

Neuroendocrine Tumours



Course for Board Examination in Endocrinology
November, 2008

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NEUROENDOCRINE TUMORS

- ❑ a heterogeneous family of tumours developing from the diffuse endocrine system

- ❑ this system includes
 - endocrine glands (the hypophysis, the parathyroids, and the NE adrenal)

 - endocrine islets within glandular tissue (C cells of the thyroid; or inside pancreas)

 - cells dispersed between exocrine cells, such as endocrine cells of the digestive and respiratory tracts

NEUROENDOCRINE TUMORS

Endocrine glands

the hypophysis → pituitary adenomas

the parathyroids → parathyroid adenomas

the NE adrenal → pheochromocytomas (chromaffin-cell tumours)

Endocrine islets

C cells of the thyroid → medullary thyroid carcinoma (MTC)

Pancreas → pancreatic endocrine tumours (PNET)

Endocrine cells → carcinoid tumors



traditionally - exclude pituitary and parathyroid tumours

What does having a NET mean?

- ✿ Most tumours are slow growing (60% metastatic at diagnosis)
- ✿ Most express somatostatin receptors (SSR_2 & SSR_5)
- ✿ Most produce/secrete some amines/peptides

Specific for a given tumour (specific markers), for ex.:

- Serotonin (5-HIAA) - carcinoid
- Insulin - insulinomas
- Gastrin - gastrinomas
- Somatostatin - somatostatinomas
- Calcitonin - MTC
- Catecholamines - pheochromocytomas

General for all tumours (general markers)

- Chromogranin-A
- subunits of glycoproteins (α -hCG), NSE, etc.

WHO Classification (clinico-pathological)

3 main categories

Well-differentiated NE tumors

(benign or low grade malignancy)

cell monomorphism

<2 mitoses/mm²; Ki-67<2%

Well-differentiated NE carcinoma

(WDNEC)

cell polymorphism

>2 mitoses/mm²; Ki-67>2%

metastases and/or invasiveness

Poorly differentiated NE carcinomas

(PDNEC)

necrosis & atypia

>10 mitoses/mm²; Ki-67>15%

weak reactivity for granular markers

◆◆◆◆

Mixed exocrine-endocrine carcinomas

Tumour-like lesions

D.Y.

- 66y old male patient, m+4
- **Past medical history:**
 - 1998 - Anterior wall MI+CABG
 - Dilative ischemic cardiomyopathy
 - Moderate to Severe LV dysfunction
 - Hyperlipidemia
- 2004 - US+CT of the abdomen: multiple liver SOL, up to 3.6cm (hemangiomas?!); negative red blood cell scintigraphy

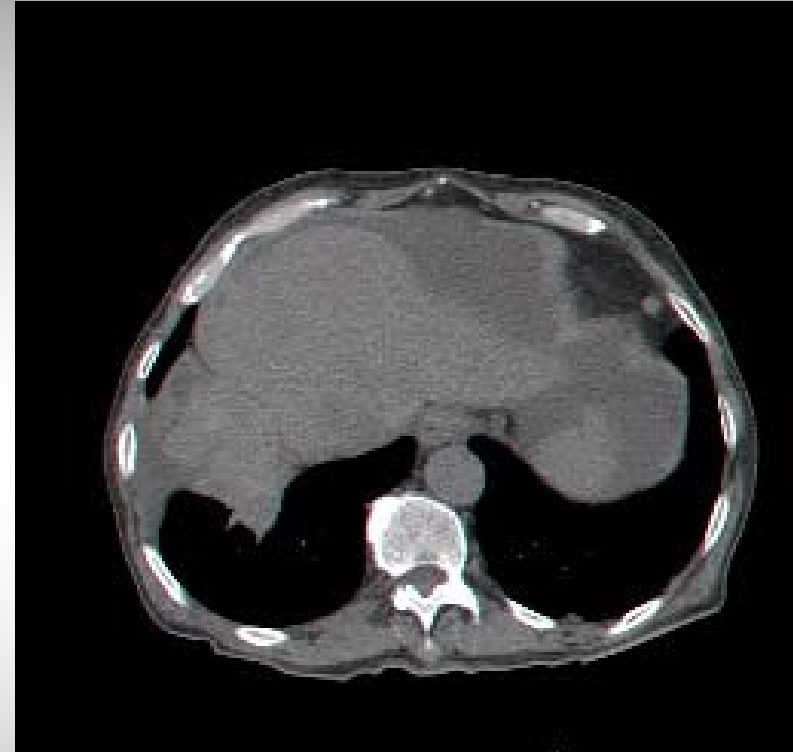
D.Y. - cont.

- **Present time-2007:** patient complained about loose stools (X3-4/day), appetite and weight loss, increasing legs edema and anasarca, abdominal fullness and diffuse abdominal pain
- Echocardiography - new finding of Severe TR

D.Y. - cont.

US & CT of the abdomen (6/2007):

- a "chain" of few nodules, on the diaphragm, from ant. to post., up to 3.5cm (m/p liver origin)
- multiple nodules inside and around the liver, involving the omentum and mesentery, and dispersed in the abdomen cavity and pelvis, up to 3.5 cm.



Ct abdomen
2007

D.Y. - cont.

- Lab tests:
 - Mild anemia, microcytic/hypochromic (HGB=12.1g/dL)
 - Normal liver test, except GGT=146 U/L and A.PHOS=168 U/L
 - Normal kidneys function
 - **5-HIAA-urine 24h** (normal range 2-10 mg/24h):
 - 61.50 mg/24h (12.2006)
 - 100.00 mg/24h (04.2007)
 - **CGA** (normal range 19.4-98.1 ng/ml): 166.0 ng/ml

D.Y.-cont.

