Sunday November 6, 2011

Session I – Thyroid Cancer Presentations

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Thyroid Cancer: Treatment Approach to Small Volume Low Risk Disease

Anna M. Sawka, MD, PhD, FRCPC

This presentation will focus on medical management of small volume low risk (early stage) papillary thyroid cancer. Disease definition, epidemiologic trends, and disease prognosis will be discussed. The speaker will focus primarily on the current evidence relating to the use of adjuvant radioactive iodine treatment in this setting.

Notes

Current Concepts in Head & Neck Surgery
Toronto, Ontario, Canada

Surgical Management of Papillary Thyroid Cancer

November 6, 2011

Ashok R. Shaha, M.D., F.A.C.S.
Professor of Surgery
Jatin P. Shah Chair in Head and Neck Surgery
Memorial Sloan-Kettering Cancer Center
New York, NY

"New York: The Nation's Thyroid Gland"

-- Christopher Morley

Thyroid Literature

Medline

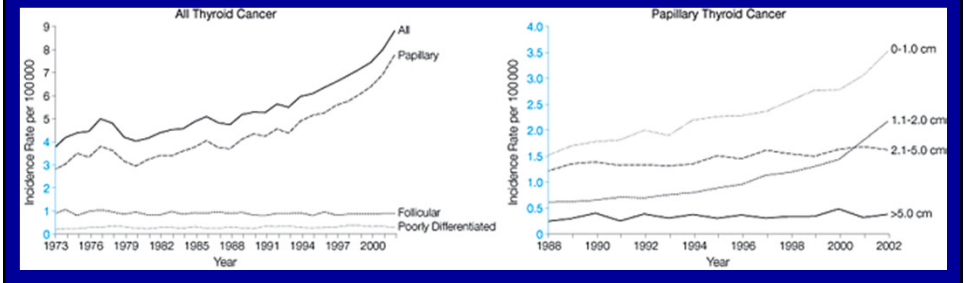
Thyroid disease	**136,053**
Thyroid tumors	**33,554**

- New Paper on Thyroid Disease – Every 3 Hours
- New Paper on Thyroid Cancer – Every 8 Hours

Thyroid Google search 36 million

Thyroid Cancer Google search 21 million

Trends in Incidence of Thyroid Cancer and Papillary Tumors by Size in the United States



Davies, L. et al. JAMA 2006;295:2164-2167.

Incidentaloma of the Thyroid

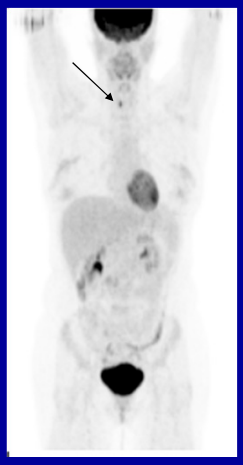
Clinical –

- Routine physical exam
- Obstetrics – Check up
- Pregnancy – Prenatal

Imaging –

- CT
- MRI – Trauma, cervical spine
- Ultrasound – Carotid, breast

PET Scan –



PET Incidentaloma

PET Associated Incidental Neoplasms (PAIN)

- Focal vs Diffuse Uptake
- 50% malignancy in patients with focal uptake
- Oncocytic pathology, tall cell or insular tumors

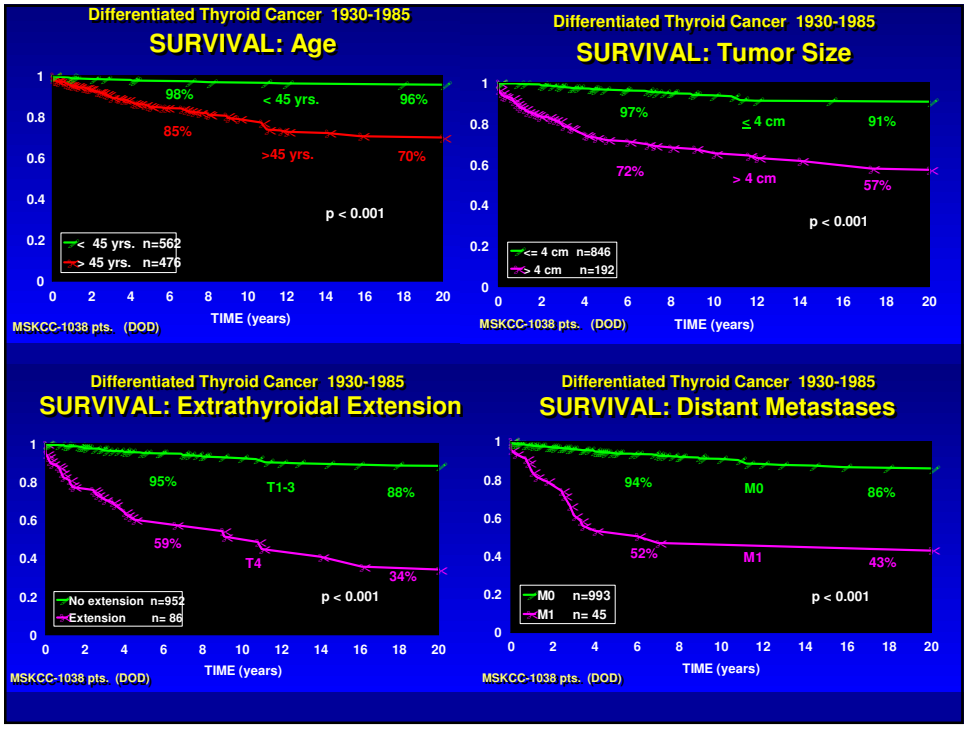
Katz, Shaha. J Am Coll Surg 2008.

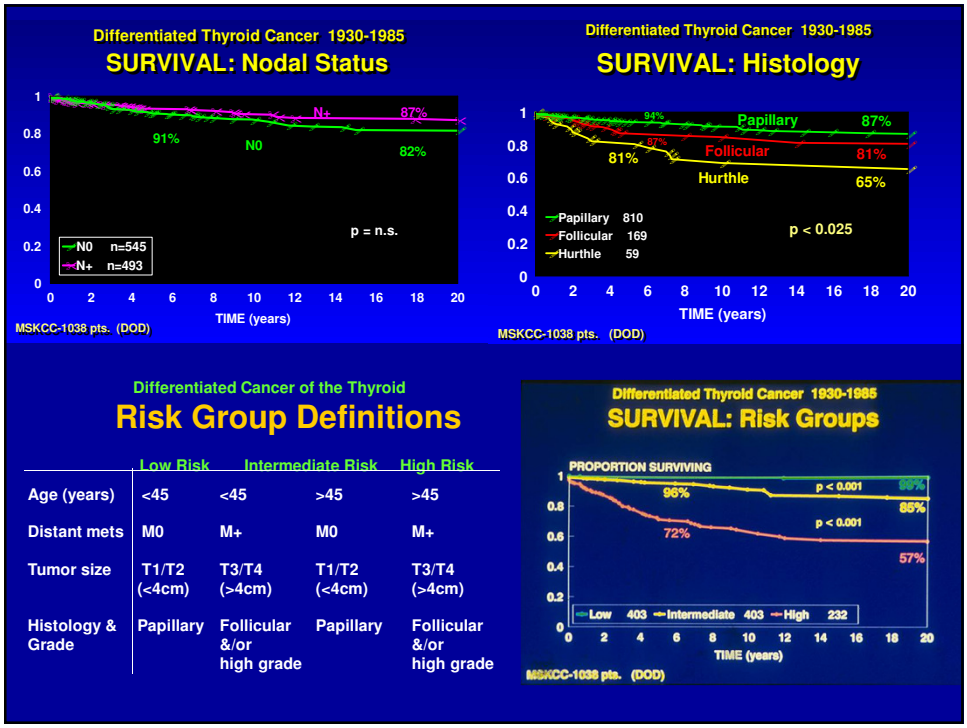
Thyroid Cancer

A Unique Human Neoplasm

- Age is the most important prognostic factor
- No stage III & IV cancers in pts below 45
- Multicentricity of thyroid cancer is frequent – no prognostic impact
  Microscopic tumor – "laboratory cancer"
- Nodal metastasis has no impact on outcome
- Impact of extrathyroidal spread
- Grade of the tumor & histologic poorly differentiated features


CLINT EASTWOOD
THE GOOD
THE BAD
AND THE UGLY

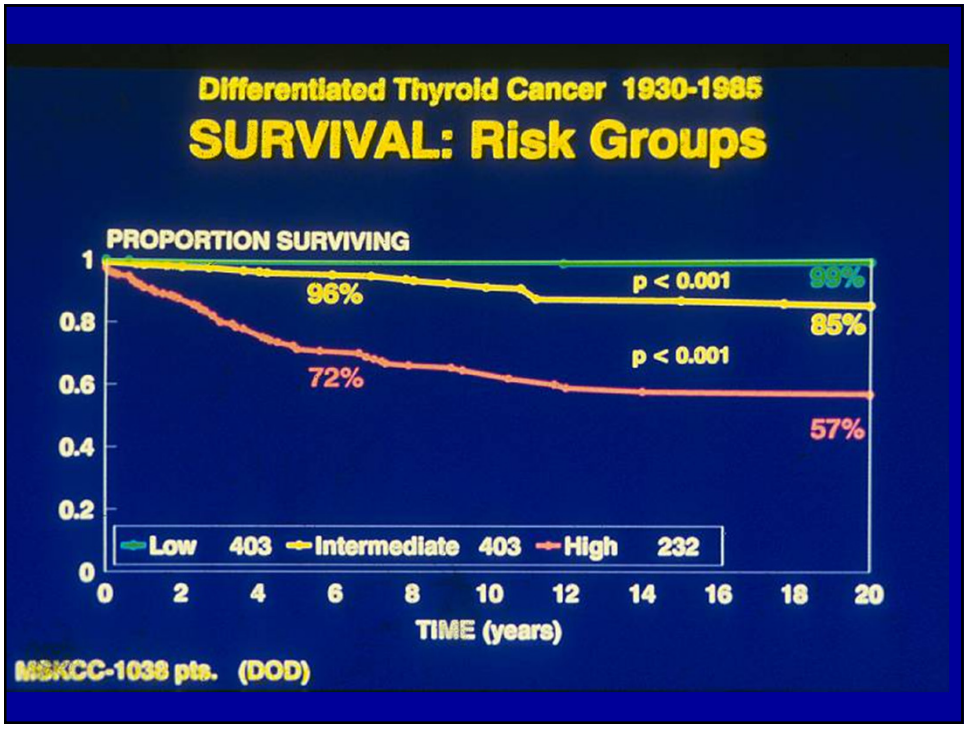

Differentiated Thyroid Cancer 1930-1985
SURVIVAL: Age
98%
< 45 yrs.
96%
85%
>45 yrs.
70%
p < 0.001
< 45 yrs. n=562
> 45 yrs. n=476
MSKCC-1038 pts. (DOD)
TIME (years)
Differentiated Thyroid Cancer 1930-1985
SURVIVAL: Tumor Size
97%
≤ 4 cm
91%
72%
> 4 cm
57%
p < 0.001
<= 4 cm n=846
> 4 cm n=192
MSKCC-1038 pts. (DOD)
TIME (years)
Differentiated Thyroid Cancer 1930-1985
SURVIVAL: Extrathyroidal Extension
95%
T1-3
88%
59%
T4
34%
p < 0.001
No extension n=952
Extension n= 86
MSKCC-1038 pts. (DOD)
TIME (years)
Differentiated Thyroid Cancer 1930-1985
SURVIVAL: Distant Metastases
94%
M0
86%
52%
M1
43%
p < 0.001
M0 n=993
M1 n= 45
MSKCC-1038 pts. (DOD)
TIME (years)

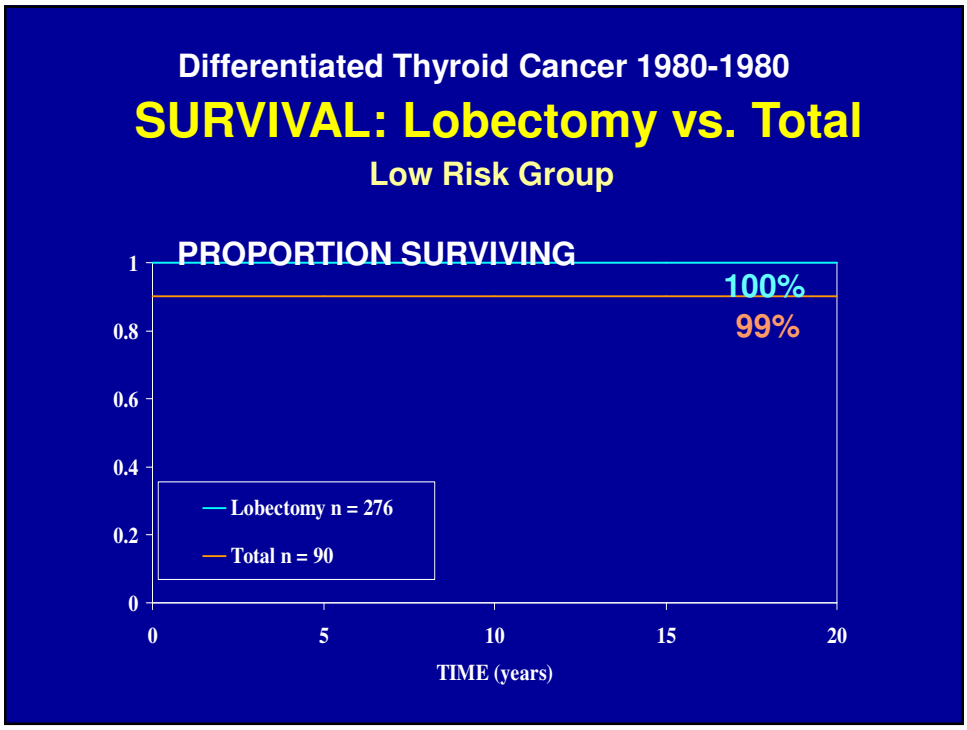


Differentiated Cancer of the Thyroid

Risk Group Definitions

	Low Risk	Intermediate Risk		High Risk
Age (years)	<45	<45	>45	>45
Distant mets	M0	M+	M0	M+
Tumor size	T1/T2 (<4cm)	T3/T4 (>4cm)	T1/T2 (<4cm)	T3/T4 (>4cm)
Histology & Grade	Papillary	Follicular &/or high grade	Papillary	Follicular &/or high grade


Differentiated Thyroid Cancer 1930-1985
SURVIVAL: Risk Groups
PROPORTION SURVIVING
1
0.8
0.6
0.4
0.2
0
96%
p < 0.001
98%
85%
72%
p < 0.001
57%
Low 403
Intermediate 403
High 232
0 2 4 6 8 10 12 14 16 18 20
TIME (years)
MSKCC-1038 pts. (DOD)


Differentiated Thyroid Cancer 1980-1980
SURVIVAL: Lobectomy vs. Total
Low Risk Group
PROPORTION SURVIVING
1
0.8
0.6
0.4
0.2
0
100%
99%
Lobectomy n = 276
Total n = 90
0 5 10 15 20
TIME (years)

"The fact that total thyroidectomy can be performed safely does not necessarily mean that it is indicated in all patients with thyroid cancer..."

"An operation not worth doing is not worth doing well."

