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60 year old male with rising calcitonin levels

February 1st, 2018

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No disclosures



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Objectives

- To discuss the role of calcitonin in follow up of patients with medullary thyroid cancer
- To define the roles of imaging studies for patients with increased calcitonin levels





Case Presentation

60 year old male with medullary thyroid cancer

- Referred by Endocrine surgery to Endocrinology here for a rising calcitonin level
- Background
 - Found to have a neck lump in 2009, FNA at OSH
 - Underwent right thyroidectomy OSH in 2009 , once diagnosed with MTC referred to Endocrine Surgery here





Pre op Evaluation for Medullary Thyroid Cancer

Labs

- plasma metanephrines Normetanephrine 59, Metanephrine 20
- serum calcium, PTH 9.4
- Calcitonin, CEA 176, 4.4
- RET germline mutation A mutation was NOT detected

Imaging

- CT Neck Chest, Abdomen, Pelvis
mediastinal LNs Enlarged Para tracheal, anterior



ROS

- Constitutional: **Positive for fatigue. Unexpected weight change (lost 20lbs in 8 months)** Negative for chills and fever.
- HENT: **some hoarseness, and he has to clear his throat frequently**
- Respiratory: Negative for shortness of breath and stridor. **Positive for cough and shortness of breath**
- Cardiovascular: Negative for chest pain.
- Gastrointestinal: Negative for abdominal pain and vomiting, **trouble swallowing (with pills only), diminished appetite**
- Neurological: Negative for tremors and syncope.
- Genitourinary: Positive for urgency.
- Musculoskeletal: **Positive for knee pain and back pain.**
- Psychiatric/Behavioral: Negative for confusion. **Positive for decreased concentration (forgetfulness). The patient is nervous/anxious (he notes occasional panic attacks).**
- All other systems reviewed and are negative.



Background

- May 2011: completion left thyroidectomy, lateral LN dissection (II,III,IV, V) with auto parathyroid transplantation
- Follows up with OSH Endocrinology, Calcitonin 131 > 150
- Imaging CT neck, chest: no evidence of any overt neck masses
- *'...radiographic imaging and clinical evaluation does not point to any source for the calcitonin levels...'*



Background

	2009	2010	Nov 2011	May 2013	Oct 2013	Jan 2014	Sep 2014	Nov 2014
Calcitonin (< 16)	176 > 130	150	255	353	333	446	469	563
CEA (0-3.4)						18.7		

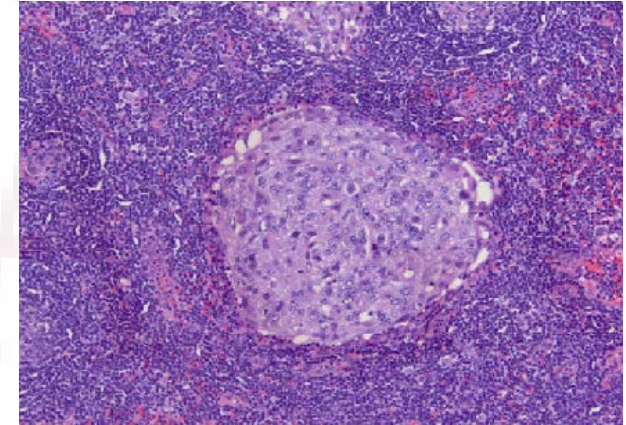
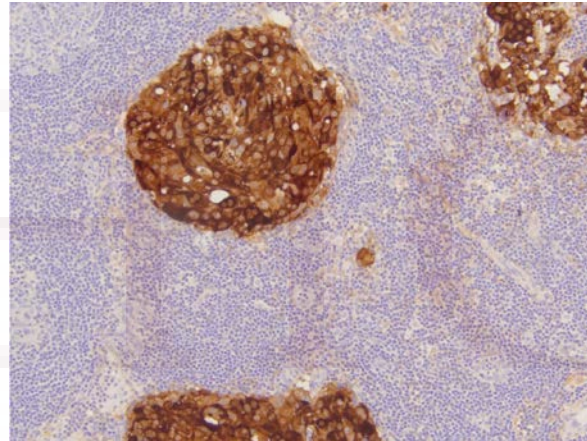
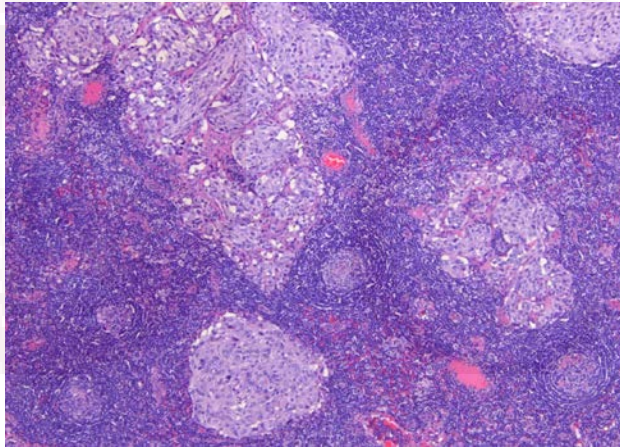
- Oct 2014: Repeat CT Neck, Chest was ordered and re referred to Endocrine surgery



