

Thyroid Cancer: Update and Review of ATA Guidelines

Sunday

April 9, 2017

**Mid Eastern Chapter, Society Nuclear
Medicine and Molecular Imaging**

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Conflicts of Interest

- **Clinical Thyroid Cancer Trials**
- **Astra Zeneca, Pfizer, ThyroSeq**
- **Advisor, LioTriDev**

Objectives

- 1. To understand how to diagnose thyroid cancer.**
- 2. To learn how to apply ATA Guidelines to patients with thyroid cancer.**
- 3. To understand the relevant molecular clinical aspects of thyroid cancer.**

Thyroid Nodules and Cancer

- **Epidemiology**
- **Clinical Findings**
- **Management**
- **Thyroid Cancer**
- **Research**

**Revised American Thyroid Association Management
Guidelines for Patients with Thyroid Nodules
and Differentiated Thyroid Cancer**
**The American Thyroid Association (ATA) Guidelines
Taskforce on Thyroid Nodules and Differentiated Thyroid
Cancer**

**David S. Cooper, M.D (Chair), Thyroid 19: 167, 2009
(November).**

Bryan Haugen, M.D. (Chair), Thyroid, 26: 1, 2016.

Prevalence of Thyroid Nodules

- In an autopsy study, **12%** of thyroid glands contained one nodule, **37%** multiple nodules; **2.1%** of all glands contained thyroid cancer (Mortensen JD, et al, JCEM 15: 1270, 1955).
- Using thyroid sonograms in a clinical study, **22%** of thyroid glands contained solitary and **45%** contained multiple thyroid nodules (Ezzat et al, Arch Int Med 154:1828, 1994).

Thyroid Nodules and Cancer

- Epidemiology
- **Clinical Findings**
- Management
- Thyroid Cancer
- Research

Clinical Findings Associated with an Increased Risk That a Thyroid Nodule Is Malignant

Table 1. Clinical Findings Associated with an Increased Risk That a Thyroid Nodule Is Malignant.*

History of differentiated thyroid cancer in at least one first-degree relative

History of external-beam radiation or exposure to ionizing radiation as a child or adolescent

Prior tissue or cytologic diagnosis of thyroid carcinoma

Male sex

Focal uptake of ^{18}F -fluorodeoxyglucose by the thyroid

Personal or family history of multiple endocrine neoplasia type 2 or familial medullary thyroid cancer

Serum calcitonin level >50 to 100 pg/ml

Residence near a nuclear-reactor accident

* Adapted with permission from the American Thyroid Association (ATA) guidelines.⁴

Burman KD, Wartofsky L. N Engl J Med 2015;373:2347



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Causes of Thyroid Nodules

- **BENIGN**

- Adenoma
- Cysts
- Thyroiditis
- Infections
- Infiltrative Diseases
- Thyroglossal duct cyst
- Teratoma

- **NON THYROIDAL CAUSES**

- Parathyroid cyst or adenoma
- Thymoma
- Lipoma
- Cystic hygroma
- Brachial cleft cyst
- Paraganglioma
- Salivary Gland Tumors

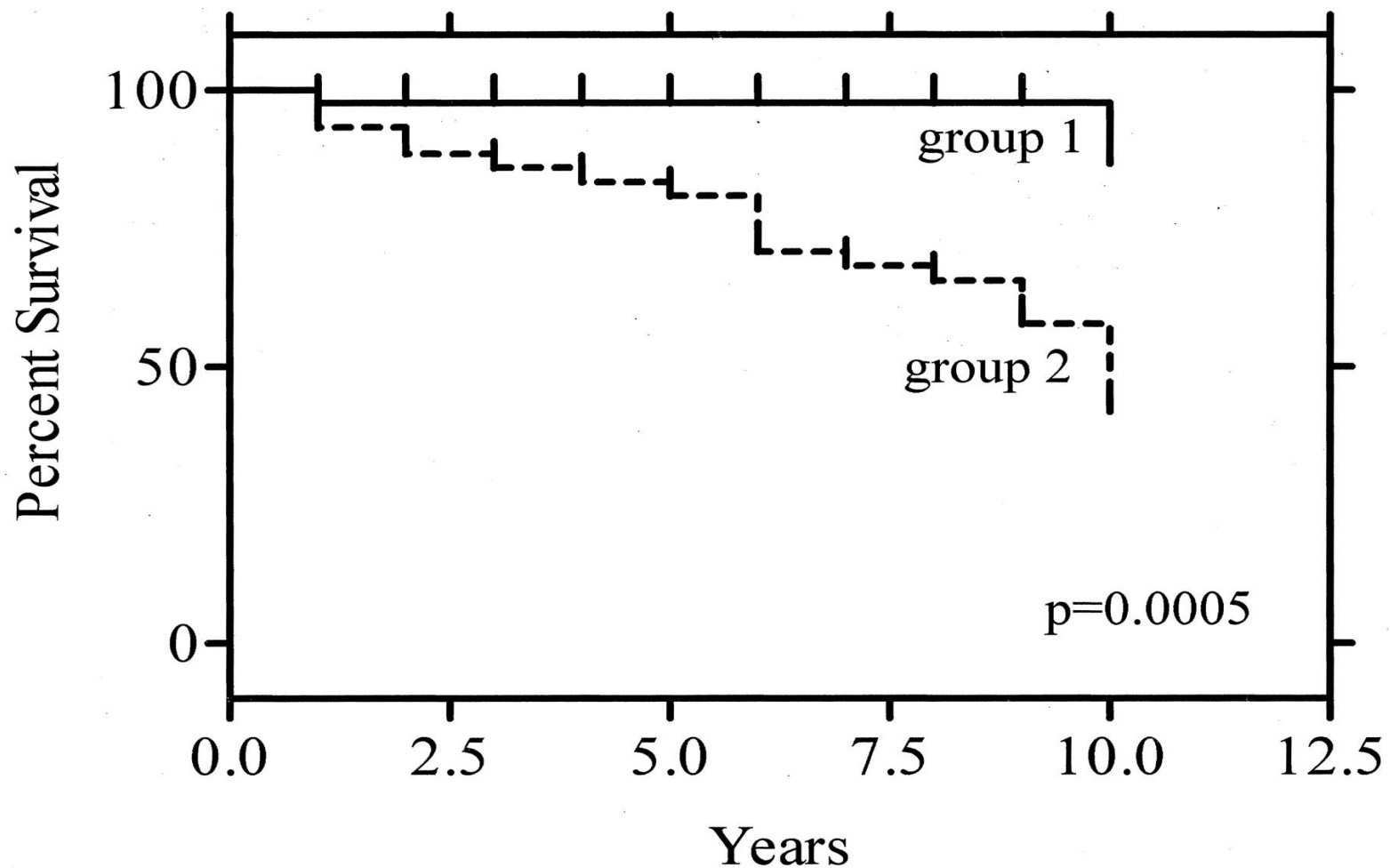
- **MALIGNANT**

- Papillary cancer
- Follicular cancer
- Medullary cancer
- Anaplastic cancer
- Lymphoma
- **Metastatic cancer**
- Renal, Breast, Melanoma, Colon

Calcitonin Measurement

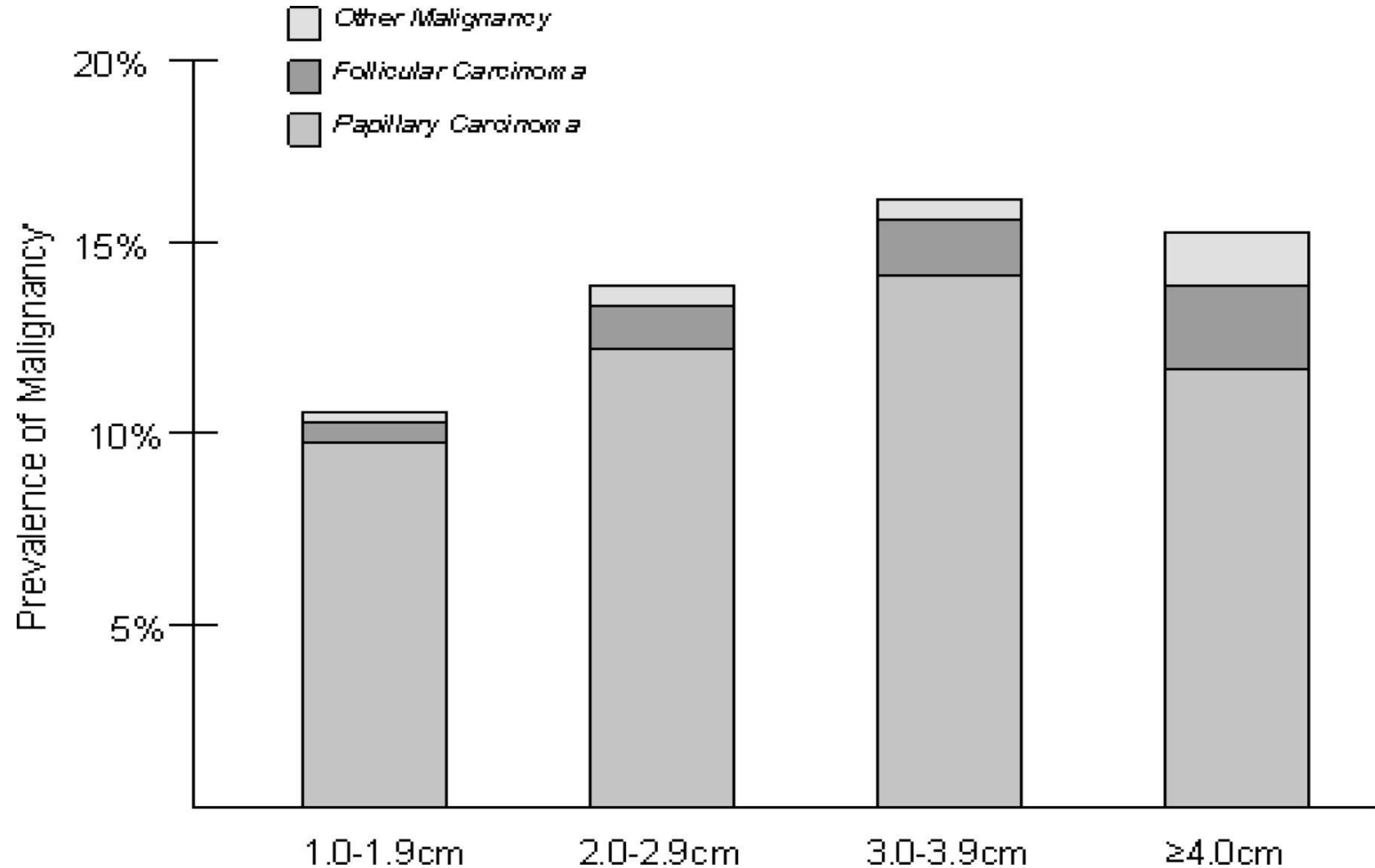
- RECOMMENDATION 4
- **The panel cannot recommend either for or against routine measurement of serum calcitonin in patients with thyroid nodules.**
- **(No recommendation, Insufficient evidence)**

FIG. 4. The survival curve of MTC patients diagnosed after the introduction of routine measurement serum CT in nodular thyroid disease (group 1) and in a historical group (group 2)



Elisei, R. et al. J Clin Endocrinol Metab 2004;89:163-168

Thyroid nodule size and the types and distribution of thyroid malignancy.



