Risk Adapted Follow-Up

Individualizing Follow-Up Strategies

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Disclosures

No relevant conflicts of interest
Spectrum of Thyroid Cancer

Natural History
- Histology
- Size of Tumor
- Metastases
- Age at Diagnosis
- Mutational Profile

Response to Therapy
- Surgery
- RAI
- EBRT

Subclinical to Lethal
Changing Paradigms in the Management of Thyroid Cancer

"Traditional Paradigm"
One Size Fits All
Total thyroidectomy
RAI remnant ablation
All with same follow up

"Risk Adapted Paradigm"
Management recommendations based
individualized risk assessment

Increased Emphasis on Assessing Risk & Predicting Outcomes
Risk Stratification

Is she a high risk or low risk patient?

- 22 year old female
- Total thyroidectomy & left MRN dissection
- 2.5 cm, multifocal, well differentiated PTC
- 20/32 lymph nodes positive
- No extrathyroidal extension
- No vascular invasion
- Post-op serum Tg 25 ng/mL (TSH 1 mIU/mL)
Potentially Important Risks

- Recurrence?
- Death from thyroid cancer?
- Complications from surgery?
- Side effects from RAI?
- Initial therapy will be ineffective?
- Distant metastases?
- Needing additional therapy?
- Disease is not RAI avid?
- Not a good Tg producer?
- FDG PET avid?
Risk Stratification in Thyroid Cancer

Static Approach

Risk of Death from Thyroid Cancer
AMES, AGES, MACIS, TNM

Diagnosis → Thyroid Surgery → RAI Ablation → Follow up
Risk Stratification in Thyroid Cancer

Static Approach

Risk of Death from Thyroid Cancer
AMES, AGES, MACIS, TNM

Risk of Recurrence
ATA, LATS, ETA

Diagnosis → Thyroid Surgery → RAI Ablation → Follow up
Risk Stratification in Thyroid Cancer

Static Approach

Risk of Death from Thyroid Cancer
AMES, AGES, MACIS, TNM

Diagnosis → Thyroid Surgery → RAI Ablation → Follow up

Risk of Recurrence
ATA, LATS, ETA
Modified 2009 ATA Risk System
Risk as a Continuum
Risk Adapted Approach to Management

Real Time Prognostication
Response to Therapy Assessment
Delayed Risk Stratification
Dynamic Risk Stratification
Ongoing Risk Assessment

Tuttle, Tala, Shaha et al, Thyroid 2010

“Reconfiguring the Course”
Picture by C Emerson
Editor, Thyroid, 2010
Focus of Yeh

Initial Static Risk Assessments
*Guide initial treatment and early follow-up recommendations*

Dynamic Risk Stratification
*Continually modify those risk estimates as new data becomes available*

Re-evaluate Management Plans
*Stay the course Testing strategy Interventions*

Momesso, Tuttle. *Endo Metab Clinic NA, 2014.*
Results That Modify Risk

Clinical utility far beyond simple disease detection

- Change in serum thyroglobulin over time
- Change in serum Tg antibodies over time
- Results of stimulated thyroglobulin determinations
- Results of follow up Neck US
- Results of RAI scanning
- Other cross sectional imaging
- Results of FDG PET imaging
- Physical examination

Tuttle. Endocrine Practice 2008.
Response To Therapy Definitions

Excellent Response
No clinical, biochemical, or structural evidence of disease

Biochemical Incomplete Response
Persistent abnormal thyrogblobulin values in the absence of localizable disease

Structural Incomplete Response
Persistent or newly identified loco-regional or distant metastases

Indeterminate Response
Non-specific biochemical or structural findings which cannot be confidently classified as either benign or malignant

Risk Adapted Approach to Management

Multiple studies have standardized and validated this approach.
Risk Adapted Approach to Management

Initial Static Risk Assessments
*Guide initial treatment and early follow-up recommendations*

Dynamic Risk Stratification
*Continually modify those risk estimates as new data becomes available*

Why is dynamic risk stratification necessary?
Shouldn't initial risk assessments provide all the guidance we need?

Re-evaluate Management Plans
Stay the course
Testing strategy
Interventions

Momesso, Tuttle. Endo Metab Clinic NA, 2014.
Initial Risk Models Do Not Accurately Predict Final Outcomes

Proportion to which a mathematical model accounts for the variation (dispersion) of a given data set
Why do initial risk models predict final clinical outcomes so poorly?

Errors in Initial Risk Stratification

Histology
Inadequate initial staging

Biological Behavior Is Not Always Predictable
Poorly differentiated thyroid cancers
Follicular cancers with wide extensive vascular invasion

Impact of Therapy
Completeness of initial surgery
RAI avidity
TSH responsiveness
Describing Best Response to Initial Therapy

25 yr old male
Total thyroidectomy & RAI ablation
3.5 cm tall cell variant PTC, 14/19 LN + (2.5 cm, +ENE)

<table>
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<th>Time</th>
<th>Excellent</th>
<th>Biochemical Incomplete</th>
<th>Structural Incomplete</th>
<th>Indeterminate</th>
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<tbody>
<tr>
<td>3 mo</td>
<td>Tg &lt;0.2</td>
<td>Tg 15</td>
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<td>TgAb neg</td>
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<td>TgAb +</td>
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<tr>
<td>6 mo</td>
<td>Tg &lt;0.2</td>
<td>Tg 9</td>
<td>Tg 20</td>
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<tr>
<td></td>
<td>US neg</td>
<td>US neg</td>
<td>US +</td>
<td>US +/-</td>
</tr>
<tr>
<td>12 mo</td>
<td>Tg &lt;0.2</td>
<td>Tg 5</td>
<td>Tg 35</td>
<td>Tg 35</td>
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<tr>
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<td>Imaging neg</td>
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Risk Estimates Using Response to Therapy Assessment

