2014 Recommendations for the follow up of Patients with DTC

Using Initial and Ongoing Risk Assessment to guide Clinical Management

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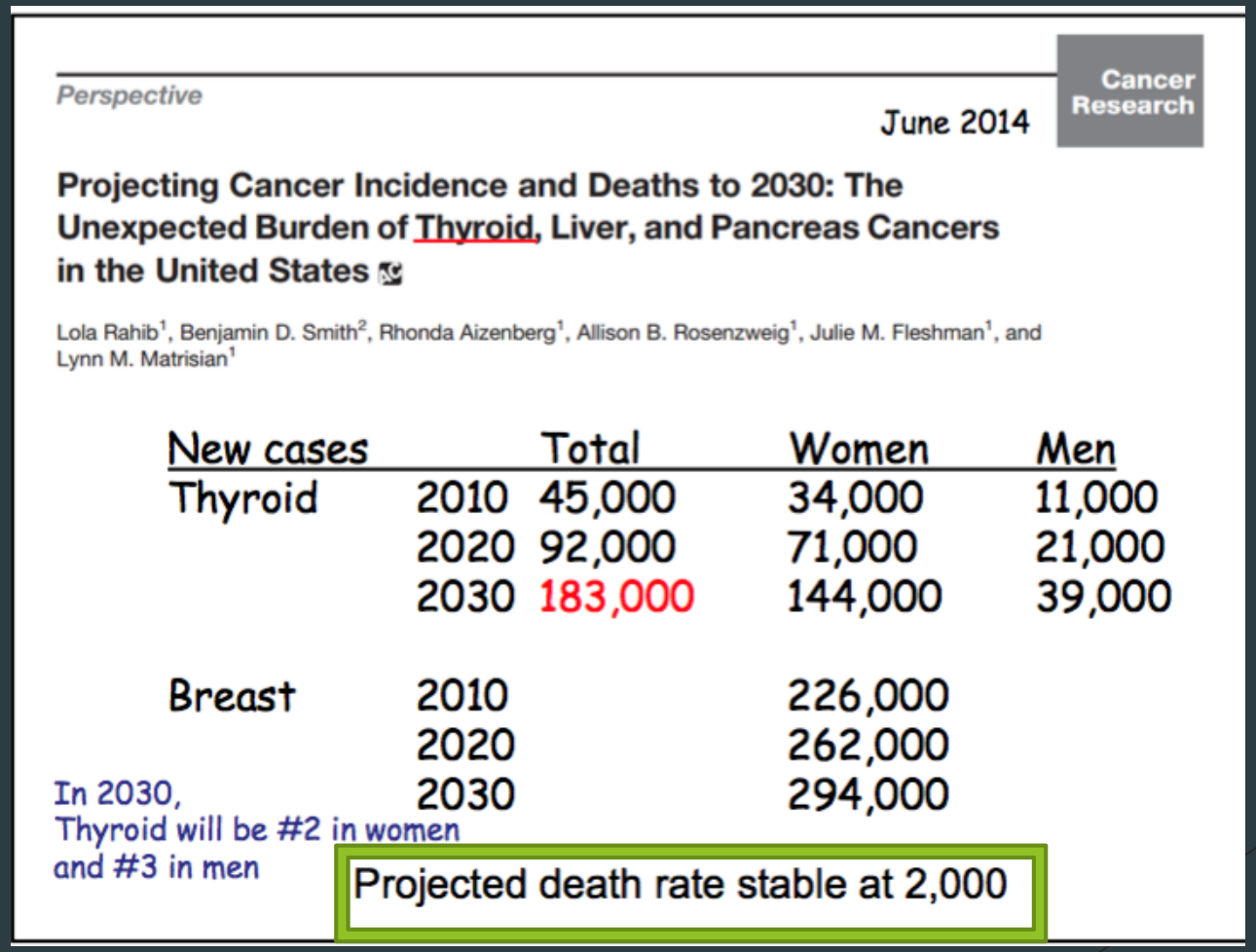
SPED Ponce
April,2016

DIMENSIONS OF THE PROBLEM

- @ 50% of increase in incidence attributed to tumors < than 1 cm
- No change in # of cancers > than 4 cm. 10%
- Peak incidence :40-50 y/o
- 1996-2006: 40% ⬆ in thyroidectomy procedures
- 28% of thyroid cancers are an incidental finding in thyroid surgery
- Increasing incidence partially reflects earlier detection

Projecting Cancer Incidence and Deaths to 2030



Perspective

June 2014

Cancer Research

Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States

Lola Rahib[1], Benjamin D. Smith[2], Rhonda Aizenberg[1], Allison B. Rosenzweig[1], Julie M. Fleshman[1], and Lynn M. Matrisian[1]

New cases		Total	Women	Men
Thyroid	2010	45,000	34,000	11,000
	2020	92,000	71,000	21,000
	2030	183,000	144,000	39,000
Breast	2010		226,000	
	2020		262,000	
	2030		294,000	

In 2030,
Thyroid will be #2 in women
and #3 in men

Projected death rate stable at 2,000

Differentiated Thyroid Cancer Guidelines

Are the New Guidelines Different from the 2009 Guidelines?

Goal: to be evidenced-based & Helpful

	2009	2015
recommendations	80	101
Sub-recommendations	103	175
references	437	998
tables	5	17
figures	5	8

- New questions-8
- New recommendations -21
- Significantly changed recommendations -21

Guideline Grading System

Strength of Recommendation		Quality of Evidence	
SR	Strong recommendation	H	High-quality evidence
WR	Weak recommendation	M	Moderate-quality evidence
NR	No recommendation	L	Low –quality evidence
		I	Insufficient evidence

Changing Paradigms in the Management of Thyroid Cancer

"Traditional Paradigm"
One size fits all
TT, RAI remnant ablation
All with same follow up

"Risk Adapted Paradigm"
Management recommendations based on individualized risk assessment

Increased emphasis on Assessing Risk & predicting Outcomes

Tuttle, Shaka
Thyroid 2010

Staging for Differentiated Thyroid Cancer

- Initial postop Staging (TNM,MACIS) predict disease-specific mortality not recurrences
- ATA Risk Stratification system to estimate risk of persistent/recurrent disease (modified 2014)
- ATA response to therapy (New 2014) Dynamic Risk Stratification based on response to treatment

R47 Role of Postoperative Staging and Risk Stratification AJCC

Estimates disease-specific mortality

TNM staging system for thyroid cancer	
Primary tumor (T)*	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension, limited to the thyroid
T1a	Tumor 1 cm or less, limited to the thyroid
T1b	Tumor more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension, limited to the thyroid
T3	Tumor more than 4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroid extension (eg, extension to sternothyroid muscle or perithyroid soft tissues)
T4a	Moderately advanced disease
	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b	Very advanced disease
	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
All anaplastic carcinomas are considered T4 tumors	
T4a	Intrathyroidal anaplastic carcinoma
T4b	Anaplastic carcinoma with gross extrathyroid extension
Regional lymph nodes (N)¶	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
N1b	Metastasis to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII)
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Anatomic stage/prognostic groups[Δ]			
Papillary or follicular (differentiated)			
Under 45 years			
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
45 years and older			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
Stage IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

SR,MQE

Haugen BR 2015 ATA

rec 48a 2009 ATA Initial Risk Stratification System is rec. for DTC pts. treated with TT, based on its utility in Predicting risk of disease recurrence and/or persistence **(SR,MQE)**

- **LOW RISK**

- Classic or PTC FV +
- No local or distant mets.
- Complete resection
- No tumor invasion
- No vascular invasion and
- If given, no RAI uptake outside thyroid bed

- **INTERMEDIATE RISK**
- **Microscopic ETE**
- **Cervical LN mets**
- **Aggressive histology or**
- **AL invasion**

- **HIGH RISK**
- **Macroscopic gross ETE**
- **Incomplete tumor resection**
- **Distant mets. or**
- **inappropriate Tg elevation**