Background Pathology

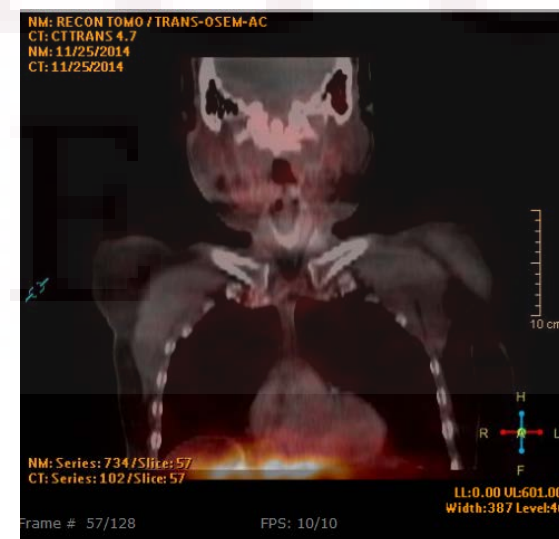
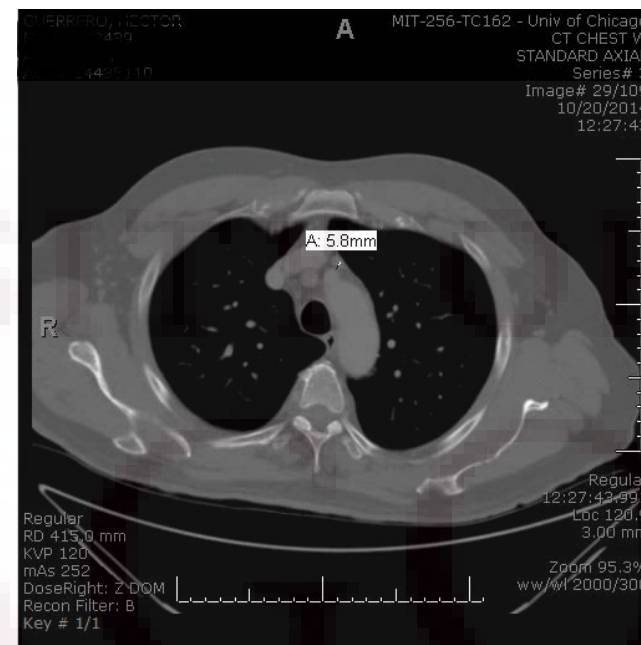
No tumor left thyroid lobe...

Immunostains for calcitonin, synaptophysin, chromogranin and CEA strongly positive in lymph nodes.



Background Imaging

- Feb 2014 PET CT scan: Without convincing abnormal FDG activity to suggest metastatic disease
- Oct 2014: Repeat CT Neck, Chest: Small pre vascular and right upper mediastinal LNs 9x14mm (previously 7x11mm in 2011)
- Re referred to Endocrine surgery
- Nov 2014 Octreotide Scan: No evidence of disease
- Dec 2014 MRI Liver: No evidence of disease
- Referred to Endocrinology here

