Thyroid Cancer

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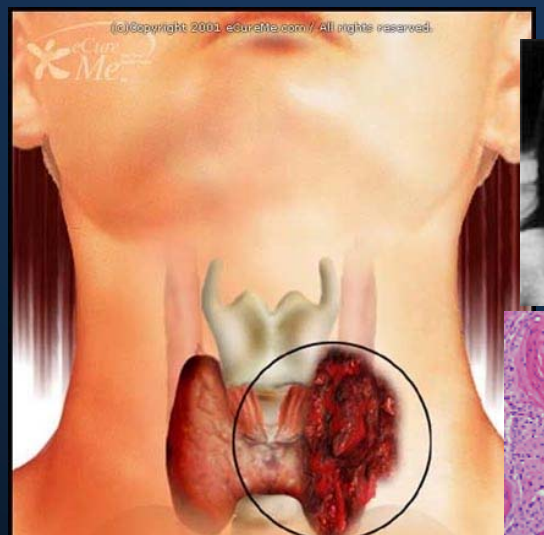
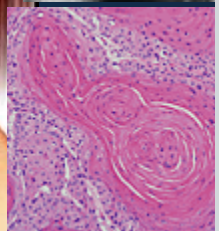
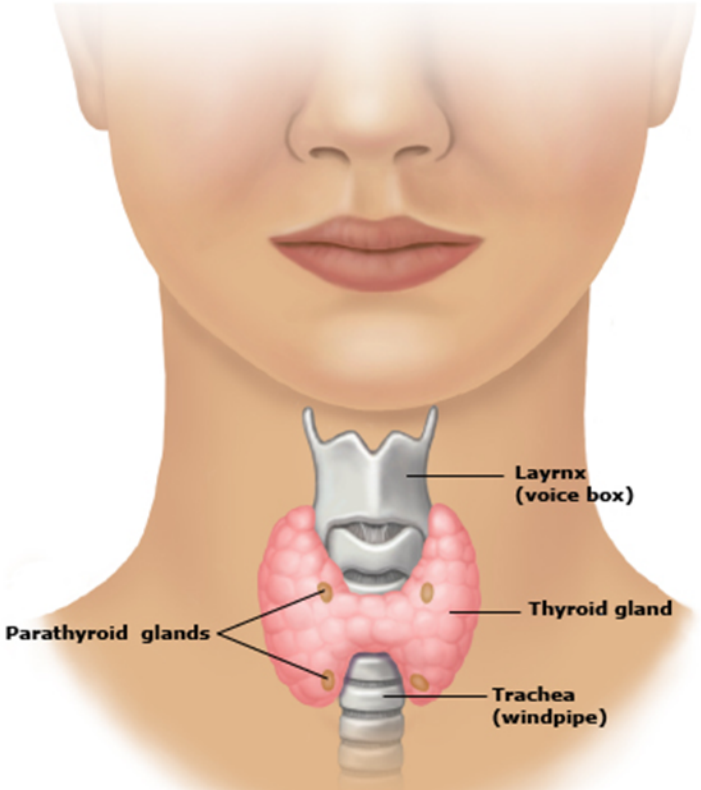




Objectives

- Review thyroid cancer types
- Review thyroid cancer epidemiology and risk factors
- Review thyroid cancer presentation
- Review thyroid cancer staging
- Review thyroid cancer treatment

Thyroid gland



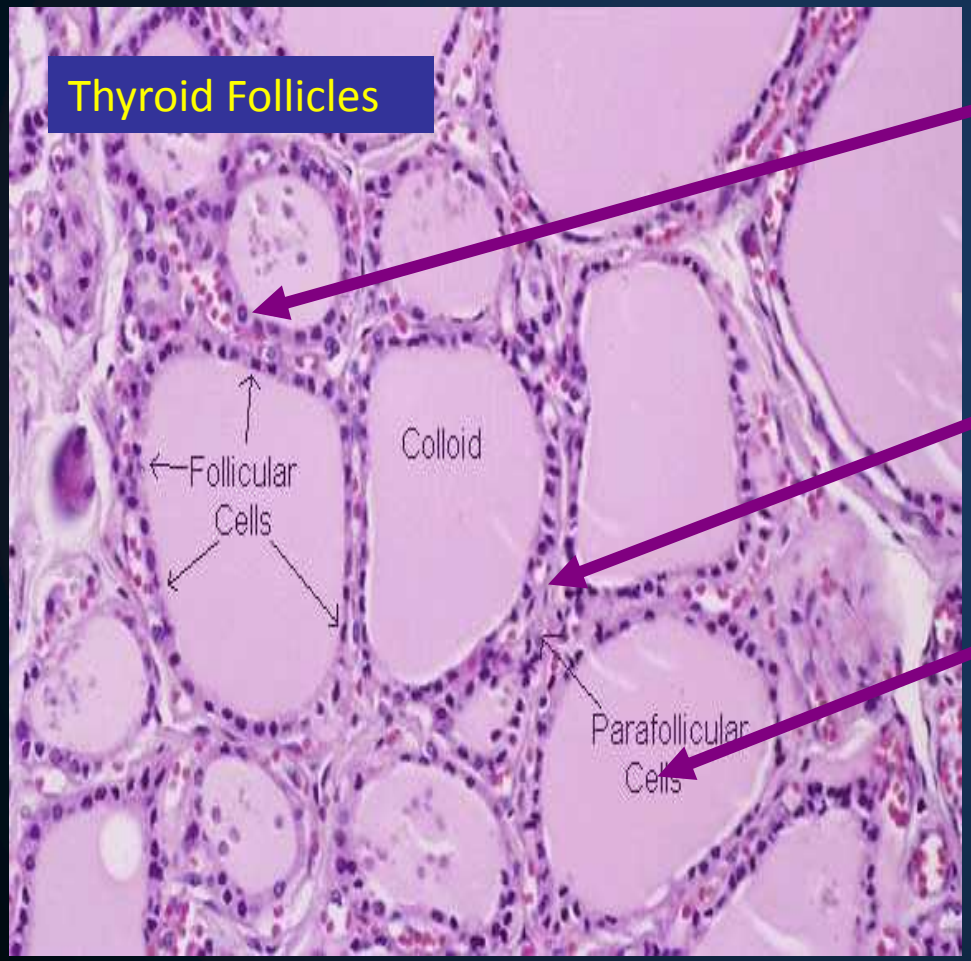
The thyroid is a butterfly-shaped gland in the middle of the neck. It sits just below the larynx (voice box). The thyroid makes two hormones, called triiodothyronine (T3) and thyroxine (T4), which control how the body uses and stores energy.

UpToDate

Thyroid function:

- Affects nearly all organs
- Regulates metabolism
- Calcium and phosphorus homeostasis

Thyroid Histology



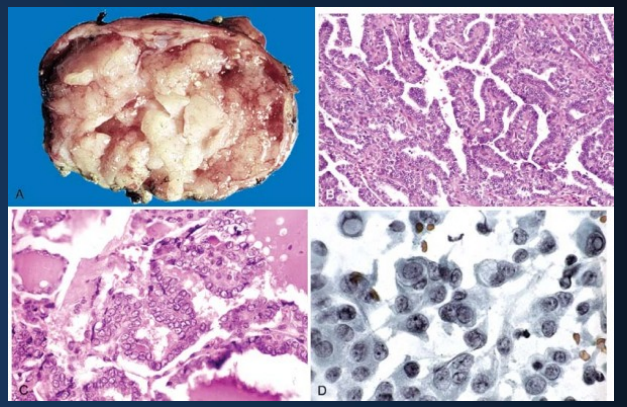
Follicular Cells: stimulated by TSH to convert thyroglobulin to T4

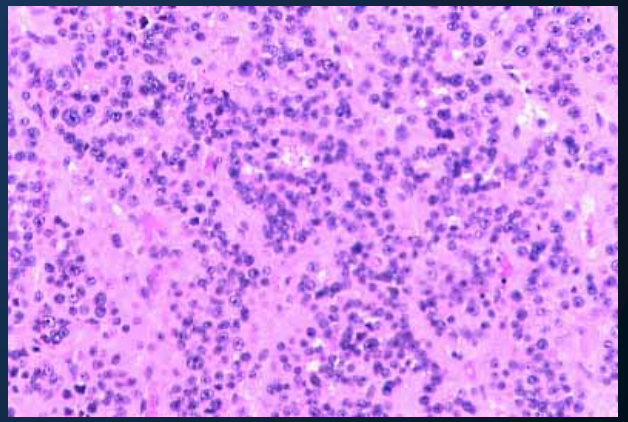
Parafollicular (C) cells: synthesize calcitonin

Colloid: storage material for thyroglobulin

Thyroid Malignancies

- Cancers of Follicular Epithelial Cells
  - Differentiated Thyroid Cancer
    - Papillary Thyroid Carcinoma
    - Follicular Thyroid Carcinoma
    - Hurthle Cell Carcinoma
  - Poorly Differentiated Thyroid Cancer
    - Derived from Follicular or Papillary Thyroid Carcinomas?
  - Undifferentiated Thyroid Cancer
    - Anaplastic Thyroid Carcinoma
- Cancer of Parafollicular (C) Cells
  - Medullary Thyroid Carcinoma





Thyroid Malignancies

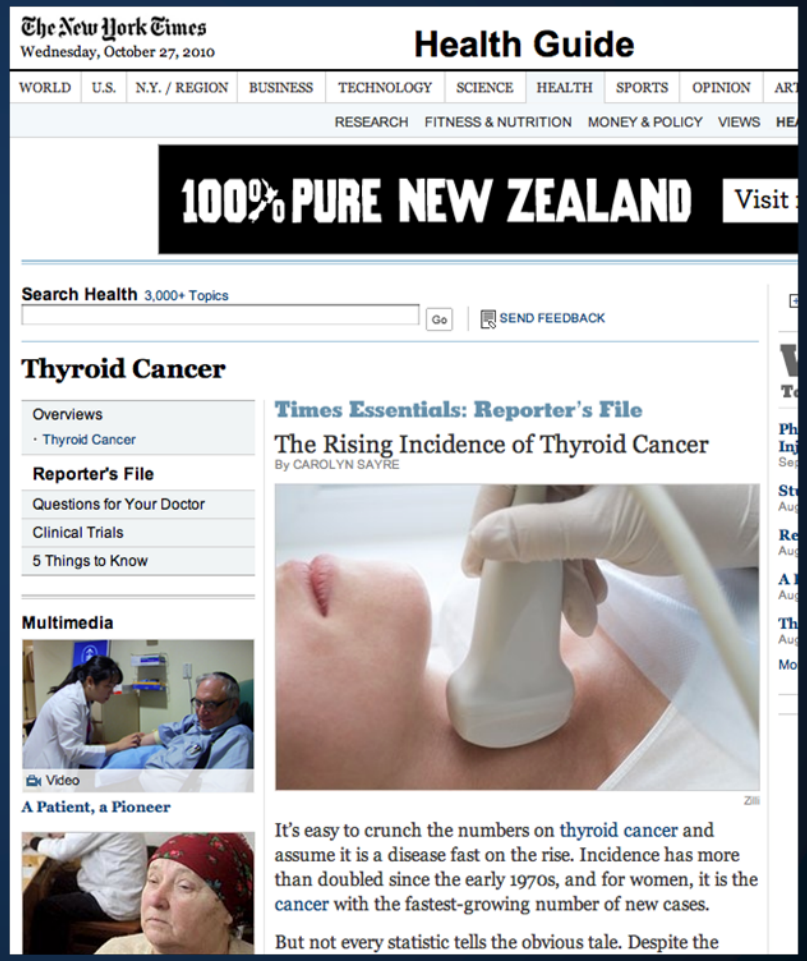
Tumor type	Prevalence	Age	Distant Metastases	Survival rate (5yr)
Papillary thyroid carcinoma	**85-90%**	20-50	5-7%	>90%
Follicular thyroid carcinoma	**<10%**	40-60	20%	>90%
Poorly differentiated thyroid carcinoma	Rare-7%	50-60	30-80%	50%
Undifferentiated thyroid carcinoma	2%	60-80	20-50%	1-17%
Medullary thyroid carcinoma	3%	30-60	15%	30-80%

Nature Reviews. April 2006, p.292-306.

Thyroid Cancer Epidemiology

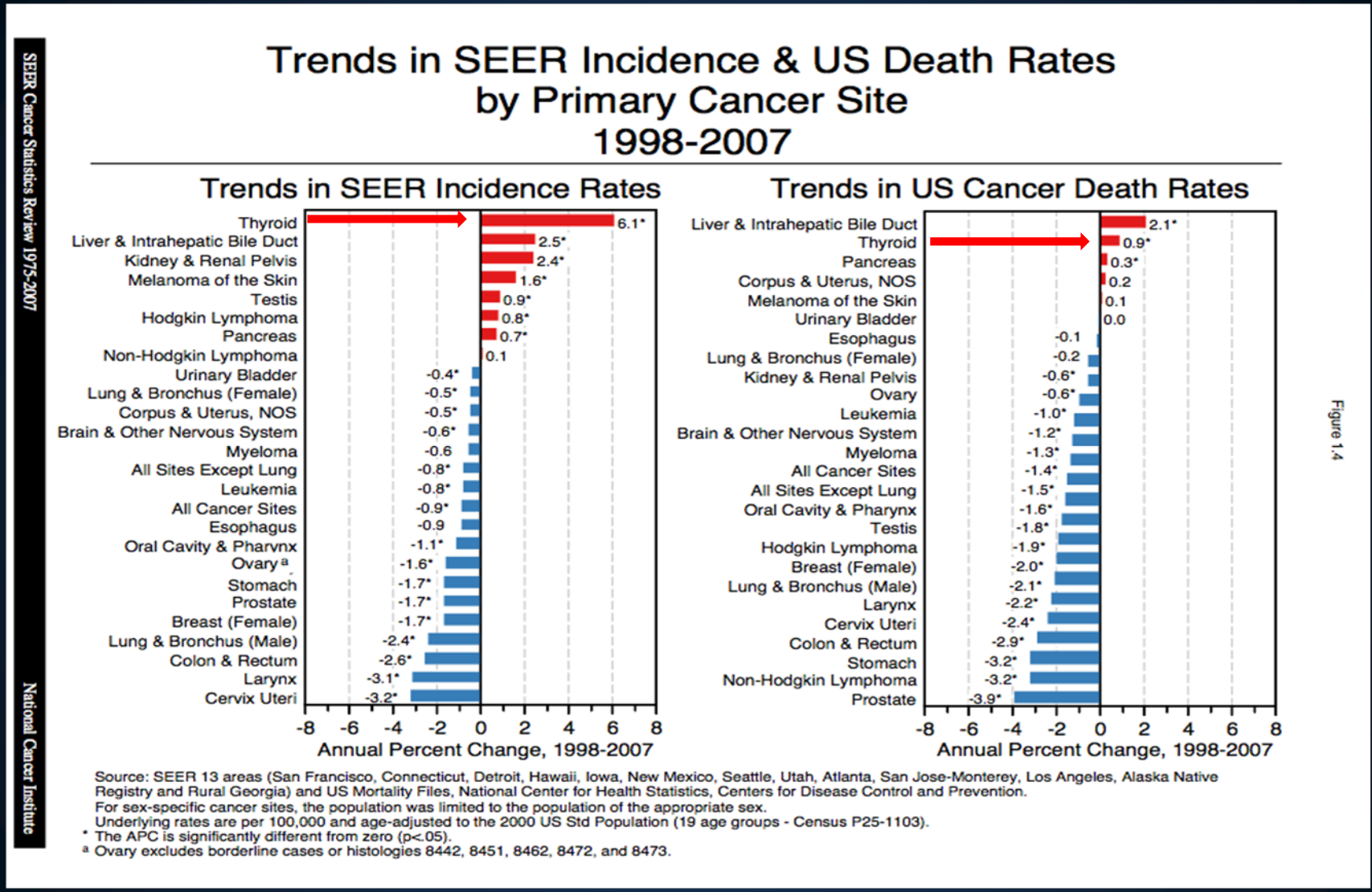
- Thyroid Cancer is the most common endocrine malignancy

- age- and gender-adjusted incidence has increased faster than that of any other malignancy
  - 23,500 cases in 2005
  - 37,200 cases estimated in 2009
  - 44,670 cases estimated in 2010
- Prevalence is high and increasing
  - 2004: 366,000 men and women alive with history of thyroid cancer
  - 2006: 434,256



Horner MJ, et al. *SEER Cancer Statistics Review, 1975-2006*, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2006/, based on November 2008 SEER data submission, posted to the SEER web site, 2009.