Kamran S C et al. JCEM 2013;98:564-570

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& METABOLISM

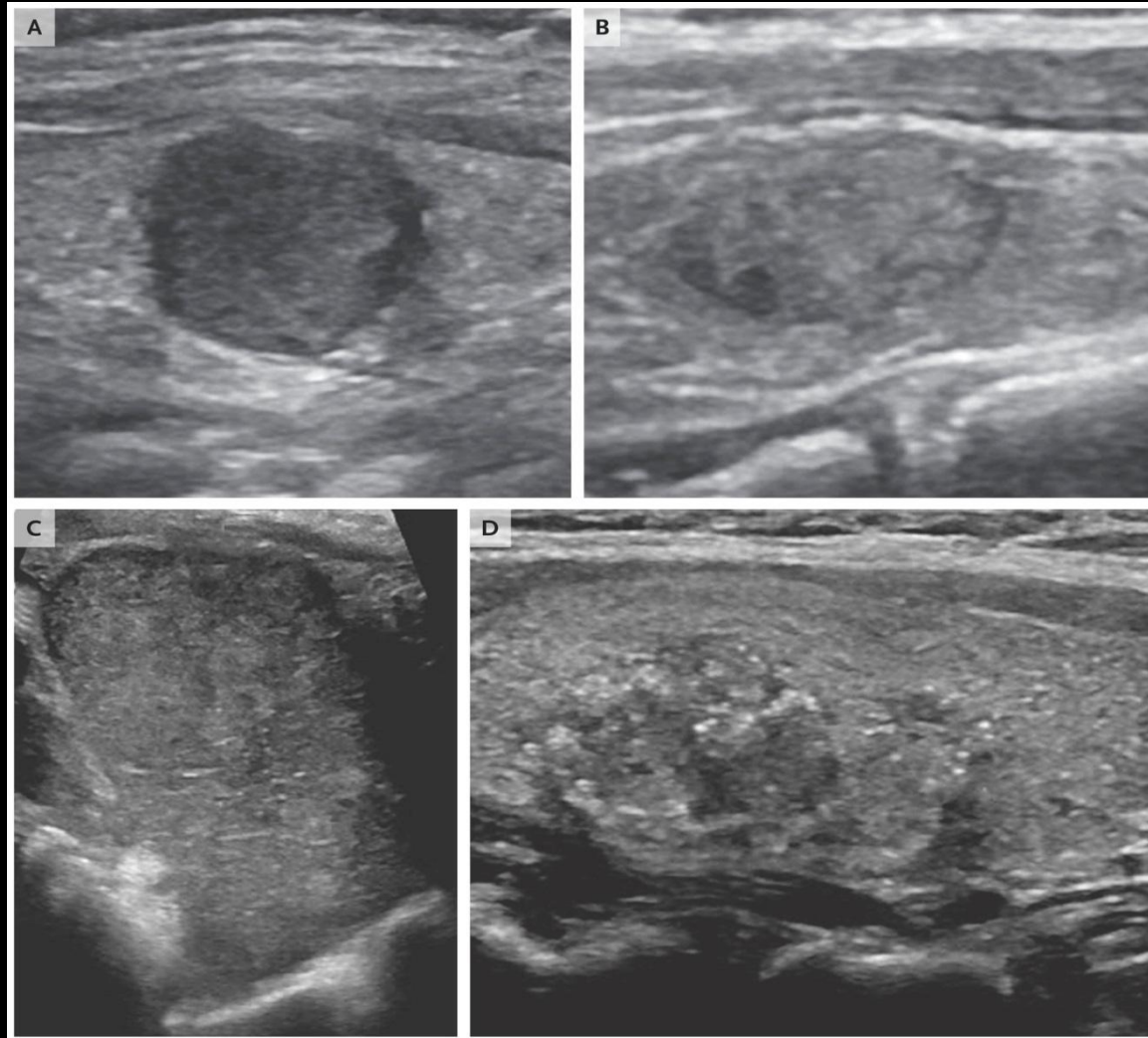
Thyroid Nodules and Cancer

- Epidemiology
- Clinical Findings
- **Management**
- Thyroid Cancer
- Research

Thyroid Sonography

- RECOMMENDATION 6
- **Thyroid sonography with survey of the cervical lymph nodes should be performed in all patients with known or suspected thyroid nodules.**
- **(Strong recommendation, High-quality evidence)**

Ultrasonographic Images of Thyroid Nodules

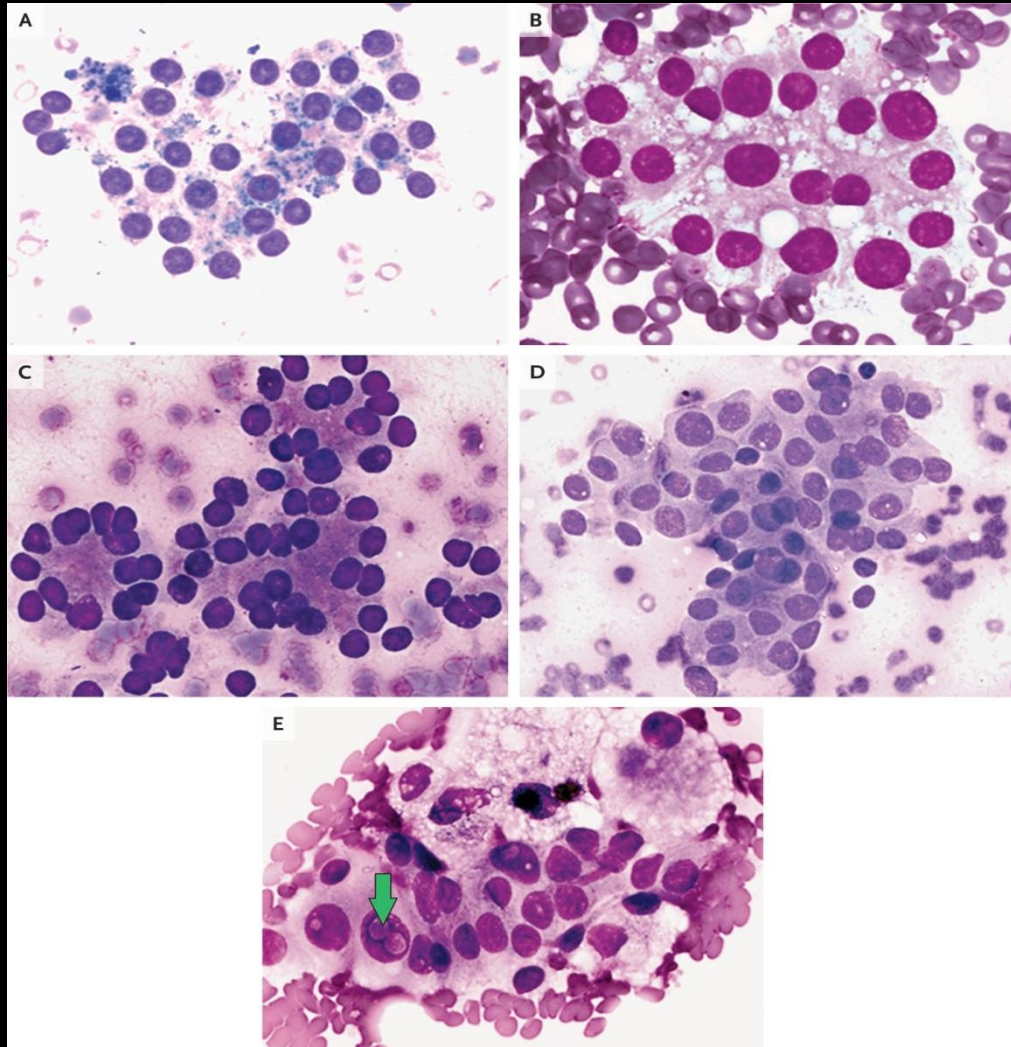


Burman KD, Wartofsky L. N Engl J Med 2015;373:2347



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Thyroid Fine-Needle Aspiration Specimens



Burman KD, Wartofsky L. N Engl J Med 2015;373:2347.



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Diagnostic Categories of Thyroid Nodules and Risk of Cancer

Table 2. Diagnostic Categories of Thyroid Nodules and Risk of Cancer.*

Diagnostic Category†	Percent Risk of Cancer‡ <i>median (range)</i>
Nondiagnostic or unsatisfactory	20 (9–32)
Benign	2.5 (1–10)
Atypia of undetermined significance or follicular lesion of undetermined significance	14 (6–48)
Follicular neoplasm or suspicious for a follicular neoplasm	25 (14–34)
Suspicious for malignancy	70 (53–97)
Malignant	99 (94–100)

* Adapted with permission from the 2015 ATA guidelines.¹³

† The categories are those of the Bethesda System for Reporting Thyroid Cytopathology.²⁹

‡ Values are based on the meta-analysis of eight studies reported by Bongiovanni et al.³⁰ The risk was calculated on the basis of the number of nodules in each diagnostic category that were surgically excised, and the time between thyroid fine-needle aspiration and surgery can vary among individual cases and among studies. In our review of the published literature, the false negative rate of a nodule with a benign finding on fine-needle aspiration is about 5 to 10%.^{30–32} The false negative rate of a thyroid fine-needle aspiration depends on multiple factors, including the adequacy of the sample obtained, the experience of the cytologist, and the size of the nodule.

Burman KD, Wartofsky L. N Engl J Med 2015;373:2347



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Oncogenic Alterations

Papillary thyroid cancer (About 70% have alteration):

RET/PTC rearrangement: Ret is a transmembrane receptor tyrosine kinase.

BRAF mutations: a cytoplasmic serine/threonine tyrosine kinase type 1.

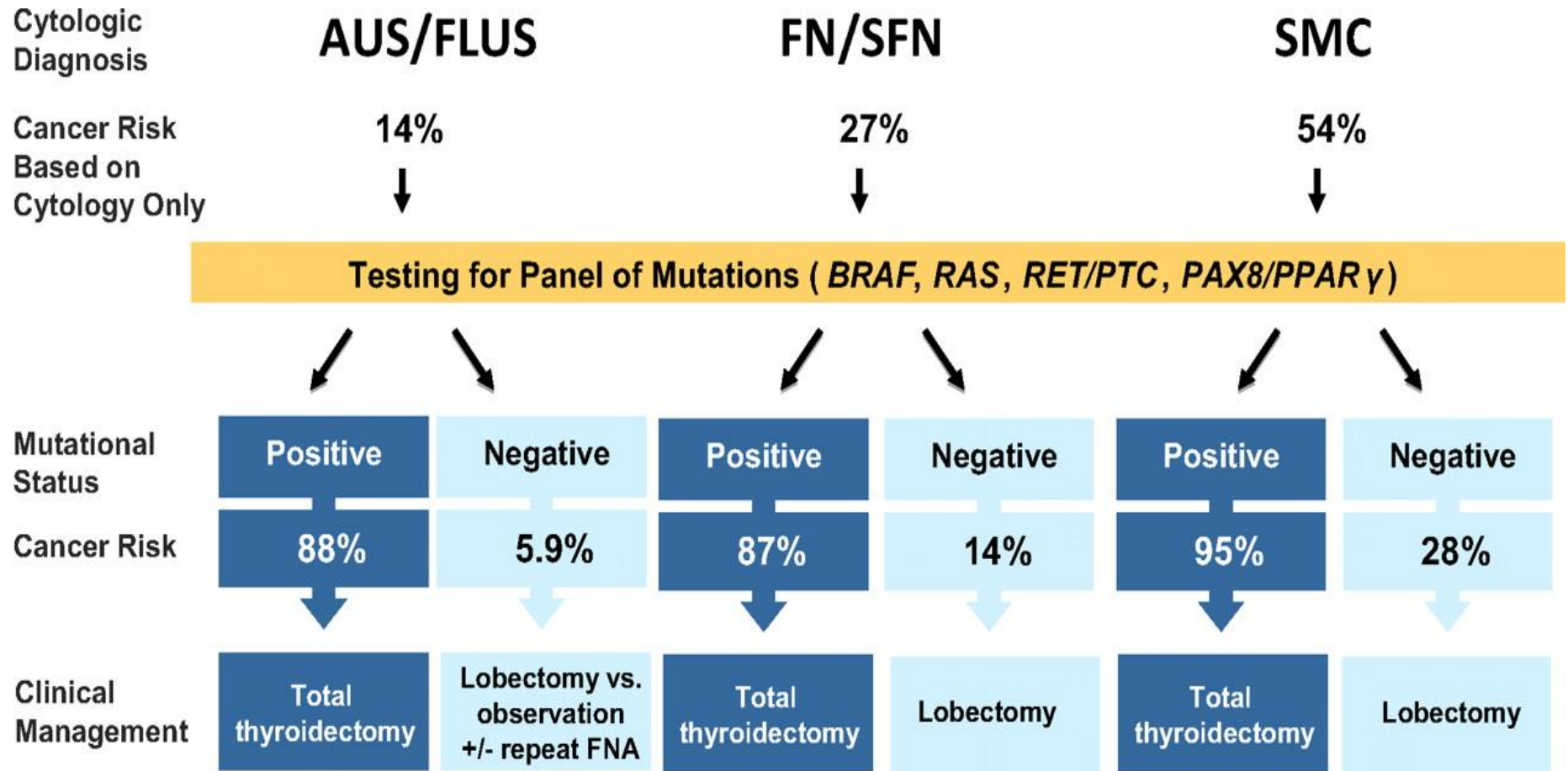
Ras mutations: Ras superfamily of small GTPases.

