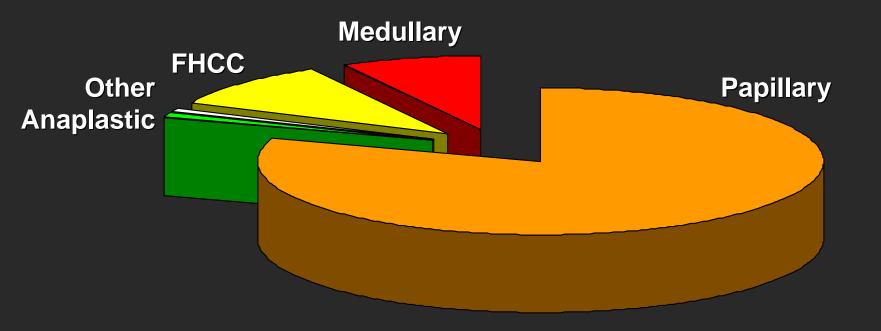


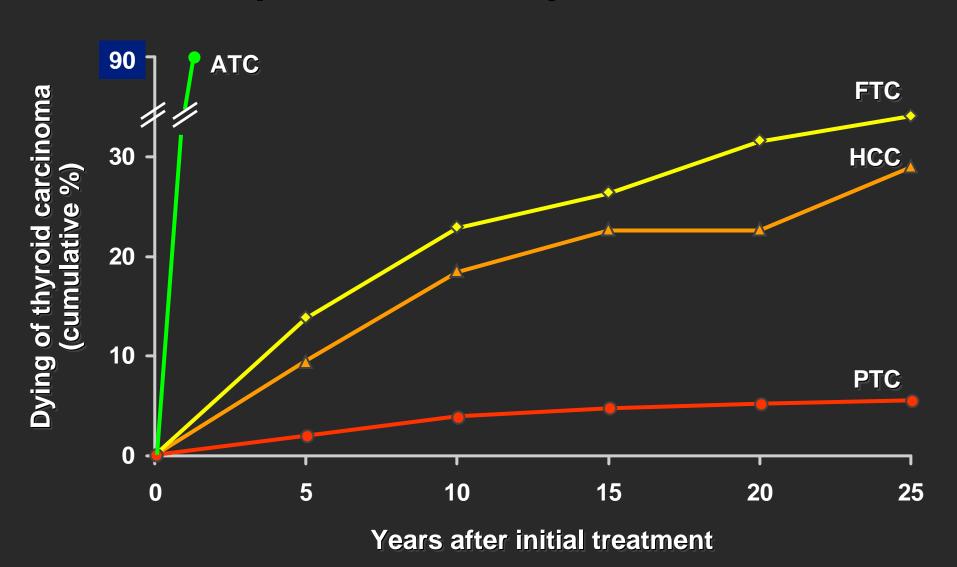
Differentiated Thyroid Cancer Objectives

- Overview and When To Suspect
- Preoperative Evaluation
- Extent of Thyroidectomy
- Extent of Lymphadenectomy
- RAI
- TSH Suppression
- Special Cases

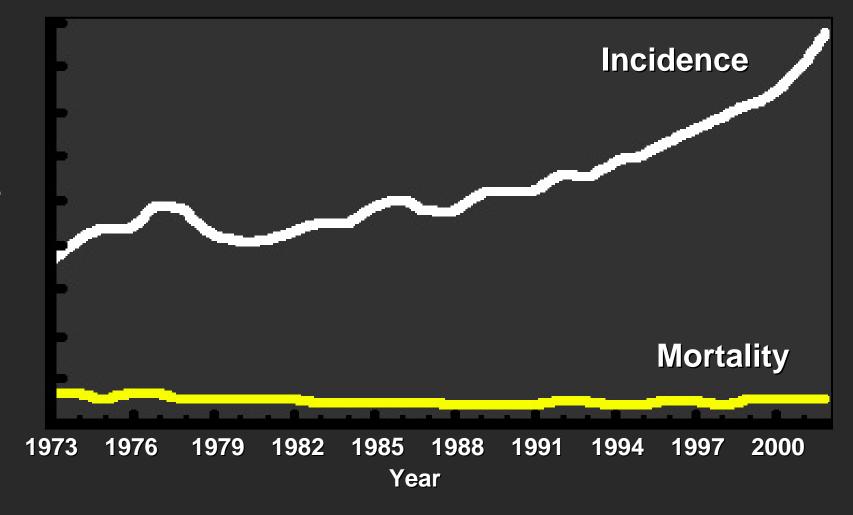
THYROID MALIGNANCIES



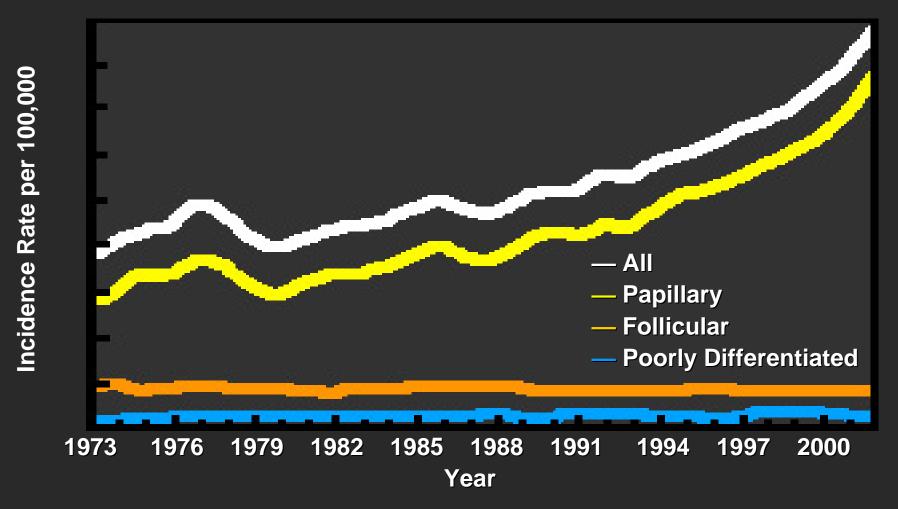
Cause-Specific Mortality Rates in FCDC



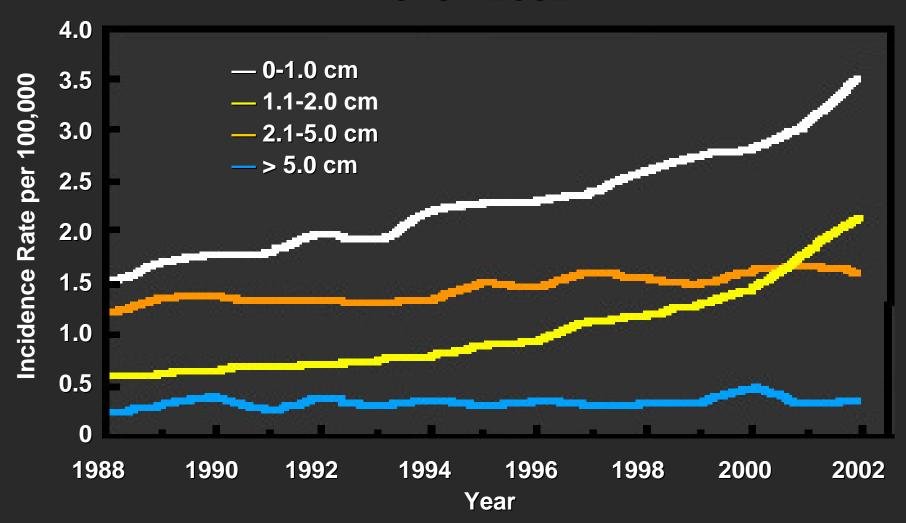
Thyroid Cancer Incidence 1973 - 2002



Thyroid Cancer Incidence 1973 - 2002



Thyroid Cancer Incidence 1973 - 2002



The Problem-Or Is It?

 15% of Americans harbor thyroid Ca (45,000,000 people)

 47,000 will be clinically detected this year (80 cases per million)

1,500 patients will die

Papillary Thyroid Cancer (PTC)

- Most common endocrine malignancy
- 80% of new cases worldwide
- Extent and type of therapy → controversial
- No long-term prospective controlled trials

Surgery for PTC

"...Adjust(ing) the radicalness of therapy to the dangerousness of the cancer"

"The punishment should fit the crime"

Cady -- 1997
Hayes Martin Lecture
Society of Head and Neck Surgeons

Preoperative Evaluation

• Tier 1: History, Exam (US), FNA, TSH

 Tier 2: Nodal mapping (US), CXR, Vocal Cord Exam

 Tier 3: CT with contrast, Triple Endoscopy

Thyroid Nodules Raised Suspicion

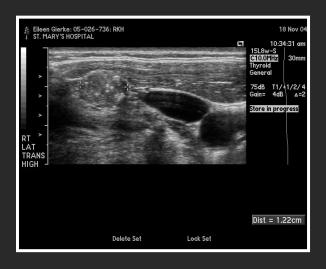
- Age < 20 years
- Male sex
- History of head or neck irradiation
- Nodule > 4 cm
- Compressive symptoms including dysphagia, dysphonia, hoarseness, dyspnea, and cough

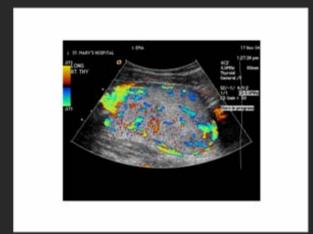
Thyroid Nodules High Suspicion

- Family history of MTC, MEN 2, PTC, Cowden's, FAP
- Rapid tumor growth, esp. on L-T4
- Firm or hard nodule
- Fixed to adjacent structures
- Paralyzed vocal cord
- Regional lymphadenopathy
- Distant metastasis

Ultrasound Suspicious Nodules

- Hypoechoic lesion plus one of the following:
 - Microcalcifications
 - Irregular border
 - Central vascularity
 - Taller rather than wide





National Cancer Institute Thyroid Fine-Needle Aspiration State of Science Conference

- Benign
- Malignant
- NEW Suspicious for malignancy (risk 50-75%)
- NEW Follicular lesion of undetermined significance (risk 5-10%)
- Nondiagnostic (7%) (<6 follicular groups with 10-15 cells x2)

FNA

<u>Nodules</u>	<u>Number</u>	
Benign	12,480	(69.0%)
Malignant	654	(3.5%)
Suspicious	1,784	(10.0%)
Non-Diagnostic	3,265	(21.0%)
Total	18,183	

Suspicious FNA

• 10 – 20% of FNA

• 15-75% are malignant

Needle Biopsy or FNA

Non diagnostic: Repeat with US

Malignant : Surgery

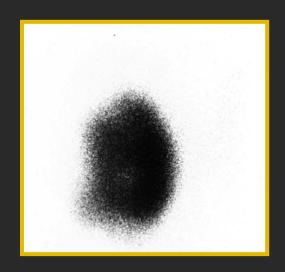
Benign : Follow

Suspicious : Surgery

Hot Nodule

About 5% of nodules

Almost always benign!



