THE GENETICS OF MEDULLARY THYROID CANCER

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WHY GERM LINE GENETICS AND FHX ARE IMPORTANT CLINICALLY IN MTC

- May predict MTC aggressiveness
- Tell us whether to expect pheo and HPT
- May help us in deciding how much neck dissection

RET-PROTO-ONCOGENE

- Location: Chromosome 10q11.21
- Discovered to be responsible for MEN 2 1993
- Exon count: 20 (in toto but only 7 of clinical interest)
- Seven exons of interest for MTC: 8, 10, 11, 13-16
- Dimeric membrane-bound tyrosine kinase receptor functioning as a growth promoter (cysteine residues) and constituituvely activated with MEN Syndromes:
  - Auto-dimerization with MEN 2A
  - Constituitively activated monomeric receptor with MEN 2B
- *RET* mutations affect expression of many other genes: calcitonin, CEA, etc
- 61 mutations on the 7 exons that cause MEN2 and Familial MTC: 95-98% sensitivity

AGGRESSIVE CLINICAL BEHAVIOR AT PRESENTATION

- 50% present with AJCC 7th Edition Stage III or IV disease- disease in LN's, or with macroscopic extrathyroidal spread or with distant metastasis
- 30% of patients present with diarrhea (most with advanced disease)
- 5 year survival 50% for stage III
- 5 year survival 40% for stage IV
- Another perspective:
  - No metastatic nodes seen or resected- 38% with residual disease
  - Positive nodes- 90% with residual disease

Why as a surgically-oriented endocrinologist, I must know about MTC diagnosis preoperatively and some centers want germ line assessment before surgical intervention , if possible

GENETIC BACKDROP

- 80% sporadic MTC without germline mutations
  - 50% of these will have *RET* mutations- most often of codon 918 of exon 16 in their thyroid tumors (like MEN 2B but only in the tumor, not germ cells)
  - 25% RAS mutations and 25% other
- 20% with germline mutations of the *RET* gene
  - MEN 2A present in 20's and 30's with MTC, pheo and HPT- 98% of their RET mutations in exon 10-11
    - Affected codons 609, 611, 618 and 620 in exon 10
    - Also codon 634 in exon 11
    - May consider deeper dive with sequencing of other pertinent exons- 8,13,14,15 and 16
  - MEN 2B present with aggressive MTC (bilat) and pheo and MS/Dev defects- 95% Codon 918 on exon 16 and often de novo with parents and sibs unaffected
    - Codon 918 in exon 16 (>95% of cases)
    - Codon 883 in exon 15
  - Familial Medullary Thyroid Cancer- 4 people from the same family- usually only MTC and likely to have advanced disease and disease in LN's at presentation
    - Mutations in codons 609, 611, 618 and 620 of exon 10 (like MEN 2A)
    - Also mutations in codon 768 in exon 13 and codon 804 in exon 14

ATA MODIFIED 2015 RET GUIDELINES

ATA Risk Level	RET Mutation	MEN2 Sub Type	Age of MTC	ATA TX Recs
Moderate	533, 603, 606, 609, 611, 618, 620, 640, 631, 666, 768, 777, 790, 804, 833, 844, 891, 912	FMTC & MEN2A	>5	5-10 in childhood or In adulthood if Calcitonin becomes elevated
High	634, 883	MEN2A	<5	At or before age 5 based on serum calcitonin levels
Highest	918	MEN2B	<1 y	First year or first months of life

ATA GUIDELINES FOR MTC GENETIC COUNSELING- 2015

- The recommended method of initial testing for MEN2A is either a single or multi-tiered analysis to detect *RET* mutations in exon 10 (codons 609, 611, 618, and 620), exon 11 (codons 630 and 634), and exons 8, 13, 14, 15, and 16

- Sequencing of the entire coding region should be reserved for situations in which no *RET* mutation is identified or there is a discrepancy between the MEN2 phenotype and the expected genotype