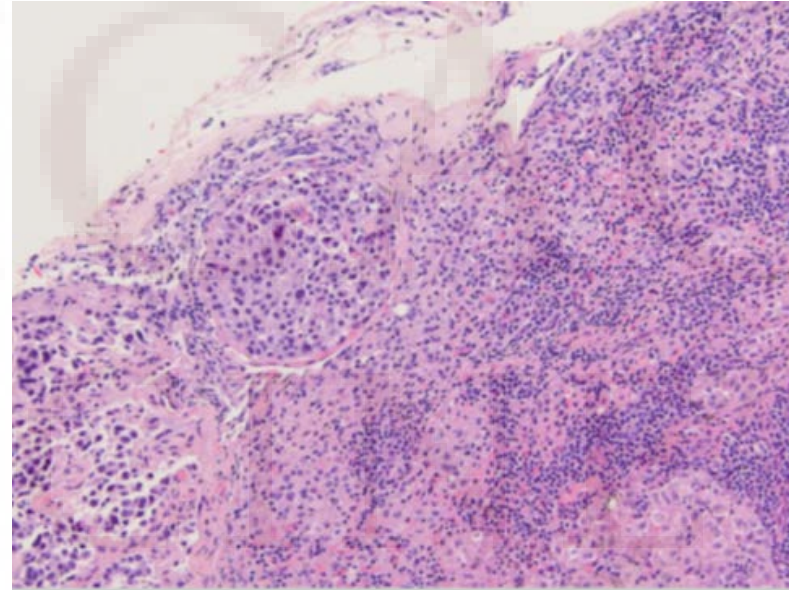
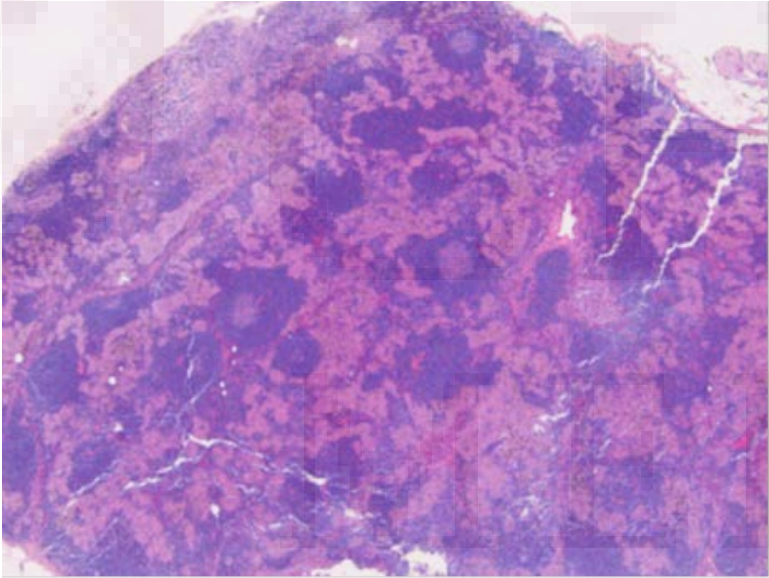


Background Case Treatment: Surgery

Dec 10 2014:

Left neck dissection negative

Lymph node metastases 11/13, largest 1.4 cm



Other PMH/PSH:

- BPH
- DVT
- HTN
- Post surgical hypothyroidism

- Pulmonary embolus
- Renal cell cancer (s/p laparoscopic left partial nephrectomy 2012)
- Rheumatoid arthritis
- partial right parotidectomy for lipoma

Allergies:

IV contrast – Hives

Medications:

- alprazolam 1 mg bid prn
- apixaban 5 mg bid
- diltiazem 240 mg daily
- fenofibrate 160 mg daily
- finasteride 5 mg daily
- fluticasone 2 Sprays prn
- hydroxychloroquine 200 mg daily
- leflunomide 20 mg daily
- levothyroxine 125 mcg daily
- lisinopril 40 mg daily
- omeprazole 20 mg
- trazodone 150 mg every night

Family history:

CAD Father/Brother
Breast cancer Sister
Papillary Thyroid Cancer Sister
HTN Sister

Social history:

Former smoker 1 ppd for 5 years,
quit > 30yrs ago, no alcohol, no illicit
drugs
Not currently working



Physical Exam

Constitutional: He is oriented to person, place, and time. He appears well-developed and well-nourished. No distress.

HENT: NCAT, EOMI, PERRL

Neck: Normal range of motion. Neck supple. No palpable thyroid tissue, no cervical adenopathy.

Cardiovascular: Normal rate, S1 + S2 no M/R/G

Pulmonary/Chest: CTAB no wheeze/rales/rhonchi

Neurological: A&O x 3. No cranial nerve deficit.

Skin: Skin is warm and dry. No erythema.

Psychiatric: normal mood and affect.



Labs

	Nov 2014	Jan 2015	Mar 2015	July 2015	Nov 2015	Jan 2016	May 2016	Nov 2016	April 2017	
Calcitonin	563	387	316	429	549	416	854	759	906	
CEA	18.7	11.9	12.6	12.4	12.4	14.6		16.2	16.4	





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How would you suggest to localize the lesion?