RAS/RAF/MAPK signaling pathway

PI3K/PDK1/Akt signaling pathway

Ouyang et al, Clin Cancer Research 12:1785,06.

Proposed clinical algorithm for management of patients with cytologically indeterminate thyroid FNA applying the results of mutational analysis



Nikiforov Y E et al. JCEM 2011;96:3390.

Afirma® Overall Performance: FLUS, FN, and SMC

All indeterminates N=265

	Cancer (N=85) Pathology	Benign (N=180) Pathology
Suspicious (Afirma)	78	87
“Benign” (Afirma)	7	93

SN: 92%

SF: 52%

PPV: 47%

NPV: 93%

False Negative Thyroid FNA

- RECOMMENDATION 23
- **Given the low false-negative rate of US-guided FNA cytology and the higher yield of missed malignancies based upon nodule sonographic pattern rather than growth, the follow-up of thyroid nodules with benign cytology diagnoses should be determined by risk stratification based upon US pattern.**
- **Nodules with high suspicion US pattern: repeat US and US-guided FNA within 12 months.**
- **(Strong recommendation, Moderate-quality evidence)**

AUS/FLUS

- **RECOMMENDATION 15**
- **For nodules with AUS/FLUS cytology, after consideration of worrisome clinical and sonographic features, investigations such as repeat FNA or molecular testing may be used to supplement malignancy risk assessment in lieu of proceeding directly with a strategy of either surveillance or diagnostic surgery. (Weak recommendation, Moderate-quality evidence)**

FN/SFN

- RECOMMENDATION 16
- **Diagnostic surgical excision is the long-established standard of care for the management of FN/SFN cytology nodules. However, after consideration of clinical and sonographic features, molecular testing may be used to supplement malignancy risk assessment data in lieu of proceeding directly with surgery. (Weak recommendation, Moderate-quality evidence)**

Indeterminate FNA

- **Nodules with low to intermediate suspicion US pattern: repeat US at 12–24 months. If sonographic evidence of growth (20% increase in at least two nodule dimensions with a minimal increase of 2 mm or more than a 50% change in volume) or development of new suspicious sonographic features, the FNA could be repeated or observation continued with repeat US, with repeat FNA in case of continued growth. (Weak recommendation, Low-quality evidence)**

Indeterminate Nodules

- **Nodules with very low suspicion US pattern (including spongiform nodules): the utility of surveillance US and assessment of nodule growth as an indicator for repeat FNA to detect a missed malignancy is limited. If US is repeated, it should be done at about 24 months.**
- **(Weak recommendation, Low-quality evidence)**

Surgery

- 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 (Strong recommendation, Moderate-quality evidence)**

Surgery

- RECOMMENDATION 20
- **Because of increased risk for malignancy, total thyroidectomy may be preferred in patients with indeterminate nodules that are cytologically suspicious for malignancy, positive for known mutations specific for carcinoma, sonographically suspicious, or large (>4 cm), or in patients with familial thyroid carcinoma or history of radiation exposure.(Strong recommendation, Moderate-quality evidence)**

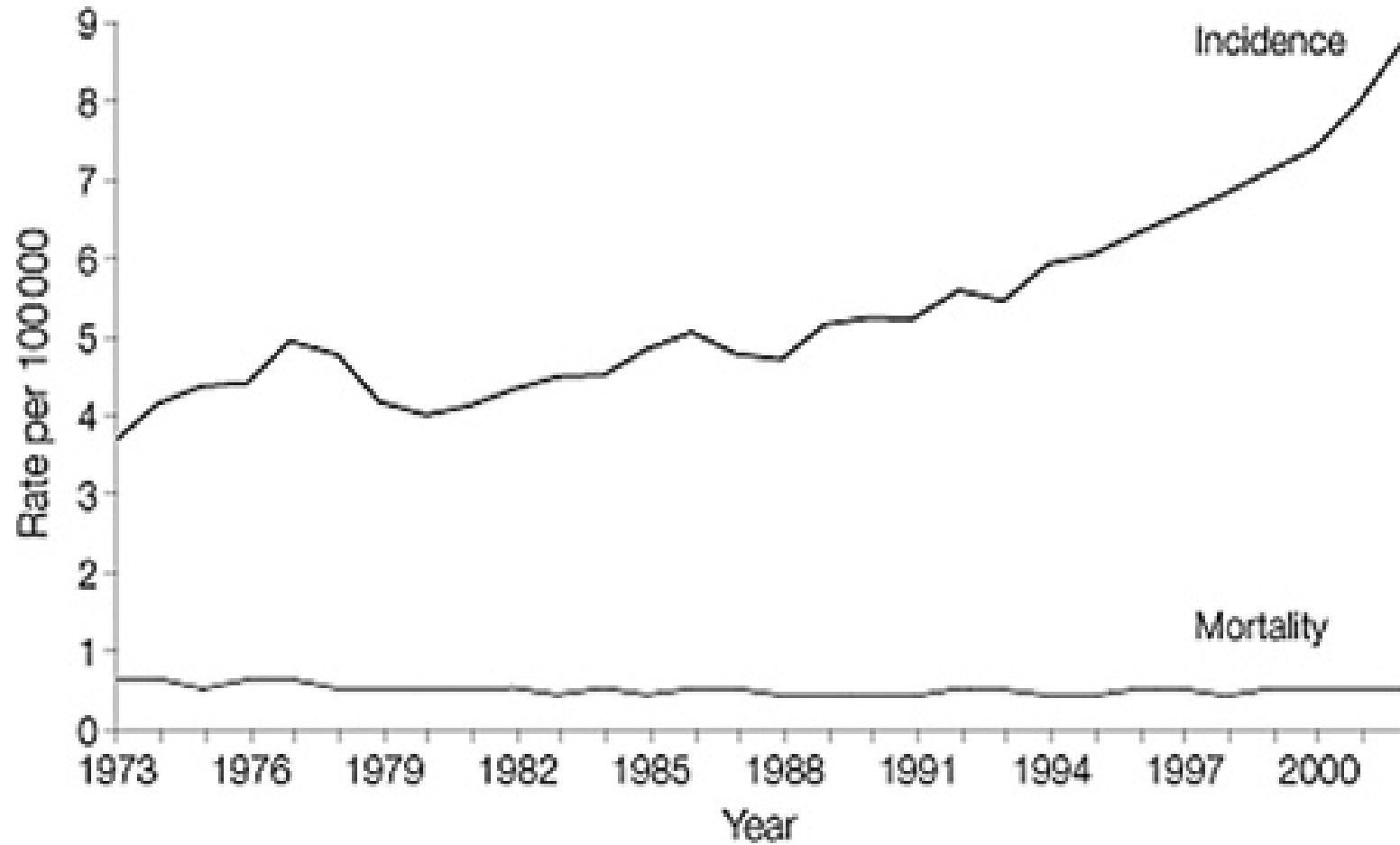
Thyroid Nodules and Cancer

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Thyroid Cancer Incidence and Prevalence

- Approximately 65,000 new cases of thyroid cancer are diagnosed annually and the incidence is increasing by 5–6% per year in the United States.
- Thyroid cancer prevalence approximately 450,000 in the United States.
- The majority of patients with thyroid cancer have an excellent prognosis, **WHEREAS** patients who have distant metastasis have only 50% 5-year survival rate.

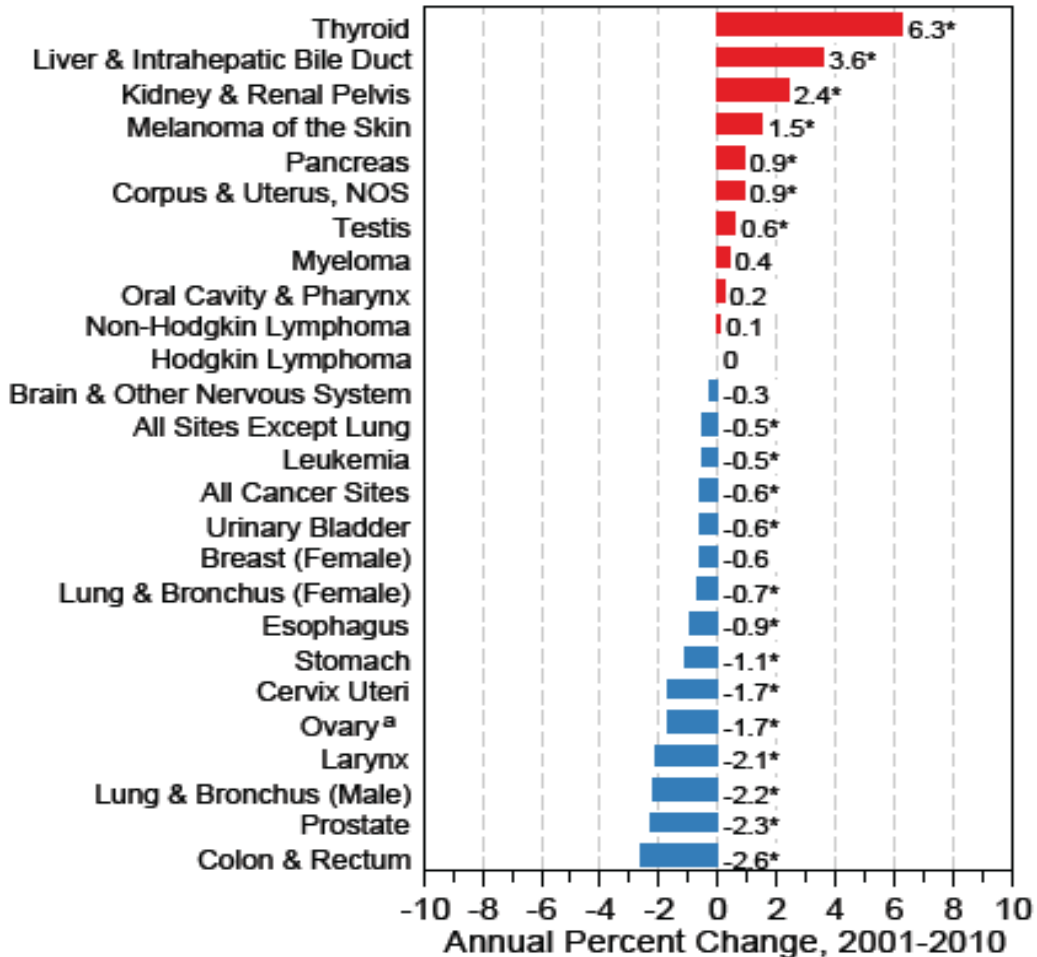
Thyroid Cancer Incidence and Mortality, 1973–2002



