

1 **Thyroid Cancer**

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2 **Objectives**

- Understand thyroid cancer types
- Understand thyroid cancer epidemiology and risk factors
- Understand thyroid cancer presentation
- Understand thyroid cancer staging
- Understand thyroid cancer treatment
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3 **Thyroid Anatomy and Physiology**

2 Thyroid function:

- Thyroid critical for brain and somatic development
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- Affects nearly all organs
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- Regulates metabolism
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- Calcium and phosphorus homeostasis

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5 **Thyroid Follicular Cell**

6 **Thyroid Histology**


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- Follicular Cells: stimulated by TSH to convert thyroglobulin to T4
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- Parafollicular (C) cells: synthesize calcitonin
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- Colloid: storage material for thyroglobulin
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7 **Thyroid Malignancies**

-  1 • 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

8 **Thyroid Malignancies**

9 **Thyroid Cancer Epidemiology**

- Thyroid Cancer is the most common endocrine malignancy
 - Papillary Thyroid Cancer most common thyroid cancer
- 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
 - 48,020 cases estimated in 2011
- Prevalence is high and increasing
 - 2004: 366,000 men and women alive with history of thyroid cancer
 - 2008: 458,403

10 **US Death Rate Increasing**

11 **Thyroid Cancer AJCC Staging**

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(Papillary and Follicular)

14 **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
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15 **Differentiated Thyroid Cancer (DTC) Risk Factors**

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- 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
 - Risk persists for 40 years

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- Fukushima??
- After nuclear accident
 - Potassium iodide can protect thyroid from I 131
 - Give as soon as possible
 - Risk of hyper/hypothyroidism

16 **Differentiated Thyroid Cancer (DTC)** **Risk Factors**

- Genetic
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 - Component of several inherited syndromes:
 - Familial adenomatous polyposis, Gardner syndrome, Cowden disease, Turcot syndrome, Carney complex
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 - “Familial 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:
 - 3.2 when a parent is diagnosed
 - 6.2 when a sibling is diagnosed
 - 11.2 if a female has a sister diagnosed

17 **Prognosis of Differentiated Thyroid Cancer**

- One of the least morbid solid tumors
- Regional lymph node metastasis
 - < 45 No effect on overall survival
 - > 45 increased risk of death by 46%
- 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

18 19 20 **PET and Prognosis**

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21 **Diagnosis**

- FNA is standard diagnostic procedure when a thyroid nodule is found
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- Most thyroid nodules are benign
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 - 5-10% chance of malignancy
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 - 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
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 - Up to 90% of women > 70 and up to 60% men > 80 have nodular goiter

22 **FNA RESULTS**23 **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

24 **What is the appropriate operation for differentiated thyroid cancer?**
American Thyroid Association Management Guidelines THYROID vol 16, 2006

25 **Surgical Resection**

26 **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

27 **Thyroid Follicular Cell**

28 **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)

29 **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 suprathreshold 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

30 **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
 - 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
 - Systemic chemotherapy?
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31 **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

32 **Systemic Chemotherapy in Advanced Thyroid Cancer**

33 **Thyroid Cancer Signaling**

34 **Differentiated (Papillary and Follicular) Thyroid Cancer Clinical Trials**

35 **Kinase Inhibitors**

- Responses likely related to VEGFR inhibition
- FDA approved for use in other malignancies
- None approved for use in DTC
- Sorafenib:
 - inhibits RAF, PDGFR, VEGFR2 and 3, RET, KIT
- Sunitinib:
 - Inhibits VEGFR-1 and 2, PDGFRs, KIT, FLT3, RET
- Pazopanib:
 - Inhibits VEGFR
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36 **Sorafenib Best Response**

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39 40 41 **DC after 12 weeks of sorafenib**42 **NCCN Recommendation for Advanced/Metastatic DTC**

“for clinically progressive or symptomatic disease: clinical trials for non-radioiodine responsive tumors: consider small molecule kinase inhibitors (such as sorafenib, sunitinib, or pazopanib) or systemic therapy”

43 44 **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 \leq 10% disease-specific mortality

45 **Clinical Presentation**

- Patient characteristics:
 - Median age: 65
 - 60-70% occur in women
 - 20% of patients have history of differentiated thyroid cancer (DTC)
 - 20-30% have concurrent DTC
- 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
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46 **Prognosis**

- “good” prognostic factors
 - Disease confined to the thyroid
 - Local or regional metastases (rather than distant)
 - Tumor size < 6 cm
- “bad” prognostic factors
 - Male

- Older age
- Dyspnea
- Tumor > 6 cm
- Distant mets at diagnosis

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47 **Survival by Extent of Disease**

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

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48 **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 randomized trials
 - Selection bias

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49 **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

50 **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

51 **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
 - Combretastatin/Carbo/Taxol: 55 pts
 - Carbo/Taxol alone: 25 pts
- Improved OS with HR 0.71
- For patients < 60, OS 10.9 vs. 3.1 months with addition of combretastatin
- Larger trial is planned
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52 53 54 55 **Medullary Thyroid Cancer**56 **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

57 **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

58 **Inherited MTC**
Autosomal Dominant Syndromes59 60 **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
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61 **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

62 **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

63 **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

64 **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

65 **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 Read⁹ and M Schlumberger⁷

66 **Study design**

67 **PFS (primary endpoint)**

68 **Objective tumor assessments**

69 **Phase I study of XL184**

70 **Phase I Study of XL184**

71 **Sorafenib in MTC**

72 **AEE After 6 Weeks of Sorafenib**

73 **NCI Clinical Trials in Advanced Thyroid Cancer**

74 **Phase I/II trial of ZD6474 (Vandetanib;ZACTIMA) plus the Bortezomib (Velcade), in 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.
- 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

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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

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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
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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.
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78  **QUESTIONS?**