Collin Thomas
Chapel Hill

Indications for Total Thyroidectomy

- Grossly palpable disease in both lobes
- High risk patient with high risk tumor
- Radiated patient
- Young patient with large nodal metastasis to facilitate RAI
- Patient with distant metastasis likely to require RAI

Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer

Estimating Risk of Recurrence
2009 Update

Low Risk

Classic PTC
No local or distant mets
Complete resection
No tumor invasion
No vascular invasion
If given, no RAI uptake outside TB

Intermediate Risk

Microscopic ETE
Cervical LN mets
Aggressive Histology
Vascular invasion

High Risk

Macroscopic gross ETE
Incomplete tumor resection
Distant Mets
Inappropriate Tg elevation

Increasing Incidence of Total Thyroidectomy

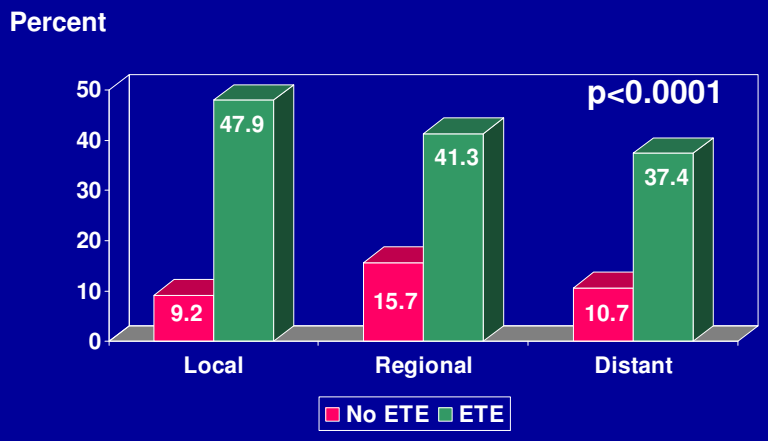
- Preop U/S showing bilateral nodules
- Preop consultation with Endocrinologist suggesting total and RAI
- Patients perceive fear of recurrence and paper confirmation of negative scan
- Thyroglobulin follow up
- Follow up with repeated U/S showing tiny nodules (Hashimoto's)
- Dr. Google

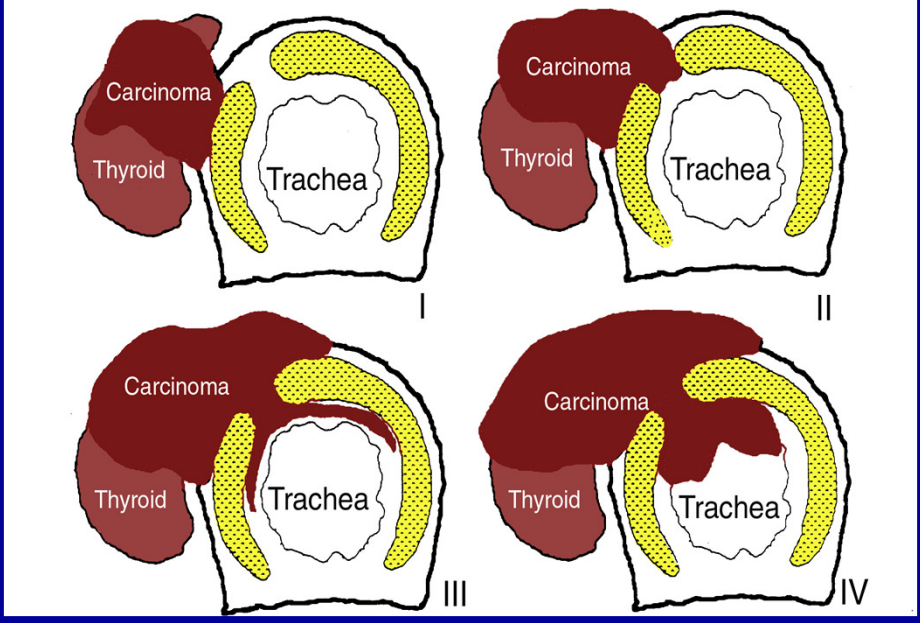
Surgical Principles

- Evaluate the risk groups
- Evaluate the prognostic factors
- Evaluate the extent of disease
- Evaluate extrathyroidal extension
- Cost effective/Evidence based management
- Avoid overtreatment and treatment related surgical & medical complications

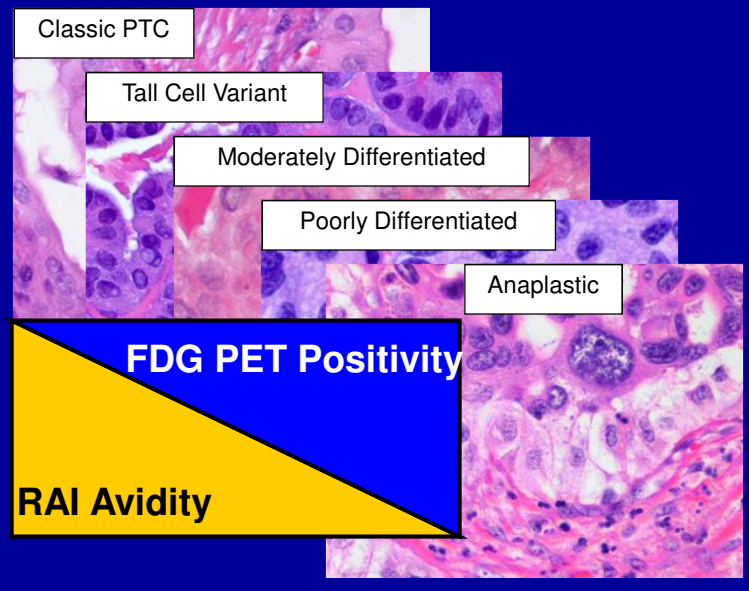
Thyroid Carcinoma with Extrathyroid Extension

Treatment Failure





Continuum of Papillary Thyroid Cancer



Management of Neck in Thyroid Cancer

Clinically Negative Intraoperative Management

- Look for TE groove nodes
- Look for sup mediastinal nodes
- Look for jugular nodes
- If any of these enlarged - do the respective clearance
- Central compartment clearance

Management of Neck in Thyroid Cancer

Clinically Positive Intraoperative Management

- "Berry picking" not recommended, higher incidence of neck recurrence
- Modified neck dissection
- Preserving SCM
  - IJV
  - Accessory nerve
  - Submandibular sal gland (Level I)
- RND - rarely indicated

Patients with multiple positive neck nodes from papillary ca may have additional paratracheal, sup mediastinal, or lateral neck nodes, and may remain with persistent mild hyperthyroglobulinemia. We may not achieve biochemical cure.

Shaha 2005.

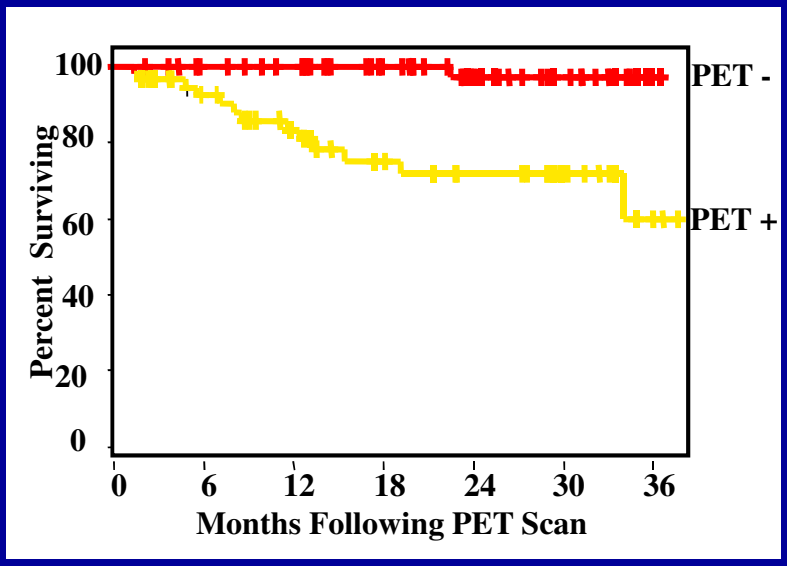
Prophylactic central compartment dissection in thyroid cancer: A new avenue of debate

Ashok R. Shaha, MD, FACS, *New York, NY*

- **Surgical experience is an important consideration while debating the issue of central compartment dissection**
- **Recurrence in the low-risk group necessitating central compartment reoperation is quite rare and in the high-risk group it is probably unavoidable**
- **It is important to develop a balance between the risk of recurrence against the benefit from elective nodal dissection**
- ***Primum non nocere – FIRST DO NO HARM***

Surgery 2009; 146;1224-7

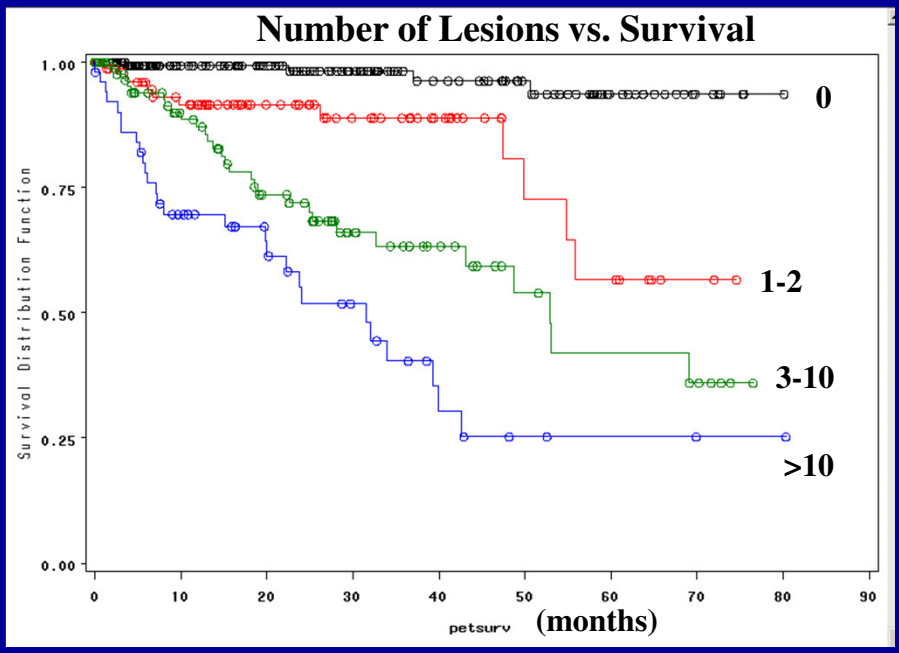
Prognostic Implication of ^{18}FDG PET



n=125 (14 deaths)

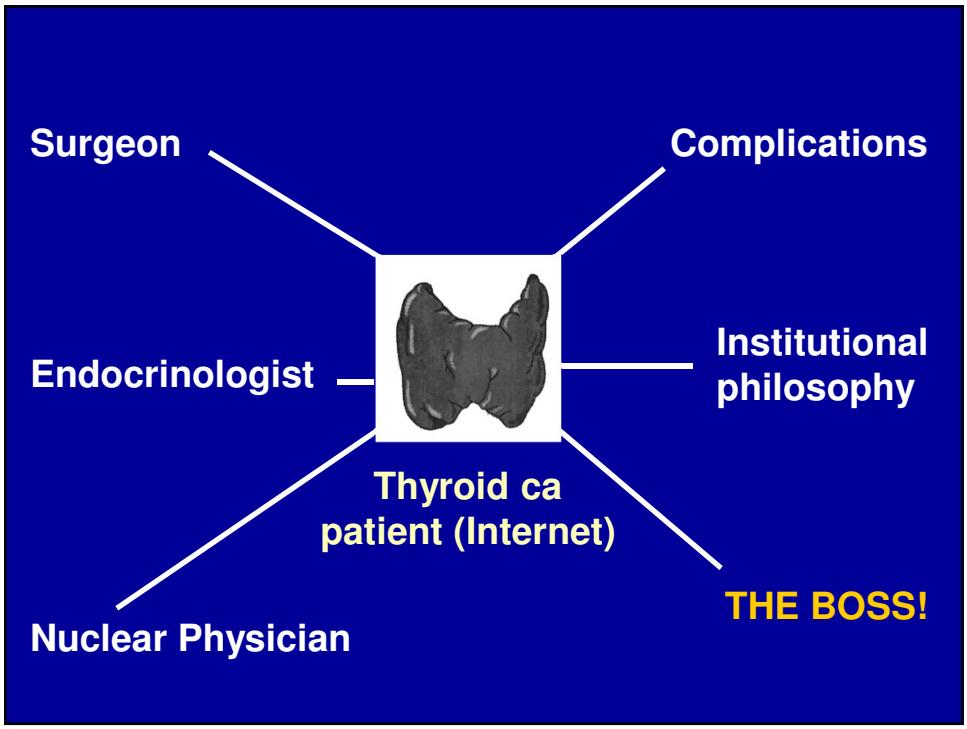
Wang et el. JCEM 85:1107-1113, 2000

Number of Lesions vs. Survival



Thyroid Cancer

	20 yr survival	Treatment
Good Low	99%	Lobectomy. Appropriate surgery based on extent of disease.
Bad Intermediate	85%	Total thyroidectomy. Select extent of thyroidectomy based on extent of disease. RAI in select cases.
Ugly High	57%	Total thyroidectomy. RAI. Ext RT in selected cases.



Notes

Medullary Carcinoma of the Thyroid Gland

Nov. 6. 2011

Current Concepts in
Head and Neck Surgery
Toronto

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Medullary Carcinoma of the Thyroid (MTC)

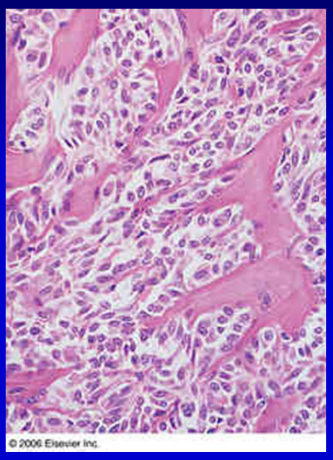
- Pathology
- Genetics
- Clinical syndromes
- Evaluation and work-up
- Surgical treatment
- Postop management
- MEN2 – screening & management
- New therapies

Background

- Natural history
  - Indolent disease process
  - Usually diagnosed on physical examination as a solitary neck nodule
  - Early spread to regional lymph nodes is common
  - Distant metastases occur to the lung, liver, bone, and brain
  - Overall more aggressive than differentiated cancers
  - Sporadic (SMTC) = 75%, Inherited (IMTC) = 25%
  - SMTC usually is unilateral
  - IMTC are typically multicentric and bilateral
  - Produce several tumor markers (Calcitonin, CEA, Corticotropin, Serotonin, Melanin → paraneoplastic syndromes)
  - Does not concentrate iodine (RAI not effective!)

Background

- Etiology
  - "Cancer that develops in C cells of the thyroid (NCI)"
  - A distinct thyroid carcinoma
  - Originates in the parafollicular C cells of the thyroid gland
  - Sporadic MTC accounts for 75% of cases, and inherited MTC constitutes the rest
  - Inherited MTC occurs in association with multiple endocrine neoplasia (MEN) syndromes, but non-MEN familial MTC also occur



Pathology

- Occurs most commonly in upper midportion of gland where C-cells are most abundant
- Variety of histopathological patterns
  - Usually bland, round or oval cells in nests or trabeculae
  - May be spindle shaped
- Stromal amyloid deposits in >25% of cases
- 90% calcitonin immunohistochemical stain positive

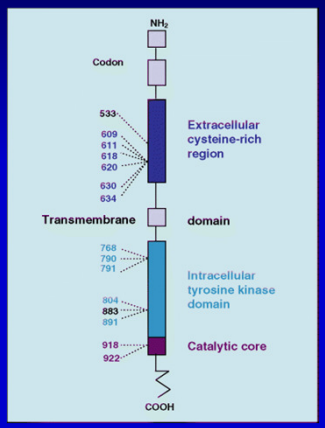
Immunohistochemistry

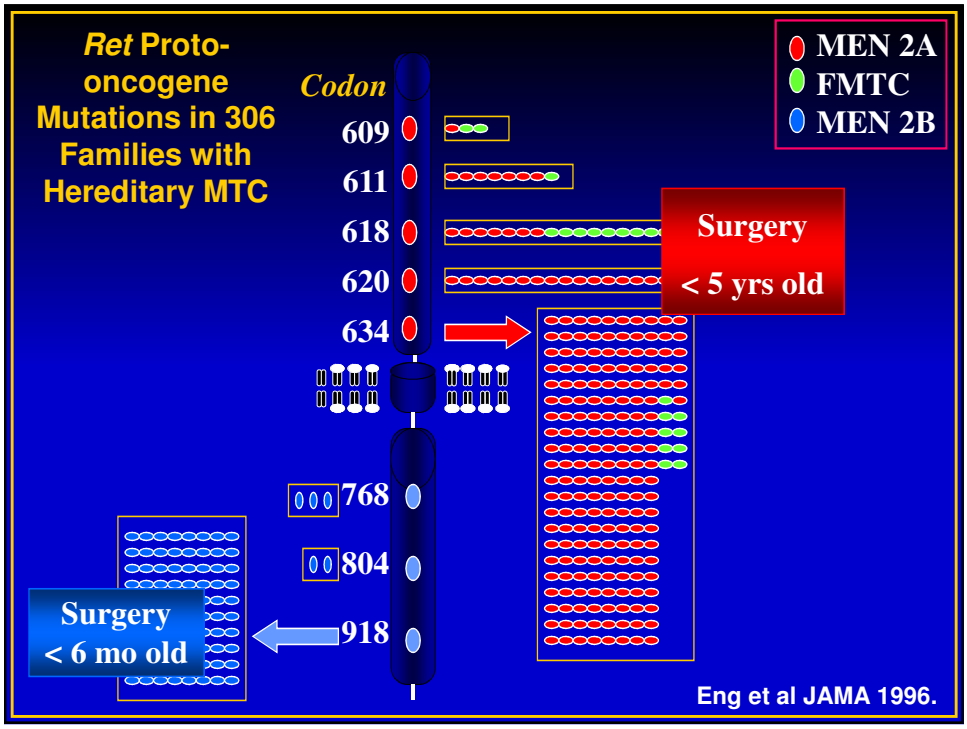
- Schroder et al
  - Calcitonin 100%
  - Cytokeratin 100%
  - CGRP 92%
  - CEA 77%
  - NSE 75%
  - Vimentin 53%
  - Serotonin 27%
  - HCG 23%
  - Bombesin 18%
  - Somatostatin 12%
  - S-100 0%
  - ACTH 0%
  - Thyroglobulin 0%

Schroder et al. Cancer 1988;61:806-16

Background

- RET protooncogene
  - Plasma membrane–bound tyrosine kinase enzyme
  - Chromosome 10
  - Mutations → overactive Ret protein → C-cell hyperplasia → Cancer
  - IMTC: 98% RET germline mutations (AD inheritance pattern)
  - SMTC: 40-50% RET somatic mutations





THE SPECTRUM OF MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES AND HEREDITARY MEDULLARY THYROID CARCINOMA

MEN Syndromes		Hereditary MTC	
MEN I	MEN-IIa	MEN-IIb	Familial MTC
Werner's Syndrome	Sipple's Syndrome	MTC	MTC
Pituitary adenomas	MTC	Pheochromocytoma	
Pancreatic islet cell tumor	Pheochromocytoma	Marfanoid habitus	
Adrenal cortical adenomas			
Hyperparathyroidism	Hyperparathyroidism	Multiple mucosal intestinal ganglioneuromas	