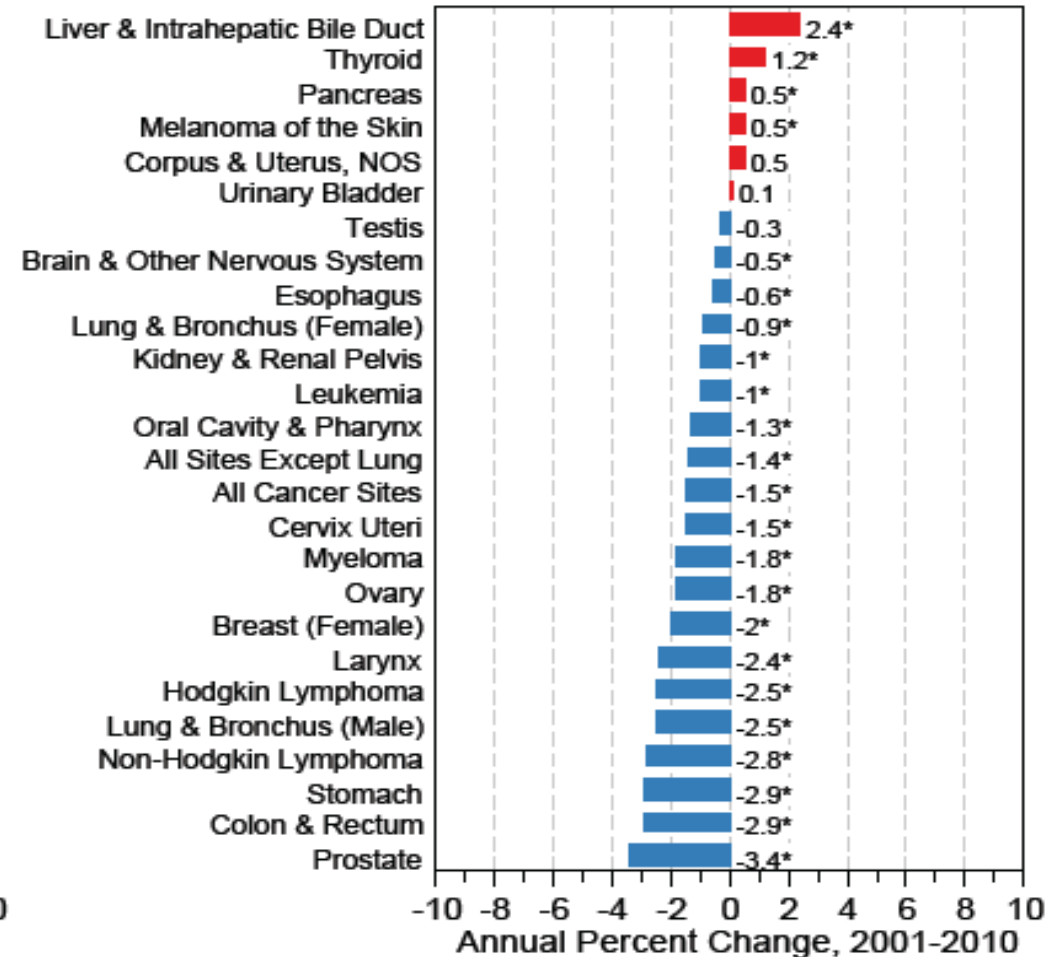
Davies and Welsh, JAMA 295: 2006;2164.

Trends in incidence and mortality, 2001-2010

Trends in SEER Incidence Rates



Trends in US Cancer Death Rates



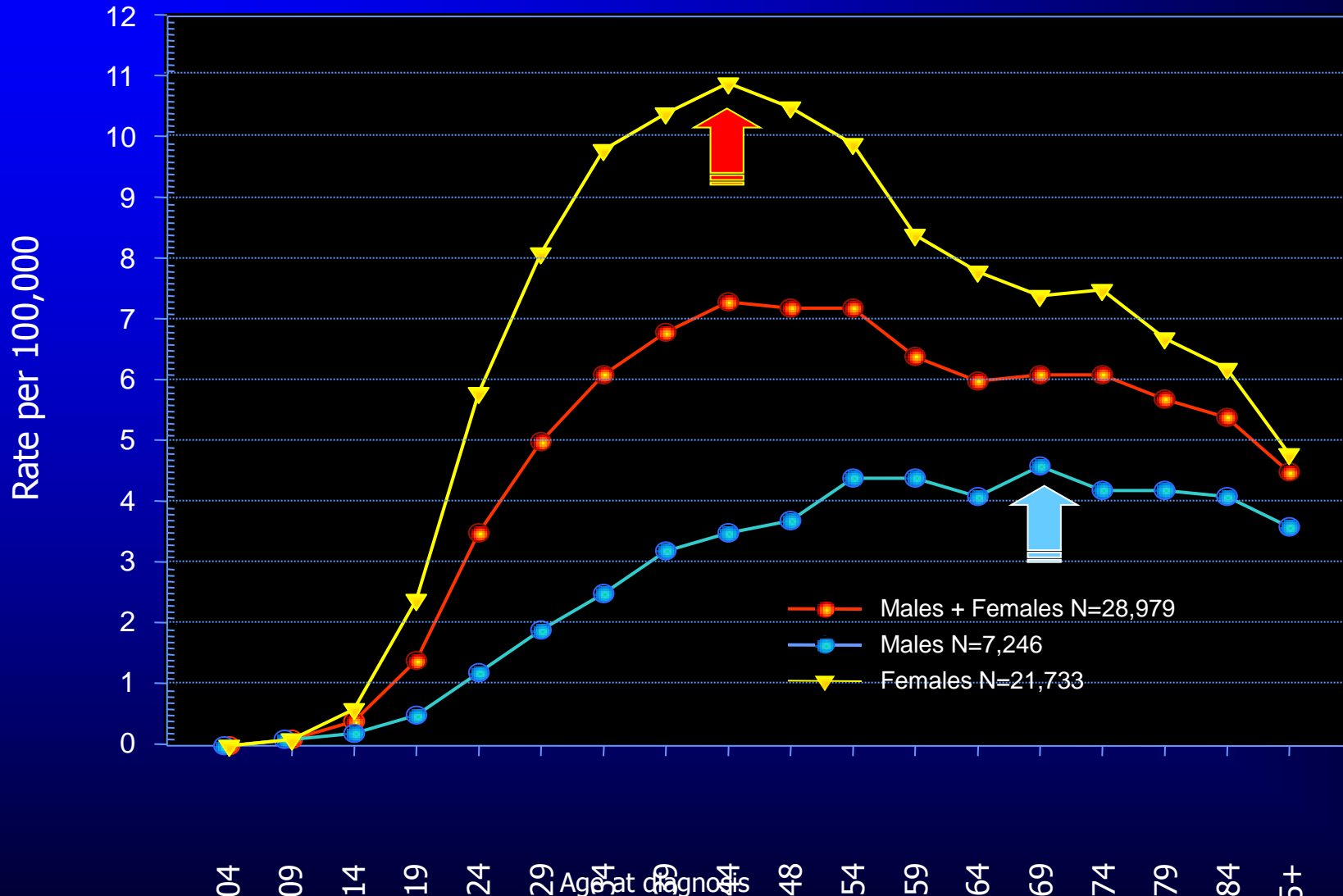
Increasing Incidence of Thyroid Cancer (1973-2002)

- 5 year survival for papillary thyroid cancer increased from **92.7%** in 1974 to **97.4%** in 2001 ($p < .05$).

HOWEVER

- **The rates of distant metastases in men increased from 4% to 9%.**
- From 1992-2000, the annual percentage change in thyroid cancer mortality increased in men by **2.4%**. This is the largest increase of any type of cancer.
- **Understanding the specific mechanisms involved in thyroid cancer progression and metastases is critical in order to develop new diagnostic and therapeutic modalities specifically for these patients.**
- Davies and Welsh, JAMA 295: 2164, 2006.
- Mazzaferri JAMA 295: 2179, 2006.

Incidence and Age of Onset of Thyroid Cancer



Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence, SEER 9 Regs Public-Use, Nov 2003 Sub (1973-2001), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2004, based on the November 2003 submission. Tumors with only one primary and microscopically confirmed

Incidence & Mortality Rates

53,856 patients (1985-1995)

	Incidence	10-year Relative Survival
Papillary	80%	93%
Follicular	11%	85%
Hürthle	3%	76%
Medullary	4%	75%
Anaplastic	2%	14%

Hundahl, S. A., Fleming, I. D., Fremgen, A. M., and Menck, H. R.A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the US, 1985-1995. Cancer 83, 2638-2648. 1998.

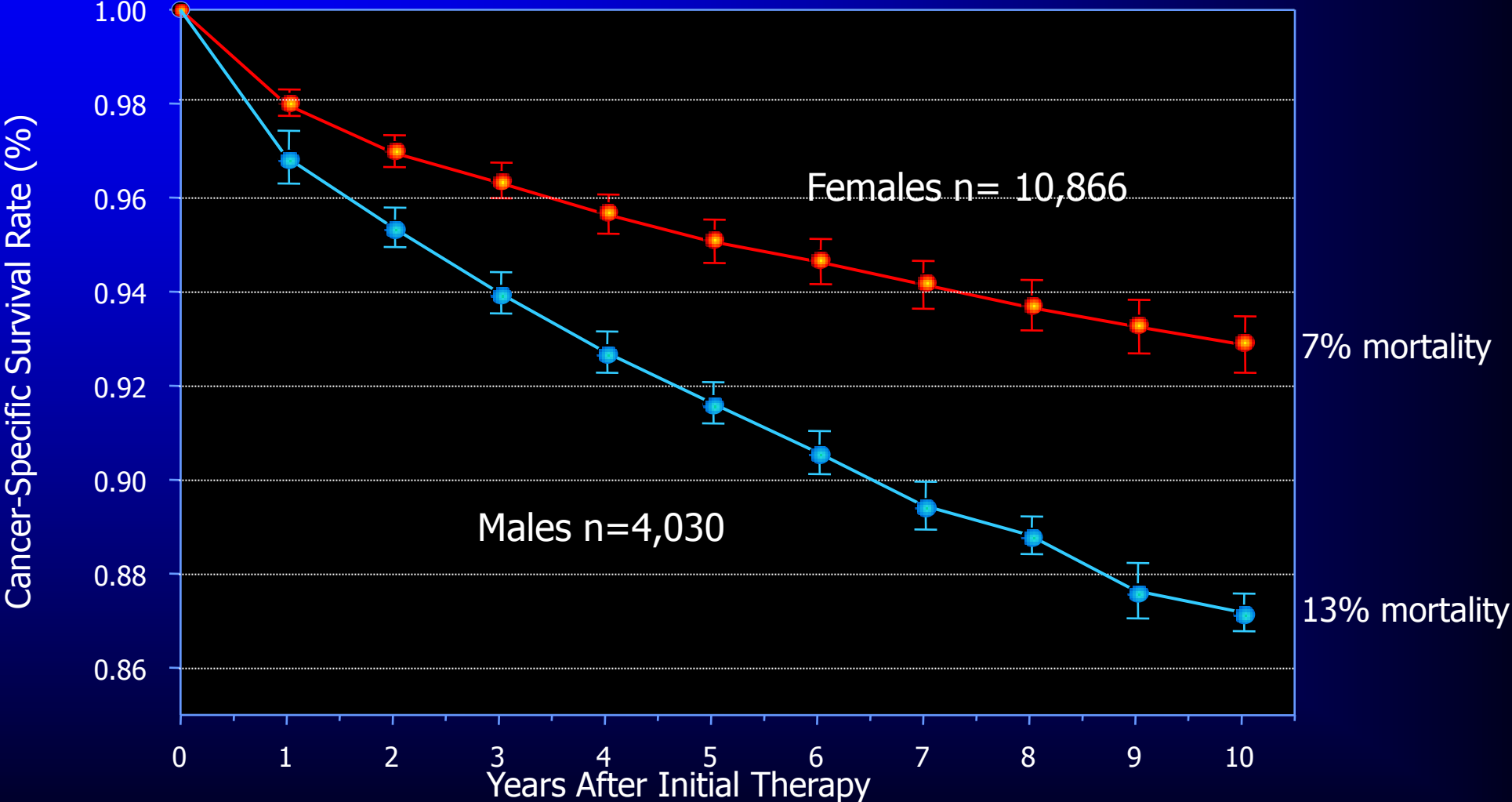
Incidence & Mortality Rates

53,856 patients (1985-1995)