US Death Rate Increasing



Highest rate of increase in any cancer for both men and women < and > 65

Death rate increasing for men and women

Differentiated Thyroid Cancer

(Papillary and Follicular)

Differentiated Thyroid Cancer (DTC) Epidemiology

- Gender: female: male = 2.5:1
- Race: Caucasian: African Americans = 2:1
- Median age at diagnosis for PTC:
  - Women: 40-41 years
  - Men: 44-45 years
- Median age at diagnosis for FTC:
  - Women: 48 years
  - Men: 53 years

Differentiated Thyroid Cancer (DTC) Risk Factors

- Radiation exposure
  - Survivors of atomic fall-out
  - Children exposed to external beam radiation
  - Children living in Chernobyl (nuclear accident)
  - Younger age at exposure: Higher risk
    - Controversial whether exposure after age 15 confers increased risk

Differentiated thyroid cancer (DTC) Risk Factors

- Genetic
  - Component of several inherited syndromes:
    - Familial adenomatous polyposis, Gardner syndrome, Cowden disease, Turcot syndrome, Carney complex
  - “Famililal nonmedullary thyroid carcinoma”
    - Appears to be low penetrance, heterogeneous
    - Case control study (n=339)
      - 10-fold increased risk of thyroid cancer in relatives of thyroid cancer patients
    - Swedish retrospective analysis (n=1953 cases)
      - Familial risk:
      - 3.21 when a parent is diagnosed
      - 6.24 when a sibling is diagnosed
      - 11.19 if a female has a sister diagnosed

Pal T; J Clin Endocrinol Metab 2001

Hemminki K; J Clin Endocrinol Metab 2005

Thyroid Cancer AJCC Staging

Stage	Follicular or Papillary*		Medullary	Anaplastic
	<45yo	>45yo	Any age	Any age
I	M0	T1	T1	
II	M1	T2-3	T2-4	
III		T4 or N1	N1	
IV		M1	M1	Any T, N, or M

*The most advanced a patient <45 yo can be is stage II

Thyroid Cancer Stage Distribution

Histologic Subtype	I (%)	II (%)	III (%)	IV (%)	Unknown (%)	Total
Papillary	**46.9**	14.4	10.3	2.1	16.4	**34,794**
Follicular	**41.2**	26.7	6.9	7.2	17.9	**5271**
Hurthle Cell	**20.8**	35.1	9.3	5.7	29	**1310**
Undifferentiated/ Anaplastic	0	0	0	100	0	741
Medullary	16.5	29.6	26.9	11	16	1550
Total	51.5	16.8	10.3	4.8	16.6	
Cases	22,486	7335	4491	2091	7263	43,666

50% of Differentiated Thyroid Cancers are Stage I

CANCER December 15, 1998 / Volume 83 / Number 12

Prognosis of Differentiated Thyroid Cancer

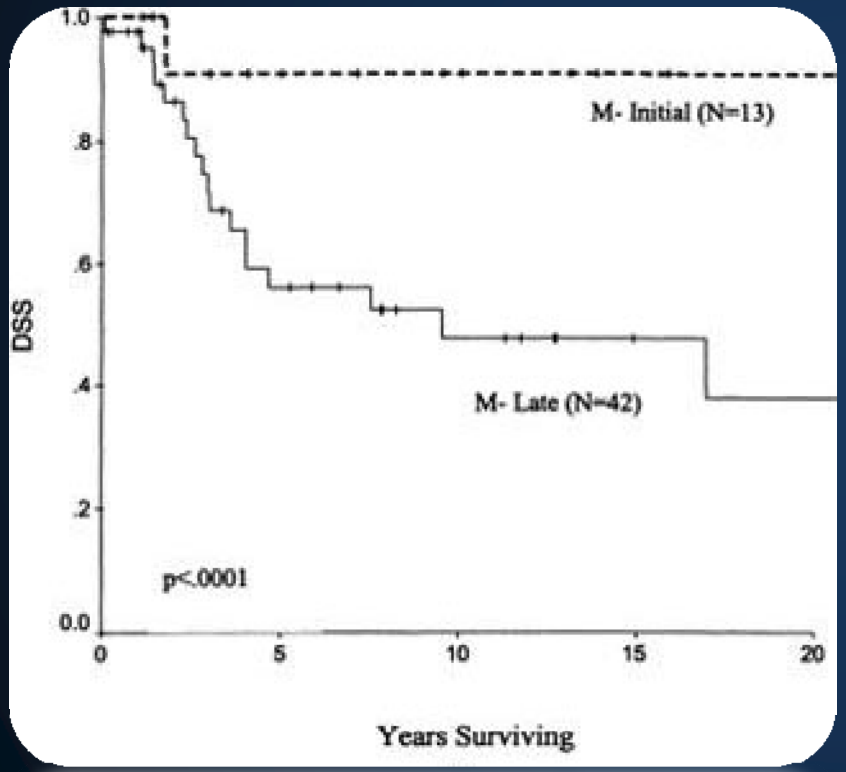
- One of the least morbid solid tumors
- Regional lymph node metastasis does not correlate with overall survival—does correlate with local recurrence
- 2/3 of patients have local disease at dx
- 33-61% of patients with PTC have clinically apparent cervical lymph node involvement at dx
- 1-2% PTC have distant mets at dx
- 2-11% FTC have distant mets at dx
- Distant mets at dx: 43-90% of patients will die of thyroid cancer

TNM Stage and Prognosis

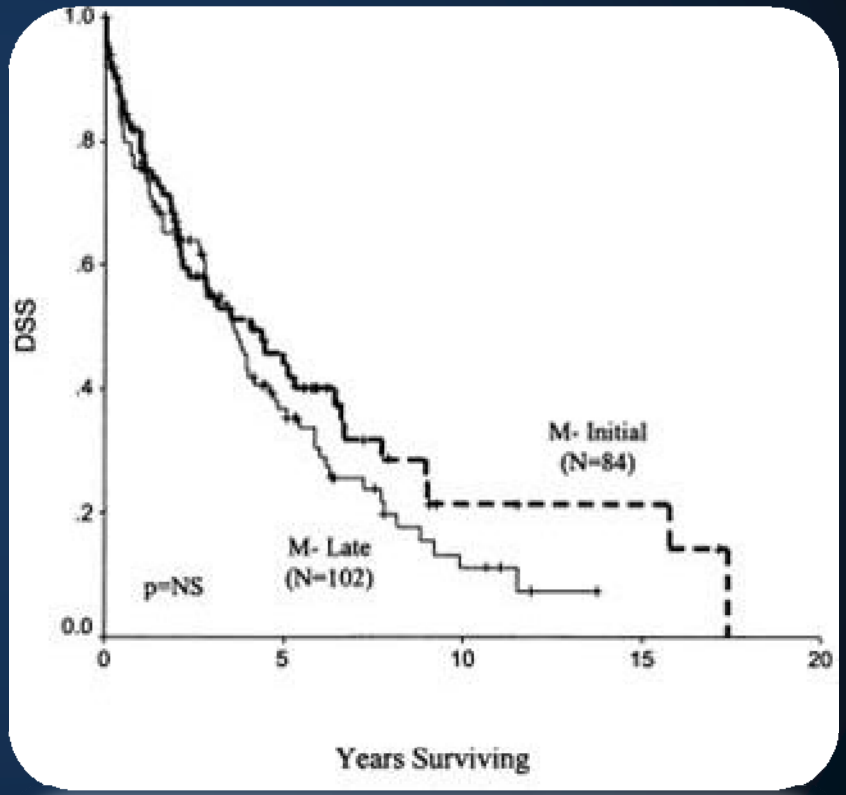
Stage	Recurrence (%)	Death (%)
I	15.4	1.7
II	22	15.8
III	46.4	30
IV	66.7	60.9

N = 700 (PTC=620, FTC=80)
Median follow-up duration = 10.6 yrs
Loh, et al. JCEM 1997

Age and Prognosis in Metastatic Differentiated Thyroid Cancer



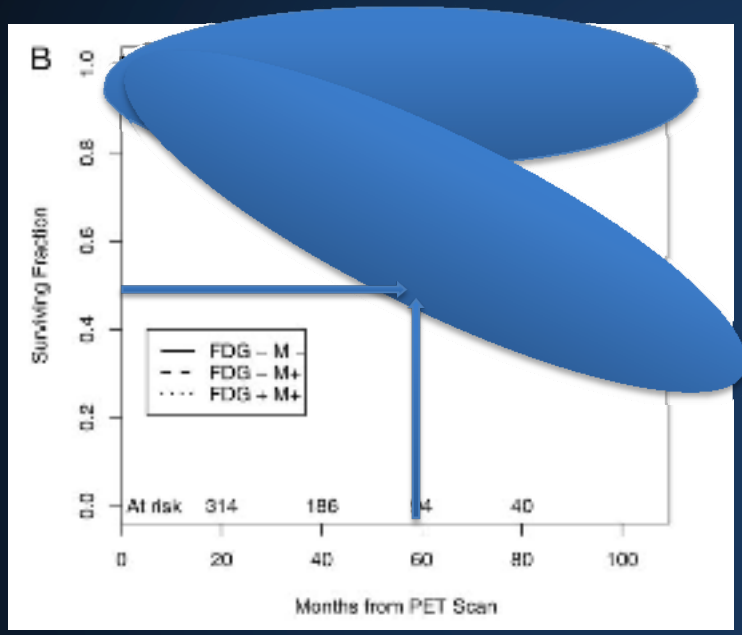
Age < 45



Age > 45

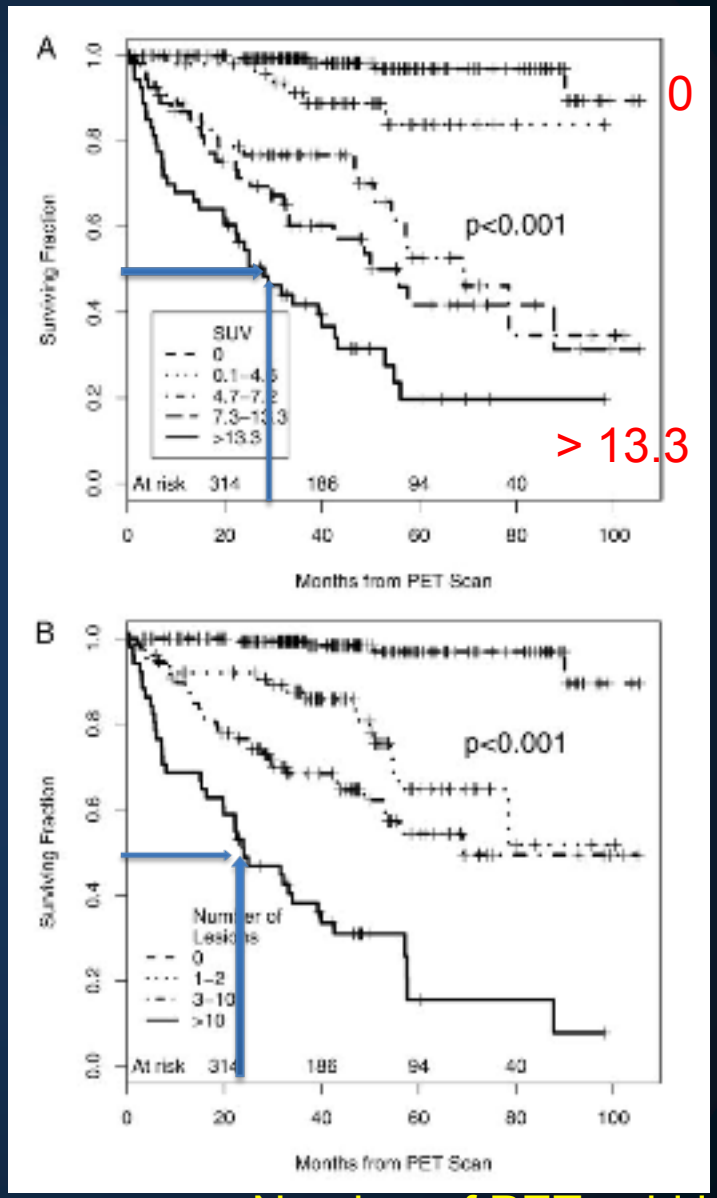
Shoup, et al. JCAS 2003

PET and Prognosis



SUV and number of PET-avid lesions influences prognosis in differentiated thyroid cancer

SUV value

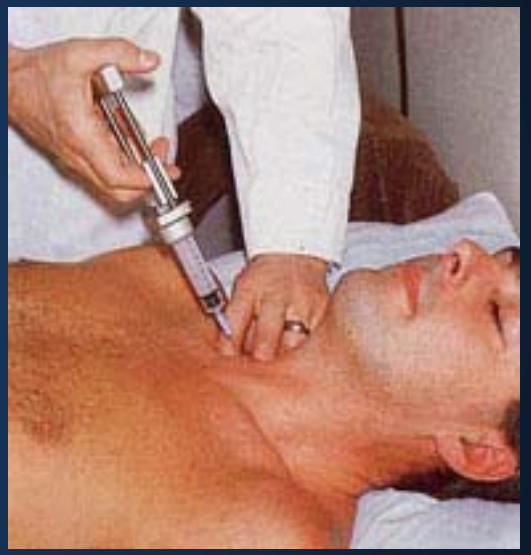


Number of PET-avid lesions

Robbins, et al. JCEM, Feb 2006, 91 (2): 498-505

Diagnosis

- FNA is standard diagnostic procedure when a thyroid nodule is found
- Most thyroid nodules are benign
  - 5-10% chance of malignancy
  - Higher rate of cancer in:
    - Men
    - Age < 20 or > 70
    - History of childhood neck radiation:
      - 33-37% chance malignancy
    - Enlarging nodule
    - Fixed nodule/vocal cord paralysis
    - h/o Graves' disease
    - Family h/o PTC, MTC, MEN 2
  - Up to 90% of women > 70 and up to 60% men > 80 have nodular goiter



FNA RESULTS

FNA result	N	%
Benign	526	87.7
Malignant	28	4.7
Suspicious for malignancy	10	1.6
Insufficient material	36	6
Total	600	100

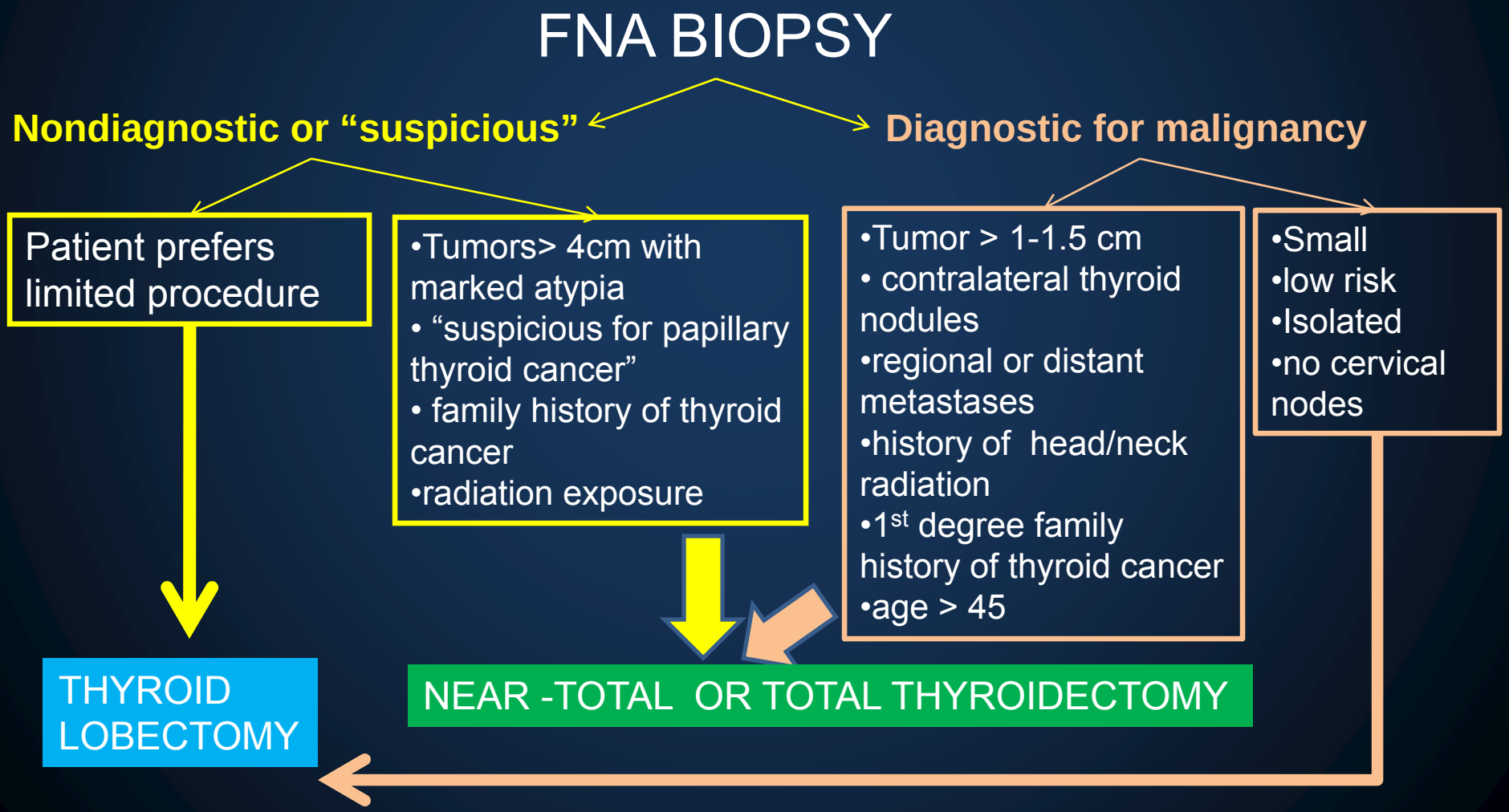
Binesh F, Pak J Med Sci 2008;24(3):382-5.