MEN=multiple endocrine neoplasia;
MTC=medullary thyroid carcinoma

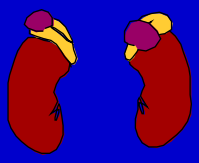
Multiple Endocrine Neoplasia, Type 2

MEN 2A

Medullary Thyroid Carcinoma
> 90-100%

Parathyroid Hyperplasia
10-20%

Pheochromocytoma
40-60%

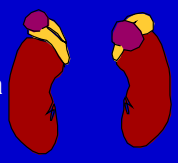


MEN 2B

Medullary Thyroid Carcinoma
> 98%

Mucosal Neuromas
>98%

Pheochromocytoma
40-60%



Genotype–Phenotype Correlations and Risk Levels for Aggressive Medullary Thyroid Cancer

Mutation	Exon	ATA risk level[a]	MTC risk level[b]	FMTC[c]	MEN 2A[d] MTC	PHPT	PHEO	CLA	HSCR	MEN 2B[d] MTC	PHEO	References
G321R[e]	5	A		+	MA	–	–	–	–	–	–	(100)
531/9 base pair duplication	8	A		+	MA	–	–	–	–	–	–	(364)
532 duplication[e]	8	A		+	?	–	–	–	–	–	–	(177)
C515S[e]	8	A		+	MA	–	–	–	–	–	–	(365)
C533C	8	A		+	MA	–	R	–	–	–	–	(99,366–368)
R600Q[e]	10	A		+	MI	–	–	–	–	–	–	(369)
K603E[e]	10	A		+	MI	–	–	–	–	–	–	(370)
Y606C[e]	10	A		+	?	–	–	–	–	–	–	(371,372)
C609F/R/G/S/Y	10	B	1	+	MA	MI	R	–	+	–	–	(14,46,85,373–375)
C611R/G/F/S/W/Y	10	B	2	+	MA	MI	R	–	+	–	–	(46,85)
C618R/G/F/S/Y	10	B	2	+	MA	MI	MI	–	+	–	–	(46,85)
C620R/G/F/S/W/Y	10	B	2	+	MA	MI	MI	–	+	–	–	(46,85,374)
C630R/F/S/Y	11	B		+	MA	R	R	–	–	–	–	(73,376,377)
D631Y[e]	11	B		+	?	–	–	–	–	–	–	(378)
633/9 base pair duplication	11	B		+	MA	MI	MI	–	–	–	–	(379)
C634R	11	C	2	–	MA	MI	MA	+	–	–	–	(46,85,380,381)
C634G/F/S/W/Y	11	C	2	+	MA	MI	MA	+	–	–	–	(46,85,380–382)
634/12 base pair duplication	11	B		+	MA	MI	–	–	–	–	–	(383)
635/insertion ELCR;T636P	11	A		+	MA	–	–	–	–	–	–	(371)
S649L	11	A		+	MI	R	–	–	–	–	–	(14,124,384,385)
K666E[e]	11	A		+	MI/MA	–	MI	–	–	–	–	(371)
E768D	13	A	1	+	MA	R	R	–	–	–	–	(46,73,90,378)
N777S[e]	13	A		+	MI	–	–	–	–	–	–	(386)
L790F	13	A	1	+	MA	R	R/MI	–	–	–	–	(86,378)
Y791F	13	A	1	+	MA	MI	MI	–	–	–	–	(86,378,387)
V804L	14	A	1	+	MA	MI	R	–	–	–	–	(46,86,388)
V804M	14	A	1	+	MA	R	R	–	–	–	–	(46,86,388,389)
V804M+V778I[f]	13/14	B		+	MA	–	–	–	–	–	–	(390)
V804M+E805K	14	D		–	–	–	–	–	–	MA	MA	(71)
V804M+Y806C	14	D		–	–	–	–	–	–	MA	MA	(72–74)
V804M+S904C[g]	14/15	D		–	–	MI	–	–	–	MA	–	(101)
G819K[e]	14	A		+	?	–	–	–	–	–	–	(14)
R833C[e]	14	A		+	?	–	–	–	–	–	–	(391)
R844Q[e]	14	A		+	?	–	–	–	–	–	–	(14,378)
R866W[e]	15	A		+	MA	–	–	–	–	–	–	(392)
A883F	15	D	3	–	–	–	–	–	–	MA	MA	(393,394)
S891A	15	A	1	+	MA	R	R	–	–	–	–	(14,395–397)
R912P	16	A		+	MI	–	–	–	–	–	–	(14,398)
M918T	16	D	3	–	–	–	–	–	–	MA	MA	(46)

[a]Risk from aggressive MTC: level D is highest risk.
[b]Risk from aggressive MTC from the Seventh International Workshop on MEN (2): level 1, high risk; level 2, higher risk; level 3, highest risk.
[c]Presence (+) of inherited MTC in the absence of PHPT or PHEO has been described, although the number of family members and number of family generations studied and duration of follow-up is variable. Historically, mutations initially considered diagnostic of FMTC have eventually demonstrated some penetrance of the MEN 2A phenotype. The absence (–) of association with FMTC indicates that inheritance of MTC in isolation is very unlikely.
[d]Organ-specific penetrance: MA, majority; MI, minority; R, rare.
[e]Mutations based on limited families/case reports and may represent variants of unknown significance.
[f]Phenotype associated with corneal nerve thickening.
[g]Phenotype associated with mucosal neurilemmomas.

American Thyroid Association Risk Level and Prophylactic Thyroidectomy Testing and Therapy

ATA risk level	*Age of RET testing*	*Age of required first US*	*Age of required first serum Ct*	*Age of prophylactic surgery*
D	ASAP and within the 1st year of life	ASAP and within the 1st year of life	6 months, if surgery not already done	ASAP and within the 1st year of life
C	<3–5 years	>3–5 years	>3–5 years	Before age 5 years
B	<3–5 years	>3–5 years	>3–5 years	Consider surgery before age 5. May delay surgery beyond age 5 years if stringent criteria are met.[a]
A	<3–5 years	>3–5 years	>3–5 years	May delay surgery beyond age 5 years if stringent criteria are met.[a]

[a]A normal annual basal ± stimulated* serum Ct, normal annual neck US, less aggressive MTC family history, and family preference.
ASAP, as soon as possible.

Treatment – Team Approach

- Head and Neck Surgery
- Endocrinology
- Cytopathology
- Pathology
- Radiology
- Radiation Oncology
- Genetics

Presentation

- Upper lobe nodule common
- 50% metastatic cervical nodes initially
- 15% airway compression or invasion
- Most patients in fourth decade of life
  - Sporadic patients older (5-6th decade) than FMTC or MEN IIA (3rd decade)
  - Most MEN IIB in 1st or 2nd decade
- Gender distribution equal

Evaluation

- Thorough history for symptoms
  - Local invasion
  - Systemic
    - Pheochromocytoma
    - Distant mets (diarrhea, bone pain)
- Comprehensive family history
- Complete head and neck examination

Treatment

- Surgery is only curative method
- I-131 and thyroid suppression Rx ineffective unlike well-diff thyroid ca
- Plan surgery appropriate for individual patient
- Calcitonin serves as marker for persistent or recurrent disease
- Adjuvant post-op XRT in select cases

Preoperative Evaluation

- Serum tumor markers
  - Calcitonin (nl <10 pg/ml)
  - CEA
- Screen for pheochromocytoma
  - 24-hour urine catecholamines and metanephrines
  - If co-existing, treat prospectively
- Screen for hyperparathyroidism
  - Serum calcium; if elevated, PTH

Primary Tumor Management

- Total thyroidectomy - general agreement
- Glandular involvement multifocal
  - Familial forms - 90%
  - Sporadic - 20% (intraglandular spread)
  - 20% "sporadic" prove to be familial
- Resect tumor completely if local invasion
- Thyroid replacement therapy post-op

Extent of Treatment

- Extent of thyroid surgery
  - Does everyone need a total thyroidectomy?
- Extent of neck surgery
  - Does everyone need central compartment nodal dissection?
  - Who needs a lateral neck dissection?
  - Uni- or bilateral?
- Adjuvant therapy
- What defines cure from MTC?
- What do you do when persistently elevated CT?

Surgical Management and Outcomes

- American Thyroid Association MTC management guidelines
- Review of data supporting "Recommendation 61-65" related to best surgical management in Sporadic MTC

Surgical Management and Outcomes

Recommendations are made on 3 main clinical scenarios:

- Surgery for low volume (intra-thyroidal) disease
- Surgery for limited local and limited or no distant disease
- Surgery for advanced local and extensive distant metastasis

Surgical Management and Outcomes

Surgery for low volume (intra-thyroidal) disease

(No evidence of of cervical lymph node metastasis per physical exam or USG)

- **"Clinical facts"**
- **High rate of lymph node metastasis**
- **Detection of node status both pre and intra-operatively is suboptimal**
- **Re-operations are associated with higher rates of surgical complications**

Surgical Management and Outcomes

Recommendation 61:

Patients with known or highly suspected MTC with no evidence of local or distant disease:

Total thyroidectomy and prophylactic central compartment (level VI) neck dissection (Grade B)

- **Importance of central neck clearance at the initial surgery was recognized (decrease recurrence and central neck complications)**
- **Prophylactic lateral neck dissection was omitted**
- **Best reserved for patients with preoperative positive imaging**

Surgical Management and Outcomes

Surgery for limited local and limited or no distant disease (+CNC and -LNC per imaging with no or limited distant disease)

"Clinical facts"

- Most patients with lymph node metastasis are not biochemically curable despite aggressive surgery
- Resection of local disease may decrease risk of local recurrence and complications

Surgical Management and Outcomes

Recommendation 62:

Patients with limited local (CN) and limited or no distant disease:

Total thyroidectomy and central compartment neck dissection (Grade B)

Recommendation 63:

Patients with limited locoregional (CN+LN) and limited or no distant disease:

Total thyroidectomy with central and lateral compartment neck dissection (Grade B)

Recommendation 64:

Patients with presence of distant metastatic disease:

Less aggressive surgical approach appropriate to preserve function to speech, swallowing and PTG

Maintain locoregional disease control and prevent central neck morbidity (Grade C)

Surgical Management and Outcomes

Surgery for advanced local and extensive distant metastasis

"Clinical facts"

- MTC patients represents a wide spectrum of tumor behavior
- Often unpredictable and indolent in nature even in the settings of extensive distant metastasis
- Management more challenging than for low stage disease
- Preservation of function and quality of life are important
- Palliative measures can be complex and multidisciplinary

Surgical Management and Outcomes

Recommendation 65:

Surgery for advanced local or distant metastasis

Less aggressive neck surgery may be appropriate to maintain local disease control and function (Grade C)

Recommendation 66:

Patients with extensive distant disease

A palliative neck procedure may still be needed (pain, tracheal compression). Otherwise, neck disease may be observed and surgery deferred (Grade C)

Radiation Therapy

- Slight improvements in locoregional disease-free survival in select cases reported
- Consider for:
  - Extraglandular invasion
  - Microscopic residual disease
  - Nodal ECS
  - Inoperable locoregional tumors
  - Symptomatic bone metastases
- Weigh benefits against sequelae

The Role of Radiation Therapy in the Treatment of Medullary Thyroid Cancer

Stephanie A. Terezakis, MD,[a] and Nancy Y. Lee, MD,[b] *Baltimore, Maryland, and New York, New York*

© Journal of the National Comprehensive Cancer Network | Volume 8 Number 5 | May 2010

- Review article
  - Despite aggressive surgery, patients at high risk for local recurrence may benefit from adjuvant EBRT?
  - Although the role of EBRT in the management of these tumors has thus far been poorly defined, EBRT should be considered as a treatment option for patients with locally advanced MTC to optimize locoregional control
- EBRT may impact locoregional control, however the literature has failed to find evidence of improved survival in these patients

Follow-Up

- Calcitonin and CEA 2 to 3 months post-op
- If calcitonin >100, evaluate for residual neck disease +/- distant metastases
- MEN-IIA and MEN-IIB:
  Annual screen for pheochromocytoma and hyperparathyroidism

Persistent Hypercalcitonemia

- Baseline calcitonin
- Serial calcitonin levels
- Calcitonin doubling time
- Symptoms
- Work-up – imaging studies (CT, MRI, PET, Octreotide scanning)
- Treatment – symptomatic relief (surgery, RT, systemic chemotherapy, targeted therapy)

Surgical Management and Outcomes

Management of metastatic disease

- **Complex and unpredictable and a topic in itself!**
- **Surgery/ chemo/ embolization/ EBRT and new investigational drug therapies should all be considered**

Surgical Management and Outcomes

Posted on September 13, 2010

Vandetanib efficacious in medullary thyroid cancer

Samuel A Wells/NCI/ International Thyroid Congress, Paris 2010

- **ZACTIMA Efficacy in Thyroid cancer Assessment by NCI**
- **Vandetanib – a once daily selective inhibitor of RET**
- **Phase 3 study**
- **331 patients with unresectable, locally advanced or metastatic MTC disease were included in the study**
- **Promising results with a statistical significant advantage in progression-free survival is seen with Vandetanib vs placebo**
- **PFS of 19 months in placebo, not reached a time of presentation (24months) in the Vandetanib arm**

Outcomes

- Outcomes variable
- Overall survival 70% 5-year
  55% 10-year
- Children with detected MEN-IIA and FMTC
  - Most cured after thyroidectomy
- Palpable tumor at presentation
  - 50% have persistent disease post-op
- Some patients have indolent disease despite distant metastases

Prognostic Factors

Clinical, pathologic, and biochemical/molecular factors:

- Stage
- Type: Sporadic, MEN-IIB, MEN-IIA, FMTC
- RET codon mutations 768,790,791,804
- ECS; bilateral nodes
- Older age; male gender
- Elevated CEA, calcitonin (>10,000 pg/ml)

Summary

- MTC - uncommon thyroid malignancy
- Neuroendocrine C-cell tumor, secretes calcitonin, allows for diagnosis and f/u
- Various forms, sporadic and hereditary, with spectrum of clinical behavior
- RET gene mutations identify at-risk patients
- Surgery is the only effective treatment
- Better adjuvant therapy is needed

Medullary Thyroid Cancer: Management Guidelines of the American Thyroid Association

The American Thyroid Association Guidelines Task Force*

Richard T. Kloos (Chair),[1] Charis Eng,[2] Douglas B. Evans,[3] Gary L. Francis,[4] Robert F. Gagel,[5] Hossein Gharib,[6] Jeffrey F. Moley,[7] Furio Pacini,[8] Matthew D. Ringel,[9] Martin Schlumberger,[10] and Samuel A. Wells Jr[11]

Background: Inherited and sporadic medullary thyroid cancer (MTC) is an uncommon and challenging malignancy. The American Thyroid association (ATA) chose to create specific MTC Clinical Guidelines that would bring together and update the diverse MTC literature and combine it with evidence-based medicine and the knowledge and experience of a panel of expert clinicians.

Methods: Relevant articles were identified using a systematic PubMed search and supplemented with additional published materials. Evidence-based recommendations were created and then categorized using criteria adapted from the United States Preventive Services Task Force, Agency for Healthcare Research and Quality.

Results: Clinical topics addressed in this scholarly dialog included: initial diagnosis and therapy of preclinical disease (including *RET* oncogene testing and the timing of prophylactic thyroidectomy), initial diagnosis and therapy of clinically apparent disease (including preoperative testing and imaging, extent of surgery, and handling of devascularized parathyroid glands), initial evaluation and treatment of postoperative patients (including the role of completion thyroidectomy), management of persistent or recurrent MTC (including the role of tumor marker doubling times, and treatment of patients with distant metastases and hormonally active metastases), long-term follow-up and management (including the frequency of follow-up and imaging), and directions for future research.

Conclusions: One hundred twenty-two evidence-based recommendations were created to assist in the clinical care of MTC patients and to share what we believe is current, rational, and optimal medical practice.

Thyroid 2009; 19(6):565-612.

MTC History - Timeline

- **1906: First described in the German literature by Jaquet.**
- **1959: Hazard et al provided the first definite histological description**
- **1961: Sipple published the first case report on the association of thyroid cancer with pheochromocytoma**
- **1966: Williams et al suggested its C cell origin**
- **1985: RET oncogene was first identified**
- **1987-94: Mutations responsible for distinctive (MEN) syndromes identified**
- **2001: RET oncogene classification system put in place based on genotype-phenotype correlations**

Notes

Management of Central Compartment Recurrence

Jeremy Freeman

Recurrent or persistent well-differentiated thyroid cancer poses a dilemma for the endocrine surgeon in terms of diagnosis and treatment. Many times there is difficulty in detection and localization. Once this is determined, there is then difficulty in deciding on the optimal treatment for that patient.

The anatomy and patterns of spread of well-differentiated thyroid cancer will be examined.

Incidence and surveillance strategies will be discussed.

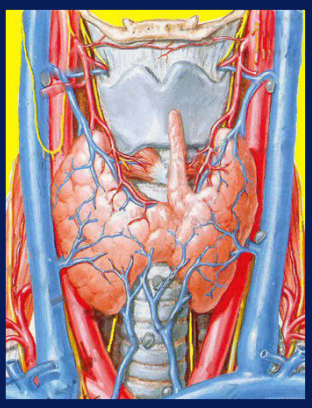
Once localization is ascertained then the algorithm for treatment will be reviewed. The options of alcohol ablation, surgery and observation will be discussed.

The operation of central compartment dissection in the face of previous surgery will be described.

Finally the results of treatment of the presenter's experience will be reported.