Cooper Thyroid 2009;19:1167
Haugen Thyroid 2016;26:1

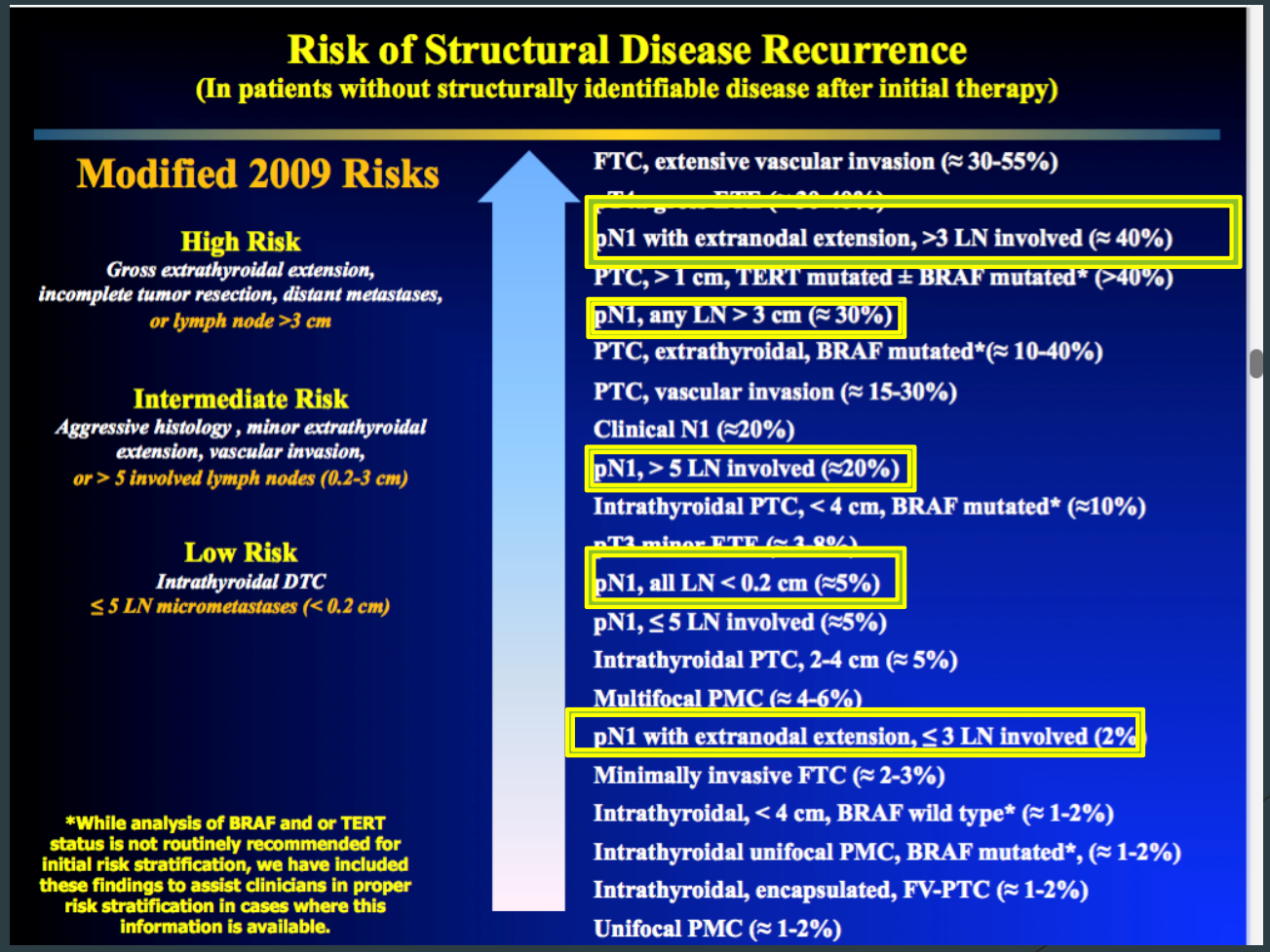
ATA Initial Risk Stratification 2015 Modifications

ATA risk stratification system to estimate risk of persistent/recurrent disease

Low risk	Intermediate risk	High risk
Papillary thyroid cancer with all of the following present:	**Any of the following present:**	**Any of the following present:**
No local or distant metastases	Microscopic invasion into the perithyroidal soft tissues	Macroscopic tumor invasion
All macroscopic tumor has been resected	Cervical lymph node metastases or ^{131}I avid metastatic foci in the neck on the post-treatment scan done after thyroid remnant ablation	Incomplete tumor resection with gross residual disease
No invasion of locoregional tissues	Tumor with aggressive histology or vascular invasion (eg, tall cell, insular, columnar cell carcinoma, Hürthle cell carcinoma, follicular thyroid	Distant metastases
Tumor does not have aggressive histology (eg, tall cell, insular, columnar cell carcinoma, Hürthle cell carcinoma, follicular thyroid cancer, hobnail variant)	Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension*	Postoperative serum thyroglobulin suggestive of distant metastases
No vascular invasion	Multifocal papillary thyroid microcarcinoma with extrathyroidal extension and *BRAF* V600E mutated (if known)*	Pathologic N1 with any metastatic lymph node ≥3 in largest dimension*
No ^{131}I uptake outside the thyroid bed on the post-treatment scan, if done		Follicular thyroid cancer with extensive vascular invasion (>4 foci of vascular invasion)*
Clinical N0 or ≤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)*		

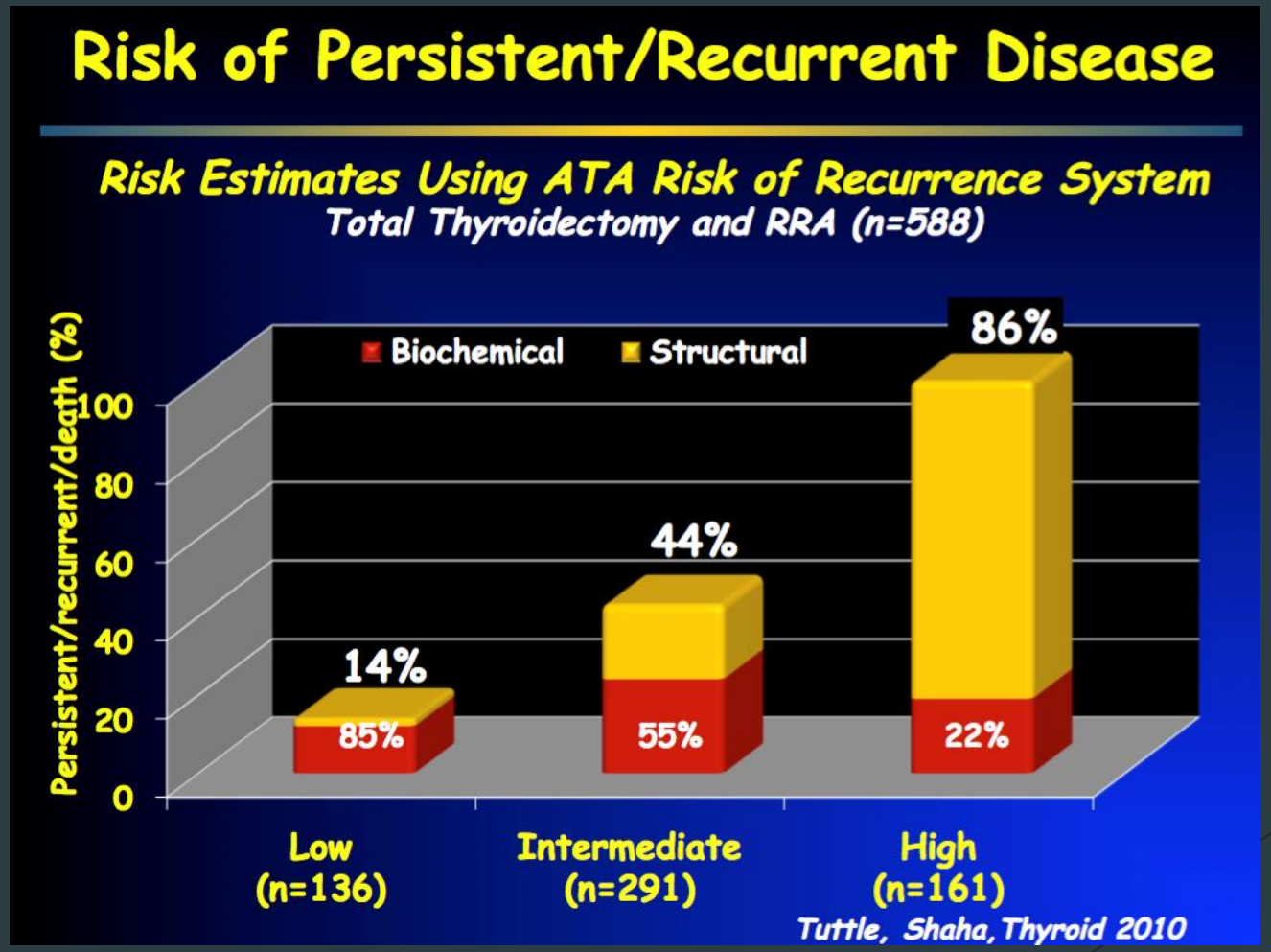
Risk of Structural Disease Recurrence

(In patients w/out structurally identifiable disease after initial therapy)



- The prognostic significance of nodal mets from PTC can be stratified based on the size and # of metastatic LN, as well as the presence of ENE

Risk of Persistent/Recurrent Disease



Pitoia et al Thyroid 2013;23:1401

Dynamic Risk Stratification

Integrating Response to Therapy in Monitoring Management

Recommendation 49 (SR,LQE)

Initial risk estimates should be **continuously modified** during follow-up, because the risk of recurrence and disease specific mortality can **change over time** as a function of the clinical course of the disease and response to therapy

Proposed Terminology to Classify Response to Therapy B26

Excellent response
No clinical, biochemical, or structural evidence of disease
Biochemical, incomplete response Persistent abnl. **Tg** values in the absence of localizable disease
Structural Incomplete Persistent or newly identified loco-regional or distant metastasis
Indeterminate Response (acceptable) Non-specific biochemical or structural findings which cannot be confidently classified as either benign or malignant

Assessing Response to Therapy

	Excellent response	Indeterminate (good)	Incomplete response
Suppressed Tg	<0.2 ng/ml	Detectable, but < 1 ng/ml	> 1 ng/ml
Stimulated Tg	<1 ng/ml	< 10 ng/ml	>10 ng/ml
Tg trend	Low	Declining	Stable or rising
Tg antibodies	Absent	Absent or declining	Persistent or rising
Neck exam imaging	Normal negative	Normal Indeterminate Clinically insignificant	Palpable disease Positive
	Lower risk estimates	**Stable risk estimate**	**Raise risk estimate**