Ultrasound

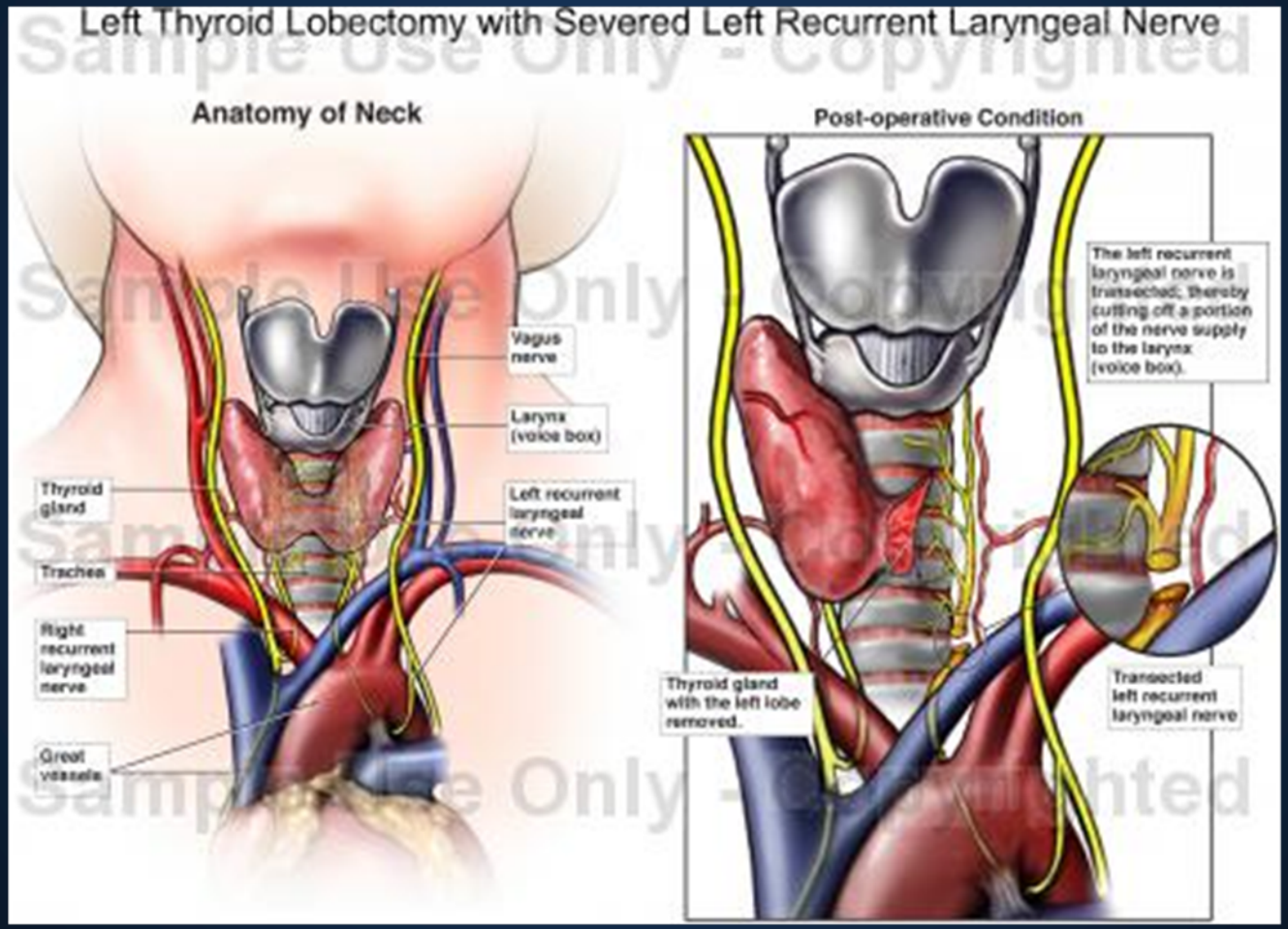
- Size assessment of nodule
- Detection of multiple nodules not discerned by palpation
- Assisting in FNA
- Distinguishing benign from malignant thyroid nodules—characteristics suggestive of malignancy
  - Microcalcification
  - irregular margins
  - spotty intranodular flow
  - hypervascularity

What is the appropriate operation for differentiated thyroid cancer?

American Thyroid Association Management Guidelines THYROID vol 16, 2006



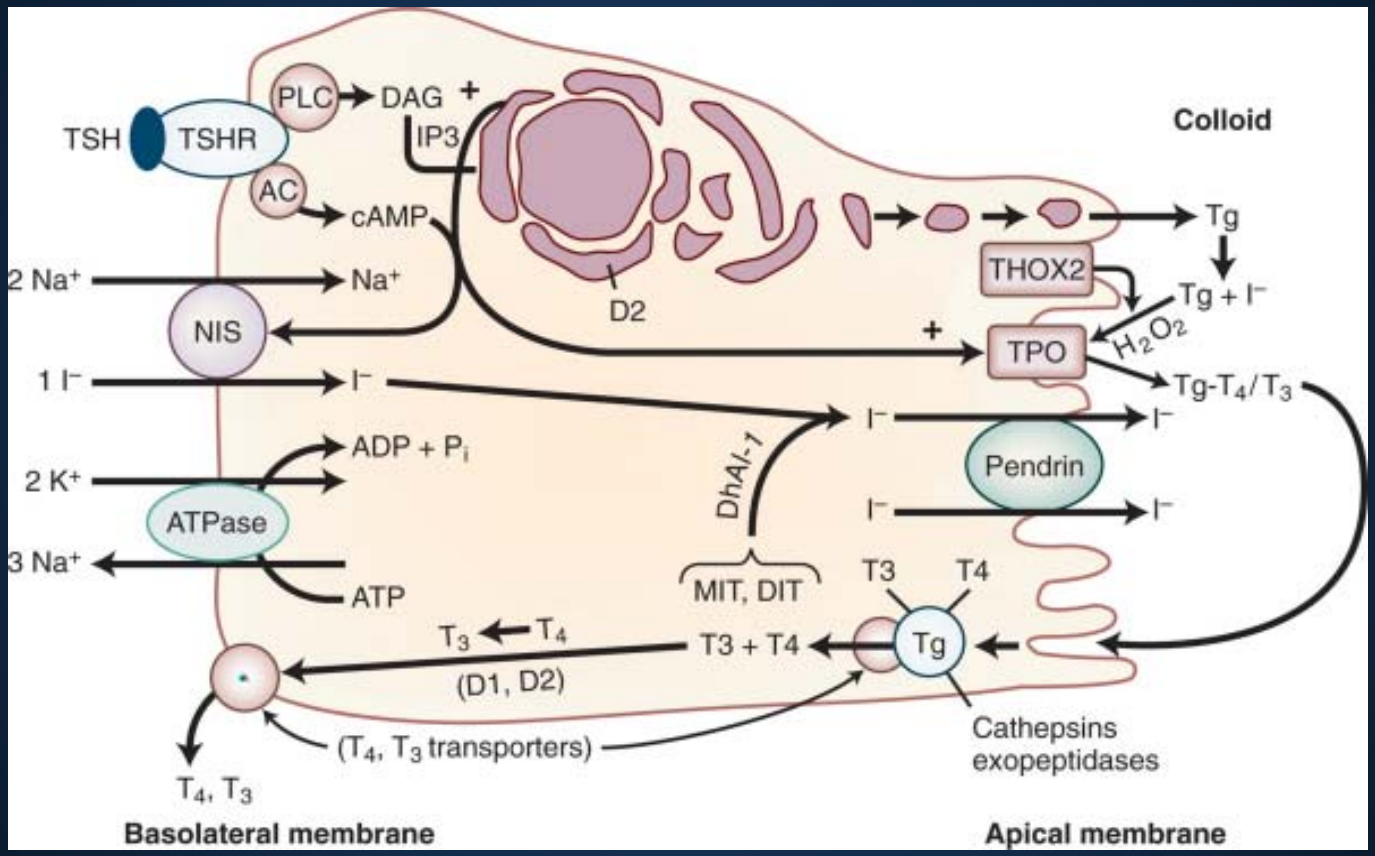
Surgical Resection



Postoperative Radioiodine

- Recommended for nearly all patients who get a total or near-total thyroidectomy in the USA
  - Stages III and IV disease
  - All Stage II disease if < 45 yo, most if > 45
  - Selected patients with stage I disease
    - Multifocal disease
    - Nodal mets
    - Extra thyroidal or vascular invasion
    - More aggressive histologies

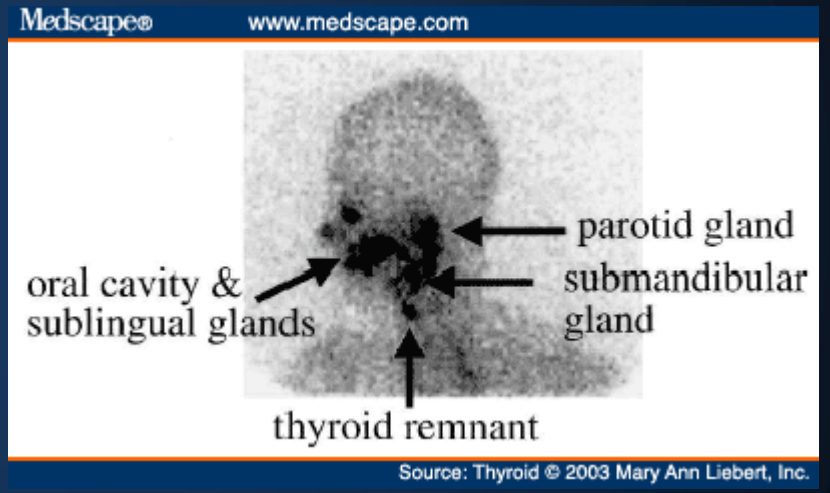
Thyroid Follicular Cell



Postoperative treatment and surveillance are based on differentiated thyroid cancer maintaining characteristics of normal thyroid follicular cells

Postoperative Radioiodine

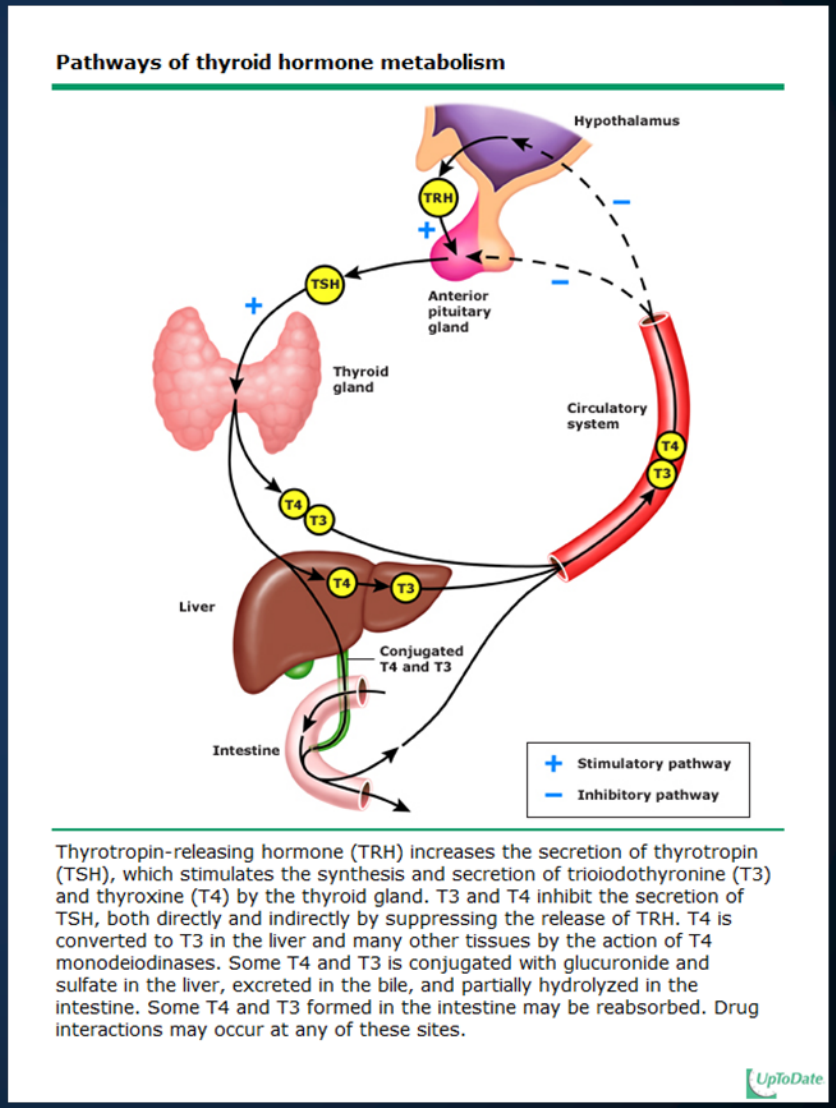
- Goals:
  - Eliminate post-surgical thyroid remnant
    - Decrease local recurrence
    - Facilitate long-term surveillance with RAI (radioiodine) scans and/or stimulated thyroglobulin measurements
  - Destroy micrometastatic disease



- No prospective studies have been done to determine which patients benefit
- Requires TSH stimulation
  - Can be done by stopping thyroid hormone replacement and allowing endogenous TSH levels to rise
  - For low risk patients, can give rhTSH (thyrotropin)

TSH Suppression Therapy

- Differentiated thyroid cancer cells express the thyrotropin receptor on the cell membrane
  - Responds to TSH stimulation
    - Increases rates of cell growth
- Use supratherapeutic doses of LT4
  - TSH suppression to < 0.1mU/L may improve outcomes in high risk patients
  - TSH 0.1-0.5 is appropriate for low risk patients
- Adverse effects of TSH suppression—subclinical thyrotoxicosis:
  - Exacerbation of angina, increased risk of atrial fibrillation, increased risk of osteoporosis in post menopausal women



Management of recurrent disease

- Surgical resection if neck disease +/- post op TSH-stimulated Tg, DxWBS, and RAI therapy
- If more extensive disease:
  - Radioiodine if uptake on WBS
  - External beam radiotherapy
  - Systemic chemotherapy?