Notes

Management of Central Compartment Recurrence



Current Concepts in Head and Neck Surgery

November 5-6, 2011

Mt Sinai Hospital/University of Toronto

Jeremy L. Freeman, MD, FRCSC, FACS

Professor of Otolaryngology—head and neck surgery
Professor of Surgery, University of Toronto
Temmy Latner/Dynacare Chair in Head and Neck Oncology
Otolaryngologist-in-Chief, Mount Sinai Hospital

Mt Sinai Hospital/University of Toronto

No disclosures

Mt Sinai Hospital/University of Toronto

Indication for Re-operation for Thyroid Cancer

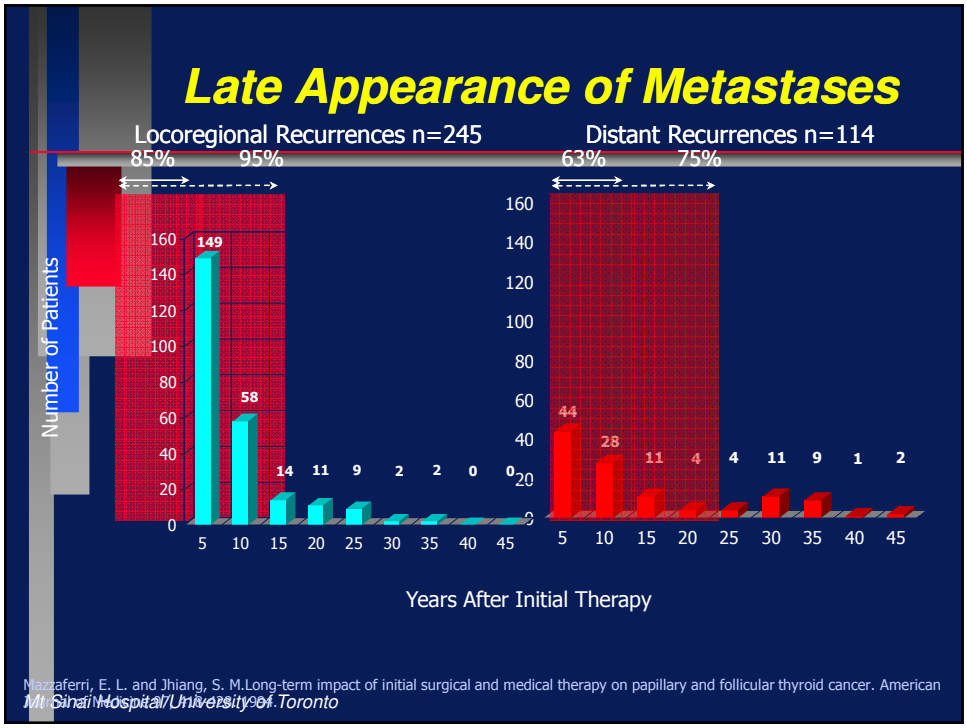
1. Previous subtotal thyroidectomy for high risk malignancy
2. Central Compartment Recurrence (including upper mediastinum)
3. Lateral Neck Recurrence
4. Visceral Recurrence
5. Medullary Carcinoma Recurrence

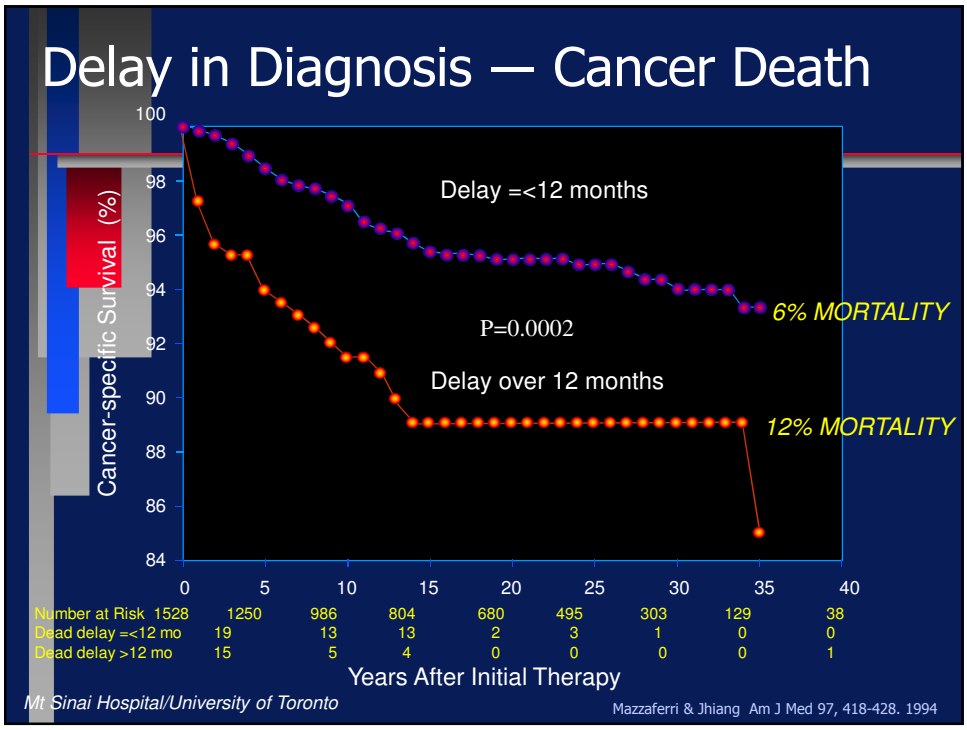
Tumor Status After Initial Therapy

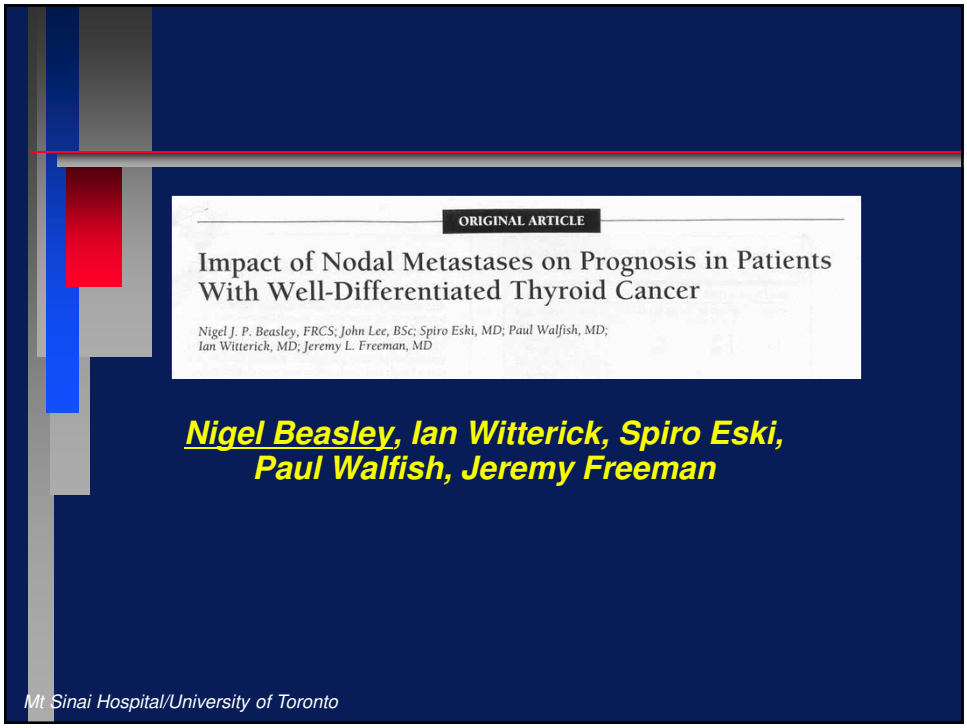
Patients are free of disease after therapy when all of the following criteria are fulfilled:

- Complete resection of identifiable tumor
- No uptake outside thyroid bed on RxWBS
- Negative neck ultrasound exam
- Undetectable Tg (<1 ng/mL) during both
  - Thyroid hormone suppression of TSH
  - TSH stimulation (THW or rhTSH)

DELAYED IDENTIFICATION OF TUMOR
The Consequences


Late Appearance of Metastases
Locoregional Recurrences n=245
85%
95%
Distant Recurrences n=114
63%
75%
Number of Patients
149
58
14
11
9
2
2
0
0
44
28
11
4
4
11
9
1
2
Years After Initial Therapy
Mazzaferri, E. L. and Jhiang, S. M.Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. American
Mt Sinai Hospital/University of Toronto


Delay in Diagnosis — Cancer Death
Cancer-specific Survival (%)
Delay =<12 months
6% MORTALITY
P=0.0002
Delay over 12 months
12% MORTALITY
Number at Risk 1528 1250 986 804 680 495 303 129 38
Dead delay =<12 mo 19 13 13 2 3 1 0 0
Dead delay >12 mo 15 5 4 0 0 0 0 1
Years After Initial Therapy
Mt Sinai Hospital/University of Toronto
Mazzaferri & Jhiang Am J Med 97, 418-428. 1994



Neck node metastases

- *Shah (1992)*
  - *931 patients, most had thyroid lobectomy, no I^{131}*
  - *nodal stage not significant for recurrence or survival*
- *McConahey (1986)*
  - *859 patients, most had total thyroidectomy, no I^{131}*
  - *nodal stage not significant for recurrence or survival*
- *Mazzaferri (1994)*
  - *1355 patients, most had total thyroidectomy and I^{131}*
  - *nodal stage predicts recurrence and survival*

Thyroid cancer database

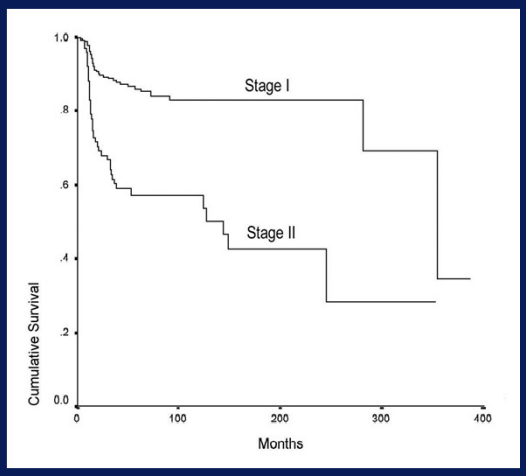
- 522 consecutive patients with well differentiated thyroid carcinoma (1964 -1999)
- All treated at Mount Sinai hospital by one endocrinologist and three surgeons
- Median follow up 68 months (0-413)
- 29 deaths; 10 from well differentiated thyroid carcinoma
- 347 Stage I - intrathyroidal disease
- 118 Stage II - intrathyroidal disease with neck nodes metastases

Location of nodal metastases

- 44 central compartment - paratracheal, anterior laryngeal
- 7 superior mediastinum
- 28 lateral neck - level IV (also II, III, V)
- 22 multiple
- (16 unknown)

Disease free survival

- Stage I vs Stage II
- Kaplan Meier method
- Median FU 49 months (1-354)
- p=0.0001 - logrank test (univariate)
- p=0.0001 - Cox's regression (multivariate) relative hazard 4.0



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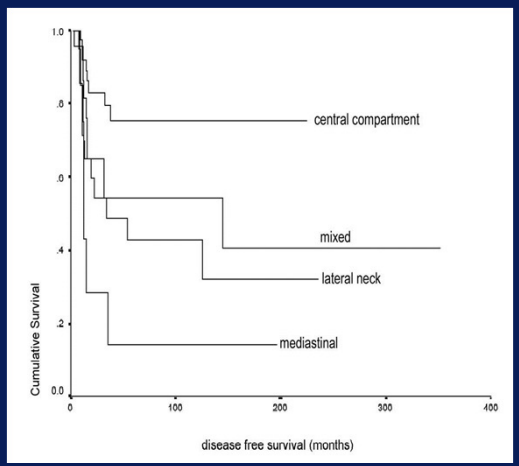
Disease free survival

- location of nodes
- Kaplan Meier method
- p=0.0032 - logrank test (univariate)



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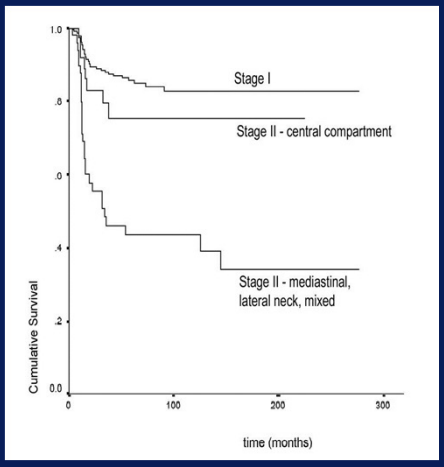
Disease free survival

- Stage I vs Stage II (central compartment vs mediastinal, lateral neck and mixed)
- Kaplan Meier method
- p=0.0001 - logrank test (univariate)



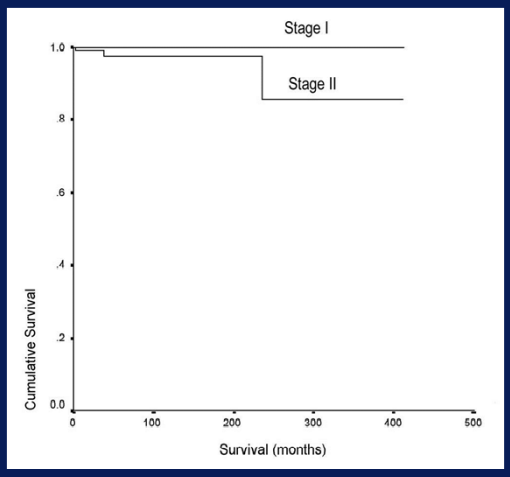
Recurrences

N = 110 (21.1%)

Local only	=	14
Regional	=	54
Distant	=	8
Loc + Reg	=	5
Reg + Dist	=	2
Loc + Dist	=	1
Site(s) Unknown	=	26

Overall Survival

- *Stage I vs Stage II*
- *Kaplan Meier method*
- *Median FU 69 months (0-413)*
- *p=0.0052 - logrank test (univariate)*
- *p=0.731 - Cox's regression (multivariate)*



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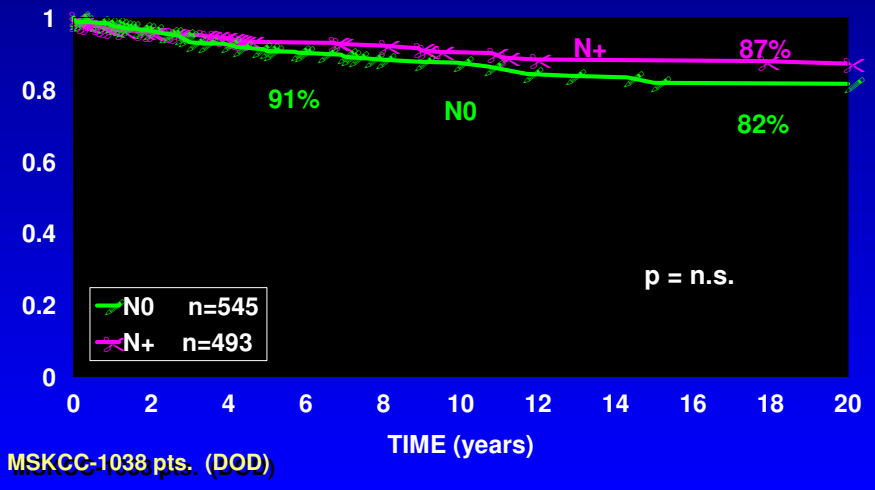
Differentiated Thyroid Cancer 1930-1985

SURVIVAL: Nodal Status



MSKCC-1038 pts. (DOD)

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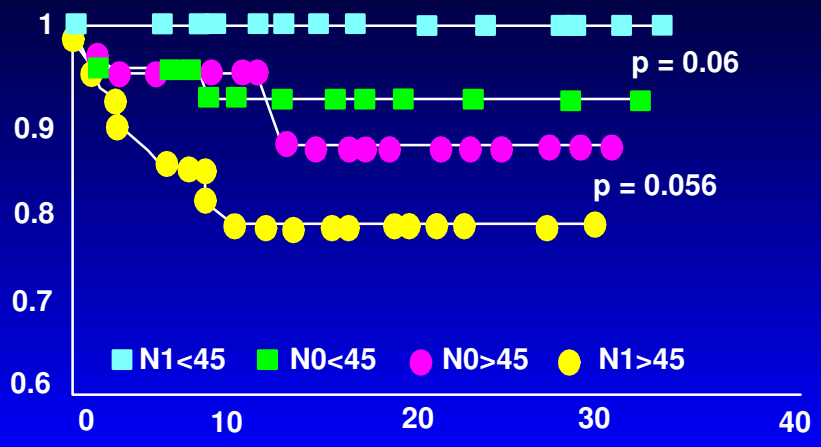
Differentiated Thyroid Cancer

Survival: Age & Nodal Status



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Management and Outcome of Recurrent Well-Differentiated Thyroid Carcinoma

Carsten E. Palme, MBBS, FRACS; Zeeshan Waseem, BA; S. Naweed Raza, BSc; Spiro Eski, MD; Paul Walfish, MD, FRCPC; Jeremy L. Freeman, MD, FRCSC

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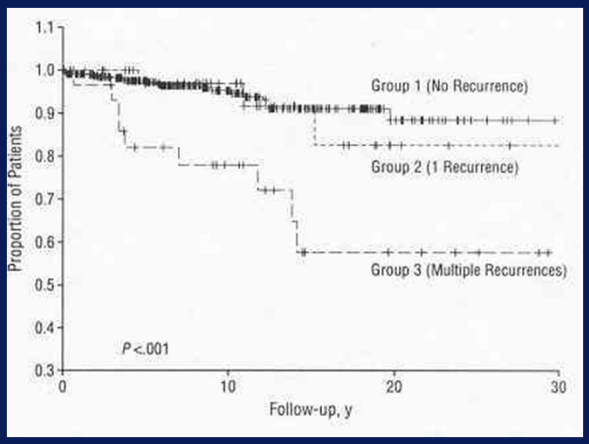