- Abdominal SOL biopsy (31.07.2007):

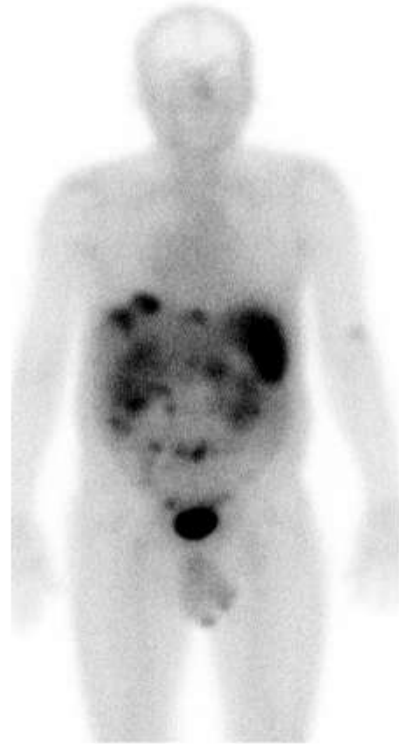
Well differentiated NET

- Immunohistochemical staining: + for synaptophysin, chromogranin
- Ki67 index of proliferation = 2%

D.Y. - cont.

- **Octreoscan (6.08.2007):**

→ High uptake in all lesions



Discussion - What to do next?

Well-differentiated terminal ileum NET
metastatic to the liver and to
abdominal cavity
&
Carcinoid heart disease

Treatment Modalities

Surgery

- ✿ The only treatment that can achieve cure
- ✿ Also in metastatic disease (improve symptoms, QoL & survival)
- ✿ **CHD**

Medical treatment

- ✿ **Somatostatin Analogues (SSAs)**
- ✿ Interferon (INF)
- ✿ mTOR inhibitors - RAD001
- ✿ TKIs
- ✿ **Somatostatin-Receptor Targeted Radiotherapy (PRRT)**
- ✿ Chemotherapy (Temozolomide)
- ✿ Combination of these therapies

RFA, Chemoembolization

D.Y. - cont.

- The patient was hospitalized for a few times d/t right heart failure and decompensation
- He was presented to the cardiologists/heart surgeon meeting - for TVR consideration
- Present treatment:
 - furosemide, carvedilol, enalapril, aldospirone, aspirin
 - sandostatin LAR 40 mgx1/month
- Decreasing but not normalization in 5-HIAA, down to 30mg/24h

D.Y.-cont.

Cardiac catheterization revealed:

- Patent LIMA to RIMA
- Moderate stenosis of proximal SVG to PDA and PLB
- Patent arterial grafts
- Moderate to severe LV dysfunction
- Severe TR

D.Y. - cont.

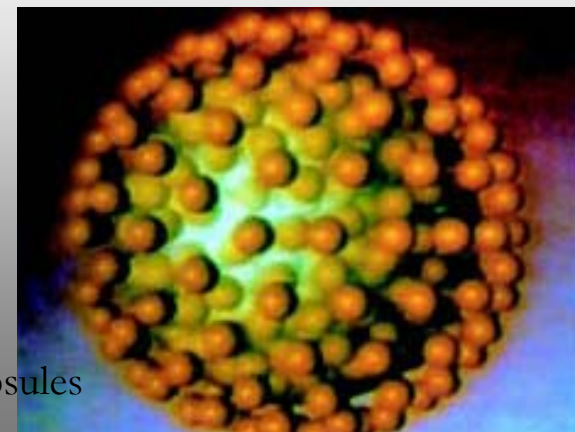
- **PRRT (somatostatin analogue radionuclide therapy):**
since 2004 until 2007 there is a clear documentation
for disease progression

Somatostatin (SS)

- an inhibitory neuropeptide (Roger Guillemin & Andrew Schally, 1973)
- two natural forms (SS₁₄ and SS₂₈)
- **Inhibitory functions**: endocrine/exocrine secretions; neurotransmission; motor and cognitive functions; intestinal motility, absorption of nutrients and ions, vascular contractility; cell proliferation.
- the biological actions - G protein-coupled receptor family: 5 membrane receptors (SSTR₁-SSTR₅)
- SSTR₂ and SSTR₅ - most commonly expressed in NETs
- **There is considerable variation in SSTR subtype expression among the different tumor types and among tumors of the same type** (de Herder *et al.*, 2003)

Somatostatin (SS)

- very short half life of the natural compound (about 3 minutes)
- synthetic analogues:
 - **short-acting** (octreotide, administered sc several times per day)
 - **medium-acting** (lanreotide, administered every 10-14 days)
 - **long-acting** (octreotide LAR, and lanreotide autogel, with a monthly administration)



Octreotide LAR molecule, consisting of microcapsules

Antiproliferative effect of SSAs in different studies

SSA	Dosage day	N	CR	PR	SD	PD	Reference
Lanreotide	3000 μ g	22	0	1	7	14	Faiss, 2003
Lanreotide	30mg/14d	35	0	1	20	14	Aparicio, 2001
Octreotide	600-1500 μ g	52	0	0	19	33	Arnold, 1996
Octreotide	1500-3000 μ g	58	0	2	27	29	Di Bartolomeo, 1996
Octreotide	600 μ g	10	0	0	5	5	Arnold, 1993
Lanreotide	1.5mg	24	1	1	11	11	Faiss, 2003
Total		201	47%			106 (53%)	

CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

PRRT

Endocrine-Related Cancer (2005) **12** 683–699

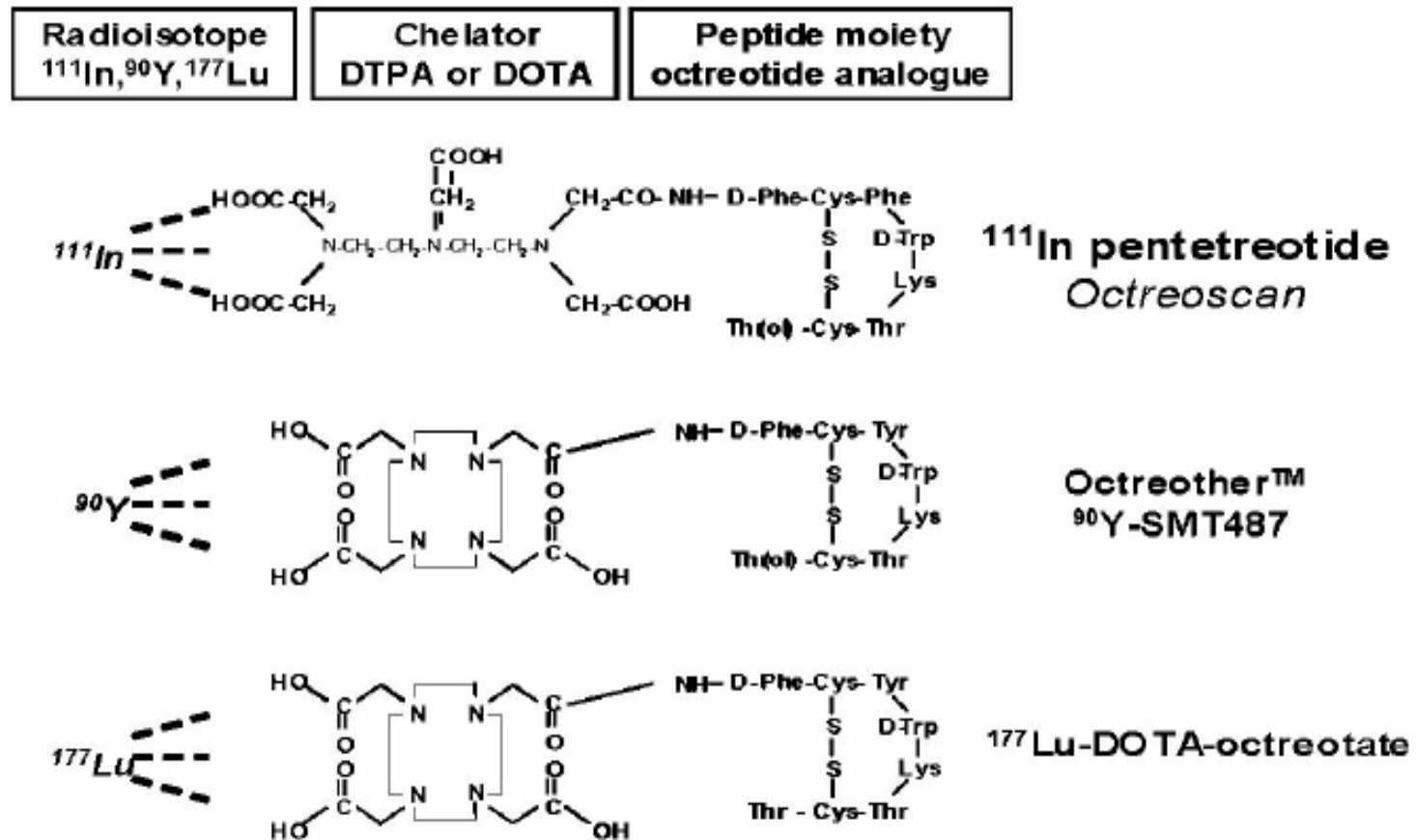


Figure 2 Chemical structure of currently used octreotide-based radiopharmaceuticals for the treatment of gastroenteropancreatic and other neuroendocrine tumours (Octreother™ = ^{90}Y -SMT487 = ^{90}Y -DOTATOC).

Table 5 Patient selection criteria for targeted radiotherapy

Indications

Inoperable/metastatic GEP
Increased uptake
at tumour sites
Haematological
considerations*
Hb >10 g/l
WBC >3.0 × 10⁹/l
PLT >100 × 10⁹/l
Biochemical considerations
Urea <10 mmol/l
Creatinine <160 µmol/l
GFR >40 ml/min
Good performance
status

Contraindications

Myelosuppression
Bone-marrow metastatic
disease
Renal impairment
Extensive hepatic
involvement
Poor performance
status
Pregnancy/lactation
Previous therapy with
radiopharmaceutical
Exceeding a dose limit

Hb, haemoglobin; WBC, white blood cells; PLT, platelets;
GFR, glomerular filtration rate; GEP, gastroenteropancreatic
tumours.

*Attention is required in patients previously treated with
chemotherapy.

Table 4 Tumour responses and side-effect profile of treatment using various radiopharmaceuticals based on somatostatin analogues in patients with GEP tumours

Radiopharmaceutical	Reference	No. of patients	Tumour response			Toxicity*	
			CR/PR	SD	PD		
¹¹¹ In	Valkema <i>et al.</i> 2002	26	~ 80%		10 (38%)	3 (11%) AML/MDS	
	Anthony <i>et al.</i> 2002	26			3 (12%)	11 grades 3–4 haematologic, 3 liver, 1 renal	
⁹⁰ Y	Buscombe <i>et al.</i> 2003	16				4 (25%)	–
	Waldherr <i>et al.</i> 2001	74				8 (11%)	8% grades 3–4 1 renal
	Waldherr <i>et al.</i> 2002 Valkema <i>et al.</i> 2003	54				10 (19%)	38% grades 3–4 haematological, 1MDS, 1 liver, 1 renal
¹⁷⁷ Lu	Bodei <i>et al.</i> 2004b	141				(18%)	
	Kwekkeboom <i>et al.</i> 2005	131				22 (18%)	Up to 1.5% grade 3 haematological, 1 liver, 1 renal

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; AML: acute myeloid leukaemia; MDS: myelodysplastic syndrome.

*Assessment followed WHO criteria (grades 3–4 toxicity is presented only).

“CARCINOID HEART DISEASE:PRESENTATION, DIAGNOSIS, AND MANAGEMENT” (*Fox,D and Khattar,R; Heart 2004*)

- the vast majority of patients with carcinoid heart disease develop right heart failure caused by severe dysfunction of the tricuspid and pulmonary valves.
- **These patients usually die as a result of severe TR and progressive heart failure (usually in 1 year after symptoms onset) rather than as a result of carcinomatosis.**
- valve surgery - considered even in metastatic disease, unless the metastatic process is likely to lead to imminent demise.
- important **to operate early or soon after the onset of cardiac symptoms**, as delay can result in worsening right ventricular failure and increase the risk of surgery.