RAI-Refractory Thyroid Cancer

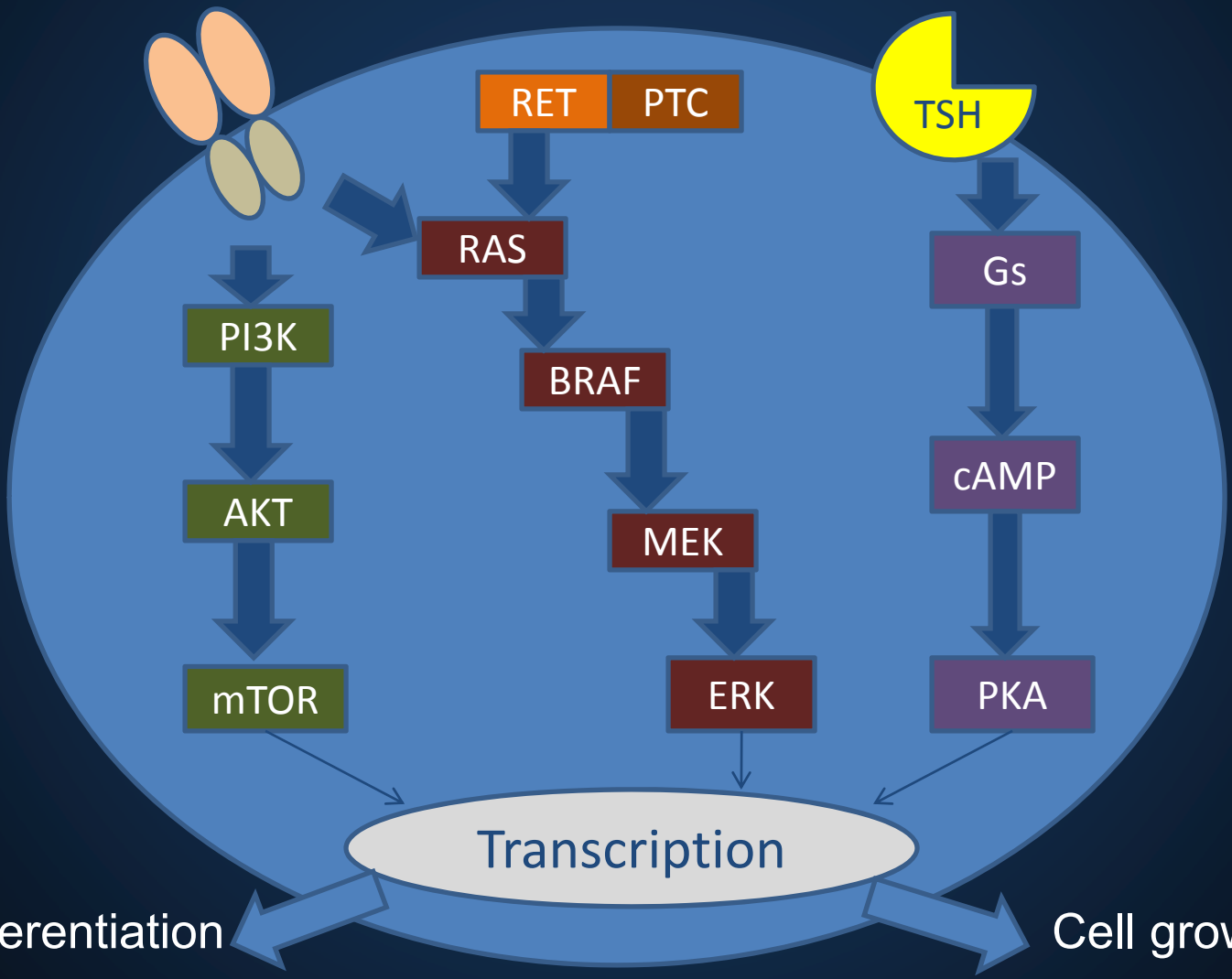
- PET avidity is inversely proportional to RAI uptake
- 25-50% metastatic thyroid cancers lose iodine concentrating ability
- Standard chemotherapy has disappointing response rates, significant toxicity
  - Doxorubicin is only FDA-approved therapy
  - PFS = 2 months
  - OS = 8 months

Shimaoka, et al. Cancer 56, 1985

Systemic Chemotherapy in Advanced Thyroid Cancer

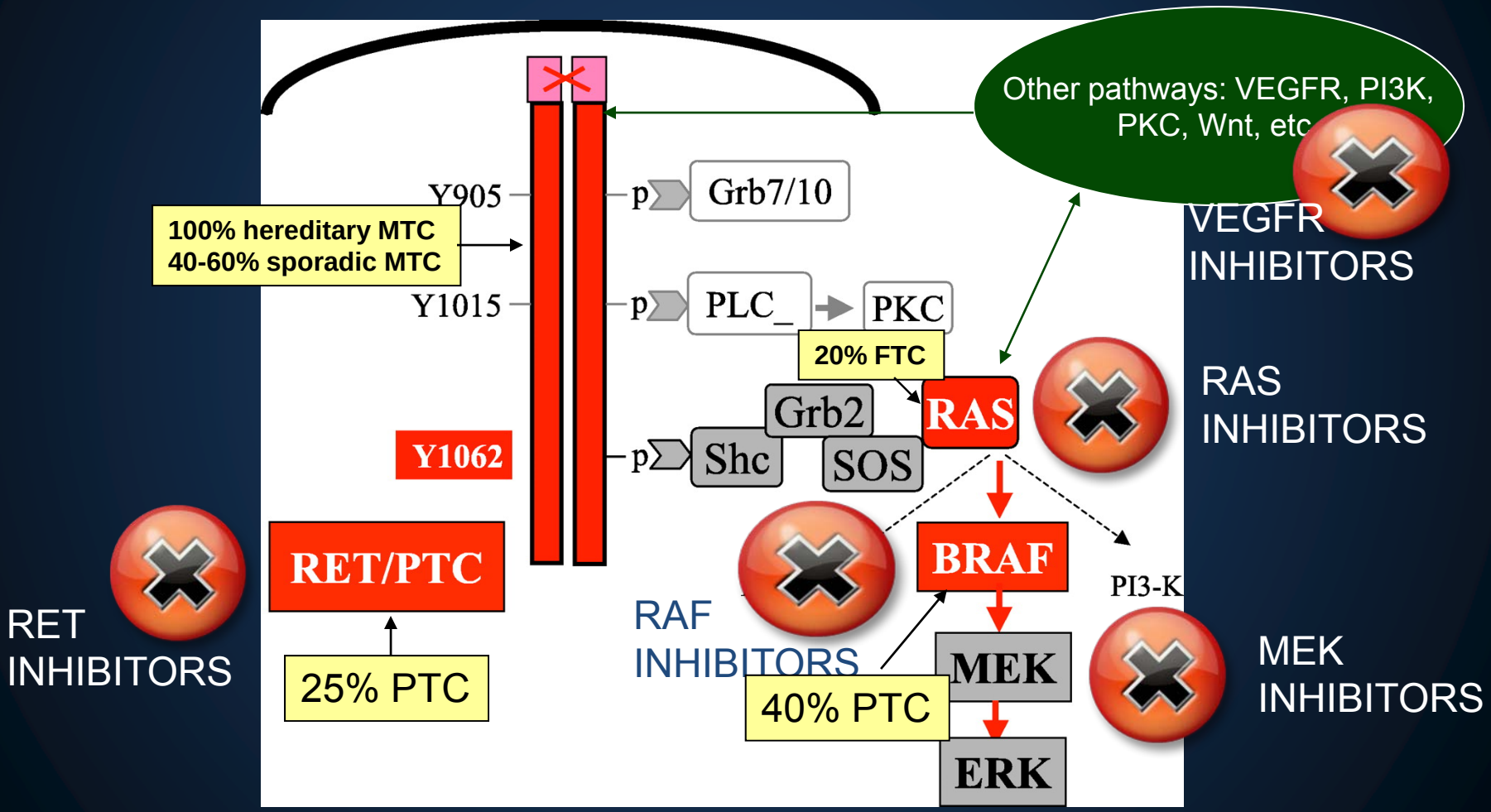
Study	Subtype (N)	ORR	OS
Doxorubicin (Gottleib and Hill. 1974 NEJM 290(4); 193-197)	Differentiated (15) Medullary (5) Anaplastic (9)	37%	4-11 months
Doxorubicin vs. **Doxorubicin + Cisplatin** (Shimaoka et al, 1985 Cancer 56 (9); 2155-60)	Differentiated (35) Medullary (10) Anaplastic (39)	17 vs. 26%	5 vs. 7 months
Doxorubicin + Cisplatin (Williams et al, 1986 Can Treat Rep 70(3); 405)	Differentiated (7) Medullary (6) Anaplastic (7)	9.1%	11.8 months
Doxorubicin + Cisplatin + Bleomycin (De Besi, et al, 1991 J Endo Invest 14; 475-480)	Differentiated (8) Medullary (9) Anaplastic (5)	42%	11 months

Thyroid Cancer Signaling



Kondo, Nature Reviews, 2006

TARGETS FOR THERAPY



Differentiated (Papillary and Follicular) Thyroid Cancer Clinical Trials

Agent	Histology (N)	OR (%)	SD (%)	Benefit (%)
Sorafenib	PTC (41) Shah JCO	15	56	**71**
	DTC/MTC (50) Brose ASCO 2009	36	46	**82**
Sunitinib	DTC (12) Ravaud,ASCO 2008	13	83	**96**
	DTC (35) Cohen ASCO 2008	17	74	**91**
	DTC/MTC (35) Carr CCR 2010	31	46	**77**
Motesanib	DTC (93) Sherman, NEJM 2008	14	67	**81**
Pazopanib	DTC (37) Bible, Lancet 2010	49	43	**92**

Sorafenib

- inhibits RAF, PDGFR, VEGFR2 and 3, RET, KIT
- Rationale for its use in DTC
- Most feel response related to VEGFR inhibition
- Approved for use in renal cell carcinoma and hepatocellular carcinoma
- 2 phase 2 trials in thyroid cancer
- Ongoing phase 3 trial of sorafenib vs. placebo

Sorafenib Studies

	University of Pennsylvania Gupta-Abramson, et al	The Ohio State University Kloos, et al
Patients	Metastatic, iodine refractory, unresectable or locally advanced (N=30)	Metastatic, iodine refractory, unresectable or locally advanced (N=56)
Progression needed?	Yes, within 12 mo by RECIST	No, 50% had RECIST progression within 12 mo
Papillary	18	41
Follicular/Hurthle Cell	9	11
ATC/Poorly Differentiated	2	4
Medullary	1	(reported separately)
Treatment	Sorafenib 400mg BID	Sorafenib 400mg po BID
Primary Endpoints	RECIST response, TTP	RECIST response

Journal of Clinical Oncology, Vol 26, No 29 (October 10), 2008: pp. 4714-4719

Journal of Clinical Oncology, Vol 27, No 10 (April 1), 2009: pp. 1675-1684

Sorafenib Studies

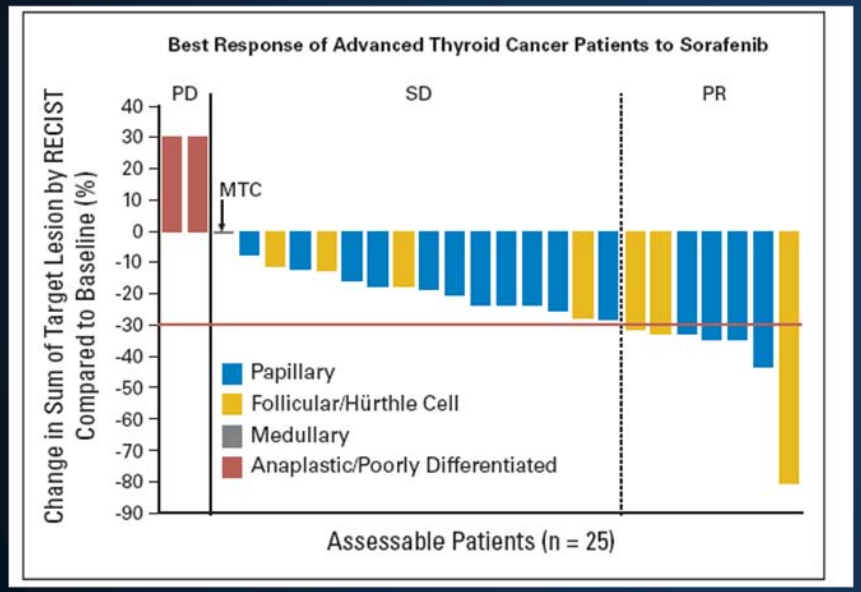
RECIST Response	University of Pennsylvania Gupta-Abramson, et al N=25	The Ohio State University Kloos, et al N=49
Complete Response	0	0
Partial Response	7 (23%)	6 (11%)
Stable Disease	16 (53%)	34 (61%)
Progressive Disease	2 (3%)	9 (21%)
PFS	79 weeks (~ 20 mo)	PTC – no prior chemo 16 mo PTC – prior chemo 10 mo FTC/HCC – 4.5 mo

Journal of Clinical Oncology, Vol 26, No 29 (October 10), 2008: pp. 4714-4719

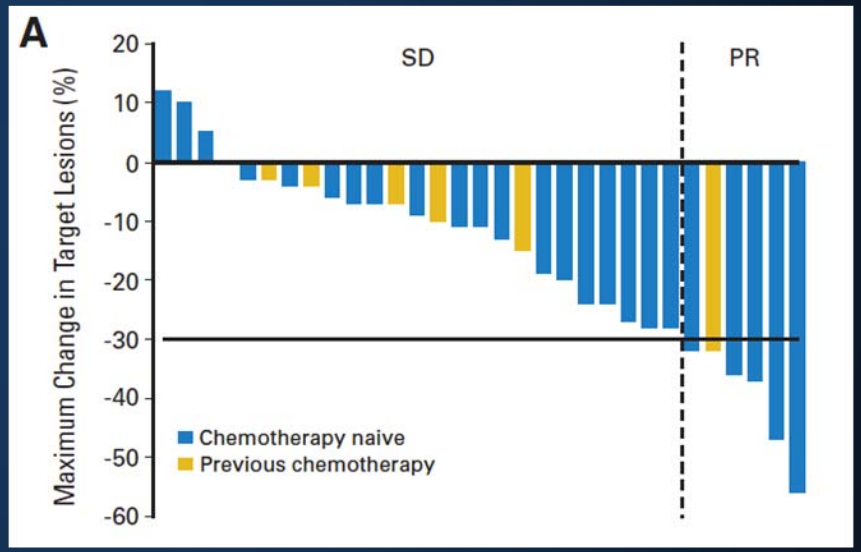
Journal of Clinical Oncology, Vol 27, No 10 (April 1), 2009: pp. 1675-1684

