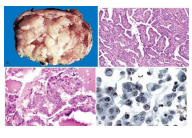
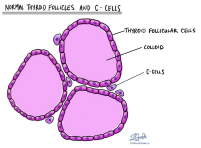
Outline

- Thyroid Malignancies
  - Differentiated thyroid cancer (papillary and follicular)
  - Medullary thyroid cancer
  - Anaplastic thyroid cancer
- Adrenocortical carcinoma
- Pheochromocytoma/paraganglioma

Thyroid Malignancies

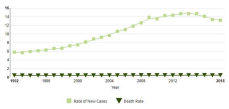
- Cancers of Follicular Epithelial Cells
  - Differentiated Thyroid Cancer
    - Papillary Thyroid Carcinoma
    - Follicular Thyroid Carcinoma
    - Hürthle Cell Carcinoma
  - Poorly Differentiated Thyroid Cancer
    - Derived from Follicular or Papillary Thyroid Carcinomas?
  - Undifferentiated Thyroid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





Thyroid Cancer Epidemiology

Estimated New Cases in 2021	44,280
% of All New Cancer Cases	2.3%
Estimated Deaths in 2021	2,200
% of All Cancer Deaths	0.4%

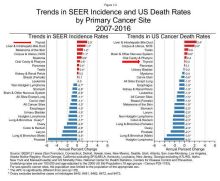


5-Year Relative Survival
98.3%
2011–2017

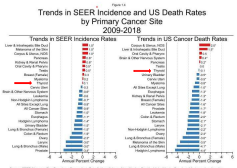
- Thyroid Cancer is the most common endocrine malignancy
  - **Papillary Thyroid Cancer** most common thyroid cancer

SEER Cancer Stat Facts: Thyroid Cancer. National Cancer Institute. Bethesda, MD.

Incidence and Death Rates



Women:men = 3:1
Median age = 51



Between 2009 and 2017, the American College of Radiology, the American Thyroid Association (ATA) and the US Preventive Services Task Force issued strong recommendations against biopsy of very small thyroid nodules and those lacking suspicious features and screening of thyroid cancer in the asymptomatic population

SEER Cancer Stat Facts: Thyroid Cancer. National Cancer Institute. Bethesda, MD.

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%

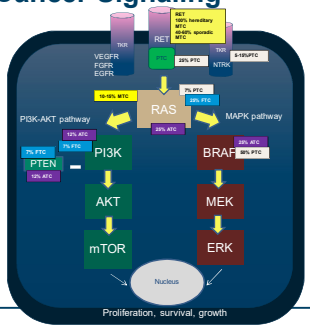
Nature Reviews. April 2006, p.292-306.

Thyroid Cancer AJCC Staging

Stage	Follicular or Papillary* <55yo	Follicular or Papillary* ≥55yo	Medullary Any age	Anaplastic Any age
I	M0	T1-2N0	T1N0	
II	M1	T1-2N1 T3	T2-3N0	
III		T4a	T1-T3N1a	
IVa		T4b	T1-T3N1b T4a	T1-T3aN0
IVb		M1	T4b	T1-T3aN1 or >T3a
IVc			M1	M1

*The most advanced a patient <55 yo can be is stage II

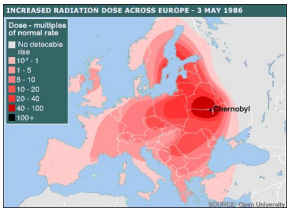
Thyroid Cancer Signaling



Differentiated Thyroid Cancer (Papillary and Follicular)

Differentiated Thyroid Cancer (DTC) Risk Factors

- **Radiation exposure**
  - Younger age at exposure: Higher risk
    - Controversial whether exposure after age 15 confers increased risk
- **Genetic**
  - Component of several inherited syndromes:
  - Familial adenomatous polyposis
    - Gardner's syndrome
    - Turcot syndrome
  - Cowden syndrome
  - Carney complex

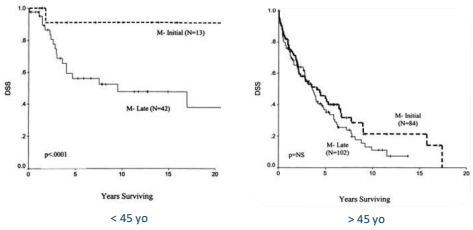


Disease Specific Survival By Stage

Stage	N	10-yr Disease Specific Survival
I	7736	99.5
II	441	94.7
III	707	94.1
IV	600	67.7

THYROID
Volume 26, Number 3, 2016

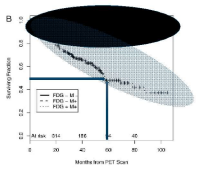
Age and Prognosis



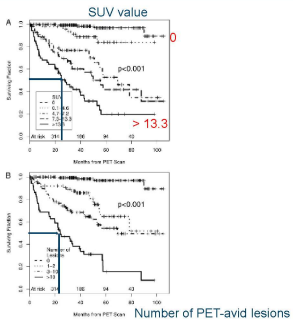
< 45 yo > 45 yo

Shoup, et al. *JCAS* 2003

PET and Prognosis



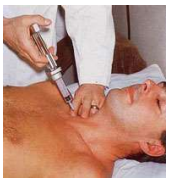
SUV and number of PET-avid lesions influences prognosis in differentiated thyroid cancer



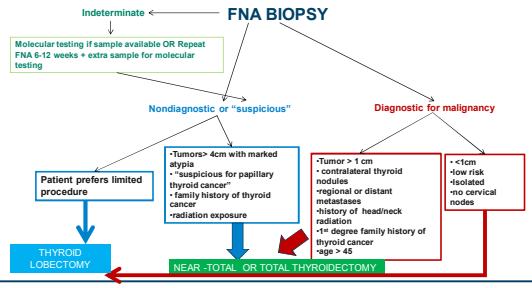
Robbins, et al. *JCEM*, Feb 2006, 91 (2): 498-505

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

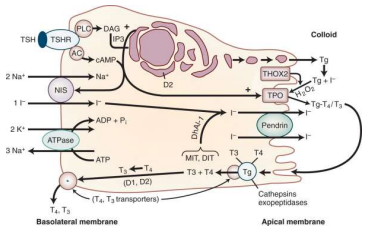


What is the appropriate surgical management?