Factors Associated with Progression of CHD

- *Moller,JE et al; NEJM 2003* - 32 patients: **serotonin levels**
- *Zuetenhorst JM et al; Cancer 2003*: **total exposure to serotonin** is even more important than the level of serotonin in the development of carcinoid heart disease.

Chromaffin-cell Tumours

L.A.

- 75y old female patient, Sephardic origin, d+3
- Past medical history:
 - ❖ Type 2 DM, on metformin - controlled
 - ❖ HTN, on enalapril, amlodipine, propranolol well controlled in the past
 - ❖ Chronic Mild Bronchitis, s/p smoking
 - ❖ Hypothyroidism, on LT4 replacement treatment
 - ❖ 1999 - S/P sigmoidectomy and chemotherapy d/t adenocarcinoma of colon

L.A. - Present disease

In 1999

- Excision of a left extra-adrenal lesion (no adrenal seen in the excised material)
- Path report:
 - ❖ 4 cm lesion
 - ❖ focal capsular invasion
 - ❖ no vascular invasion
 - ❖ the lesion reached the surgical margins
 - ❖ low mitotic activity
 - ❖ IHC: + for CgA, SYN, NSE; - for ACTH
- Dg: chromaffin-cell tumour
 - Since then, no related follow-up

L.A. - Present disease, cont.

In 12.2006: abdomen CT (before correction of abdominal wall hernia)

- ❖ a 1.1cm suspect lesion - on the right posterior wall of urinary bladder (confirmed by US)
- ❖ a ~ 1cm nodule in the right adrenal

CT, 2006



CT, 2006



L.A. - Present disease, cont.

- ❑ 4.2007 - **cystoscopy**: a solid oval lesion, no malignant cells on urine cytological examination

- ❑ 6.2007 - **endoscopic lesion biopsy** :
 - ❖ In the lamina propria there is tumour comprised of cells arranged in nests, variable in size and with nuclear atypia
 - ❖ Rare mitoses, no necrosis
 - ❖ IHC + for NSE, CgA, SYN
 - ❖ Low Ki-67% (stained in isolated nuclei)

- ❑ Dg: **chromaffin-cell tumour**

	Lab test	18/9/07	27/12/07
	Urea	27mg/dl	38 mg/dl
	Creatinine	0.9mg/dl	0.9 mg/dl
	Sodium	138mEq/L	140 mEq/L
	Potassium	4.9 mEq/L	5.2 mEq/L
	Glucose	112mg/dl	126 mg/dl
	Calcium (8.5-10.5)	10.7 & 10.6 mg/dl	10.0 mg/dl
	Phosphorus	4.1 mg/dl	3.2 mg/dl
	Albumin/Total Protein	4.3 g/dl /7.7 g/dl	4.0 g/dl /7.3 g/dl
	Alk.Phosphatase	70 U/L	71 U/L
	GOT	29 U/L	28 U/L
	GPT	17 U/L	18 U/L
	GGT	23 U/L	22 U/L
	LDH	350 U/L	413 U/L
	Magnesium (1.9-2.5)	1.81 mg/dL	1.83 mg/dL
	Vitamin D 25-OH (20-58)	-	15.7 ng/ml
	PTH (10-65)	119 ng/L	-

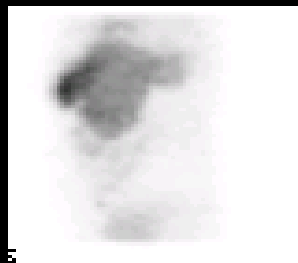
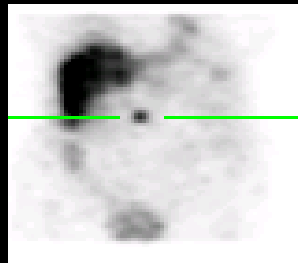
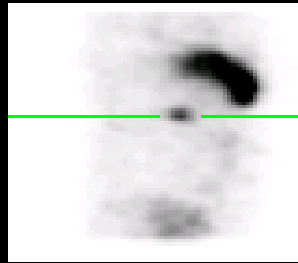
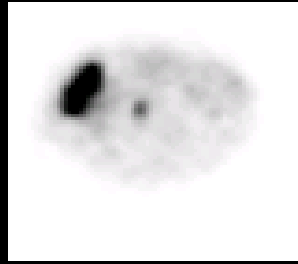
Lab test - cont.	10/07	12/07
Epinephrine-U 24h (0-20 mcg/24h)	3	8
Norepinephrine-U 24h (10-75 mcg/24h)	44	55
Dopamine-U 24h (10-400 mcg/24h)	147	142
VMA-U 24h (0.0-6.7 mg/24h)	2.5	4.2
Metanephrines	?	?
Normetanephrine/creatinine (95-452 µg/gr cr)	-	500
Calcitonin (<5.0 pg/ml)		<2.00
Chromogranin A (19.4-98.1 ng/ml)	516	

L.A. - Present disease, cont.

