or no?

Conflicting data

Favour
3. Samaan NA et al., JCEM 1992
6. Jonklaas J et al., Thyroid 2006

Against
5. Sugitani I & Fujimoto Y, Endocr J 1999
Conflicting data

Accurate risk assessment appears to be the key to identifying DTC patients who are likely to benefit from postoperative radioiodine
131I therapy: yes or no?

Need to estimate the risk of residual disease

Low risk

131I NO
n=290

131I YES
n=495

Follow-up:
6 yrs (2.5-25)

Disease 1 (0.4%)

Disease 0

Patients

- Tumor staging: T1-T2, Nx/N0, M0
- Not aggressive hystologic subtype (e.g., tall cell subtype)
- Not locally invasive (angiolympathic invasion)

Durante et al., JCEM, 2012
**131I therapy: yes or no?**

**Need to estimate the risk of residual disease**

**Low/Intermediate risk**

131I NO
n=120

Follow-up: 5 yrs (0.5-34)

Disease 5 (4.1%)

**Patients**

- T1b-T3 (<4 cm)
- Nx/N0/N1 (minimal lymph node involvement)
- Post-surgery, not stimulated Tg <10 ng/ml (negative TgAb)

Vaisman et al., Clin Endocrinol, 2011
Need for prospective randomized studies

A prospective randomized trial in low to intermediate risk thyroid cancer patients is now underway in Europe

PTC
Non aggressive histological features
pT1b, pT2, pT3, intrathyroidal only
pNX, N0, N1a

FTC/ Hürthle cell cancer
Minimally invasive
pT1b, pT2, intrathyroidal

This strategy shift is reflected in the 2009 ATA guidelines, which recommend tailoring case management to individual risk levels.
### 131I therapy: yes or no?

**The 2009 ATA guidelines recommendations**

<table>
<thead>
<tr>
<th>131I NO</th>
<th>“Grey zone”</th>
<th>131I YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 (≤1 cm)</td>
<td>T1 (1-2 cm)</td>
<td>T3 (&gt;4 cm)</td>
</tr>
<tr>
<td>N0/Nx</td>
<td>T2</td>
<td>T4</td>
</tr>
<tr>
<td>Recommendation E</td>
<td>Recommendation I</td>
<td>Recommendation B</td>
</tr>
<tr>
<td>Recommendation I</td>
<td>Recommendation C</td>
<td>Recommendation B</td>
</tr>
<tr>
<td></td>
<td>T3 (extrathyroidal)</td>
<td>M1</td>
</tr>
<tr>
<td></td>
<td>Recommendation I</td>
<td>Recommendation A</td>
</tr>
<tr>
<td></td>
<td>N1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recommendation C</td>
<td></td>
</tr>
</tbody>
</table>

**Low risk**

**Low-Intermediate risk**

**Intermediate-High risk**
Clinical cases

- **Histology:** PTC, classic variant, 12 mm (pT1b, Nx) – Stage I
  - 51 yrs

- **Histology:** PTC, follicular variant, 18 mm, extrathyroidal extension, 2 out of 21 metastatic lymph nodes (pT3, N1a) – Stage III
  - 63 yrs

Early follow-up

- ✓ Risk: LOW
- ✓ ¹³¹I: NO

- ✓ Risk: INTERMEDIATE
- ✓ ¹³¹I: YES

What dose?

How prepare the patient?
The 2009 ATA guidelines recommendations

“If post-operative $^{131}$I is used, the ATA guidelines advise using the *lowest activity* needed to ensure successful remnant ablation”

What is the lowest $^{131}$I activity for remnant ablation?