Haugen, et al. *THYROID* Volume 26, Number 1, 2016

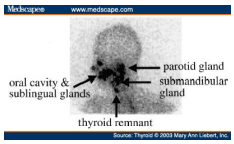
Thyroid Follicular Cell



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)



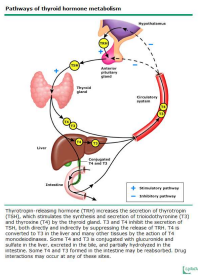
Postoperative Radioiodine

- Not recommended for low-risk disease
  - < 1cm, unifocal, etc.
- Recommended for select intermediate-risk patients
  - Microscopic invasion, aggressive histology, N1
- Routinely recommended for high-risk disease
  - Distant metastases, N1 > 3 cm, residual disease, etc.

Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016; 26:1.

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
  - TSH suppression can be reduced after 5 years
- Adverse effects of TSH suppression—subclinical thyrotoxicosis:
  - Exacerbation of angina, increased risk of atrial fibrillation, increased risk of osteoporosis in post menopausal women



Thyrotropin-releasing hormone (TRH) increases the secretion of thyrotropin (TSH), which stimulates the synthesis and secretion of triiodothyronine (T3) and thyroxine (T4) by the thyroid gland. T3 and T4 inhibit the secretion of both the TRH by the hypothalamus and TSH by the anterior pituitary gland. T4 is converted to T3 in the liver and many other tissues by the action of T4 monodeiodinases. Some T4 and T3 is conjugated with glucuronide and sulfate in the liver, excreted in the bile, and partially hydrolyzed in the intestine. Some T4 and T3 formed in the intestine may be reabsorbed. Drug interactions may occur at any of these sites.

Management of Recurrent Disease

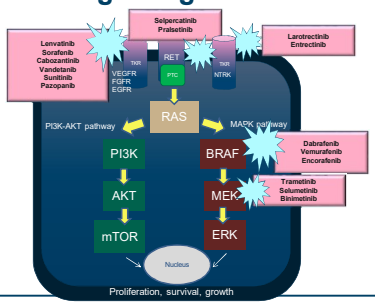
- Surgical resection if limited disease
  - +/- RAI therapy depending on uptake, prior dose
- If more extensive disease:
  - RAI if uptake on iodine scan
    - NOTE: **IV contrast SHOULD NOT BE GIVEN** for CT scans if RAI is still a potential option
    - Treatment of choice, can result in CR
      - Young patients, small pulmonary nodules
  - External beam radiotherapy
  - Bisphosphonates
  - Systemic therapy
  - Observation

RAI-Refractory Thyroid Cancer

- Distant metastases in 10-15% DTC patients
- 35-50% metastatic thyroid cancers lose iodine concentrating ability
- RAI rarely results in complete remission
  - Young women with small volume disease (lungs)
- PET avidity is inversely proportional to RAI uptake
- Standard chemotherapy had disappointing response rates, significant toxicity

Shimaoka, et al. Cancer 56, 1985

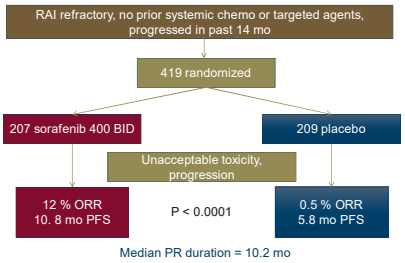
Thyroid Cancer Signaling



Approved Drugs

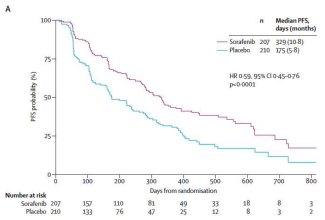
Differentiated (PTC, FTC)
Sorafenib
Lenvatinib
Larotrectinib Entrectinib (NTRK fusion)
Selpercatinib Pralsetinib (RET fusion)

Sorafenib vs. Placebo in Locally Advanced or Metastatic DTC



Median PR duration = 10.2 mo

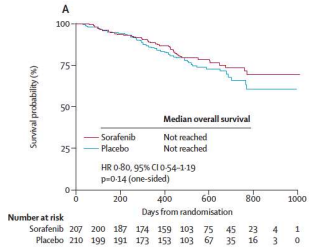
Sorafenib in DTC Progression Free Survival



FDA approved Nov 2013 for the treatment of locally recurrent or metastatic, progressive differentiated thyroid carcinoma (DTC) refractory to radioactive iodine treatment.

Brose, et al. *Lancet.* 2014 Apr 23.

Sorafenib in DTC Overall Survival



150 (71%) of placebo patients crossed over to sorafenib

Brose, et al. *Lancet.* 2014 Apr 23.

