Medullary Thyroid Carcinoma:
Treatment and Follow-up
AME-AACE - Verona, 27-29 ottobre 2006

Surgical Treatment:

Initial Approach and Re-Intervention

Corrado Pedroni M.D.

Department of Otolaryngology
Head & Neck Surgery
Arcispedale Santa Maria Nuova
Reggio Emilia

MTC: Primary Surgical Management

"Issues"

- **Sporadic vs hereditary MTC**
- **Clinically apparent vs screen detected MTC**
- **Indications and extent of lymph node dissection**
- **Management of parathyroid glands**

Clinical MTC: Primary Surgical Treatment

- **surgery is the only curative treatment**
- **external-beam radiotherapy and chemotherapy are ineffective**
- **recurrence and survival rates depend upon the adequacy of initial surgery**

Clinical MTC: Primary Surgical Treatment

- **minimal surgical procedure, regardless of form and stage: total thyroidectomy and central neck dissection**
- **indication for lateral neck dissection is still controversial**

Clinical MTC: Primary Surgical Treatment

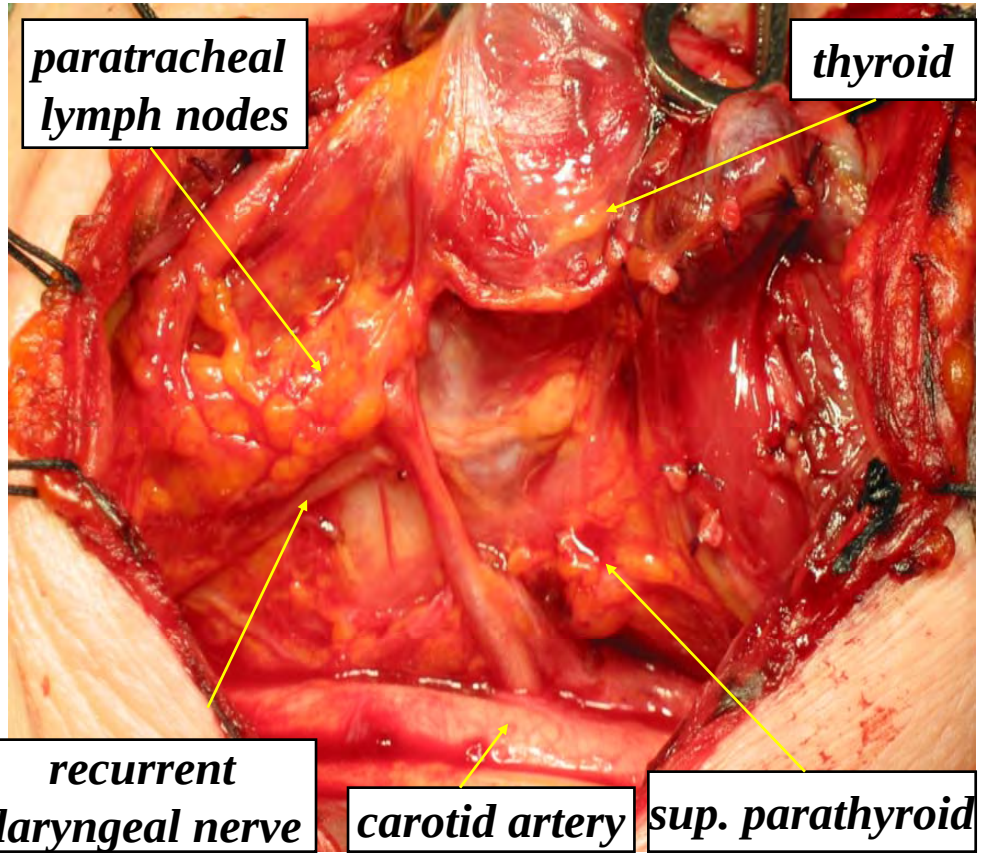
According to

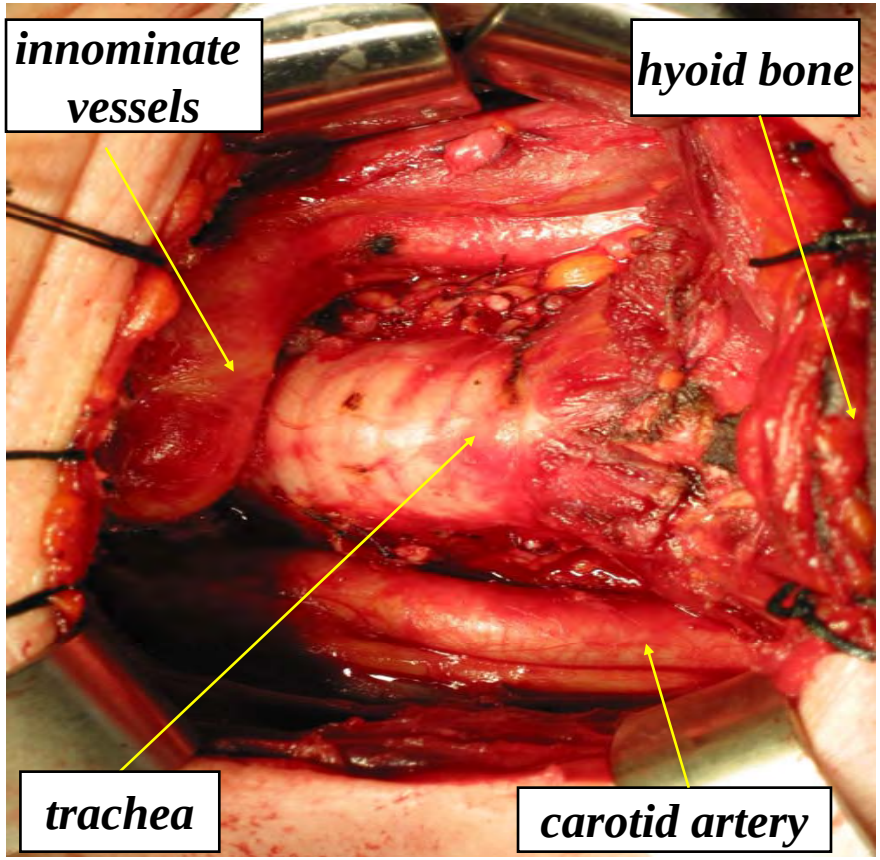
- **SSO guidelines** (1997), **Mayo** (Heshmati, 1997), **MSKCC** (Shaha, 1998): **lateral ND only for N+**

- **NCCN guidelines** (2006):
  ipsilateral ND for sporadic MTC > 1 cm N0

- **AACE/AAES guidelines** (2001), **German guidelines** (1996), **IGR** (Scollo, 2003), **M.D. Anderson CC** (Fleming, 1999):
  ipsilateral ND for unilateral sporadic MTC N0
  bilateral ND for hereditary MTC and for N+

- **Washington Univ.** (Moley, 1999), **Halle Univ.** (Machens, 2002):
  bilateral ND even for unilateral sporadic MTC N0





Central neck dissection

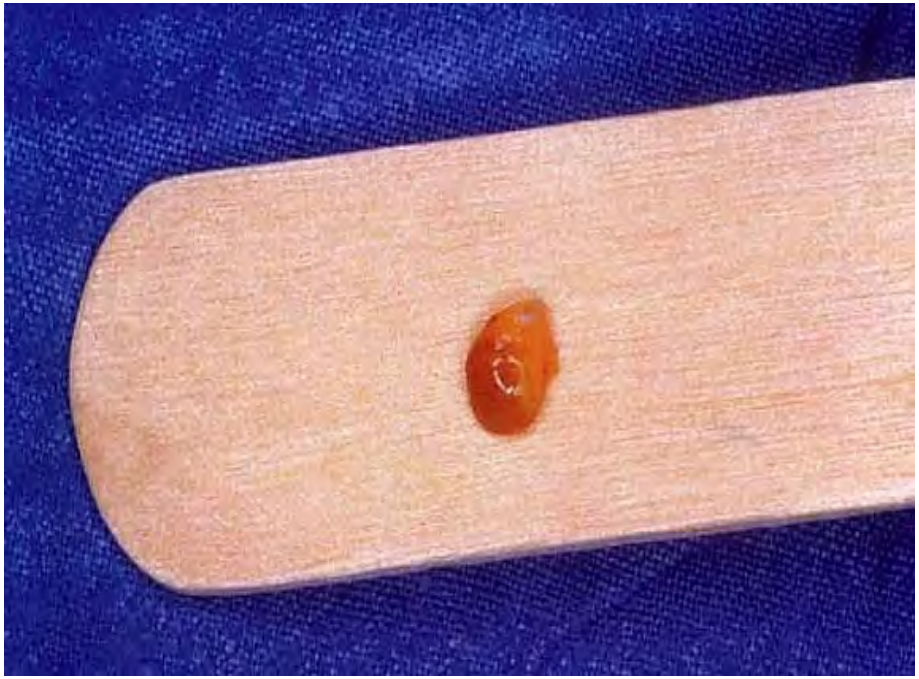
anatomical limits

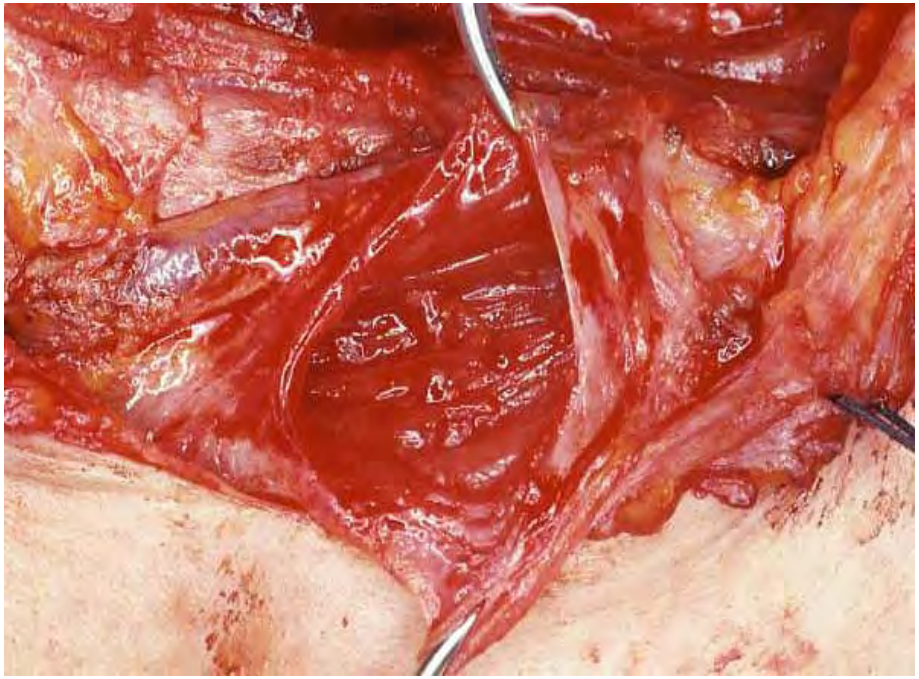
- *hyoid bone*
- *innominate vessels*
- *carotid sheath*

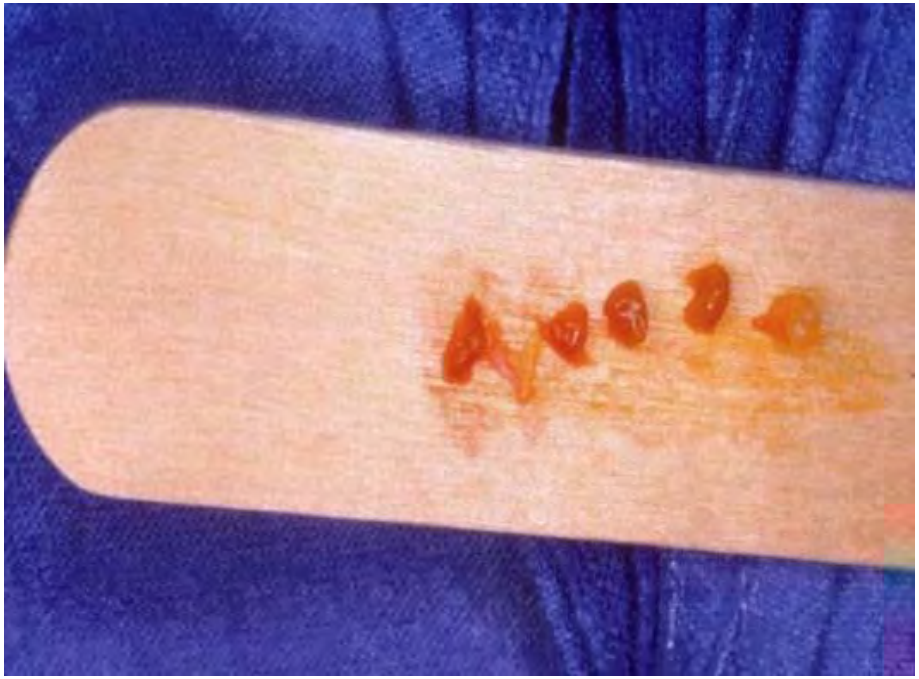
"high point"

preservation of the recurrent laryngeal nerves and parathyroid glands

The inferior parathyroid gland is sliced into few mm 5 pieces, confirmed histologically (so as not to autograft a lymph node metastasis), and auto-transplanted into individual pockets in the SCM muscle





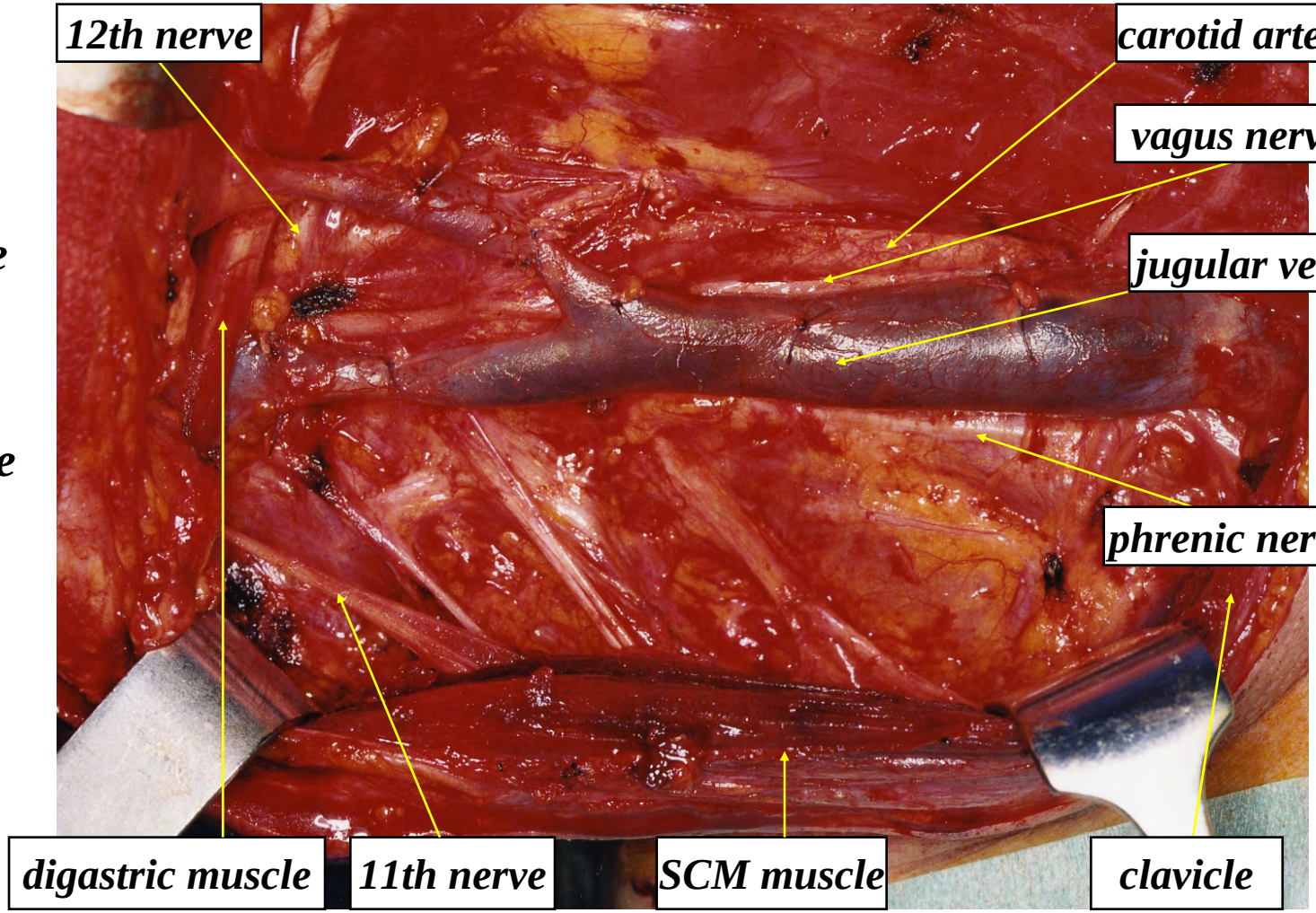


MTC: Management of parathyroid glands in Central Neck Dissection

- **parathyroids glands preserved in situ by means of limited central neck dissection** *(Gagel, 1993)*
- **inferior parathyroidectomy with autotransplantation to the SCM muscle** *(Evans, 2000)*
- **total parathyroidectomy with autotransplantation to the SCM muscle** *(Cohen, 2003)*

anatomical limits

- *digastric muscle*
- *clavicle*
- *carotid sheath*
- *trapezius muscle*



Lateral neck dissection

"high point"

preservation of the 11th, nerve, jugular vein and SCM muscle

Clinical MTC: Primary Surgical Treatment

Reasons for total thyroidectomy

- **hereditary MTC: multifocal and bilateral**
- **sporadic MTC: bilateral in 20-30% of cases (intraglandular lymphatic spread)**
- **hereditary background unknown at the time of primary operation (5% of index cases) or not even detected (rare RET mutations)**
- **radio-iodine treatment not effective**

Clinical MTC: Primary Surgical Treatment

Reasons for more extensive neck dissection

- **high incidence of lymph node metastasis in the central and lateral neck compartments**

Locoregional lymph node involvement in MTC

Author	Central	Ipsilateral	Contralateral	Mediastinal
Fleming, 1999 40 pz	(80%)	(78%)	(25%)	NA
Moley, 1999 73 pz	(79%)	(75%)	(47%)	NA
Machens, 2002 161 pz	(52%)	(43%)	(19%)	(17%)
Scollo, 2003 101 pz	(48%)	(49%)	(24%)	NA

Clinical MTC: Primary Surgical Treatment

Reasons for more extensive neck dissection

- high incidence of lymph node metastasis in the central and lateral neck compartments
- **high rates of regional recurrence after total thyroidectomy ± selective lymphadenectomy**

Cervical Recurrence of MTC requiring Reoperation

Author	n°	Median follow-up (yr)	n° with Cervical Recurrence
Simpson, 1982	16	NA	8 (50%)
Saad, 1984	143	6	39 (27%)
van Heerden, 1990	40	12	26 (65%)
Gharib, 1992	52	24	18 (35%)
Kallinowski, 1992	40	6	26 (65%)
Dralle, 1994	39	5	23 (59%)
Marzano, 1995	25	5	10 (40%)
Fuchshuber, 1998	28	19	6 (21%)
Fleming, 1999	40	3	5 (13%)

Clinical MTC: Primary Surgical Treatment

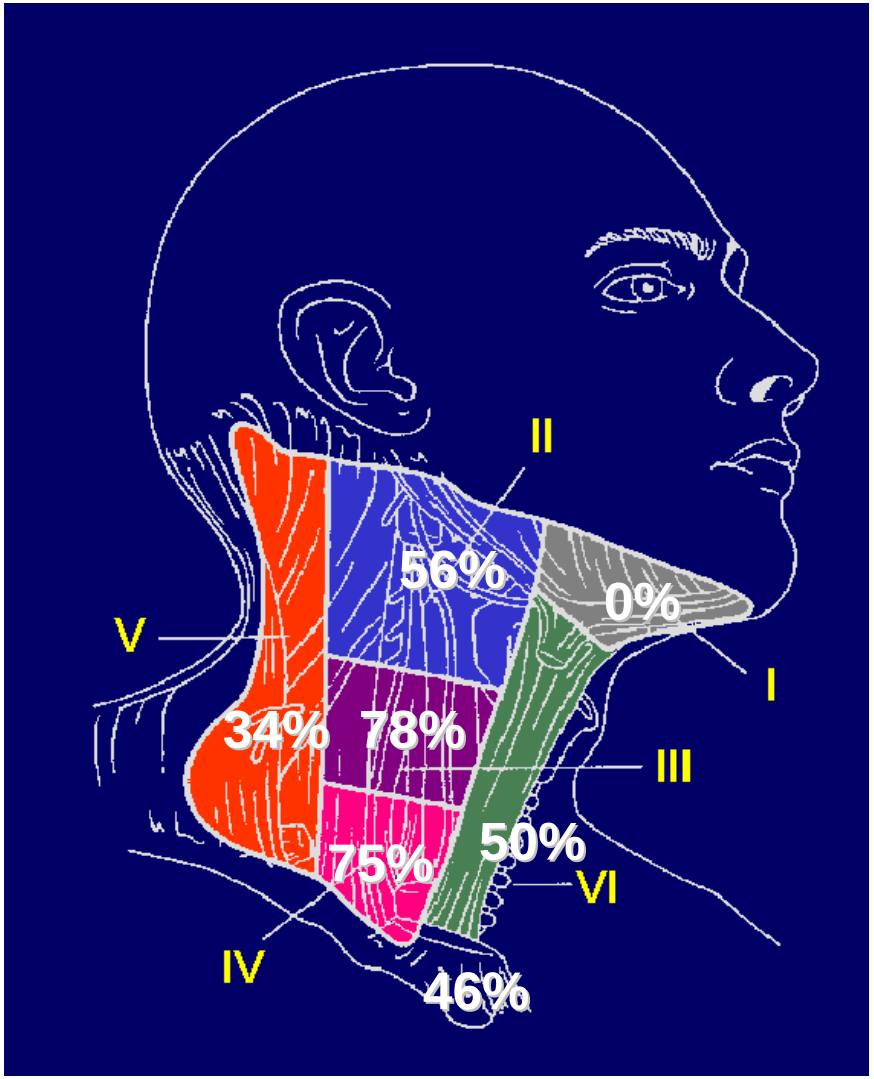
Reasons for more extensive neck dissection

