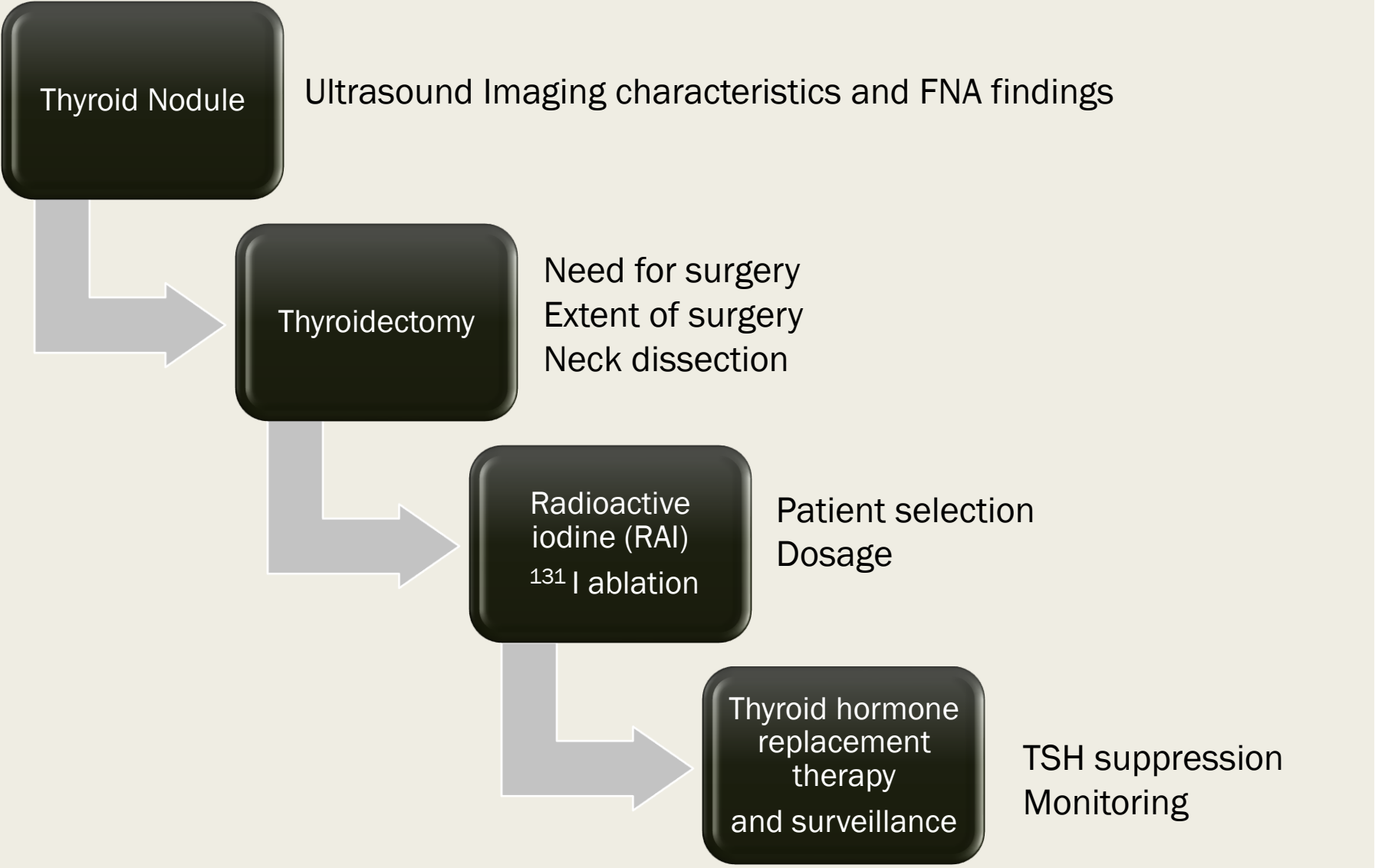


PANEL DISCUSSION

EVIDENCE-BASE CASE
DISCUSSION

Management of a thyroid nodule



Case 1

- A 42 years old woman with a 2 cm, isoechoic, solid left thyroid nodule on Ultrasound imaging.
- FNA consistent with papillary thyroid carcinoma.
- Stage 1, ATA low risk
- Extent of surgery?
- Management of neck?