Sorafenib Best Response

Gupta Abramson,et al



Kloos, et al



Journal of Clinical Oncology, Vol 26, No 29 (October 10), 2008: pp. 4714-4719

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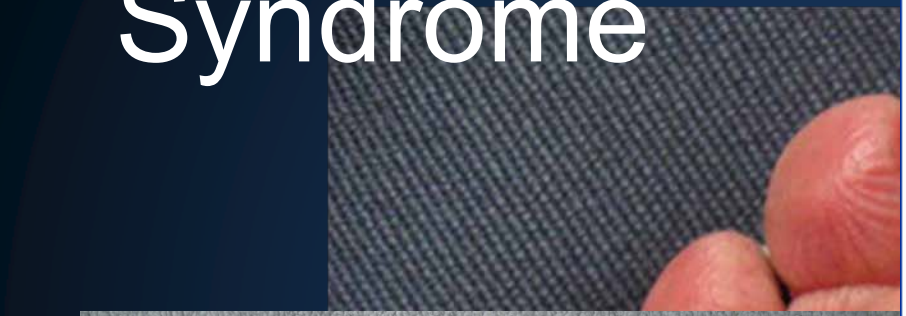
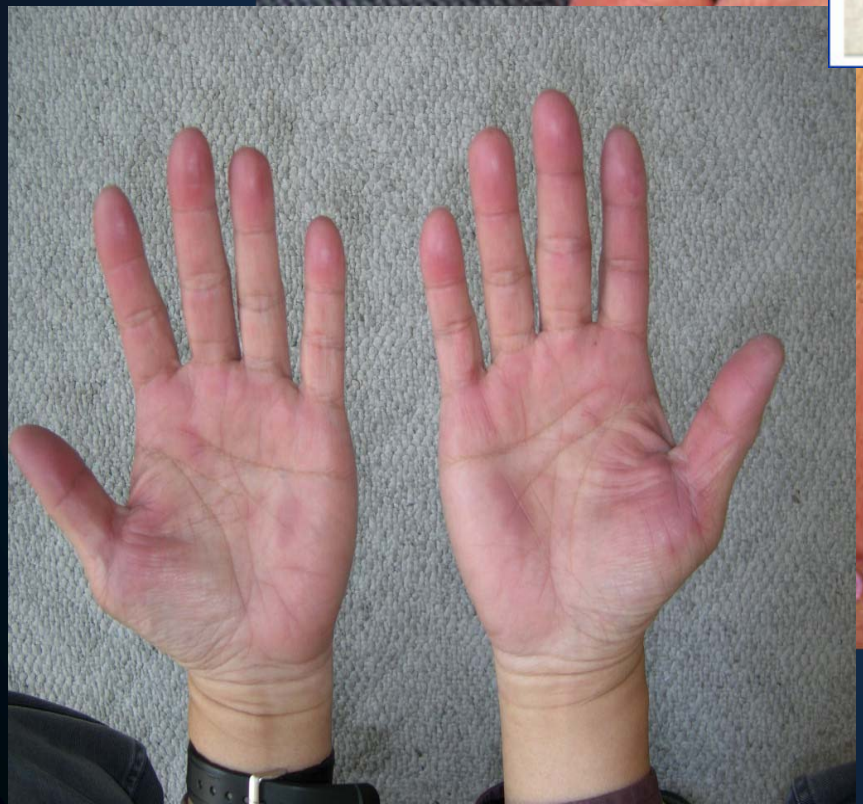
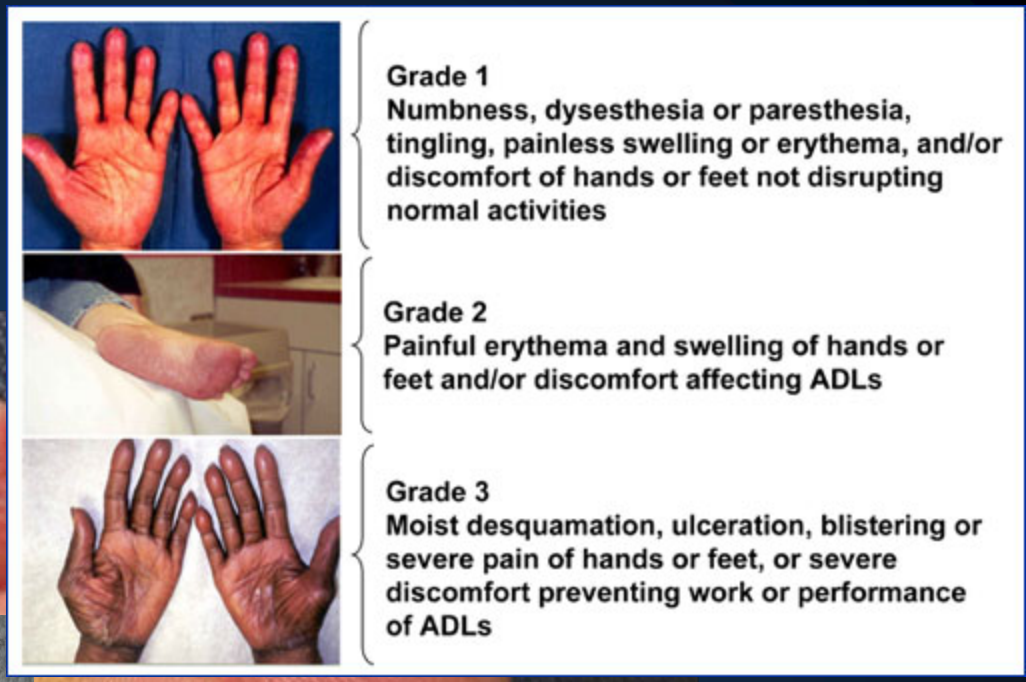
Hand Foot Syndrome



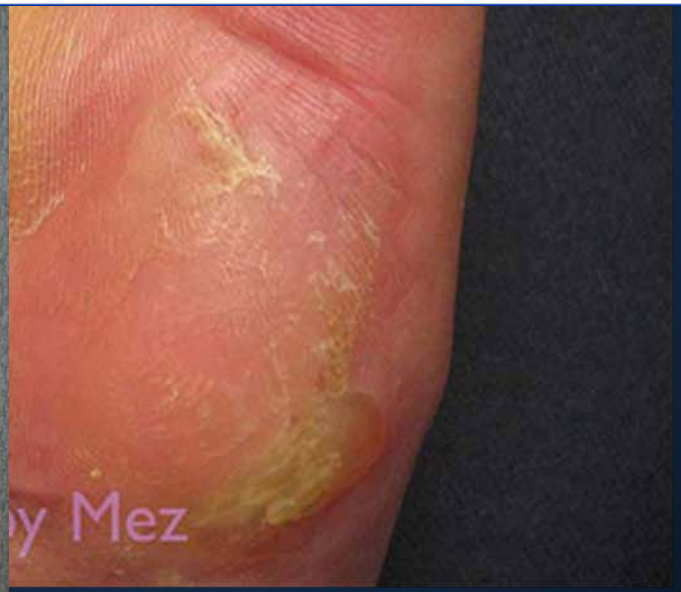




Grade 1
Numbness, dysesthesia or paresthesia, tingling, painless swelling or erythema, and/or discomfort of hands or feet not disrupting normal activities

Grade 2
Painful erythema and swelling of hands or feet and/or discomfort affecting ADLs

Grade 3
Moist desquamation, ulceration, blistering or severe pain of hands or feet, or severe discomfort preventing work or performance of ADLs



Sunitinib

- Multitargeted tyrosine kinase inhibitor approved for renal cell carcinoma and gastrointestinal stromal tumor (GIST)
- Targets VEGFR-1 and 2, PDGFRs, KIT, FLT3, RET

Sunitinib

	University of Washington Carr, et al.	University of Chicago Cohen, et al
Patients	Differentiated or medullary thyroid cancer refractory to curative therapy	Differentiated or medullary thyroid cancer refractory to curative therapy
Progression needed?	No, disease had to be PET avid	Yes, RECIST progression within 6 months
Papillary	18	16
Follicular/Hurthle Cell	9	22
ATC/Poorly Differentiated	1	0
Medullary	7	25
Treatment	Sunitinib 37.5 mg daily	Sunitinib 50 mg QD 4-weeks on/2-weeks off
Primary Endpoints	RECIST response	RECIST response

Clin Cancer Res; 16(21) November 1, 2010

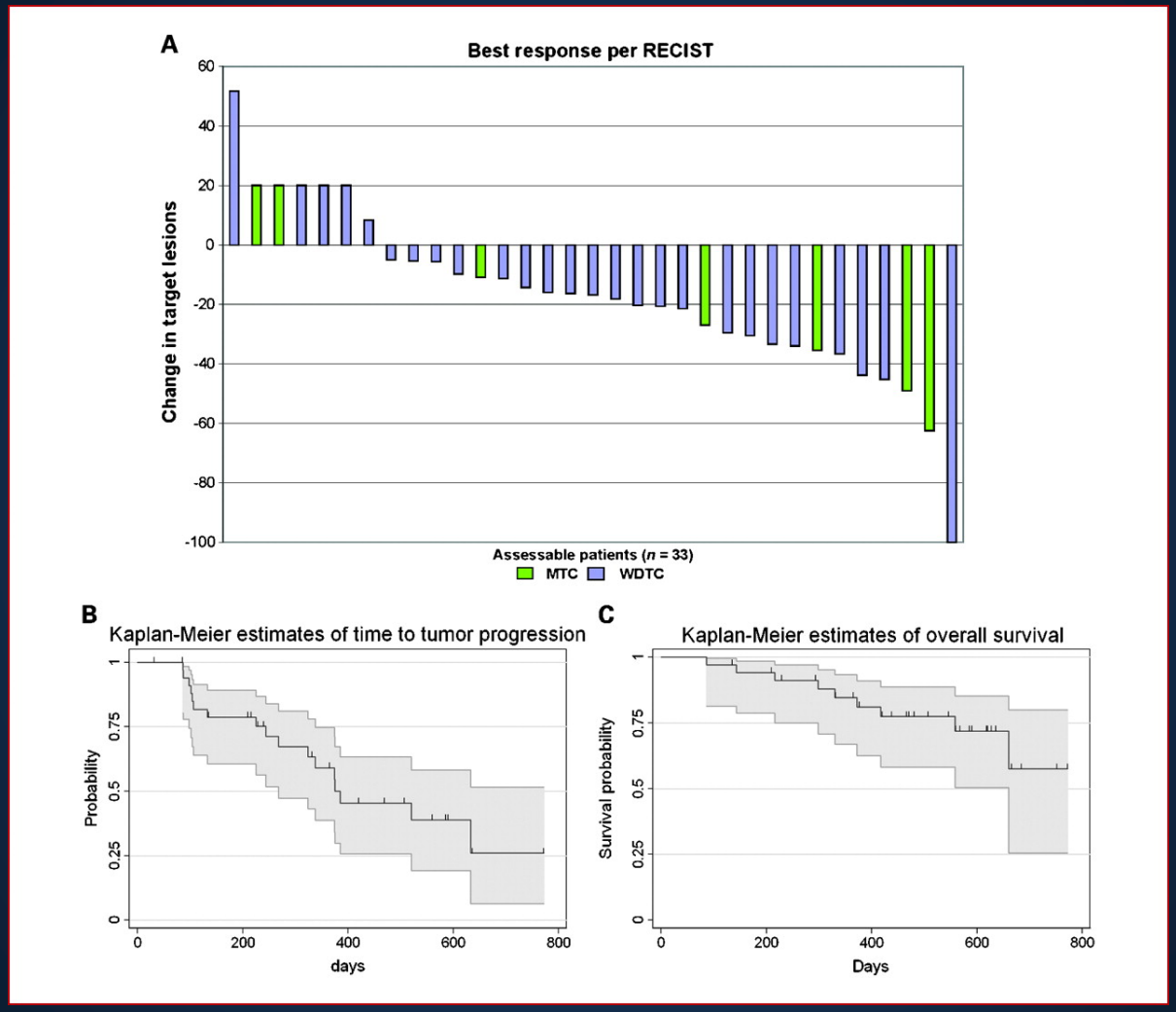
ASCO (abstract 6025) 2008, ASCO (abstract 5504) 2010

Sunitinib

RECIST RESPONSE	University of Washington Carr, et al. N=35	University of Chicago Cohen, et al N=35 (of 38 DTC patients)
Complete Response (CR)	1 (3%)	0
Partial Response (PR)	10 (28%)	6 (17%)
Stable Disease (SD)	16 (46%)	26 (74%)
Stable Disease (SD) > 6 months	13 (37%)	?
Progression	6 (17%)	3 (9%)
Time To Progression	12.8 mo	28 weeks (7 mo)

Median duration of response: 8 months
Median TTP: 12.8 months

A, maximum percent change in target lesions from baseline in all patients with evaluable disease (n = 33; 1 patient was removed from the study because of adverse event before evaluation and 1 patient did not have measurable disease per RECIST at baseline).



Carr L L et al. Clin Cancer Res 2010;16:5260-5268

Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study

Keith C Bible, Vera J Suman, Julian R Molina, Robert C Smallridge, William J Maples, Michael E Menefee, Joseph Rubin, Kostandinos Sideras, John C Morris III, Bryan McIver, Jill K Burton, Kevin P Webster, Carolyn Bieber, Anne M Traynor, Patrick J Flynn, Boon Cher Goh, Hui Tang, Susan Percy Ivy, Charles Erlichman, for the Endocrine Malignancies Disease Oriented Group, Mayo Clinic Cancer Center, and the Mayo Phase 2 Consortium

RECIST RESPONSE	N= 37
Complete Response (CR)	0
Partial Response (PR)	18 (49%)
Papillary	5 (33%)
Follicular	8 (73%)
Hurthle Cell	5 (45%)
Stable Disease (SD)	3 (43%)
Progression	1 (14%)

p = NS

Histologic subtype	N= 37
Papillary	15
Follicular	11
Hurthle Cell	11

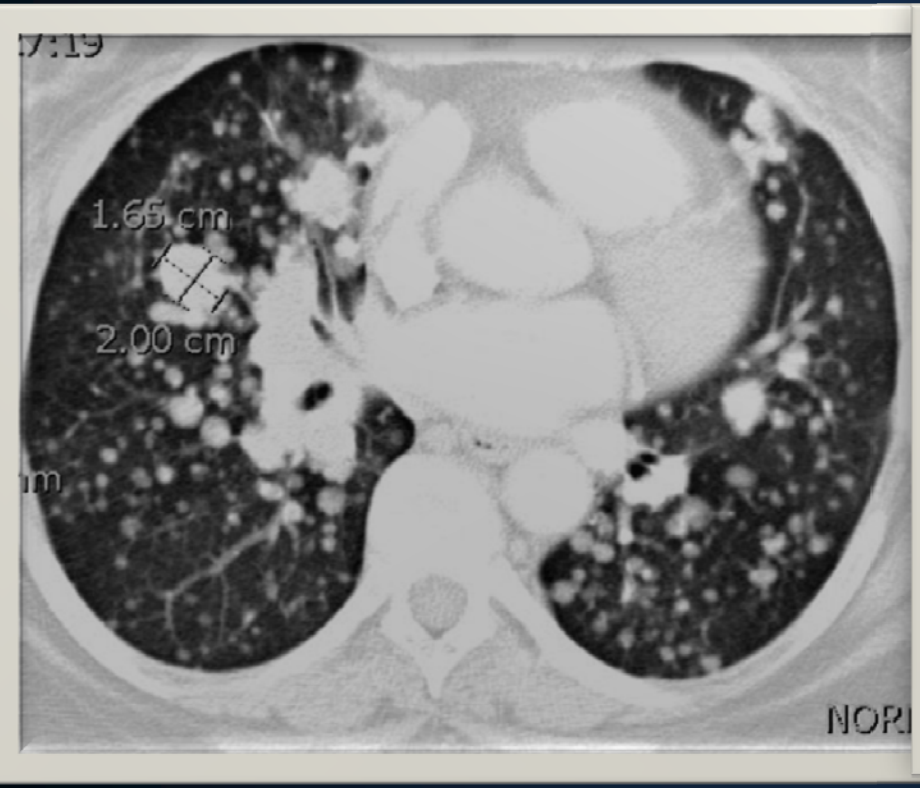
Differentiated Thyroid Cancer Clinical Trials

	Agent and regimen	Radioiodine-resistance required	Threshold for progression	Patients with any RECIST response (n/total [%])	Median survival (months)	
					Progression-free	Overall
Cohen et al[11]	Axitinib 5 mg twice daily	Yes	None	14/45 (31%)	18·1*	NR
Iten et al[12]	[^{90}Yttrium-DOTA]-TOC median cumulative administered activity 12·6 GBq (range 1·7–29·6 GBq)	Yes	<12 months	NR	NR	16·8
Gupta-Abramson et al[13]	Sorafenib 400 mg twice daily	Yes	<12 months	7/27 (26%)	19·75	NR
Kloos et al[14]	Sorafenib 400 mg twice daily	No	None	6/52 (12%)	12·6	25·5
Aim et al[15]	Thalidomide 800 mg daily	Yes	<12 months	5/28 (18%)†	4†	17†
Sherman et al[16]	Motesanib 125 mg daily	Yes	<6 months	13/93 (14%)	40	NR
Argiris et al[17]	Interferon alfa 2b, 12 million units/m² subcutaneously on days 1–5, and doxorubicin, 40 mg/m² intravenously on day 3; 28-day cycles	Yes	None	1/14 (7%)	5·9	26·4
Mrozek et al[18]	Celecoxib 400 mg twice daily	Yes	<12 months	1/32 (3%)	NR	NR
Woyach et al[19]	Vorinostat 200 mg twice daily (2 weeks on, 1 week off)	Yes	None	0/16	NR	NR
Pennell et al[20]	Gefitinib 250 mg daily	Yes	None	0/17	3·7*	17·5*

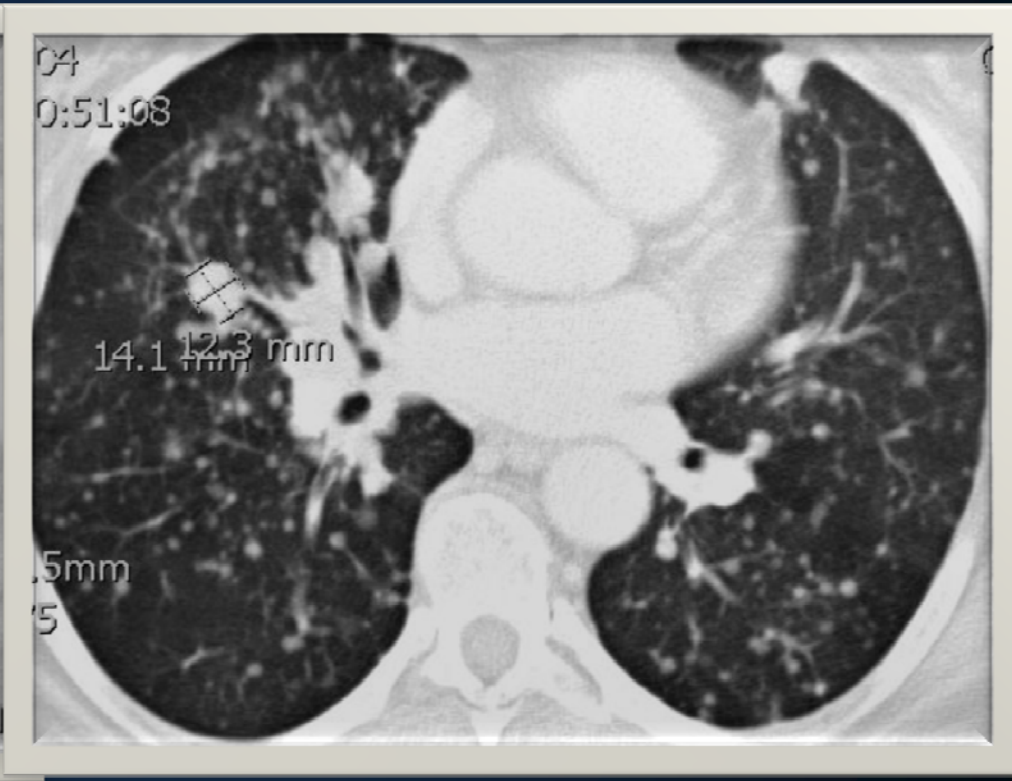
NR=not reported. RECIST=Response Evaluation Criteria in Solid Tumors. *Includes patients with anaplastic and medullary thyroid cancers. †Includes patients with medullary thyroid cancers.