- high incidence of lymph node metastasis in the central and lateral neck compartments
- high rates of regional recurrence after total thyroidectomy ± selective lymphadenectomy
- **the most frequently involved nodal levels, in order, are III, IV, II, VI, VII, V** *(Ellenhorn, Shah, 1993)*

MTC: Distribution nodal metastases

Ellenhorn, Shah et al. Impact of therapeutic regional lymph node dissection for medullary carcinoma of the thyroid gland. Surgery, 1993

level I	0%
level II	56%
level III	78%
level IV	75%
level V	34%
level VI	50%
level VII	46%



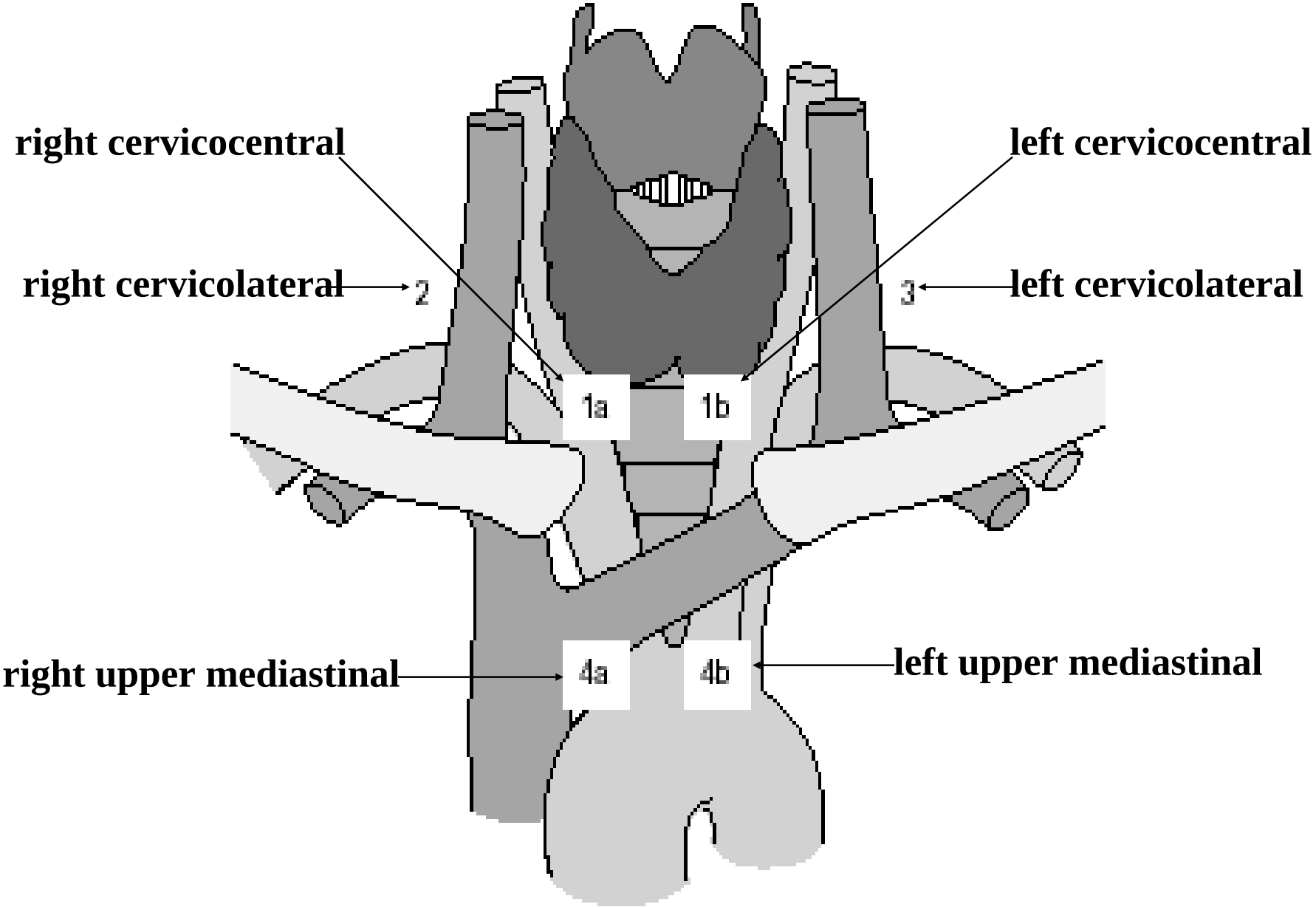
Clinical MTC: Primary Surgical Treatment

Reasons for more extensive neck dissection

- high incidence of lymph node metastasis in the central and lateral neck compartments
- high rates of regional recurrence after total thyroidectomy ± selective lymphadenectomy
- the most frequently involved nodal levels, in order, are III, IV, II, VI, VII, V *(Ellenhorn, Shah, 1993)*
- **four compartment-oriented lymphadenectomy decreases regional recurrence rates (from 59% to 10%) and improve length of survival** *(Gimm, 1998)*

Four compartment-oriented lymphadenectomy

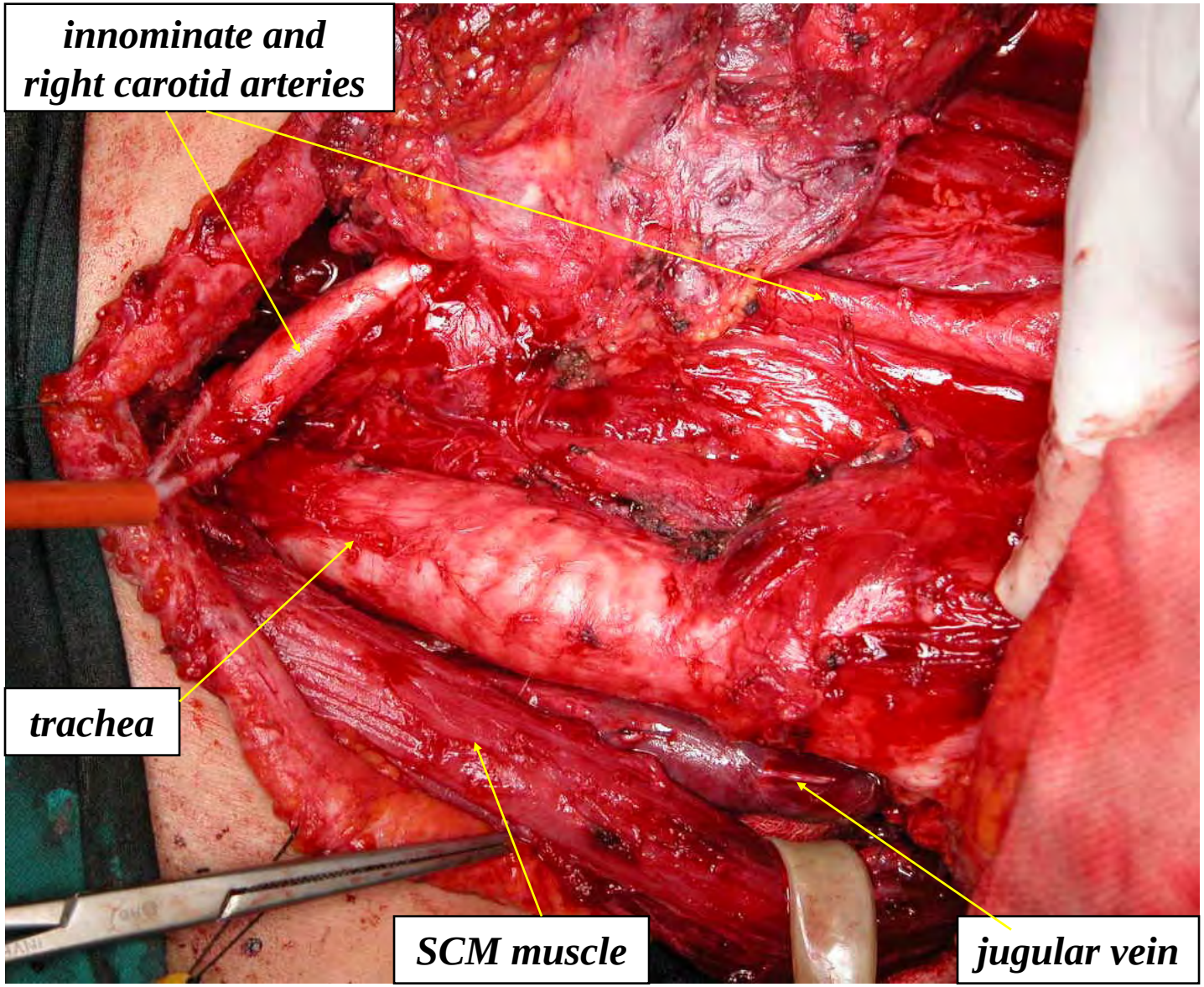
(Dralle, 1994)



Clinical MTC: Primary Surgical Treatment

Upper mediastinal dissection

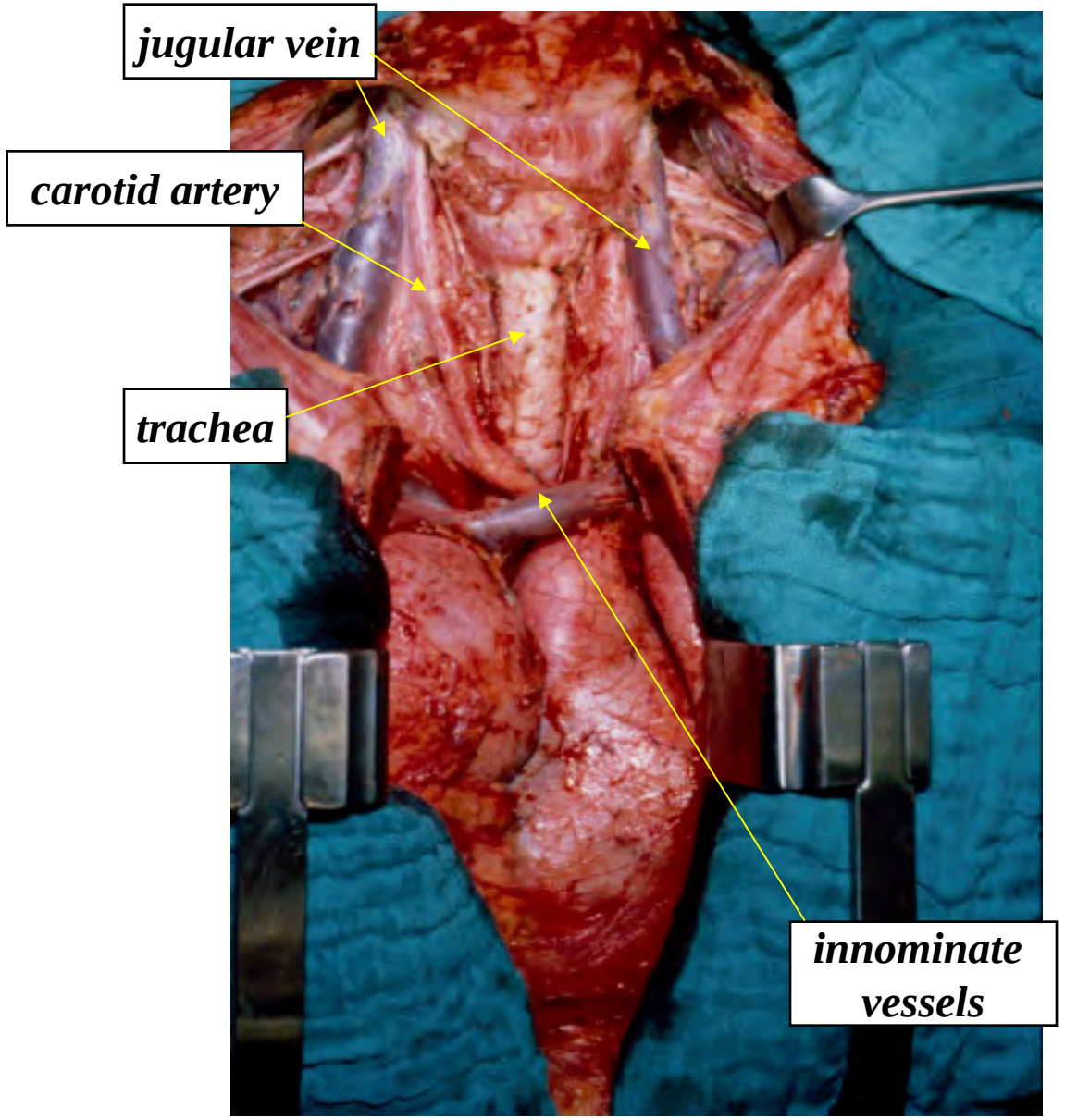
- **when central compartment is involved**
- **generally through a standard cervical incision**
- **through median sternotomy only if mediastinal metastases are imaged preoperatively**
- **most surgeons do not perform elective median sternotomy for removal of possible occult metastasis** ***(Fleming, 1999; Cohen & Moley, 2003; Scollo, 2003)***



Total thyroidectomy and central (levels VI and VII) and bilateral levels II–V node dissections

anatomical limits

- *innominate vessels*
- *tracheal bifurcation*



Trans-sternal mediastinal dissection

Hereditary MTC: Surgical Treatment

RET gene mutation,
no clinically detected disease

prophylactic total thyroidectomy

± central neck dissection

timing of surgery

- **MEN2A, FMTC: before of 5 or 10 years**
- **MEN2B: before of 6 months or at diagnosis**

Prophylactic thyroid management according to RET genotype

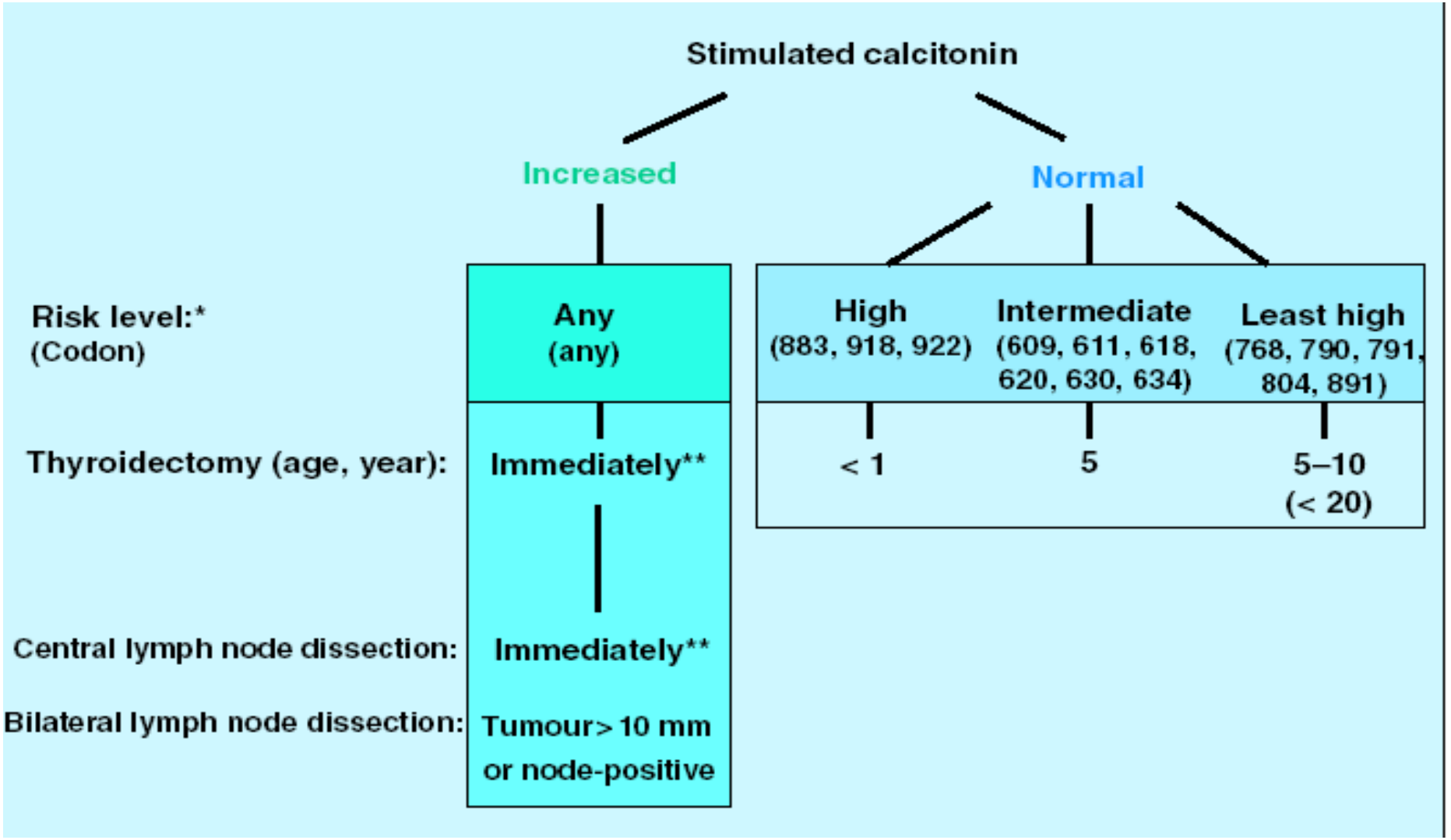
based on the 1999 consensus statement from the 7th International Workshop on MEN; where no consensus was reached, recommendations are based on recent literature *(Machens for EUROMEN Study Group 2003, 2004; Dralle, 1998)*

Risk level	RET genotype (mutation in codon)	Thyroidectomy before age (years)	Central lymph node dissection before age (years)
3 Highest	883, 918, 922	0.5	0.5
2 High	630, 634	5	≥ 10
2 High	609, 611, 618, 620	5	≥ 20
1 Least hight	768, 790, 791, 804, 891	5 or 10	≥ 20

Timing of thyroidectomy in RET gene carriers

(University of Halle Algorithm)

(Machens, 2005))



MTC: Management of parathyroid glands in MEN 2A

- **selective removal only of the abnormal parathyroid glands** ***(Decker, 1997)***
- **subtotal parathyroidectomy with preservation of a well vascularized portion of a single gland in situ** ***(Heshmati, 1997)***
- **total parathyroidectomy with immediate autotransplantation of a portion of a single gland to the nondominant forearm brachioradialis muscle** ***(Wells, 1994)***

MTC: Reoperations for ↑ CT

- **CT (basal and stimulated) is a highly sensitive marker of persistent or recurrent disease**
- **after primary surgery, more than 50% of patients will have persistent elevation of CT levels**
- **when examination of the neck and metastatic search are negative, occult cervical disease has presumed**
- **the management of occult metastatic MTC is controversial: surgical reoperation or conservative observation are the best available options**

MTC: Reoperations for ↑ CT

- ***Tisell** (1986), **Buhr** (1993), **Moley** (1993)* **and** ***Dralle** (1994)* **have recommended aggressive microsurgical neck dissection**
- **20-30% of patients may have normal stimulated CT levels after such neck reoperative surgery**
- **microdissection takes longer, the surgical technique is more difficult and complications are greater than conventional neck dissection**
- **during reoperative surgery, *Gimm & Dralle** (1997)* **found pulmonary micrometastasis in 28% of patients and *Moley** (1997)* **liver metastases in 25%**