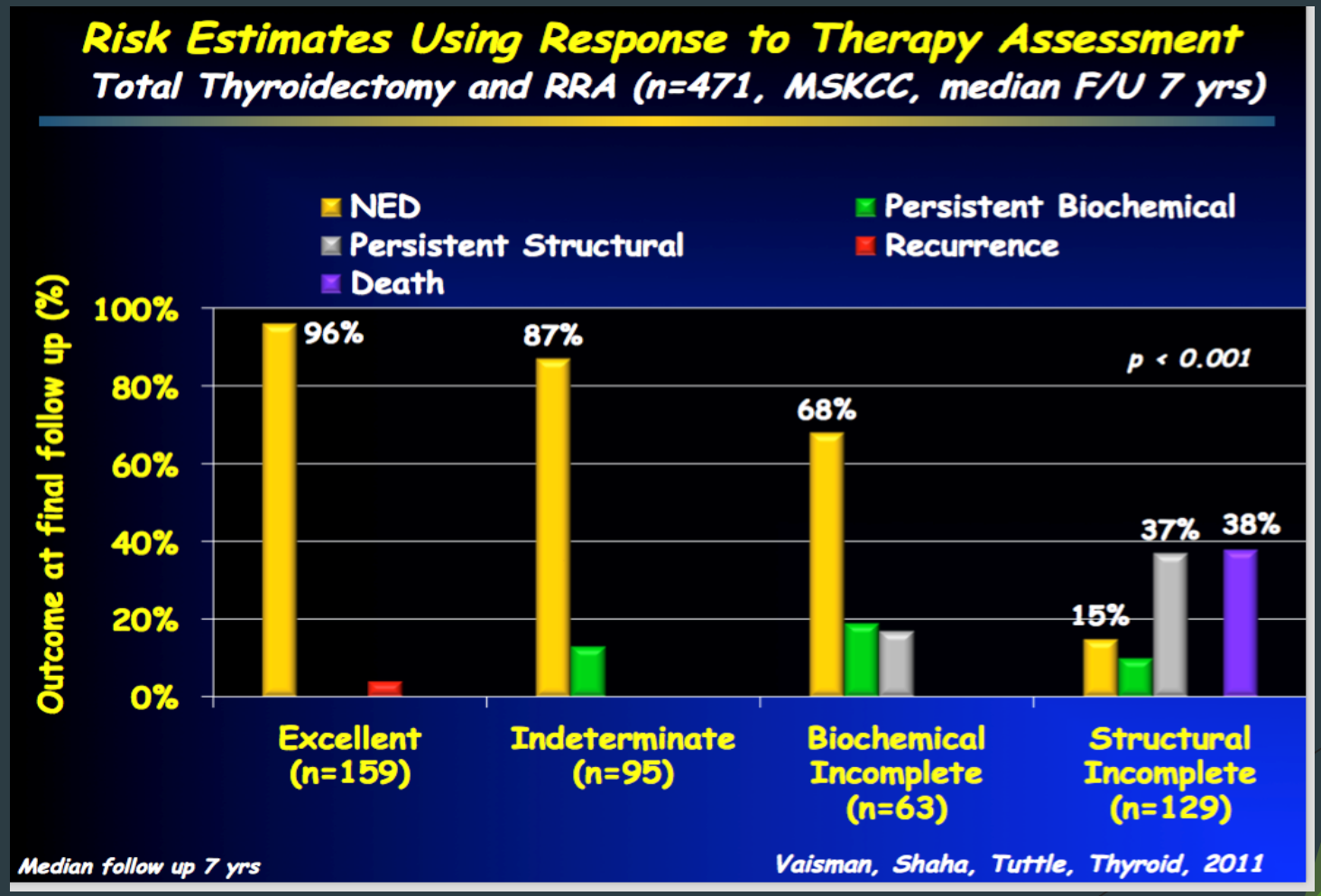
ATA Initial Risk Stratification

Estimates of pts. who subsequently had NED in each Risk Category

Postoperatively classify each patient as:	No evidence of disease following Thyroidectomy ± I131 ablation
Low risk for recurrence intrathyroidal DTC, no ETE, vascular invasion ,or metastasis ≤5 LN micrometastasis (<0.2cm)	**86-91%**
Intermediate risk (everything else) Higher risk variants of PTC (tall cell,columnar)	**57-63%**
High risk Gross ETE Incomplete tumor resection Distant mets	**14-16%**

Thyroid 2016 vol 26

Risk Estimates Using Response to Therapy Assessment



Clinical Implications of Response to Therapy

Category	Definitions	Clinical outcome	Management implications
excellent	Negative imaging AND either Suppressed Tg<0.2 OR Stimulated Tg <1 ng/ml	1-4% recurrence < 1% disease specific death	↓ in intensity and frequency of f/up and degree of TSH suppression
Biochemical incomplete	Negative imaging AND Suppressed TG >1 ng/ml OR stimulated Tg >10 ng/ml OR rising TG Ab levels	At least 30% spontaneously evolve to NED 20% achieve NED after additional Tx 20% develop structural disease	Observation with stable or declining Tg values If ↑, additional investigation
Structural incomplete	Structural or functional evidence of disease with any Tg level	50-85% continue to have persistent disease despite additional Tx Disease specific death rates 11% with locoreginal mets 50% with distant mets	In some, additional Tx or ongoing observation depending on multiple C-P features
indeterminate	Non-specific findings on imaging studies Non stimulated Tg detectable, but < 1 ng/ml Stimulated Tg level detectable, but < than 10 ng/ml	15-20% will have structural disease identified during f/up < 1% disease-specific death	continued observation with mild TSH suppression Serial imaging & serum Tg monitoring

Initial treatment

Goals of Initial Therapy

- Remove the primary tumor, disease that has extended beyond the capsule, and c LN mets
  - **Completeness of surgical resection is an imp. determinant of outcome.**
- Minimize risk of disease recurrence and metastatic spread
  - **Adequate surgery is the most imp. variable influencing prognosis.**
- Facilitate postoperative Tx with RAI, where appropriate.
- Permit accurate staging and risk stratification of the disease.
  - **Accurate post-op risk assessment is a crucial element in the Tx of DTC**
- Permit accurate long-term surveillance for disease recurrence
- Minimize treatment-related morbidity

Operative Approach for a Biobsy Diagnostic for Follicular Cell- derived Malignancy

Recommendation 35 A (SR,MQE)

- For patients with thyroid cancer > 4cm or with gross ETE (clinical T4), clinical N1, or distant metastasis the initial surgical procedure should include a near total or total thyroidectomy and gross removal of all primary tumor unless there are contraindications

Thyroid 2016;26:1-133

Operative Approach for a Biobsy Diagnostic for Follicular Cell- derived Malignancy

Recommendation 35 B (SR,MQE)

- For pts. With thyroid cancer >1 cm and <4 cm w/out ETE, and cN0, the initial surgical procedure can be either a NTT , TT or a unilateral lobectomy.
- Thyroid lobectomy may be the initial procedure for low –risk PTC & FTC
- However, the team may choose TT to enable RAI therapy or to enhance follow up based upon disease features and/or patient preferences
- DEBATE CONTINUES

Thyroid 2016;26:1-133

Proper Patient Selection for Lobectomy (SR,MQE)

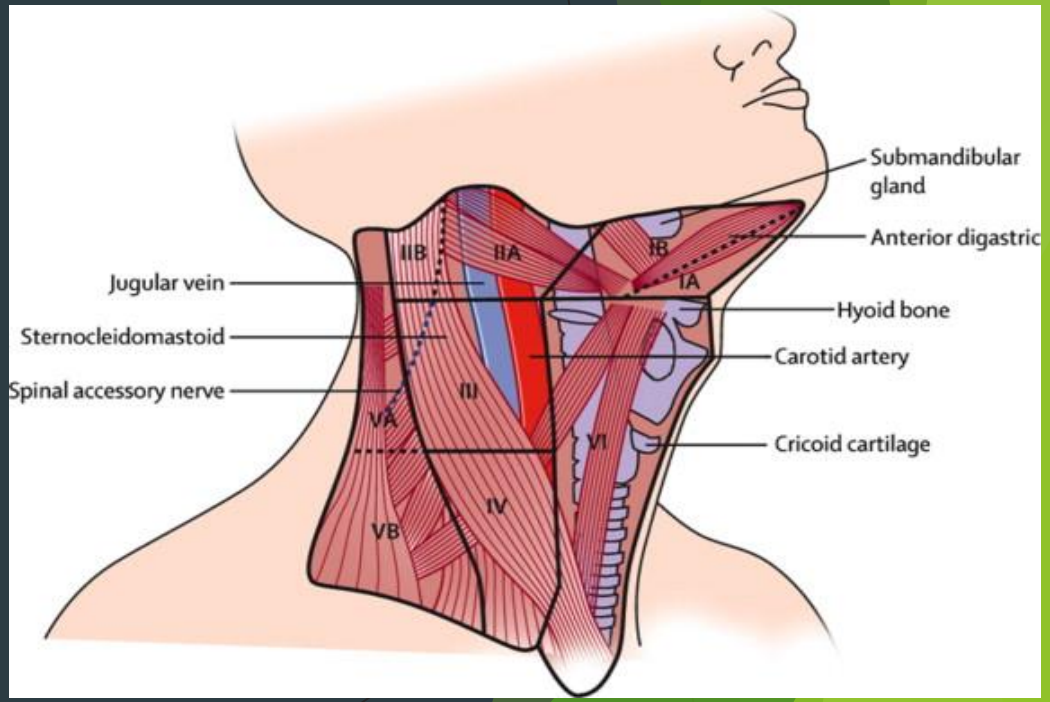
- Intrathyroidal PTC
  - < 1cm w/out ETE and confined to 1 lobe
  - Multifocal microPTC with < than 5 foci
- Pre-op Neck US
  - Clinical N0
  - Contralateral lobe essentially normal
- Shared management decision
- Willing to accept
  - Slightly higher recurrence rate
  - possibility of need for completion thyroidectomy

Lymph Node Dissection

- Rec 36 A **Therapeutic** central-compartment (level VI) neck dissection for pts with **clinically** involved central nodes should accompany TT to provide clearance of disease from the central neck (strong Rec)
- B. **Prophylactic** central compartment neck dissection should be considered in pts. with PTC with **cN0 who have advanced primary disease (T3 or T4) or with cN1b** or if the inf. will be used to plan further steps in therapy (weak rec)
- C. No need for prophylactic central neck dissection for T1/T2 PTC and cN0 and for most FTC (strong Rec)

Lymph Node Dissection

- R 37 Therapeutic lateral neck compartment LN dissection should be performed for patients **with biobsy-proven** metastatic lateral cervical lymphadenopathy (Strong rec)



Radioiodine Treatment

Goals of Radioiodine

- **Remnant ablation**
  - Of residual normal thyroid tissue to facilitate detection of recurrent disease ie Tg
- **Adjuvant**
  - Destroy suspected, but unproven residual disease, especially in pts. At increased risk of recurrence
- **Treatment**
  - Intended to improve disease-specific mortality & disease-free survival by Tx persistent disease in higher risk pts.