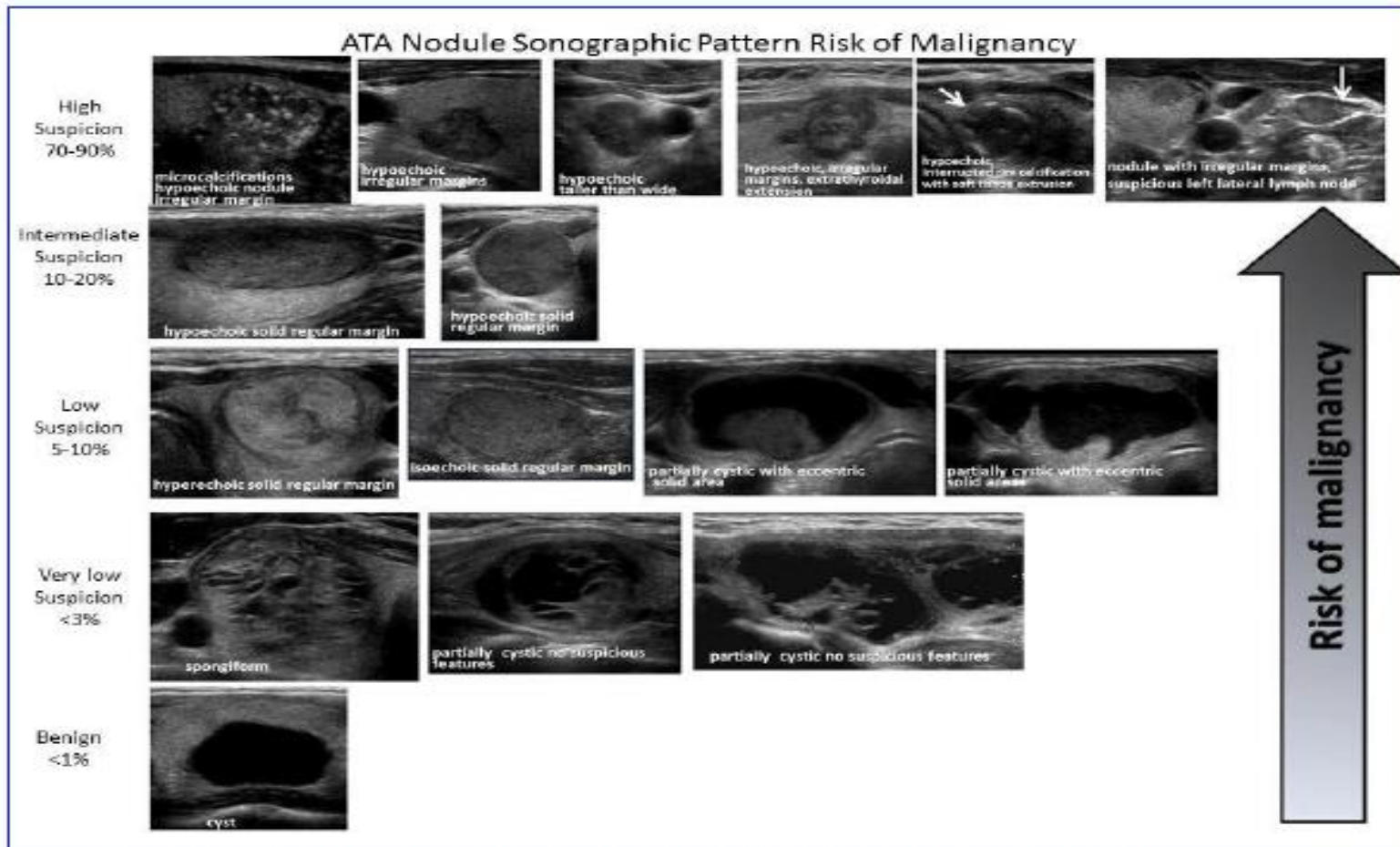


Figure 2. ATA nodule sonographic patterns and risk of malignancy

Haugen BR, Alexander EK, Bible KC, 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*. 2016;26(1):1-133.