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Dotatate Scan



What is the Dotatate Scan?

Dotatate aka 1,4,7,10- tetraazacyclododecane-1,4,7,10-tetraacetic acid(DOTA),-Tyr3octreotate

NET have Somatostatin receptors expressing tumors

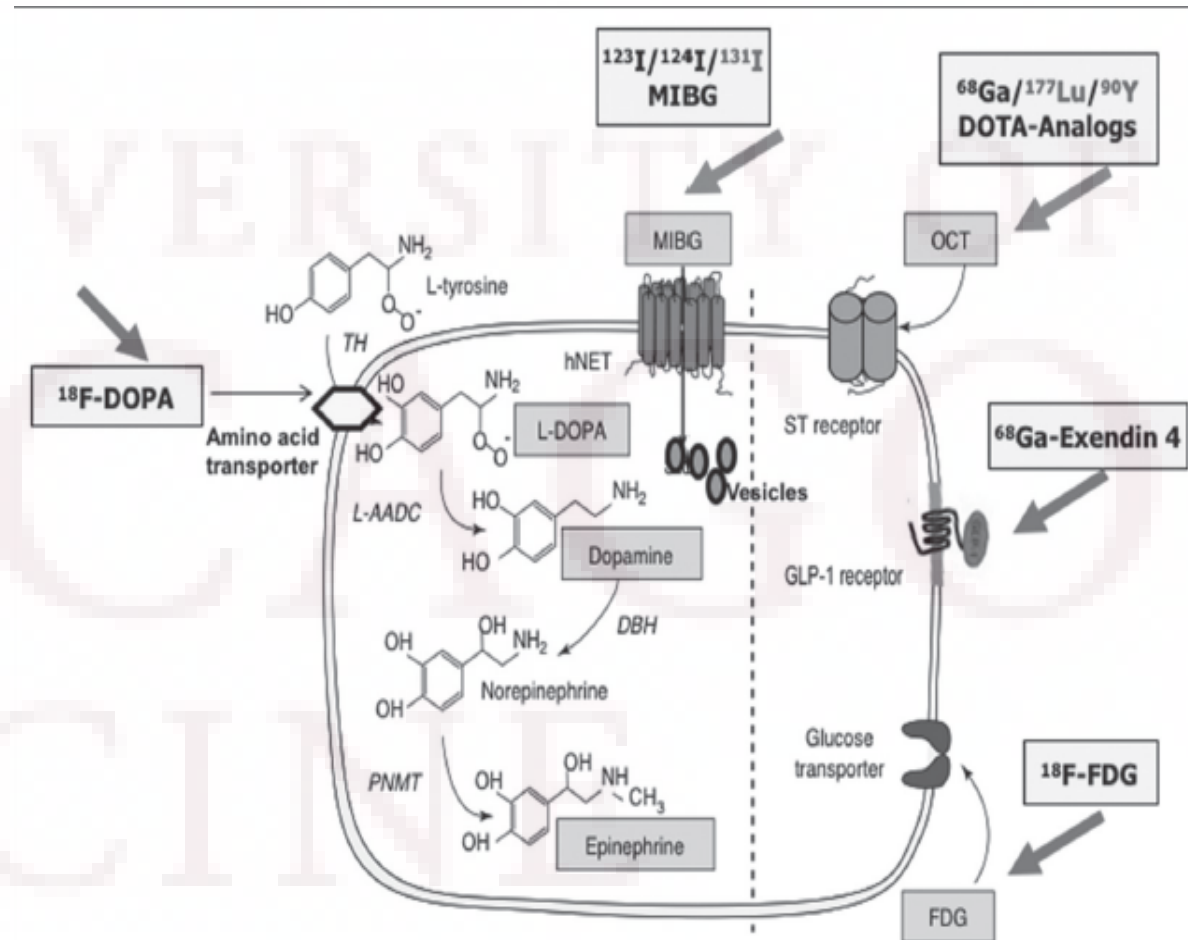
Bind to peptides, R_p mediated internalized and intracellular retention

This can be exploited in imaging by chelating with positron-emitting radionuclides, usually gallium-68-Dotatate (Peptide receptor imaging)

This permits imaging in a PET camera which has better sensitivity and higher resolution than the gamma camera, which results in better image quality.