Total Thyroidectomy and RRA (n=471, MSKCC, median F/U 7 yrs)

Outcome at final follow up (%)

- **NED**
- **Persistent Biochemical**
- **Persistent Structural**
- **Death**

<table>
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<tr>
<th>Outcome</th>
<th>Excellent (n=159)</th>
<th>Indeterminate (n=95)</th>
<th>Biochemical Incomplete (n=63)</th>
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<tr>
<td>NED</td>
<td>96%</td>
<td>87%</td>
<td>68%</td>
<td>37%</td>
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<tr>
<td>Persistent Biochemical</td>
<td>15%</td>
<td></td>
<td>38%</td>
<td>15%</td>
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<tr>
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*Median follow up 7 yrs*

*p < 0.001*

Vaisman, Shaha, Tuttle, Thyroid, 2011
**Risk of Persistent/Recurrent Disease**

**Risk Estimates Using Response to Therapy Assessment**

*Total Thyroidectomy and RRA (n=471)*

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<th>Risk Level</th>
<th>All patients</th>
<th>Excellent</th>
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<tr>
<td>Low (n=104)</td>
<td>16%</td>
<td>2%</td>
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<tr>
<td>Intermediate (n=241)</td>
<td>43%</td>
<td>3%</td>
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<td>High (n=126)</td>
<td>84%</td>
<td>14%</td>
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*p < 0.001*

*Tuttle, Shaha Thyroid 2010*
Response to Therapy Risk Stratification Models Provide Better Prognostic Information

Pitoia et al. Thyroid, 2013
Using Response to Therapy Categories to Describe Clinical Status at Any Time Point

25 yr old male
Total thyroidectomy & RAI ablation
3.5 cm tall cell variant PTC, 14/19 LN + (2.5 cm, +ENE)

ATA 2009 Intermediate Risk Patient
AJCC Stage I

3 mo
- Tg 0.3
- TgAb +
- Indeterminate Response

6 mo
- Tg 4
- TgAb rising
- US neg
- Biochemical Incomplete Response

12 mo
- Tg 8
- TgAb rising
- Imaging +
- Structural Incomplete Response
### Using Response to Therapy to Guide Clinical Management

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# Response To Therapy Definitions

*Tg cut points based on initial therapy*

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Momesso, Tuttle J CEM 2016
Risk Adapted Approach to Management

Initial Static Risk Assessments
Guide initial treatment and early follow-up recommendations

Dynamic Risk Stratification
Continually modify those risk estimates as new data becomes available

Old Concept
New Names
Validated/Operationalized
Personalized, Individualized
Thyroid Cancer Management

Re-evaluate Management Plans
Stay the course
Testing strategy
Interventions

Momesso, Tuttle. Endo Metab Clinic NA, 2014.
Case 1

37 year old female
Total thyroidectomy and RAI ablation
3.5 cm classic PTC, 12/23 + LN (largest 2.5 cm)
6 weeks post-op: Tg 3.4 ng/mL, TSH 0.6 mIU/L, TgAb neg
Post therapy scan show only uptake in thyroid bed

6 month later
Tg 2.0, TSH 0.1 mIU/L

1 year later
Tg 2.1 ng/mL, TSH 0.1 mIU/L
Neck US normal
Chest CT normal
Using Response to Therapy to Guide Clinical Management

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Alternate History

37 year old female
Total thyroidectomy and RAI ablation
3.5 cm classic PTC, 12/23 + LN (largest 2.5 cm)
6 weeks post-op: Tg 0.1 ng/mL, TSH 0.6 mIU/L, TgAb neg
Post therapy scan show only uptake in thyroid bed

6 month later
Tg < 0.1, TSH 0.1 mIU/L

1 year later
Tg < 0.1 ng/mL, TSH 0.1 mIU/L
Neck US normal
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Alternate History

37 year old female

Total thyroidectomy, left neck dissection and RAI ablation
3.5 cm classic PTC, 12/23 + LN (largest 2.5 cm)

6 weeks post-op:  Tg 3.4 ng/mL, TSH 0.6 mIU/L, TgAb neg
Post therapy scan show only uptake in thyroid bed

6 month later
Tg 3, TSH 0.1 mIU/L

1 year later
Tg 3.8 ng/mL, TSH 0.1 mIU/L
Neck US: right neck, 1.3 and 1.2 cm abnormal LN
FNA + PTC in 1.3 cm LN
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Alternate History

37 year old female

Total thyroidectomy, left neck dissection and RAI ablation
3.5 cm classic PTC, 12/23 + LN (largest 2.5 cm)
6 weeks post-op: Tg 26 ng/mL, TSH 0.6 mIU/L, TgAb neg
Post therapy scan diffuse uptake in both lungs
Chest CT multiple 3-4 mm nodules bilaterally

6 month later
Tg 15, TSH 0.1 mIU/L

1 year later
Tg 10 ng/mL, TSH 0.1 mIU/L
Neck US normal
Chest CT: the same or slightly better
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