	Incidence	Percent of Deaths
Papillary	80%	53%
Follicular	11%	16%
Hürthle	3%	7%
Medullary	4%	10%
Anaplastic	2%	14%

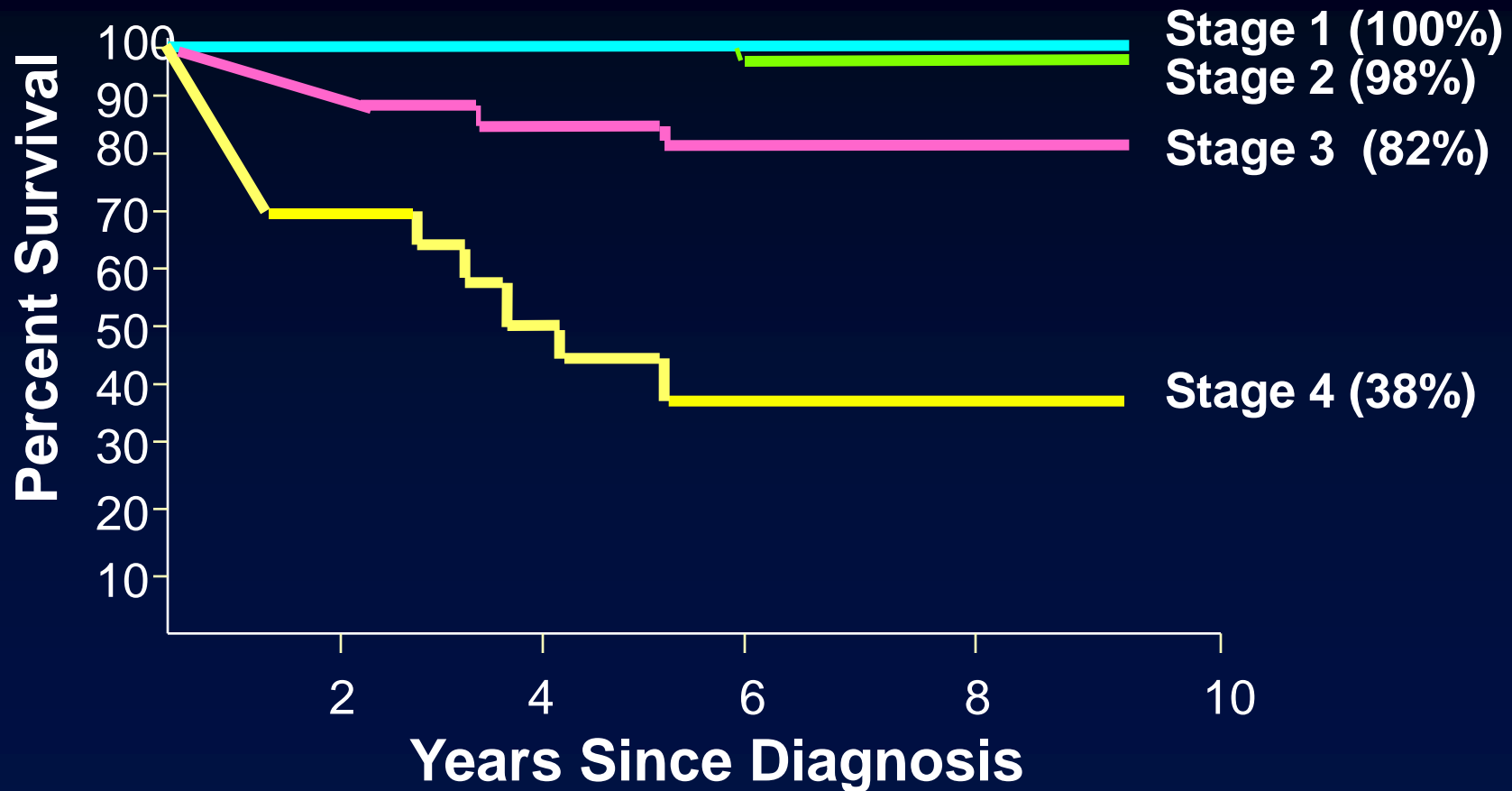
Cause-specific Survival Men and Women Age 40+

Papillary and Follicular Thyroid Cancer



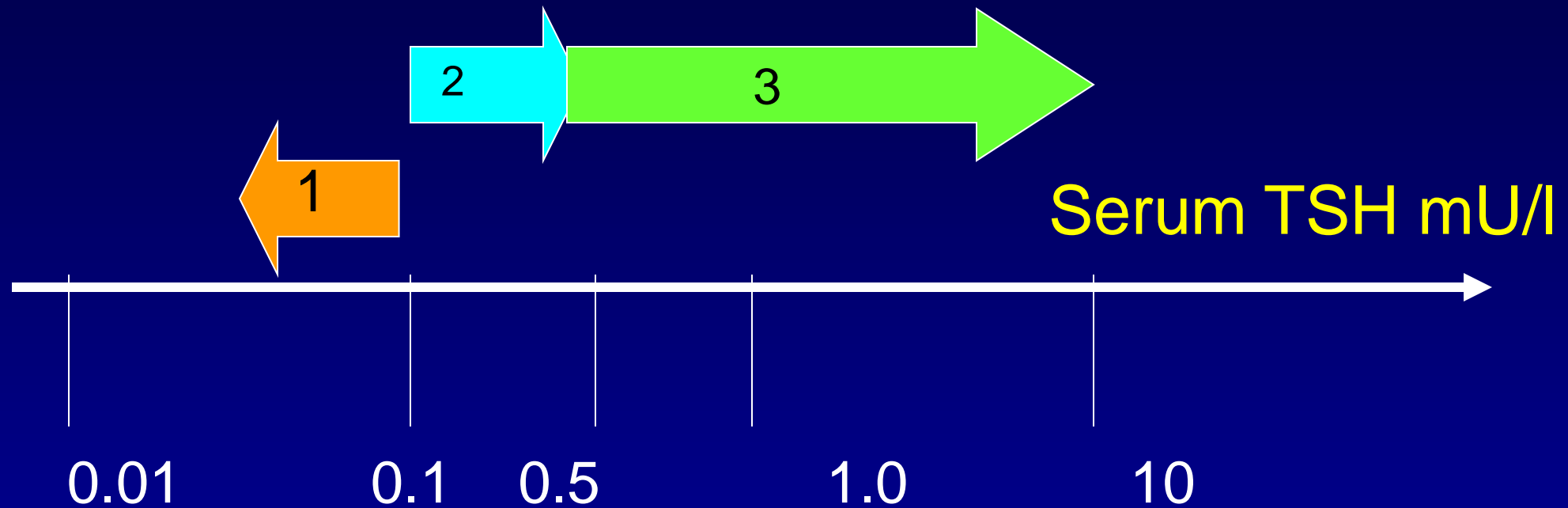
Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Public-Use, Nov 2003 Sub (1973-2001), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2004, based on the November 2003 submission. Tumors with only one primary and microscopically confirmed

Effect of Current Therapy: Thyroid Cancer Survival



Sherman, et. al. Cancer 1998;83:1012-1021.

TSH in Thyroid Cancer Long-Term



1. persistent disease < 0.1
2. disease free, higher risk 0.1-0.5
3. disease free, low risk 0.3-2

ATA RISK STRATIFICATION

- **LOW RISK**

- No local or distant metastases
- All microscopic tumor resected
- No locoregional tumor invasion
- No aggressive histology or vascular invasion
- If ¹³¹I given, no uptake outside of thyroid bed on post-Rx scan

ATA RISK STRATIFICATION

- **INTERMEDIATE RISK**

- (+) microscopic perithyroidal invasiveness
- (+) lymph nodes or uptake outside thyroid bed
- (+) aggressive histology or vascular invasion

- **HIGH RISK**

- Macroscopic invasion of tumor
- Incomplete tumor resection
- Distant mets or Tg suggestive of distant mets

WHO TO ABLATE? RECOMMENDATION 51: Decision based on ATA risk of recurrence stratification system post thyroidectomy

- Do not give RAI for “**low risk**” DTC* **Weak**
Recommendation; Low Quality evidence
- Do not give RAI for unifocal Micro PTC*
Strong Recommendation; Moderate Quality evidence
- Do not give RAI for multifocal Micro PTC * **Weak**
Recommendation; Low Quality evidence

*absent any other higher risk features

WHO TO ABLATE? ATA GUIDELINES: 2015

Decision based on ATA risk of recurrence stratification system post thyroidectomy

- Yes, RAI ablation for **Intermediate risk**
 - selected patients with 1–4 cm tumors confined to thyroid and LN metastases
 - Other high risk features (when combination of age, tumor size, LN status, and histology predicts an intermediate/ high risk of recurrence or death)
 - *Weak Recommendation; Low Quality evidence*

WHO TO ABLATE? ATA GUIDELINES: 2015

Decision based on ATA risk of recurrence stratification system post thyroidectomy

- Yes, RAI ablation for **High risk**
 - known distant metastases
 - Extrathyroidal extension regardless of tumor size
 - tumor size >4 cm even absent other high risk features.