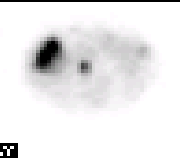
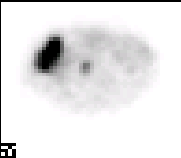
- **^{123}I -MIBG** (12.2007):
 - ❖ No uptake in the tumour inside urinary bladder
 - ❖ Abnormal uptake in the right adrenal area
 - ❖ Abnormal uptake in the left thyroid lobe



Patient Name: JACQ W. WSA
Position: L: 435386
Study Area: 1
Date: 11/21/2011 11:23
Manufacturer Model: TC
RADIO MEDICAL CENTER
10000 MIDLAND AVE. FORT WORTH, TX



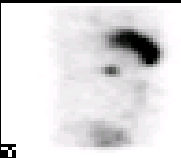
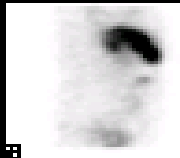
04 - Posterior



Head to Feet

Transaxial

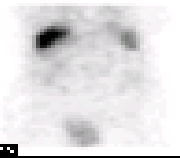
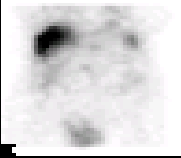
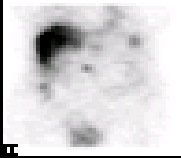
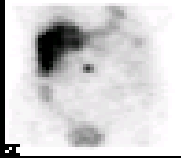
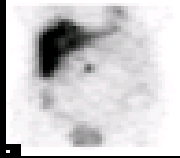
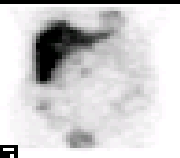
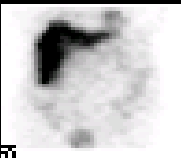
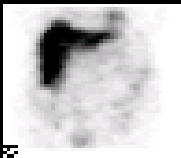
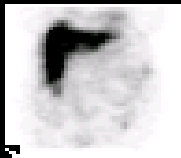
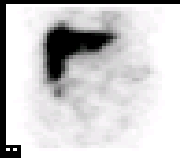
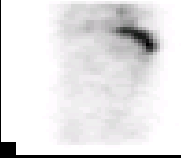
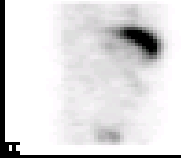
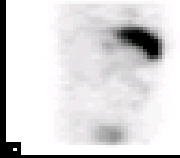
SI scan thickness: 9.50 mm



Slightly Left

Right

SI scan thickness: 9.50 mm



Superior to Posterior

Coronal

SI scan thickness: 9.50 mm

L.A. - Present disease, cont.

In 01.2008

- abdomen CT, 1 year from the previous
 - ❖ a ~ 1cm nodule in the right adrenal, not changed when the previous CT was revised
 - ❖ a 1.1cm lesion on the right posterior wall of urinary bladder, without change

L.A. - Present disease, cont.

- **Genetic testing** (-) for MEN2, SDHD/B
- 9/2008
 - palpitations
 - BP~140-160/90-100
 - pulse=100/min
- CT abdomen & pelvis (7.08.08)
 - Rt. Adrenal nodule w/o significant change
 - No nodule inside the urinary bladder (?!)
- Abdominal US, negative

CT 8.2008



Lab test - cont.	10/07	12/07	10/08
Epinephrine-U 24h (0-20 mcg/24h)	3	8	5
Norepinephrine-U 24h (10-75 mcg/24h)	44	55	44
Dopamine-U 24h (10-400 mcg/24h)	147	142	103
VMA-U 24h (0.0-6.7 mg/24h)	2.5	4.2	-
Metanephrines (10-300 µg/24h)	-	113	195
Normetanephrine/creatinine (95-452 µg/gr cr)	-	500	704
Creatinine-U 24h (800-1800 mg/TV)	-	850	920
Normetanephrine (90-450 µg/24h)	-	413	633
Calcitonin (<5.0 pg/ml)	-	<2.00	-
Chromogranin A (19.4-98.1 ng/ml)	516	-	pending

L.A. - discussion:

❖ Working Diagnosis: Multiple extra-adrenal and adrenal chromaffin-cell tumours, progressively functional

❖ What to do next?

Surgery: lap excision of the adrenal chromaffin-cell tumours ?

or

continue follow-up and change medical treatment

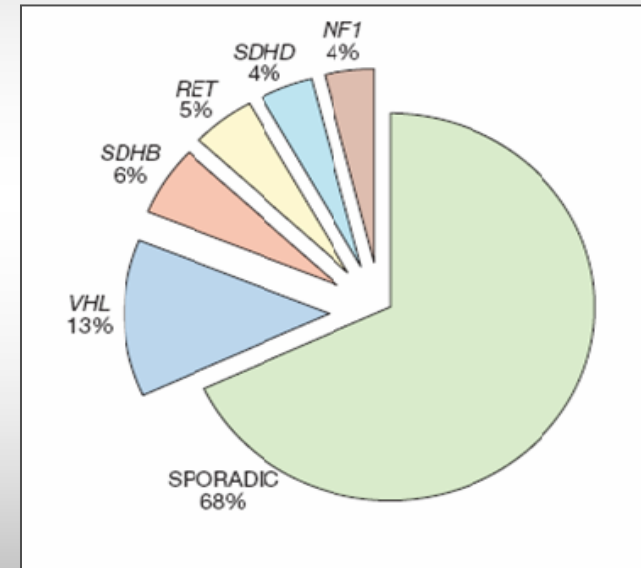
CCT: Sporadic versus Familial

- Most, sporadic
- **Familial syndrome** (bilateral/multifocal)
 - ❖ von Hippel-Lindau disease
 - ❖ Multiple Endocrine Neoplasia type 2
 - ❖ Neurofibromatosis type 1
 - ❖ Carney's syndrome

**Always consider the possibility of familial disease:
up to 26% in "sporadic" cases**

Susceptibility Genes for Chromaffin-cells Tumors

- the **RET** proto-oncogene (**MEN-2**)
- the **VHL** tumor-suppressor gene (von Hippel-Lindau disease)
- the newly identified **SDH** genes (familial paraganglioma and pheochromocytoma)
 - ❖ *SDHD (head and neck paragangliomas)*
 - ❖ *SDHB (malignant and extra-adrenal pheochromocytomas)*
 - ❖ *SDHC (extra-adrenal pheochromocytomas)*



*Data from the European-American Pheochromocytoma-Paraganglioma Registry
Schiavi F et al., JAMA, 2005; Peczkowska M. et al., Nature Clinical Practice, 2008*

Malignant Chromaffin-cells Tumors

Susceptibility Genes

Table 2 Hereditary pheochromocytoma: facts and figures.