- Patients with the MEN2B phenotype should be tested for the *RET* codon M918T mutation (exon 16) and, if negative, the *RET* codon A883F mutation (exon 15). If there are no mutations identified in these 2 exons, the entire *RET* coding region should be sequenced

- Genetic counseling and genetic testing for *RET* germline mutations should be offered to first-degree relatives of patients with proven hereditary MTC; parents whose infants or young children have the classic phenotype of MEN2B; patients with cutaneous lichen amyloidosis(CLA: 634 and 804M); and infants or young children with Hirschsprung Disease (HD) and exon 10 *RET* germline mutations, and adults with MEN2A and exon 10 mutations who have symptoms suggestive of HD (609, 611, 618 and 620)

REMEMBER

- 95-98% of the pertinent MEN2 mutations are detected with sequencing of ***RET*** exons 8, 10, 11, 13-16
- Codon 918 is a very bad actor (also 634, 883)
- Surrounding SNP's (single nucleotide polymorphisms-they don't change the protein coded for) likely modify disease expression and timing

MOST FREQUENT RET MUTATION CARRIES A VERY LOW LIFETIME RISK OF MTC-DR. TURNBULL ICR IN SUTTON, UK

- Analyzed the entire Exome Aggregation Consortium database for MTC allele frequencies
- 11 of the 61 known RET mutations were present in the database
- Her group then calculated the number of alleles they would expect to observe for each pathogenic mutation assuming that a fully penetrant allele cannot be more common than the disease it causes
- Codon 804 mutations were 5x more common than any other RET mutation
- They estimated that the observed frequency of codon 804 equates to a penetrance of 4%
- Findings: "In spite of the ATA recommendation truly prophylactic thyroidectomy for codon 804 is likely inappropriate"

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MEMORIAL CENTER FOR INTEGRATIVE ENDOCRINE SURGERY MTC EXPERIENCE 2011-2018

- 22 patients with molecular or cytologic evidence of MTC- 18 of whom had sporadic MTC
- One false negative adenomatous goiter patient
- 3 MEN 2A patients
  - One an exon 11 634S Mutation in her 20's with Medullary Ca and calcitonin 8 post op
  - Two from a family with exon 10 620S Mutation in 20's and 30's with medullary Ca and pheos
- One patient who underwent surgery with us with an outside Bethesda 3 thyroid FNA and stage 4 metastatic breast cancer with a high CEA of 100 presumed to be breast Ca related who turned out to have a 3.5 cm MCT (calcitonin <7 post op)

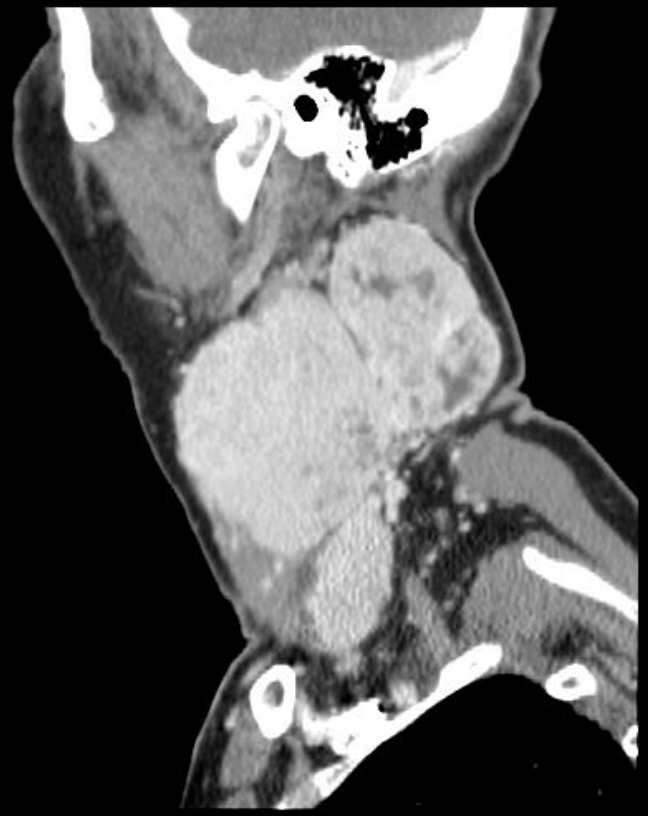
MEMORIAL CENTER FOR INTEGRATIVE ENDOCRINE SURGERY MTC EXPERIENCE 2011-2018 (OTHER CANCERS)