Preoperative Evaluation

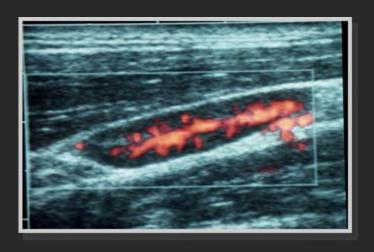
• Tier 1: History, Exam (US), FNA, TSH

 Tier 2: Nodal mapping (US), CXR, Vocal Cord Exam

 Tier 3: CT with contrast, Triple Endoscopy

Benign Cervical Node





- Slender
- Fatty hilum
- Hilar blood flow

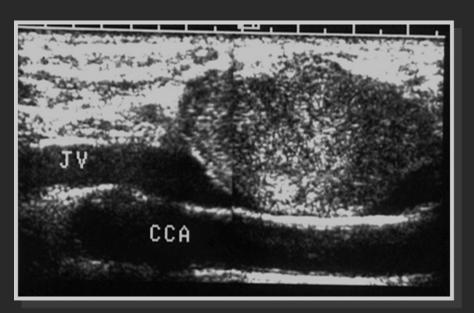
Malignant Lymph Node

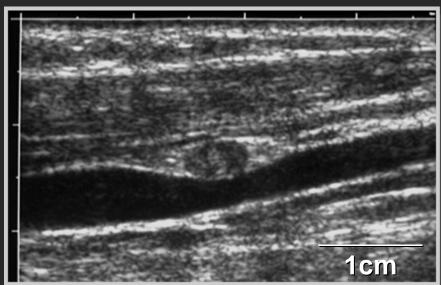


Cystic change



Malignant Neck Node

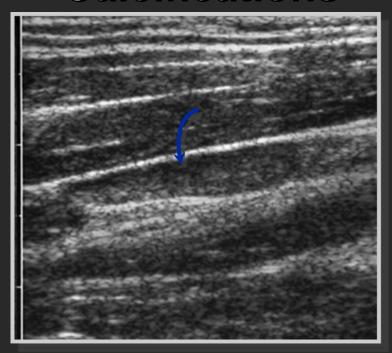


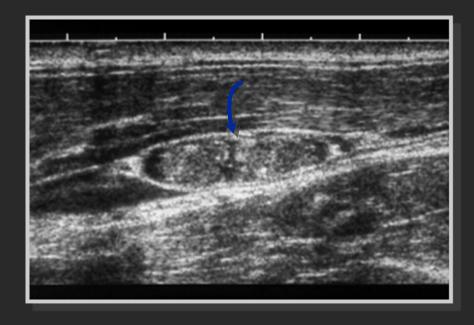


Vascular indentation

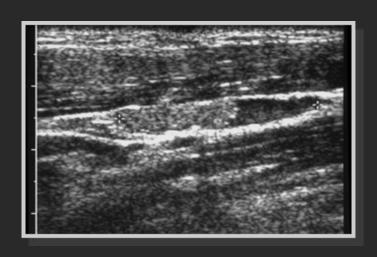
Malignant Neck Node

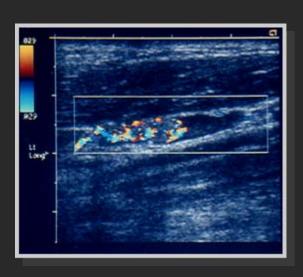
Calcifications





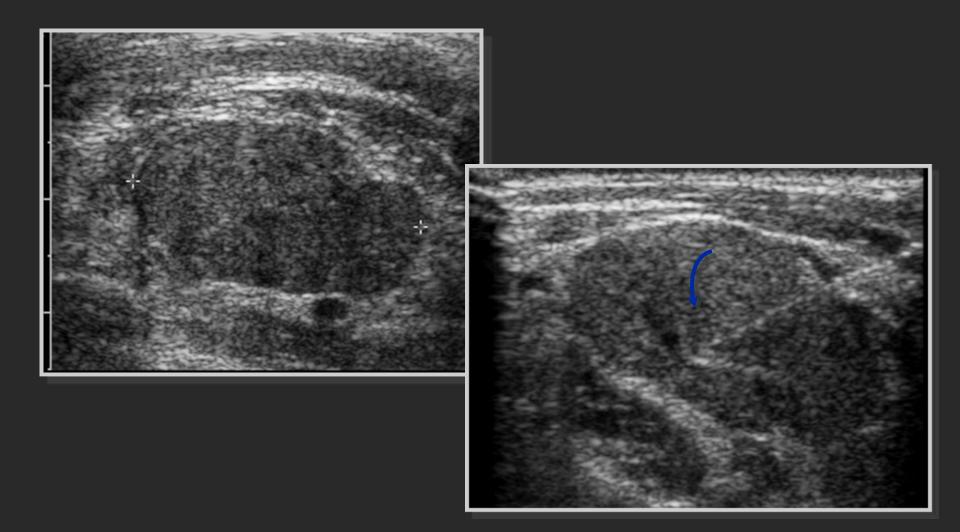
Malignant Neck Node

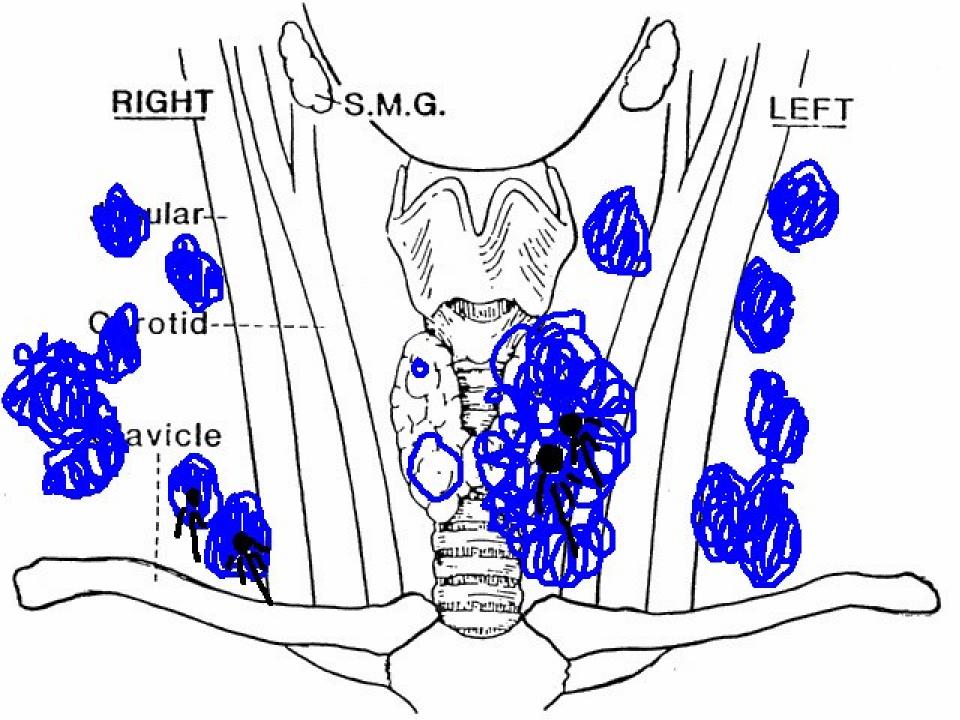




Alteration in architecture and flow

Lymph Node Biopsy





Value of Preoperative Ultrasound in PTC

Mayo Clinic: 770 pts (1999-2004)

US identified nonpalpable lateral nodes:
 15% in first time operations

Reops-NLLN's: 64%; NCLN's: 28%

 US altered extent of operation in 41% of initial and 43% of reoperative pts. with palpable nodes



Preoperative Evaluation

• Tier 1: History, Exam (US), FNA, TSH

 Tier 2: Nodal mapping (US), CXR, Vocal Cord Exam

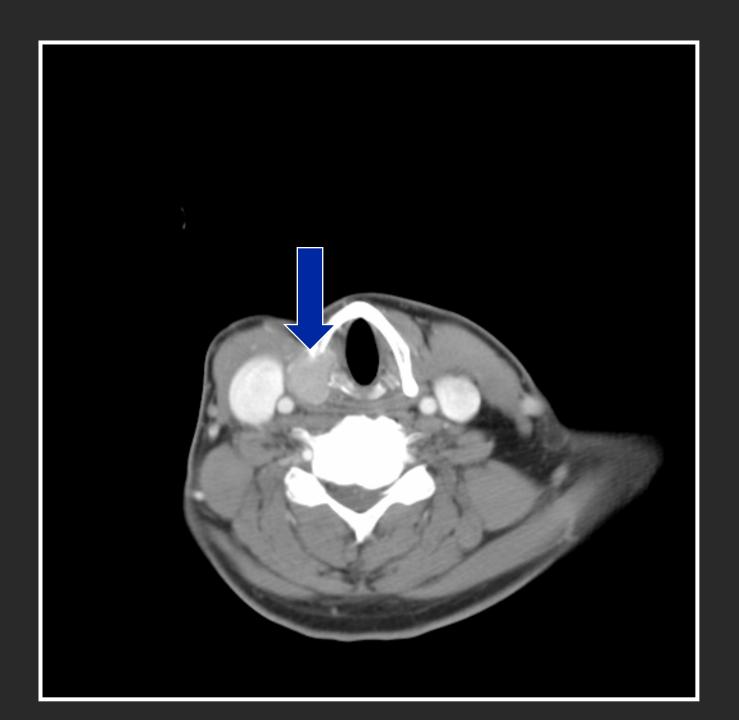
 Tier 3: CT with contrast, Triple Endoscopy

75 year old male with hoarseness



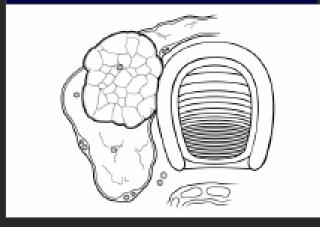


8cm grossly invasive FTC

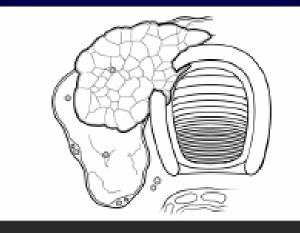


Stages of Tracheal Invasion in Thyroid Cancer

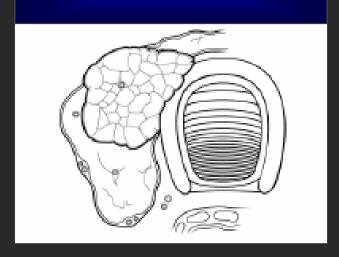
Invasion of perichrondrium without infiltration of cartilage or soft tissue between cartilages



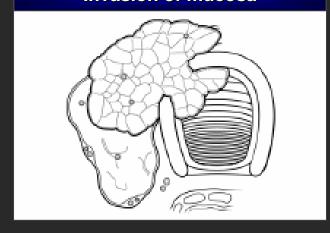
Invasion of lamina propria of tracheal mucosa

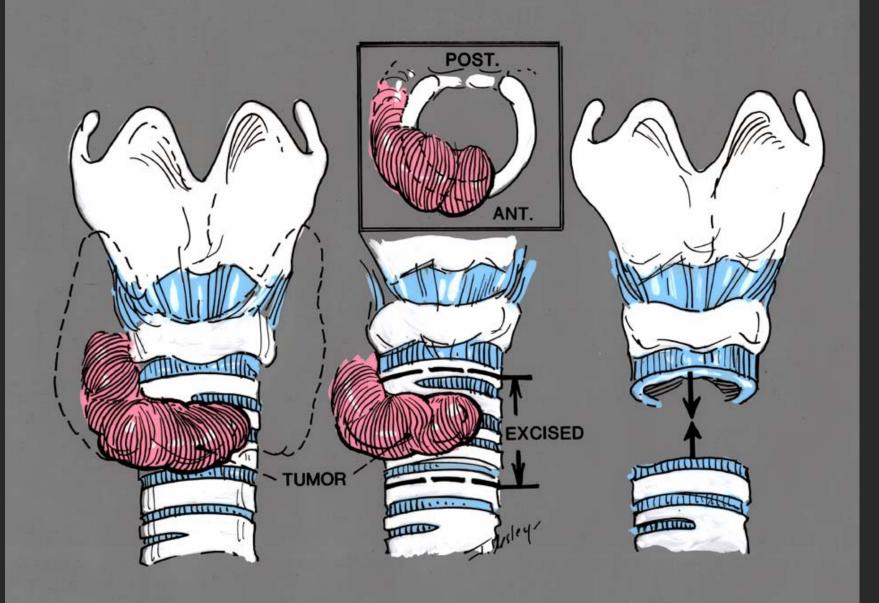


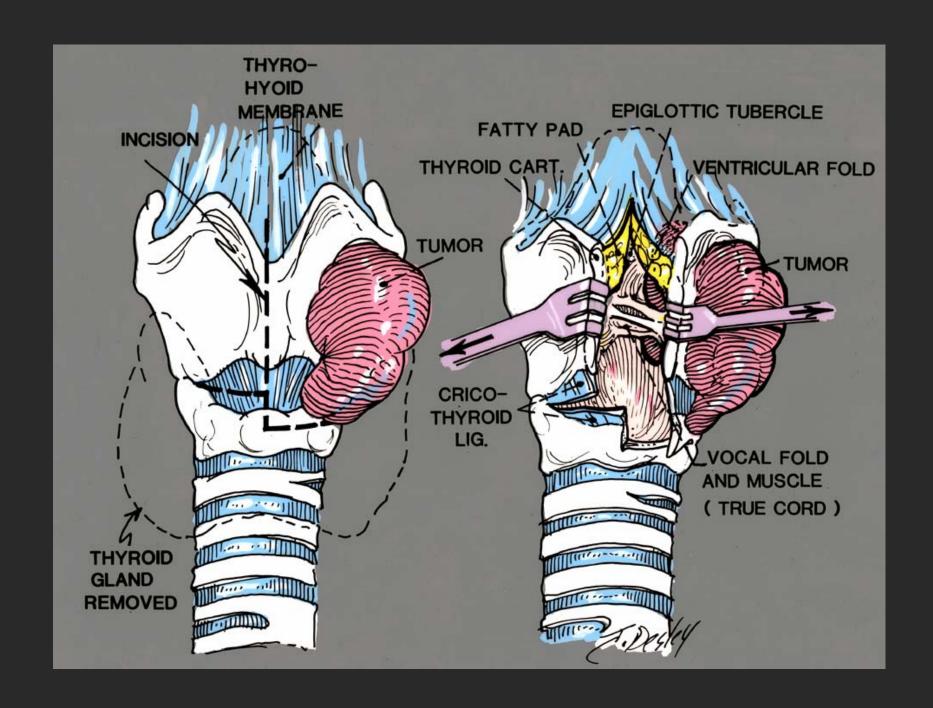
Invasion of cartilage

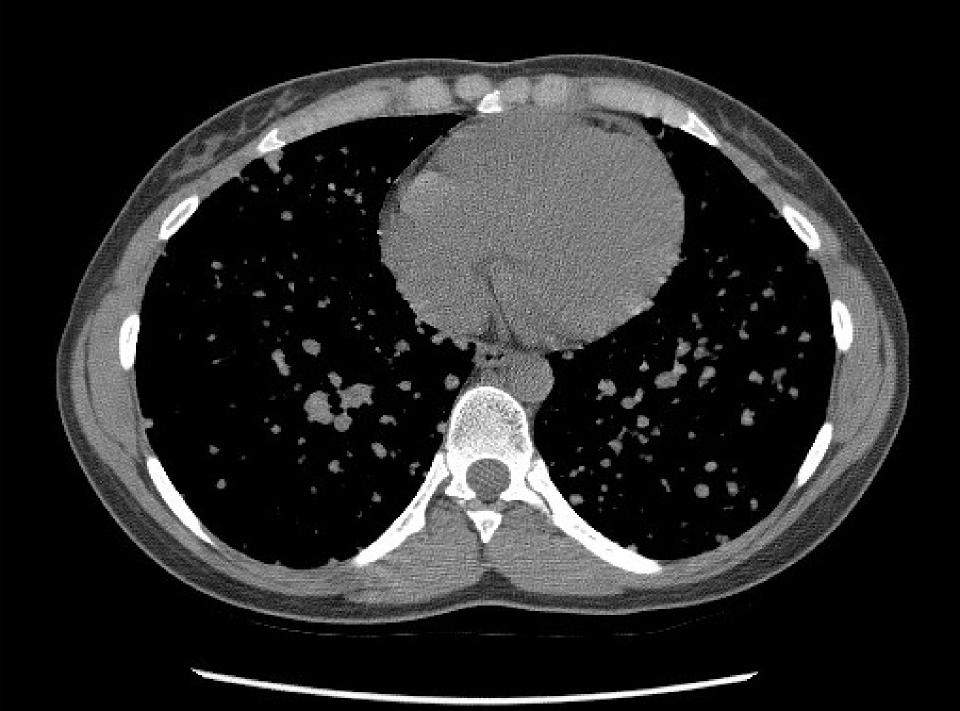


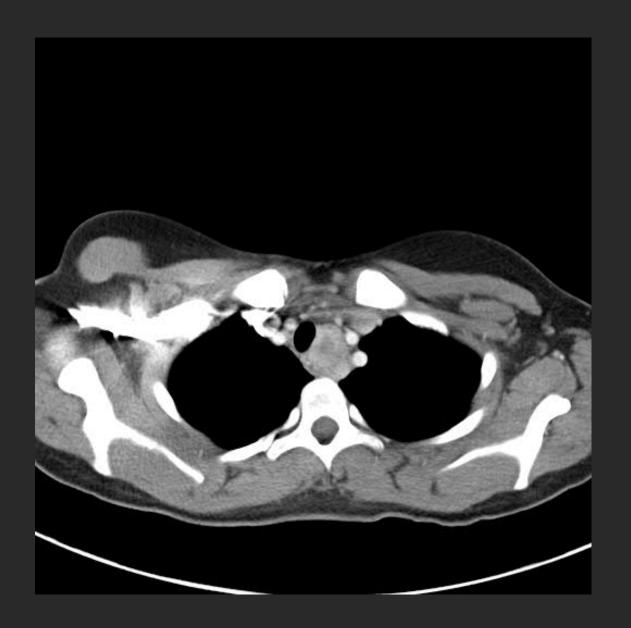
Invasion of mucosa











Thyroid Nodules Goals

Treat thyroid cancer!