	Gene				
	VHL	RET	NF1	SDHD	SDHB
Frequency in 'sporadic' tumors (%) [*]	6–10	1–5	unknown	2–8	4–9
Predisposition to malignancy (%)	3	<3	11	<2	66–83
Tumor catecholamine phenotype [†]	NE	E	E	unknown	unknown
Adrenal disease	++	++	++	+	+
Extra-adrenal disease	+	–	+	++	++

^{*}Frequencies of germ-line mutations in apparently sporadic pheochromocytoma and predispositions to malignancy are derived from several sources of data (Walther *et al.* 1999; Aguiar *et al.* 2001; Neumann *et al.* 2002; Bryant *et al.* 2003; Bauters *et al.* 2003; Gimenez-Roqueplo *et al.* 2003).

[†]Tumor catecholamine phenotypes are designated as either epinephrine-producing (E) or predominantly norepinephrine-producing (NE).

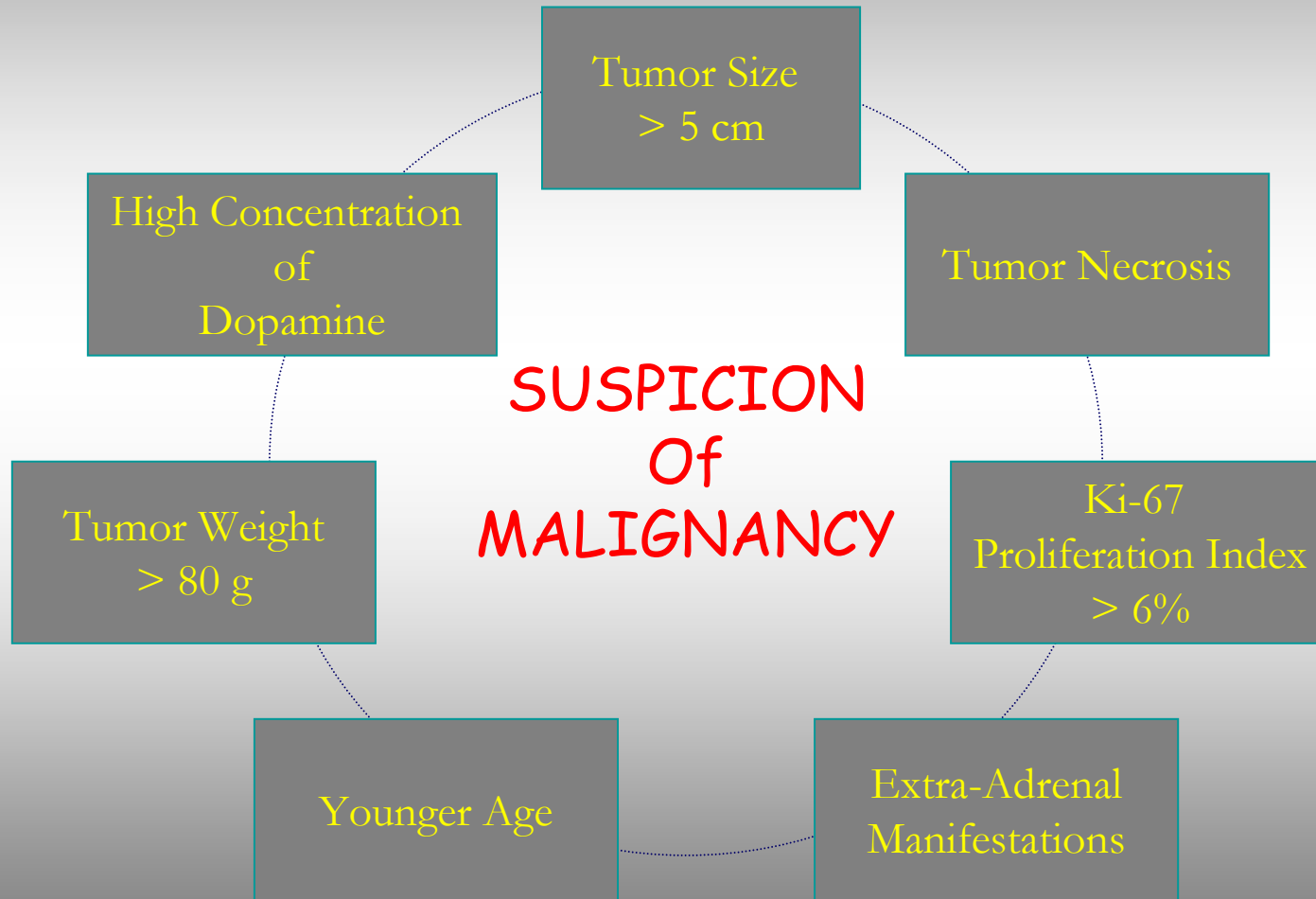
++; +; –, Relative likelihoods of adrenal or extra-adrenal disease from high to low.

*Data from the European-American Pheochromocytoma-Paraganglioma Registry
Eisenhofer G. et al., Frontiers of Hormone Research, 2004*

SDHB Tale of Malignant Behavior

- a tumor suppressor gene
- malignancy is common (up to 83%) in carriers of mutated SDHB
- usually extra-adrenal tumors (~ 92%)
- high penetrance (~ 80%) by age 50
(i.e. 80% of carriers will have at least one tumor by the age of 50)
- young age of onset (~ 36 years)
- **SDHB mutations - are associated with shorter survival**

Markers of Malignancy



Malignant Chromaffin-cells Tumors

Pharmacological Symptomatic Control

- a continue requirement for metastatic or incompletely resectable invasive tumors
- α -receptor blockers and calcium channel antagonists, followed by β -adrenergic receptor blockade often reduce hormone-mediated symptoms
- exceptionally: α -methyl paratyrosine (Demser) to inhibit catecholamine synthesis (extensive disease)

Chromaffin-cells Tumors

Surgical Treatment

- Surgical excision/debulking is a mainstay of therapy, including in metastatic tumours
- Rationale:
 - ❖ to reduce target organs exposure to high levels of catecholamines
 - ❖ to increase MIBG uptake into the remaining lesions