RAI Ablation Considerations in the cN0 Neck R51

Risk Category	Description	Improves Survival	Decreases Recurrence	Post-Surgical RAI Indicated?
ATA low risk T1a N0,Nx M0,Mx	Tumor size ≤1cm (uni-or multi-focal)	No	No	**No**
ATA low risk T1b,T2 N0, Nx M0,Mx	Tumor size >1-4 cm	No	Conflicting data	**Not routine** – may be considered for patients with aggressive histology or vascular invasion (ATA intermediate risk)
ATA low to intermediate risk T3 N0,Nx M0,Mx	Tumor size >4 cm	Conflicting data	Conflicting data	**Consider** - Need to consider presence of other adverse features. Advancing age may favor RAI use in some cases, but specific age and tumor size cut-offs subject to some uncertainty
ATA low to intermediate risk T3 N0,Nx M0,Mx	Microscopic extra-thyroidal extension, any tumor size	No	Conflicting data	**Consider** - Generally favored based on risk of recurrent disease. Smaller tumors with microscopic ETE may not require RAI

Thyroid 2016;26:1-133

RAI Ablation Considerations in the cN1 Neck

Risk	Description	Improves Survival	Decreases Recurrence	Post-Surgical RAI Indicated?
ATA low to intermediate risk T1-3 N1a M0,Mx	Central compartment neck lymph node metastases	No, except possibly in subgroup of patients ≥ 45 years of age	Conflicting data	**Consider – Generally favored**, due to somewhat higher risk of persistent or recurrent disease, especially with increasing number of large (>2-3 cm) or clinically evident lymph nodes or presence of extra-nodal extension. Advancing age may also favor RAI use. However, there is insufficient data to mandate RAI use in patients with few (<5) microscopic nodal metastases in central compartment in absence of other adverse features.
ATA low to intermediate risk T1-3 N1b M0,Mx	Lateral neck or mediastinal lymph node metastases	No, except possibly in subgroup of patients ≥ 45 years of age	Conflicting data	**Consider - Generally favored**, due to higher risk of persistent or recurrent disease, especially with increasing number of macroscopic or clinically evident lymph nodes or presence of extra-nodal extension. Advancing age may also favor RAI use.

Haugen et al. ATA Guidelines Thyroid 2015

ATA Guideline on RAI Remnant Ablation

- Recommended for T3-4 or M1
- Recommended for selected cases in 1-4 cm thyroid cancers with:
  - LN mets
  - High risk features
    - Age > 45,tumor invasion, aggressive histology, incomplete resection
- NOT rec for pts with
  - Unifocal cancer < 1cm w/out other higher risk features
  - Multifocal cancer when all Foci are < 1 cm Rating E

Haugen et al Thyroid Vol 26, 2016

Long-Term Management

What is the Role of TSH Suppression During T4 Therapy in the Long-term Follow –up of DTC? R 70

Response to therapy	Serum TSH (mU/L)
Structural incomplete response	<0.1
Biochemical incomplete	0.1-0.5
High-risk disease but excellent response	0.1-0.5
Excellent response or indeterminate response (especially those with a low risk of recurrence)	0.5-2
Pts who have NOT undergone remnant ablation ;nl neck us, low or undetectable Tg on T4, Tg or Tg Abs that are NOT rising	0.5-2.0

What is the Role of Serum Tg Measurement in the follow-up of DTC

- R 62 serum Tg abs should be quantitatively assessed with every measurement of serum Tg. Ideally, should be assessed longitudinally in same lab and using same assay
- Initially, should be checked q 6-12 mos . > frequent if ATA high risk
- In ATA low –and intermediate risk pts that achieve an Excellent response to Tx, time interval between serum Tg measurements q 12-24 mos
- In ATA high risk pts (regardless of response to Tx) and all pts with biochemically incomplete, structurally incomplete, or indeterminate response check serum Tg at least q 6-12 mos for several yrs

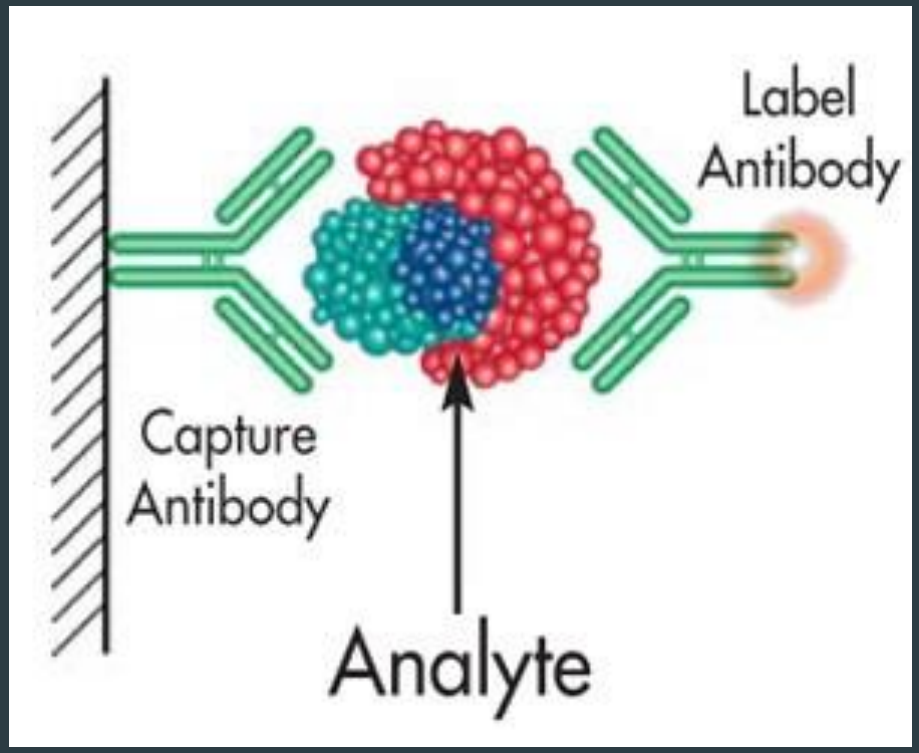
What is the Role of Serum Tg Measurement in follow-up of DTC ?

- R 63 In ATA low risk & intermediate-risk pts who have had ablation, neg. cervical US , serum Tg should be measured at 6-18 mos on T4 treatment with a sensitive Tg assay. Assay should be calibrated against the CRM 457 std. (strong)
- Repeat TSH-stimulated Tg testing is NOT rec for low and intermediate-risk pts. with an excellent response to therapy Tg on T4 Rx < 0.1-0.2 with a sensitive assay)
- Subsequent TSH-stimulated serum Tg with an indeterminate, biochemical incomplete, or structural incomplete response following either additional therapies or a spontaneous ↓ in Tg values on T4 Tx
- subsequent stimulated testing is RARELY needed for those with NED .

Pearls & Pitfalls of Serum Tg Measurements

- Serum Tg is **NOT** a reliable tumor marker immediately post op or post RAI
- 6 week wait to reassess serum Tg status post op or post RAI
- Must maintain CONSTANT TSH value
- Serum Tg only reliable as a marker if TSH is Stable
- Serum Tg measurements in the presence of Tg Abs. may NOT be reliable

Two-antibody "Sandwich" Immunometric Assays



Clinical decision-making and Management recommendations in ATA low Risk DTC

- Initial therapy : TT
- Evaluation of post-operative Disease Status
- Consider post-op serum Tg
- Neck US