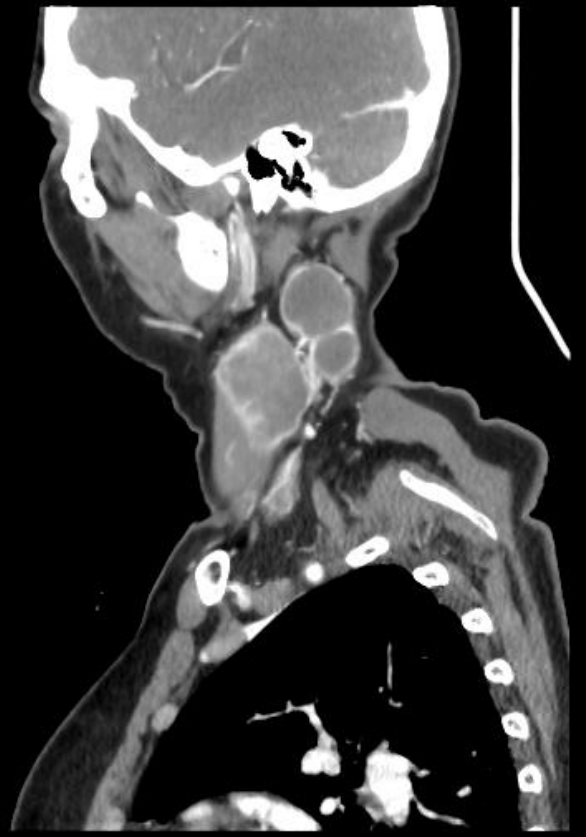
- Two patients died over the 7 years of follow-up both from the consequences of second metastatic cancers- Stage 4 Breast and Stage 4 undifferentiated rectal Ca
- Beware of the referral from oncology of the patient with breast or colon cancer, elevated CEA and a thyroid nodule- think MTC
- Three patients with MTC and multifocal PTC's doing well

NON-SECRETORY MTC

- One patient with an aggressive non-secretory MTC needing Tx, CLND, RLLND and external beam neck irradiation: Pre-op CEA 2.0 and calcitonin 6.9
- Cytology suspicious for MTC
- Malignancy Classifier positive for MTC
- Expression Panel- negative for MTC
- Immunohistochemistry- Negative for calcitonin and PAX 8, positive for CEA and chromogranin A