Chromaffin-cells Tumors

[¹³¹I] MIBG Therapy

- selectively concentrated in chromaffin storage granules (VMAT1 and 2)
- usually, multiple medium doses of about 200 mCi (7.4 GBq) are administered
 - ❖ symptoms improvement, up to 75%
 - ❖ partial tumor response in 24-45%
 - ❖ stable disease up to 57%
- disease progression after approximately 2 yr - common

Chromaffin-cells Tumors

Somatostatin Analogs

- Disappointing
 - ❖ 10 patients - Sandostatin-LAR
 - ❖ no changes in major parameters (BP, plasma catecholamine and CgA, urinary metanephrines) or in symptoms
 - ❖ octreotide ineffectiveness - d/t low SSTR expression (SSTR_{2a} is expressed in only ~25%)

Chromaffin-cells Tumors

Radiolabelled Somatostatin Analogs

- for patients showing a high tumour uptake on scintigraphy
- several radiopharmaceuticals (^{111}In -DOTA-octreotide, ^{90}Y -DOTA-octreotide and ^{177}Lu -DOTA-octreotate, and ^{111}In and ^{90}Y -DOTA-lanreotide)
- disease stabilisation in a few patients
- side effects: leucopenia and thrombocytopenia

Novel Anti-Neoplastic Therapies

- Imatinib mesylate (Glivec) - ineffective in a small number of cases
- Everolimus (mTOR inhibitor, RAD001, Novartis) - some efficacy in NETs
 - ❖ ineffective in two patients with malignant paragangliomas
- New promising targets for therapy - under investigation
 - ❖ the human telomerase (the over-expressed hsp90 or hTERT)
 - ❖ the angiogenic pathways
 - ❖ tumor sensitization to ^{131}I -MIBG radiotherapy
 - ❖ gene therapy

Gross D.J. et al, Endocrine-Related Cancer, 2006

Sausville E.A. et al., Current Cancer Drug Targets, 2003

Chromaffin-cell Tumors

Conclusions

- **Risk factors for malignant disease:**
 - ❖ large size of the primary tumor
 - ❖ an extra-adrenal location of the primary tumor
 - ❖ the presence of an SDHB mutation
 - ❖ significant production of dopamine
- A considerable proportion of the patients respond to MIBG radiotherapy, after palliative surgery.
- In the presence of metastases, the average 5-yr survival is approximately 50%.
- It is unclear whether these responses have an overall impact on survival or QoL (no RCTs).

Medullary Thyroid Carcinoma

- A 53 year old male patient with a slowly enlarging left neck mass - 2.5 cm
- FNA- Medullary Thyroid Carcinoma
- Pre-op
 - ❖ CLT = 1540 (normal up to 5)
 - ❖ CEA = 132 (normal up to 5)
 - ❖ Normal catecholamines & metanephrines
- Total thyroidectomy with left neck dissection

Medullary Thyroid Carcinoma- cont.

- Post-op:
 - At 5 days: CLT=525, CEA=56
 - At 2 months: CLT=432, CEA=27
 - At 6 months: CLT=554, CEA=42
 - At 1y: CLT=920 (DT~6m), CEA=53
- US neck: a small mass in the thyroid bed, 1.7 cm

Medullary Thyroid Carcinoma- cont.

- Chest CT: miliary nodules in both lungs
- MRI abdomen: small mass inside the liver
- Bone scan & MRI of the spine: normal
- Octreoscan/MIBG: no uptake

MTC - *types*

- Sporadic
- Multiple Endocrine Neoplasia (MEN)
 - Type 2A
 - Type 2B
- Familial Medullary Thyroid Carcinoma (FMTC)

Genetic Testing

- RET Proto-oncogene mutations
 - codon 634 the most frequent
 - codon 918 : > 98% of MEN 2B
 - 95% sensitive in index case
 - 100% sensitive in family members
- Test: all MTC patients (controversial at old ages)
- all 1st degree relatives after a positive test

Characteristics

FAMILIAL


- Multifocal/bilateral
- More aggressive
- Onset 2nd or 3rd decade
- Earlier onset in women

SPORADIC

- Unifocal
- More indolent
- Onset 6th or 7th decade
- No gender disparity

Prognosis

5 year survival

- 50% Overall
 - 75% Without metastasis or invasion
 - 25% With metastasis or invasion
 - CLT-DT
 - <6m
 - 6m-2y
 - >2y
- 

MTC - Adjuvant therapy

- **Chemotherapy**
 - No established role
- **Radiation**
 - controversial
 - palliation
 - residual local disease

TKIs & RET proto-oncogene

- RET includes a TK in its structure
- Each TK is divided into three domains:
 - ❖ N-terminal extracellular domain
 - ❖ hydrophobic transmembrane domain
 - ❖ a cytoplasmic tyrosine kinase domain