Strong Recommendation; Moderate Quality evidence

Molecular Testing

- RECOMMENDATION 52
- **The role of molecular testing in guiding postoperative RAI use has yet to be established; therefore, no molecular testing to guide postoperative RAI use can be recommended at this time.**
- **(No recommendation, Insufficient evidence)**

Follow up

- **ATA high-risk patients (regardless of response to therapy) and all patients with biochemical incomplete, structural incomplete, or indeterminate response should continue to have Tg measured at least every 6–12 months for several years.**
- **(Weak recommendation, Low-quality evidence)**

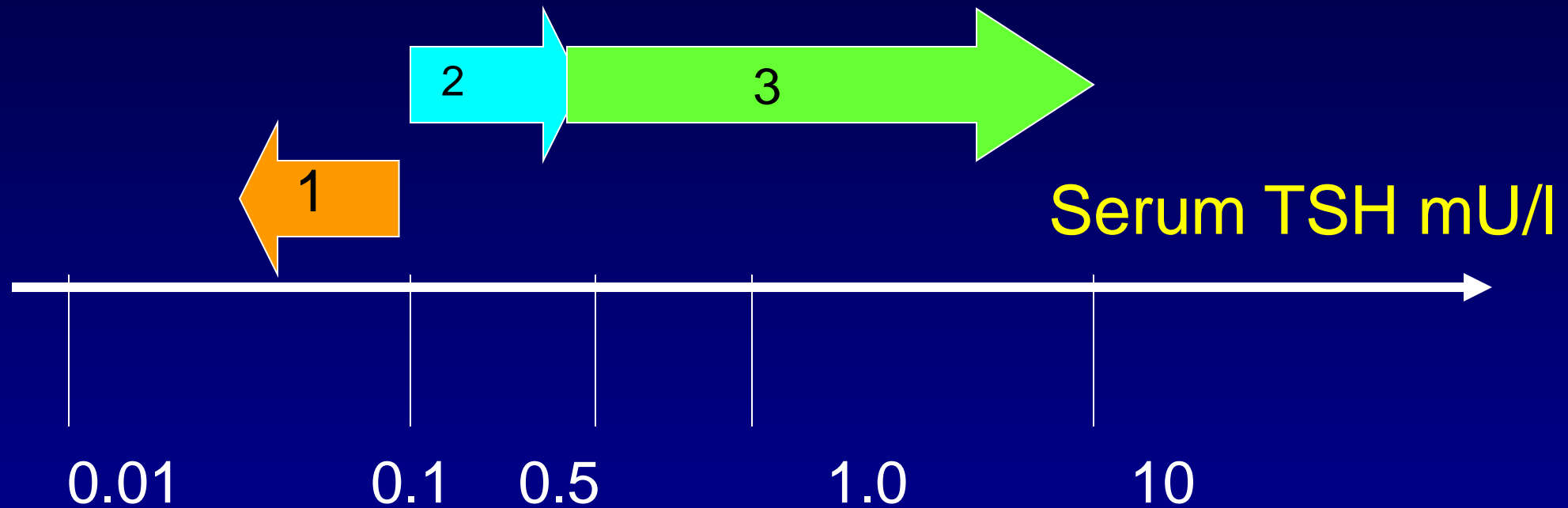
Follow Up

- **RECOMMENDATION 63**
- **In ATA low-risk and intermediate-risk patients who have had remnant ablation or adjuvant therapy and negative cervical US, serum Tg should be measured at 6–18 months on thyroxine therapy with a sensitive Tg assay (<0.2 ng/mL) or after TSH stimulation to verify absence of disease (excellent response). (Strong recommendation, Moderate-quality evidence)**

Cross-Sectional Imaging

- **RECOMMENDATION 33**
- **Preoperative use of cross-sectional imaging studies (CT, MRI) with intravenous (IV) contrast is recommended as an adjunct to US for patients with clinical suspicion for advanced disease, including invasive primary tumor, or clinically apparent multiple or bulky lymph node involvement**

TSH in Thyroid Cancer Long-Term



1. persistent disease <0.1
2. disease free, higher risk 0.1-.5
3. disease free, low risk 0.3-2

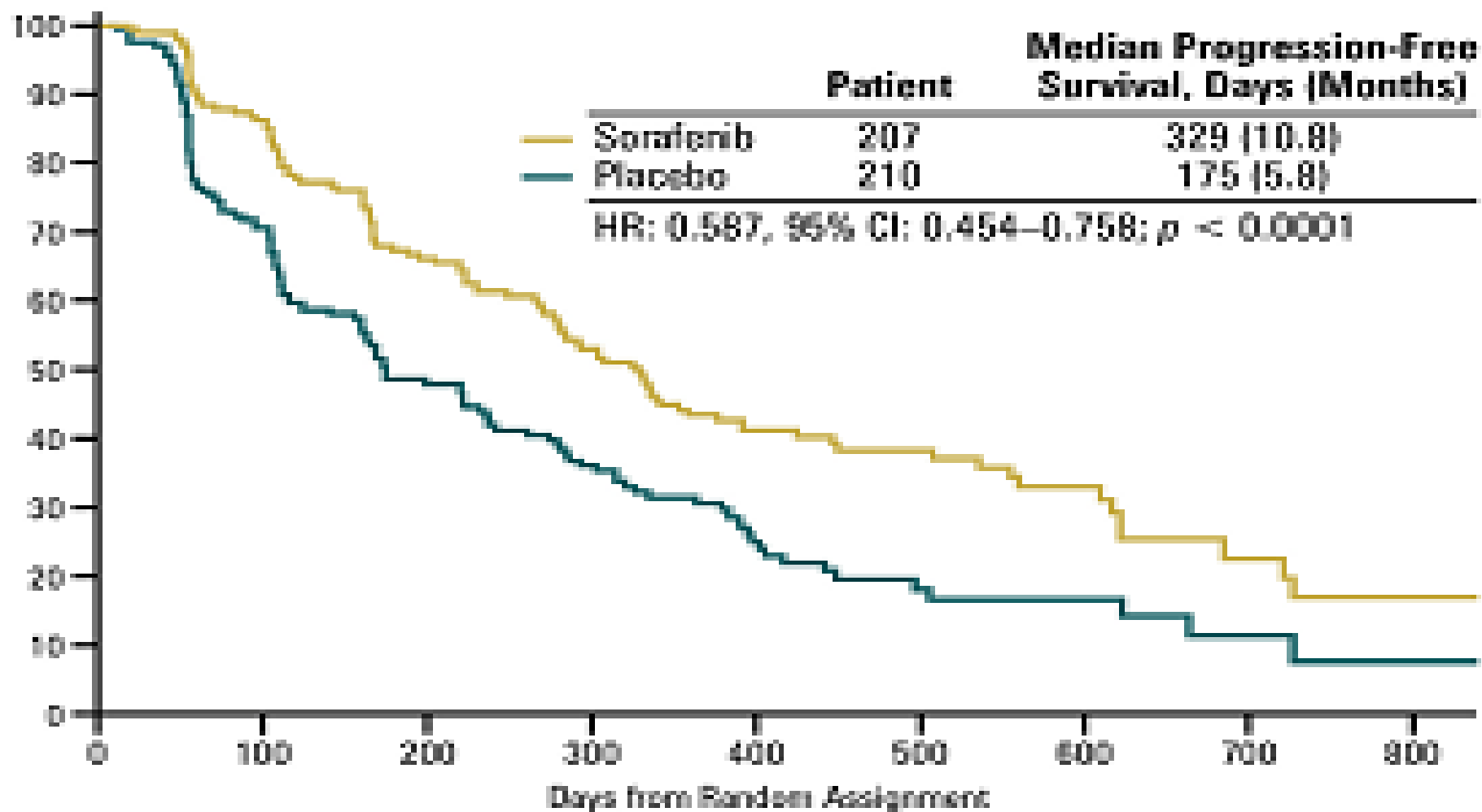
Case; Metastatic Thyroid Cancer

- **“Referral for participation in clinical trials should be considered for patients with progressive or symptomatic metastatic disease. For those patients who do not participate in clinical trials, treatment with tyrosine kinase inhibitors should be considered.”**

Sorafenib

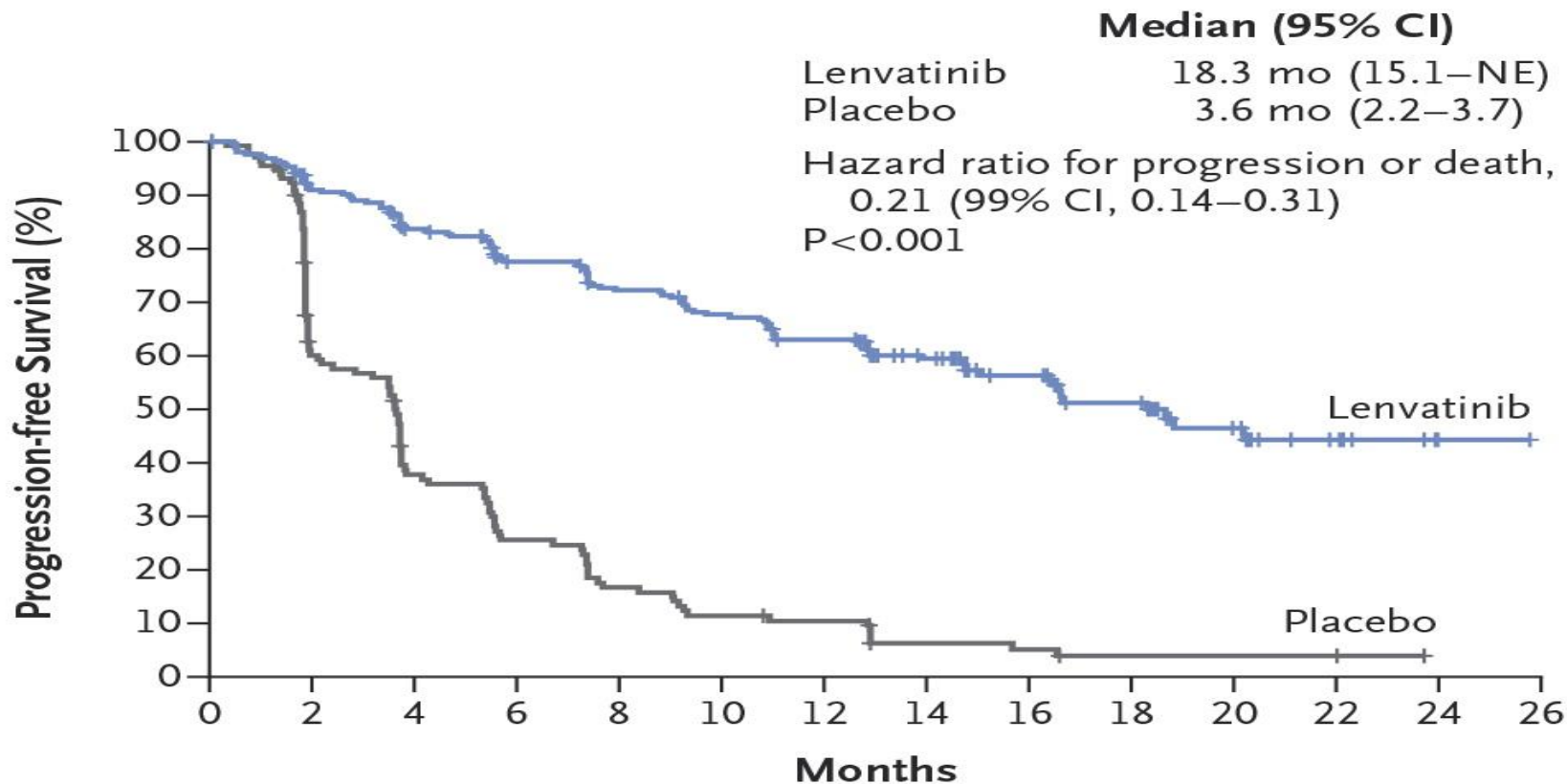
Sorafenib and Lenvatinib are indicated for the treatment of patients with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DTC) that is refractory to radioactive iodine treatment.

(By Independent Central Review)



Brose et al, ASCO, June 2013
Brose et al, Lancet 384: 319, 14

Kaplan–Meier Estimate of Progression-free Survival: Lenvatinib vs. Placebo



No. at Risk

Lenvatinib	261	225	198	176	159	148	136	92	66	44	24	11	3	0
Placebo	131	71	43	29	19	13	11	5	4	2	2	2	0	0

Common Side Effects of Tyrosine Kinase Inhibitors

- Malaise
- Hypothyroidism
- **Hand foot syndrome**
- Liver
- Edema
- **Skin rash**
- Cardiac
- Hypertension
- **Proteinuria**

Hand Foot Syndrome with TKI

Tsai et al, JCO 24: 5768, 2006.