↓

RAI remnant ablation Not routinely recommended

↓

Initial TSH goal
0.5-2.0 mU/l

↓

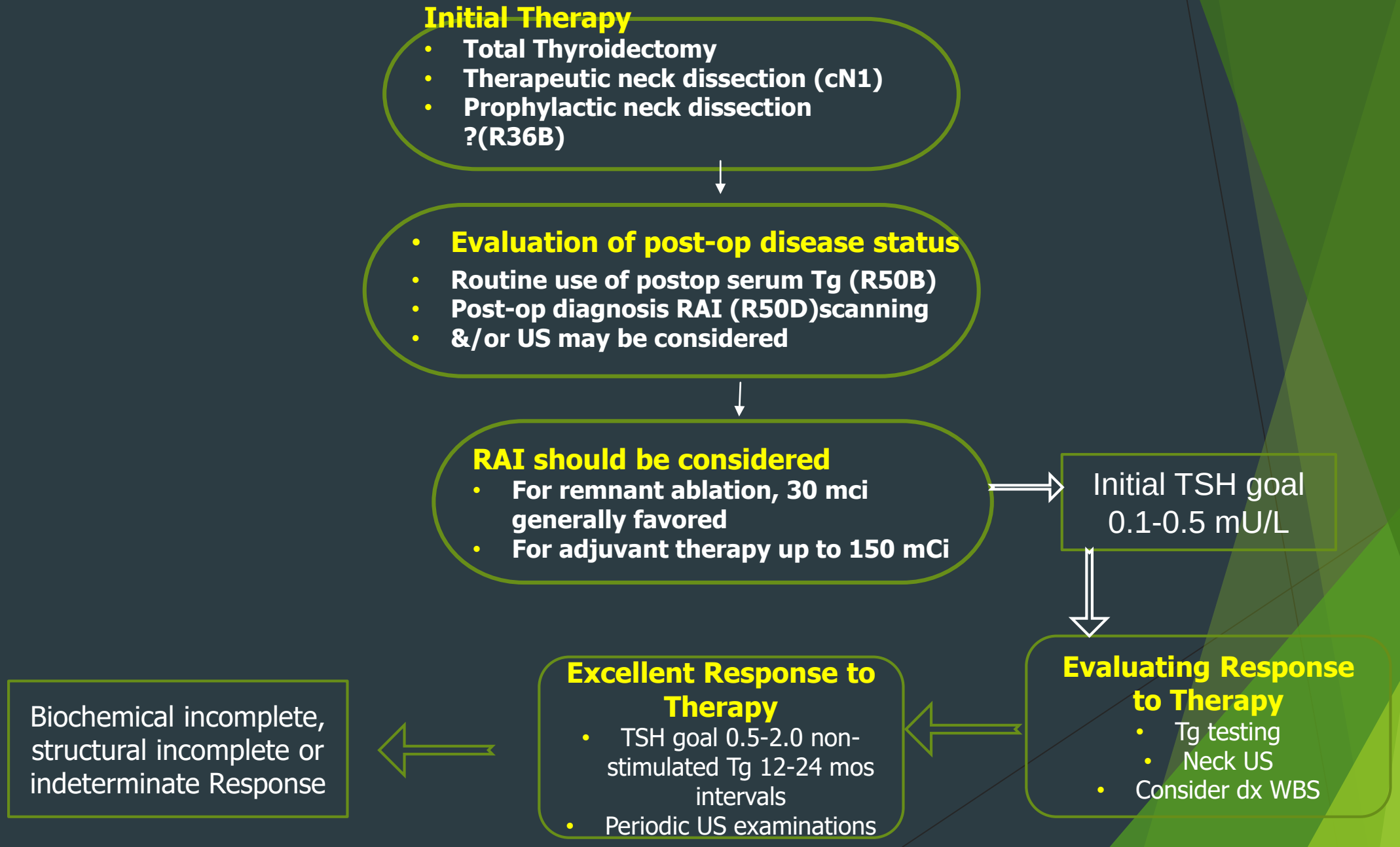
Evaluation Response to Therapy
- Neck US
- Consider Tg testing

↓

- Excellent response to Tx
- 1ary f/up with clinical exam and non- stimulated Tg
- TSH goal 0,5-2.0 mU/l
- Non-stimulated Tg 12-24 mos intervals
- Periodic US exam

Biochemical incomplete (rising serum Tg)
Structural incomplete or indeterminate response

Clinical decision-making and Management recommendations in ATA Intermediate Risk DTC



After the 1st Year of fup When do Structural Neck Recurrences Occur?

ATA Initial Risk	Recurrence (5 yrs.)	%
Low	**77%**	0.8%
Intermediate		2.5%

- 948 pts. **With no evidence of structural disease on 1 year post US** followed for subsequent neck recurrence (median Fu 10.4 yrs.)

Clinical Decision making and Management Rec. in ATA HIGH RISK DTC Patients

- Initial Therapy
- TT
- Therapeutic neck dissection (cN1)

- Evaluation of Post-op disease ``````````````Status
- Routine use of serum Tg
- Post op diagnostic RAI scanning and/or US may be considered

RAI should be considered

- For adjuvant Tx, up to 150 mci are generally recommended
- For known structural disease, empiric 100-200mci

Initial TSH Goal
<0.1 mU/L

- Excellent response
- TSH 0.1-0.5 for at least 5yrs
- Yearly f/up and Tg x at least 5 yrs
- Consider periodic US/CT/MRI

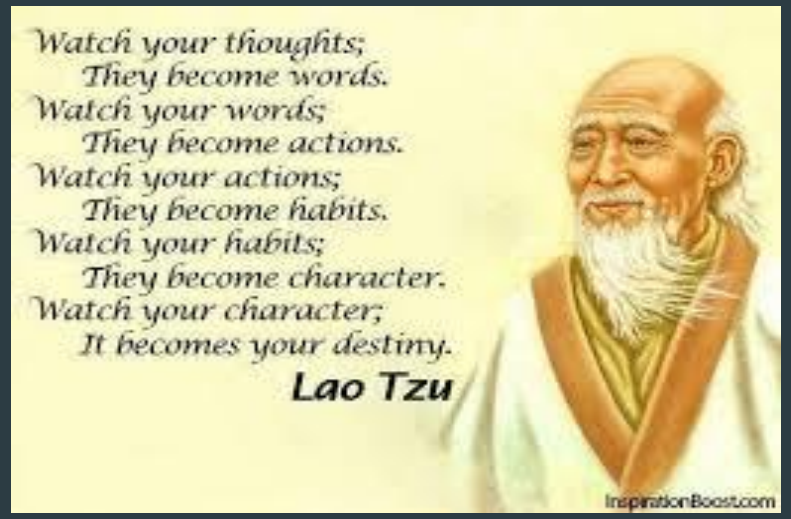
- Evaluate Response to Therapy
- Tg testing, Neck US
- Consider CT/MRI imaging and/or FDG/PET scan
- Consider WBS

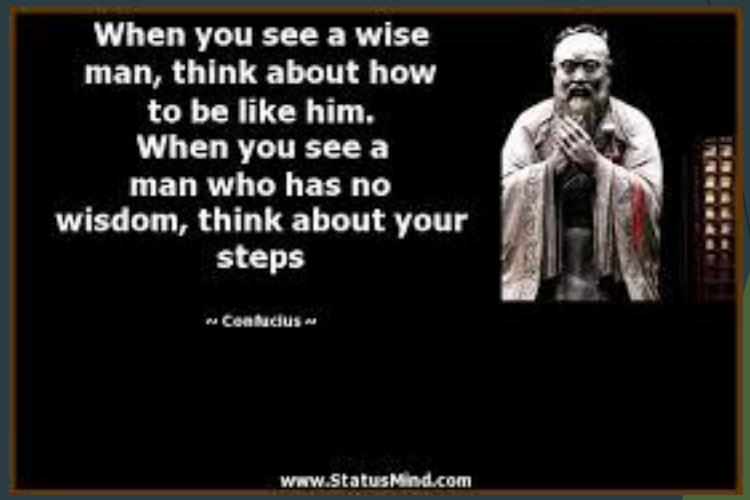
- Bioch incomplete, structural incomplete or indeterminate response
- TSH goal <0.1 indefinitely

2015 ATA Guidelines DTC Substantial Changes

- Stage (AJCC/TNM), ATA recurrence risk, response to therapy
- the aggressiveness of intervention and f/up to the specific risks associated with the tumor in an individual patient
- These initial management plans are then modified over time as additional data accumulate
- Restratify based on response to therapy
- Other features:
  - More detailed pathologic reports
  - selective use of radioiodine
  - Cross-sectional imaging for higher risk disease

Thank You!


Watch your thoughts;
They become words.
Watch your words;
They become actions.
Watch your actions;
They become habits.
Watch your habits;
They become character.
Watch your character;
It becomes your destiny.
Lao Tzu
InspirationBoost.com


When you see a wise man, think about how to be like him.
When you see a man who has no wisdom, think about your steps
~ Confucius ~
www.StatusMind.com

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- **INTERMEDIATE RISK**
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- **Cervical LN mets**
- **Aggressive histology or**
- **AL invasion**

- **HIGH RISK**
- **Macroscopic gross ETE**
- **Incomplete tumor resection**
- **Distant mets. or**
- **inappropriate Tg elevation**

Cooper Thyroid 2009;19:1167
Haugen Thyroid 2016;26:1

What is the Role of US & other Imaging Techniques (RAI SPECT/CT,CT,MRI,) During Follow-up?

- R65 post op, cervical US to evaluate the thyroid bed and central & lateral cervical LN should be performed at 6-12 mos. And then periodically, depending upon pts. Risk for recurrence & Tg status (strong)
- If a + result will change Tx, suspicious LN $\geq 0.8 - 1\ \mathrm{cm}$ should be biobsied for cytology with Tg measurement in the wash out fluid
- Low risk pts. Who have had remnant ablation, neg. cervical US, and a low seru Tg on T4 (,0.2) or stimulate (<1 ng/ml) may be followed with Pex and serum Tg while on T4

What is the Role of US & other Imaging Techniques : FDG-PET scanning During Follow-up?

- R 68 FDG-PET scanning should be considered in high-risk patients with elevated serum Tg (generally >10 ng/ml) with negative RAI imaging
- FDG-PET is > sensitive in pts. With an aggressive histologic subtype, tall cell, poorly differentiated, & Hurthle cell ca.
- FDG uptake on PET in metastatic DTC pts. Is a major negative predictive factor for response to RAI Tx, & a negative prognostic factor for survival
- It can also identify lesions with high FDG uptake that may be > aggressive and should be targeted for therapy
- False + frequency 0-39% .this high # , justifies FNAB with cytology and Tg measurement in cases in which surgery is planned, based on FDG-PET results

Differentiated Thyroid Cancer: Management During First year

Risk of Recurrence			
	Low	**Intermediate**	**high**
Suppressed Tg	**At 3, 6 mos post op**	At 3-6 mo postop	At 3 to 6 mo postop
Stimulated Tg	At 6 to 12 mos post RAI, otherwise not done	At 6-12 mo post RAI	Not needed since suppressed Tg is elevated
Neck US	At 6-12 mos	At 6 to 12 mo	Every 6-12 mo
MRI,CT	Not indicated	Not indicated	If Tg elevated or high clinical suspicion
FDG-PET	Not indicated	Not indicated	If Tg elevated >10 ng/ml
Serum TSH level	0.5 to 2 mU/L	<0.1	<0.1 mU/L
Diagnostic WBS	Usually not indicated	May be done at same time of stimulated Tg	Case-specific