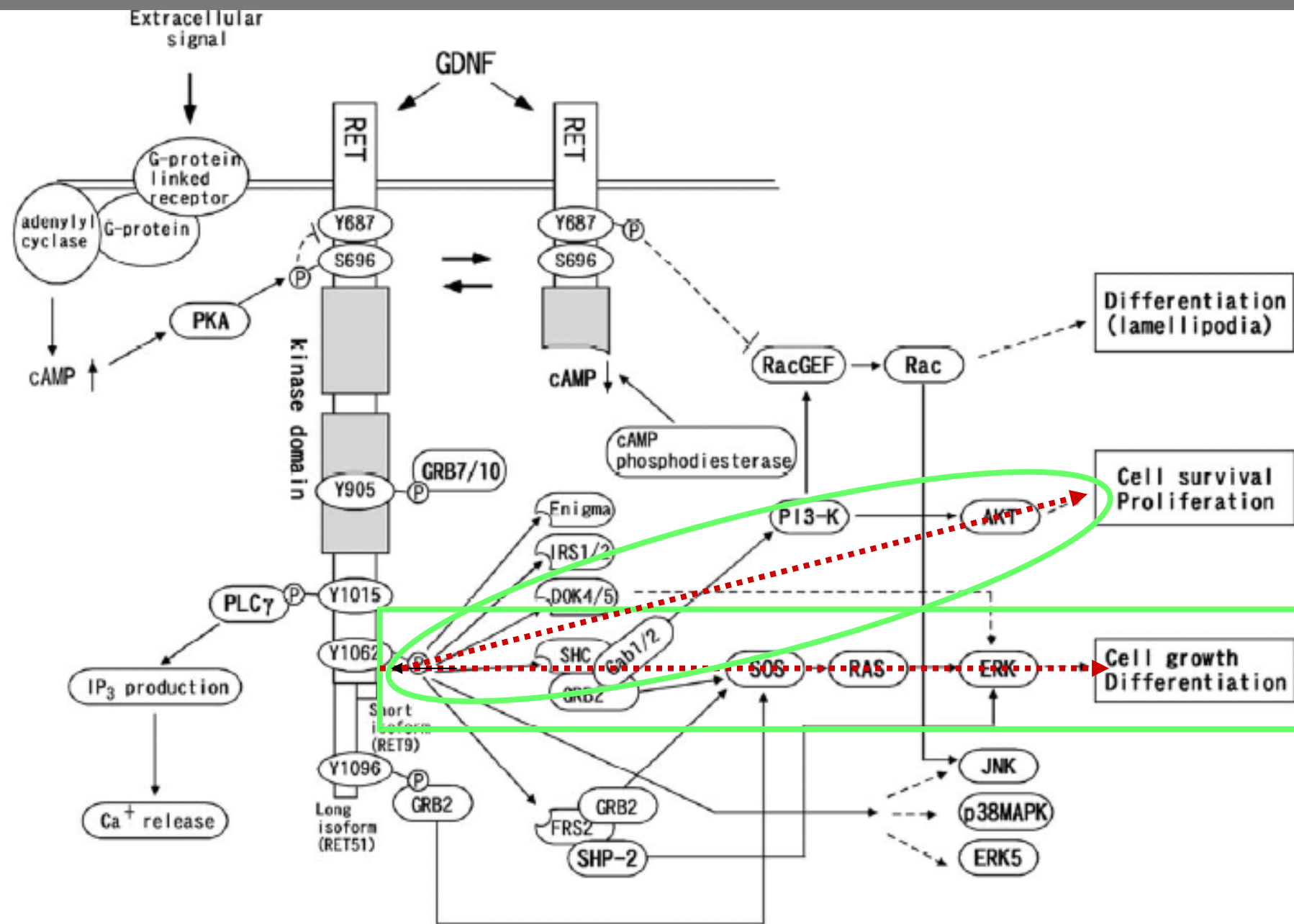


Fig. 1. Intracellular signaling pathways through activated RET.

Strategies to inhibit RET

- Dominant Negative receptor forms
- Ligand competing peptides
- Aptamers
- Small molecules tyrosine kinase inhibitors (TKI)
 - Bind to RET ATP binding pocket
 - Overlapping specificities : inhibit VEGFR2, PDGFR2, EGFR

Clinical trials of TKI in MTC

- ZD6474 (Zactima, vandetanib); Astra Zeneca

- ❖ VEGFR inhibitor, TK inhibitor
- ❖ Phase II, non RCT; multicenter; international; ongoing, not-recruiting

Wells et al, interim data on 15 cases

- Mean duration of Therapy 136 days
 - ❖ PR in 3
 - ❖ SD in 10
 - ❖ PD in 2
- Sustained decreased 50% of CLT in 12/15 > 6 weeks.
 - ❖ Some patients had a > 90% decreased levels of CLT
 - Suspicion: loss of tumor cell differentiation.
 - Question: is CLT a reliable marker when using TKI ?
- Decreased CEA levels
- Sides effects: diarrhea, nausea, rash, fatigue
- Associated effects: inhibition of VEGFR2.

Clinical trials of TKI in MTC, cont.

- Sorafenib (Nexavar; Bayer)
 - ❖ oral multi-kinase inhibitor
 - ❖ blocks the Raf kinase and VEGF receptors 2 & 3 to target tumor cell growth and angiogenesis, as well as PDGFR-B, KIT, FLT-3, and RET.
 - ❖ FDA approved for use in RCC & HCC
 - ❖ **AE:** HTN, skin, weakness, GIT; rare: bleeding, heart

Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings

Effect of sorafenib in symptomatic metastatic MTC

F. Kober et al; Kaiserin Elisabeth Spital, Vienna, Austria

- 5 patients with excessive CLT levels
- symptoms in all: diarrhea, severe pain
- all had prior thyroidectomy and cervical \pm mediastinal LN dissection, 4 pts had prior octreotide therapy, 3 prior chemotherapy.

Results:

- at 4 weeks: all pts were free of CLT-related symptoms.
- at 3 months: CLT decreased $>50\%$ of baseline in all, $>90\%$ in 2.
- at 3 months: 2 pts with severe metastasis-related pain were off analgesics
- tumour response: at 6 months, CR -1, PR -1, SD 3.

Due to AE, Sorafenib dosage was reduced to 50% of the initial dose in all patients. Marked TSH - elevations were observed in 3 pts which indicates a direct influence to the hypothalamic-pituitary-axis.

Conclusion: Sorafenib has to be considered as an effective treatment of symptomatic, metastatic MTC.

Clinical trials of TKI in MTC, *cont.*

- Sunitinib (Sutent)

- ❖ oral multiple receptor TK inhibitor
- ❖ **AE:** CHF, HTN, bleeding, CBC decrease, liver disturbances, GIT
- ❖ Phase III as 1st -line in advanced RCC - promising (MSKCC).
- ❖ In GIST: 62% of patients - abnormal TSH; 36% - hypothyroidism → the drug could be useful in Thyroid CA