Avoid unnecessary surgery !

 Select pts for appropriate adjuvant therapies

Staging and Risk Assessment-

Determine Risk of Death/Recurrence

Application of TSH suppression

Application of remnant ablation with I-131

 Application of Radioiodine Scanning and/or stimulated Tg testing

Papillary and Follicular Thyroid Cancer

- 1,355 patients (OSU, US Air Force)
- Median follow-up: 15.7 years

30 years: Survival 76%
 Recurrence 30%
 CSM 8%

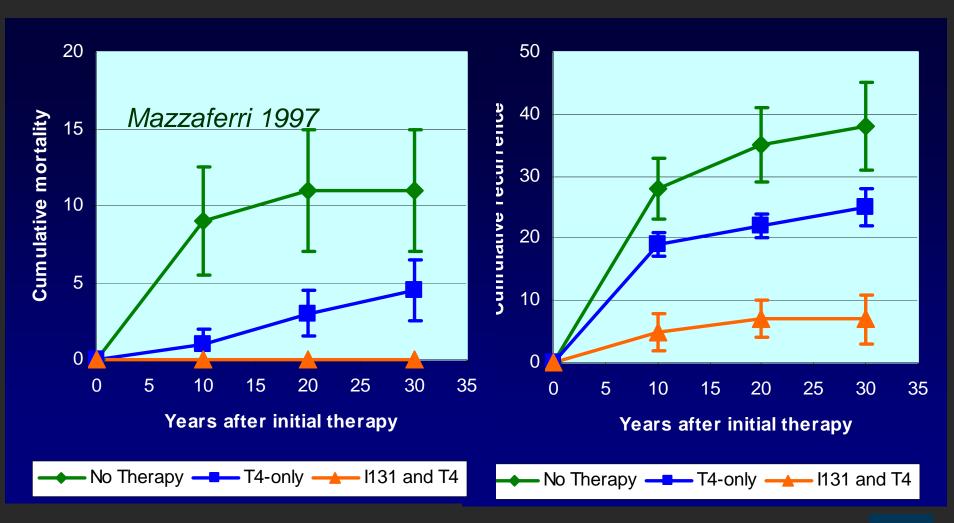
Mazzaferri EL. Am J Med 1994;97:418

Papillary and Follicular Thyroid Cancer

- Cancer death rate reduced by:
 - female sex
 - surgery more extensive than lobectomy
 - 131 plus thyroid hormone therapy
- Recurrence reduced to less than 1/3 with RRA vs T4 alone

Mazzaferri EL. Am J Med 1994;97:418

Impact of I¹³¹ on DTC Recurrence and Mortality

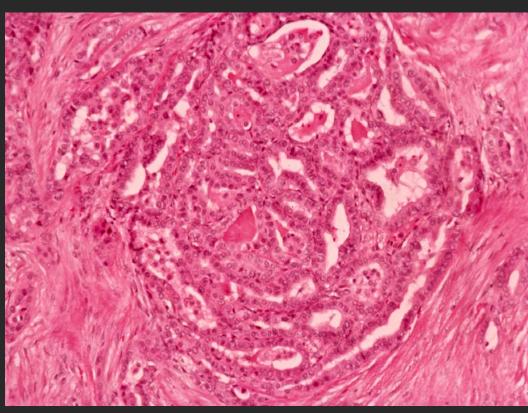


Papillary Thyroid Cancer

Is all of this true?

Risk Assessment in Thyroid Carcinoma





1.5mm Papillary microcancer

Risk Assessment in Thyroid Carcinoma



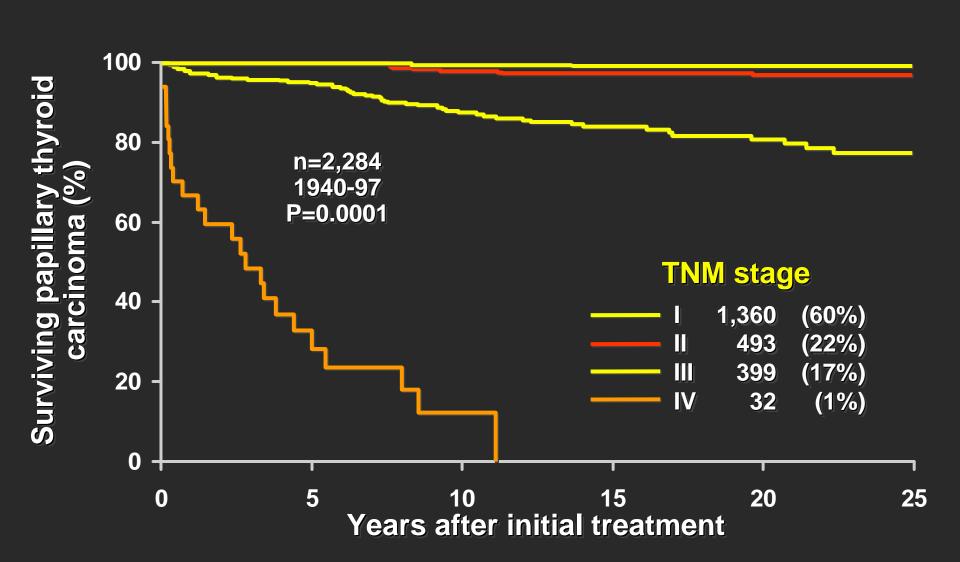


8cm grossly invasive FTC

pTNM Staging for FCDTC 2002 Classification

	<45 years	≥45 years		
1	TxNxM0	T1N0M0		
Ш	TxNxM1	T2N0M0		
III		T3N0M0 / T1-3N1aM0		
IVA	-	T4aNxM0 / T1-3N1bM0		
IVB	-	T4bNxM0		
IVC	-	TxNxM1		

PTC Survival by TNM Stage



PTC Prognostic Factors

Well-Established Independent Prognostic Factors Less Certain
Prognostic Factors

Age

Extrathyroidal tumor invasion

Primary tumor size

Distant metastases

Incomplete tumor resection

Gender

Lymph node metastases

Tumor multicentricity

Vascular invasion

Morphologic variants of

PTC*

*tall cell, columnar cell, diffuse sclerosing

Kebebew & Clark, 2001

Prognostic Schemes for DTC

	EORTC	AGES	AMES	MACIS	OSU	SKMMC
Age	X	X	X	X		X
Sex	X		X			
Size		X	X	X	X	X
Multicentricity					X	
Grade		X				X
Histology	X	PTC	X	PTC		X
Invasion	X	X	X	X	X	X
Nodes					X	X
Metastases	X	X	X	X	X	X
Complete excision				X		

Differentiated Thyroid Carcinoma MACIS (PTC)

Metastasis (distant)

Age (at diagnosis)

Completeness of primary tumor resection

Invasion of extrathyroidal structures

Size (of primary tumor)

MACIS Prognostic Scoring System

```
Score = 3.1 (if age = 39 yrs) or 0.08 \times age (if age = 40 yrs)
```

- + 0.3 X tumor size (cm-max diameter)
- + 1 (if incompletely resected)
- + 1 (if locally invasive)
- + 3 (distant spread)

Survival by MACIS Score @ 20 yrs

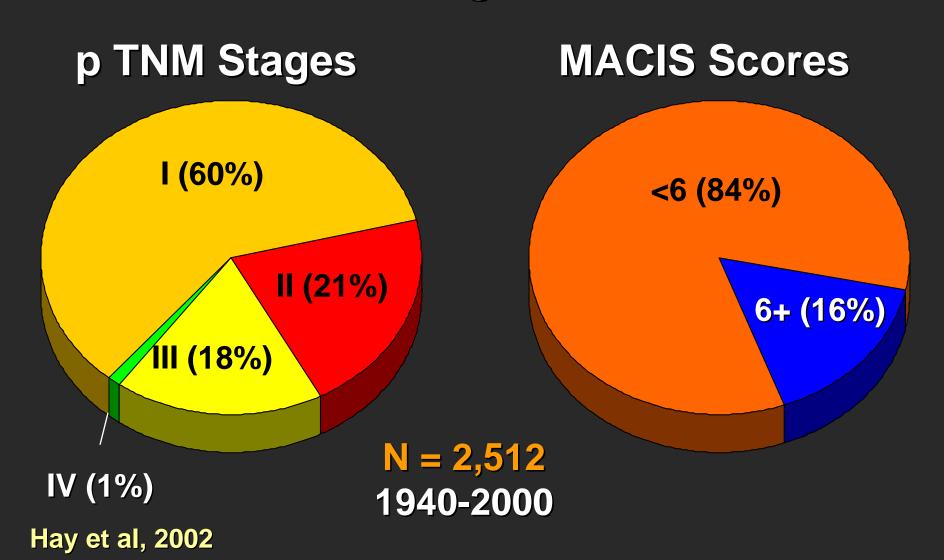
• <6 99%

6.00-6.9989%

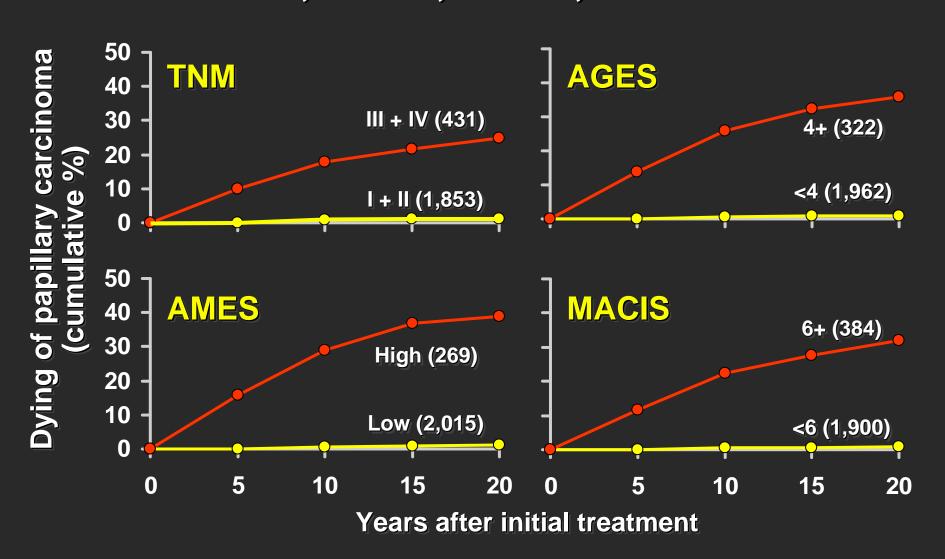
• 7.00-7.99 56%

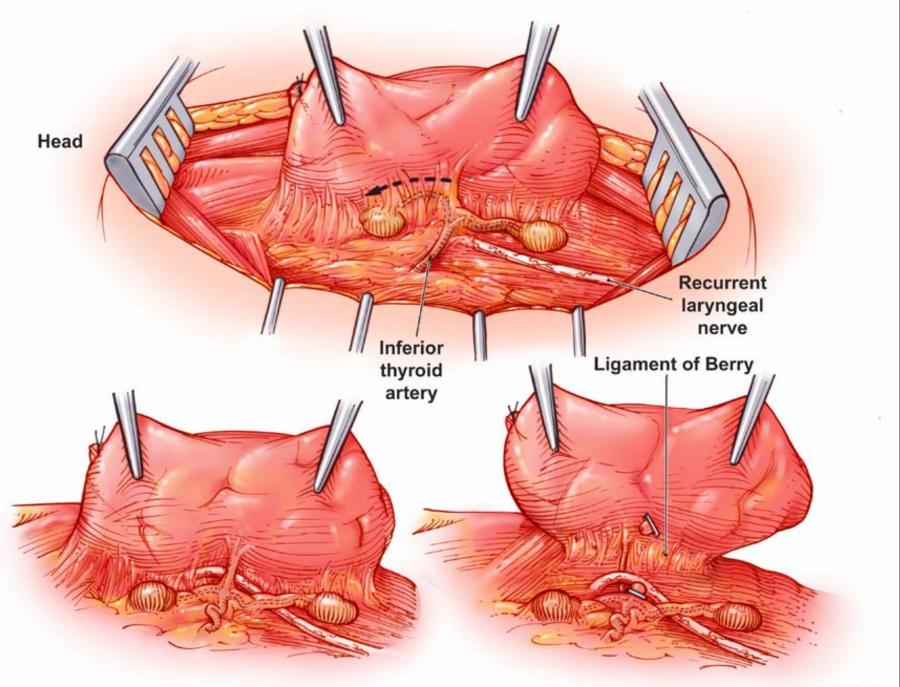
• >8 **24%**

Papillary Thyroid Carcinoma 1940-2000 Presenting Disease



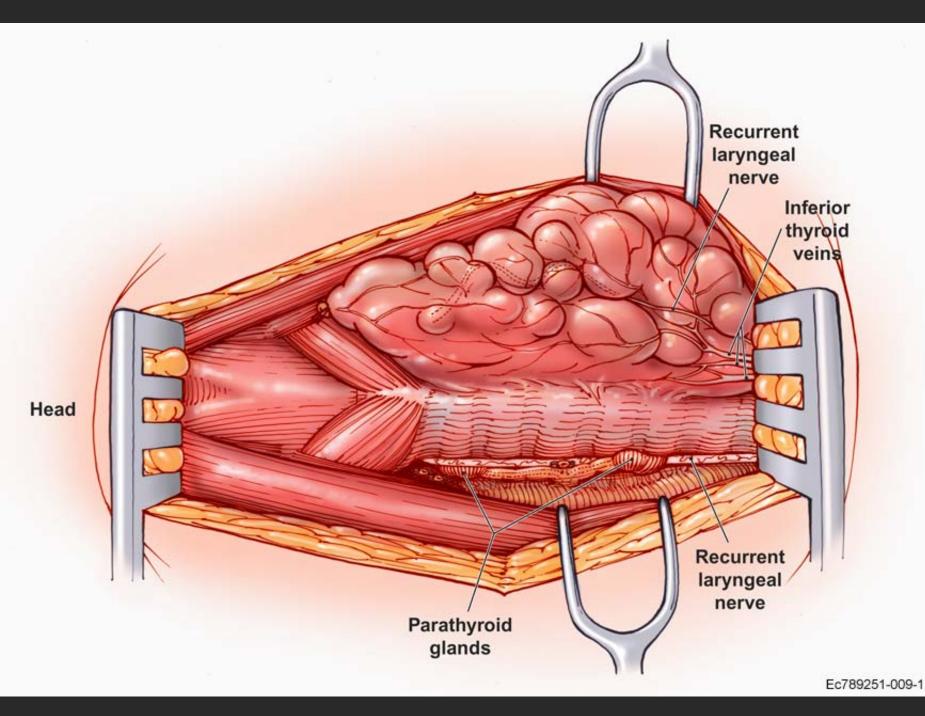
CSM from PTC in High- and Low-Risk Groups TNM, AGES, AMES, MACIS