Reoperative cervical surgery for MTC

Author	n°	Image +	Bilateral MRND	CT-PG negative after Reoperation
Norton, 1980	7	0	0	1/7 (14%)
Tisell, 1986	11	1	10	4/11 (36%)
Van Heerden, 1990	11	11	NA	0/11 (0%)
Frank-Raue, 1992	14	6	NA	3/14 (21%)
Dralle, 1994	55	NA	NA	8/55 (15%)
Abdelmoumene, 1994	13	3	2	1/13 (8%)
Buhr, 1995	53	0	24	8/53 (15%)
Gimm & Dralle, 1997	34	27	34	9/34 (26%)
Moley, 1997	45	22	30	17/45 (38%)
Fleming, 1999	29	16	25	4/29 (14%)

Complications after reoperation for recurrent MTC (36 patients)

(Gimm & Dralle, 1997)

complication	n°	%
permanent unilateral palsy of recurrent nerve	3	8,3%
permanent hipoparathyroidism	9	25%
transient Horner's syndrome	2	5,5%
transient paresis of brachial plexus	1	2,7%

MTC: Reoperations for ↑ CT

- **most patients with elevated CT levels, following TT and ND, survives many years (86% 10-year survival) without clinical evidence of metastatic disease** ***(van Heerden, 1990)***

- **in patients who have undergone primary complete neck dissection, reoperative cervical surgery should be considered only if imaging studies document recurrent disease**

- **an elevated CT level alone may be followed conservatively if the patient is asymptomatic**

Medullary Thyroid Carcinoma
The Problem of Follow-up

Bryan McIver MB PhD

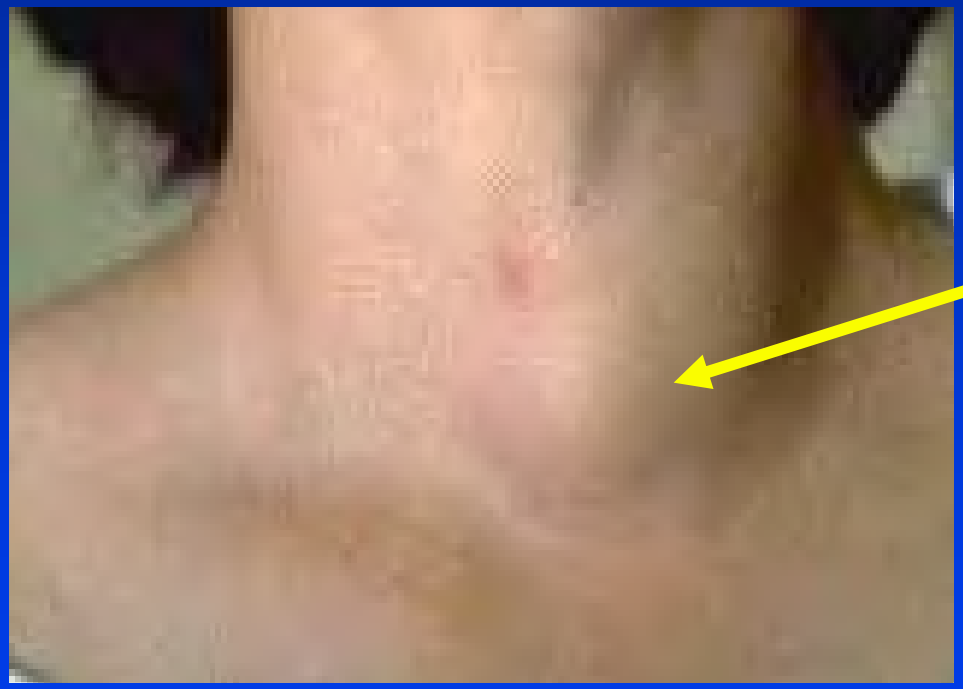
Mayo Clinic
Rochester MN

October 28th 2006

Verona, Italy

mayo

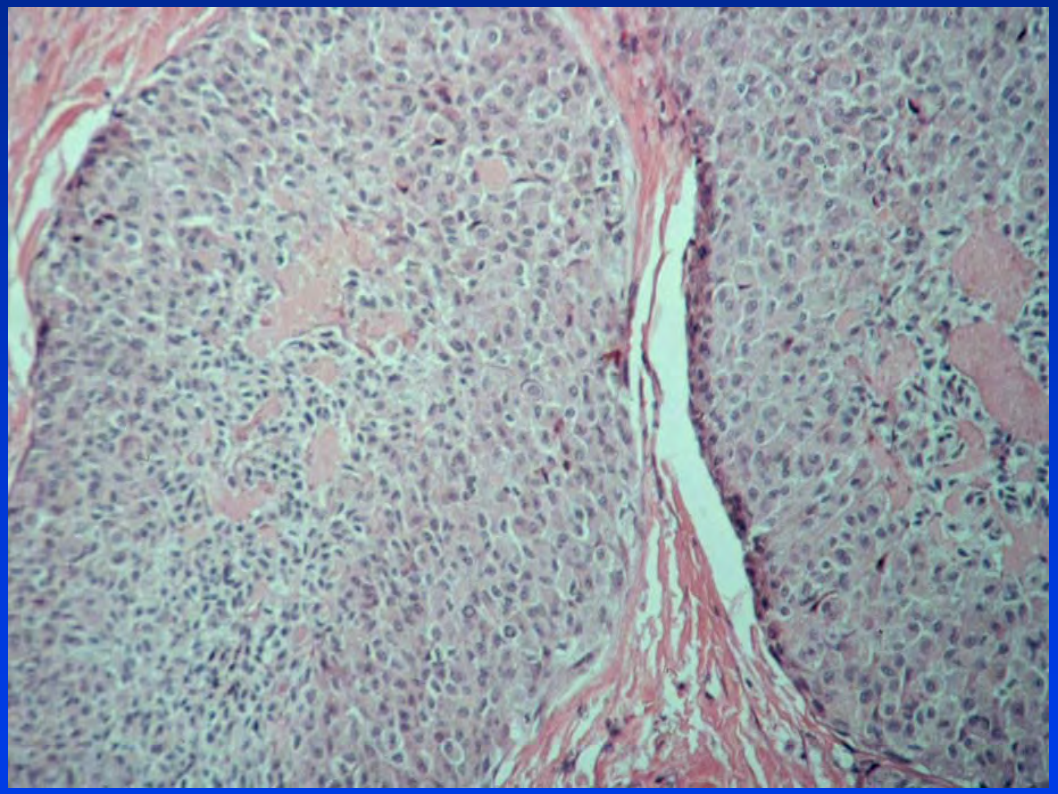
Thyroid Nodule



Solitary nodule,
left lobe of thyroid

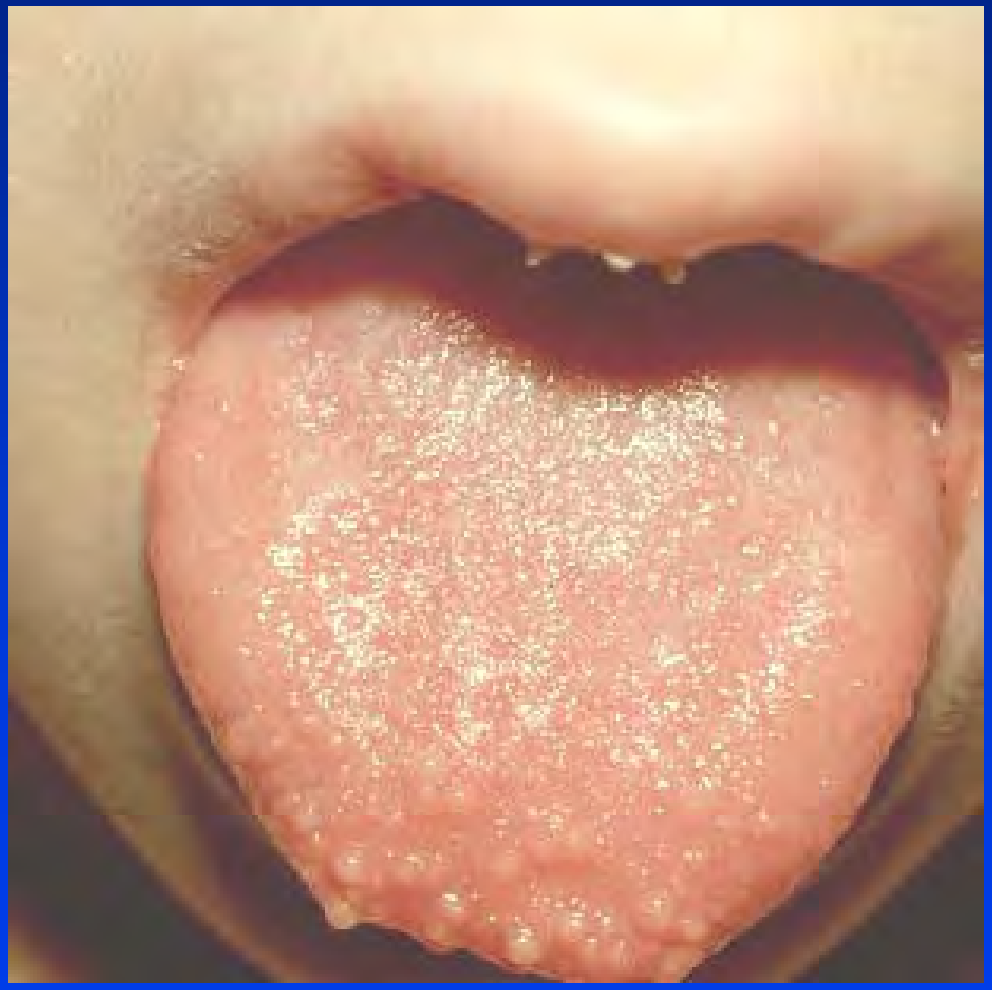
Medullary Carcinoma of Thyroid

- Sheets of spindle-shaped cells
- Amyloid deposition
- Most aggressive of the differentiated thyroid cancers
- Neural crest origin
- No iodine uptake
- Calcitonin and CEA

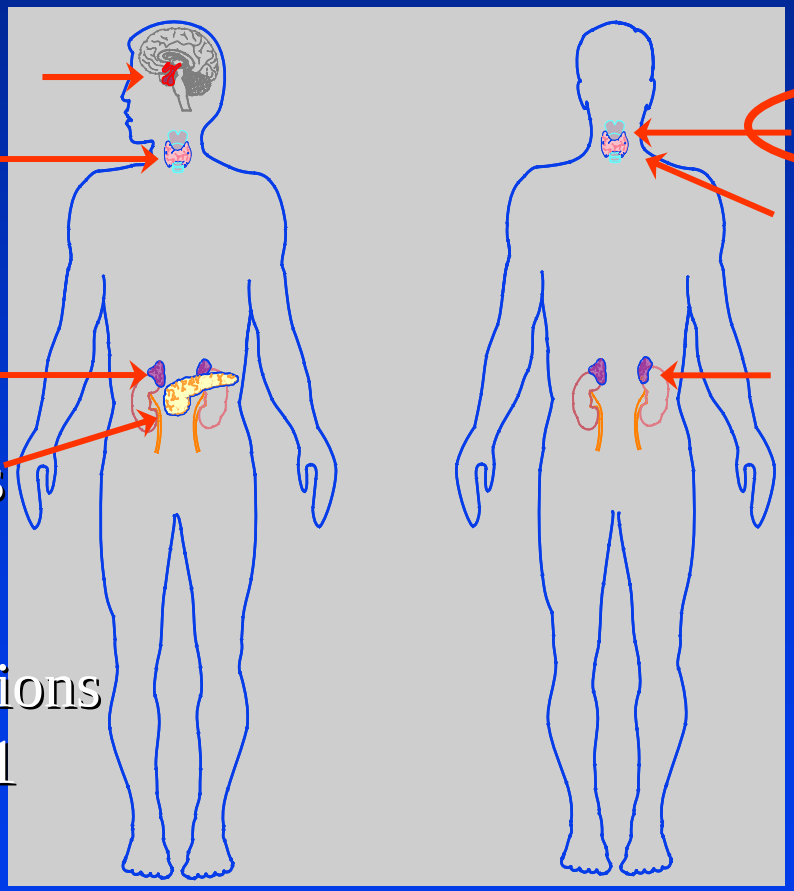


mayo

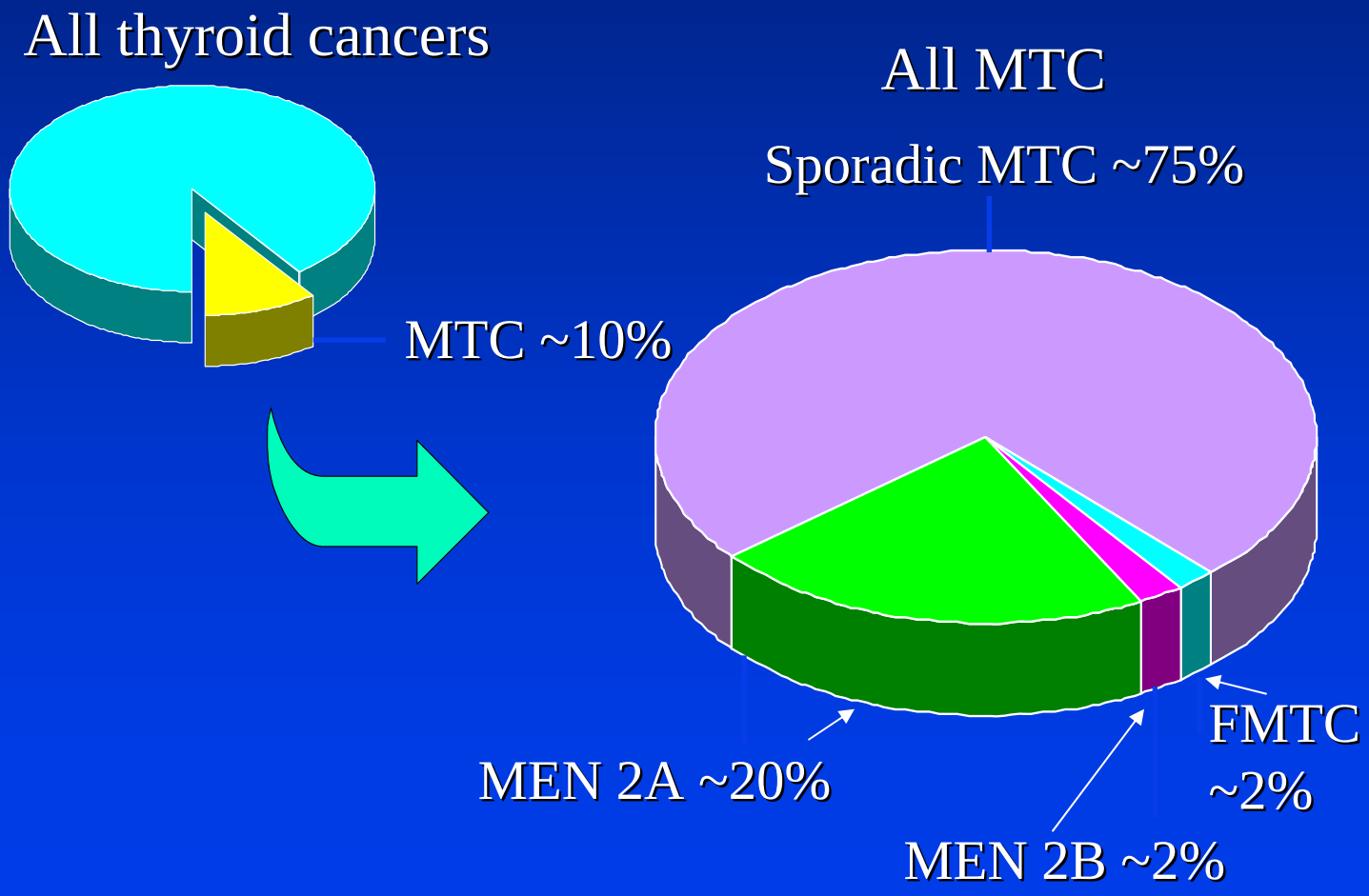
The Tongue



MEN 1 and MEN 2 Are Hereditary Cancer Syndromes



Medullary Thyroid Carcinoma (MTC) Is the Hallmark of MEN 2



Sporadic vs Hereditary MTC

Sporadic MTC

- Unifocal
- Later age at onset
- C-cell hyperplasia rare or absent
- No family history
- No associated endocrinopathies

Hereditary MTC

- Multifocal
- Early age at onset
- C-cell hyperplasia
- Family history in some cases
- Associated endocrinopathies in MEN 2A and 2B

Clinical Presentation of Medullary Thyroid Carcinoma

Type	MTC Distribution	Familial Pattern	Associated Abnormalities
Sporadic	Unilateral	No	None
MEN 2A	Bilateral	Yes	Pheochromocytomas Hyperparathyroidism
MEN 2B	Bilateral	Yes/No	Pheochromocytomas Mucosal neuromas Ganglioneuromas Marfanoid phenotype
FMTC	Bilateral	Yes	None

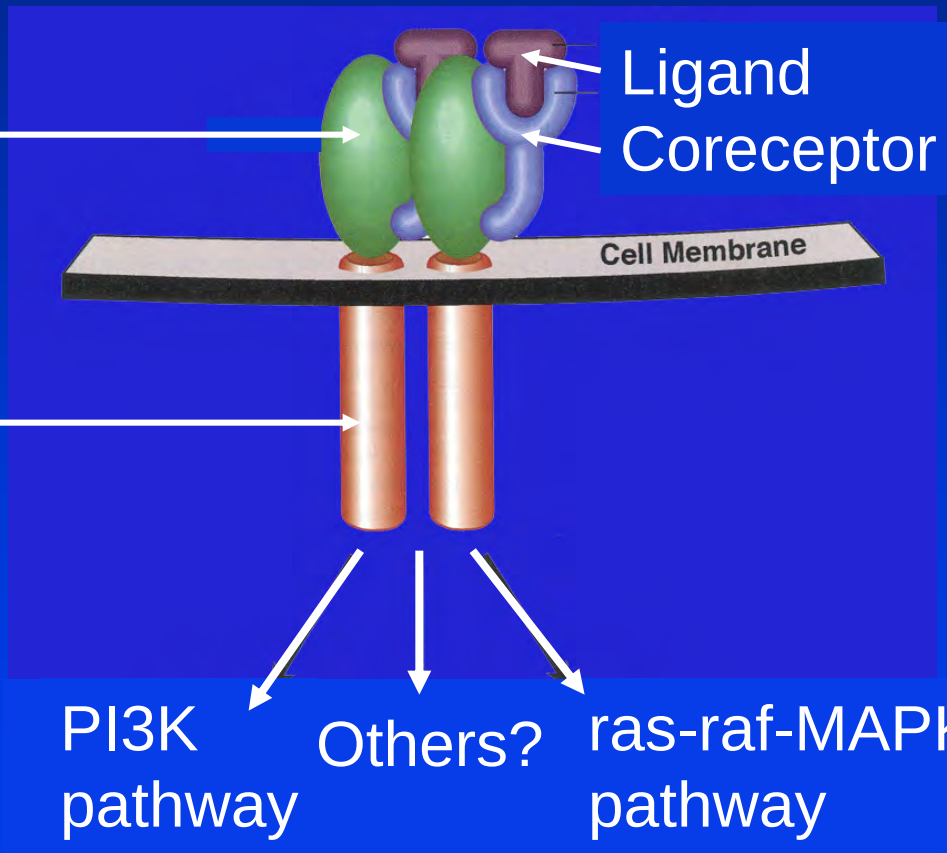
Genetics of MEN 2 Syndromes

- *RET* proto-oncogene on chromosome 10
- Autosomal dominant transmission
- 21-exon gene codes for membrane-associated tyrosine kinase receptor
- Mutated *RET* gene remains activated leading to tumorigenesis