Pearls & Pitfalls of Tg Assays

- **Euthyroid @ 12 gms.**
  - Tg 3-40 ng/ml
  - Suppressed TSH : 1.5-20 ng/ml
- **Lobectomy @ 5 gms.**
  - Tg: 0.75-10 ng/ml
- **Total thyroidectomy**
  - Tg <0.5 ng/ml

- Functional sensitivity: lowest Tg concentration that an assay can reliably & consistently measure under clinically relevant conditions with < than 20% CV
  - 1st generation assays 0.5-1 ng/ml
  - 2nd generation "sandwich" IMRA .05-0.1 ng/ml
- Are stimulated Tg levels useful in the era of hs Tg assays?
- Tg <0.1 only 2.5% have sTg ≥ 2.0 ng/ml

Differentiated Thyroid Cancer: Management Year 1 to 2

Risk Of Recurrence			
	Low	**Intermediate**	**high**
Stimulated Tg	Not needed	At 12 to 18 mos if not done during 1st yr	Not needed
Neck US	Yearly	Yearly	Every 6-12 mos
Diagnostic WBS	Not indicated	Not usually done	Case –specific
MRI,CT	Not indicated	Not indicated	If Tg elevated or high clinical suspicion
FDG-PET	Not indicated	Not indicated	If Tg elevated >10 ng/ml
Serum TSH level	0.3-2.0 mU/L	<0.1 mU/L	<0.1 mU/l
Suppressed Tg	Q 6 mos	Q 6 mos	Q 6 mos

Differentiated Thyroid Cancer: Monitoring Long-term (> 2 yrs)

Response to Therapy					
	excellent	**Biochemical incomplete**		**Structural incomplete**	**indeterminate**
Suppressed Tg	Every year	Ever 6 mo		Every 6 mo	6-12 mo
Stimulated Tg	Not needed	May be repeated at 2-3 year intervals if suppressed Tg <0.6 ng/ml		Not needed	Repeat stimulated Tg may re-classify patient
Neck US	Consider at 3-5 yr interval		Yearly for 5 yrs	Yearly for 5 yrs	6 to 12 mo interval for 5 yrs

Adjuvant Management

		Level
High and intermediate-risk patients	TSH suppression therapy to maintain TSH <0.1	B
Low risk patients +/- RAI	TSH suppression to maintain TSH at or slightly below nl range (0.1-0,5 mU/L)	B
External beam radiation therapy	➢ 45 y/o with grossly visible extrathyroidal extension and high likelihood of microscopic residual disease ➢ Pts with gross residual tumor in whom further surgery or RAI would likely be ineffective	B
Chemotherapy		F

What is the Role of US & other Imaging Techniques: CT and MRI

- R69 cross-sectional imaging of the neck and upper chest (CT,MRI) with IV contrast should be considered
  - In the setting of bulky, widely distributed recurrent nodal disease where US may not completely delineate disease
  - In the assessment of possible invasive recurrent disease where potential aerodigestive tract invasion requires complete assessment
  - When neck US is felt to be inadequately visualizing possible nodal disease (high Tg, negative neck US)
- B CT imaging of the chest w/out IV contrast (imaging pulmonary parenchyma) or with IV contrast(imaging mediastinum) should be considered in high risk DTC pts. With ↑TG (generally > 10 ng/ml) or rising Tg abs. with or w/out negative RAI imaging

Radioiodine Remnant Ablation/Adjuvant Therapy R 51

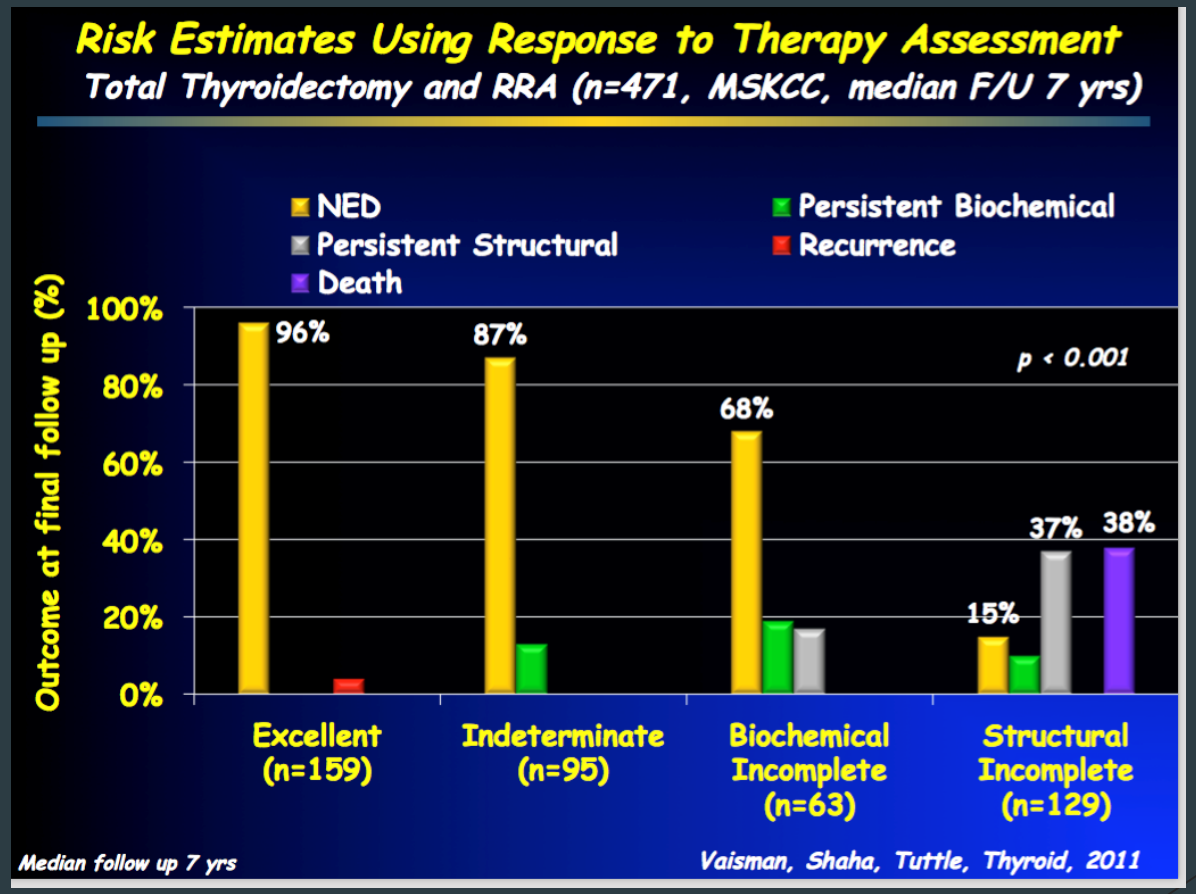
ATA recurrence risk TNM staging	description	Post surgical RAI, indicated?
ATA low risk T1a,NO,Nx/M0,Mx	T1≤1cm(unifocal or multifocal)	No
ATA low risk T1b,T2/N0,M0,Mx	T1-4cm	Not routine
ATA low to intermediate T3/N0,Nx/Mo,Mx	T >4 cm or minimal ETE	Consider
ATA low to intermediate T1-3/N1a/Mo,MX	Central compartment LN mets	Consider (size and #)
ATA low to intermediate risk Any T1-T3/N1b/Mo,Mx	Lateral compartment LN mets	Consider size, number, age)
ATA high risk T4/any N/any M	Gross ETE	Yes
ATA High risk M1,any T, any N	Distant metastasis	Yes

Risk Adapted Initial Follow Up

follow up after Initial therapy

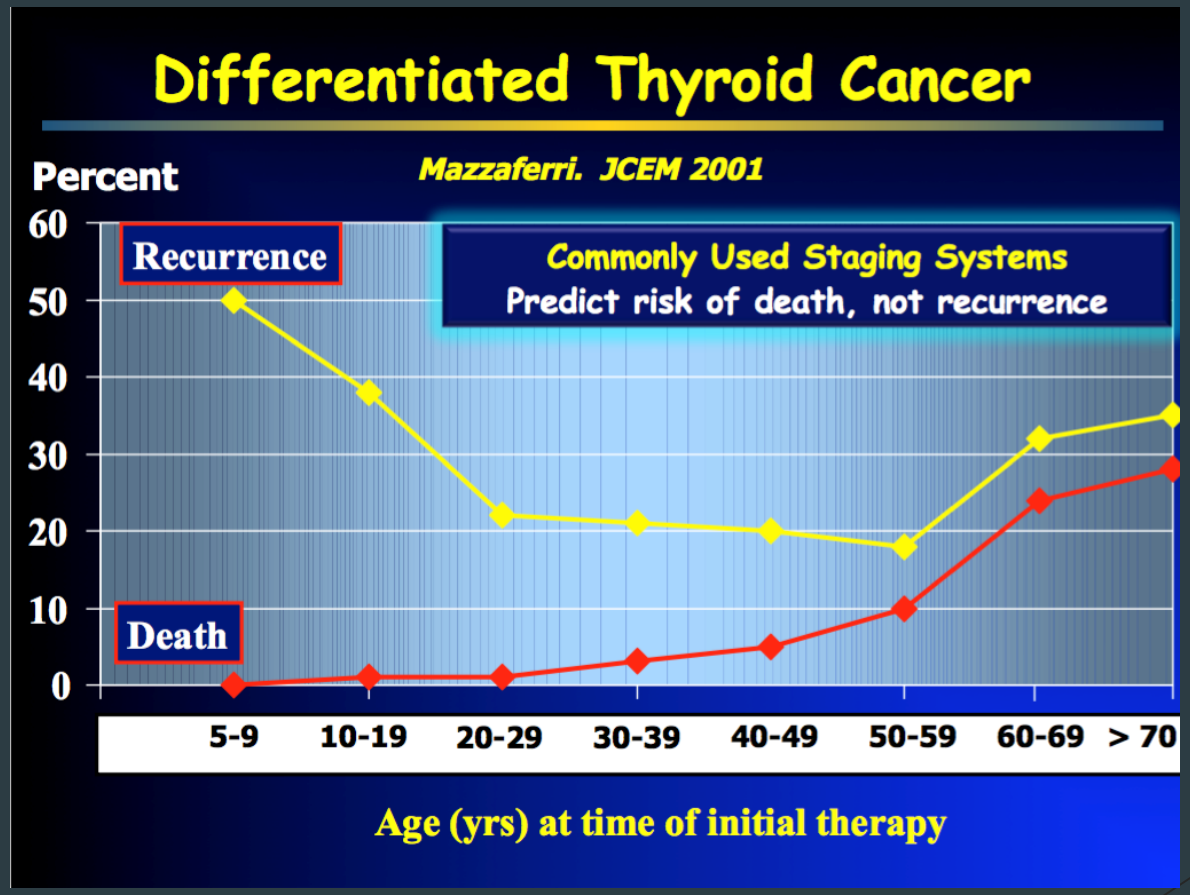
	6 mo	12mo	18mo	24mo
Non-Stim Tg	+	+	+	+
US		+		+
Stimulated Tg*			*	
Diagnostic WBS			**Inter/high**	
CT/MRI		**High**		**High**
FDG PET		**high**		**high**