The most commonly used tracers or radiopeptides 68Ga-DOTATOC, 68Ga- DOTATATE and 68Ga-DOTANOC

Couple with radioactive isotopes use for PRRT (peptide receptor radio therapy) for tumor shrinkage by delivering high dose radiation to intracellular components of cancer. Effect not seen with cold somatostatin analogues.



Adapted from Ilias et al. *Trends Endocrinol. Metab* 2005; 16:66



Imaging

- Numerous studies have demonstrated superior accuracy of ⁶⁸Ga-DOTATATE/DOTATOC compared with either conventional radiologic imaging or ¹¹¹In-octreotide scintigraphy for evaluation of NET, with a pooled sensitivity of 93% and specificity of 96% in a recent large meta-analysis
- Technetium-99m-DMSA-V was mainly used in the detection of MTC but the sensitivity was counterbalanced by instability of the component and low specificity with non-tumoral uptake such as in areas of inflammation, bone fractures and other types of tumors. It is now unavailable commercially
- Indium-111-octreotide sensitivity ranging from 37% to 75%
- ¹²³I-MIBG SPET/CT, which detects uptake in intra-cellular granules ¹⁸F-FDG PET/CT which detects increased metabolic activity and utilization of glucose by tumor cells recurrences are only detected in 40% of cases
- improved resolution of PET compared to SPET imaging with ¹²³I-MIBG or ¹¹¹In-octreotide
- Gallium-68-Dotatate has also been shown to detect bone metastases that were not suspected clinically or radiologically



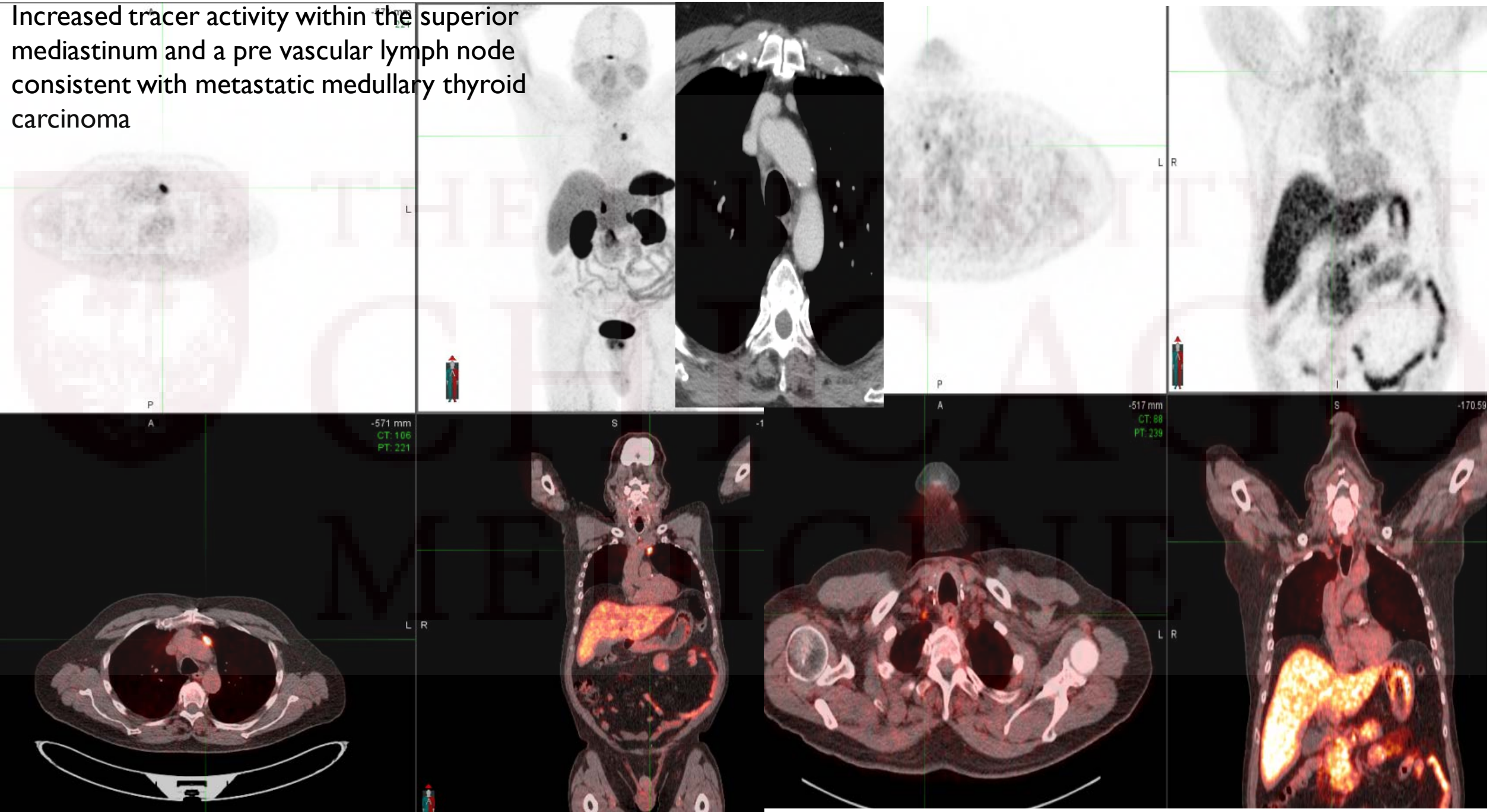
Clinical Indications for the Dotatate Scan