Table 7. The Bethesda system for reporting thyroid cytopathology: Diagnostic categories and risk of malignancy¹

Diagnostic category	Estimated/predicted risk of malignancy by the Bethesda system (%) ¹	Actual risk of malignancy in nodules surgically excised (% , median (range)) ²
Nondiagnostic or Unsatisfactory	1-4	20 (9-32)
Benign	0-3	2.5 (1-10)
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS)	5-15	14 (6-48)
Follicular Neoplasm or Suspicious for a Follicular Neoplasm (FN/SFN)	15-30	25 (14-34)
Suspicious for Malignancy (SUSP)	60-75	70 (53-97)
Malignant	97-99	99 (94-100)

¹As reported in The Bethesda System by Ali & Cibas, 2009 (1076)

²Based on the meta-analysis of 8 studies reported by Bongiovanni et al. (103). The risk was calculated based on the portion of nodules in each diagnostic category that underwent surgical excision and likely is not representative of the entire population, particularly of non-diagnostic and benign diagnostic categories.

Role of Radiofrequency ablation (RFA)



Role of Radiofrequency ablation (RFA)

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ORIGINAL ARTICLE

WILEY

Radiofrequency ablation and related ultrasound-guided ablation technologies for treatment of benign and malignant thyroid disease: An international multidisciplinary consensus statement of the American Head and Neck Society Endocrine Surgery Section with the Asia Pacific Society of Thyroid Surgery, Associazione Medici Endocrinologi, British Association of Endocrine and Thyroid Surgeons, European Thyroid Association, Italian Society of Endocrine Surgery Units, Korean Society of Thyroid Radiology, Latin American Thyroid Society, and Thyroid Nodules Therapies Association

Lisa A. Orloff MD¹ | Julia E. Noel MD¹  | Brendan C. Stack Jr MD²  |

At present, candidate primary tumors should demonstrate the following characteristics:

- (1) unifocal microcarcinoma confined to the thyroid gland, without evidence of extrathyroidal extension or capsular contact
- (2) cytologic confirmation of papillary thyroid cancer without aggressive subtype
- (3) no evidence of metastatic lymphadenopathy
- (4) High risk, ineligible for, or declines surgery.

Case 2

- 21 years old male with 3.5 cm, hypoechoic, solid thyroid nodule on ultrasound.
- FNA reported as revealed Follicular lesion of undeterminate significance (FLUS), Bethesda III
- Management?
- Role of PET scan in indeterminate nodules?

■ RECOMMENDATION 18

¹⁸F-DG-PET imaging is not routinely recommended for the evaluation of thyroid nodules with indeterminate cytology. (Weak recommendation, Moderate-quality evidence)



Review

Performance of ^{18}F -FDG PET/CT in Selecting Thyroid Nodules with Indeterminate Fine-Needle Aspiration Cytology for Surgery. A Systematic Review and a Meta-Analysis

Marco Castellana ¹, Pierpaolo Trimboli ², Arnoldo Piccardo ³, Luca Giovanella ^{2,4} and Giorgio Treglia ^{2,5,6,*}

Table 3. Summary estimates of the diagnostic performance of ^{18}F -FDG PET/CT in selecting thyroid nodules with indeterminate FNA for surgery.

Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)	Likelihood Ratio for Positive Results (95% CI)	Likelihood Ratio for Negative Results (95% CI)	Diagnostic Odds Ratio (95% CI)
74% (55–87)	58% (48–67)	34% (25–44)	74% (41–100)	1.7 (1.4–2.0)	0.4 (0.2–0.7)	3.5 (1.7–7.1)
$I^2 = \text{NA}$	$I^2 = \text{NA}$	$I^2 = 57\%$	$I^2 = 99\%$	$I^2 = 17\%$	$I^2 = 93\%$	$I^2 = 32\%$

Legend: I^2 = I-square test result for heterogeneity; NA = not available for bivariate meta-analysis; 95% CI = 95% confidence interval.