Extent of Thyroidectomy (PTC) Recommendations

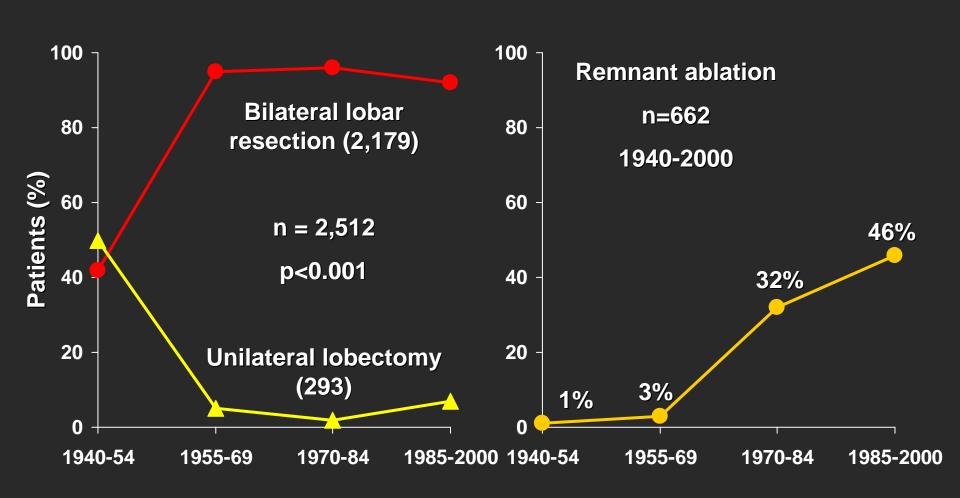
- American Thyroid Association Near-total or Total
- AACE
 Near-total or Total
- Society of Surgical Oncology
 Low Risk: Unilateral Lobectomy
 High Risk: Total thyroidectomy



Papillary Thyroid Cancer (PTC)

- Societal recommendations
 - -Bilobar resection (BLR) = Near total / Total thyroidectomy
 - Radioiodine remnant ablation (RRA)

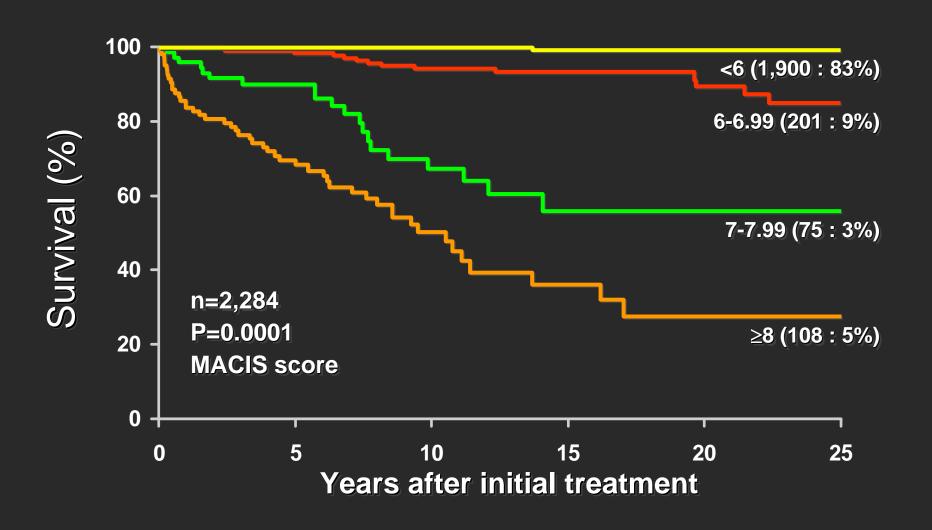
Papillary Thyroid Carcinoma 1940-2000 Trends in Extent of Surgery & RRA



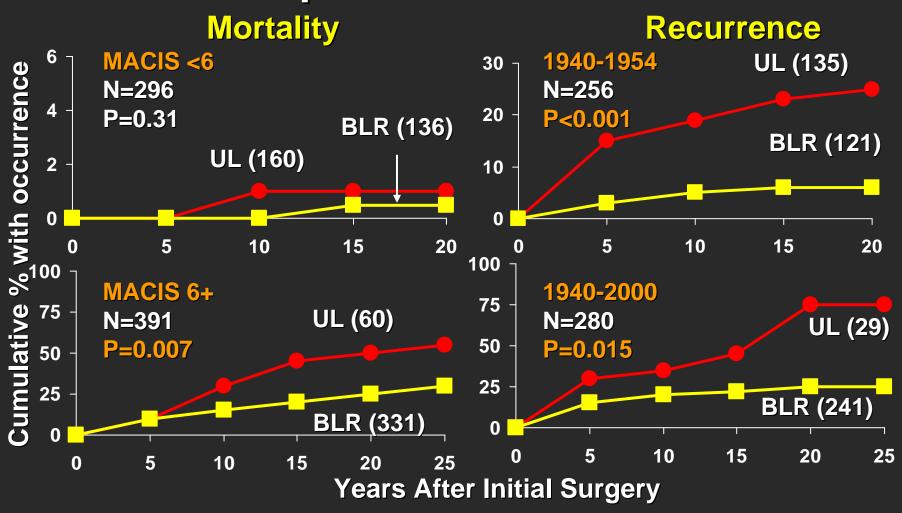
Papillary Thyroid Cancer (PTC)

- Why? (Multicentric Cancer)
 - Improves cause-specific mortality (CSM)
 - Reduces tumor recurrence (TR)
 - Facilitates radioiodine scanning and use of therapeutic RAI
 - Improves effectiveness of thyroglobulin (Tg) screening

Cause-Specific Survival by MACIS Score 1940-97



Papillary Thyroid Carcinoma Comparison of Outcome



PTC

In low-risk patients:

- No survival benefit: unilateral lobectomy vs bilobar resection
 - Hay et al 1987
- TR higher with unilateral procedure
 - Grant et al 1988, Hay et al 1988

Risk of Locoregional Recurrence Unilateral Lobectomy

4x-7x higher compared to BLR @ 20 years

Low-Risk DTC Patients: Limited Surgery? Local Recurrence

- **Patient anxiety**
- **1** Physician anxiety
- 1 Surgeon anxiety
- 1 Need for reoperation
- **1** Time away
- **↑** Cost

PTC

In high-risk patients

- CSM and TR rates higher: unilateral lobectomy vs BLR
 - Hay et al 1987

Low-Risk DTC Patients: Limited Surgery? Total Thyroidectomy (Morbidity)

- The risk of permanent hypoparathyroidism is significantly greater than lesser resections in many series
- 3% vs 1.4% @ Mayo Clinic (Total vs NT)
- Rates as high as 15-20% have been reported

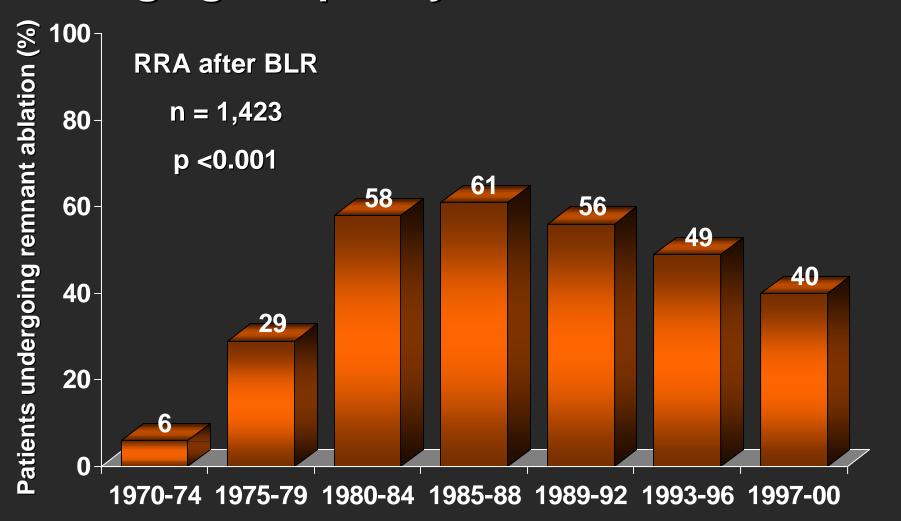
Hay et al. Surgery 1998; 124:958-966

PTC

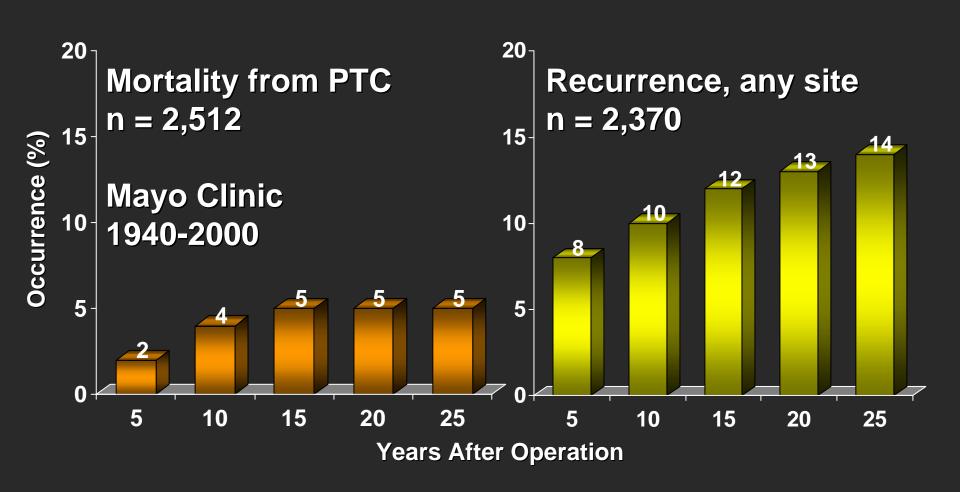
Near-Total vs Total Thyroidectomy (BLR)

- No difference in CSM or TR in either low- or high-risk groups
 - Hay et al 1987

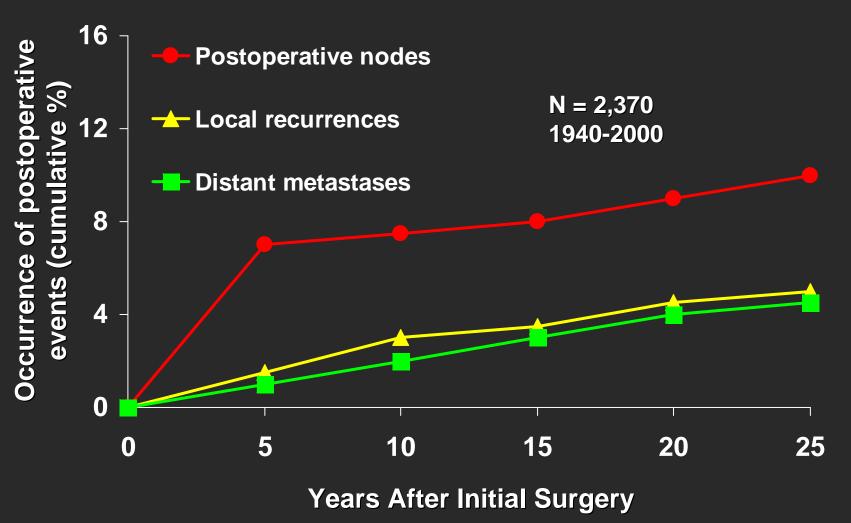
Papillary Thyroid Carcinoma 1970-2000 Changing Frequency of Remnant Ablation



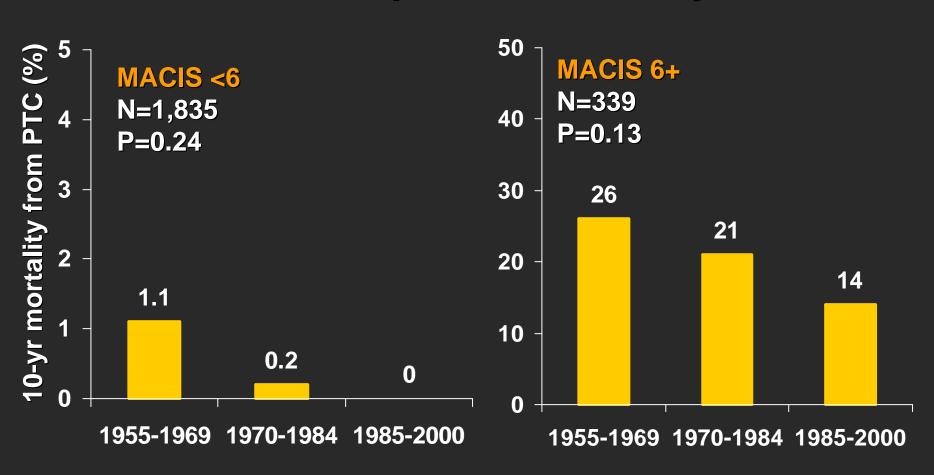
Papillary Thyroid Carcinoma 1940-2000 Overall Outcome