Adverse Events

	Sorafenib		Placebo	
	Any %	Grade 3/4 %	Any %	Grade 3/4 %
Any AE	99	-	88	-
SAE	37	-	26	-
Hand-foot	76	20/0	10	-
Diarrhea	69	5/0.5	15	1/0
Alopecia	67	-	8	-
Rash or desquamation	50	5/0	12	-
Fatigue	50	5/0.5	25	1/0
Weight loss	47	6/0	14	1/0
Hypertension	41	10/0	12	2/0

Brose, et al. *Lancet.* 2014 Apr 23.

Lenvatinib in patients with 131I-refractory differentiated thyroid cancer

- VEGFR1-3, FGFR1-4, PDGFRβ, RET, KIT inhibitor
- Randomized 2:1, double blind, placebo controlled study
- RAI refractory, PD within 13 mo.
- 392 patients, 54% PTC
- Crossover permitted after progression (83%)
- Dose was 24 mg daily

N Engl J Med 2015; 372:621-630

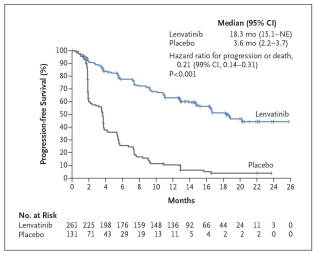
Lenvatinib vs. Placebo - Efficacy

Efficacy	Lenvatinib (n=261)	Placebo (n=131)
ORR	**169 (65%)**	2 (2%)
CR	**4 (2%)**	0
PR	**165 (63%)**	2 (2%)
SD > 23 weeks	40 (15%)	39 (30%)
PD	18 (7%)	52 (40%)
Median time to response (mo)	2 (1.9-3.5)	-
Median duration of response	30 months	-
Median PFS (mo)	18.3	3.6
Deaths % p = 0.10	27%	36%

Median OS = Not Evaluable

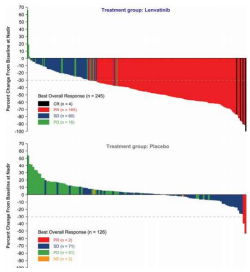
Lenvima package insert 2015

Lenvatinib vs. Placebo - Progression-Free Survival



N Engl J Med 2015; 372:621-630

Analysis of Overall Tumor Shrinkage



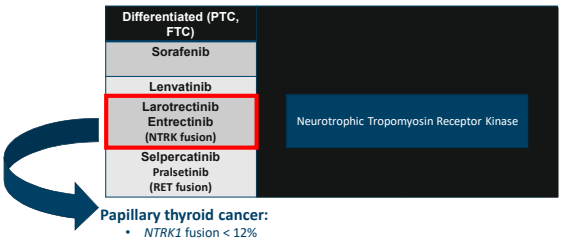
N Engl J Med 2015; 372:621-630

Lenvatinib vs. Placebo - Adverse Events

Adverse Event	Lenvatinib 24mg N=261 All Grades %	Grades 3-4 %	Placebo N=131 All Grades %	Grades 3-4 %
hypertension	73	44	16	4
diarrhea	67	9	17	0
Fatigue/asthenia	67	11	35	4
Arthralgia/myalgia	62	5	28	3
Decreased appetite	54	7	18	1
Weight loss	51	13	15	1
nausea	47	2	25	1
Hand/foot	32	3	1	0
Rash	21	0.4	3	0

Lenvima package insert 2015

Approved Drugs



Papillary thyroid cancer:

- *NTRK1* fusion < 12%
- >15% in Italian population, < 10% in others
- *ETV6-NTRK3* radiation associated

TRK Inhibitors – Larotrectinib and Entrectinib

EFFICACY BY SOLID TUMOR TYPE

Response rates in various tumor types (as assessed by a BIRC,* N=55)[1]

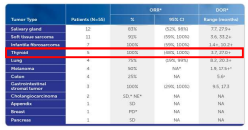


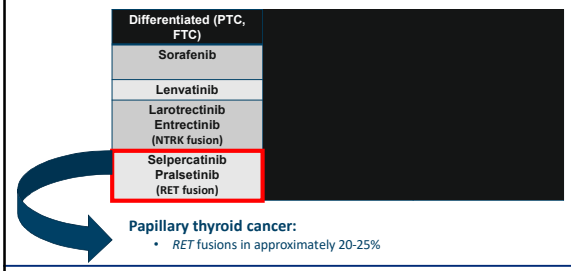
Table 9: Efficacy by Tumor Type

Tumor Type	Patients N = 54	ORR %	ORR 95% CI	DOR Range (months)
Sarcoma	13	46%	19%, 75%	2.8, 15.1
Non-small cell lung cancer	10	70%	35%, 93%	1.9*, 20.1*
Salivary (MASC)	7	86%	42%, 100%	2.8, 16.5*
Breast cancer	6	83%	36%, 100%	4.2, 14.8*
Thyroid cancer	5	20%	NA	7.9
Colorectal cancer	4	25%	NA	4.8*
Neuroendocrine cancers	3	PR	NA	5.6*
Pancreatic cancer	3	PR, PR	NA	7.1, 12.9
Gynecological cancers	2	PR	NA	20.3*
Cholangiocarcinoma	1	PR	NA	9.3

* Censored
MASC = mammary analogue secretory carcinoma, NA = not applicable, PR = partial response

rozlytrek_prescribing.pdf
https://www.hcp.vitrakvi-us.com/about-vitrakvi/efficacy/