Thyroid Nodules and Cancer

- **Epidemiology**
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- **Research**

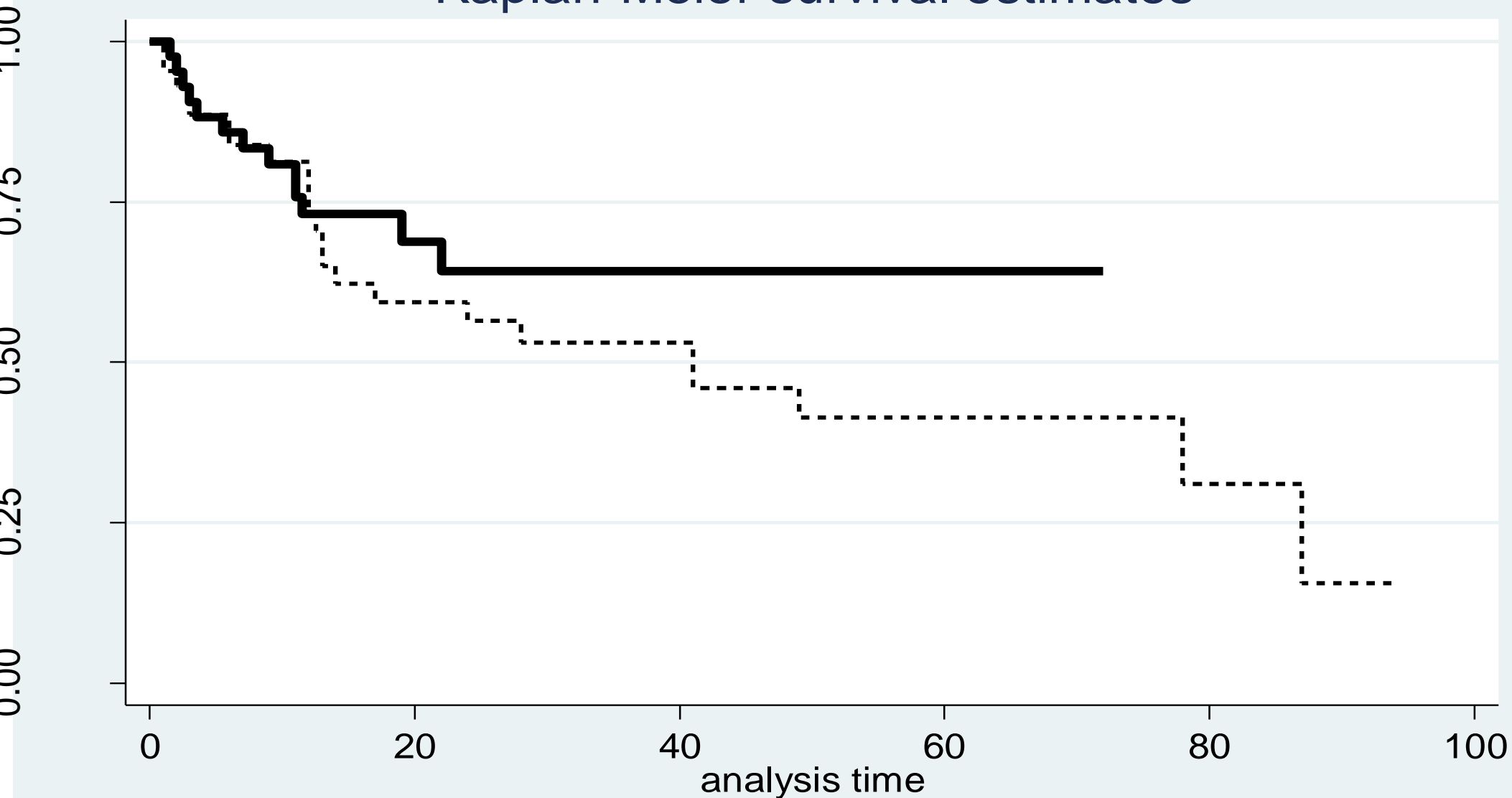
**EFFICACY OF DOSIMETRIC VERSUS EMPIRICALLY DETERMINED
PRESCRIBED ACTIVITY OF ¹³¹I
FOR THERAPY OF DIFFERENTIATED THYROID CANCER**

- **87 patients: 43 exclusively treated with dosimetry and 44 with empiric therapy.**
- **Mean follow-up 51 months.**
- **Multivariate analysis, controlling for age, gender and status of metastases revealed that D-Rx group was 70% less likely to progress (OR 0.29, p=0.052) and more likely to obtain complete remission compared to the E-Rx group (OR 8.2, p=0.029).**

**EFFICACY OF DOSIMETRIC VERSUS EMPIRICALLY DETERMINED
PRESCRIBED ACTIVITY OF ¹³¹I
FOR THERAPY OF DIFFERENTIATED THYROID CANCER**

- **Complete remission was significantly higher in D-Rx vs E-Rx in this group of patients (35.7% vs 3.3%, p=0.009)(Loco-regional Disease).**
- **The rates of partial response, stable disease and progressive disease, and the frequency of side effects were not significantly different between the two groups.**

Kaplan-Meier survival estimates



----- treatment = Empiric_fixed ——— treatment = Dosimetry

**EFFICACY OF DOSIMETRIC VERSUS EMPIRICALLY DETERMINED
PRESCRIBED ACTIVITY OF ¹³¹I
FOR THERAPY OF DIFFERENTIATED THYROID CAN**

- **Conclusion**
- **The potential higher efficacy with a similar safety profile of D-Rx treatment compared to E-Rx supports the rationale for employing individually prescribed activity in high risk patients with DTC.**

RhTSH versus LT4 Withdrawal

- **RECOMMENDATION 54**
- **In patients with ATA low-risk and ATA intermediate-risk DTC without extensive lymph node involvement (i.e., T1–T3, N0/Nx/N1a, M0), in whom RAI remnant ablation or adjuvant therapy is planned, preparation with rhTSH stimulation is an acceptable alternative to thyroid hormone withdrawal for achieving remnant ablation, based on evidence of superior short-term quality of life, noninferiority of remnant ablation efficacy, and multiple consistent observations suggesting no significant difference in long-term outcomes.**
- **(Strong recommendation, Moderate-quality evidence)**

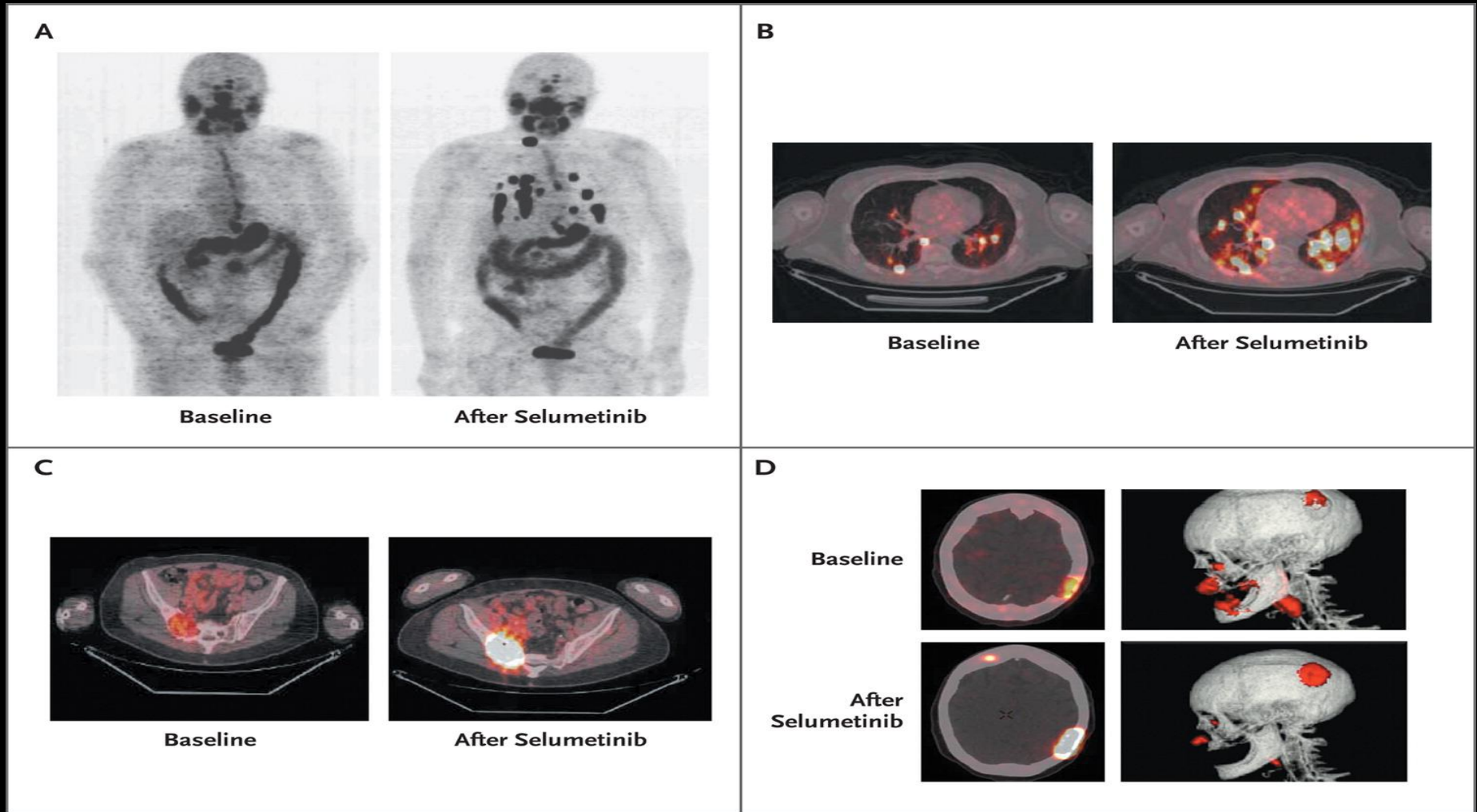
RhTSH versus LT4 Withdrawal

- In patients with ATA intermediate-risk DTC who have extensive lymph node disease (multiple clinically involved LN) in the absence of distant metastases, preparation with rhTSH stimulation may be considered as an alternative to thyroid hormone withdrawal prior to adjuvant RAI treatment.
- (Weak recommendation, Low-quality evidence)

RhTSH versus LT4 Withdrawal

- In patients with ATA high-risk DTC with attendant higher risks of disease-related mortality and morbidity, more controlled data from long-term outcome studies are needed before rhTSH preparation for RAI adjuvant treatment can be recommended.
- (No recommendation, Insufficient evidence)

Iodine-124 PET-CT Scans Obtained before and after Selumetinib Treatment in Selected Patients with Positive Responses.