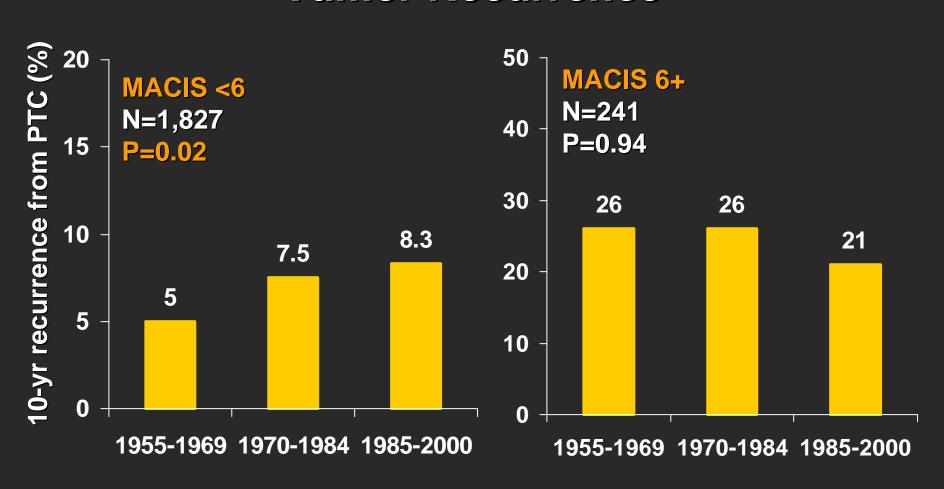
Papillary Thyroid Carcinoma 1940-2000 Overall Outcome



Papillary Thyroid Carcinoma 1955-2000 Cause Specific Mortality



Papillary Thyroid Carcinoma 1955-2000 Tumor Recurrence



Radio-iodine Remnant Ablation

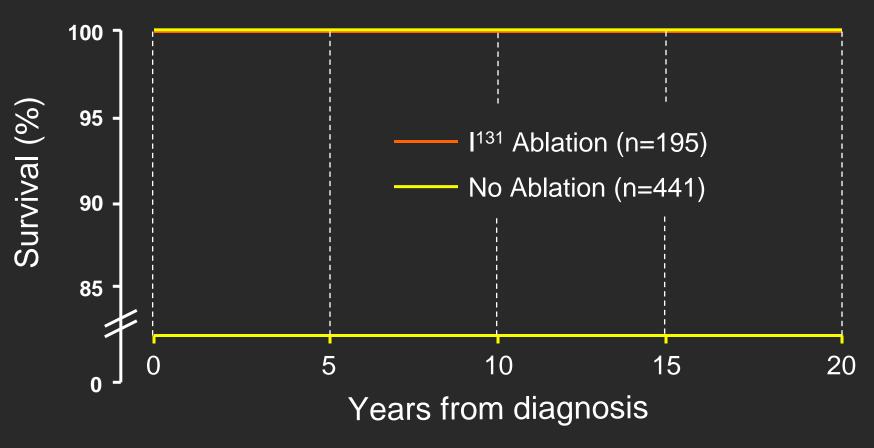
"Routine" Administration

- I-131 in moderate dose is safe
- Ablation of the thyroid remnant decreases the risk of recurrent disease
- All patients should be offered this therapy

"Selective" Administration

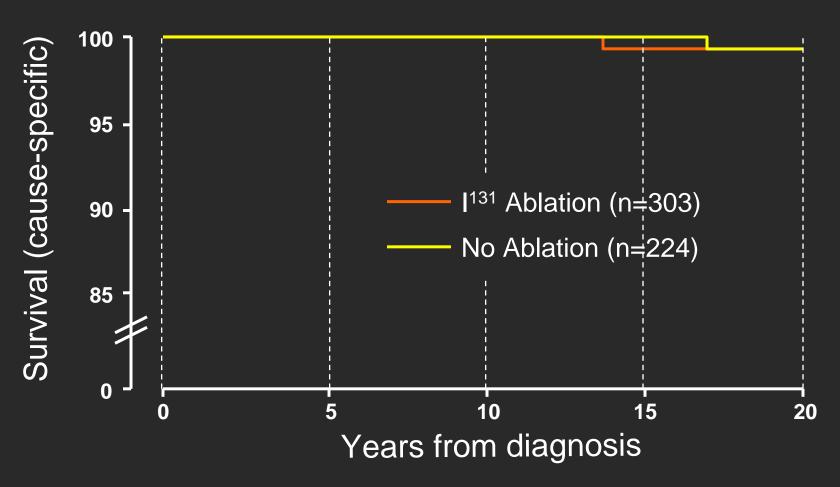
- Morbidity from I-131, while rare, does occur
- Most patients with DTC are at very low risk of death or recurrence
- Treatment should be offered selectively

Survival (T_xN₀M₀, MACIS<6)



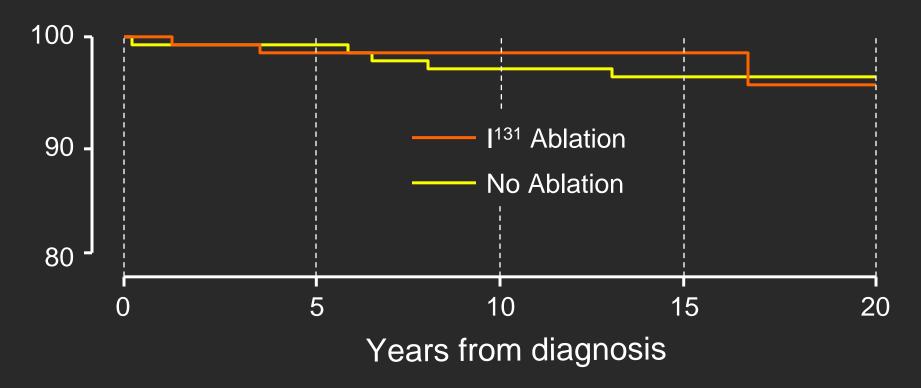
636 node negative patients; total or near-total TTX; 1970 - 2000

Survival (T_xN₁M₀, MACIS<6)



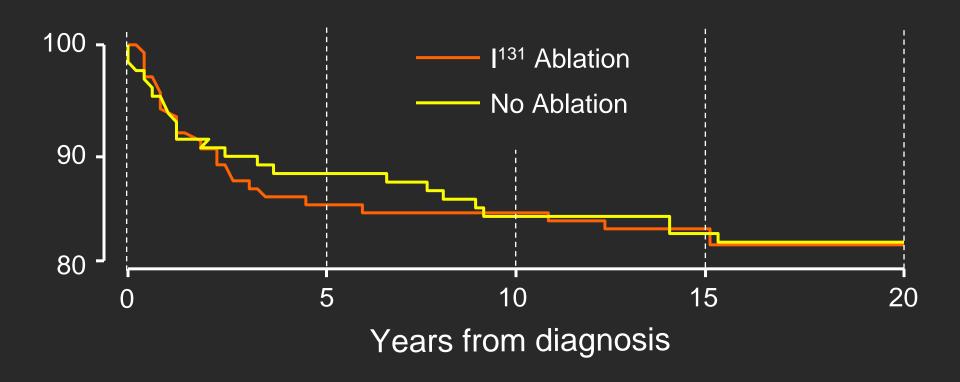
527 node positive patients; total or near-total TTX; 1970 - 2000

Recurrence $(T_xN_0M_0, MACIS<6)$



636 node negative patients; total or near-total TTX; 1970 - 2000

Recurrence $(T_xN_1M_0, MACIS<6)$

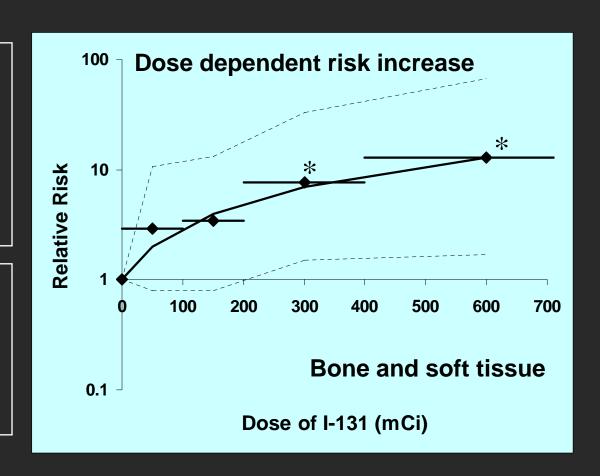


527 node positive patients; total or near-total TTX; 1970 - 2000

Carcinogenesis with I¹³¹

3 populations
(Sweden, Italy, France)
6841 patients
Mean dose I¹³¹ 162 mCi
Mean F/U of 13 years
Incidence of 2nd malignancy

Increased risk for cancer of:
Salivary gland 7.5
Bone & soft tissue 4.0
Uterus / female genital 2.3
Colorectal 1.3



Post-operative Remnant Ablation: ATA Guidelines 2009

- RRA recommended for
 - Patients with Stage III and IV disease
 - >45 years, node positive, invasive, metastatic
 - Patients with Stage II disease (<45 years)
 - <45 years, metastatic
 - "Most" older patients with Stage II disease
 - >45 years with larger tumors (> 2 cm)
 - "Selected" patients with Stage I disease
 - "multifocal; nodes; invasion; non-PTC"

Recommendation 32

- RAI ablation is recommended for all patients with:
- Distant metastases, gross extrathyroidal extension and tumor size > 4 cm
- Even in the absence of other high risk features

Recommendation 32

Radioiodine ablation may be helpful for tumors 1-4 cm in diameter, in patients with lymph node metastases, or other high risk features including histologic variants that would place the patient in an intermediate or high risk group

Recommendation 32

 Remnant ablation is not recommended for unifocal or multifocal cancers <1cm in the absence of other high risk features



Most recurrences in PTC (esp. low-risk) are nodal

Regional Lymph Node Metastases

- Influence on prognosis is questionable
 - Effect on survival (rarity)
 - Little if any in most cases
 - Older patients
 - -Bilateral jugular nodes (extensive)
 - -Extracapsular spread, matted nodes
 - –Locally advanced primary

Possible exceptions

Why Perform Cervical Lymphadenectomies

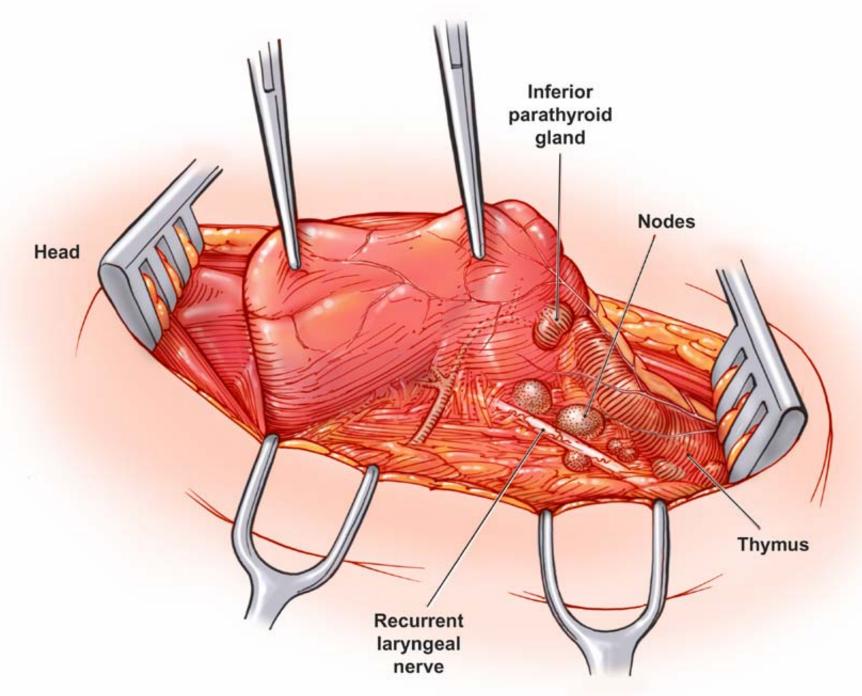
- Positive nodes in select groups worsen prognosis
- Nodes beget nodes → ↑ recurrence
- May become destructive over time (especially older patients)
- Cannot rely upon RAI to fix shoddy surgery

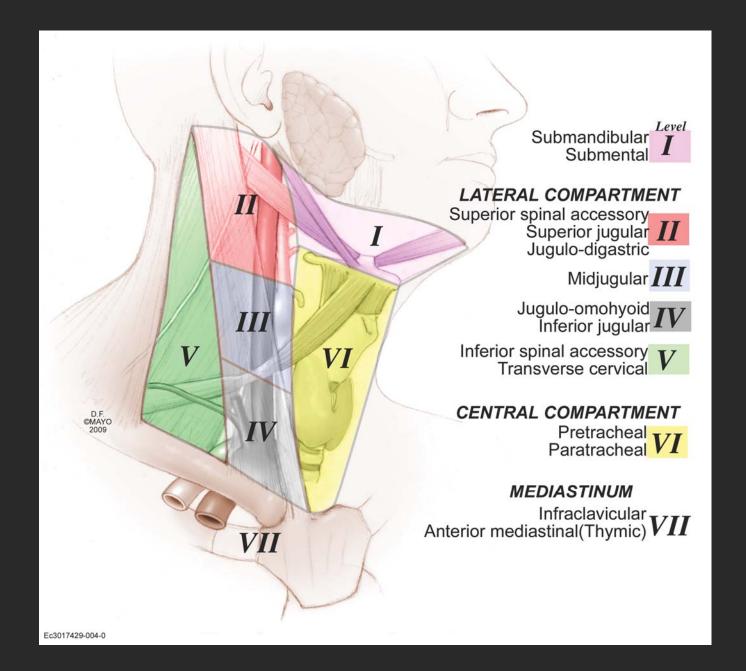
Why Perform Cervical Lymphadenectomies?