ADVANCED MTC NEO-ADJUVANT CASE- PRE AND POST 1.5 MONTHS OF LENVATINIB 20 MG

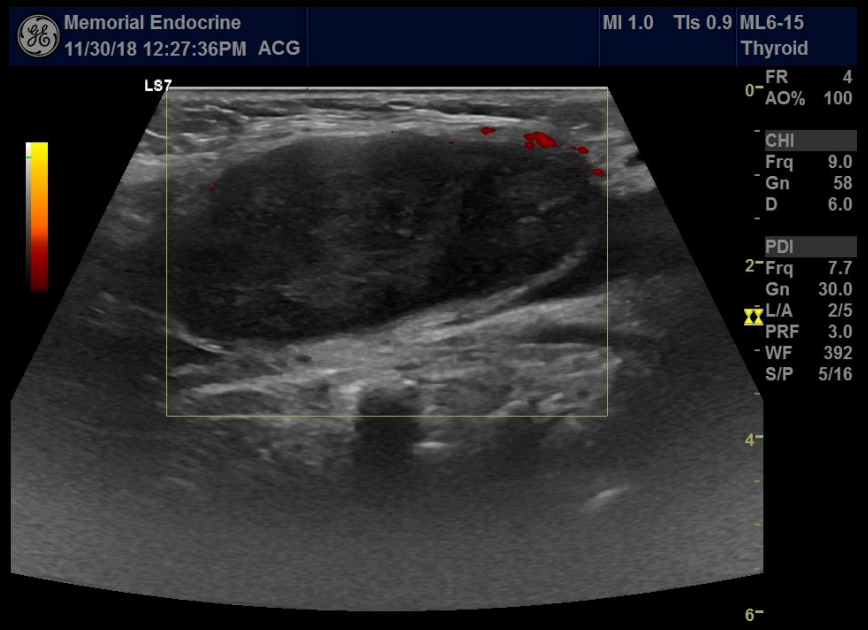




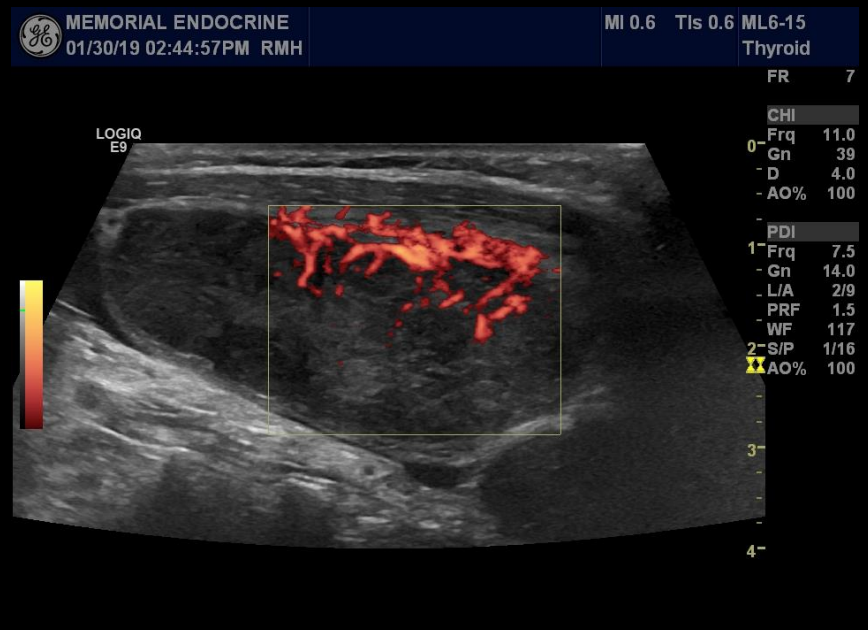
Calcitonin 33,000-5,000 an 85% drop

CEA 218-55 a 75% drop

ADVANCED MTC ON (3 MONTHS) AND OFF LENVATINIB 20 MG (10 DAYS)