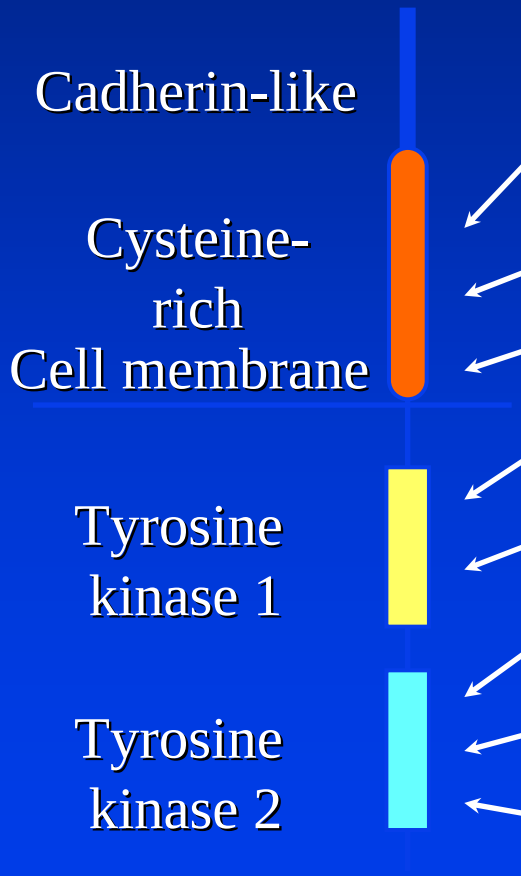
RET in Medullary Carcinoma

MEN 2a

MEN 2b



Mutations of the *RET* Proto-Oncogene: MEN 2A



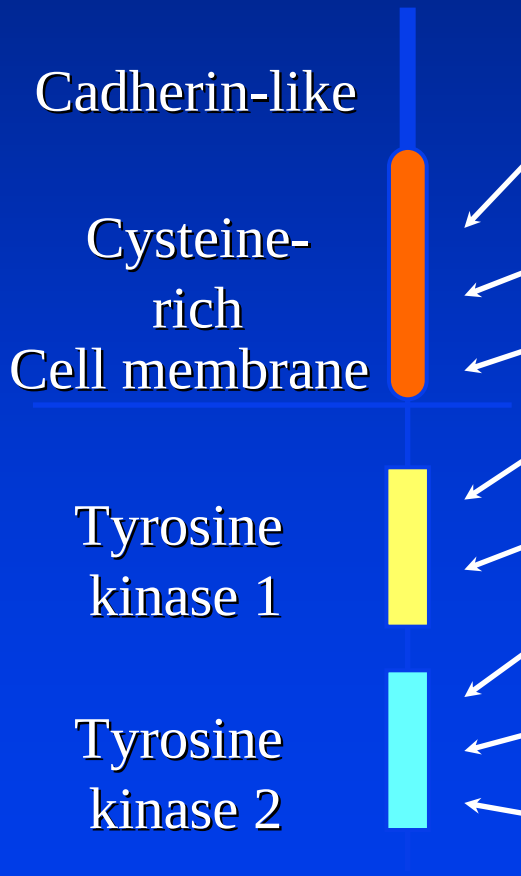
Exon	Codon
10	609, 611, 618, 620
11	630,631
11	634
13	768, 790, 791
14	804, 806, 844
15	883
15	891
16	918

MEN 2A:

codon 634 mutation accounts for 85%; most others in exons 10 and 11 with very rare mutations reported elsewhere in gene.

mayo

Mutations of the *RET* Proto-Oncogene: MEN 2A

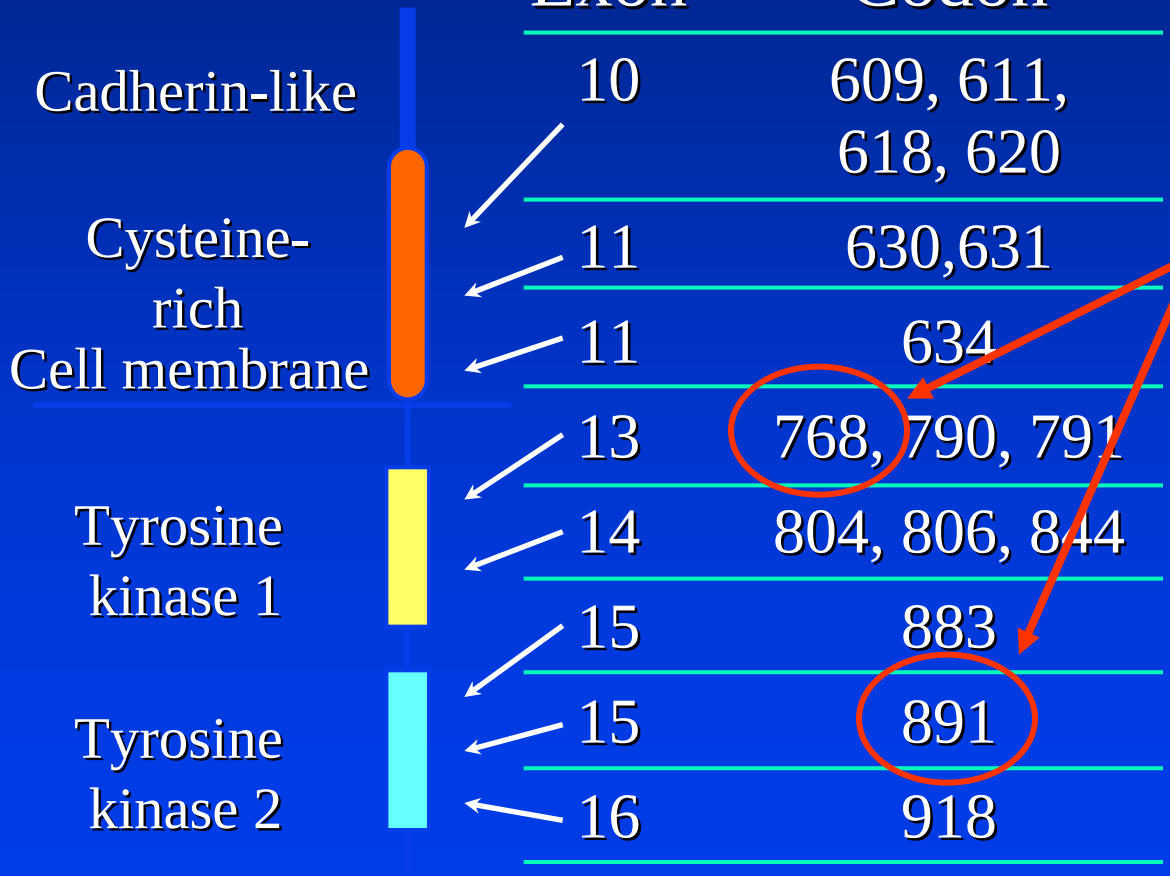


Exon	Codon
10	609, 611, 618, 620
11	630,631
11	634
13	768, 790, 791
14	804, 806, 844
15	883
15	891
16	918

MEN 2B:

codon 918 mutation accounts for 95%; codon 883 also implicated in a few cases

Mutations of the *RET* Proto-Oncogene: MEN 2A



Exon	Codon
10	609, 611, 618, 620
11	630,631
11	634
13	768, 790, 791
14	804, 806, 844
15	883
15	891
16	918

FMTC:

codons 768 and 891 mutations may be unique to FMTC, others – including 634 – overlap with MEN2A

RET Mutations in Families With MEN 2

Phenotype	% *RET* mutation
MEN 2A	97
MTC, pheo, PTH	99
MTC, pheo, no PTH	100
MTC, PTH, no pheo	95
MEN 2B	88
FMTC	85
Other MTC	92

N=477

Eng C et al. *JAMA* 276:1575, 1996

mayo

Genetic counseling

- 95% MEN2A inherited. Family should be evaluated carefully
- Nearly all FMTC inherited
- >50% MEN2B *de novo* mutation, but testing and careful family evaluation warranted.
- Offspring of gene carrier has 50% risk in all types.

Who Should be Offered RET Testing?

- Any patient with MTC

  ~20% will be due to germline mutation

  Even older patients with no FH have been reported positive

- Predictive testing in relatives of patients with known *RET* mutations and/or diagnosis of MEN 2A, MEN 2B, or FMTC

mayo

Benefits and Limitations of *RET* Mutation Testing for MEN 2

Benefits

- Identifies most *RET* mutation carriers, in whom early intervention may be lifesaving
- Identifies non mutation carriers, who require no further evaluation

Limitations

- No detectable mutations in some families

mayo

Biochemical Screening for MEN 2 in Affected Individuals

MTC

- Pentagastrin- and calcium-stimulated calcitonin

Pheochromocytoma

- Urinary catecholamines and metabolites
- Abdominal ultrasound or CT scans

Hyperparathyroidism

- Serum calcium and PTH

RET Mutation Testing Is More Accurate Than Calcitonin Testing

Improved sensitivity

- Normal calcitonin levels in 14 unaffected children with *RET* mutations
- 8 of the 14 children (57%) had microscopic MTC

Improved specificity

- 68 subjects with no *RET* mutations
- 6 of the 68 (9%) had elevated calcitonin, leading to prophylactic thyroidectomy – none had MTC

Lips CJ et al. *N Engl J Med* 331:828, 1994

mayo

Prophylactic Thyroidectomy in *RET* Mutation Carriers

- Lifetime risk of MTC is ~100% in affected patients
- Prophylactic thyroidectomy is thought to reduce both morbidity and mortality
- Surgery usually uncomplicated and thyroid replacement hormone readily available
- Parathyroid tissue may be conserved *in situ* or resected and autotransplanted

Management of MEN2

- Pheo screening: 8% positive at time of MTC diagnosis. Adrenalectomy should preceed thyroidectomy.
- For patients with negative pheo screening, annual repeat biochemical screening advised. Role of imaging unclear.
- Consider screening FMTC kindreds for pheo in case they “convert” to MEN2A

Management of MEN2

- Screening for parathyroid adenoma/hyperplasia: annual biochemical screening for all clinical phenotypes
- Beware “eucalcemic hyperparathyroidism”, especially in Vitamin D deficient areas; consider measurement of PTH as well as Calcium

Timing controversial (Brandi 2001)

For MEN2B-type mutations, earliest possible, even in first month of life.

For mutations in codons 611, 618, 620, 634 thyroidectomy under age 5 years

For others, thyroidectomy ages 5-10.

Follow-up of at-risk individuals in kindreds with negative *RET* screening

- Prophylactic thyroidectomy not routinely offered – *but could it be justified?*
- Annual calcitonin stimulation test recommended but note 5% of population may manifest C-cell hyperplasia of some degree.
- Annual biochemical screening for pheo and HPT.

Follow-up Strategies in MTC

- Basal calcitonin and CEA
- Stimulated calcitonin
- Ultrasound scan
- CT / MRI / Bone scan
- Octreotide scan
- PET scan

Follow-up Strategies in MTC

- Basal calcitonin and CEA
- Stimulated calcitonin
- Ultrasound scan
- CT / MRI / Bone scan
- Octreotide scan
- PET scan

But who needs which tests?

mayo

Post-operative Surveillance of MTC

- Basal Calcitonin (CT) and CEA
- Undetectable CT at 3 mo. post-op suggests “cure” in early stage patients
- Stimulated CT may be true “gold standard”, not yet recommended routinely
- Repeat CT and CEA after 6 months and then annually
- Anatomic imaging for detectable or rising CT
- High disease stage warrants aggressive evaluation

mayo

2002 UICC/AJCC Staging for MTC

Stage	All ages
I	T1N0M0
II	T2N0M0
III	T3N0M0 / T1-3N1aM0
IVA	T4aNxM0 / T1-3N1bM0
IVB	T4bNxM0
IVC	TxNxM1

Greene et al 2003

mayo

AJCC/UICC Tumor Classification

	Vth Edition	*VIth Edition*
Tx	Not evaluated	Not evaluated
T0	No tumor seen	No tumor seen
T1	≤1cm	≤2cm
T2	1 - 4 cm	2 - 4 cm
T3	>4cm (no invasion)	>4cm, or minimal invasion
T4	Any invasion	Extensive invasion*

*T4a = larynx, esoph, trach, RLN; T4b = prevertebral fascia, vessels; except in ATC, where T4a = intrathyroidal; T4b = any invasion

mayo

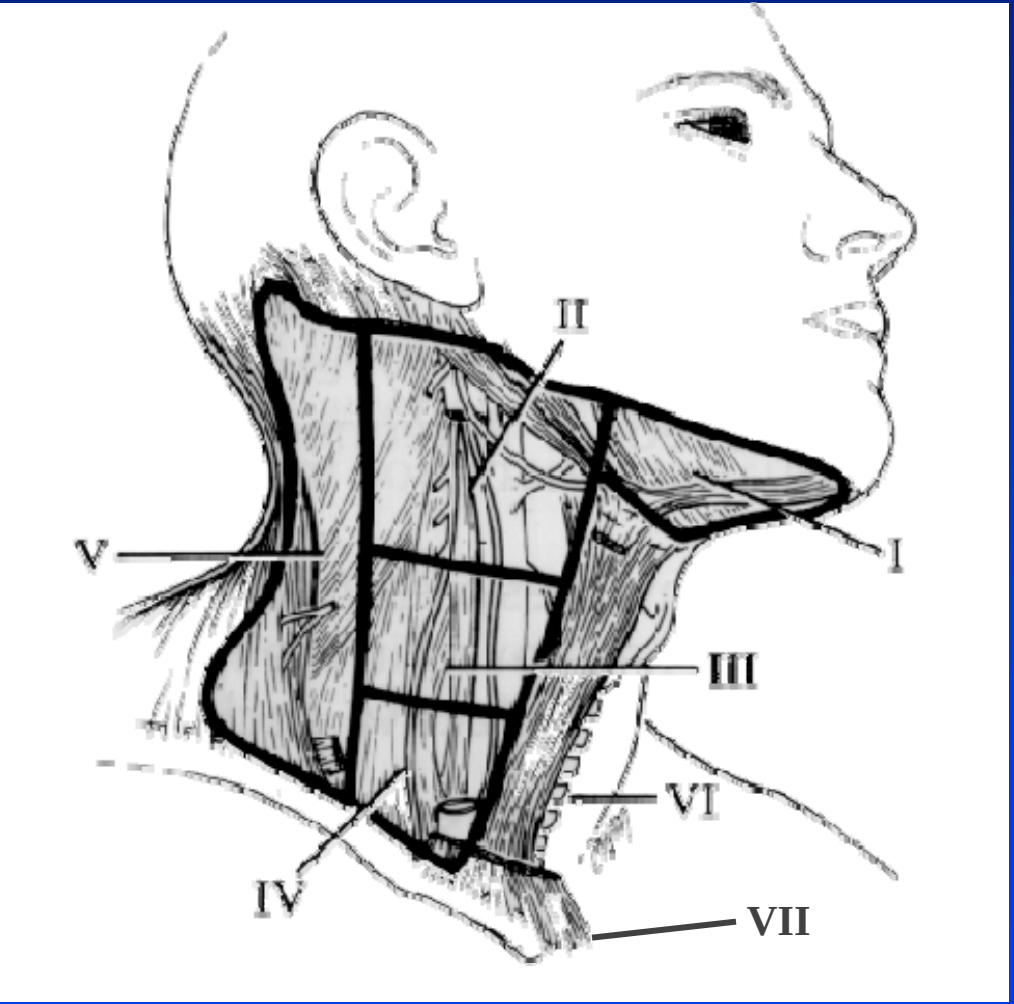
AJCC/UICC Node Classification

	Vth Edition	*VIth Edition*
Nx	**Not evaluated**	**Not evaluated**
N0	**No nodes involved**	**No nodes involved**
N1a	**Ipsilateral nodes**	**Level VI nodes***
N1b	**Bilateral, midline, contralateral or mediastinal nodes**	**Levels I-V or VII nodes**

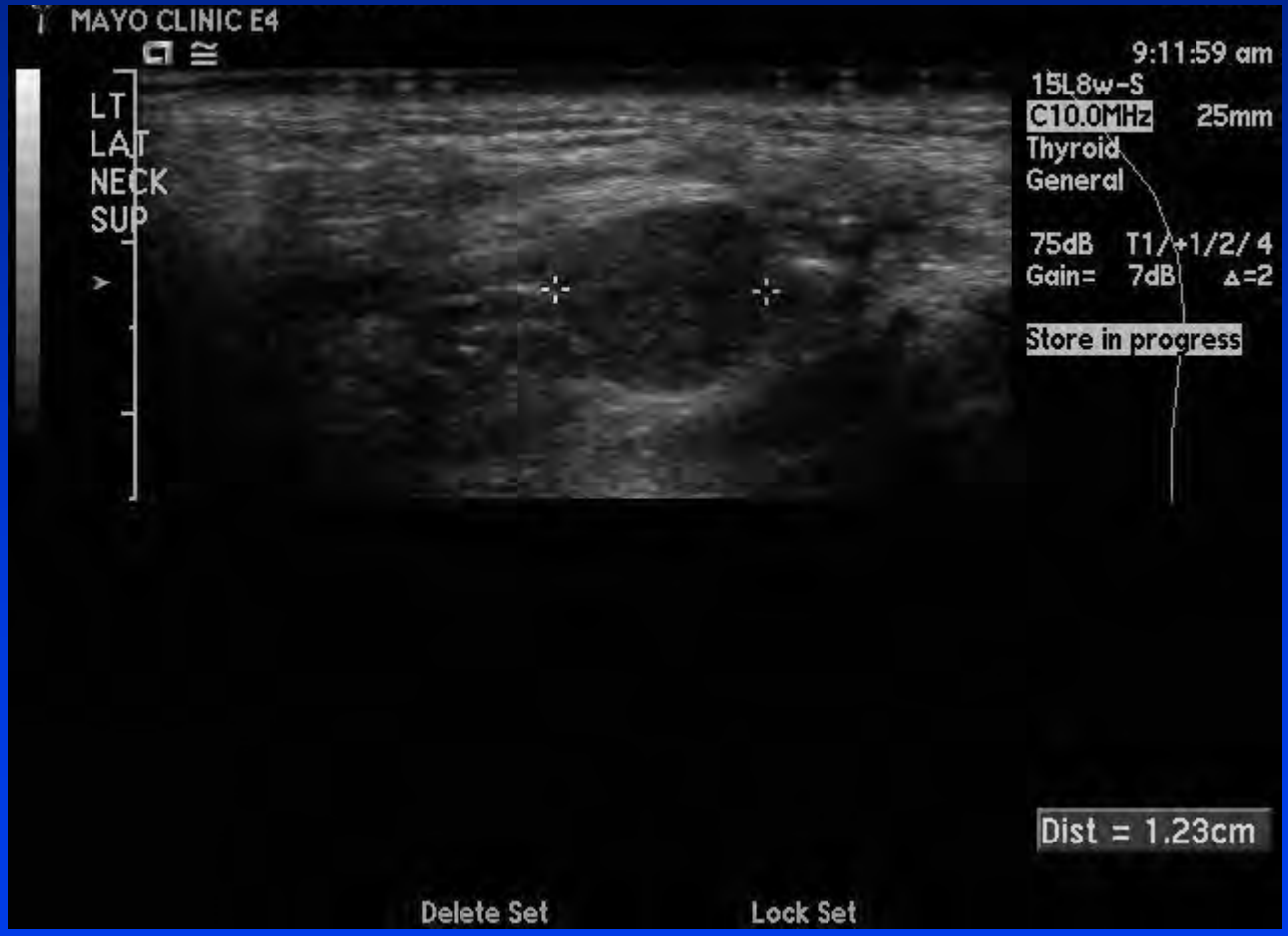
***Includes pretracheal, paratracheal, prelaryngeal and Delphian nodes**