- Thyroglobuli 00 (withdrawal, Thyroge ulated)

 Hindo Iution ultrasound

 - Radioiodine and PET scans
 - Tg mRNA





PTC

"Berry-Picking" vs Formal Nodal Dissection

- Nodal recurrences increased in all series
- Reoperations more difficult
 - Increased morbidity
- Metastatic carcinoma in lymph nodes > 3 mm always associated with disease in smaller lymphatics
 - Noguchi et al 1970, 1987

Best to avoid going back to the central compartment

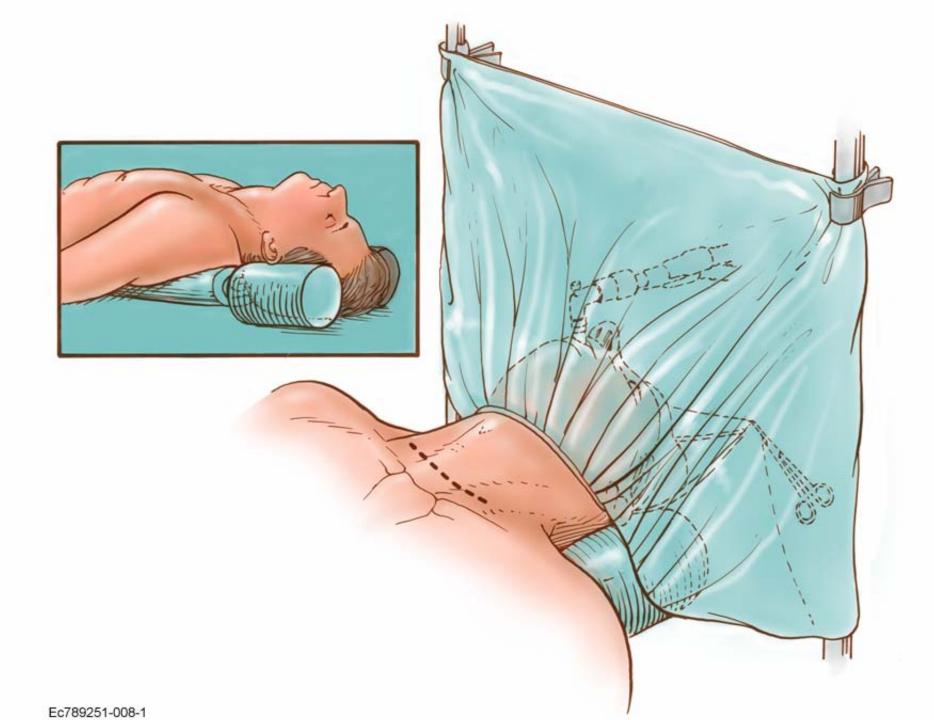
Routine Removal of Central Compartment Nodes

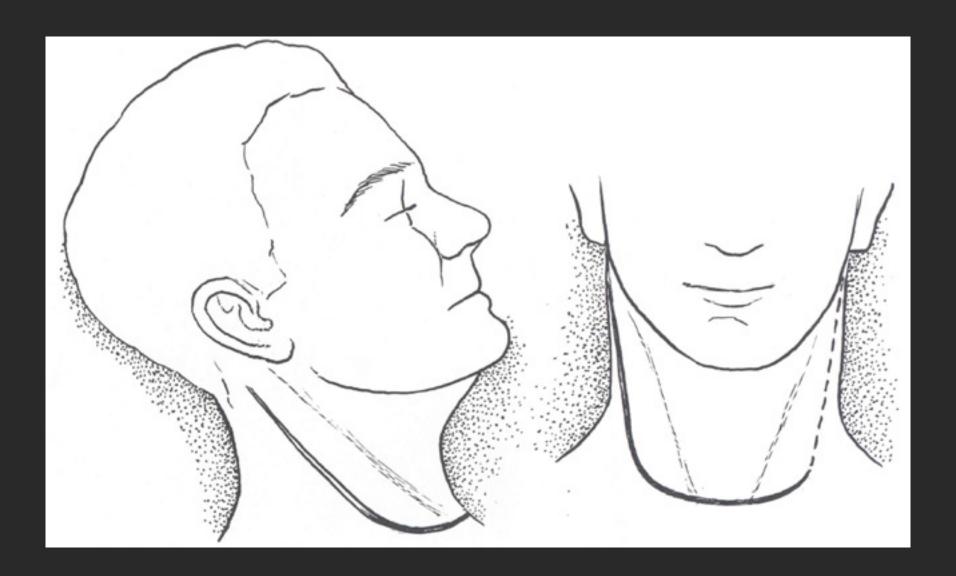
- Advocated by some groups
- Only if FS ⊕
- Only for larger 1° tumors (> 1-2 cm)
- Only if grossly involved
- Increased hypoparathyroidism, neuropraxia

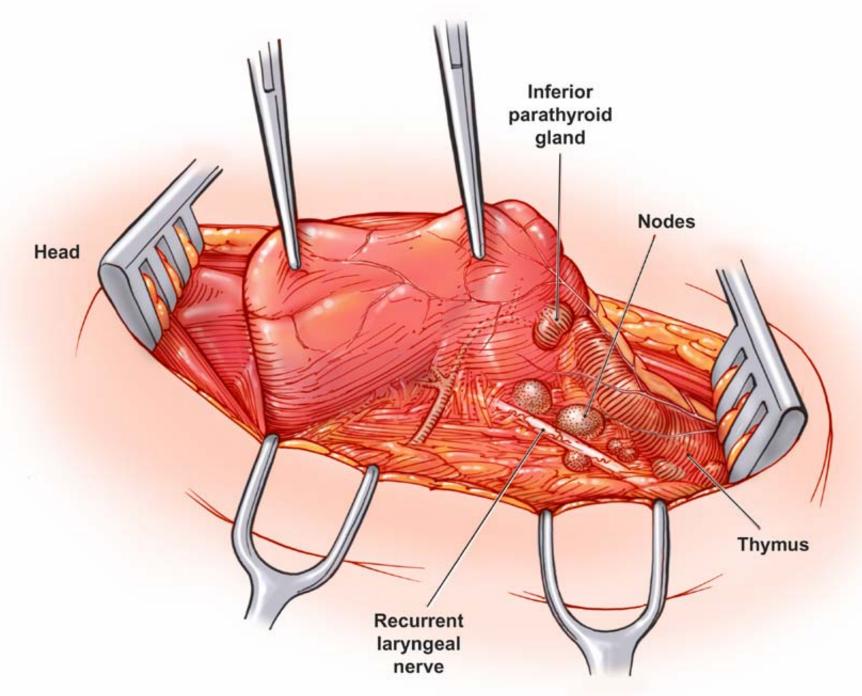
They Will Come Back To Haunt Us and Our Patients

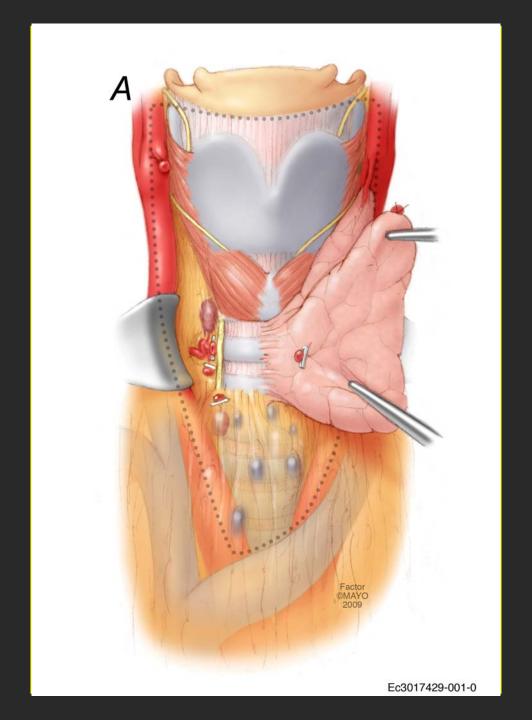
Lateral Neck Dissection

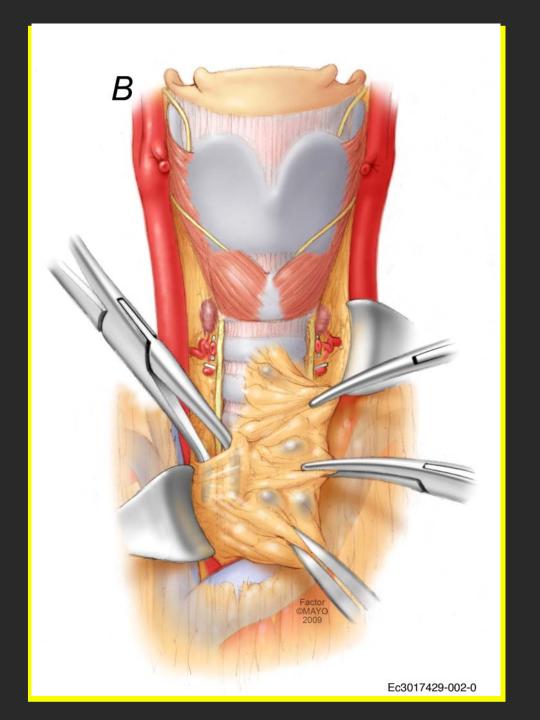
- Therapeutic
 - Biopsy positive
 - Ultrasound positive
 - -Gross involvement