Approved Drugs



Papillary thyroid cancer:
- *RET* fusions in approximately 20-25%

Selpercatinib – RET Fusion Thyroid Cancer

- 27 patients with RET fusion-positive thyroid cancer refractory to RAI
  - 19 previously treated with sorafenib, lenvatinib, or both
  - 8 systemic therapy naïve
- 160 mg po BID
- Tumor Types:
  - PTC = 78%
  - PDTC = 11%
  - ATC = 7%
  - Hurthle Cell = 4%

https://uspl.lilly.com/retevmo/retevmo.html#pi

Selpercatinib – RET Fusion Thyroid Cancer

Table 13 Efficacy Results in LIBRETTO-001 (*RET* Fusion-Positive Thyroid Cancer)

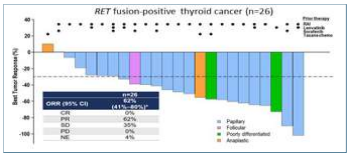
	RETEVMO Previously Treated (n = 19)	RETEVMO Systemic Therapy Naïve (n = 8)
Overall Response Rate[1] (95% CI)	79% (54%, 94%)	100% (63%, 100%)
Complete response	5.3%	12.5%
Partial response	74%	88%
Duration of Response		
Median in months (95% CI)	18.4 (7.6, NE)	NE (NE, NE)
% with ≥ 6 months[2]	87	75

[1]Confirmed overall response rate assessed by BICR.
[2] Based on observed duration of response
NE = not estimable

FDA approved May 2020

https://uspl.lilly.com/retevmo/retevmo.html#pi

Selpercatinib



- Most common toxicities:
  - Dry mouth, diarrhea, constipation, nausea, hypertension, fatigue, edema, rash, headache
- Very low rate of grade 3-4 toxicity

https://uspl.lilly.com/retevmo/retevmo.html#pi

Pralsetinib – RET Fusion Thyroid Cancer

- 9 patients –disease progression following standard therapy
- 100% had papillary thyroid cancer
- 5 patients had prior sorafenib and/or Lenvatinib
- 5 patients had a history of CNS metastases
- 400 mg once daily

https://www.gene.com/download/pdf/gavreto_prescribing.pdf

Pralsetinib – RET Fusion Thyroid Cancer

Table 13: Efficacy results for *RET* fusion-positive thyroid cancer (ARROW)

Efficacy Parameters	GAVRETO N=9
Overall Response Rate (ORR)[a] (95% CI)	89 (52, 100)
Complete Response, %	0
Partial Response, %	89
Duration of Response (DOR)	**(N=8)**
Median in months (95% CI)	NR (NE, NE)
Patients with DOR ≥ 6 months[b], %	100

NR = Not Reached; NE = Not Estimable
[a] Confirmed overall response rate assessed by BICR
[b] Calculated using the proportion of responders with an observed duration of response at least 6 months or greater

https://www.gene.com/download/pdf/gavreto_prescribing.pdf

Pralsetinib – RET Fusion Thyroid Cancer

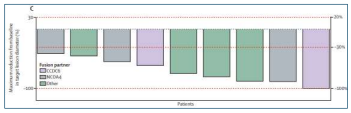


Table 6: Adverse Reactions (≥ 15%) in *RET*-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW

Adverse Reactions	GAVRETO N=138 Grades 1-4 (%)	GAVRETO N=138 Grades 3-4 (%)
Musculoskeletal		
Musculoskeletal Pain[1]	42	0.7*
Gastrointestinal		
Constipation	41	0.7*
Diarrhea[2]	34	5*
Abdominal Pain[3]	17	0.7*
Dry mouth	17	0
Stomatitis[4]	17	0.7*
Nausea	17	0.7*
Vascular		
Hypertension	40	21*
General		
Fatigue[5]	38	6*
Edema[6]	29	0
Pyrexia	22	2.2*
Nervous System		
Headache[7]	24	0
Peripheral Neuropathy[8]	20	0
Dizziness[9]	19	0.7*
Dysgeusia[10]	17	0
Respiratory		
Cough[11]	27	1.4*
Dyspnea[12]	22	2.2*
Skin and Subcutaneous		
Rash[13]	24	0
Metabolism and Nutrition		
Decreased Appetite	15	0

1 Musculoskeletal Pain includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain
2 Diarrhea includes colitis, diarrhea

DTC Summary

- Papillary thyroid cancer is the most common type
- Main risk factors: radiation as a child and family history
- Mainstay of treatment is surgery, often followed by RAI ablation and TSH suppression
- Distant metastases can sometimes be eradicated with RAI therapy
- IV contrast should not be given to patients who are potential candidates for RAI (if needed quickly)

DTC Summary – RAI refractory disease

- *Sorafenib AND lenvatinib are approved for treatment of locally recurrent or metastatic, progressive differentiated thyroid carcinoma (DTC) refractory to radioactive iodine treatment (not tested head to head)
- *Sorafenib and lenvatinib improved PFS, but not OS, therefore, timing of therapy and discussion of risks and benefits with patients is imperative
- *For patients with TRK fusions, larotrectinib or entrectinib are options
- *For patients with RET fusions, selpercatinib or pralsetinib are options
- *Dabrafenib/Trametinib are not FDA approved for BRAF-mutated DTC

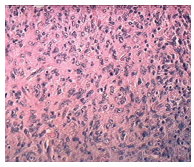
Anaplastic Thyroid Cancer

Anaplastic Thyroid Cancer

- **Rare**
  - incidence: 1-2 cases/million annually
  - 2-5% of all thyroid cancer (600-1000 patients in US/year)
- **Aggressive**
  - Median survival 3-6 months
  - 90% with regional/distant metastases at diagnosis
- **Lethal**
  - Nearly 100% disease-specific mortality
  - Papillary thyroid cancer has ≤10% disease-specific mortality