mayo

Cervical Node-bearing Regions



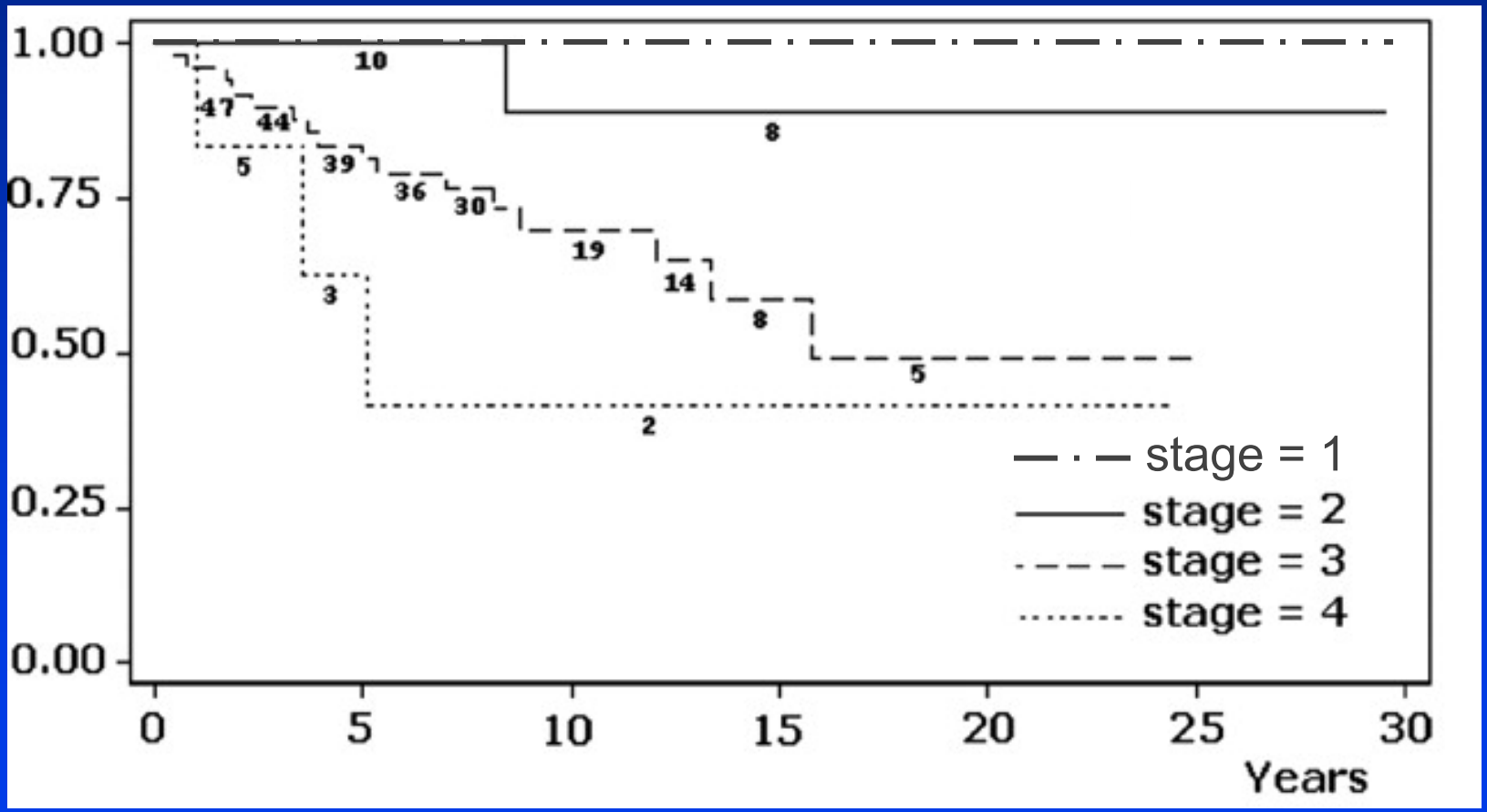
Ultrasound in MTC



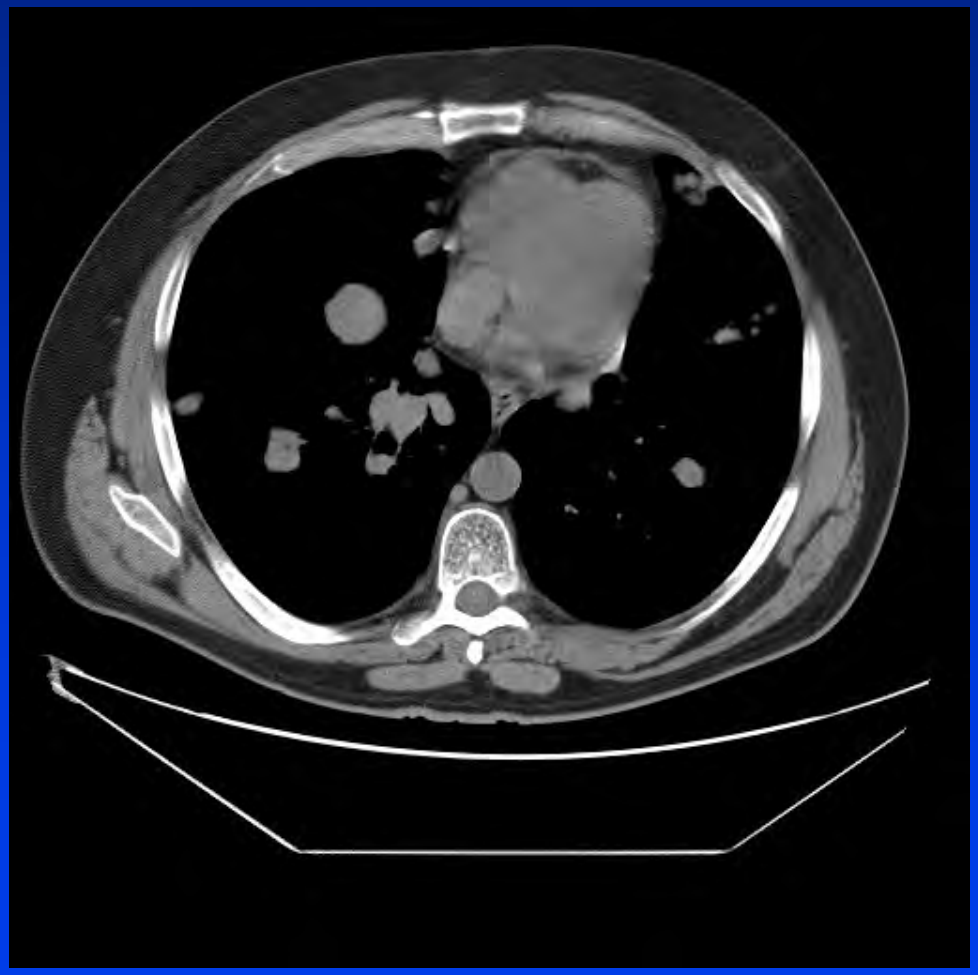
AJCC/UICC Metastatic Classification

	Vth Edition	*VIth Edition*
Mx	**Not evaluated**	**Not evaluated**
M0	**No distant metastases**	**No distant metastases**
M1	**Distant metastases**	**Distant metastases**

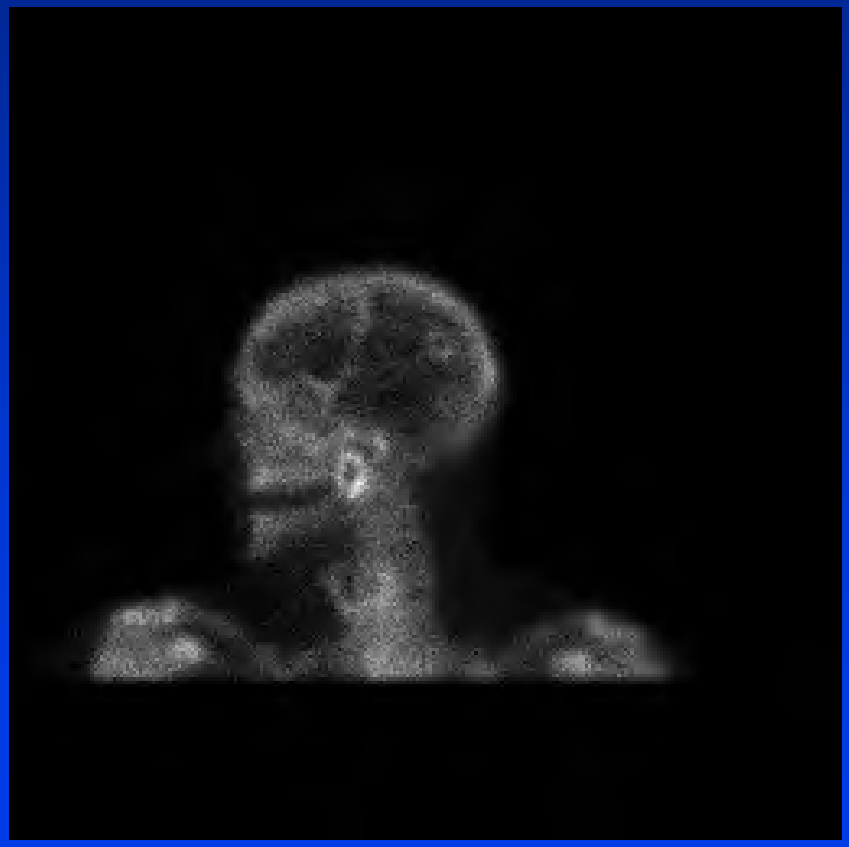
MTC Survival by Stage

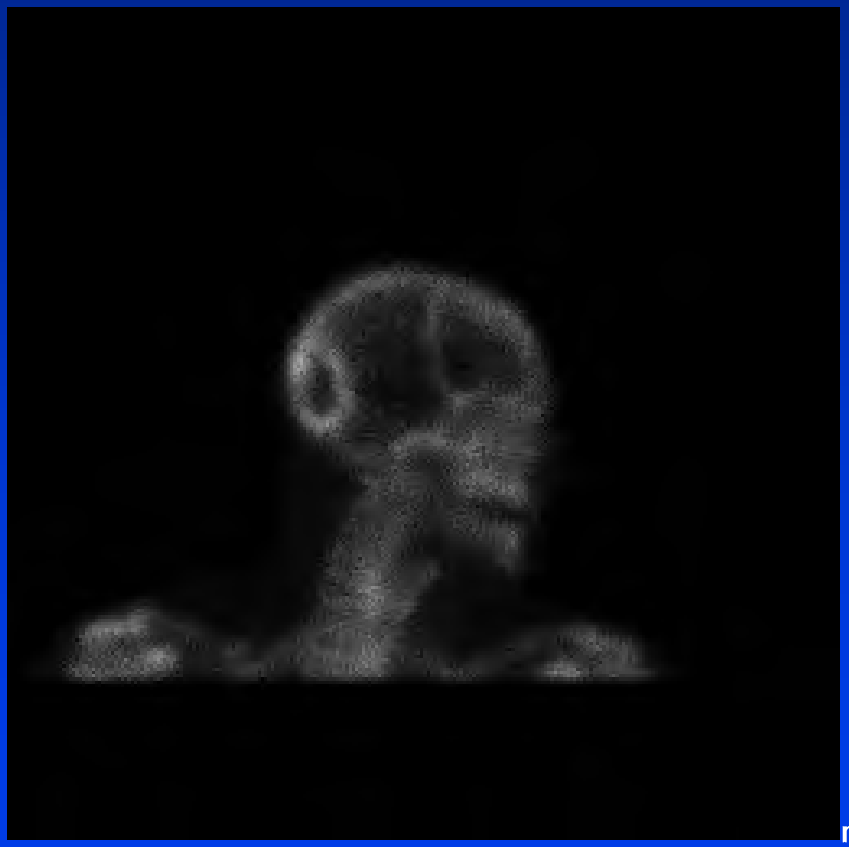


Anatomic Imaging – CT Scan



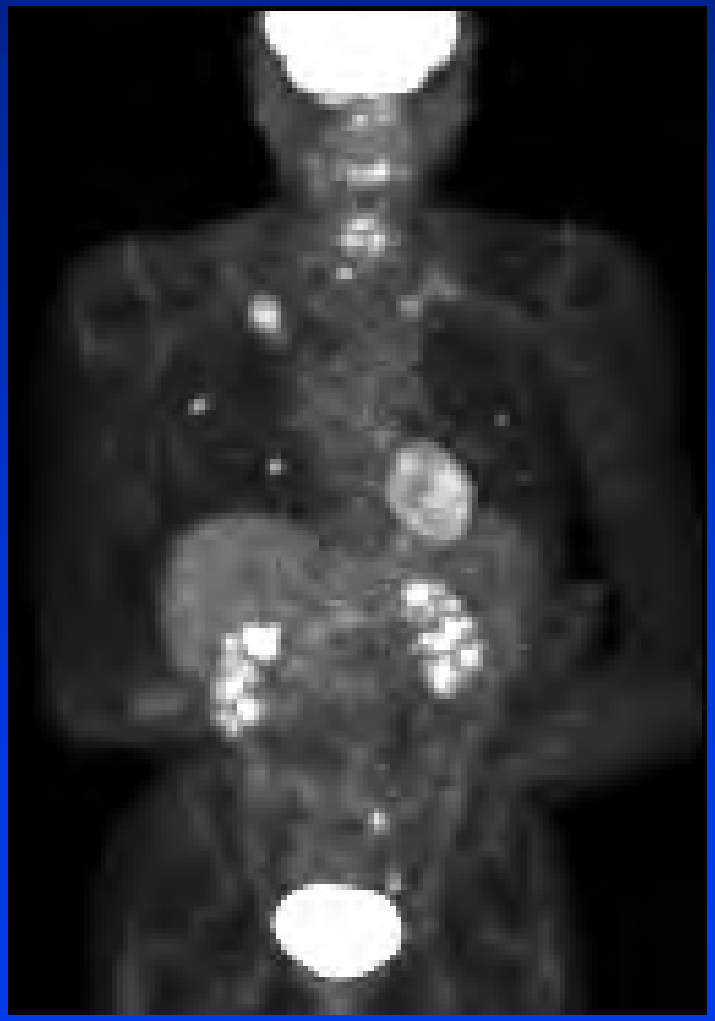
Skeletal Metastases in MTC



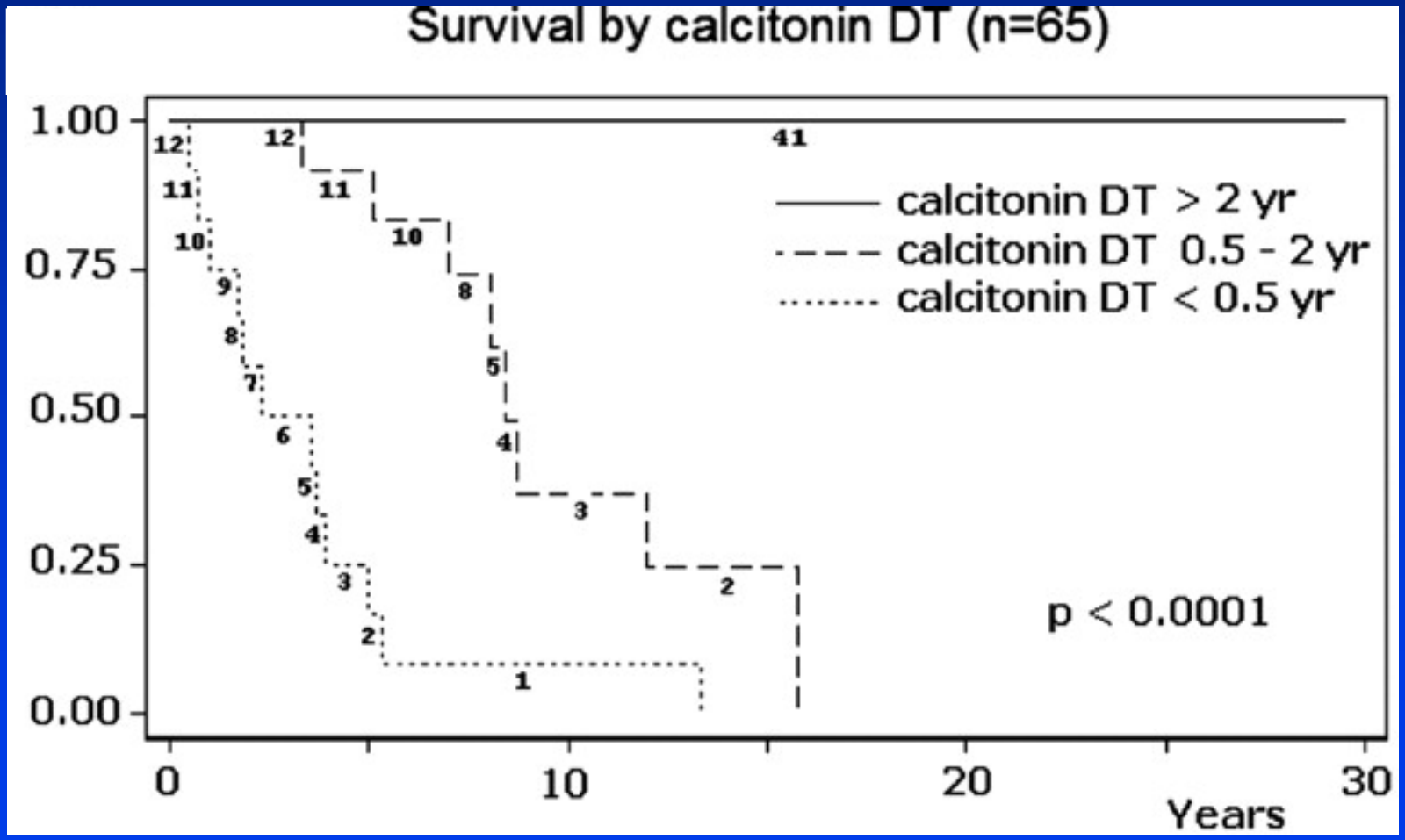


Octreotide Scanning in MTC

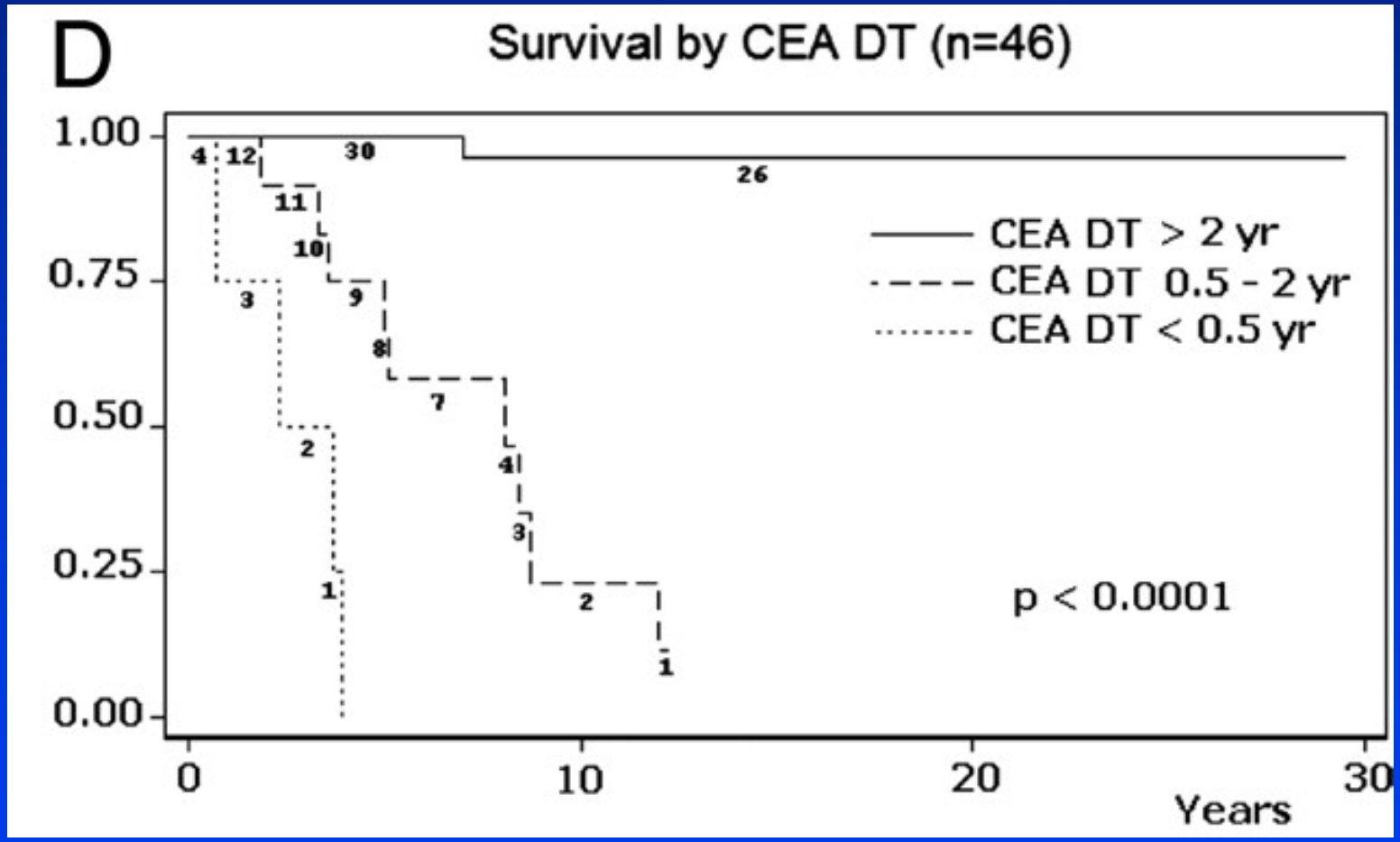
Calcitonin-positive, PET-positive



MTC Survival as a Function of Rate of Change of Calcitonin



MTC Survival by delta[CEA]



Conclusions

- Apparently sporadic MTC may be familial: RET screening is appropriate in all cases
- Screening for pheo, hyperparathyroidism is needed life-long in FMTC, or MEN2 patients
- Nodal metastatic spread of MTC occurs early, making biochemical cure difficult
- Stable or slowly increasing CT may be consistent with long life-expectancy, especially in early stages
- Careful anatomic assessment is necessary for patients with detectable or rising CT and CEA

mayo

6th AME National Meeting
3rd Joint Meeting with AACE

Update in Clinical Endocrinology
Verona – October 27-29, 2006

Advanced Medullary Thyroid Carcinoma: Medical Therapy

Bologna nel 1505 (veduta prospettica da un dipinto di Francesco Francia, la *Madonna del Terremoto*).
Bologna in 1505 (prospective view taken from the painting of the *Madonna del Terremoto* by Francesco Francia).