R36 – Recommendation B (ATA guidelines, 2009)
Randomized clinical trials: ESTIMABL, HiLo

131I remnant ablation

DTC patients
Total thyroidectomy

- rhTSH plus thyroid hormone therapy
  - 30 mCi (1.1 GBq)
  - 100 mCi (3.7 GBq)

- Withdrawal
  - 30 mCi (1.1 GBq)
  - 100 mCi (3.7 GBq)

ESTIMABL: Schlumberger M et al., NEJM, 2012
HiLo: Mallick U et al., NEJM, 2012
Successful remnant ablation

**ESTIMABL**

- 30 mCi rhTSH: 90%
- 100 mCi Withdrawal: 93%

**HiLo**

- 30 mCi rhTSH: 84%
- 100 mCi Withdrawal: 87%

**ESTIMABL:** Schlumberger M et al., *NEJM*, 2012

**HiLo:** Mallick U et al., *NEJM*, 2012
If residual microscopic disease is suspected or documented, or if there is a more aggressive tumor histology (e.g., tall cell, insular, columnar cell carcinoma), then higher activities (100–200 mCi) may be appropriate.
Clinical case #4

- Follicular thyroid carcinoma (pT2, N0, M1 – Stage IVc – Risk: High)
- RxWBS (3.7 GBq): RAI avid pulmonary and mediastinal lesions
- 18-FDG uptake at PET scan

**Benefit from $^{131}$I therapy?**
131I therapy: yes or no?

131 treatment

Survival & 131I avidity

Group 1:
- 131I-avid lesions
- remission

Group 2:
- no/low 131I uptake
- persistent disease

Group 3:
- 131I-avid lesions
- persistent disease

Survival after metastasis discovery

Durante C, JCEM, 2006
131I therapy: yes or no?

18-FDG-PET scan: estimating RAI response

Survival at 60 months

- RAI + FDG - 95%
- RAI + FDG + 45%
- RAI - FDG + 45%

RAI: radioactive iodine
FDG: [18F]fluoro-2-deoxy-D-glucose

Robbins et al. J JCEM 2006
**131I therapy: yes or no?**

**RAI refractory disease**

1. Index lesion that did not take up 131I on a RAI scan
2. RAI-avid index lesion that did not respond to therapeutic RAI treatment
3. 18F-Fluoro-deoxy glucose avid PET lesions
What is the risk of persistent disease?

Do they need $^{131}\text{I}$ therapy?

Are they disease-free or they still have persistent disease?

Early follow-up
After total or near total thyroidectomy with or without thyroid remnant ablation, disease free comprises ALL of the following:

- No disease clinical evidence
- No tumor's imaging evidence
- Serum Thyroglobulin undetectable during TSH suppression and stimulation
- No anti-thyroglobulin antibodies

ETA Consensus, 2006
ATA guidelines, 2009
The tools of follow up

First line

Neck US

Tg ± rhTSH

Second line

Other imaging modalities

ETA Consensus, 2006
ATA guidelines, 2009
Neck US: why?

Stage at diagnosis

- Persistent or recurrent disease is almost always associated with spread to the cervical lymph nodes
- It usually precedes distant metastasis

**Intrathyroidal**
- **Regional metastases**
- **Distant metastases**
- **Unknown**

SEER summary stage 2000-2007
Neck US: specificity

High specificity

- Cystic change
  Specificity 100%

- Calcifications
  Specificity 100%

Low specificity

- Loss of the fatty hilus
  Specificity 29%

- Rounded shape
  Specificity 64%

- Peripheral vascularity
  Specificity 82%

Leboulleux S, JCEM, 2009
Sensitivity (%)

NeckUS (± FNAB) has a higher sensitivity when compared to stimulated Tg determination in detecting locoregional disease

Pacini F et al., JCEM, 2003
Torlontano M et al., JCEM, 2004
The 2009 ATA guidelines recommendations

**Neck US**

- Following surgery, cervical US to evaluate the thyroid bed and central and lateral cervical nodal compartments should be performed at 6–12 months and then periodically

R48 - Recommendation rating: B

**DxWBS**

- Low-risk patients with an undetectable Tg on thyroid hormone and a negative US do not require routine DxWBS during follow-up
- It may be of value in the follow-up of patients with high or intermediate risk of persistent disease

R46-47 - Recommendation rating: F-C
The tools of follow up

First line

- Neck US
- Tg ± rhTSH

Second line

- Other imaging modalities

ETA Consensus, 2006
ATA guidelines, 2009
Thyroglobulin (Tg)

No $^{131}$I therapy:

may I use serum Tg measurement during the follow-up?