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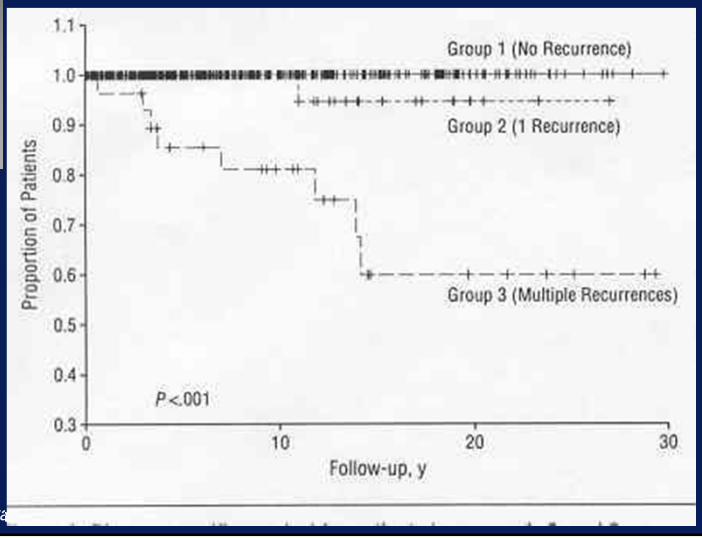


The Journal of Otolaryngology, Volume 34, Number 1, 2005

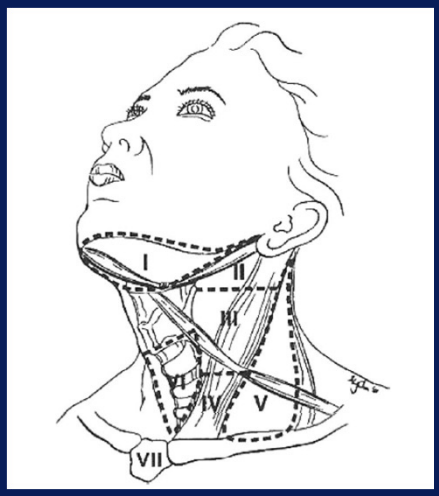
Surgical Strategy for Thyroid Bed Recurrence in Patients with Well-Differentiated Thyroid Carcinoma

Carsten E. Palme, MB BS, FRACS, and
Jeremy L. Freeman, MD, FRCSC, FACS

Carsten E Palme MB BS FRACS
Jeremy L Freeman MD FRCSC FACS

Mt Sinai Hospital/University of Toronto

Neck Levels



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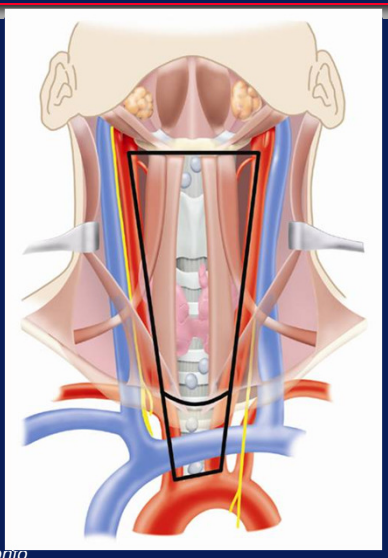
The Central Compartment



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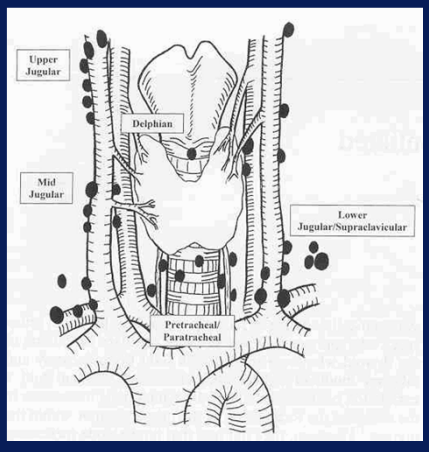
Pattern of Spread



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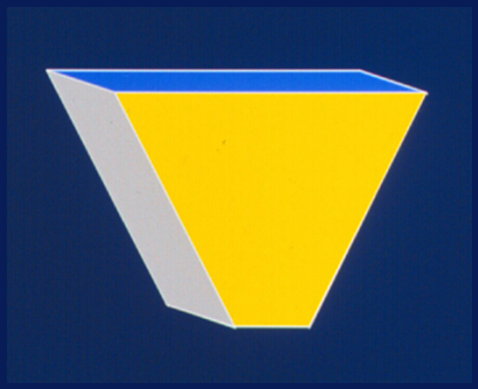
Upper Mediastinum



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Central Compartment Recurrence (including upper mediastinum)

- Detection=Clinically, Radiographically, Biochemically (Tg, stimulated or non-stimulated) +/- Cytopathology

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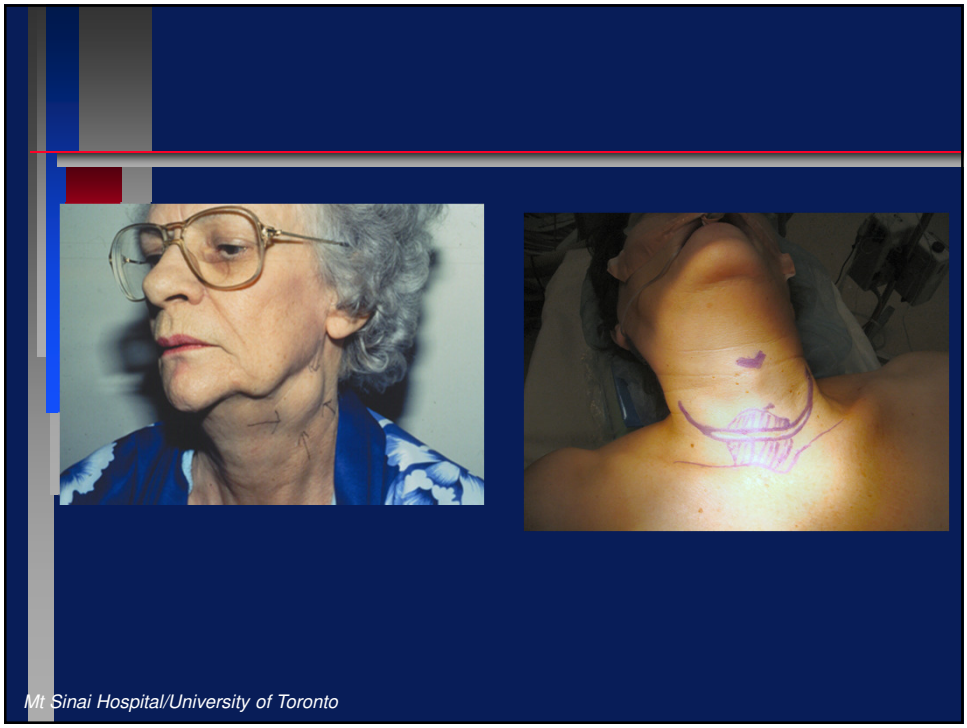
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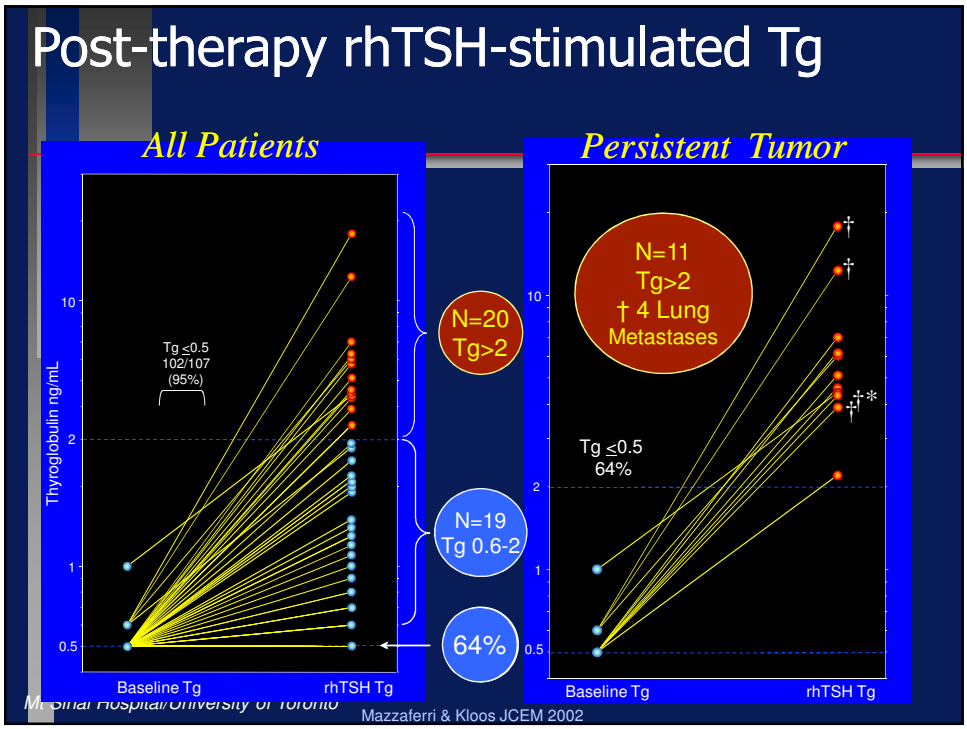
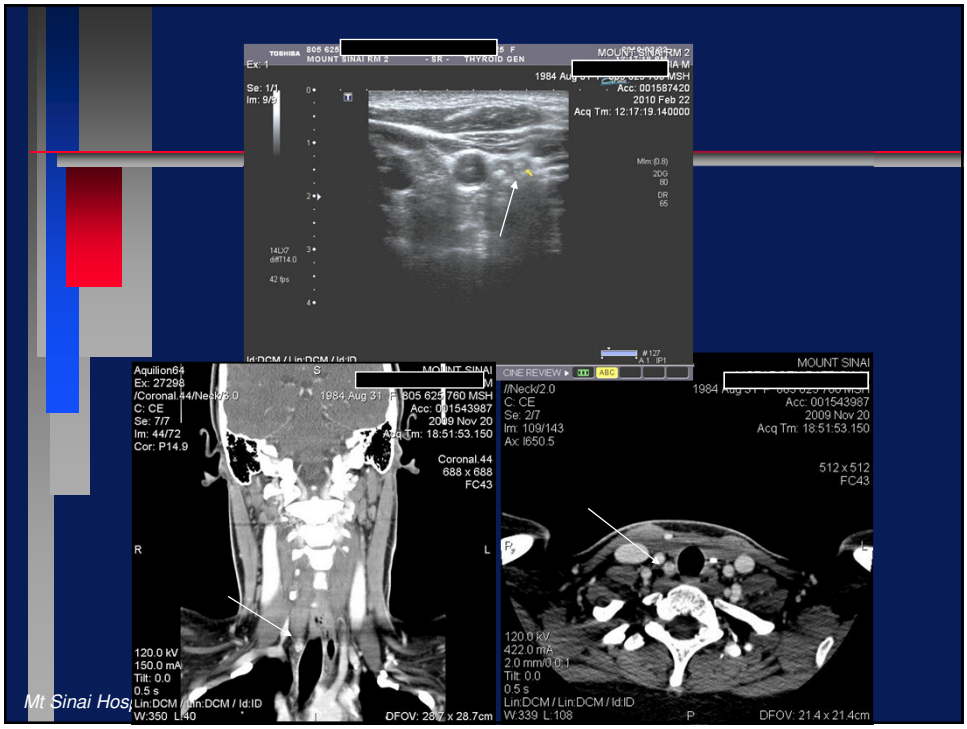
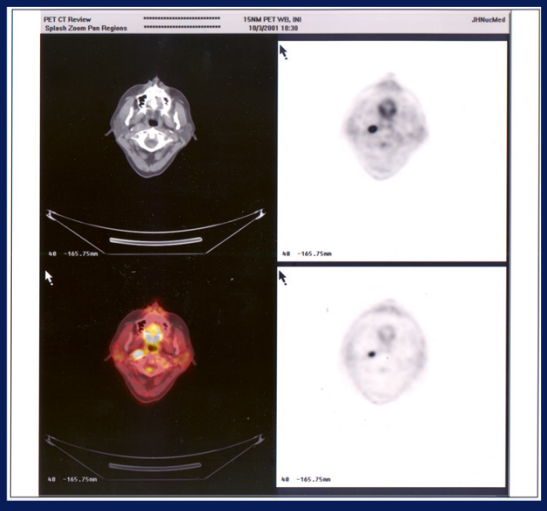

Post-therapy rhTSH-stimulated Tg
All Patients
Persistent Tumor
Thyroglobulin ng/mL
10
2
1
0.5
Tg ≤0.5
102/107
(95%)
Baseline Tg
rhTSH Tg
N=20
Tg>2
N=19
Tg 0.6-2
64%
N=11
Tg>2
† 4 Lung
Metastases
Tg ≤0.5
64%
Mt Sinai Hospital/University of Toronto
Mazzaferri & Kloos JCEM 2002



Mt Sinai Hos

PET-CT



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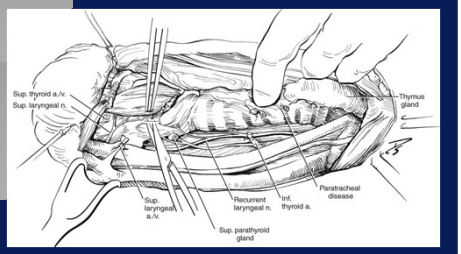
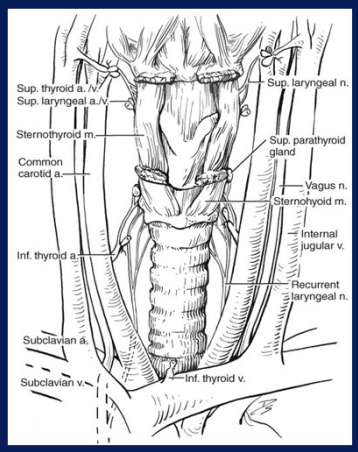
Management of the Small Neck Recurrence

- Reoperation on the central or lateral compartment
- Alcohol ablation
- Observation (World Congress on Thyroid Cancer)

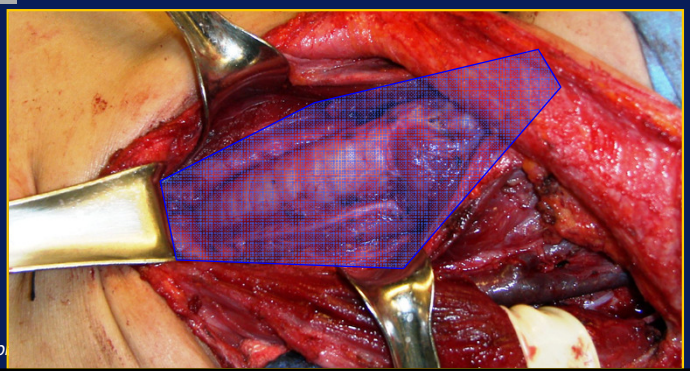
Central Compartment Re-operation





Neck Dissections

- Lateral Neck Dissection
- Central compartment dissection



Mt Sinai Hosp

The Question of Prophylactic Central Compartment Dissection

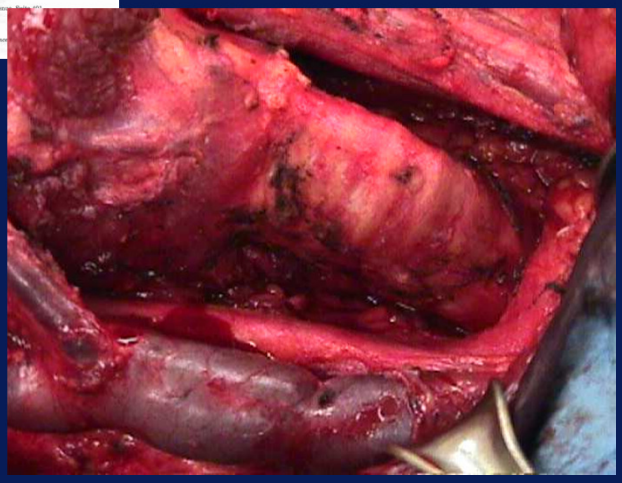
Why, When, and How Much?