Nadia Cremonini

Unità Operativa di Endocrinologia
e Malattie del Ricambio
Ospedale Maggiore-Bellaria, Bologna

➥1959 – Hazard JB et al:

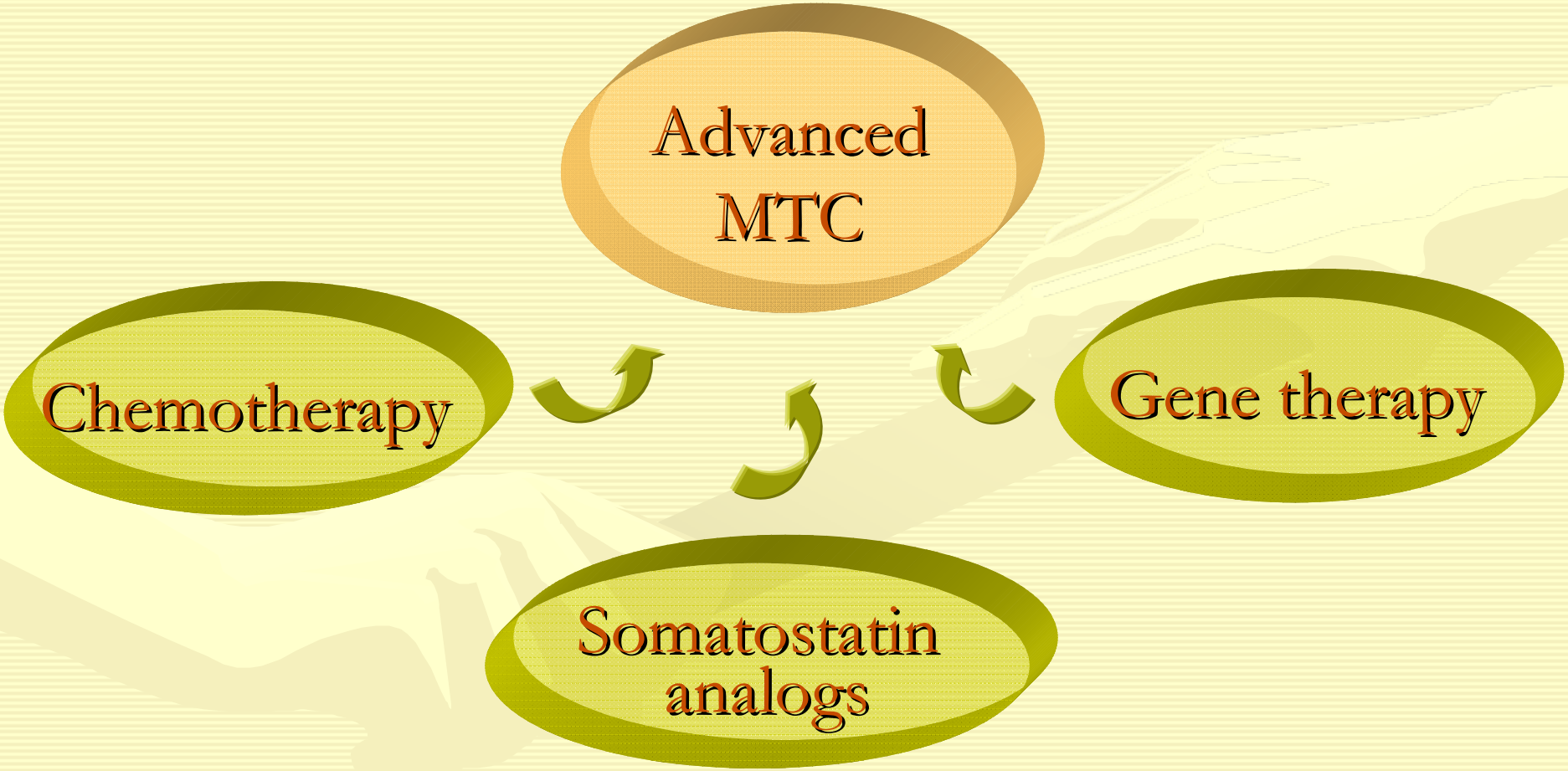
Medullary (solid) carcinoma of the thyroid – a clinicopathological entity. *JCEM, 19:152*

➥2006:

- Surgical removal of all neoplastic tissue in the neck is the only potentially curative treatment in localized medullary thyroid carcinoma

- Medical treatment of advanced medullary thyroid carcinoma represents an important challenge

Which Medical Therapy for Advanced Medullary Thyroid Carcinoma?



Medullary Thyroid Carcinoma: Chemotherapy

- Limited efficacy
- Studies using CHT: usually small, single-institution studies
- Frequently the studies report results about Patients with MTC together with results about Patients with other thyroid cancers or neuroendocrine tumors

  ↳ hard to assess results specifically for MTC
- Response criteria to the treatment in the different reports: not homogeneous
- Not performed large randomized trials

BUT…

CHEMOTHERAPY IS NOT A PARTICULARLY ATTRACTIVE OPTION FOR PATIENTS WITH METASTATIC MTC

Antiproliferative Agents in Metastatic Medullary Thyroid Carcinoma

	No. Patients	Complete response	Partial response	Progression of disease	No Change
DOXORUBICIN	41	1 (2.4 %)	12 (29 %)	21 (51%)	7 (17%)
Burgess & Hill (1978) Husain et al (1978) Leight et al (1980) Harada et al (1981) Simpson et al (1982) Droz et al (1884) Shimaoka et al (1985)					
DOXORUBICIN + CISPLATINUM	45	1 (2.2 %)	10 (22.2 %)	14 (31%)	14 (31%)
Droz et al (1984) Shimakoa et al (1985) Sridhar et al (1985) Williams et al (1986) De Besi et al (1991) (+ Bleomicin) Scherubl et al (1990) (+ Vindesine)					
DACARBAZINE + 5-FU	36	1 (2,7 %)	9 (25%)	11 (30.5)	15 (41.6%)
Petursson (1988) Wu et al (1994) (+ Vinristine) Schlumberger et al (1995) Bayetta et al (1998) (+ Epirubicine) Orlandi et al (2001)					
DOXORUBICIN + STREPTOZOCIN /5-FU + DACARBAZINE	20	/	3 (15%)	7 (35%)	10 (50%)
Nocera et al (2000)					

(modified from Orlandi F et al, Endocrine-Related Cancer 2001;8:135)

A Phase I Trial Combining High-dose ^{90}Y-hMN-14 anti-CEA Antibody with Doxorubicin and Peripheral Blood Stem Cell Rescue in Advanced Medullary Thyroid Cancer

14 Patients, 4 F 10 M
Age: 16 – 75 yr

Treatment Plan

- 1st d: PBSC harvest
  G-CSF/leukapheresis
- after 6-8 d: ^{111}In-hMN-14 Scan
- after 6-8 d: ^{90}Y-hMN-14
  740-1850 MBq/m^2
- after 1 d: DOXORUBICIN
  60 mg/m^2
- after 7-12 d: PBSC reinfusion
  + G-CSF

ANTITUMOR RESPONSE
Follow-up CT scans

- Disease Progression:
  7 Patients
- Stable disease (and stable tumor markers): 4 Patients
  (follow-up: 3, 3.5, 5.6 e 8.5 months)
- Minor Response:
  2 Patients
- 1 Patient after initial response showed severe disease progression:
  he died 8 mo after treatment

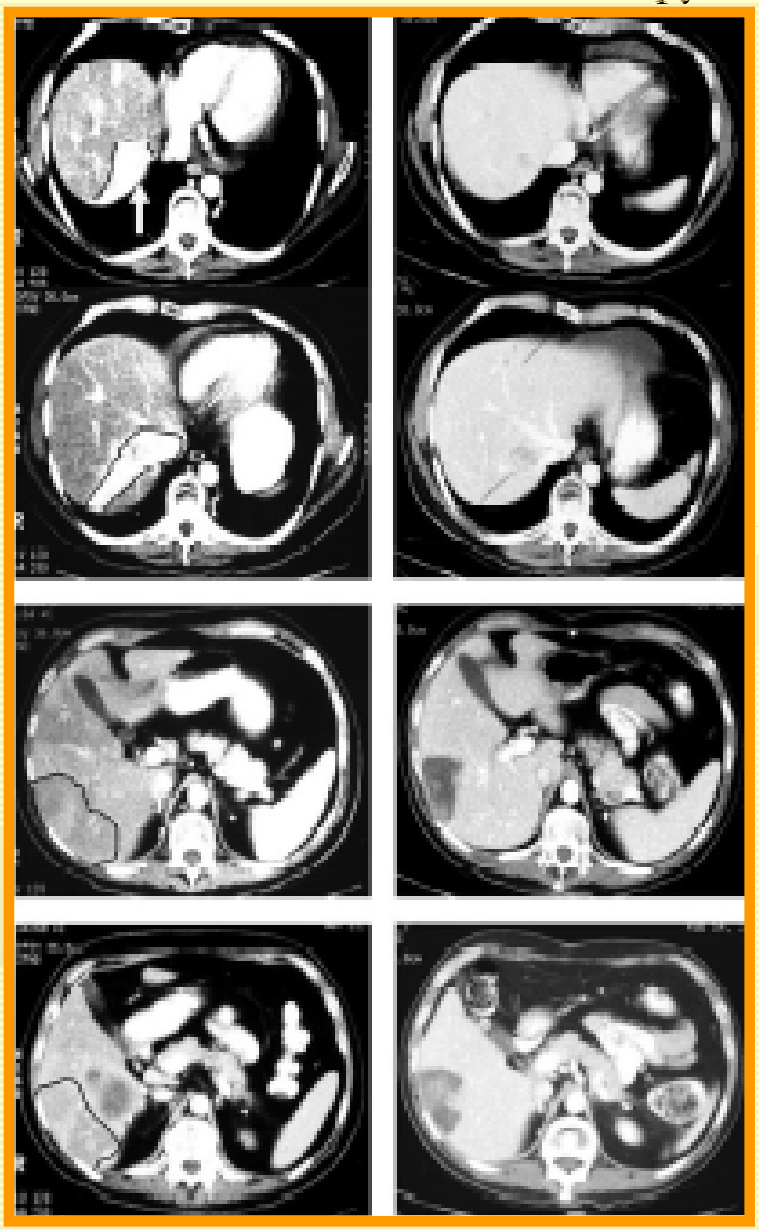
(Sharkley RM et al, J Nucl Med 2005;46:620)

A Phase I Trial Combining High-dose ^{90}Y-hMN-14 anti-CEA Antibody with Doxorubicin and Peripheral Blood Stem Cell Rescue in Advanced Medullary Thyroid Cancer

(Sharkley RM et al, J Nucl Med 2005;46:620)

"…Evidence of antitumor response in these patients with advanced cancer was modest, but encouraging ; this type of treatment may be more successful if applied to more limited, earlier-stage disease. "

Baseline 3 mo after therapy



41 -y-old man

Treatment of Advanced Medullary Thyroid Cancer with Chemotherapy: When?

Indolent clinical course of medullary thyroid carcinoma

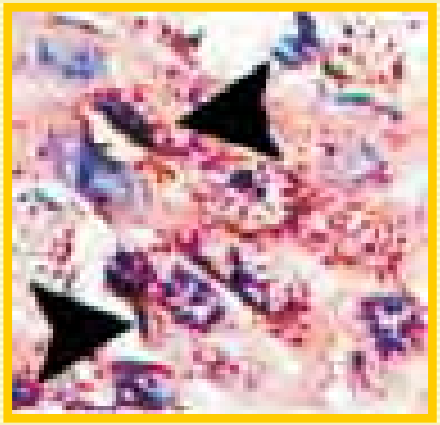
High survival rates in many patients despite the presence of distant metastases

CHT in patients with metastatic MTC: no consistent benefit

Survival rate: not modified by chemotherapy

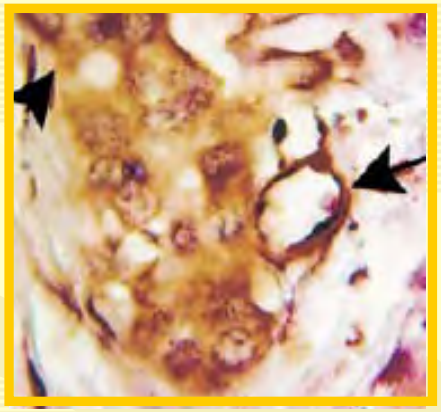
Chemotherapy should be used in a minority of patients with rapidly progressive, measurable, metastatic disease

Somatostatin Receptor Types in Medullary Carcinoma of the Thyroid

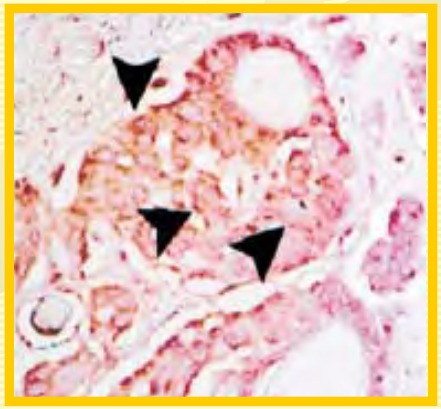


SST1:
27/51 MTC specimens
53%
7 focal
20 diffuse

SST2:
22/51 MTC specimens
43%
11 focal
11 diffuse



SST3:
24/51 MTC specimens
47%
7 focal
17 diffuse



SST5:
29/51 MTC specimens
57%
10 focal
19 diffuse

- **65% of the tumours express > 1 sst subtype**
- **SST4 virtually undetectable (2/51, 4%)**

(Papotti M et al, Clin Endocrinol 2001;54:641)

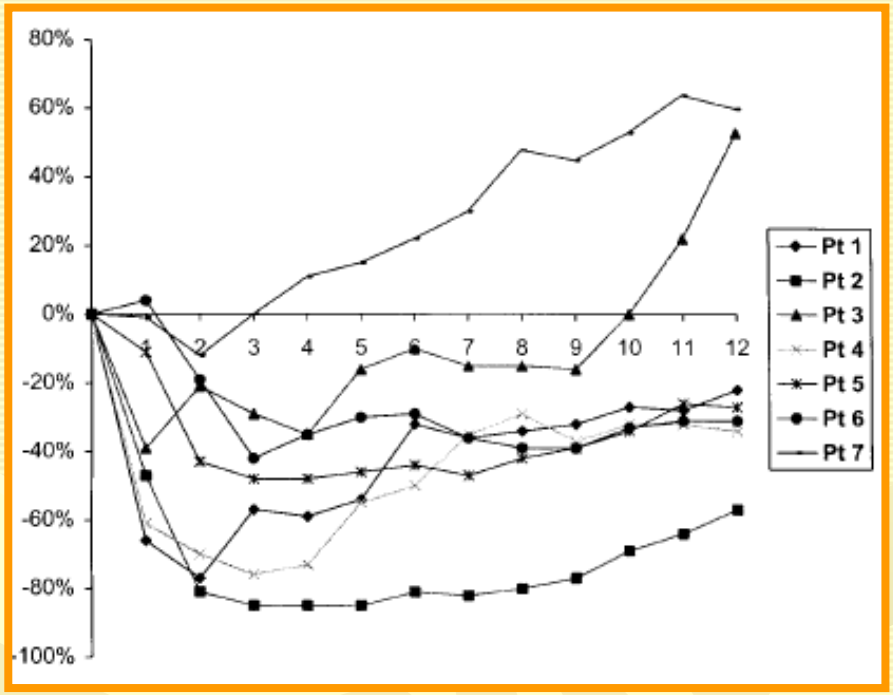
Somatostatin Analogs in the Treatment of MTC

Author and year	Number patients	Octreotide (µg/die)	Duration (months)	Changes CT levels	Changes in measur. lesions
Modigliani (1989)	18	300-1500	1-2	Decr 11, Incr 7	**Decr 5**
Giuliana (1989)	18	300-1500	1-2	Decr 10, Incr 8	NS
Mahler (1990)	3	600-2000	3-17	Decr & Incr	NS
Fugazzola (1991)	5	150-900	0.5-7	Decr 1, Incr 2	Incr 2
Modigliani (1992)	14	500	3	Decr 4, Incr 7	NC2, **Decr 1**,Incr 6
Kvols (1992)	3	1500	1-8	No change	Incr 3
Frank-Raue (1993)	7	300-600	3-9	Decr 2	**Decr 1**
Ronga (1995)	5	300-600	3-9	Decr	**Decr 5**
Di Bartolomeo (1996)	12	1500-3000	5	Decr & Incr	NC 4, Incr 8
Lupoli (1996)	6	150-300 (+INF)	12	Dec r6	No change
Diez (2002)	5	1(300) – 4 LRTlar*	3	Decr 1, NC 2, Incr 2	NC 2, Incr 3

* Lanreotide 30 mg/14-28 days, Decr: decrease, Incr: increase, NS: not studied, NC: no change

- Reduction of Calcitonin levels below 50 % of baseline values → reported in isolated patients
- An initial decrease in CT levels is followed by a subsequent rise
- CEA concentration are unmodified
- Isolated reports about modest reduction of volume in cervical nodes or liver metastases

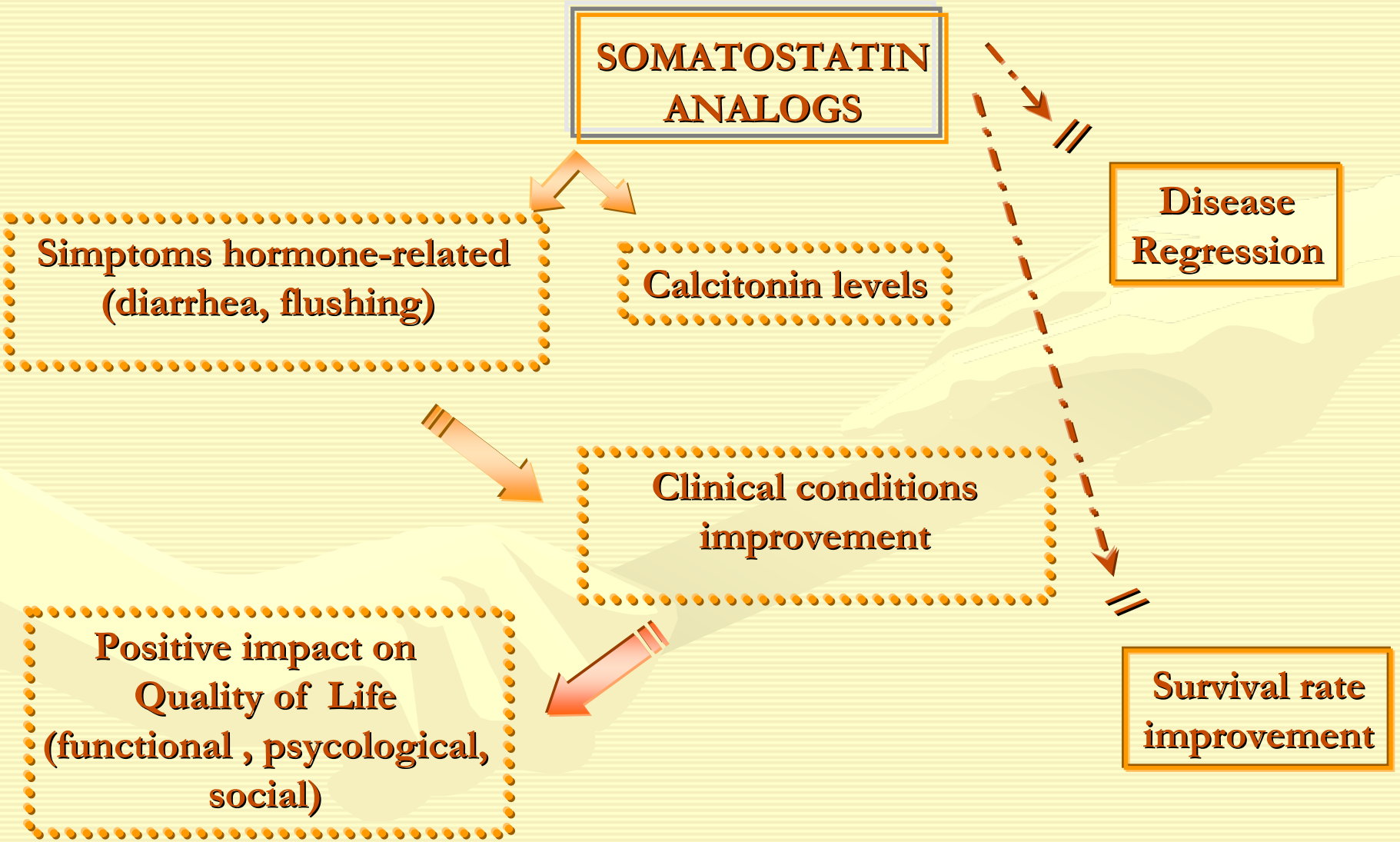
Slow Release Lanreotide in Combination with Interferon-α2b in the Treatment of Symptomatic Advanced Medullary Thyroid Carcinoma



- 7 Patients, 3 M, 4 F (29-57 yr)
- Lanreotide : 30 mg/14 d (6 mo)
  then: 30 mg/10 d (6 mo)
  1 month after: + INF-α2b 5000000 UI 3/week
- Clinical benefit: 5/7 Pt
- Disease stabilization: 3/7 Pt
- Minor tumor regression: 2/7 Pt
- Progressive disease: 2/7 Pt

(Vitale G et al, JCEM 2000,85:983)

Medullary Thyroid Carcinoma: Therapy with Somatostatin Analogs



Which Medical Therapy for Advanced Medullary Thyroid Carcinoma?