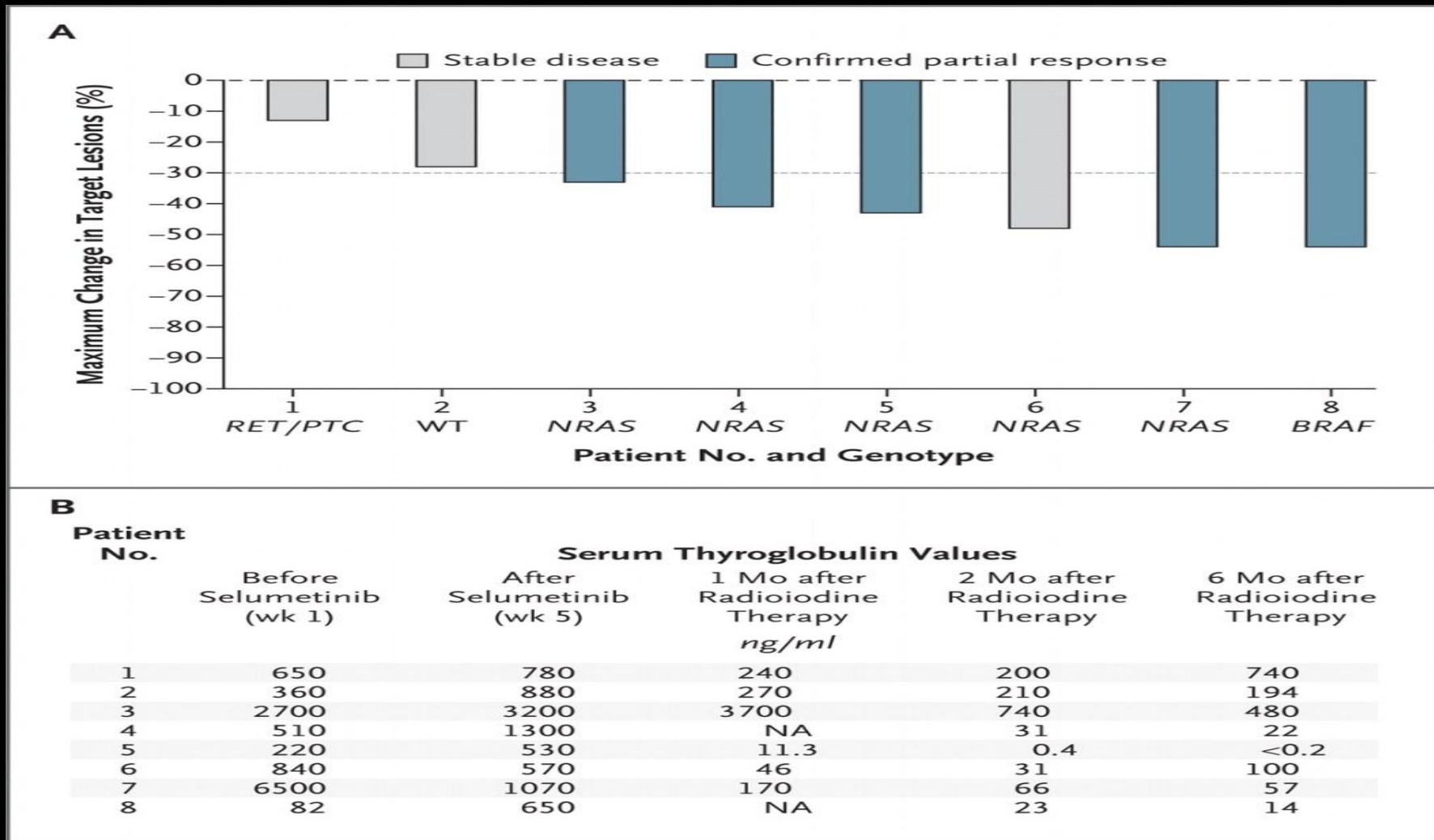


Ho AL et al. N Engl J Med 2013;368:623-632.



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Response to Iodine-131 Therapy with Selumetinib Treatment



Ho AL et al. N Engl J Med 2013;368:623-632.

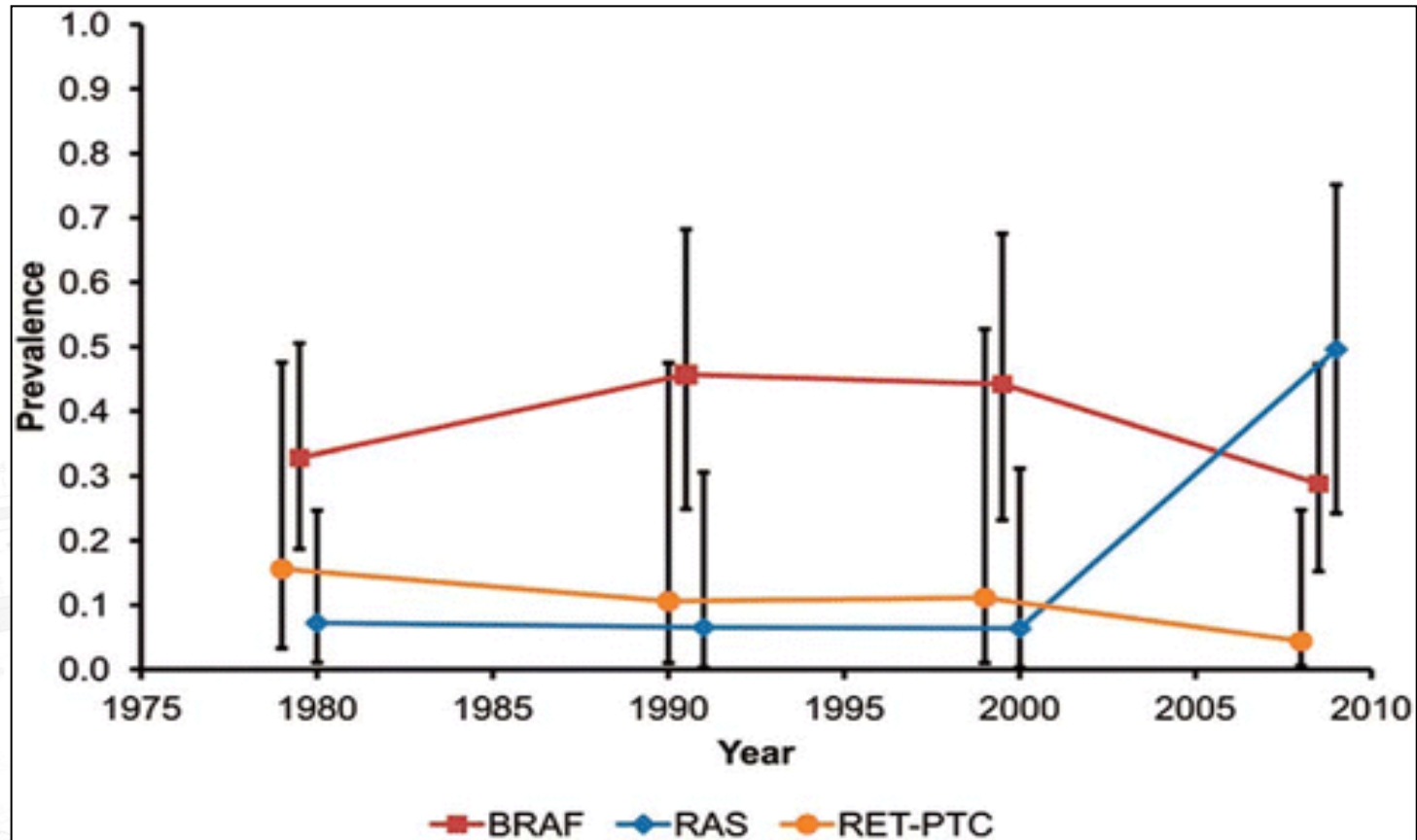


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Incidence of Mutations in PTC Over Time

- **Jung, et al. J Clin Endocrinol Metab. 2014;99:E276-E285**
- **469 consecutive PTC cases from 4 selected periods of time: 1974-1985; 1990-1992; 2000-2009.**
- **Evaluated for BRAF mutations, RAS mutations, and RET/PTC rearrangements**
- **Increase in percentage of fvPTC over time with reduction in classical PTC.**
- **Increase in percentage with microcarcinoma**
- **Increase in age 37 yo to 53 yo**

Incidence of Mutations in PTC Over Time



Jung, et al. J Clin Endocrinol Metab. 2014;99:E276-E285

The James

What activity of ^{131}I should be used for remnant ablation or adjuvant therapy?

- **RECOMMENDATION 55**
- If RAI remnant ablation is performed after total thyroidectomy for ATA low-risk thyroid cancer or intermediate-risk disease with lower risk features (i.e., low-volume central neck nodal metastases with no other known gross residual disease or any other adverse features), a low administered activity of approximately of 30 mCi is generally favored over higher administered activities.
- (Strong recommendation, High-quality evidence)

What activity of ^{131}I should be used for remnant ablation or adjuvant therapy?

- **When RAI is intended for initial adjuvant therapy to treat suspected microscopic residual disease, administered activities above those used for remnant ablation up to 150 mCi are generally recommended (in absence of known distant metastases). It is uncertain whether routine use of higher administered activities (>150 mCi) in this setting will reduce structural disease recurrence for T3 and N1 disease.**
- **(Weak recommendation, Low-quality evidence)**

Post 131-I Therapy Scans

- **A posttherapy WBS (with or without SPECT/CT) is recommended after RAI remnant ablation or treatment, to inform disease staging and document the RAI avidity of any structural disease**

PET Scans

- **^{18}F FDG-PET scanning should be considered in high-risk DTC patients with elevated serum Tg (generally >10 ng/mL) with negative RAI imaging**
- **(Strong recommendation, Moderate-quality evidence)**

CT and MRI

- **Cross-sectional imaging of the neck and upper chest (CT, MRI) with IV contrast should be considered (i) in the setting of bulky and widely distributed recurrent nodal disease where US may not completely delineate disease, (ii) in the assessment of possible invasive recurrent disease where potential aerodigestive tract invasion requires complete assessment, or (iii) when neck US is felt to be inadequately visualizing possible neck nodal disease (high Tg, negative neck US).**
- **(Strong recommendation, Moderate-quality evidence)**

CT and MRI

- **CT imaging of the chest without IV contrast (imaging pulmonary parenchyma) or with IV contrast (to include the mediastinum) should be considered in high risk DTC patients with elevated serum Tg (generally >10 ng/mL) or rising Tg antibodies with or without negative RAI imaging.**
- **(Strong recommendation, Moderate-quality evidence)**

CT and MRI

- **Imaging of other organs including MRI brain, MR skeletal survey, and/or CT or MRI of the abdomen should be considered in high-risk DTC patients with elevated serum Tg (generally >10 ng/mL) and negative neck and chest imaging who have symptoms referable to those organs or who are being prepared for TSH-stimulated RAI therapy (withdrawal or rhTSH) and may be at risk for complications of tumor swelling.**
- **(Strong recommendation, Low-quality evidence)**

Pulmonary Micrometastases

- Pulmonary micrometastases should be treated with RAI therapy and RAI therapy should be repeated every 6–12 months as long as disease continues to concentrate RAI and respond clinically because the highest rates of complete remission are reported in these subgroups.
- (Strong recommendation, Moderate-quality evidence)

RAI treatment of bone metastases ■ RECOMMENDATION 79

- **RAI therapy of iodine-avid bone metastases has been associated with improved survival and should be employed, although RAI is rarely curative.**
- **(Strong recommendation, Moderate-quality evidence)**
- **The RAI activity administered can be given empirically (100–200 mCi) or determined by dosimetry.**
- **(Weak recommendation, Low-quality evidence)**

How is RAI-refractory DTC classified?

- Radioiodine-refractory structurally evident DTC is *classified* in patients with appropriate TSH stimulation and iodine preparation in four basic ways: **(i)** the malignant/metastatic tissue does not ever concentrate RAI (no uptake outside the thyroid bed at the first therapeutic WBS), **(ii)** the tumor tissue loses the ability to concentrate RAI after previous evidence of RAI-avid disease (in the absence of stable iodine contamination), **(iii)** RAI is concentrated in some lesions but not in others; and **(iv)** metastatic disease progresses despite significant concentration of RAI.
- When a patient with DTC is classified as refractory to RAI, there is no indication for further RAI treatment.

Thyroid Nodules and Cancer

- **Epidemiology**
- **Clinical Findings**
- **Management**
- **Thyroid Cancer**
- **Research**