Case 2

- 21 years old male with 3.5 cm, hypoechoic, solid thyroid nodule on ultrasound.
- FNA reported as revealed Follicular lesion of undeterminate significance (FLUS), Bethesda III
- Management?
- Role of PET scan in indeterminate nodules?
- Would high risk mutations define Adjuvant therapy?

■ RECOMMENDATION 19

When surgery is considered for patients with a solitary, cytologically indeterminate nodule, thyroid lobectomy is the recommended initial surgical approach. This approach may be modified based on clinical or sonographic characteristics, patient preference and/or molecular testing when performed (see Recommendations 13-16). (Strong recommendation, Moderate-quality evidence)

Extent of surgery in indeterminate nodules defined by :-

- Pre surgery risk factors for malignancy – size > 4cm, family history, history of radiation
- Ultrasound features
- FNA results
- Molecular testing
- Patient preference
- Contralateral nodularity
- Medical co-morbidities

Case 3

- 49 yo woman with 2 cm unifocal, solid left thyroid nodule, with peripheral vascularity on US
- FNA – ‘Suspicious for papillary thyroid carcinoma’ – Bethesda V
- Role of mutational analysis?

Impact of Mutational Testing on the Diagnosis and Management of Patients with Cytologically Indeterminate Thyroid Nodules: A Prospective Analysis of 1056 FNA Samples

Yuri E. Nikiforov, N. Paul Ohori, Steven P. Hodak, Sally E. Carty, Shane O. LeBeau, Robert L. Ferris, Linwah Yip, Raja R. Seethala, Mitchell E. Tublin, Michael T. Stang, Christopher Coyne, Jonas T. Johnson, Andrew F. Stewart, and Marina N. Nikiforova

Departments of Pathology and Laboratory Medicine (Y.E.N., N.P.O., R.R.S., M.N.N.), Surgery (S.E.C., L.Y., M.T.S.), Otolaryngology and Head Neck Surgery (R.L.F., J.T.J.), and Radiology (M.E.T.), and Division of Endocrinology (S.P.H., S.O.L., C.C., A.F.S.), University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213

TABLE 1. Cancer probability in thyroid nodules with indeterminate cytology based on specific cytological diagnosis and results of molecular testing performed in FNA samples

	Cancer risk			
	AUS/FLUS cytology (n = 247)	FN/SFN cytology (n = 214)	SMC cytology (n = 52)	All indeterminate cytology (n = 513)
Cytology only	14%	27%	54%	24%
Any mutation identified	88%	87%	95%	89%
<i>RAS</i>	84%	85%	88%	85%
<i>BRAF</i>	100%	100%	100%	100%
<i>PAX8/PPAR-γ</i>	100%	100%	100%	100%
<i>RET/PTC</i>	na	na	100%	100%
No mutation identified	5.9%	14%	28%	11%

na, Not applicable.

BRAF V600E and *TERT* Promoter Mutations Cooperatively Identify the Most Aggressive Papillary Thyroid Cancer With Highest Recurrence

Mingzhao Xing, Rengyun Liu, Xiaoli Liu, Avaniyapuram Kannan Murugan, Guangwu Zhu, Martha A. Zeiger, Sara Pai, and Justin Bishop