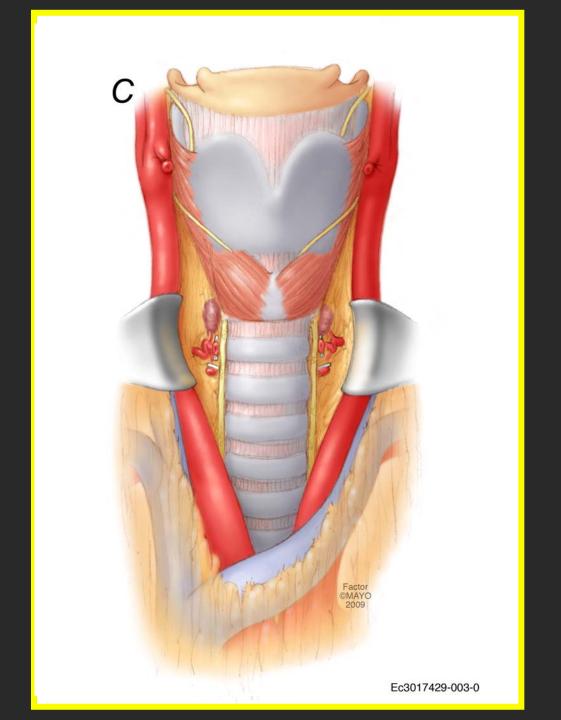


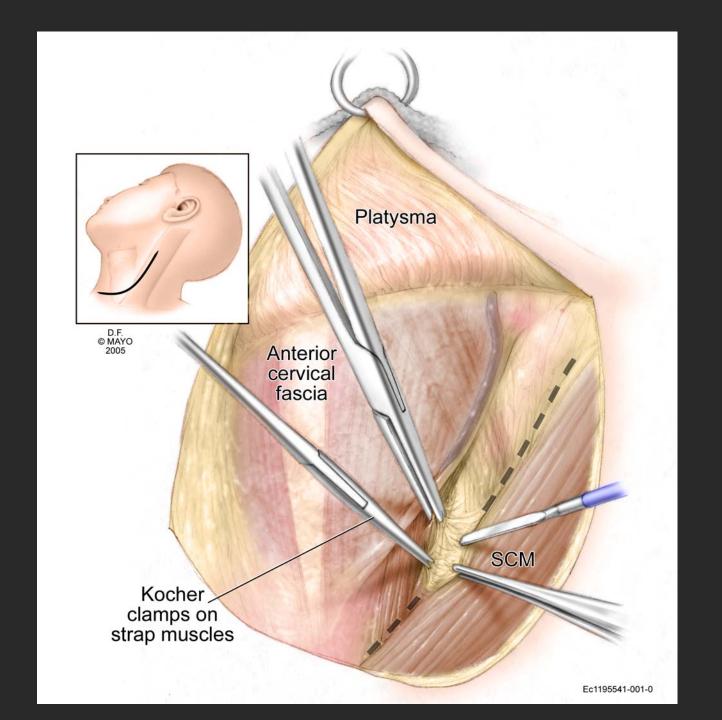


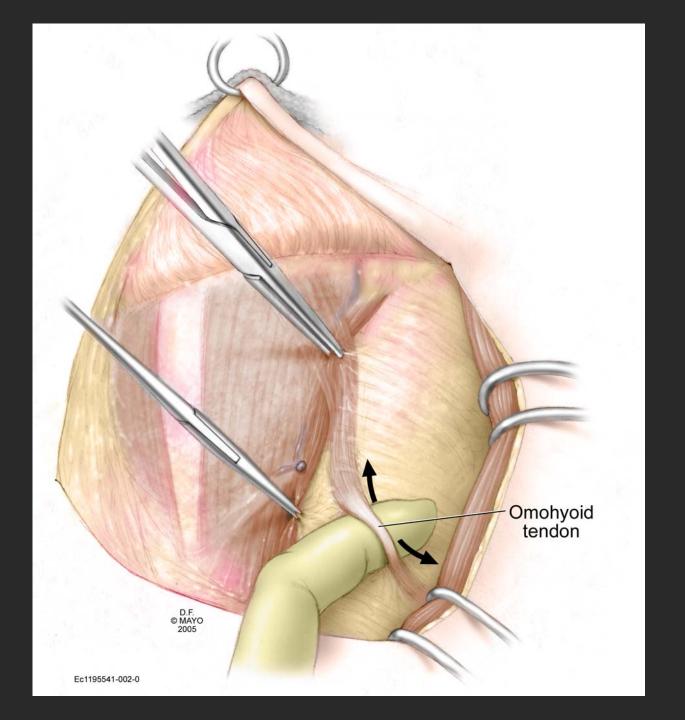


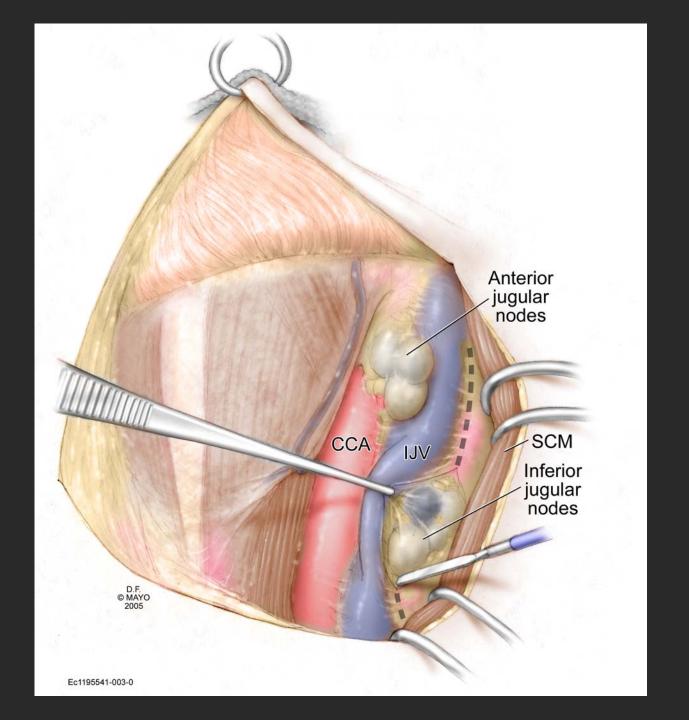


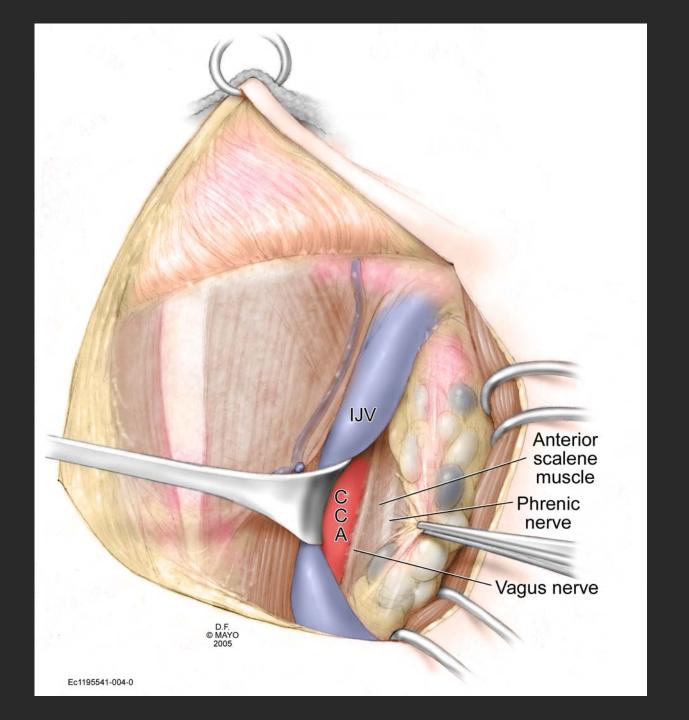


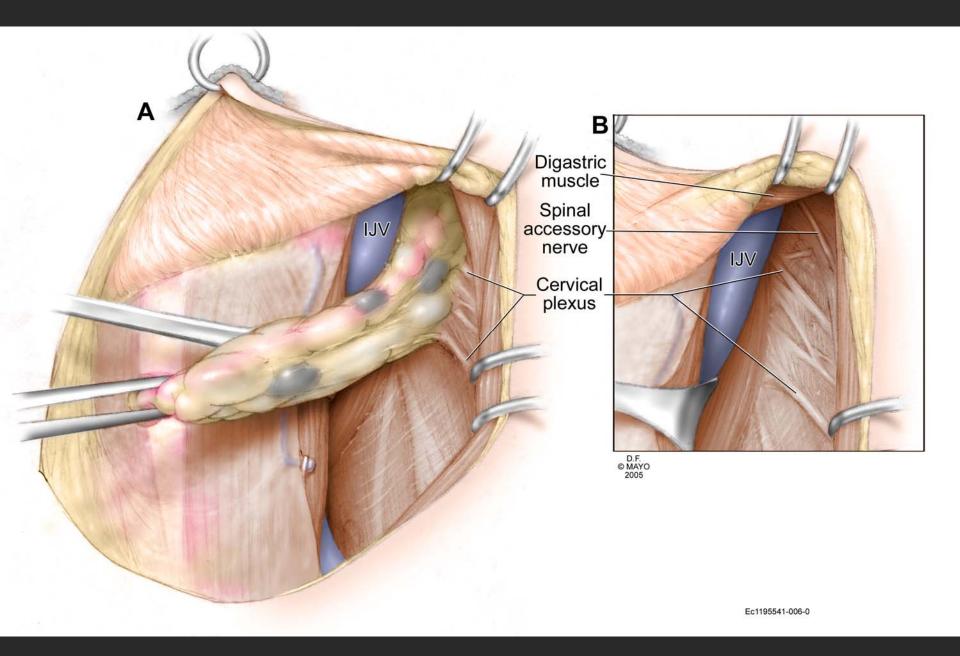


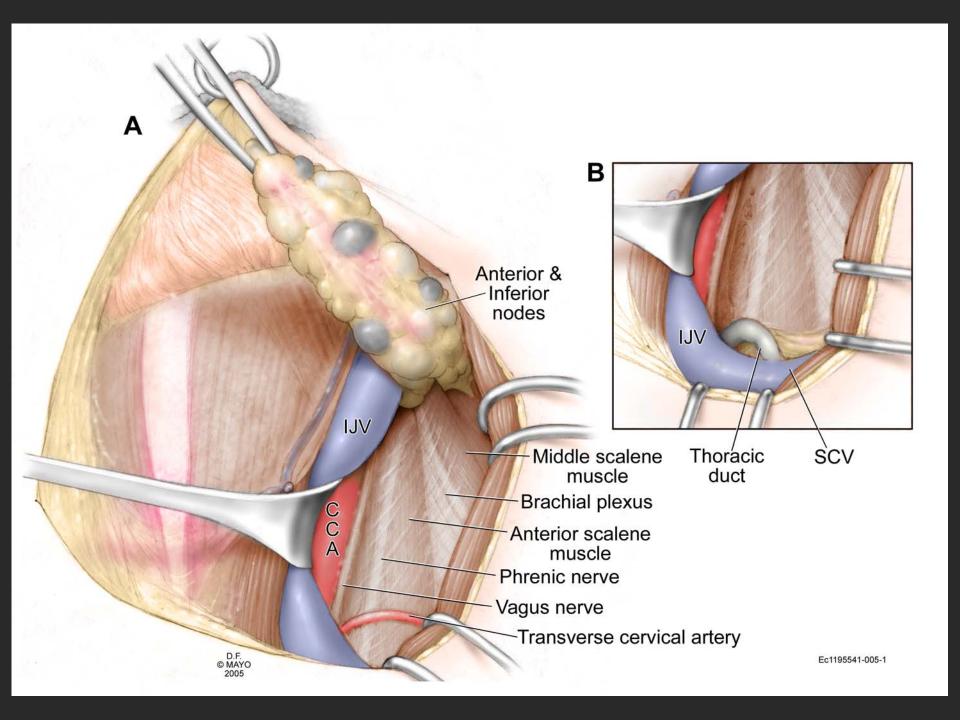












Prophylactic Central Lymph Node Dissection

Should be performed for T3 and T4 tumors. It is optional for T1 and T2 tumors (ATA Recommendations 2009)

Practical Algorithm

⊕ FNA for PTC (or suspicious)

US Mapping ± **FNA**

⊕Lateral Nodes

⊖ Lateral Nodes

Extensive Limited

MRND SND

+TTx

+CCND

Total Thyroidectomy (TTx)

CN's grossly ⊕
Multifocal
Larger tumor
Extrathyroidal

Bilateral level

VI ± VII Delphian

Pretracheal

CN's grossly ⊖
Tumor unifocal
< 1 cm
Intrathyroidal

Ipsilateral level VI Delphian

Pretracheal

MRND = modified radical neck dissection

+TTx

+CCND

SND = selective (lateral) neck dissection

Recommendations

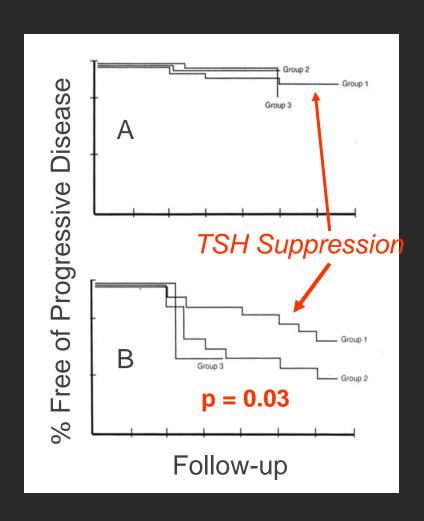
- BLR and central node dissection (CND) reduces TR in low-risk patients
- BLR and CND reduces TR and CSM in high-risk patients
- RRA does not further reduce CSM or TR in MACIS low-risk patients

TSH Suppression and Outcomes

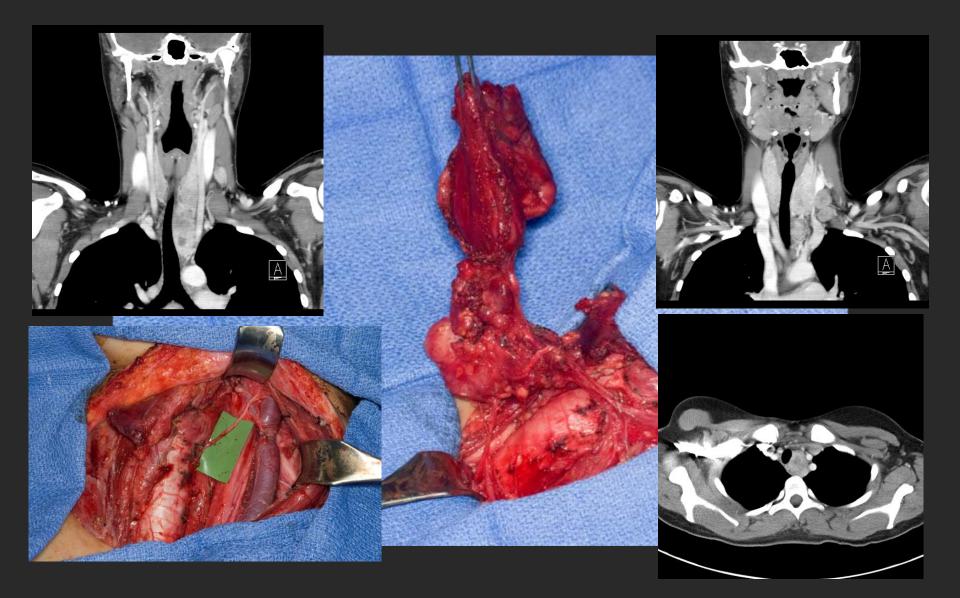
- 683 patients with DTC followed at 14 institutions up to 10 years
- Majority (90%) were PTC

A: Stage I & II

B: Stage III & IV



Childhood PTC





Long-Term Outcome in 215 Children and Adolescents with Papillary Thyroid Cancer Treated During 1940 Through 2008

Ian D. Hay · Tomas Gonzalez-Losada · Megan S. Reinalda · Jennifer A. Honetschlager · Melanie L. Richards · Geoffrey B. Thompson

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Abstract

Background Controversy exists regarding the aggressiveness of initial therapy in childhood papillary thyroid cancer (PTC). Few studies with long-term outcome exist and second primary malignancies have rarely been analyzed.

Methods We studied 215 PTC patients younger than 21 years old managed during 1940 through 2008. The patients were aged 3–20 year old (median age = 16 years); the median follow-up was 29 years. Recurrence and mortality details were taken from a computerized database.

(UL) were significantly (P < 0.001) higher than after bilateral lobar resection (BLR). During 1950–2008 radioiodine remnant ablation (RRA) was administered within 18 months to 32%; it did not diminish the 25-year regional recurrence rate of 16% seen after BLR alone (P = 0.86). Only two fatal events from PTC occurred at 28 and 30 years, for a cause-specific mortality at 40 years of only 2%. All-causes mortality rates did not exceed expectation through 20 years, but from 30 through 50 years, the number of deaths was significantly (P < 0.001) higher than predicted. Fifteen of 22

Childhood and Adolescent PTC Managed During 1940-2008 - Patients Studied -

215 consecutive PTC patients aged <21 years

January 1, 1940 - December 31, 2008

Followed to June 2009

Childhood and Adolescent PTC Treated at Mayo Clinic during 1940-2005 Conclusion

- Patients with PTC before age 21 typically were nodepositive and 1/3 recurred in 30 yr
- Extent of initial surgery, but <u>not</u> radioiodine remnant ablation, influenced recurrence rates
- PTC patients <21 yr at diagnosis enjoyed a 98% causespecific survival at 60 postop yr
- However, such patients experienced excessive allcauses mortality after 30 years

Mortality Rates from All Causes in Childhood and Adolescent PTC 1940-2008 Cohort

- Rates as predicted through 20 yr
- Significantly (p<0.001) higher than expected during years 30 through 50
- 22 deaths observed vs 11 expected
- 17/22 (77%) died from malignancy; 2 from PTC, 15 from other primaries
- 73% received some form of ionizing therapeutic radiation

Childhood and Adolescent PTC Treated at Mayo Clinic during 1940-2008

 Childhood and adolescent PTC is not a lethal diagnosis

Overzealous Treatment vs Predisposition?

 Overaggressive postoperative treatment could have long-term, possibly fatal, consequences

PAPILLARY THYROID MICROCARCINOMA

An innocuous occurrence in our opinion

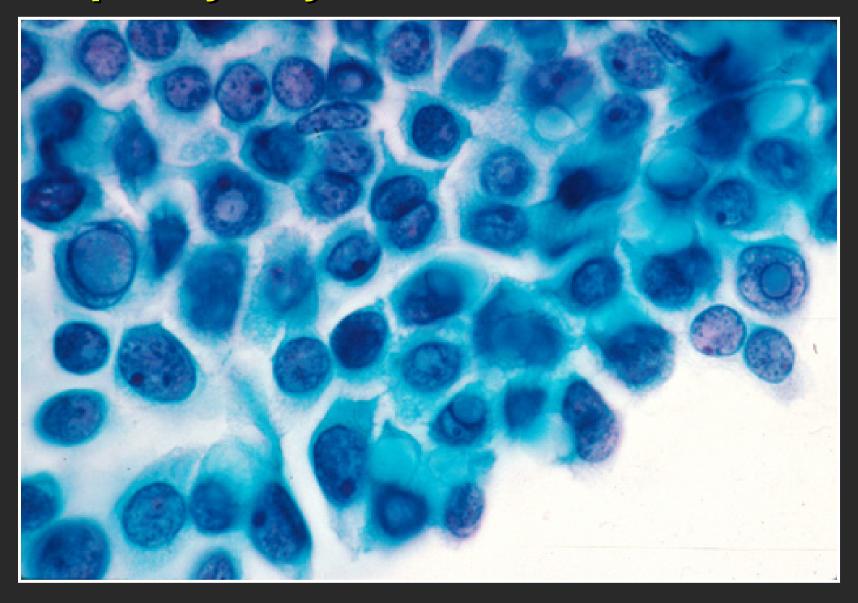
Unless higher risk features are present at the time of diagnosis