*** Or non-stimulated Tg <0.2 ng/ml**

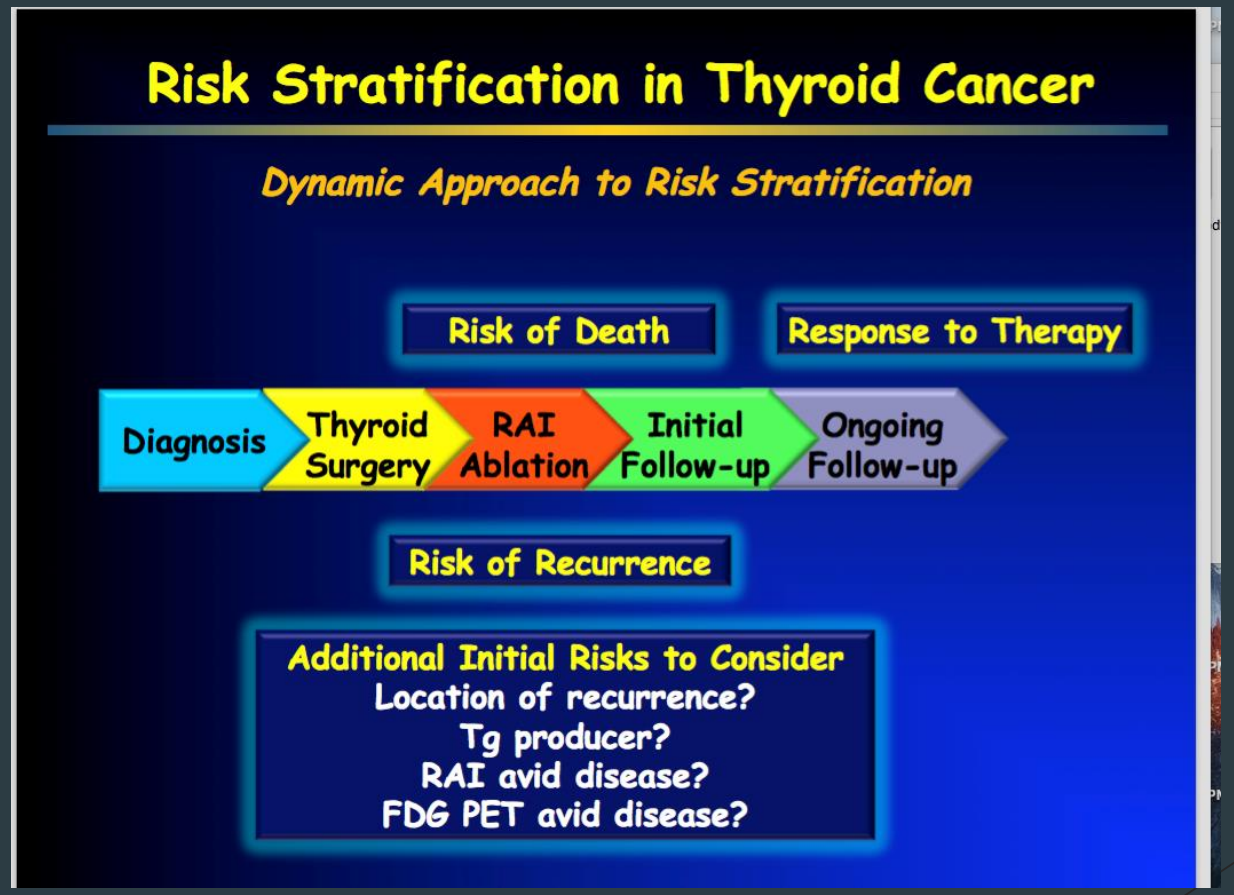

Risk Estimates Using Response to Therapy Assessment
Total Thyroidectomy and RRA (n=471, MSKCC, median F/U 7 yrs)
NED
Persistent Biochemical
Persistent Structural
Recurrence
Death
Outcome at final follow up (%)
100%
80%
60%
40%
20%
0%
96%
87%
68%
15%
37%
38%
p < 0.001
Excellent (n=159)
Indeterminate (n=95)
Biochemical Incomplete (n=63)
Structural Incomplete (n=129)
Median follow up 7 yrs
Vaisman, Shaha, Tuttle, Thyroid, 2011

Long – Term Follow-up

- 35-y/o female treated 1 year ago for a T1N1aM0 (stage 1) PTC of the right lobe with total thyroidectomy, RAI, and TSH suppression
- Undergoes the appropriate follow-up studies
  - Thyroglobulin levels
  - thyroglobulin antibodies'
  - Ultrasound


Differentiated Thyroid Cancer
Percent
Mazzaferri. JCEM 2001
60
50
40
30
20
10
0
Recurrence
Death
Commonly Used Staging Systems
Predict risk of death, not recurrence
5-9
10-19
20-29
30-39
40-49
50-59
60-69
> 70
Age (yrs) at time of initial therapy

Integrating Response to Therapy in Monitoring Management



What does Follow-up Look Like?

36 y/o female s/p lobectomy for intrathyroidal 2cm PTC

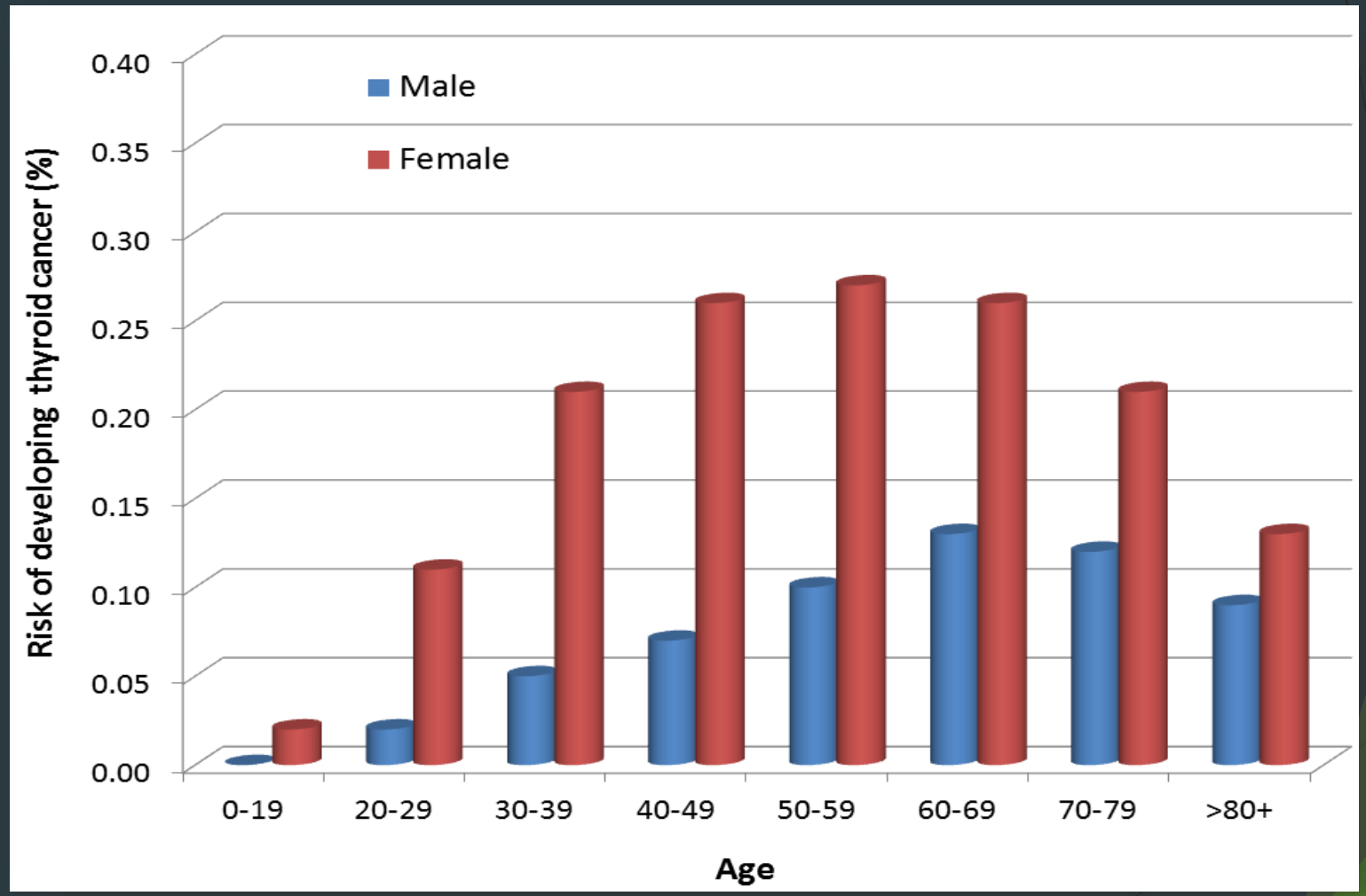
- TSH Goal
  - @ 1mIU/L
- Neck US
  - 6-12 mos
  - Yearly for a few yrs
- Non-stimulated Tg
  - Yearly