Mt Sinai Hospital/University of Toronto

Upper Mediastinal Dissection

TRANSCERVICAL SUPERIOR MEDIASTINAL LYMPHADENECTOMY IN THE MANAGEMENT OF PAPILLARY THYROID CARCINOMA

Mark L. C. Khoo, FRCS, Jeremy L. Freeman, MD



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Upper Mediastinal Dissection

TRANSCERVICAL SUPERIOR MEDIASTINAL LYMPHADENECTOMY IN THE MANAGEMENT OF PAPILLARY THYROID CARCINOMA

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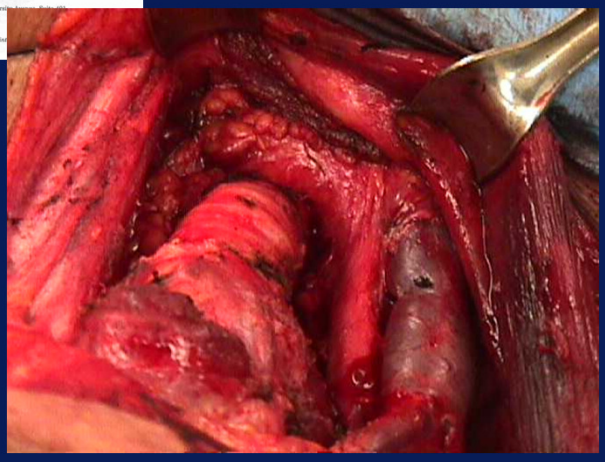

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MOUNT SINAI HOSPITAL

Efficacy and Safety of Central Compartment Neck Dissection for Recurrent Well-Differentiated Thyroid Carcinoma

Manish D. Shah, Luke D. Harris, Ramez Nassif, Dae Kim, Spiro Eski, Jeremy L. Freeman

Archives of Otolaryngology—head and neck surgery
In Press

Most Recent Results

- 154 patients operated by one surgeon (JLF)
- Vocal Cord Injury=<1.9%
- Permanent hypopara=6%
- Normalization of Tg=67%

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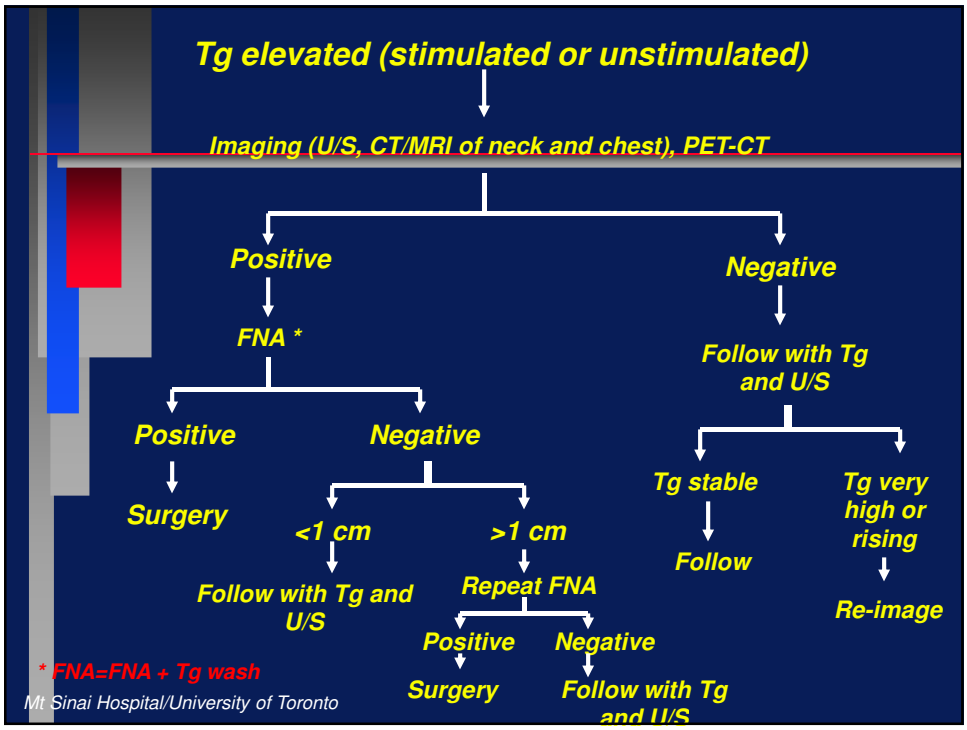
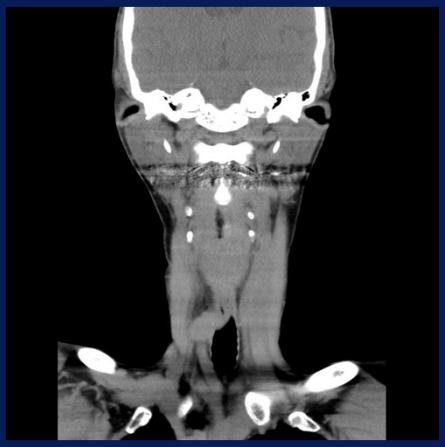


Is surgery necessary? When to operate and when not?



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Thyroid surgery—degree of difficulty

- Thyroid lobectomy
- Total thyroidectomy
- Completion thyroidectomy
- Revision central compartment dissection
- Revision central compartment dissection with visceral extirpation

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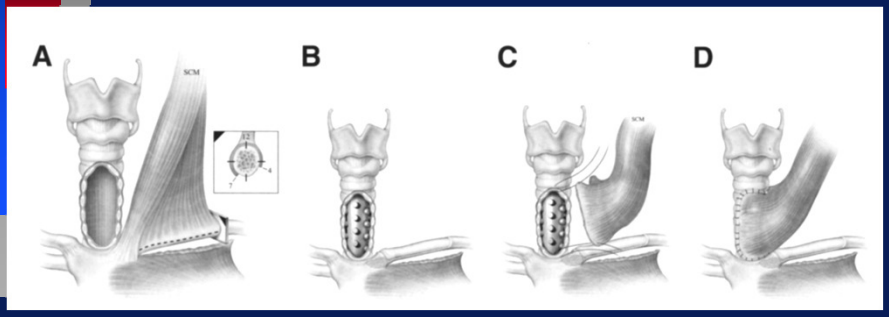
Recurrence Involving Viscera

- Primary management should be organ preservation surgery + RAI + External XRT
- It there is no hope of useful organ function, then surgical organ extirpation + RAI + External XRT

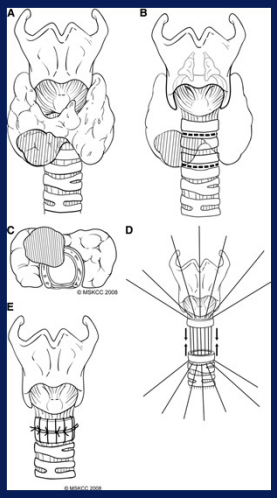
Management of Airway Invasion



Pipefitting

Mt Sinai Hospital/University of Toronto

Management of Airway Invasion



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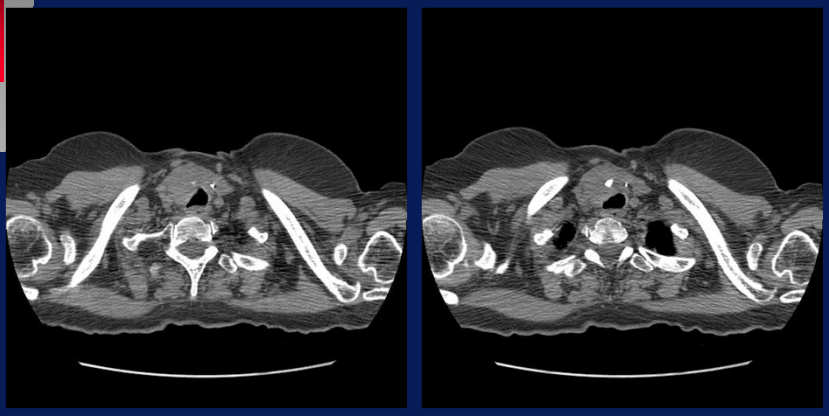
MV



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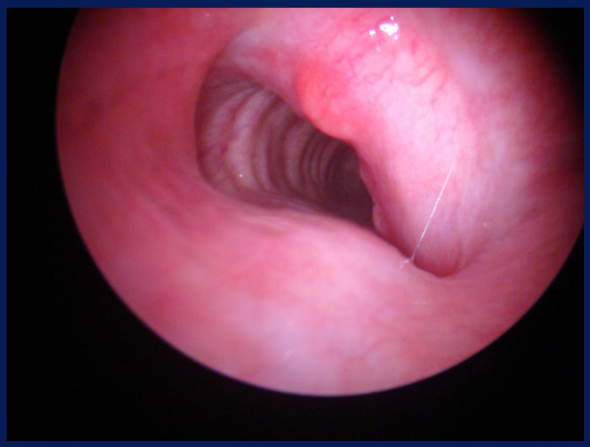

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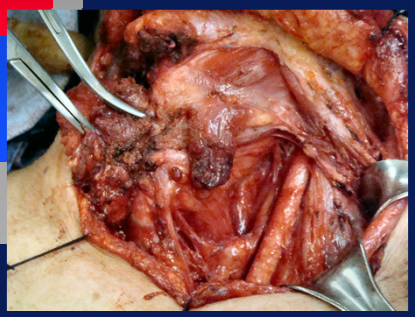

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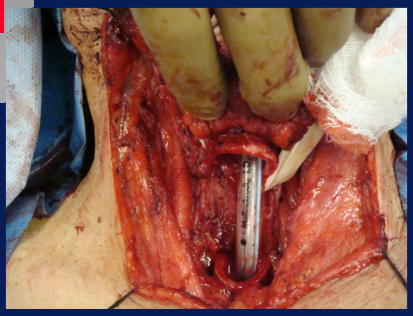

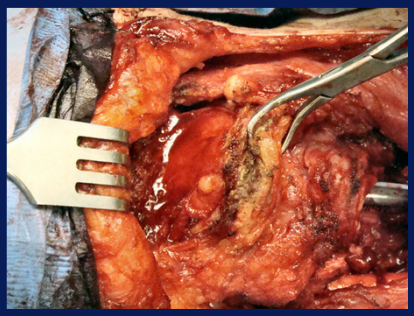

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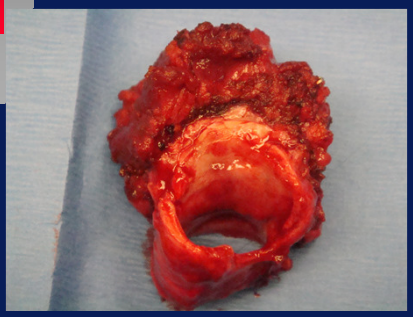

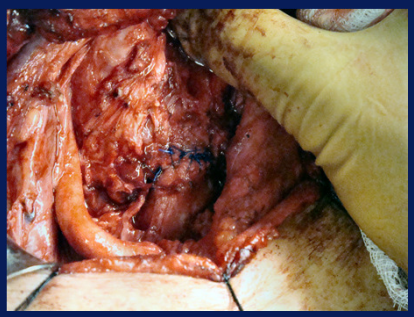

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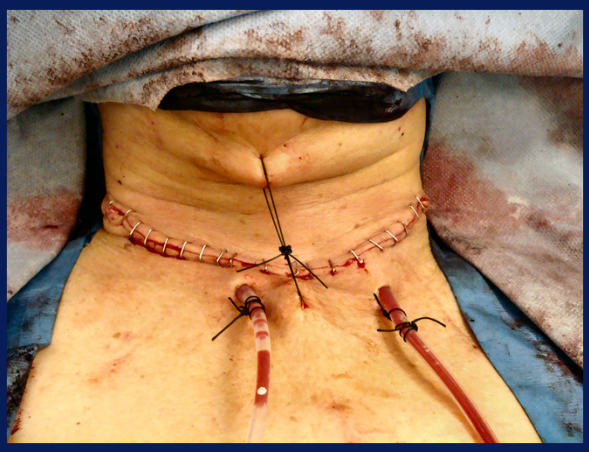

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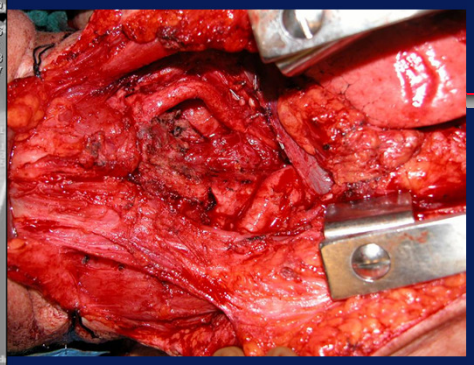

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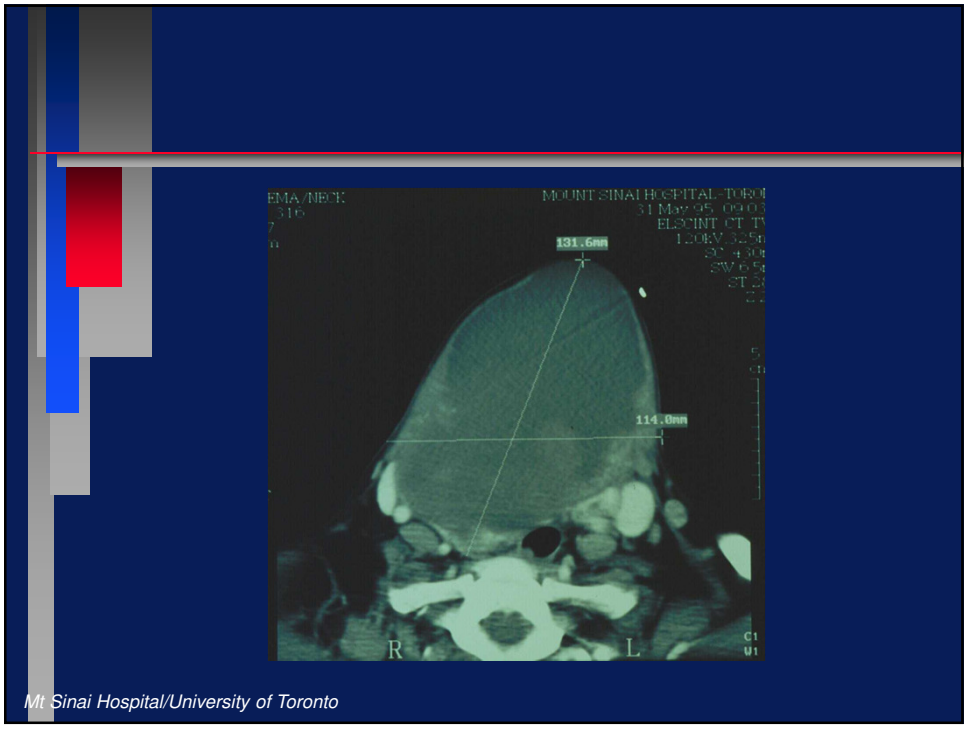

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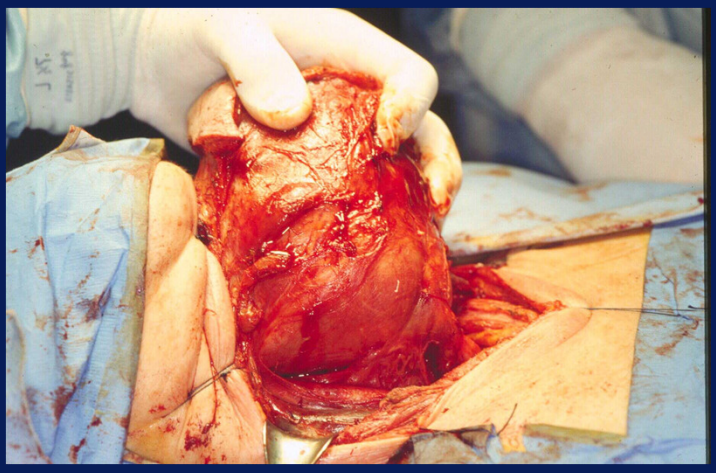

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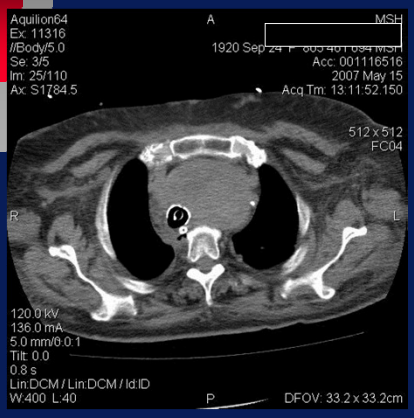

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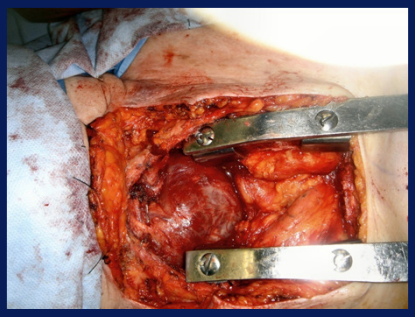

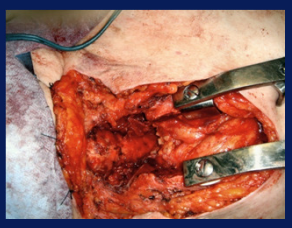

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Recurrence Involving Viscera

- Primary management should be organ preservation surgery + RAI + External XRT
- It there is no hope of useful organ function, then surgical organ extirpation + RAI + External XRT

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Conclusions

- We are seeing increasingly more recurrences from WDTC
- The detection of recurrence involves clinical evaluation/imaging/biochemistry
- Treatment is controversial and can involve observation, surgery or alcohol ablation
- Surgery is well established but there is a learning curve

Notes

Adjuvant Therapy of Differentiated Thyroid Carcinoma

J Brierley

Princess Margaret Hospital

Disclosure Information

I have no financial relationships to disclose.