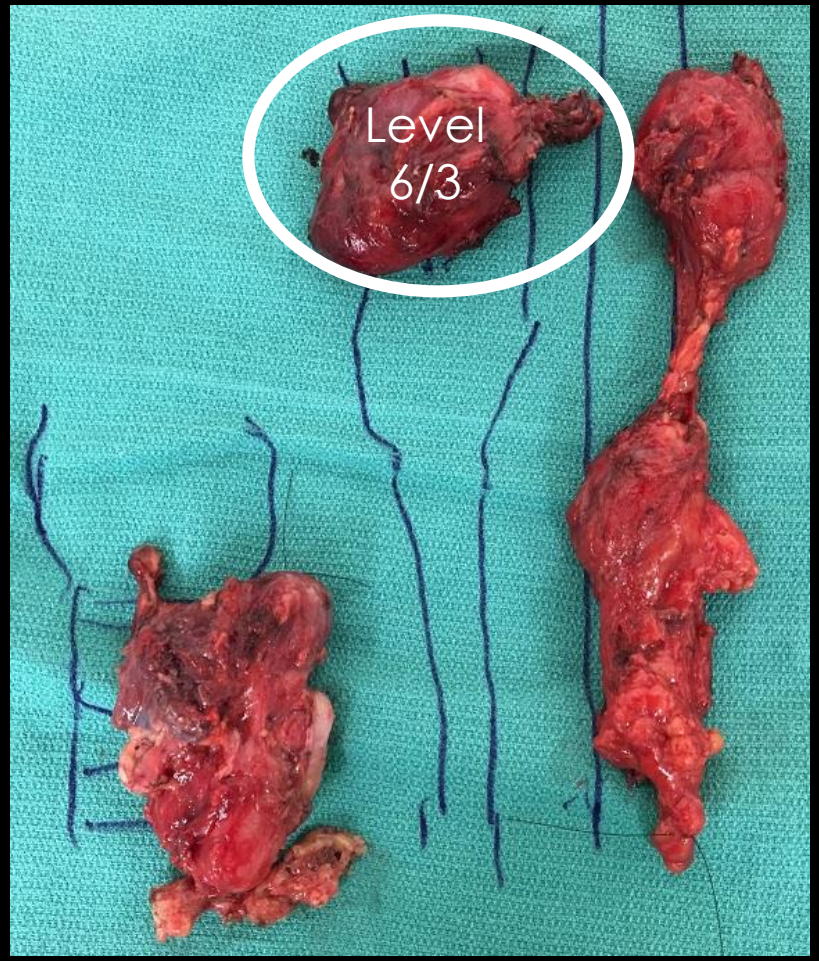


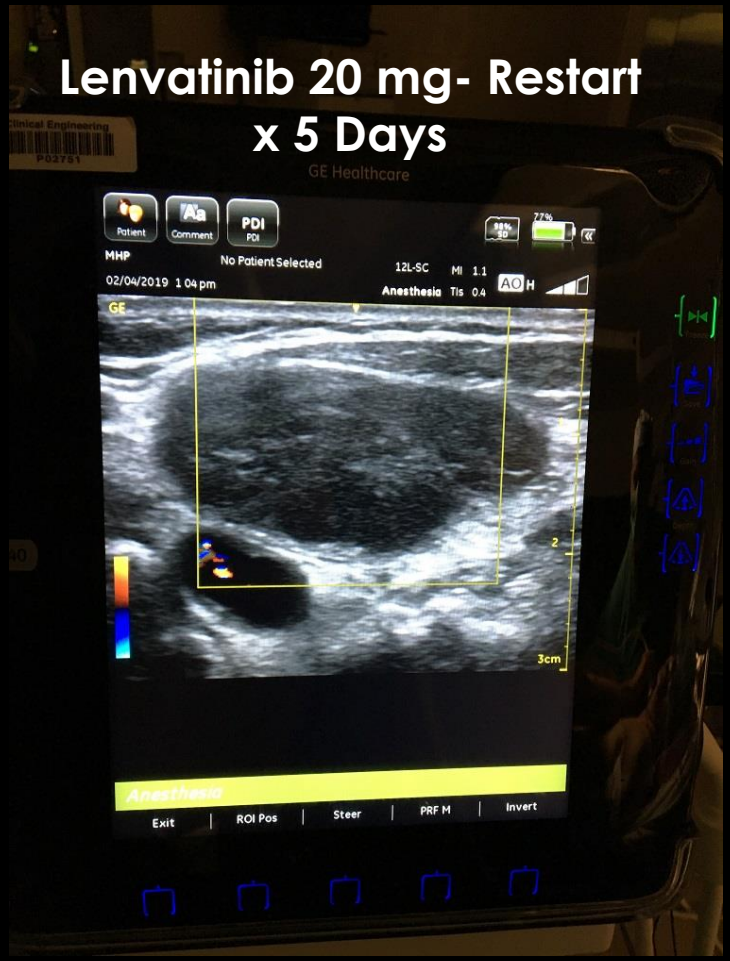
ON



OFF

OPERATIVE SPECIMEN WITH OPERATIVE DOPPLER OF LEVEL 6/3 LN





Patient describes neck as dramatically smaller after retreatment with 3 days Lenvatinib