Clinical Presentation

- **Symptoms**
  - Related to neck mass in most patients
    - Pain, compression of airway, dyspnea, dysphagia, hoarseness, cough
  - Constitutional symptoms can occur
- **Diagnosis**
  - FNA or core biopsy
  - Imaging studies
    - CT of neck and chest
    - FDG PET

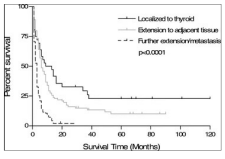


Staging

- All ATC is Stage IV
- In 2003, AJCC revised the staging:
  - IVA: tumor intrathyroidal (surgically resectable)
  - IVB: tumor extrathyroidal (not surgically resectable)
  - IVC: distant metastases
- Stage Distribution in a retrospective series (n=100):
  - Stage IVA: 11%
  - Stage IVB: 31%
  - Stage IVC: 58%

AJCC 6th Edition
Sugino, et al. Thyroid 2011

Survival by Extent of Disease



- Retrospective review
- SEER Database (1983-2002)
- 261 patients
- included those eligible for surgical resection who lived at least one month (omitted 203 patients)

Extent	Median Survival	2-year Survival %	5-year Survival %
Confined to thyroid	9 months	33	23
Local extension	6 months	16	10
Distant mets	3 months	2	---

Chen, et al. Am J Clin Oncol 2008; 31:460-464

National Cancer Database Review

Treatment	Yes (median survival)	No (median survival)
Total thyroidectomy	6.2 mo.	2.3 mo.
Radiation	5 mo.	1.8 mo.
Chemotherapy	5.9 mo.	2.3 mo.

2003-2008 (n = 699)	Median Survival
Stage IVA	9 mo
Stage IVB	4.8 mo
Stage IVC	3 mo

Goals of Therapy

- Quality of life
- Symptom management
- End of life care
- Prevent asphyxiation?
  - – death most often caused by airway compromise (50-60%)
- No therapy has been shown to clearly improve overall survival
  - No adequately powered randomized trials
  - Selection bias

Surgery

- Usually recommended for disease confined to the thyroid or if locoregional disease is surgically resectable
  - Intrathyroidal: total thyroidectomy
  - Locally advanced: depends on extent of disease – total thyroidectomy, lobectomy

Radiation Therapy

- Up to 80% of patients may respond, but most will recur locally
- Hyperfractionated accelerated radiation therapy (>40 Gy) may improve local control
  - Retrospective study of 47 patients
  - 6-month PFS = 94% vs. 65% for palliative (<40 Gy)
  - No survival benefit
- Concurrent chemoradiotherapy
  - Several small series claim potential improved local control and survival compared to historical controls
  - No definitive data regarding survival or local control
    - Selection bias
    - No proven benefit to doxorubicin, cisplatin, taxane, or combination thereof

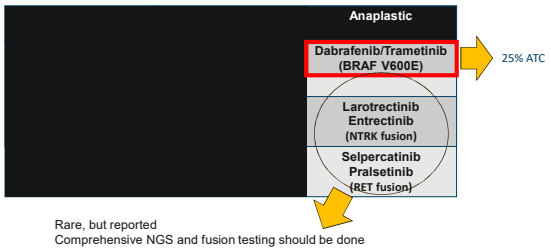
Wang et al. Cancer (2006) 107 (8)

Chemotherapy—Advanced Disease

- Doxorubicin used most commonly
  - Poor response rates
  - No improved survival
- Paclitaxel appears to have most activity
  - 20 patients with advanced disease
    - 120-140mg/m2 CIV over 96hrs q 3 weeks
    - 53% response rate
    - Median survival responders: 32 weeks
    - Median survival non responders: 10 weeks

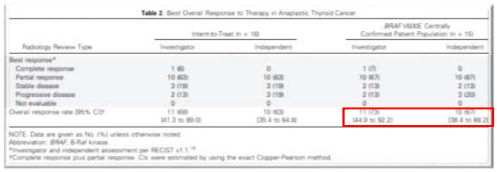
Ain, et al. Thyroid (2000): 10 (7)

Approved Drugs



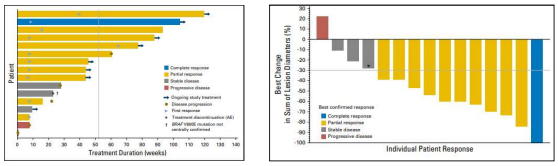
Dabrafenib and trametinib in patients with V600E-mutated ATC

- 16 patients with BRAF V600E mutated ATC
  - All had prior radiation
  - 6 had prior systemic therapy
  - Median age 72



J Clin Oncol 36:7-13. © 2017

Swimmers and Waterfalls



J Clin Oncol 36:7-13. © 2017

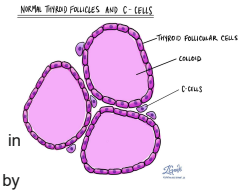
Anaplastic Thyroid Cancer - Current Management Summary

- BRAF TESTING!!!! And comprehensive NGS and fusion testing
- Dabrafenib and trametinib combination therapy for BRAFV600E mutated ATC (approximately 25% of cases)
- Surgery, radiation, and chemotherapy may improve survival for patients with local disease
- Radiation alone with hyperfractionation may achieve local control, but patients are likely to relapse
- Multimodality therapy may improve local control and prevent asphyxiation
  - Does not improve survival
  - Toxicities
- Chemotherapy alone may provide a response
  - Short duration
- No standard therapeutic recommendations, can consult the American Thyroid Association Guidelines or NCCN guidelines
- Clinical trials

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 C634R	RET M918T	RET exon 11

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 to screen for pheo
- RET mutation
- Calcitonin level