Princess Margaret Hospital

- 1. Understand when radioactive iodine is used to **treat** differentiated thyroid cancer
- 2. Understand when external beam radiotherapy is used to treat differentiate thyroid cancer

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Theoretical benefits of thyroid ablation

- RAI for Ablation – for follow up
- RAI as adjuvant therapy
- RAI as treatment for metastatic disease

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Mazzaferri

1355 patients	USAF and Ohio
1956 -1993	15.7 years follow up
Tumours ≥ 1.5cm	Stage 2 and 3

	^{131}Iodine	No ^{131}Iodine
Recurrence	16%	38% (p=0.001)
Cancer Death	3%	9% (p=0.03)

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Mazzaferri and Jhiang. Am J Med. 97: 1994

Mazzaferri

- Note included all patients with tumors > 1.5cm and no metastases
- Includes ETE and Nodal Involvement

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Mazzaferri and Jhiang. Am J Med. 97: 1994

Low risk thyroid cancer -Mayo

- 2286 patients
- 1950- 1999 median 15 years
- MACIS < 6
  - age = 60 years, tumor size = 4 cm = MACIS 6
- 10-yr CSS 100%
- Outcome the same if RAI given or not
- No need for RAI in low risk patients

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Hay et al.World J Surg. 2002

MSK - Survival

	Survival	
• Low Risk	98%	Lobectomy
• Intermediate Risk	87%	
– Low risk over 45 (no ETE,<4cm -Nodes)		
– High risk under 45 (ETE, <cm, -/+Nodes)		
• High Risk	57%	Total + RAI

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Shaha Larygoscope 2004 114(3))

Treatment
Multivariate Analysis

- LRFR
  - RAI p = 0.01 HR 0.6 (0.4- 0.9)
  - Surgery p = 0.52 HR 1.1 (0.8- 1.7)
  - RT p = 0.14 HR 1.4 (0.9- 2.1)
- 10 yr LRFR
  - RAI 86% No RAI 79%
  - Lobectomy 87% Total/N 86%
  - RT 79% No RT 88%
  - Nodes not significant

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Nodes

- In young patients nodes may not be a significant factor
  - Mayo
  - MSK
- SEER 1988 – 2003
  - 30504 papillary thyroid
  - < 45 no effect on survival p=0.535

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Zaydfudin Surgery 2008

Nodes

- 4297 N0 Patients with papillary cancer
- 125 N1a
- 621 N1b

- If N1b <5 nodes, 3cm and no ECE, survival and DFS the same as N1a

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Ito Endocrine Journal 2009, 56

Recurrence, Distant Recurrence, & Death in 1528 patients from time of Initial Treatment

Age cut of higher than 45

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Mazzaferri and Kloos. J C E & M; 86: 2001

RAI in Good Prognosis Patients

- 228 patients
  - < 60 yrs
  - < 4cm
  - No extrathyroid extension
    - 10 yrs CSS
      - RAI 96% No RAI 99% p = 0.16
    - 10 yrs LRFS
      - RAI 88% No RAI 90% p= 0.14

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RAI in patients > 60 yrs, or > 4cm, or Extrathyroid Extension

- 378 had RAI
- 123 did not
- RAI resulted in improved LRFR at 10 yrs
- 85% v 75% (p=0.01)

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National Thyroid Cancer Treatment Cooperative Study Group (NTCTCSG)

- Multi-institutional registry
- 13 institutions in United States and Canada
- 4,047 thyroid cancer patients enrolled since 1987
- Patients receive usual care at each institution--no specific protocols or management strategies

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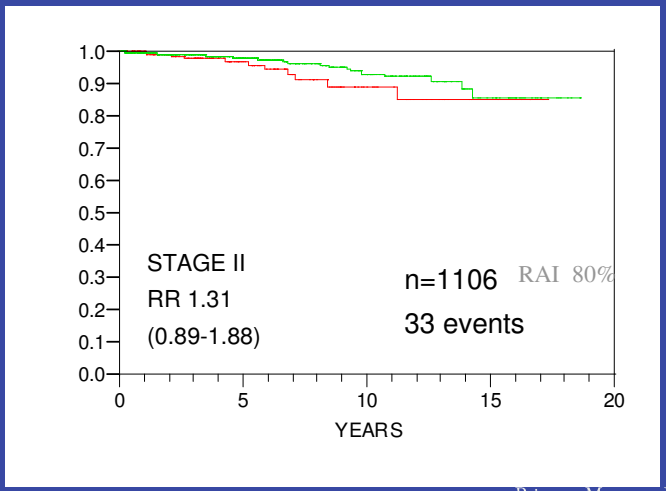
OS RAI_____ in Stage II



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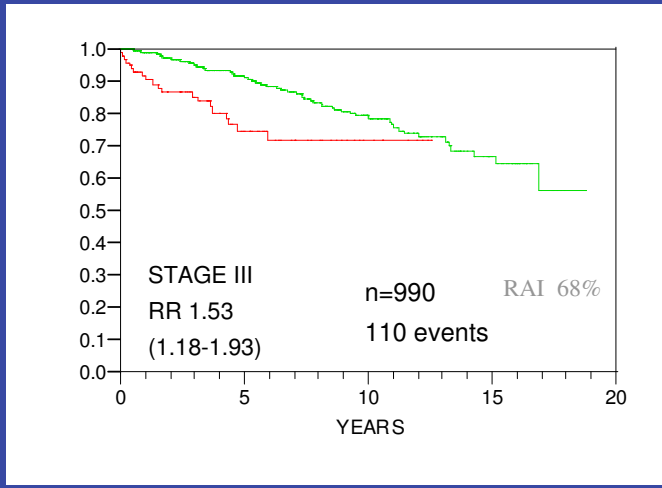
OS RAI_____ in Stage III patients

> 45, neck nodes, ETE or > 45



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Complications of ^{131}Iodine – Late all dose related?

- 15% dry mouth > 3 yrs after treatment
- 3% tear duct problems > 3 yrs after treatment
- Early menopause
- No effect female pregnancies
- Temporary oligospermia in men
- 1% risk second malignancy
- 0.4% risk leukeamia

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Conclusions

- Avoid ^{131}Iodine if unnessesary
- Reserve for increase risk of recurrence
- Older patients
- T3/4
- Lateral Nodes

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External Beam Radiotherapy

If surgery and radioactive iodine are standard therapy in differentiated thyroid cancer, is there a role for additional treatment with XRT

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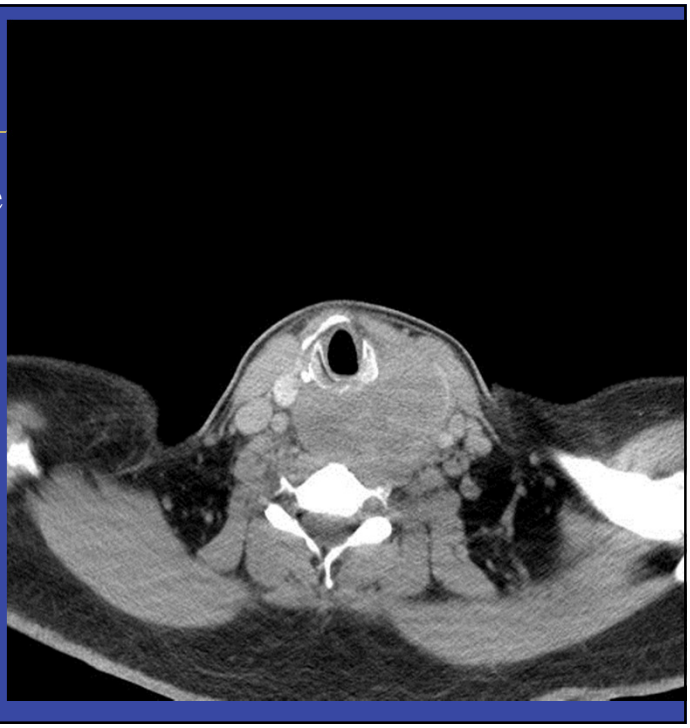
- Unresectable disease



Unresected Thyroid Cancer

- 124 gross residual disease 5 year survival
  No RT 38%
- With RT 67% (p = 0.001)

- 28 patients with gross residual disease after surgery following external beam radiotherapy
  - LRFR 10 yrs 90%
  - CSS 48%

Chow et al. Int J Radiat Oncol ; 52: 2002
Sia et al J Thyroid Res, 2010

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Differentiated Thyroid Cancer

- To identify patients who may benefit from RT
- Know the extent of disease before surgery to help plan RT
- Clinical evidence of T4 disease
  - fixed
  - painful
  - hoarse
  - large size
- CT Scan with contrast

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CT Scan

- Why CT Scan
  - Contrast allows for better identification of nodes v. vascular structures
  - Invasion of cartilage
  - Calcification
  - Does not prevent the giving of RAI!
  - *When radiologic imaging using iodine-containing contrast media has been used, any subsequent radioiodine scintigraphy or treatment must be delayed for 2–3 months. (European consensus)*

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Effect of extent of disease

- Local Invasion/T4
  - papillary 8%
- Local Recurrence
  - invasion/T4 38%
  - no invasion 25% p=0.001
- Cancer deaths
  - invasion/T4 20%
  - no invasion 9% p=0.001

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Mazzaferri and Jhiang Am J Med; 97:1994

External Radiation In Differentiated Thyroid Cancer

MDA

- 65 recurrences
- All had surgery and iodine
- Iodine uptake high in nodal recurrences
- Patients with local invasion less likely to take up iodine and to die

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Vassilopoulou-Selin et al. Cancer; 78: 1996

External Radiation In Differentiated Thyroid Cancer

- Farahati et al
  - 137 patients > 40 yrs
  - All T4
  - All had surgery and ^{131}I
  - 85 had XRT
  - XRT predictive factor for freedom from relapse (p=0.0001)

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Farahati et al. Cancer; 77: 1996

External Radiation in high risk patients

- 1958- 1984
  - 154 pts
  - Papillary thyroid cancer
  - Microscopic residual disease
  - Small but significant benefit from RT
    - 10yr CSS
      - RT 99% No RT 94% p = 0.04
    - 10yr LRFR
      - RT 93% No RT 83% p = 0.01

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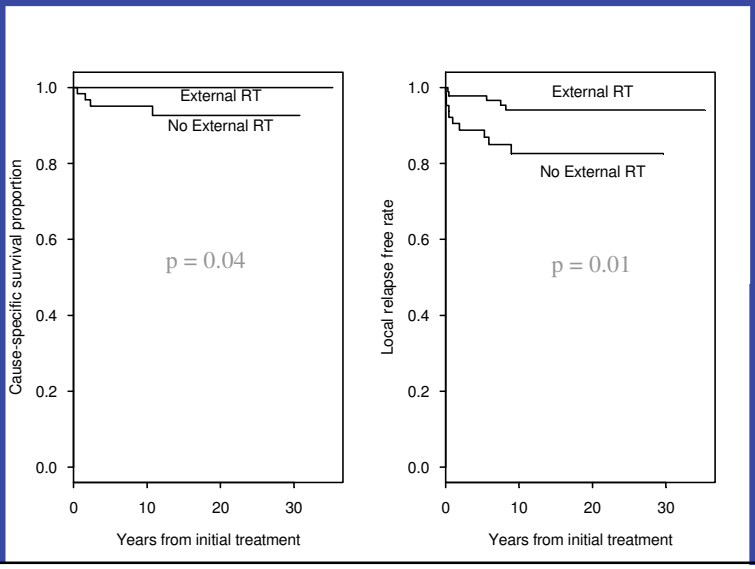
Brierley et al Clinical Endocrinology 63, 418; 2005

Effect of External Radiation in Patients with microscopic residual disease



External Radiation in high risk patients

- 1958- 1998
  - 70 pts
  - > 60 yrs
  - Extrathyroid extension
  - No gross residual disease
    - 10yr CSS
      - RT 78% No RT 59% p = 0.04
    - 10yr LRFR
      - RT 84% No RT 57% p = 0.01

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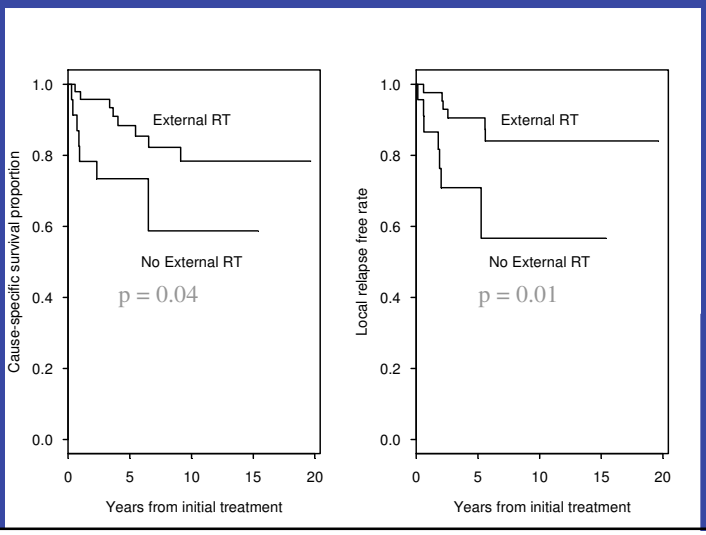
Brierley et al Clinical Endocrinology 63, 418; 2005

Effect of External Radiation in Patients over 60 with extrathyroid extension and no gross residual disease



AJCC/UICC TNM 6th Edition, 2002

- T1 ≤ 2cm in size
- T2 > 2cm ≤ 4cm
- T3 > 4cm or any tumour with minimal extrathyroid extension to sternothyroid or perithyroid tissue.
- T4a invades subcutaneous soft tissue, larynx, trachea, oesophagus, recurrent laryngeal nerve.
- T4b invades prevertebral fascia, mediastinal vessels or encases carotid.

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Current indications for RT

- Most common volume/dose:
  - thyroid bed and adjacent level III, IV, V, VI, nodal regions
  - More extensive nodes coverage only if extranodal or known nodal disease that dose not take up iodine
- Toxicity
  - Well tolerated with careful planning
  - < 10% require iv fluids
  - No grade IV toxicity (Tsang & Farahati)

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Newer Radiation Techniques

- Intensity modulated radiation therapy (IMRT)
  - Allow for more accurate delivery of radiation and sparing normal tissue
  - But can not spare larynx, tracheal or oesophagus

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Recommendations of American Thyroid Association

- RT should be considered in patients over the age of 45 with grossly visible extrathyroid extension at the time of surgery and a high likelihood of microscopic residual disease and for patients with gross residual tumor in whom further surgery or RAI would likely be ineffective

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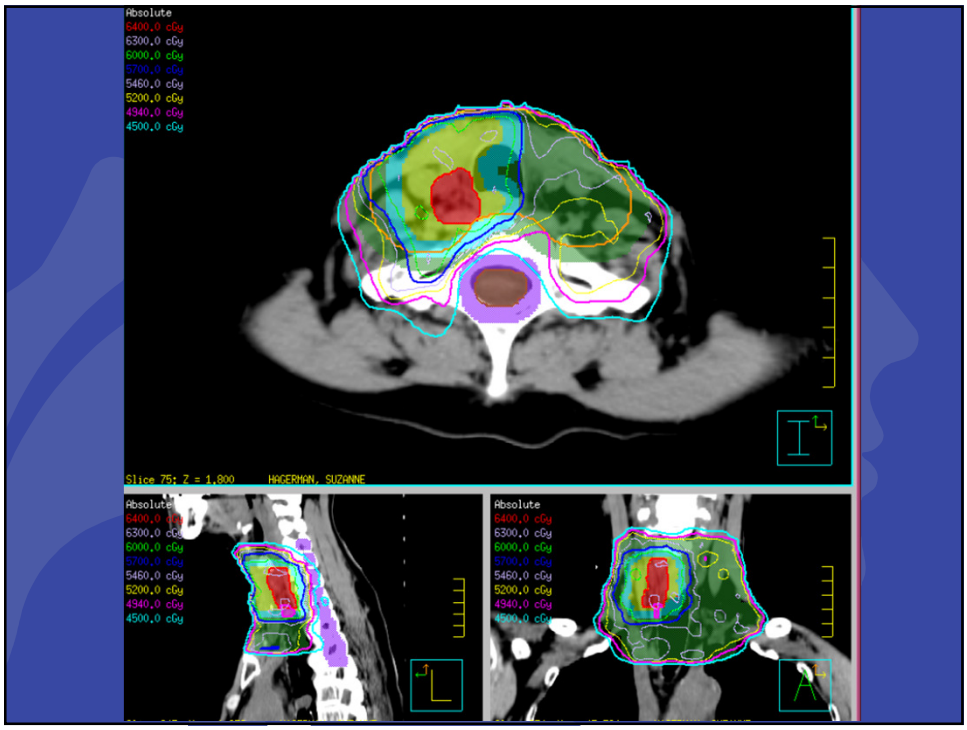
Cooper et al Thyroid 16: 109; 2006


512 x 512
STANDARD
R
L
120.0 kV
261.0 mA
5.0 mm
Tilt: 0.0
ET: 1.7 s/He
GP: 0.8 s
TS: 7.50 mm/s
SPR:
Lin:DCM / Lin:DCM / Id:ID
W:300 L:35
P
DFOV: 21.0 x 21.0cm


Absolute
6400,0 cGy
6300,0 cGy
6000,0 cGy
5700,0 cGy
5460,0 cGy
5200,0 cGy
4940,0 cGy
4500,0 cGy
Slice 75: Z = 1,800
HAGERMAN, SUZANNE

External Radiation Conclusions

- For all histologies external radiation has a role in local control in patients at high risk of recurrence
- CT Scan before surgery to identify extent of disease and aid planning of IMRT

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Conclusions

- Avoid ^{131}Iodine if unnessesary
- External radiation has a role in local control in patients at high risk of recurrence

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Notes

Current Concepts in Head and Neck Surgery 2011

Management of Parathyroid Disease

Lorne Rotstein MD, FRCSC, FACS

Peter A Crossgrove Chair in General Surgery, University Health Network, University of Toronto

Disclosures

None: no commercial interests related to this presentation

Sir Richard Owen FRS 1804-1892 Professor and Curator Hunterian Collection

The Indian Rhinoceros in the London Zoo died Nov 19,1849. The carcass was offered to Professor Owen for dissection.