***Table 4*: Summary of results of published clinical trials in differentiated thyroid cancers**

DC after 12 weeks of sorafenib



5/08 CT

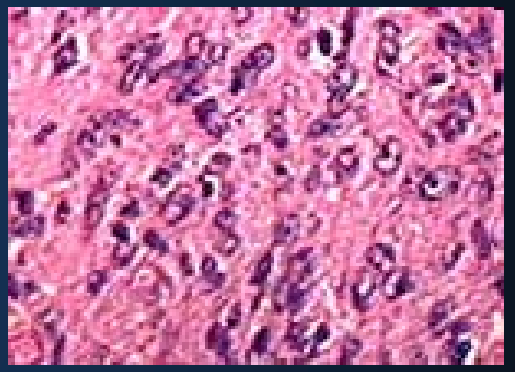


10/08 CT

Anaplastic Thyroid Cancer

Anaplastic Thyroid Cancer

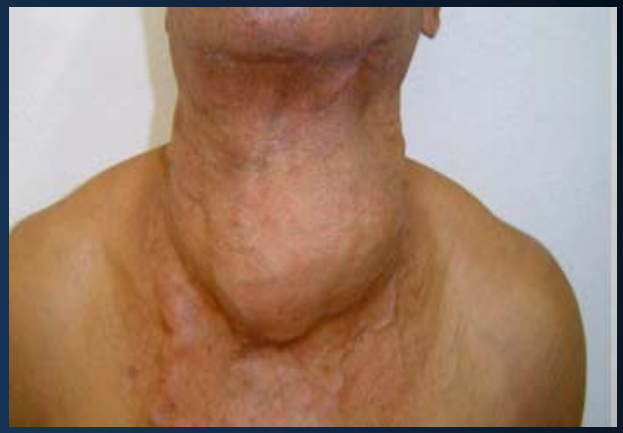
- Undifferentiated tumors
- Aggressive
  - Disease-specific mortality near 100%
- Annual incidence: 2/1,000,000
- Mean age at diagnosis: 65
- 60-70% occur in women
- 20% of patients have history of differentiated thyroid cancer (DTC)
- 20-30% have concurrent DTC



Anaplastic Thyroid Cancer

- Up to 90% have regional or distant metastases at presentation
  - Lungs most common site
- Clinical presentation:
  - Rapidly enlarging neck mass
    - Pain, upper airway compression, dyspnea, dysphagia, hoarseness, cough
  - Constitutional symptoms:
    - Anorexia, fever, weight loss

Anaplastic Thyroid Cancer



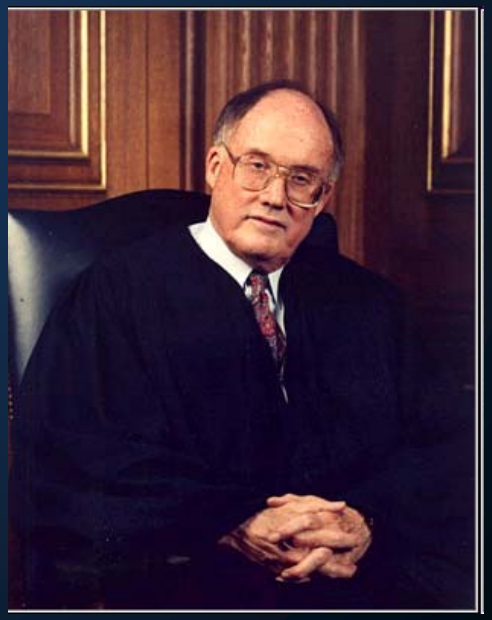
- Diagnosis:
  - FNA
  - CT neck and chest
- Prognosis:
  - Considered Stage IV at diagnosis
  - Patients with disease confined to the thyroid/regional disease survive longer than patients with distant mets
  - Tumor size:
    - < 6 cm: 2 yr survival 25%
    - > 6 cm: 2 yr survival 3-15%
- Other: older age, male sex, dyspnea : poorer prognosis

Anaplastic thyroid cancer

- Treatment:
  - Surgery: ONLY if tumor appears localized to the thyroid
    - Lobectomy with wide margins
    - Total thyroidectomy does not prolong survival and has higher complication rate
  - Adjuvant therapy:
    - No data other than uncontrolled observation
    - Most will treat with concurrent chemoradiotherapy

Metastatic or advanced ATC

- No effective therapy, uniformly fatal
- Median survival: 3-7 months
- One year survival: 20-35%
- Five year survival: 5-14%
- Death most often due to airway compromise (50-60%)
- Chemotherapy and/or radiation do not prolong survival
- Patients should participate in clinical trials

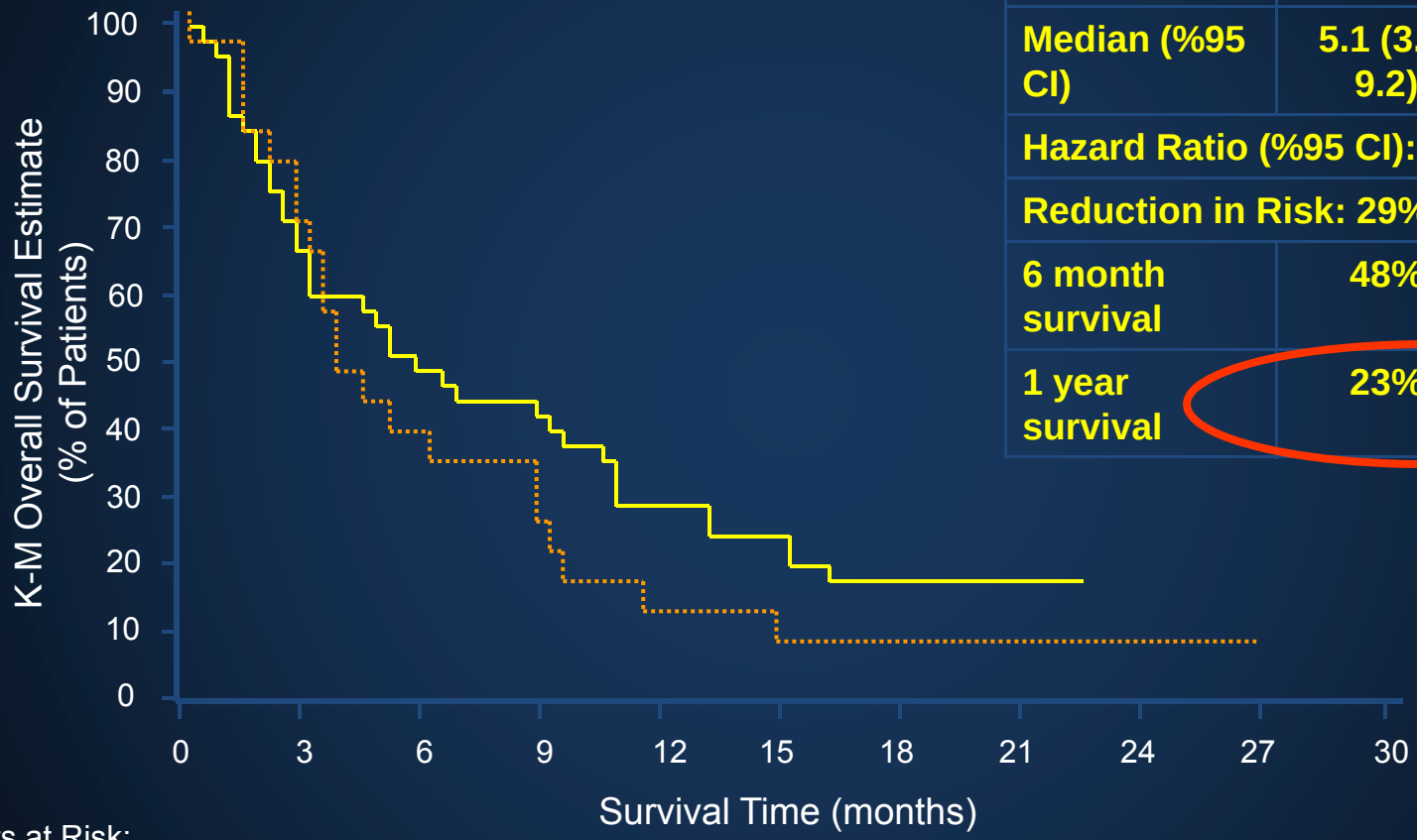


FACT Trial (Fosbretabulin + Carboplatin/Paclitaxel vs. Carboplatin/Paclitaxel Alone in ATC

- Results reported September 2010
- Phase II/III Randomized Trial
- 80 patients
  - Largest ATC trial
  - First randomized trial
  - 55 patients Fosbretabulin/Carbo/Taxol
  - 25 patients Carbo/Taxol alone

Overall Survival

Intent-to-Treat Population



	CA4P+C/P	C/P
Median (%95 CI)	5.1 (3.1, 9.2)	4.1 (2.8, 8.9)
Hazard Ratio (%95 CI): 0.71 (0.42, 1.22)		
Reduction in Risk: 29%		
6 month survival	48%	37%
1 year survival	23%	9%

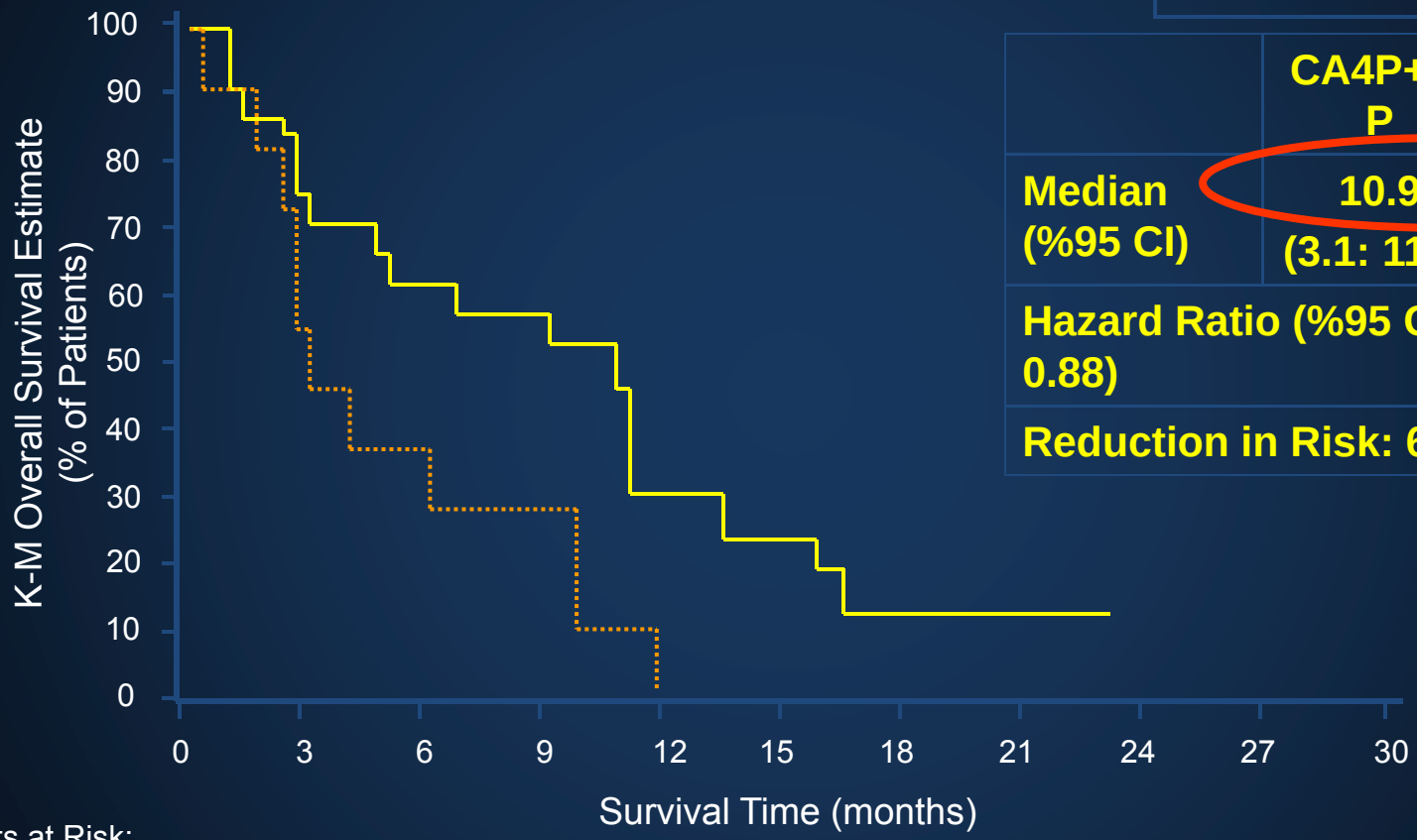
Patients at Risk:

CA4P+C/P (n=55)	36	25	18	9	6	2	2	-	-	-
C/P (n=25)	15	8	6	2	2	1	1	1	1	-

Data Cutoff: 08August2010

Overall Survival

Age ≤ 60



	CA4P+C/P	C/P
Median (%95 CI)	10.9 (3.1: 11.1)	3.1 (1.7, 9.5)

Hazard Ratio (%95 CI): 0.38 (0.16, 0.88)