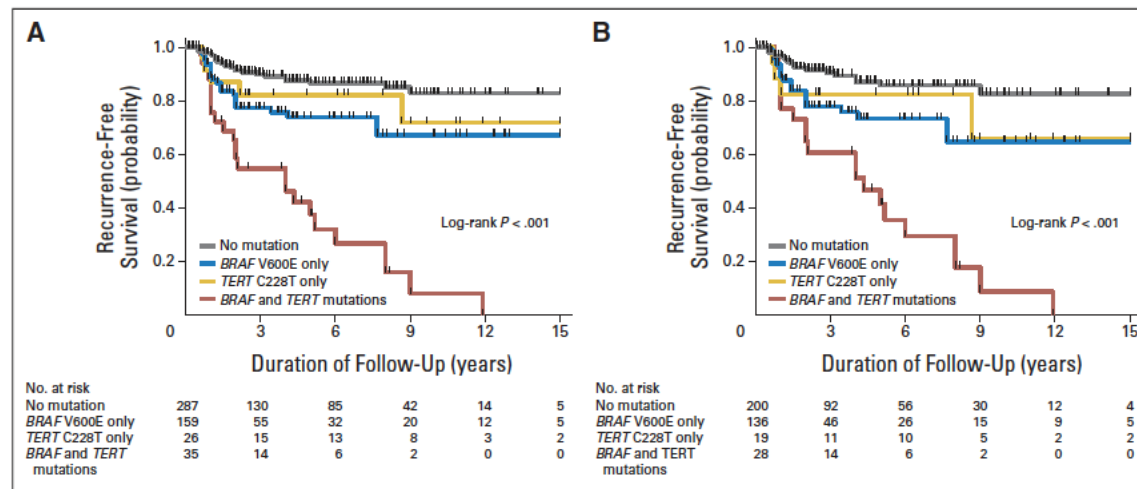


Fig 2. Kaplan-Meier analyses of the impacts of *BRAF*V600E or *TERT*C228T alone or their coexistence on disease-free survival of patients with papillary thyroid cancer (PTC). (A) Results of the analyses of patients with PTC of all types. (B) Results of the analyses of conventional variant PTC only. Four groups of patients are indicated in A and B, including patients with neither mutation (gray lines), *TERT* C228T mutation only (gold lines), *BRAF*V600E mutation only (blue lines), and coexistence of the two mutations (red lines).

Case 3

- 49 yo woman with 2 cm unifocal, solid left thyroid nodule, with peripheral vascularity on US
- FNA – ‘Suspicious for papillary thyroid carcinoma’ – Bethesda V
- Role of mutational analysis?
- Patient underwent Left hemithyroidectomy.
- Pathology – 2.3cm unifocal papillary cancer, follicular variant. With focal margin positivity
- Completion thyroidectomy? Adjuvant therapy? Role of Radioactive iodine ablation

Radioactive Iodine (RAI) therapy

- Not indicated for ATA low risk
- Not routinely indicated following surgery for unifocal or multifocal papillary microcarcinoma, in the absence of other adverse features
- Should be considered after total thyroidectomy in ATA intermediate risk patients
- Routinely recommended after Total thyroidectomy for ATA high risk patients

Case 4

- 57 yo male undergoes Total thyroidectomy with ipsilateral Level VI dissection for 2 cm papillary thyroid carcinoma with focal columnar features
- Pathology - 2.3 cm thyroid nodule confined to the thyroid gland, 1/3 Level VI lymph node positive for metastatic thyroid carcinoma
- Stage III
- Adjuvant therapy?
- Surveillance?

Estimating Risk of Recurrence in Differentiated Thyroid Cancer After Total Thyroidectomy and Radioactive Iodine Remnant Ablation: Using Response to Therapy Variables to Modify the Initial Risk Estimates Predicted by the New American Thyroid Association Staging System

R. Michael Tuttle,¹ Hernan Tala,¹ Jatin Shah,² Rebecca Leboeuf,¹ Ronald Ghossein,³ Mithat Gonen,⁴ Matvey Brokhin,¹ Gal Omry,¹ James A. Fagin,¹ and Ashok Shaha²

TABLE 8. USING THYROGLOBULIN AND RESPONSE TO INITIAL THERAPY ASSESSMENTS AT THE 2-YEAR FOLLOW-UP TIME POINT TO PREDICT LIKELIHOOD OF BEING NO CLINICAL EVIDENCE OF DISEASE AT FINAL FOLLOW-UP