Manage accordingly

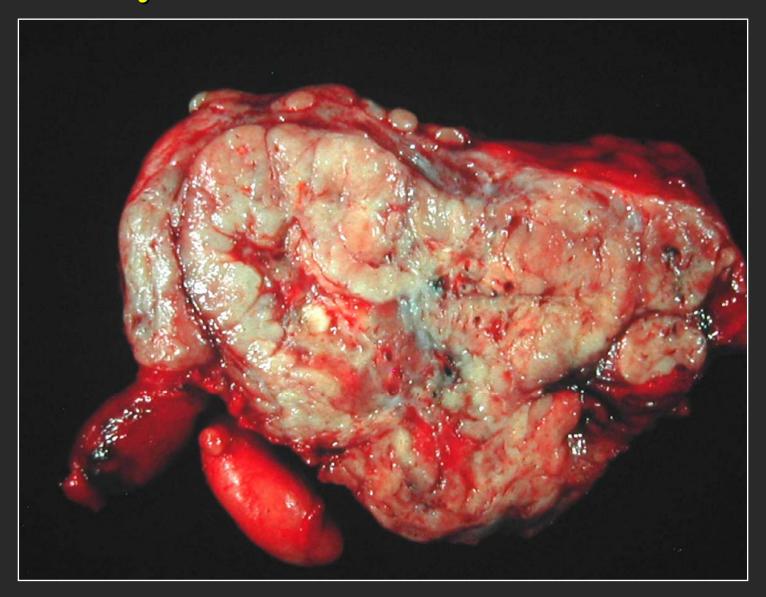
Follicular Thyroid Cancer (FTC)

- 10-15% of thyroid malignancies
- Cytology insufficient
- Capsular / vascular invasion
- 90% unifocal
- Hematogenous spread
- Lung and bone metastases: 15%
- Nodal metastases: FCC 5%

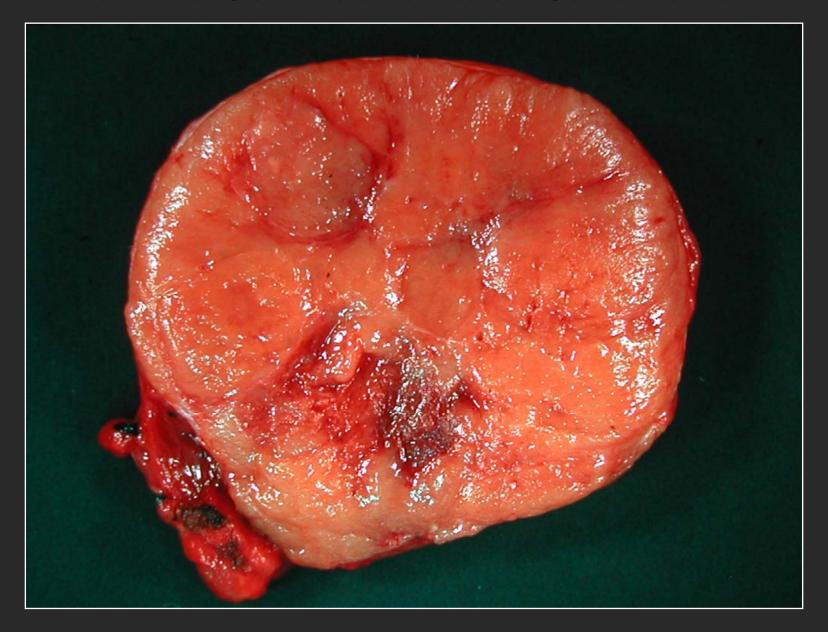
Papillary Thyroid Carcinoma-FNAB



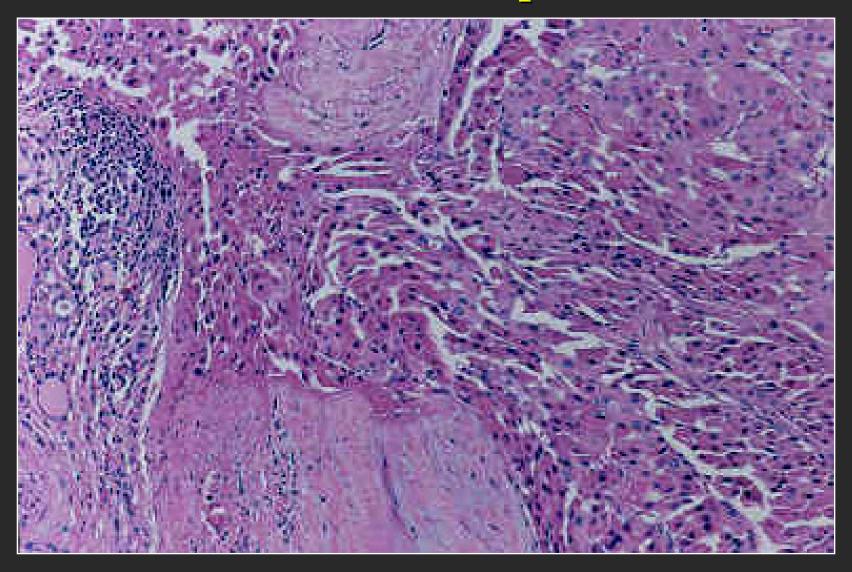
Widely Invasive Follicular Carcinoma



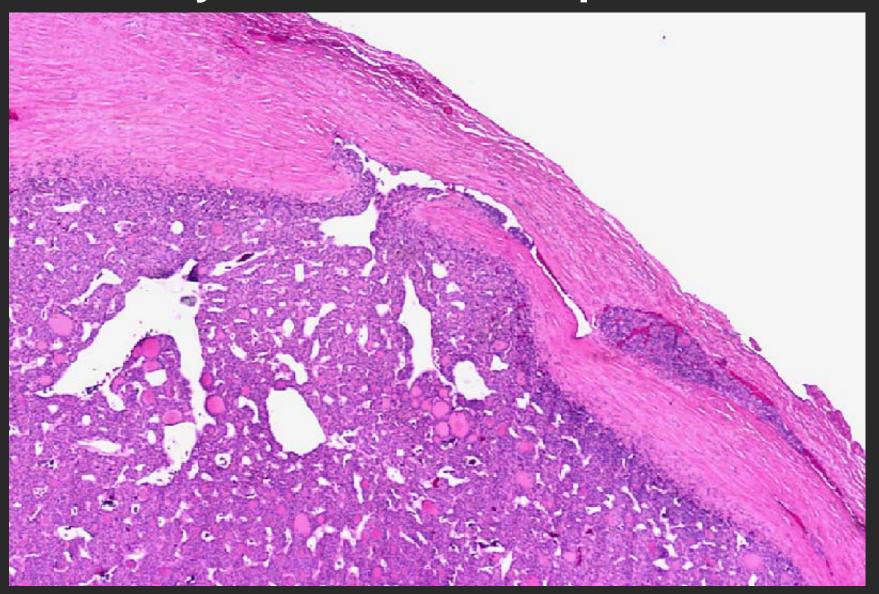
Hurthle Cell Adenoma or Carcinoma?



Follicular Carcinoma-Capsular Invasion



Follicular Carcinoma – Minimally Invasive Into Capsular Vessel



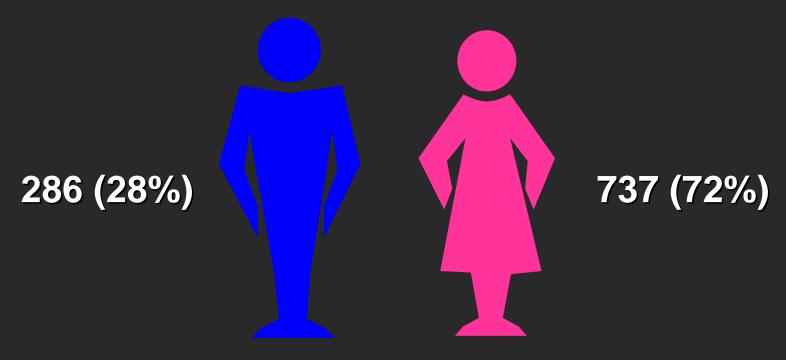
Frozen Section-Modified Toluidine Blue Stain





Follicular Neoplasms: Frozen Section

Results: 1023 Patients

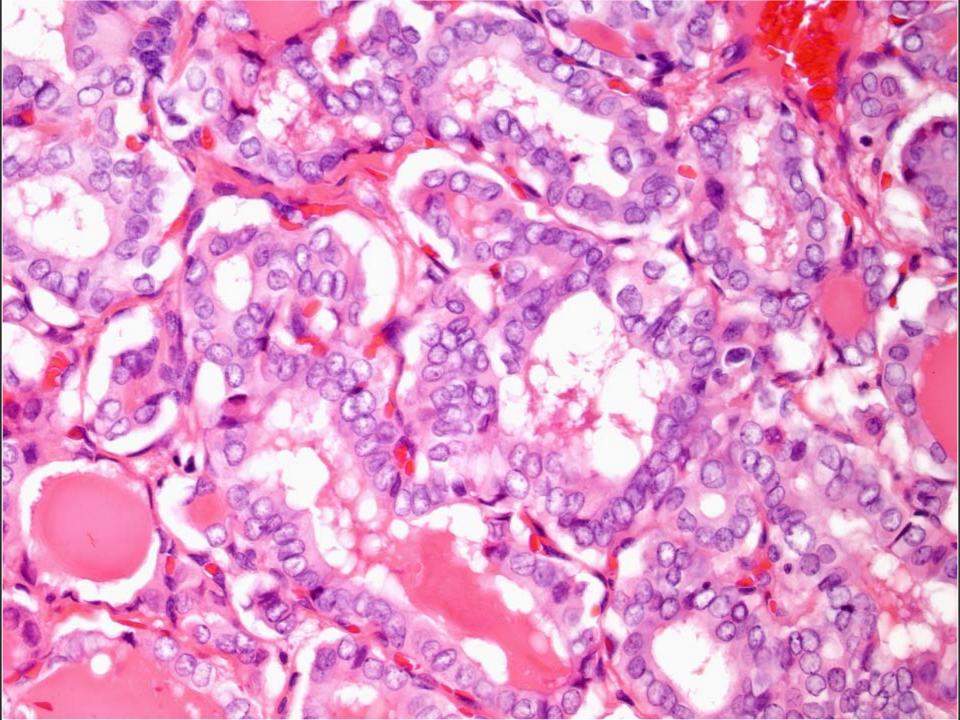


Mean age: 52.1 years

Follicular Neoplasms: Pathology

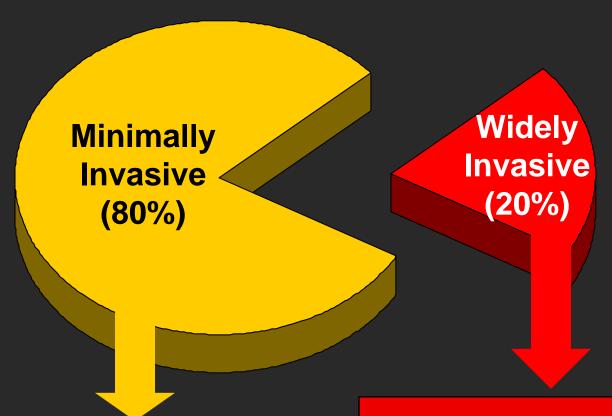
		Frozen Section		
		Ca	Non-Ca	Total
Perm	Ca	65 TP	18 FN	83
Section	Non-Ca	7 FP	933 TN	940

65/83 (78%) Ca Dx by FS



Follicular Thyroid Cancer

- Lymph node metastases (< 5%)
 - Usually associated with locally advanced tumor
 - Worse prognosis

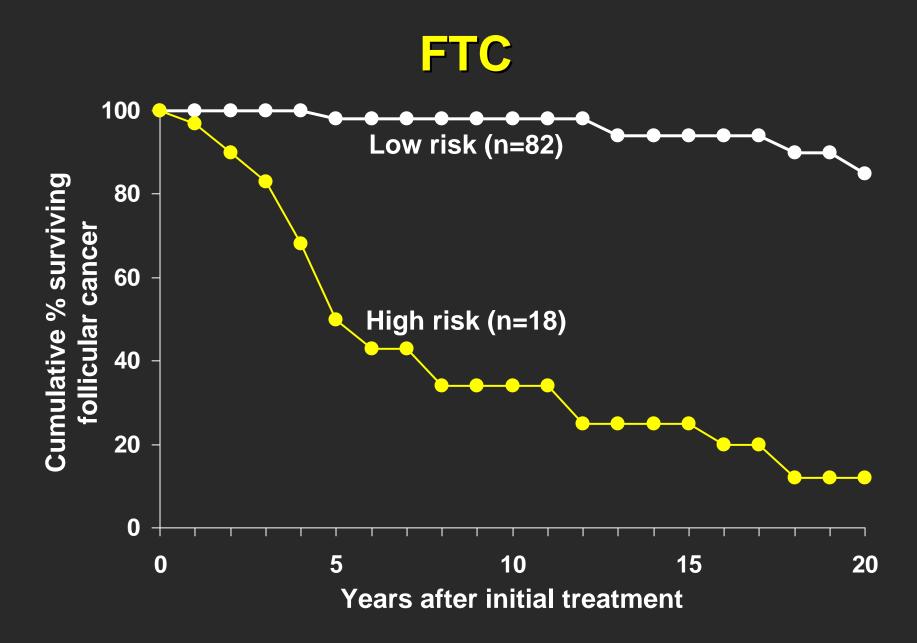


Microscopic vascular and capsular invasion

Gross involvement of vessels and contiguous structures

- Prognostic indicators
 - -Age > 50
 - Marked vascular invasion
 - Metastatic disease

- High risk (2/3 risk factors)
 - Survival: 47% and 8% @ 5 and 20 years
- Low risk (0-1/3 risk factors)
 - -Survival: 99% and 86% @ 5 and 20 years



- Tumors < 2 cm with
 - -minimal capsular invasion alone
 - √ No metastases or deaths
 - √ Recent 10-year follow-up
 - Lobectomy Alone

Hurthle Cell Cancer

- <5% of all thyroid cancers</p>
- More locally aggressive
- Less avidity for RAI
- Nodal metastases in 1/3

Follicular and Hurthle Cell Carcinoma

- Lymph node mets from FTC rare (<5%); if present consider FVPTC
- Routine CCND and LND for FTC not necessary unless positive nodes are present grossly or by US
- HCC has positive nodes in up to 30%; manage nodes like PTC

FTC/HCC

Treatment:

- Total / NT Thyroidectomy
- Sample central nodes*
- Formal node dissection when nodes ⊕
- CCND for HCC
- RRA, THST except in small tumors with minimal capsular invasion

^{*}may be only indication of FVPTC

Summary

- Total or Near-Total Thyroidectomy
- Central Compartment Lymphadenectomy (PTC, HCC)
- Lateral lymphadenectomy based on pre-op Ultrasound
- RRA based on Risk Assessment
- TSH Suppression based on Risk Assessment

If all else fails.....

Thyroid Cancer Strategy Meeting?