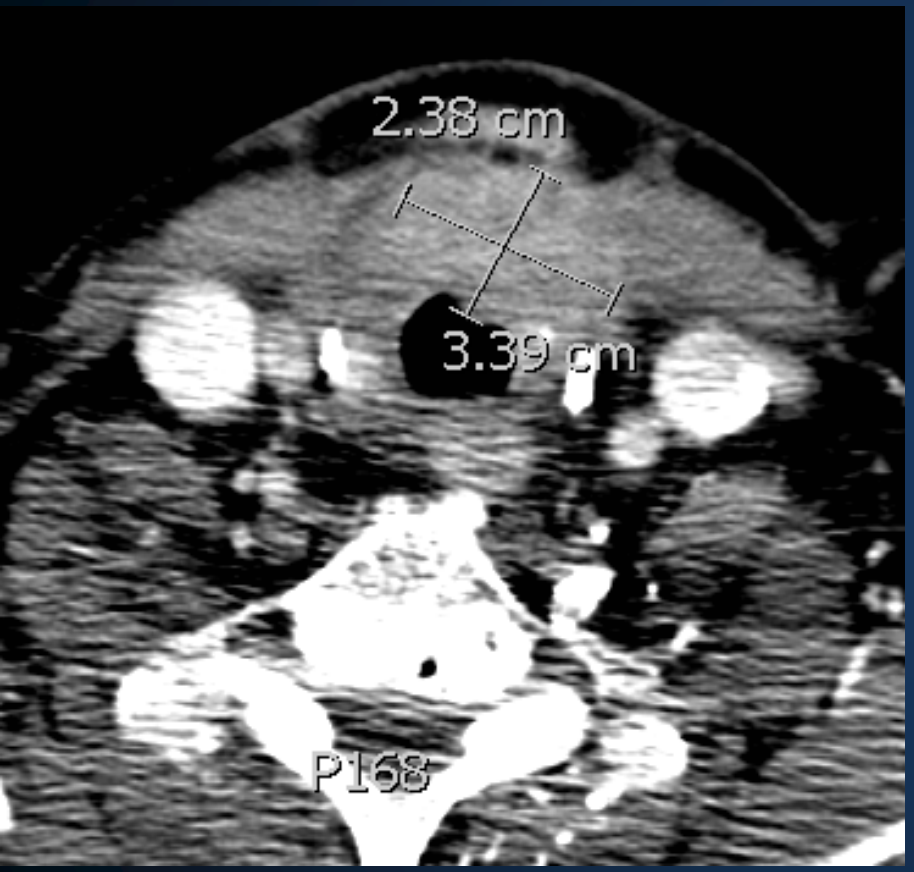
Reduction in Risk: 62%

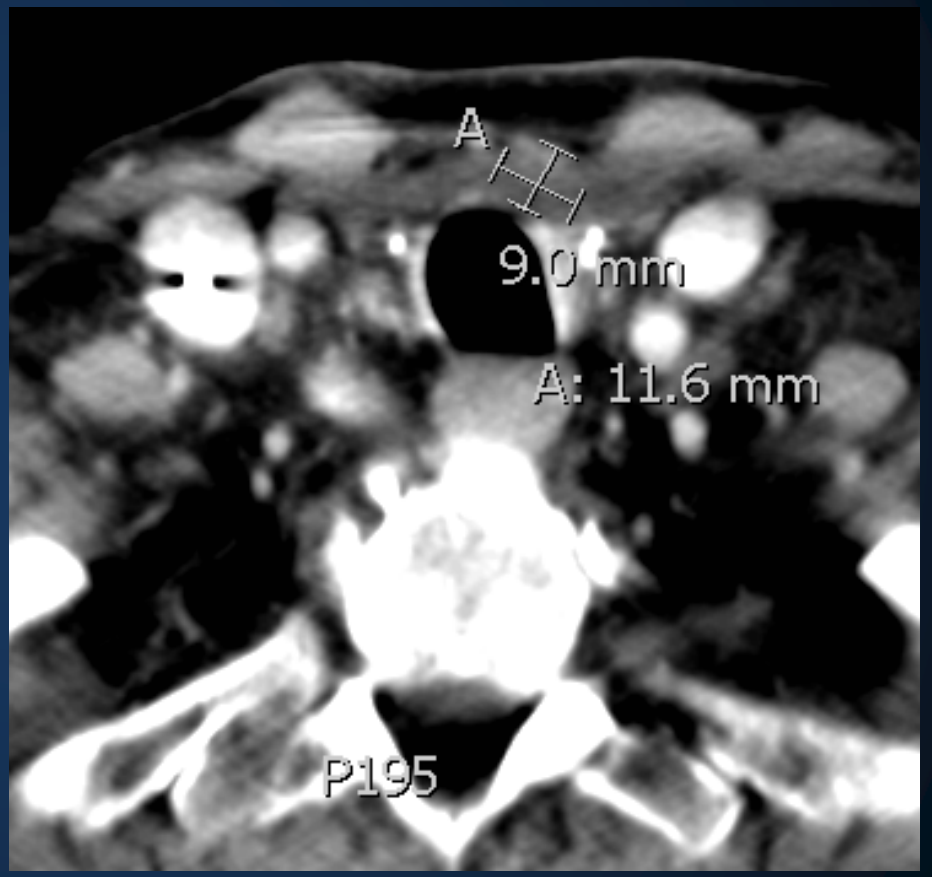
Patients at Risk:

CA4P+C/P (n=24)	18	14	11	5	4	1	1	-	-	-
C/P (n=11)	6	4	3	0	0	0	0	0	0	0

Data Cutoff: 08August2010

Anaplastic Thyroid Cancer Treated With Combretastatin, Carboplatin, Paclitaxel

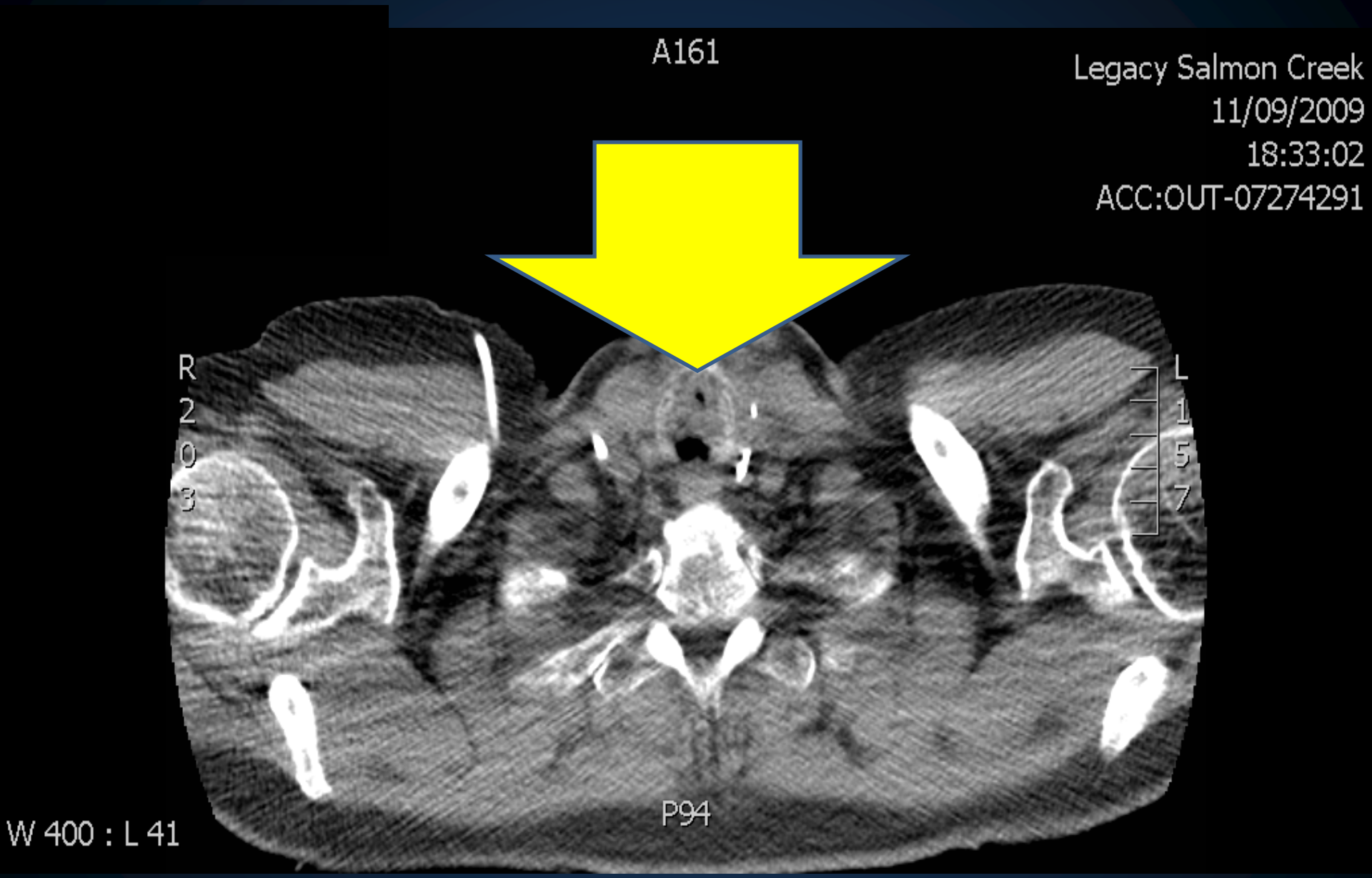




6/9/09

9/1/09

Vague thickness, difficult to see or measure any tumo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Medullary Thyroid Cancer

Medullary Thyroid Cancer

- Neuroendocrine tumor of the parafollicular (C cells)
- Produce calcitonin
- 80% are sporadic
- 20% are familial: MEN type 2 syndromes
- Sporadic MTC presents 50s-60s
- Familial MTC (MEN2) presents younger (30s)
  - Children with MEN 2B undergo thyroidectomies in infancy
  - Children with MEN 2A undergo thyroidectomies by ages 5 or 6

Medullary Thyroid Cancer

- Clinical presentation:
  - Thyroid nodule
  - 50% have cervical lymph node involvement
  - 15% have symptoms—dysphagia, hoarseness
  - 5% have distant metastases
  - Systemic symptoms:
    - Secretes calcitonin: diarrhea, facial flushing
    - Can secrete corticotrophin (ACTH): Cushing's syndrome

Inherited MTC Autosomal Dominant Syndromes

MEN 2A	MEN 2B	FMTC (Familial Medullary Thyroid Cancer)
MTC (100%)	MTC (100%)	MTC
pheochromocytoma	pheochromocytoma	
Primary parathyroid hyperplasia (hyperparathyroidism)	Mucosal neuromas	
RET C634A	RET M918T	RET exon 11

Did he have a pheochromocytoma when assassinated?

-thinner, he fainted while getting up quickly from a chair, he had periodic severe headaches and cold hands and feet.

Did 2 of his sons, Willie and Tad, also have MEN 2B?

-Photographs of them show somewhat irregular lips.

-Willie died at 11, probably of typhoid fever

-Tad at 18, reportedly of tuberculosis

His mother died at 34

Doubtful…he had already lived to 56

Inherited MTC

- Kindred can be screened for medullary thyroid cancer with calcitonin levels
  - Screening of MEN 2A families found 80% of cases—most had no thyroid abnormalities on exam
- Kindred are now screened for point mutations in the RET proto-oncogene
  - Allows for earlier diagnosis and prophylactic thyroidectomies

Clinical Evaluation

- CTs of neck, chest, abdomen, pelvis
- Bone scan
- PET/CT imaging controversial—can often miss metastases
- Serum calcium level
- 24 hour excretion of metanephrines, norepinephrine, and epinephrine
- RET mutation
- Calcitonin level

Prognosis

- Postoperative calcitonin doubling time:
  - < 6 months: 10 yr survival = 8%
  - 6-24 months: 10 yr survival = 37%
  - > 2 yrs: 10 yr survival = 100%
- Age at diagnosis:
  - < 40: 10 yr survival = 65%
  - > 40: 10 yr survival = 50%
- RET M918T mutation

Treatment of Medullary Thyroid Cancer

- Cured only by complete resection of tumor and lymph node mets
- Total thyroidectomy
  - Up to 30% have bilateral or multifocal disease
- Start thyroxine (T4) immediately post-op
    - Maintain euthyroid state
    - C-cells are not TSH responsive
    - No role for radioiodine
- Measure serum calcitonin and CEA 6 months after surgery
  - Detect residual disease
  - If undetectable, 5% 5-yr recurrence rate

Residual/Recurrent MTC

- Surgical resection
- Radiation?
  - No prospective data
  - May prolong disease progression interval
- Chemotherapy
  - Not effective
- Clinical trials with targeted agents
- Vandetanib approved for advanced, progressive or symptomatic disease on 4/6/11

Vandetanib in locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind Phase III trial (ZETA)

SA Wells,[1] BG Robinson,[2] RF Gagel,[3] H Dralle,[4] JA Fagin,[5] M Santoro,[6] E Baudin,[7] J Vasselli,[8] J Read[9] and M Schlumberger[7]

[1]*Medical Oncology Branch, National Cancer Institute, NIH, Bethesda, MD*
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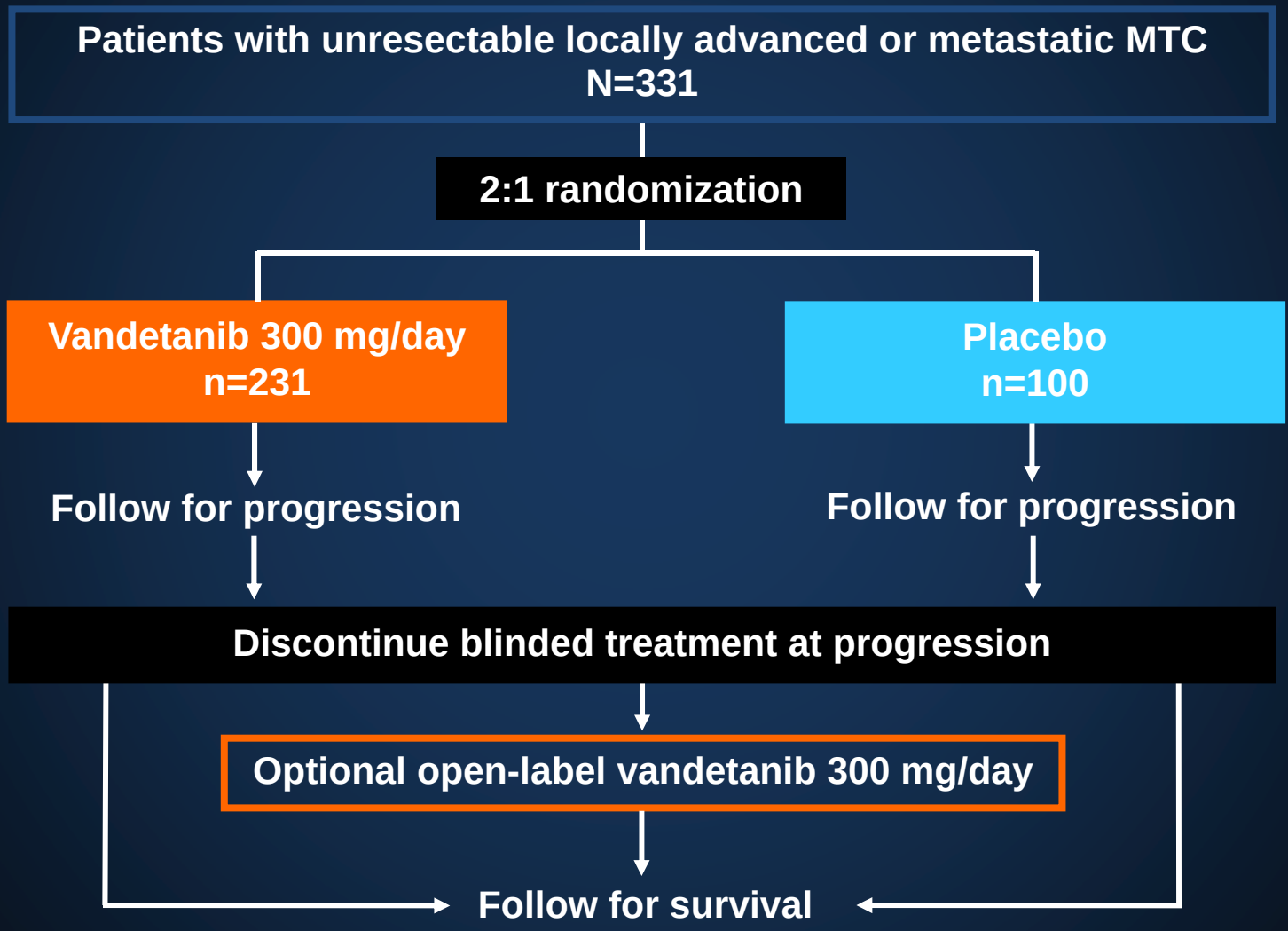
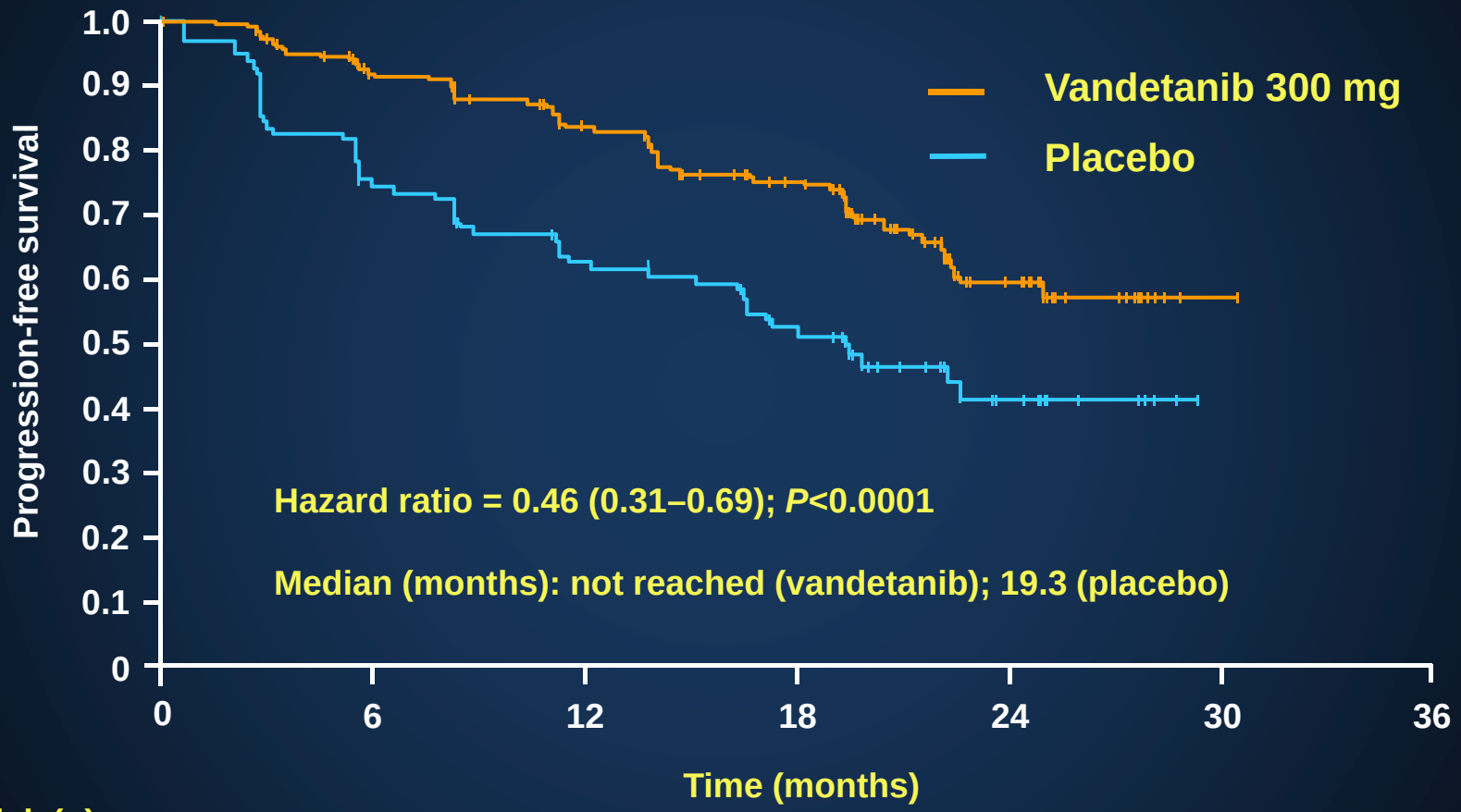
[3]*University of Texas MD Anderson Cancer Center, Houston, TX*
[4]*Martin Luther University Halle-Wittenberg, Halle, Germany*
[5]*Memorial Sloan-Kettering Cancer Center, New York,*
[6]*Universita' di Napoli Federico II, Naples, Italy*
[7]*Institut Gustave Roussy, Villejuif, France*
[8]*AstraZeneca, Wilmington, DE*
[9]*AstraZeneca, Macclesfield, UK*