Staging	Prior to resection of apparently localized disease
Localization	Primary site in patients with biochemical suspicion of NET Unknown primary with metastatic NET
Theranostic (therapy and diagnostics)	SSTR density & distribution to guide suitability for SSA therapy or PRRT
Therapeutic	Restaging response assessment Suspected disease recurrence post-surgery (e.g. rising tumor markers)



May 2017:

Increased tracer activity within the superior mediastinum and a pre vascular lymph node consistent with metastatic medullary thyroid carcinoma



Follow up

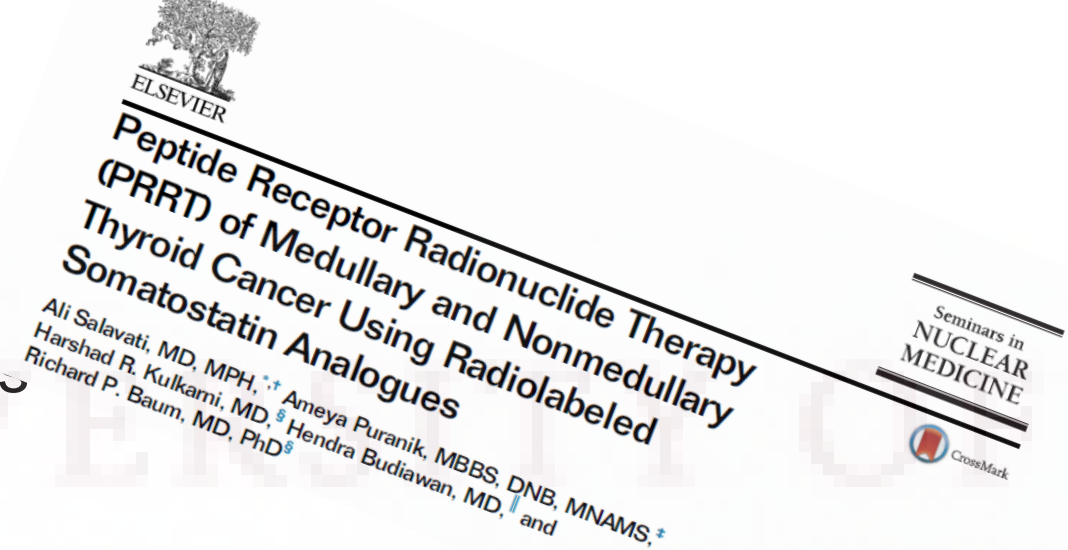
- Jan 2018 CT Neck: Evidence for progression of disease

What do we do now?



Patient treatment options:

- Continued observation and follow up
- Oncology: Role of TKI (2 FDA approved drugs cabozantinib and vandetanib)
- Role of external beam radiation
- Therapeutic application of Beta -emitting Yttrium-90 and Lutetium-177 for PRRT. (peptide receptor radionuclide therapy), individualize treatment depending on extent of disease
- LUTATHERA® (lutetium Lu 177 dotatate) FDA approved for Gastro-pancreatic Neuroendocrine tumors Jan 2018)



Take Home points

- Dotatate scan is available here for management of NET
- New targeted therapies are becoming available (Peptide receptor radionuclide therapy for treatment of NET)



Acknowledgements

- Dr Cohen
- Dr Appelbaum (Nuclear Medicine)
- Dr Vokes
- Dr Pytel (Pathology)
- Dr Zeytinoglu