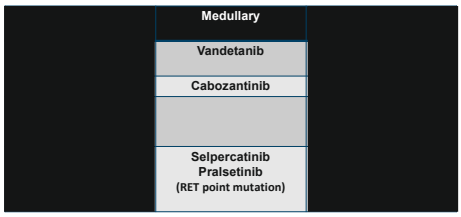
Treatment of Medullary Thyroid Cancer

- 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

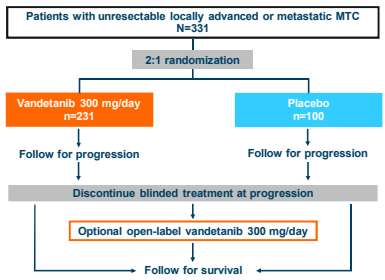
Residual/Recurrent MTC

- Surgical resection
- Radiation?
  - No prospective data, but may improve PFS
- Chemotherapy
  - Not effective
- **Vandetanib** and **Cabozantinib** approved for advanced, progressive or symptomatic disease **regardless** of RET mutation
- **Selpercatinib** and **Pralsetinib** approved for **RET-mutant** MTC

Approved Drugs

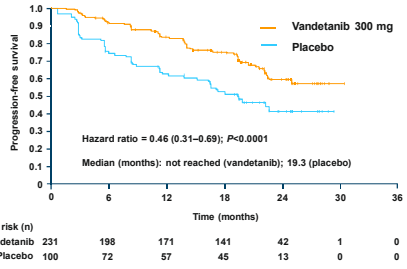


Vandetanib in MTC Study Design



Slide courtesy Samuel Wells, MD

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

Slide courtesy Samuel Wells, MD

Objective Tumor Assessments

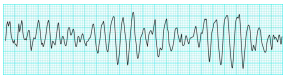
	Vandetanib 300 mg (n=231)	Placebo (n=100)
ITT analysis*		
Objective response rate	**45% (104)**	**13% (13)**
Odds ratio (95% CI)	5.48 (2.99–10.79), P<0.0001	
Excluding open-label scans		
Objective response rate	44% (101)	1% (1)
Odds ratio (95% CI)	76.91 (16.68–1366), P<0.0001	

- 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

Vandetanib Toxicities

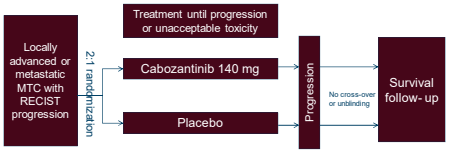
Black Box Warning: QT prolongation. Torsades de pointes and sudden death have been reported.



Most Common toxicities

Adverse Event	Vandetanib 300mg N = 231		Placebo N=99	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Diarrhea/Colitis	57 %	26 %	27 %	2 %
Rash	53 %	5 %	12 %	0
Dermatitis Acneiform/Acne	35 %	1 %	7 %	0
Nausea	33 %	1 %	16 %	0
Hypertension	33 %	9 %	5 %	1 %

An international, double-blind, randomized, placebo-controlled phase III trial (EXAM) of cabozantinib (XL184) in medullary thyroid carcinoma (MTC) patients with documented RECIST progression at baseline



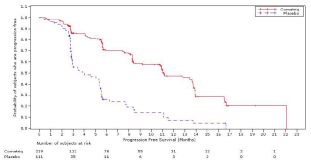
An international, double-blind, randomized, placebo-controlled phase III trial (EXAM) of cabozantinib (XL184) in medullary thyroid carcinoma (MTC) patients with documented RECIST progression at baseline

	Cabozantinib	Placebo
Median PFS (months)	11.2	4
1 year PFS	47.3%	7.2%
HR (95% CI)	0.28 (0.19, 0.40)	

	PR rate
Cabozantinib	27%
Placebo	0

P < 0.0001

Figure 1: Progression-Free Survival



Cabozantinib package insert

Cabozantinib Toxicity

MedDRA System Organ Class/ Preferred Terms	Cabozantinib (n=214)		Placebo (n=109)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
GASTROINTESTINAL DISORDERS				
Diarrhea	63	16	33	2
Stomatitis[2]	51	5	6	0
Nausea	43	1	21	0
Oral pain[2]	36	2	6	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Fatigue	41	9	28	3
Asthenia	21	6	15	1
INVESTIGATIONS				
Decreased weight	48	5	10	0
METABOLISM AND NUTRITION DISORDERS				
Decreased appetite	46	5	16	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
PPES[3]	50	13	2	0
Hair color changes/ depigmentation, graying	34	0	1	0

WARNING: PERFORATIONS AND FISTULAS, and HEMORRHAGE

See full prescribing information for complete boxed warning.

- **Perforations and Fistulas: Gastrointestinal perforations occurred in 3% and fistula formation in 1% of COMETRIQ-treated patients. Discontinue COMETRIQ in patients with perforation or fistula. (5.1)**
- **Hemorrhage: Severe, sometimes fatal, hemorrhage including hemoptysis and gastrointestinal hemorrhage occurred in 3% of COMETRIQ-treated patients. Monitor patients for signs and symptoms of bleeding. Do not administer COMETRIQ to patients with severe hemorrhage. (5.2)**

Cabozantinib package insert

Selpercatinib

- Highly selective RET inhibitor
- Subset global Ph 1/2 trial Libretto-001 trial
- Included patients with RET-mutated MTC who were treated with prior cabozantinib or vandetanib (N=55) or treatment naïve (N=88)

RET-Mutant MTC Previously Treated with Cabozantinib or Vandetanib N= 55	
Overall Response Rate	**69%**
Complete Response	9%
Partial Response	60%
Duration of Response	
Median in Months	NE (19.1, NE)
% with ≥ 6 months	76