In his detailed description of the anatomy, published in 1862, Owen refers to 'a small compact yellow glandular body attached to the thyroid at the point where the vein emerged'—a structure we now know as the parathyroid gland.

Ivar Viktor Sandstrom

- Medical student studying anatomy at University of Uppsala 1890, dissecting a dog's neck
- He identified similar structures on human cadavers and coined the term ***"glandulae parathyroidae"***
- His report was not well received and barely noticed

- 'I encountered on the thyroid of a dog a small hardly hemp-seed sized structure which was included in the same capsule as the thyroid but distinguished itself from it by a brighter colour. A superficial examination revealed an organ of a structure entirely different from that of the thyroid and particularly amply vascularised, because of which I considered it probable that here a vascular gland had been encountered, analogous to the carotid glands'.[2,3]

Eugene Gley, 1857-1930 Physiologist, Paris

- The significance of Sandström's discovery remained unappreciated until the experiments of Eugene Gley in the early 20th century
- Gley, a physiologist at the Collége de France, observed that the tetany and death caused by experimental thyroidectomy in dogs occurred only if the excised material included the glands described by Sandström. This was confirmed by several workers during the first decade of the 20th century, who went on to show that the neuromuscular abnormalities that develop in thyroidectomized animals can be prevented by transplantation of these glands.
- Relationship of these glands to Calcium metabolism unknown

Structure and Function

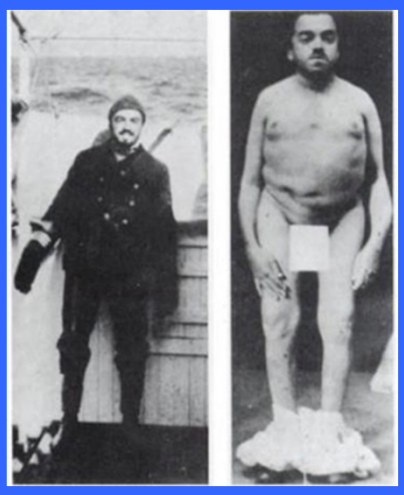
- In 1891 **Friedrich Daniel von Recklinghausen** (1833–1910) reported on a patient who had experienced recurrent fractures of several bones with negligible trauma and had subsequently shown 'bending' of the long bones with extensive fibrosis, cysts and brown tumours. This group of findings was subsequently termed 'osteitis fibrosa cystica of von Recklinghausen'.
- von Recklinghausen did not correlate the bone disease with any parathyroid abnormality.
- Most authorities at this time believed that the enlargement of the parathyroid gland noted in patients with bone disease was a compensatory event.
- In 1915, **Friedrich Schlagenhaufer** (1866–1930), professor of pathology in Vienna, suggested that an enlarged parathyroid might be the cause of bone disease and not the result of it. He presented two patients with osteomalacia each of whom was found to have a single parathyroid tumour at necropsy.[3]

Parathyroid Surgery, 1925

- The surgeon was **Felix Mandl** (1892–1957), Vienna. The patient had severe von Recklinghausen's disease. Mandl had at first thought the patient to be hypoparathyroid and he unsuccessfully transplanted four parathyroid glands from a dead accident victim.
- As a last resort, on 30 July 1925, under local anaesthesia, Mandl removed a 'yellowish-brown almond shaped tumour' measuring 25×15×12 mm from the left inferior area behind the thyroid gland.
- There was immediate improvement. Within a few days the blood and urine calcium content was considerably lower and the patient was soon able to walk.
- He was well for the next six years before developing recurrent hypercalcaemia

History of Parathyroid Surgery, USA

- Edward Churchill 1926, MGH
  - Patient Captain Charles Martell
  - 6 failed neck explorations 26-32
  - Patient pushed for mediastinal exploration with successful removal of adenoma
  - Died from tetany with laryngospasm



History of Parathyroid Surgery, Canada

- James Collip PhD
  Edmonton Alberta
- Successfully separated and purified parathyroid extract and demonstrated efficacy in treating tetany and osteoporosis, 1925
- Nobel Prize 1932

Questions in Parathyroid Disease

- Diagnostic challenges
- Indications for surgery in asymptomatic and symptomatic patients?
- What localization tests?
- What operation?
- Who should be doing this surgery?

Parathyroid
Paradigm Shift (in recognition)

1930s	2011
• Rare	• Common
• Severe disorder of stones, bones, moans	• Mild disorder, mostly asymptomatic
• Diagnosis arcane	• Symptoms of fatigue and joint pain overlap with normal aging process
	• Diagnosis easy

Hyperparathyroidism:
Biochemical Confirmation

- Reproducible elevation of serum Calcium
- Inappropriate elevation in iPTH level
- Urinary Ca greater than 100 mg/24h
  (urinary Ca/Cr clearance ratio > 0.02)

- In the setting of normal renal function

Pitfalls in Diagnosis

- Elevated iPTH normal total Ca
  - Repeat ionized Ca as in mild HPTH, more likely to be elevated
  - Check renal Fn may be secondary disease due to occult renal insufficiency
  - Vitamin D deficiency?
  - Malabsorption?
- "Normocalcemic Hyperparathyroidism" is very rare so don't book the OR

Pitfalls in Diagnosis

- Increased Ca and normal iPTH
  - If in upper range of normal, the patient does have hyperparathyroidism
  - Most will have elevated iPTH if retested under dietary Ca restriction
  - If iPTH is low, look for another cause

Pitfalls in Diagnosis

- Elevated serum Calcium, iPTH and urinary Calcium and
  Non localizing Sestamibi +/- ultrasound
- The diagnosis is a biochemical one, not radiological

Indications for Parathyroidectomy: NIH consensus 2002

- All symptomatic patients
- Asymptomatic patients if:
  - Ca++ 1.0mg/dl above normal
  - Hypercalciuria > 400 mg/day (not in 2008)
  - Creatinine clearance reduced by ≥ 30%
  - Bone mass reduction, T score 2.5 below age, gender and race matched controls
  - Presence of silent kidney stones by radiograph, or nephrocalcinosis
  - Age < 50 years

Asymptomatic Disease may not exist !

- Pasieka and Parsons, WJS, 1998
- Application of prospective questionaire re symptoms pre and post op n=(63), with matched patients having thyroid surgery (n=54) as control
- Questionnaire Items: bone pain, feeling tired, mood swings, feeling blue, feeling weak, feeling irritable, joint pain, being forgetful, headache, itchy skin, difficulty getting out of a chair, thirst

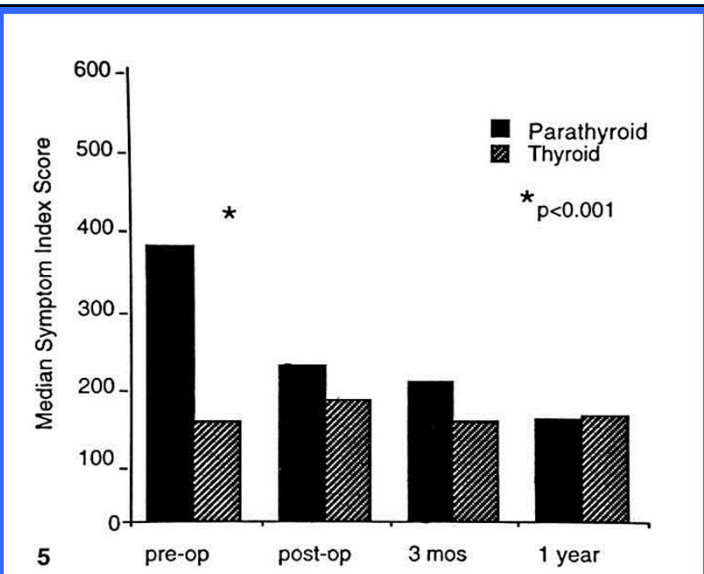


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Fig. 5. Median symptom index scores for the HPT group and thyroid comparison group. The HPT group reported significantly more symptoms than the thyroid group preoperatively. After successful surgical intervention there was no difference in the median symptom scores between the two groups.

Pasieka and Parsons Conclusions

- Most patients with hyperparathyroidism have vague symptoms
- Symptom alleviation occurs with parathyroidectomy
- 60% improvement in 'general health' sustained at one year follow-up

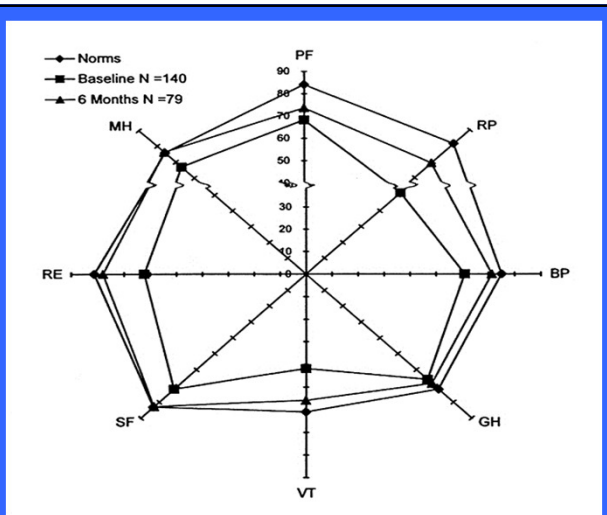


Fig 3. Radar plot showing SF-36 scores for patients with HPT at baseline (n = 140) and at 6 months (n = 79) compared with normal population. Scores for normal population taken from Ware et al.[15]

*Burney RE et al. Surgery 1999;125:930-6

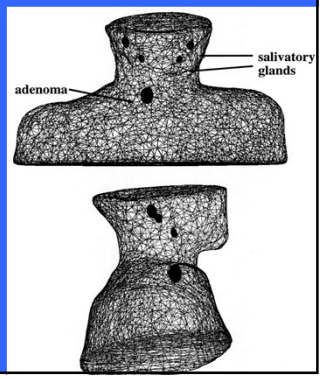
Surgery in Asymptomatic Disease?

- Symptoms are subtle and may not be recognized pre op
- Progression not always predictable
- Established bone disease difficult to reverse
- Minimal Access Parathyroidectomy well tolerated and highly efficacious

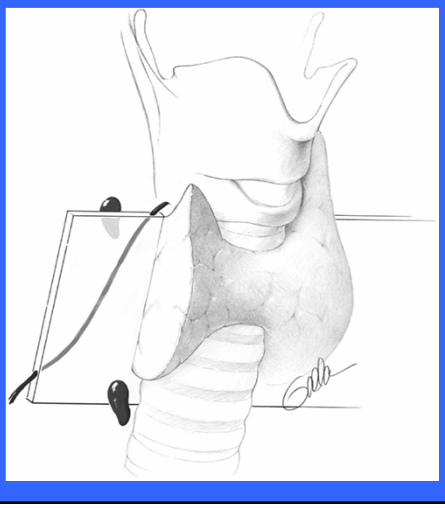
All asymptomatic patients with a clear biochemical diagnosis should be considered for surgical treatment

Localization Studies

- Sestamibi scintigraphy localizes 80-90% of abnormal glands
- Addition of SPECT increases specificity further and adds additional information regarding anatomic location
- US is inherently less specific but useful to rule out co existent thyroid disease
- If Sestamibi and US are concordant, operative success rate approaches 99%
- Other imaging, CT, MRI, PET, venous sampling, only in re operative



Inferior Anterior, Superior Posterior



Minimally Invasive Surgery Trends

- Gallbladder
- Nissen
- Adrenal
- Spleen
- Colon
- Parathyroid

Operative Management

- Focused or limited parathyroidectomy has replaced bilateral neck exploration as the standard approach
- Smaller incision, less pain, decreased OR time and LOS, lower rates of hypocalcemia
- Comparable success to BNE 97-99%

- IAES Survey 2002, 92% of respondents performed focused surgery Sacket et al, 2002

Focused Surgery: Common Features

- Central or Lateral Incision 2-4 cm
- Only the abnormal gland identified and excised
- Intraoperative Parathyroid Hormone Monitoring (IPM) used to confirm lack of additional hypersecreting glands
- Ambulatory or short stay
- Local plus, or “light” GA augmented by local

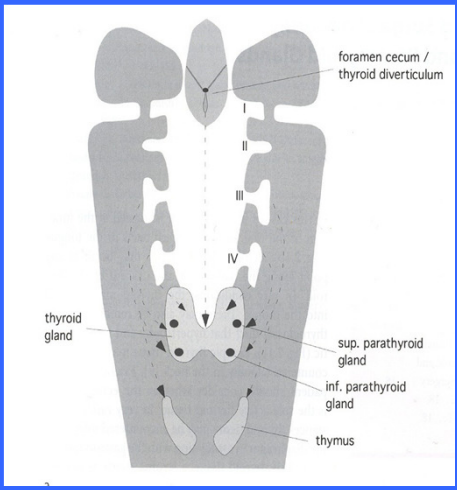
Focused Surgery: Exclusions

- Lack of localization
- More than one gland suspected on localization
- MEN or MEN kindred
- Bulky goiter
- Prior thyroid or parathyroid surgery
- Morbid obesity

Where are the parathyroids and how do I recognize them?

- Maintain a bloodless OR field
- Remember embryology
  - » Lower PTH derived from 3rd branchial cleft
  - » More variable in location, migrates with Thymus
- Inferior gland anterior, superior posterior
- Symmetry is helpful
  - » If IDed on one side, should be in same location on the other
- Parathyroids are “organoid” with characteristic shape, color, texture, surface

Parathyroid Embryology



Parathyroid Characteristics

Structure	Colour	Firm	Shape	Discrete Sliding Movement	Vascular Hilum
Thyroid	Red	Yes	Varies	No	No
Fat	Bright Yellow	No	Amorphous	No	No
Lymph Node	White-gray to red	Yes	Spherical to elliptical	+/-	No
Thymus	White-yellow	No	Amorphous	No	No
Parathyroid	Tan, brown, salmon	Soft	Elliptical, flat	Yes	Yes

Focused Surgery: IPM Criteria UHN

- Rapid assay measurement of pre excision, and post excision PTH levels at 10 and 15 minutes after removal of abnormal parathyroid tissue
- Decrease in iPTH greater than 75% defined as success
- Gland size and histology not used as criteria for continued exploration
- If decrease < 75% conversion to BND

MIP Results: UHN

- 310 patients considered 2008-2011
  - Negative Sestamibi scan 46
  - Significant Thyroid disease on U/S 28
  - 74/310 therefore selected for 4 gland or unilateral exploration
  - 236/310 (76.16%) eligible for MIP

MIP Results

- Mean LOS 18H
- Mean OR time 1.2H
- Conversion rate 3%
- Persistant hypercalcemia 2%
- RLN palsy 2/236 .88%
- Hematoma 1/236 .44%

- Safe, effective procedure in selected patients

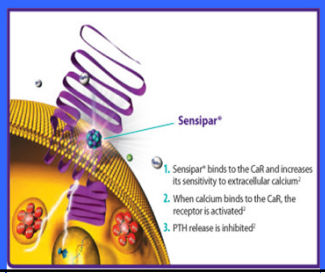
MIRP ?

- Minimally Invasive Radioguided Parathyroidectomy (MIRP) combines
  - Sestamibi injection day of OR
  - Intraoperative gamma probe for localization
  - Verification of excision by drop in count

- The reported outcomes of MIP and MIRP in terms of normocalcemia, complications, LOS, duration of surgery are virtually identical
- Most experts have stopped using radio guidance apart from Norman and Denham (Tampa)

Do we still need to do surgery in primary hyperparathyroidism?

- Cinacalcet (Sensipar) calcimimetic which binds to Ca receptor on PTH cells
- Effective agent in management of pts with secondary, tertiary hyperparathyroidism and calciphylaxis



Do we still need to do surgery in primary hyperparathyroidism?

- Blinded RCT Cinacalcet vs Observation in mild to moderate primary hyperparathyroidism n=78 l yr F/U Peacock et al CJEM 2005

- Serum Calcium normalized 88%
- Serum iPTH decreased 60%
- BMD no different than control

- Approved for primary HPTH by FDA and HPB

- Comparative utility and cost/benefit studies not yet done

Who should be doing parathyroid surgery ?

- Surgeon Outcome vs. Volume Sosa JA, 1998 JCEM
- High vs. Low vol surgeons surveyed (50 cases/yr)

Complications	1 vs 1.9%	p <0.05
Re op rate	1.55 vs 3.8%	
Mortality	0.04 vs 1%	

- Higher volume surgeons also had lower threshold to operate in mild disease

Who is doing parathyroid surgery ?

- Saunders et al, 2003, Surgery
- USA 1998-2000 14,232 parathyroidectomies by 6,100 surgeons
- Only 4% of operations done by high volume (> 27/yr) surgeons
- 91.6% of procedures done by surgeons who did 3 or less/yr

Who should be doing parathyroid surgery ?

- ***"Parathyroidectomy should be performed only by experienced, expert parathyroid surgeons"*** Bilezikian et al NIH 2002

Summary

- Biochemical diagnosis is straightforward and trumps imaging
- There may be no such thing as asymptomatic disease
- Indications for surgery should be liberal as operations get smaller less morbid
- Minimal Invasive parathyroidectomy has become the standard of care
- Experience is a key factor in determining outcome

Notes

Session V

Panel Discussion– Management of Parathyroid & Thyroid Disease

No material

Notes

Sunday November 6, 2011

Session VI – Stump the Faculty

Notes

Sunday November 6, 2011

Session VII – Video Session II

Notes