BEST EVIDENCE ENT 2014
AUGUST 2-5

Post-Treatment Surveillance

		Level
Thyroglobulin levels and Tg antibody measurement	Every 6-12 months after thyroidectomy +/- RAI	A
Thyroglobulin levels and neck ultrasound	"Periodically" for less than total thyroidectomy or total without RAI	B
Thyroglobulin level after T4 withdrawal or rhTSH stimulation 12 months after treatment	• For low-risk, clinically and U/S negative with TSH < 0.1. • Follow Tg	A
Cervical ultrasonography	6–12 months and then periodically, depending on the patient's risk for recurrent disease and Tg status	B
• Ultrasound-guided FNA of suspicious nodes >5-8 mm • Tg measurement of needle wash-out	If a positive result would change management	A
Observation of suspicious nodes <5–8 mm	If there is growth or if the node threatens vital structures.	C

Risk of developing thyroid cancer by sex and age



US Cancer Statistics (USCS): 1999-2007 Incidence and Mortality Web-based Report, released in December 2010 and available on the Centers for Disease Control and Prevention (CDC)

What does Follow-up Look Like?

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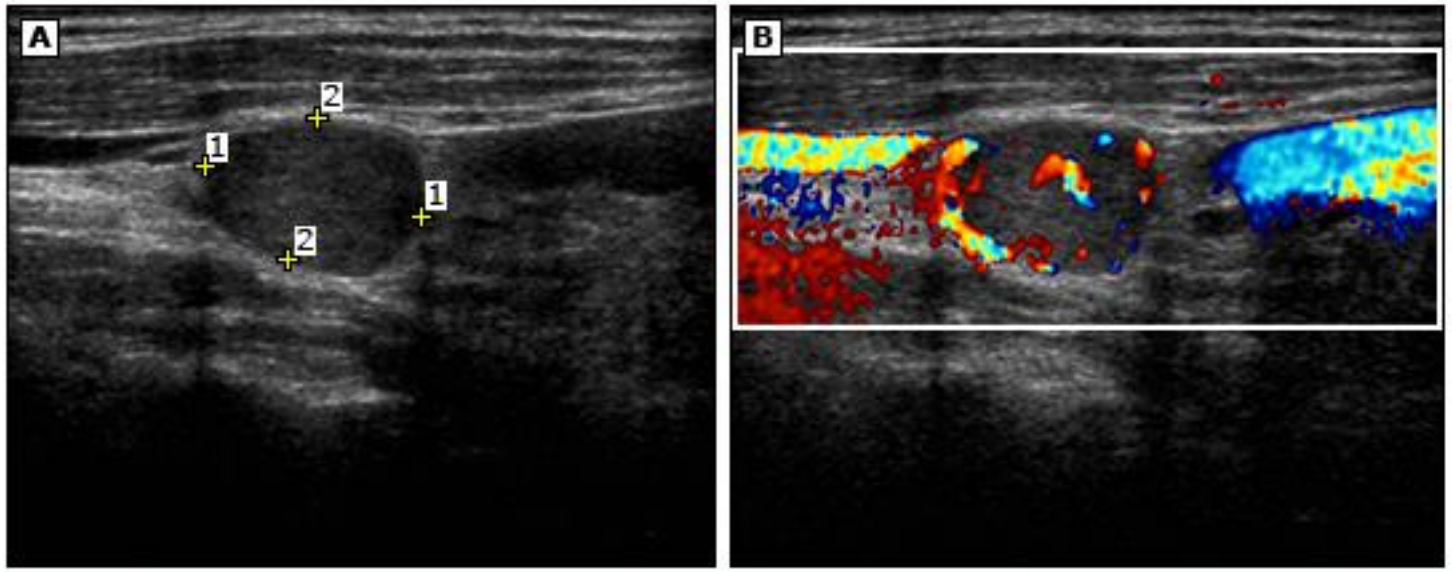
  - 6-12 mos
  - Yearly for a few yrs
- Non-stimulated Tg
  - Yearly

Thyroid ultrasound of a nonpalpable recurrent papillary thyroid carcinoma



(Panel A) An example of an abnormal lymph node demonstrating a round, heterogeneous appearance with no fatty hilum.
(Panel B) An example of an abnormal lymph node demonstrating a rounded structure with peripheral vascularity.

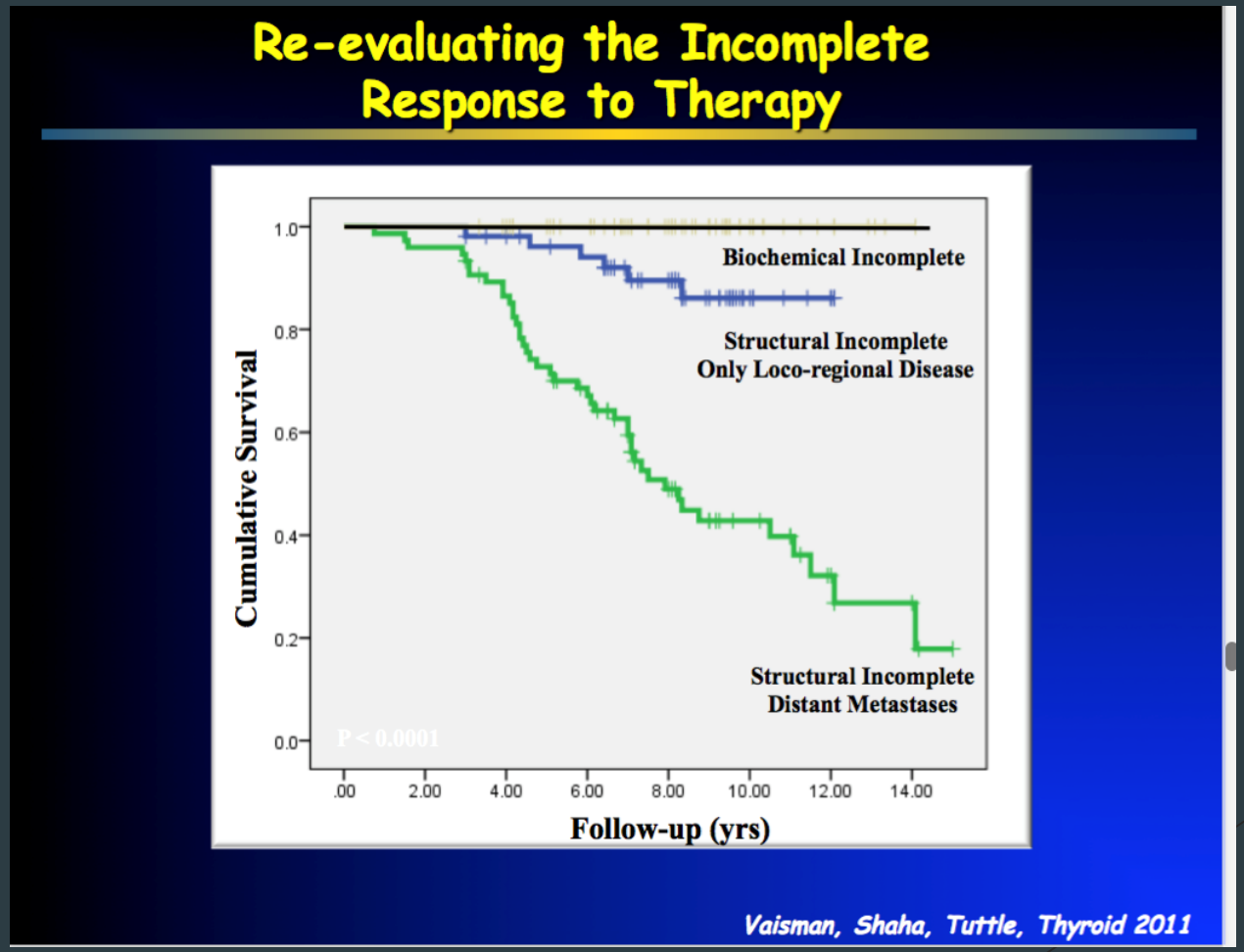
Courtesy of Dr. Stephanie Fish, Endocrinology Service, Memorial Sloan-Kettering Cancer Center, New York.

Central to Risk Stratification
Improved & standardized Histopathologic Assessment

- R 46 (new) Pathology reports should include:
  - TNM criteria
  - Vascular invasion & # of vessels
  - Number of LN examined and involved
  - Size of the largest metastatic LN focus
  - Extranodal extension

  (strong recommendation, moderate quality evidence)

Re-evaluating the Incomplete Response to Therapy



Diagnostic Whole-body RAI Scans

- R 66 after the first post treatment WBS performed post remnant ablation , low-risk and intermediate-risk patients (lower risk features) with an undetectable Tg on T4 with neg. anti-Tg Abs. and a Neg. US do NOT require routine diagnostic WBS during f/up
- R67 diagnostic WBS, either following T4 withdrawal or rhTSH, 6-12 mos. after adjuvant RAI therapy can be useful in the f/up of pts. with high or intermediate risk (higher risk features) of persistent disease and should be done with low activity I131