Cabozantinib and Vandetanib-naïve RET-Mutant MTC N= 88	
Overall Response Rate	**73%**
Complete Response	11%
Partial Response	61%
Duration of Response	
Median in Months	22 (NE, NE)
% with ≥ 6 months	61

https://uspl.lilly.com/retevmo/retevmo.html#pi

Pralsetinib

- Highly selective RET inhibitor
- Subset of global ph 1/2 ARROW trial
- Included patients with RET-mutated MTC who were treated with prior cabozantinib or vandetanib (N=55) or treatment naïve (N=21)

RET-Mutant MTC Previously Treated with Cabozantinib or Vandetanib N= 55	
Overall Response Rate	**60%**
Complete Response	2%
Partial Response	58%
Duration of Response	
Median in Months	NR (15.1, NE)
% with ≥ 6 months	96%
% with ≥ 12 months	92%

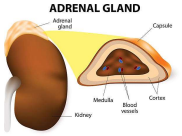
Cabozantinib and Vandetanib-naïve RET-Mutant MTC N= 21	
Overall Response Rate	**71%**
Complete Response	5%
Partial Response	67%
Duration of Response	
Median in Months	NR (NE, NE)
% with ≥ 6 months	93
% with ≥ 12 months	84

Subbiah, V. et al. The lancet. Diabetes & endocrinology (2021, June 9)

MTC Summary

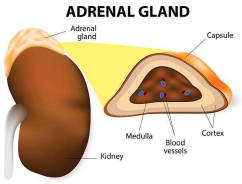
- Hereditary or sporadic neuroendocrine tumor
  - MEN 2 syndromes – germline RET mutations
  - Sporadic - ~ 50% somatic RET mutations
- Can present with systemic symptoms related to hormone production
- Surgery is the mainstay of therapy
- RAI and TSH suppression are NOT effective treatments for MTC
- Advanced progressive or symptomatic disease not amenable to surgical resection can be treated with vandetanib or cabozantinib **regardless of whether there is a RET mutation**
  - Must institute cautiously given the often indolent nature of the malignancy and potential toxicities – no overall survival benefit
- Selective RET inhibitors selpercatinib and pralsetinib are now approved for **RET mutated MTC**

Adrenal Tumors
Adrenocortical Carcinoma
Pheochromocytoma



ACC Epidemiology/Clinical Presentation

- Rare: 1-2 cases/million/year
- Bimodal age distribution
  - < 5 or 40-50
- Tumor of the adrenal cortex
  - Tumors of adrenal medulla = pheochromocytoma
- Can be "functioning" or "non-functioning"
  - ~ 60% functioning/secretory
  - Adrenal hormone secretion
    - Cortisol: Cushing's syndrome (most common ~45%)
    - Aldosterone: hypertension, hypokalemia
    - Androgen or estrogen: Virilization or feminization
- Patients with non-functioning tumors present with incidental finding or tumor-related symptoms
- Diameter of adrenal mass is predictive of malignancy
  - Most adrenal adenomas are <4 cm, most ACCs are >4 cm in diameter when discovered



ACC Pathogenesis

- Most cases are sporadic
- Inherited syndromes:
  - Li-Fraumeni (TP53 mutation): breast cancer, sarcoma, brain tumor, ACC
  - Beckwith-Wiedemann (chromosome 11p15): Wilms' tumor, neuroblastoma, hepatoblastoma, ACC
  - MEN 1 (MEN1 gene): parathyroid, pituitary, pancreatic neuroendocrine tumors, adrenal adenoma, ACC
  - SBLA syndrome (unknown cause): sarcoma, breast, lung, ACC, others

ACC Diagnosis

- Hormonal evaluation
- Rule out pheochromocytoma with plasma or urine metanephrines and catecholamines
  - Particularly prior to bx of an adrenal lesion
    - High rate of complications with pheo bx
- PET-CT has sensitivity of 100% and specificity of 98% for differentiating carcinoma from adenoma
- FNA not helpful to distinguish adrenal adenoma from carcinoma
  - Useful to distinguish adrenal met from primary adrenal lesion

ACC Staging

Most treatment studies use European Network for The Study of Adrenal Tumors ENSAT staging (differentiates resectable Stage IV from Stage IV with distant disease)

Stage	Description	TNM	5-yr survival
Stage I	Confined to adrenal gland, tumor ≤ 5 cm	T1N0M0	82%
Stage II	Same as I, but tumor > 5 cm	T2N0M0	61%
Stage III	Any size but at least one RF: Infiltration Tumor thrombus Positive LNs	 T3 T4 N1	50%
Stage IV	Distant Metastases	M1	13%

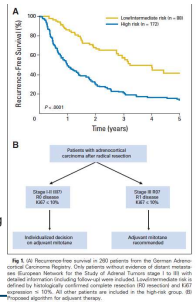
Fassnacht, et al. Cancer. 2009;115(2):243

ACC Primary Treatment

- Surgery: preferred treatment if possible for stage I-III
  - Open adrenalectomy with lymphadenectomy
  - Incomplete resection with maximum debulking may help relieve symptoms in patients with hormone-secreting tumors
- Unresectable or incomplete resection
  - Mitotane: adrenocorticolytic, decreases steroid hormone synthesis
    - Main benefit is reduce symptoms
    - Decreases symptoms in ~75% of patients
    - ~25-33% objective response rate
    - Does not prolong survival – median survival 6.5 months
- Mitotane typically used in the adjuvant setting for high-risk disease
  - histologically high-grade disease (Ki67 of >10% of tumor cells, >20 mitotic figures/50 HPF regardless of tumor size)
  - intraoperative tumor spillage
  - large tumors that are low grade but have vascular or capsular invasion
  - Treat for 5 years