<i>Initial risk stratification</i>	<i>Response to therapy variables during first 2 years of follow-up</i>	<i>NED at final follow-up</i>
Low risk (<i>n</i> = 104)	Suppressed Tg < 1 ng/mL alone	84%
	Stimulated Tg < 1 ng/mL alone	89%
	Excellent response (imaging negative ^a and suppressed Tg < 1 ng/mL)	94%
	Excellent response (imaging negative ^a and stimulated Tg < 1 ng/mL)	97%
Intermediate risk (<i>n</i> = 241)	Suppressed Tg < 1 ng/mL alone	74%
	Stimulated Tg < 1 ng/mL alone	80%
	Excellent response (imaging negative ^a and suppressed Tg < 1 ng/mL)	90%
	Excellent response (imaging negative ^a and stimulated Tg < 1 ng/mL)	94%
High risk (<i>n</i> = 126)	Suppressed Tg < 1 ng/mL alone	39%
	Stimulated Tg < 1 ng/mL alone	55%
	Excellent response (imaging negative ^a and suppressed Tg < 1 ng/mL)	80%
	Excellent response (imaging negative ^a and stimulated Tg < 1 ng/mL)	82%

n = 471 with both suppressed and stimulated Tg values available for analysis.

^aNegative imaging: normal neck US in all patients. In addition, any other functional or cross-sectional imaging obtained at the discretion of the treating physician was interpreted as having no evidence of persistent/recurrent thyroid cancer.

NED, no clinical evidence of disease.

Initial ATA risk estimates can be significantly refined based on the assessment of response to initial therapy, thereby providing a dynamic risk assessment that can be used to more effectively tailor ongoing follow-up recommendations.

Response

- ***Excellent response:*** no clinical, biochemical or structural evidence of disease
- ***Biochemical incomplete response:*** abnormal thyroglobulin or rising anti-thyroglobulin antibody levels in the absence of localizable disease.
- ***Structural incomplete response:*** persistent or newly identified locoregional or distant metastases
- ***Indeterminate response:*** non-specific biochemical or structural findings which cannot be confidently classified as either benign or malignant. This includes patients with stable or declining anti-thyroglobulin antibody levels without definitive structural evidence of disease.

Haugen et al, ATA 2015

■ RECOMMENDATION 49

Initial recurrence risk estimates should be continually 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 the response to therapy (Strong recommendation, Low-quality evidence)

Case 5

- 57 yo woman with a H/O new onset cough and hoarseness
- CT scan of the neck - 3.2 x 2 x 2 cm dominant left thyroid nodule with irregular margins, with extension into the left tracheoesophageal groove. Multiple bilateral subcentimeter nodules. Left level III/IV 3x2cm lymph node
- FNA – ‘papillary thyroid carcinoma’
- Pre-operative work up?
- Extent of surgery?

Recommendation 41

Pre-operative laryngeal examination should be performed with any patient with –

- Pre-operative voice abnormalities
- H/O cervical or upper chest surgery
- Known thyroid cancer with posterior extrathyroidal extension or central nodal metastasis.

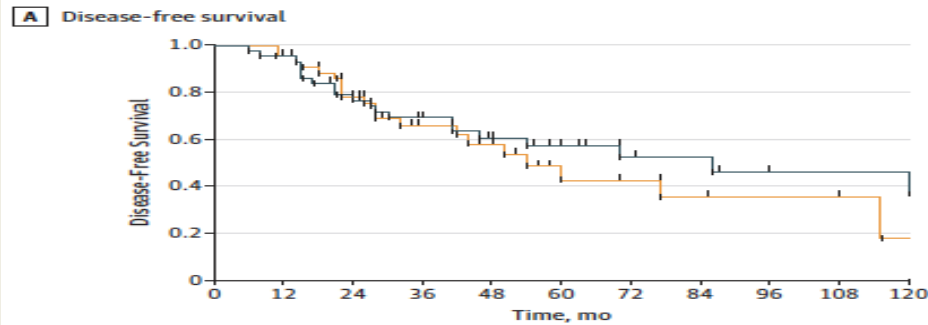
Case 5

- Underwent Total thyroidectomy with Left selective neck dissection (II-V), left central compartment neck dissection.
- Intraoperatively, minor erosion of the external cortex of cricoid cartilage. Shaving of the cartilage performed.
- Pathology – 3x2x2 cms left thyroid nodule with extrathyroidal extension into the strap muscles. 2/5 level VI lymph nodes positive with extranodal extension, left level III lymph node showed metastatic papillary thyroid carcinoma with extranodal extension.
- Adjuvant therapy? RAI vs Radiotherapy vs Both