IMMUNOMODULATORY Gene Therapy:
to induce gene expression that inhances immune responses against tumor tissues (IL 2, IL 12)

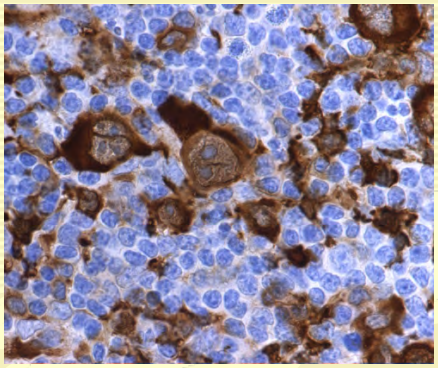
CYTOREDUCTIVE or SUICIDE Gene Therapy:
to deliver an exogenous gene that causes cell death or allows the application of cytotoxic agents (HSV-tk)

CORRECTIVE Gene Therapy:
to restore the normal function of a deleted or mutated gene, or negate the effect of a tumor-promoting gene (oncogene)(dn-RET)

IMMUNOMODULATORY combined with SUICIDE Gene Therapy

Immunotherapy for Medullary Thyroid Carcinoma by Dendritic Cell Vaccination: Clinical Trial

Active immunotherapy using autologous dendritic cells (DCs) pulsed with tumor antigens to generate a cytotoxic immune response directed against the cancer cells



TREATMENT PLAN

DCs pulsed with CT and CEA (1-5 x 10^6 cells, in 100 µl 0.9% NaCl), were administered by intracutaneous injections in upper arm, first 4 cycles/weekly, then at intervals of 4-8 wk

Patients' characteristics before and after DC vaccination therapy

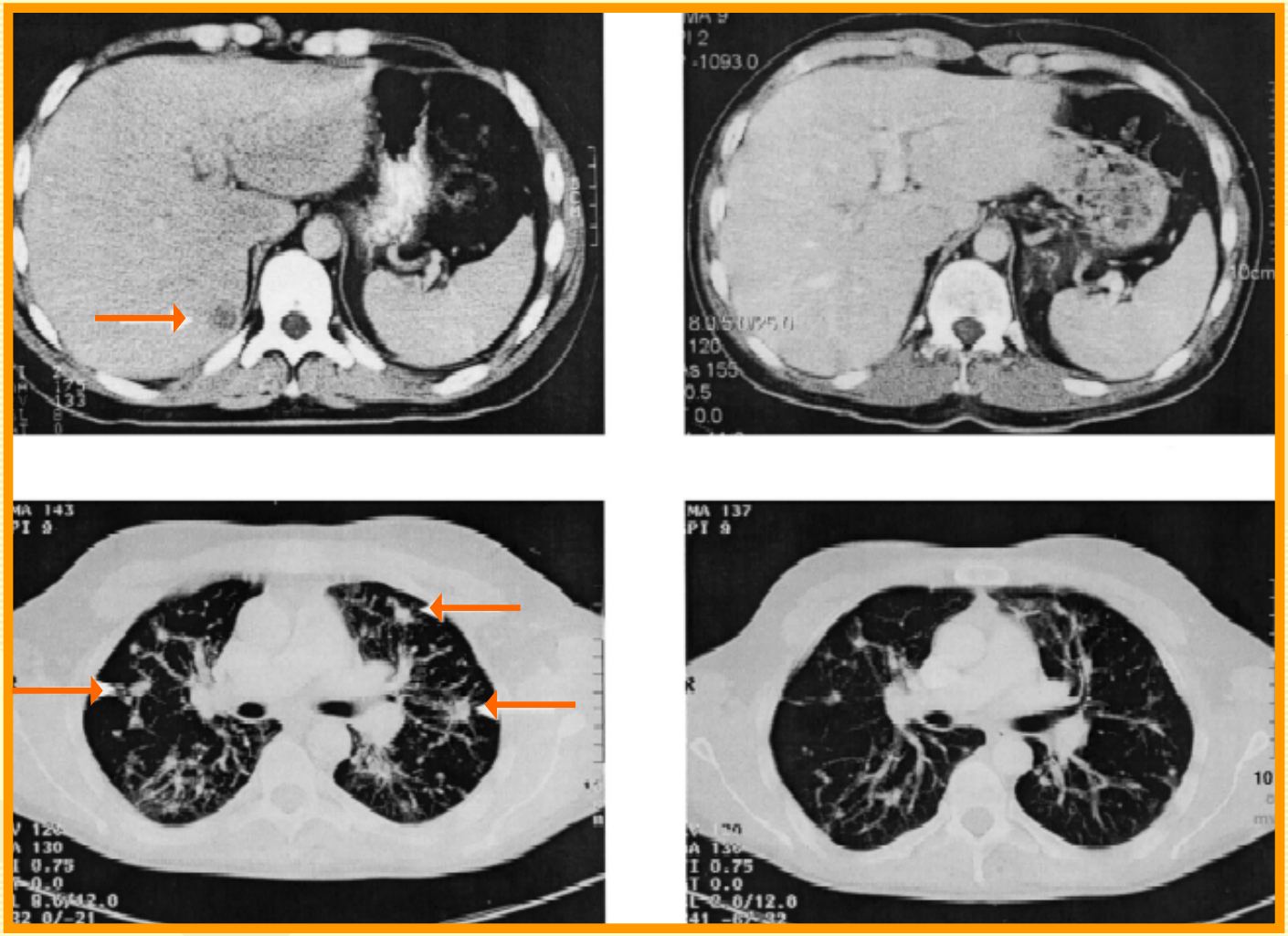
Pt	MCT	Metastases	No. of vacc.	Follow-up	CT-CEA	US/CT
1 53 f	Sp.	liver	14	16 mo	mixed response	stable disease
2 62 m	Sp.	not detectable	14	13	stable	not detectable
3 37 m	MEN2	liv. lung skin bone	12	13	part. decrease	part. remission
4 32 f	Sp.	not detectable	10	9	stable	not detectable
5 58 f	MEN2	liver	11	9	stable	stable disease
6 31 m	MEN2	not detectable	11	9	increase	not detectable
7 38 f	Sp.	liver	7	9	increase	progressive disease

(Schott M et al, J Clin Endocrinol Metab 2001;86:4965)

Immunotherapy for Medullary Thyroid Carcinoma by Dendritic Cell Vaccination

Pt 3, 37 y, M

before DC therapy



13 months after initiation of DC therapy

(Schott M et al, J Clin Endocrinol Metab 2001;86:4965)

Dendritic Cell Vaccination in Advanced Medullary Tyroid Carcinoma

TREATMENT PLAN

10 Patients (age 26-70 y), with metastatic MTC (sporadic)

Autologous tumor lysate-pulsed DCs (DCs cultured in presence of GMC-stimulating factor, IL4, TNF-α, ±INFγ)

DCs injected into a groin lymph node under US guidance. No side effects

Patients characteristics, therapy and response

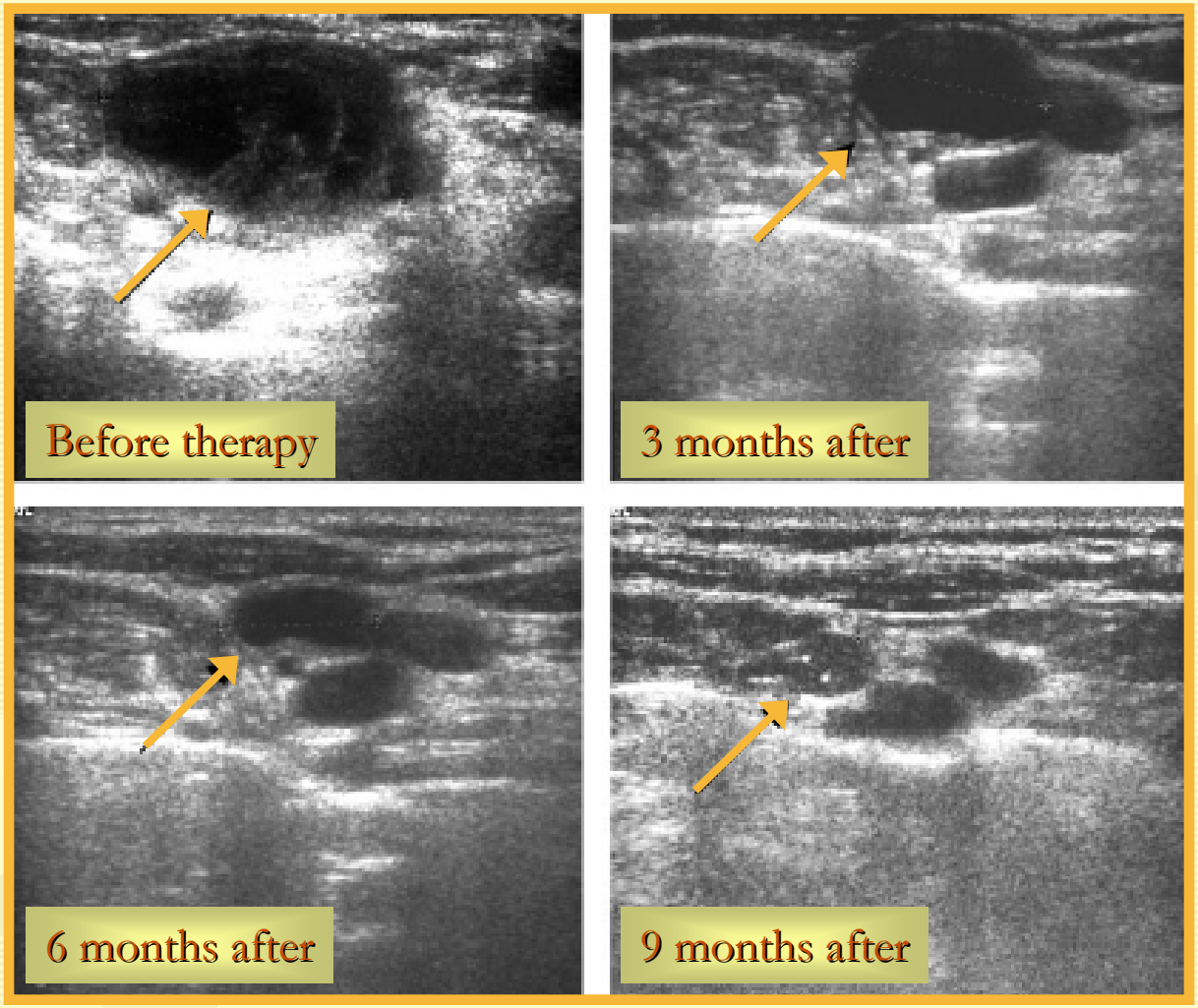
Pt	Age/Sex	Sites of disease	No. vacc.	Outcome/mo.	Survival/mo.	Follow-up
1	31 m	liver, LNs (C,M)	30	MR/30	2+32*	deceased
2	69 m	liver, lung, bne	5	PD	3+4	deceased
3	57 m	lung, LNs (C,M)	10	PD	72+9	deceased
4	61 m	lung, bone, LNs(C,M)	20	SD/24	16+29	deceased
5	26 f	LNs (C)	11	PR/29	2+29	alive
6	39 m	liver, spleen, LNs (M)	10	PR/30	140+30	alive
7	68 m	liver, lung, LNs (M)	3	PD	9+3	deceased
8	48 m	LNs (M)	10	SD/15	268+15	alive
9	59 m	LNs (C,M)	10	PR/12	64+12	alive
10	70 m	LNs (C,T)	6	PD	1+6	deceased

* Months after diagnosis until therapy + months after therapy,
LN: Lymph node; C: cervical; M: mediastinal; T: tracheal;
MR: minor response; PD: progressive disease; SD: stable disease; PR: partial response

(Stift A et al, Clin Cancer Res 2004;10:2944)

Dendritic Cell Vaccination in Advanced Medullary Tyroid Carcinoma

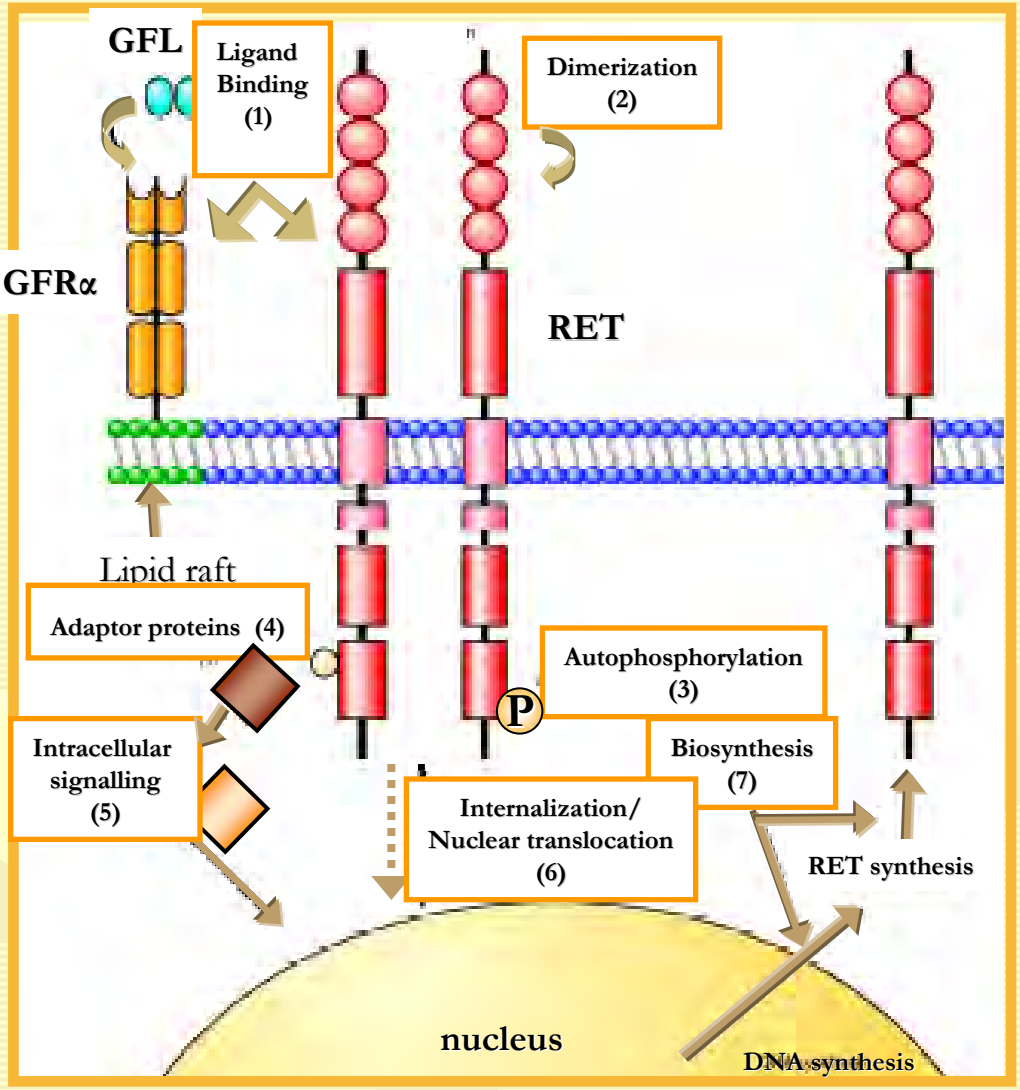
Pt 5, 26 y, F



(Stift A et al, Clin Cancer Res 2004;10:2944)

Inhibition of Oncogenic RET Function

Strategies to inhibit RET



RET Mutations

MEN2 syndromes:

germline mutations resulting in activation of the RET receptor tyrosine kinase

Sporadic MTC:

RET somatic mutations

↓

Inhibition of Oncogenic RET Function:

ATTRACTIVE TARGET FOR GENE THERAPY OF MTC

(modified from de Groot JWB et al, Endocrine Reviews 2006;27:535)

Inhibitors of RET

	Inhibitor	Class	Molecular target	Trial Phase	Reference
Molecular/biological inhibitors	Truncated RET molecule (D-N)	Peptide	RET autopho-sphorylation	Preclinical	Drosten et al(2004)
	Soluble RET ectodomain	Peptide	RET homodime-rization	Preclinical	Cerchia et al (2003)
	Aptamer	RNA	RET homodime-rization	Preclinical	Cerchia et al (2004)
Small-molecule drugs	RP1 (2-indolinone)	Kinase inh.	TK activity	Preclinical	Cucurru et al (2004)
	PP1, PP2 (pyrazolopyrimidine)	Kinase inh.	TK activity	Preclinical	Carlomagno et al (2002), (2003)
	ZD6474	Kinase inh.	TK activity	II	Wells et al (2005)
	CEP-701, CEP-751 (indocarbazole comp.)	Kinase inh.	TK activity	Preclinical	Strock et al (2003), (2006)
	Imatinib mesylate	Kinase inh.	TK activity	Preclinical	Cohen et al (2002) Ezzat et al (2005)
	Sorafenib (BAY 43-9006)	Kinase inh.	Serine/threonine and TK activity	Peclinical and Cl PhI	Carlomagno et al (2006)

(modified from Drosten M and Pützer BM Nat Clin Pract Oncol 2006; 3: 564)

Selected Therapy for Treatment of Medullary Thyroid Carcinoma in Clinical Trials

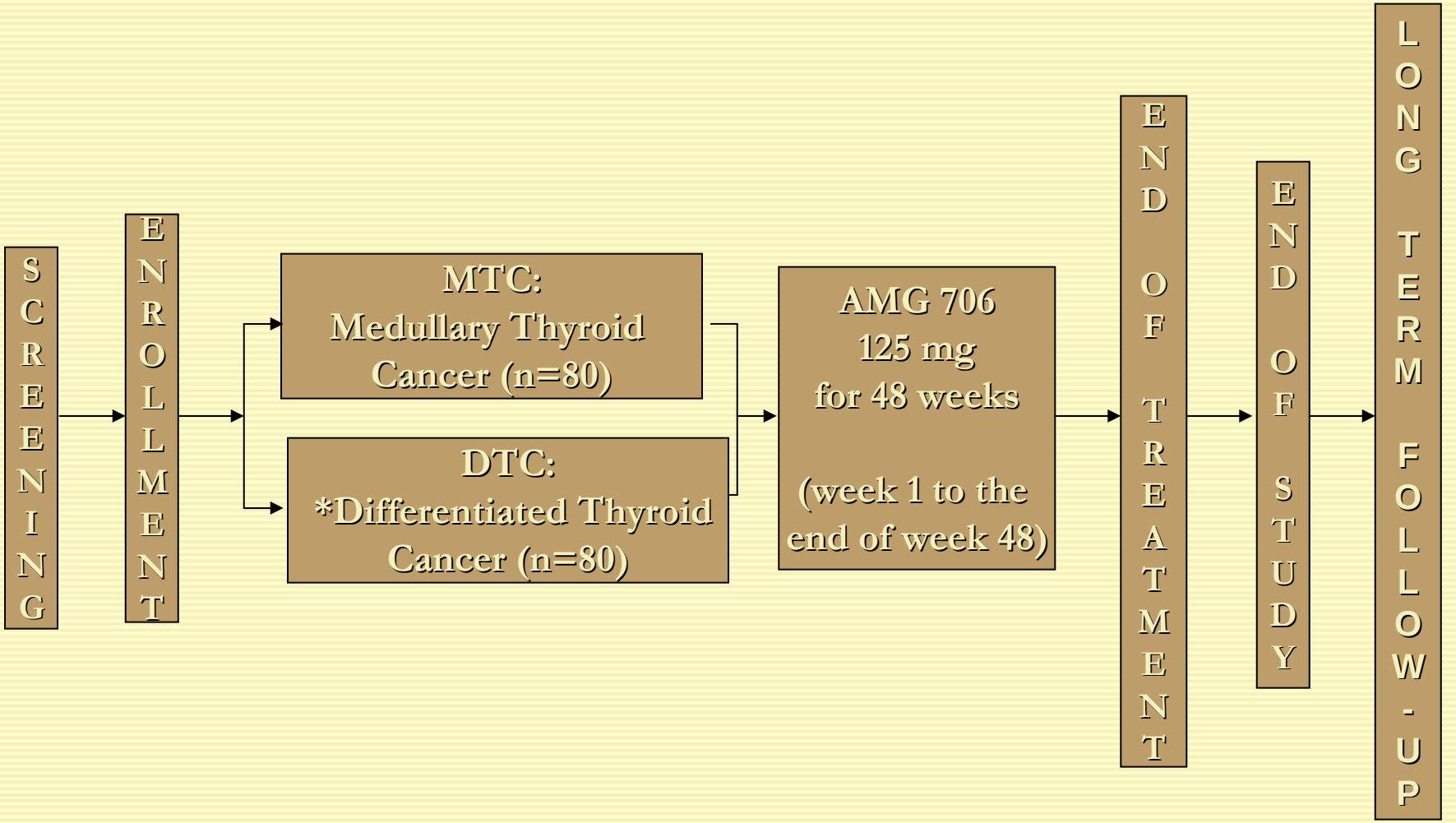
Drug	Trial phase	Class	Mechanism of action
17-allylamino- de-methoxygeldamycin	II	HSP90 inhibitor	Blocks HSP90 chaperon, implicated in folding of oncogenic patways components (indirect effect on RET)
AMG706	II	Kinase inhibitor	Inhibits multiple receptor TK
Gefitinib	II	Kinase inhibitor	Inhibitor of EGFR tyrosine kinase
AG-013736	II	Kinase inhibitor	Blocks angiogenesis by inhibiting VEGFR and PDGFR
ZD6474	II	Kinase inhibitor	Inhibits VEGFR, EGFR and RET TK
Irinotecan	II	Chemother. agent	Inhibits topoisomerase I and prevents repair of DNA strand breaks
Bevacizumab and Sorafenib	I	Humanized Ab; Kinase inhibitor	Bevacizumab blocks angiogenesis BAY43-9006 blocks RAF family kinases downstream of RET
NGR-TNF	I	Peptide fused to TNF	Inhibits angiogenesis by targeting TNF to blood vessels