Considerations for Mitotane Use

- Mitotane levels must be monitored!!!
  - Therapeutic at 14-20 mcg/ml
  - Toxicities:
    - Weakness, somnolence, confusion, lethargy, headache
    - Anorexia, nausea, diarrhea
    - Ataxia, vertigo, dysarthria
- ADIUVO trial for low to intermediate risk ACC (I-III, R0 resection, Ki67 <10) in the adjuvant setting

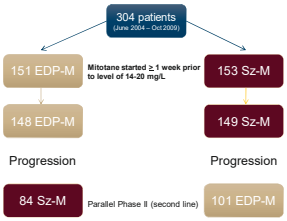


Adjuvant therapy in patients with adrenocortical carcinoma: a position of an international panel: JCO 2010.

ACC Adjuvant Therapy -- Radiation

- No prospective data, retrospective data that it improves local control, not survival
- NCCN guidelines suggest for localized, high grade tumors to "consider RT to tumor bed"
- German ACC registry:
  - recommend adjuvant RT for: microscopically incomplete (R1 or R2) or uncertain (Rx) margin, and stage III disease
  - Considered for tumor > 8 cm with invasion (not thrombus) and Ki67 > 10%, or spillage
- RT can also be used for metastatic sites as needed

FIRM-ACT Trial Treatment



EDP-M = Etoposide 100mg/m2 IV days 2,3,4; Doxorubicin 40mg/m2 day 1; Cisplatin 40mg/m2 days 3,4; oral mitotane continuously
Sz-M = streptozocin 1g IV days 1-5 (cycle 1) then 2g day 1 each cycle; oral mitotane continuously

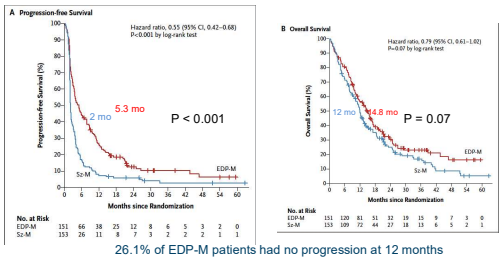
Fassnacht, et al. N Engl J Med 2012; 366:2189-2197

Best Overall Response (RECIST)

Variable	EDP-M	Sz-M	P value
Type of response n (%)			
Complete response	2 (1.3)	1 (0.7)	
Partial response	23 (21.8)	13 (8.5)	
Stable disease (≥ 8 weeks)	53 (35.1)	34 (22.2)	
Progressive disease	43 (28.5)	88 (57.5	
Did not receive treatment	3 (2.0)	4 (2.6)	
Not evaluable	17 (11.3)	13 (8.5)	
Objective response	35	14	
% (95% CI)	23.2 (16.7-30.7)	9.2 (5.1-14.9)	< 0.001
Disease control (CR + PR + SD)	88	48	
% (95% CI)	58.3 (50.0-66.2)	31.4 (24.1-39.4)	< 0.001

Fassnacht, et al. N Engl J Med 2012; 366:2189-2197

Progression-Free Survival and Overall Survival



26.1% of EDP-M patients had no progression at 12 months
7.2% of Sz-M patients had no progression at 12 months

Fassnacht, et al. N Engl J Med 2012; 366:2189-2197

Controlling hormonal excess

- Mitotane – adrenocorticolytic
- Metyrapone – inhibits last step of cortisol biosynthesis (off-label use)
- Ketoconazole – inhibits 1st step of cortisol biosynthesis (off-label use)

ACC Summary

- 60% present as functioning tumors
  - Most commonly Cushing's syndrome +/- virilism
- Diagnosis made by CT characteristics, hormone levels
- Surgery is only chance of cure
  - Stage I-III
  - Debulking for symptom control
- Mitotane is often used in the adjuvant setting and for metastatic disease +/- other systemic therapy
  - Improves adrenocortical hormone-related sx
  - Can have objective tumor responses
- FIRM-ACT trial showed that EDP-M had higher anti-tumor efficacy than Sz-M as first line therapy
  - No overall survival advantage

Pheochromocytoma

- Arises from the chromaffin cells of the adrenal medulla
- Paraganglioma is considered an "extra-adrenal pheochromocytoma"
  - Arises from the sympathetic ganglia
  - Produces catecholamines
  - Treated the same as pheochromocytoma
- Associated with hereditary syndromes in about 40% of cases: VHL, MEN2, NF1
- Very rare – 2-8 cases/million

Pheochromocytoma

- Symptoms occur in ~50% of patients and are often paroxysmal
- Classic Triad: episodic headache, sweating, tachycardia
- 85-95% will have hypertension
- Approximately 10% are malignant and 10% are multiple
- Diagnosis: measure urine and plasma fractionated metanephrines and catecholamines

Pheochromocytoma - treatment

- Surgical resection is mainstay of treatment
  - Laparoscopic appropriate if performed by experienced surgeon
  - Preoperative control of blood pressure and alpha and beta-adrenergic blockade to prevent intraoperative hypertensive crisis
  - ~95% will be cured
- Metastatic/ Malignant disease:
  - I131 attached to MIBG (iobenguane I-131) if takes up MIBG on scan
  - Octreotide
  - CVD (cyclophosphamide, vincristine, dacarbazine)
  - Lutathera (177Lu-DOTATATE) in a clinical trial, not FDA approved for pheo/paraganglioma

Thank You