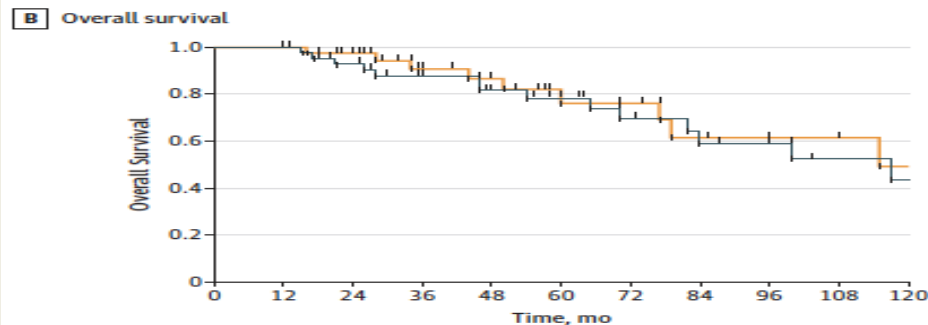
Adjuvant External Beam Radiotherapy in Locally Advanced Differentiated Thyroid Cancer

Samantha Tam, MD; Moran Amit, MD, PhD; Mongkol Boonsripitayanon, MD; Maria E. Cabanillas, MD; Naifa L. Busaidy, MD; G. Brandon Gunn, MD; Stephen Y. Lai, MD, PhD; Neil D. Gross, MD; Erich M. Sturgis, MD, MPH; Mark E. Zafereo, MD

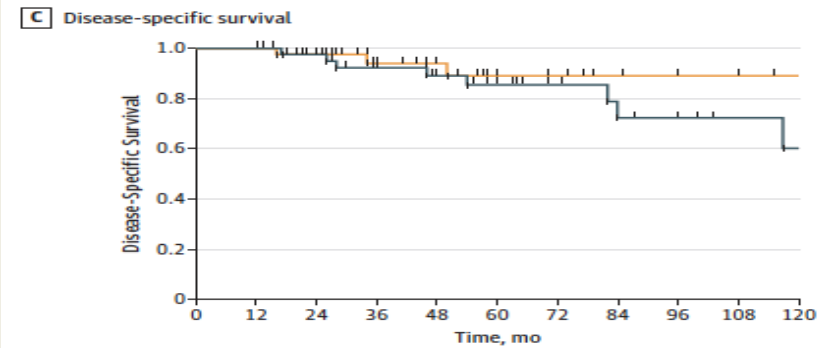
Figure 1. Disease-Free Survival, Overall Survival, and Disease-Specific Survival in Patients Undergoing RAI Alone or RAI and EBRT



No. at risk	0	12	24	36	48	60	72	84	96	108	120
RAI alone	44	42	30	19	14	8	7	6	4	3	2
EBRT and RAI	44	42	33	26	20	16	12	9	6	6	5



No. at risk	0	12	24	36	48	60	72	84	96	108	120
RAI alone	44	44	36	24	20	14	13	9	7	6	5
EBRT and RAI	44	44	39	31	26	22	17	12	10	7	6



No. at risk	0	12	24	36	48	60	72	84	96	108	120
RAI alone	44	44	36	24	20	14	13	9	7	6	5
EBRT and RAI	44	44	39	31	26	22	17	12	10	7	6

A, Log-rank $P = .46$; B, log-rank $P = .78$; C, log-rank $P = .27$. EBRT indicates external beam radiotherapy; RAI, radioactive iodine.

EBRT with RAI showed good disease control in patients with extensive soft tissue and visceral extension

Adjuvant therapy with External beam radiotherapy to be considered

- Locoregional disease/recurrence not surgically resectable
- Aerodigestive invasive cancer, R1 resection EBRT may be considered with RAI therapy
- Metastatic bony lesions for pain relief or palliation
- Brain metastasis



THANK YOU