Basal Tg

$^{131}$I -

$^{131}$I +

Tg after rhTSH
Tg “natural history”

Not ablated patients

1. 60% of pts had already undetectable Tg values at the 1st post-operative evaluation (about 12 months)

2. In the remaining 40%, Tg values remained stable or declined spontaneously over time

Durante C et al., JCEM, 2012
Tg trend & outcome

Pts in remission (77/78)  Pts with recurrence (1/78)

Serum Tg (ng/mL)

Mean values

Years

0 0.1 0.2 0.3 0.4 0.5

1 2 3 4 5 6 7

Treatment

Suspicious lymph node at neck US

Durante C et al., JCEM, 2012
Thyroglobulin (Tg)
How to manage rhTSH-Tg?

12 months after rhTSH

- Tg < 1 ng/ml
- Tg 1-10 ng/ml
- Tg > 10 ng/ml

Negative results
High NPV (~99%)

Positive results
Low PPV (20-50%)

The main contribution of rhTSH-Tg is to identify patients who are cured (the majority!!)

Torlontano M et al., JCEM, 2004; Brassard M et al., JCEM, 2011
How to manage rhTSH-Tg?

12 months Tg after rhTSH

Tg <1 ng/ml
- No other abnormalities
Long term follow-up

Tg 1-10 ng/ml
- No other abnormalities
Monitor Tg

Tg >10 ng/ml
- And/or other abnormalities
Staging ± therapy

decreasing values rising values

PPV=100%

Adapted from: ETA consensus, 2006; ATA guidelines, 2009

Baudin E et al., JCEM, 2003
Torlontano M et al., JCEM, 2004
Highly sensitive Tg: cut-off?

Optimal cut-off (according to ROC curves)

Basal Tg = 0.2–0.3 ng/ml
- Sensitivity: 65%
- Specificity: 85-87%

rhTSH-Tg = 1 ng/ml
- Sensitivity: 73-76%
- Specificity: 88-89%

How to improve sensitivity & specificity?

1. By combining highly sensitive Tg with neck ultrasound (Castagna et al., J Endocrinol Invest, 2011)

2. By observing the trend of serial serum Tg determinations (Durante C et al., JCEM, 2012)

Schlumberger M et al, JCEM, 2007
The tools of follow up

First line

- Neck US
- Tg ± rhTSH

Second line

- Other imaging modalities

ETA Consensus, 2006
ATA guidelines, 2009
Other imaging modalities

Assessment of disease extent

- Mediastinum, lung
  - CT
- Liver
  - US
  - MRI or CT dual-phase
- Bone
  - Bone scintigraphy, MRI
- Brain
  - CT or MRI

Giraudet et al, JCEM, 2007
Tg(+) & imaging(-) patients?

The 2009 ATA guidelines recommendations

“Empiric radioactive iodine therapy (100–200 mCi) might be considered in patients with elevated or rising serum Tg levels in whom imaging has failed to reveal a potential tumor source”

What is the sensitivity of RxWBS in detecting disease in these patients?

What about $^{18}$FDG PET/CT?

R75 – Recommendation C (ATA guidelines, 2009)
Tg(+) & imaging(-) patients?

**RxWBS Vs $^{18}$FDG PET/CT  $^{131}$I-WBS  $^{124}$I-PET**

Lebouleux S et al., *Thyroid*, 2012

Van Nostrand D et al., *Thyroid*, 2010
Conclusions

• We have diagnostic tools able to effectively distinguishing patients with negligible risks for persistent/recurrent disease from those with higher-risk tumors

• We are moving toward increasingly individualized, risk-tailored diagnostic/therapeutic protocols
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Tribute to Ernie Mazzaferri

Ernie in Rome