Study design



PFS (primary endpoint)



At risk (n)							
Vandetanib	231	198	171	141	42	1	0
Placebo	100	72	57	45	13	0	0

Hazard ratio <1 favors vandetanib

Objective tumor assessments

	Vandetanib 300 mg (n=231)	Placebo (n=100)
ITT analysis*		
Objective response rate	45% (104)	13% (13)
Odds ratio (95% CI)	5.48 (2.99–10.79), P<0.0001	
Excluding open-label scans		
Objective response rate	44% (101)	1% (1)
Odds ratio (95% CI)	76.91 (16.68–1366), P<0.0001	

- 24 patients randomized to placebo received open-label therapy before progression according to central read
  - 12 (50%) had an objective tumor response
- Objective responses were durable; median duration of response not reached at 24 months of follow-up

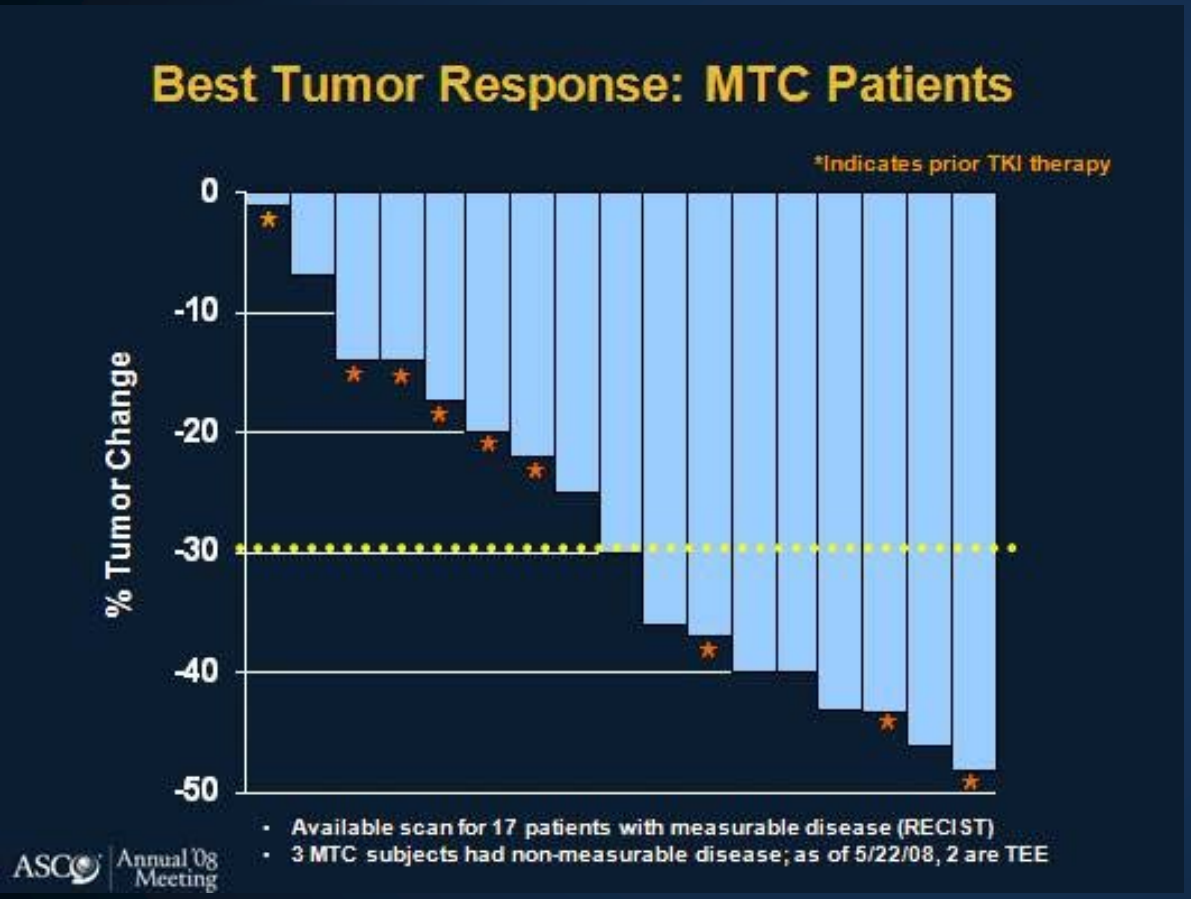
Odds ratio >1 favors vandetanib
***Including all scans until progression according to central read**

Phase I study of XL184

RECIST RESPONSE	N=34
Complete Response	0
Partial Response	10 (29%)
Stable Disease (≥ 6 months)	15 (41%)
Progressive Disease	?

Median response duration not yet reached

Phase I study of XL184

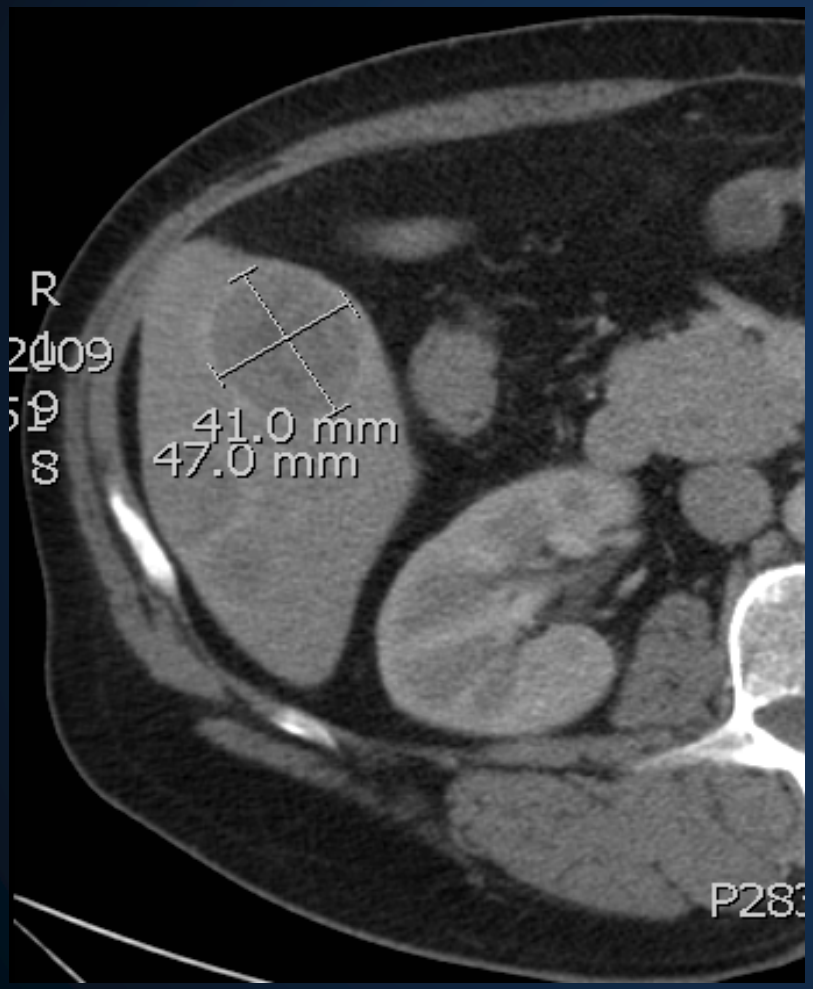


AACR 2009 Abstract 4513

- Sorafenib in metastatic MTC

Response	Hereditary N=3 (%)	Sporadic N=16 (%)
Partial Response	1 (33)	1 (6)
Stable Disease	2 (67)	14 (87)
> 20-29% decrease	0	2
>10-20% decrease	1	7
>0-10% decrease	1	5
Stable Disease > 6 months	1 (33)	10 (62)
Median Duration Stable Disease months	5 (4-6+)	12 (2-22+)
Progressive Disease	0	1 (6)

AEE After 6 Weeks of Sorafenib



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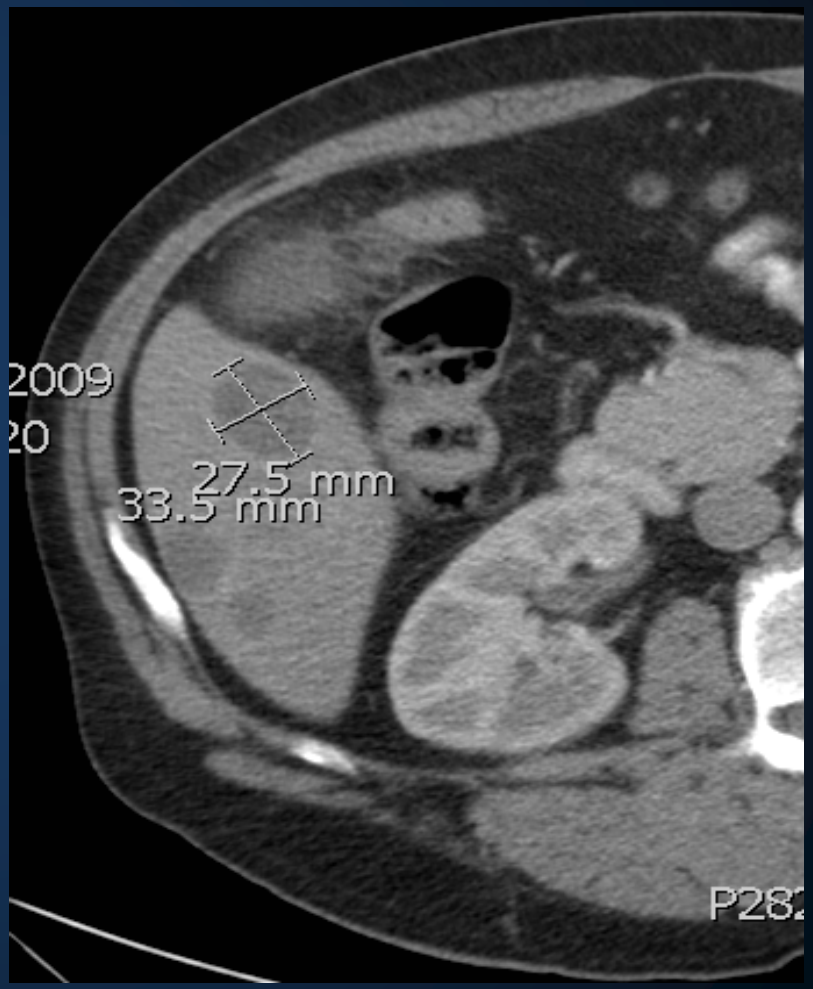

11/04/09

NCI Clinical Trials in Advanced Thyroid Cancer

STATUS	MALIGNANCY	TITLE
OPEN	Medullary Thyroid Cancer	**A Targeted Phase I/II trial of ZD6474 (Vandetanib;ZACTIMA)plus the proteasome inhibitor, Bortezomib (Velcade), in advance or metastatic Medullary Thyroid Cancer (MTC)**
OPEN	Anaplastic Thyroid Cancer	**Phase 1/ 2 Trial of EPC2407 (Crolibulin) plus Cisplatin in Adults with Solid Tumors with a Focus on Anaplastic Thyroid Cancer (ATC)**

Phase I/II trial of ZD6474 (Vandetanib;ZACTIMA) plus the Bortezomib (Velcade), in Medullary Thyroid Cancer (MTC)

- Phase I
  - Study Design:
    - assess the safety, tolerance and activity of daily oral Vandetanib and Bortezomib on days 1, 4, 8 and 11 every 28 days in adults.
  - Eligibility for phase I:
    - diagnosis of recurrent, metastatic or primary unresectable solid tumor that does not have curative standard treatment.

COMPLETE

- Phase II:
  - Study Design:
    - Compare the activity of the combination of bortezomib plus vandetanib or vandetanib alone using a 2:1 randomization
  - Eligibility for phase II:
    - Previously untreated recurrent or metastatic medullary thyroid cancer

Phase I/II trial of EPC2407 (Crolibulin) plus Cisplatin in Adults with Solid Tumors with a Focus on Anaplastic Thyroid Cancer (ATC)

Crolibulin (EPC2407):

- microtubule inhibitor that has been shown to have direct antitumor effects in vivo and in vitro
- disruption of endothelial cells with disruption of blood flow to the tumor

Phase I/II trial of EPC2407 (Crolibulin) plus Cisplatin in Adults with Solid Tumors with a Focus on Anaplastic Thyroid Cancer (ATC)

Phase I Eligibility:

- Adults ≥18 with diagnosis of recurrent, metastatic or primary unresectable solid tumor that does not have curative standard treatment.

Phase II Eligibility:

- Adults ≥18 with a diagnosis of recurrent, metastatic or primary unresectable ATC

Phase I/II trial of EPC2407 (Crolibulin) plus Cisplatin in Adults with Solid Tumors with a Focus on Anaplastic Thyroid Cancer (ATC)

Phase I Study Design:

- Dose escalation of Cisplatin Day 1 + Crolibulin Days 1,2,3 q 21 days

Phase II Study Design:

- Randomization 2:1 of patients receiving MTD of Cisplatin/Crolibulin vs. Cisplatin alone.

QUESTIONS?