(modified from Drosten M and Pützer BM Nat Clin Pract Oncol 2006; 3: 564)

AMG 706

- AMG 706 is a potent, oral, multi-kinase inhibitor
- Anti-cancer activity is achieved by selectively targeting all known VEGF, PDGF receptors, Kit and Ret. Both anti-angiogenic and direct antitumor activity have been seen in preclinical studies.
- AMG 706 is being developed as a cancer therapeutic for:
  - Monotherapy in 2nd line GIST
  - Monotherapy in thyroid cancer
  - In combination with chemo and/or panitumumab (ABX-EGF) for CRC, NSCLC, H&N Ca, pancreatic Ca, Breast Ca and other malignancies
- Development Status:
  - Phase 1a study has completed enrollment and
  - Multiple Phase 1b trials are open for accrual
  - Phase 2 trial: Gleevec-resistant GIST; finished enrollment in July '05

Study Design and Treatment Schema



*eg, follicular, papillary and Hürthle Cell

AMG 706 Clinical Trial

Milano	Prof. Licitra
Pisa	Prof. Pinchera
Siena	Prof. Pacini
Firenze	Prof. Brandi
Torino	Prof. Orlandi
Roma	Prof. Filetti

RET "signaling" inhibitor ZD6474 (4-anilinoquinazoline)

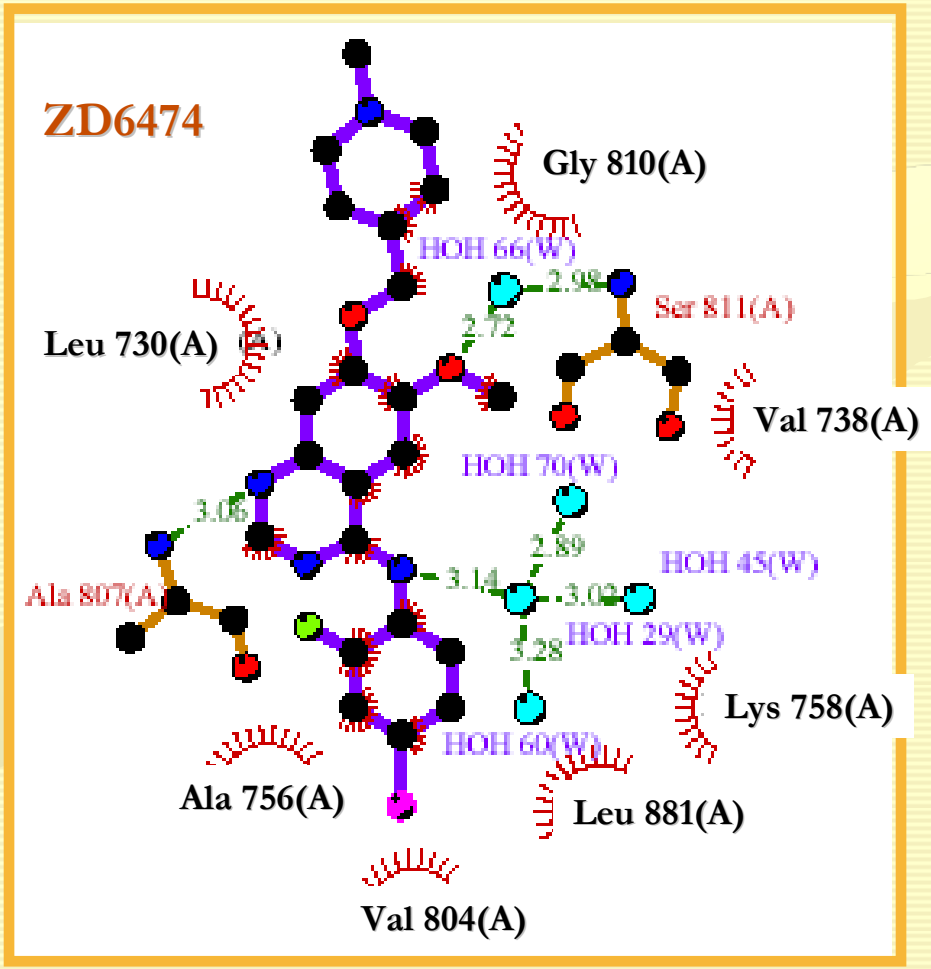
- Selective inhibitor of RET, VEGF-receptor and EGFR-receptor Kinases
- It blocks VEGF-stimulated endothelial cell migration and proliferation
- It is currently being used in clinical trials against non-small cell lung cancer and breast cancer

(Putzer BM & Drosten M, Trends Mol Med 2004)

- Antiangiogenetic effects
- Low toxicity
- Possibility of oral administration
- Oncogenic point mutation in codon 804 (V804L, V804M) is associated with resistance to RET antagonist

(Carlomagno F et al, Oncogene 2004)

Schematic diagram of ZD6474 contacts with RET



(modified from Knowles PP et al, J Biol Chem 2006)

ZD6474 Suppresses Oncogenic RET Isoforms in a *Drosophila* Model for Type 2 Multiple Endocrine Neoplasia Syndrome and Papillary Thyroid Carcinoma

Vidal M, Wells S, Ryan A, and Cagan R. Cancer Res , May 2005; 65: 3538

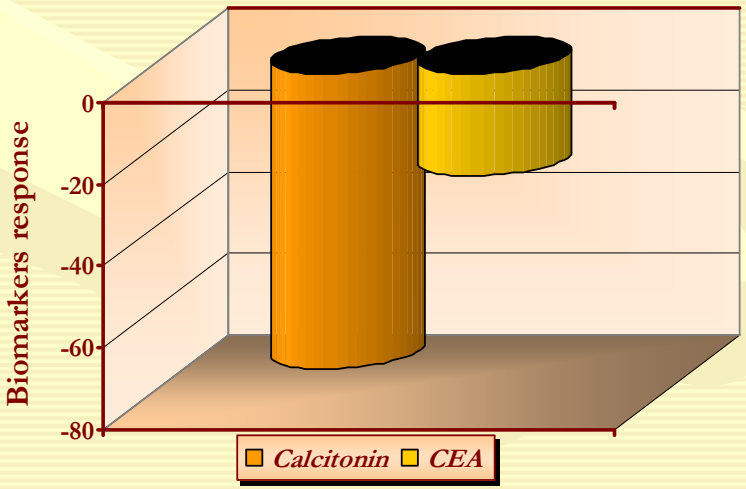
The Use of ZACTIMA (ZD6474) in the Treatment of Patients with Hereditary Medullary Thyroid Carcinoma

Wells S, You Y, Lakhani V, Bauer M, Langmuir P, Headley D, Skinner MA, Morse M, Burch W

Proc of AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics Philadelphia, Novembre 16, 2005 (Abstract B248)

The Use of ZACTIMA (ZD6474) in the Treatment of Patients with Hereditary Medullary Thyroid Carcinoma

- Phase II study
- Aim: to evaluate the anti-tumor efficacy and safety of ZD6474 in
- 11 Patients with advanced hereditary MTC
- ZD6474: 300 mg once daily oral for at least 3 months



RESULTS

- Tumor response:
  - 2 Pt. with Partial Response (shrank 30% or more)
  - 9 Pt. with Stable Disease (madian 17 weeks, range 12-31)
- Biomarkers response: average decrease
  - Calcitonin: 72 %
  - Carcinoembryonic antigen: 25 %

(Wells S et al, Proc of AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics Philadelphia, 2005)

Concluding Remarks and Future Hope

"These data are very encouraging for patients with this rare form of thyroid cancer. Neither standard chemotherapeutic regimens, nor radiation therapy, provide substantial benefits to these patients. In this small ongoing study, ZD6474 has shown promising results in patients with this disease." *(Wells S. 2005)*

We are finally seeing the emerge of new approaches for development of therapies for medullary thyroid carcinoma.

There is reason for light optimism that we may soon have new therapeutic options for our patients with advanced medullary thyroid carcinoma.

...Thank you
for your attention…

Advanced medullary thyroid carcinoma: radio-receptor treatment.

Massimo E. Dottorini
Direttore S.C. Medicina Nucleare 1
Ospedale “S. Maria della Misericordia”
Perugia

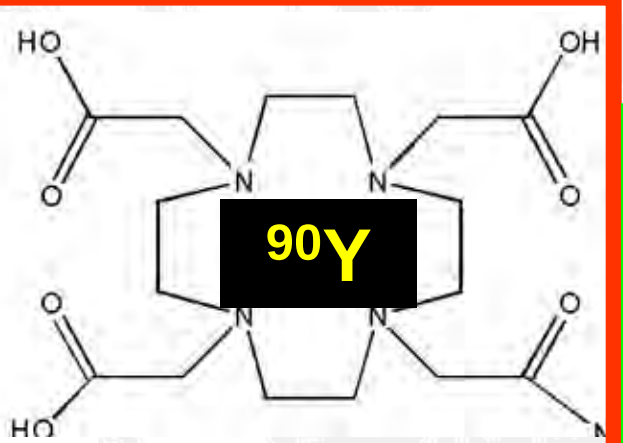
Nuclear medicine treatments of MTC

- ^{131}I-mIBG
- anti-carcinoembryonic-antigen radioimmunotherapy
- radioreceptor treatment:
  - somatostatine analogues (^{90}Y-DOTATOC)
  - CCK2/gastrin-R
- ^{131}I after human sodium iodide symporter (hNIS) gene transfer

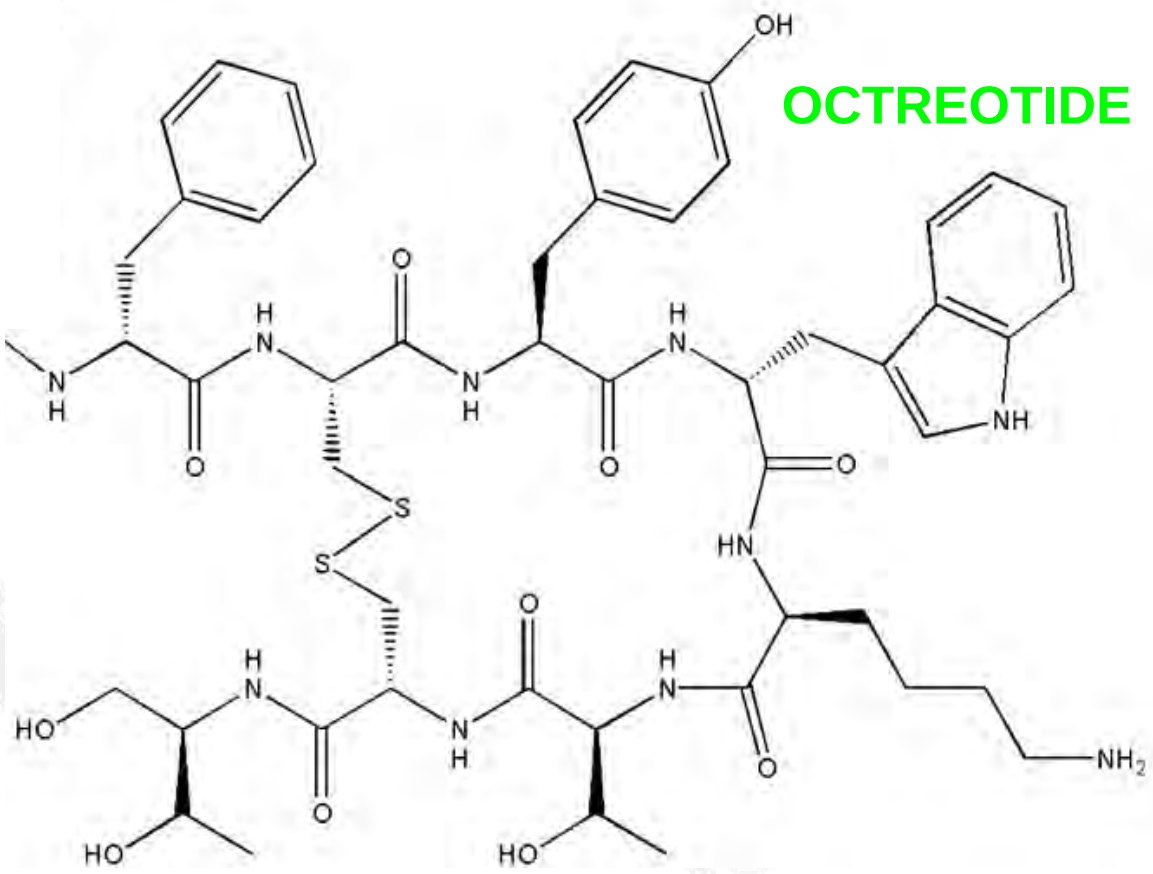
Stemma dell'Ospedale di S. Maria della Misericordia di Perugia

Massimo E. Dottorini
Direttore S.C. Medicina Nucleare 1
Ospedale "Santa Maria della Misericordia" Perugia

Somatostatin analogs: DOTATOC



[DOTA^{0}-Tyr^{3}]



Massimo E. Dottorini
Direttore S.C. Medicina Nucleare 1
Ospedale "Santa Maria della Misericordia" Perugia

Somatostatin Analogs

peptide-chelator conjugates

DTPA-octreotide	DTPAOC
DTPA-[Tyr^3]-octreotate	DTPATATE
DOTA-octreotide	DOTAOC
DOTA-[Tyr^3]-octreotide	DOTATOC
DOTA-vapreotide	DOTAVAP
DOTA-lanreotide	DOTALAN
DOTA-[Tyr^3]-octreotate	DOTATATE
DOTA-1-Nal^{3}octreotide	DOTANOC

Stemma dell'Ospedale di S. Maria della Misericordia di Perugia

Massimo E. Dottorini
Direttore S.C. Medicina Nucleare 1
Ospedale "Santa Maria della Misericordia" Perugia

Somatostatin analogs

Radionuclides

γ-emitters
(diagnosis - SPET)

^{111}**In**

^{99m}**Tc**

^{177}**Lu**

β-emitters
(therapy)

^{90}**Y**

^{177}**Lu**

Auger electrons
emitters (therapy)

^{111}**In**

positron-emitters
(diagnosis - PET)

^{68}**Ga** (generator)

^{66}**Ga**

^{18}**F**

^{86}**Y** (dosimetry)

^{64}**Cu**

Stemma dell'Ospedale di S. Maria della Misericordia di Perugia

Massimo E. Dottorini
Direttore S.C. Medicina Nucleare 1
Ospedale "Santa Maria della Misericordia" Perugia

Peptides	hsst 1	hsst2	hsst3	hsst4	hsst5
SS-28	5.2	2.7	7.7	5.6	4.0
Octreotide	>10000	2.0	187	>1000	22
CH288	23	>10000	>1000	>10000	>1000
In-DTPAOC	>10000	22	182	>1000	237
Y-DOTATOC	>10000	11	389	>10000	114
Ga-DOTATOC	>10000	2.5	613	>1000	73
Y-DOTATATE	>10000	1.6	>1000	523	187
Ga-DOTATATE	>10000	0.2	>1000	300	377
Y-DOTAOC	>10000	20	27	>10000	57
Y-DOTALAN	>10000	23	290	>10000	16

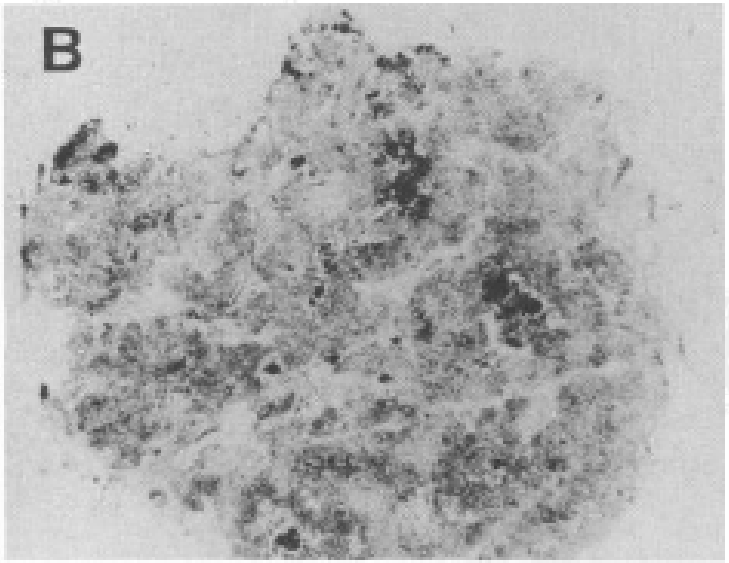
Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. Reubi JC, Schär JC, Waser B et al. Eur J Nucl Med. 2000 Mar;27(3):273-82.

Peptides	hsst 1	hsst2	hsst3	hsst4	hsst5
SS-28	3.8	2.5	5.7	4.2	3.7
Y-DOTATOC	>10000	11.4	389	>10000	204
Y-DOTAOC	>10000	20	27	>1000	58
Y-DOTALAN	>10000	22.8	290	>1000	16.3
In-DOTANOC	>10000	2.9	8	227	11.2
Y-DOTANOC	>1000	3.3	26	>1000	10.4

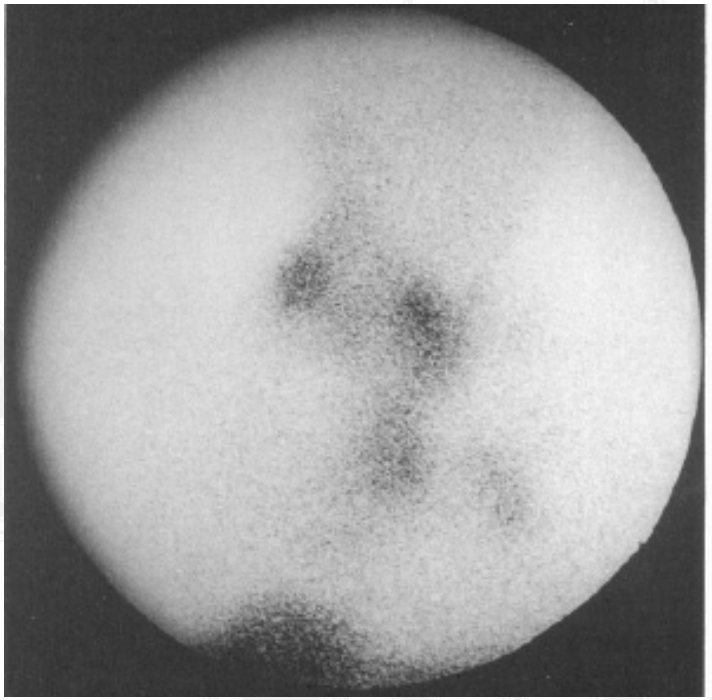
DOTANOC, a high-affinity ligand of somatostatin receptor subtypes 2,3 and 5 for labelling with various radiometals.
Wild D, Schmitt JS, Ginj M et al. Eur J Nucl Med Mol Imaging 2003;30:1338-47.

Stemma dell'Ospedale di S. Maria della Misericordia di Perugia

Massimo E. Dottorini
Direttore S.C. Medicina Nucleare 1
Ospedale "Santa Maria della Misericordia" Perugia



binding of [^{125}I-Tyr^{3}]octreotide



^{111}In-octreotide

In vivo somatostatin receptor imaging in medullary thyroid carcinoma.
Kwekkeboom DJ et al. J Clin Endocrinol Metab. 1993 Jun;76(6):1413-7.

Stemma dell'Ospedale di S. Maria della Misericordia di Perugia

Massimo E. Dottorini
Direttore S.C. Medicina Nucleare 1
Ospedale "Santa Maria della Misericordia" Perugia

IMMUNOHISTOCHEMISTRY IN 51 MEDULLARY CARCINOMA OF THE THYROID (MCT)

sst1	sst2	sst3	sst4	sst5
59%	43%	47%	4%	57%

51%: one or two sst subtypes
33%: three or more sst subtypes

Immunohistochemical detection of somatostatin receptor types 1-5 in medullary carcinoma of the thyroid.
Papotti M et al. Clin Endocrinol (Oxf). 2001 May;54(5).

20 MTC pts.
calcitonin (mean: 11 071 ng/l, range 51.2–93 450)
↓
11/20 positive (conventional imaging 11/20 positive)
↓
7/11: histology (6 confirmed 1 false positive)

- low-moderate sensitivity of ^{111}In-octreotide scintigraphy for the detection of MTC recurrence
- low relative somatostatin receptor density in MTC

Use of somatostatin analogue scintigraphy in the localization of recurrent medullary thyroid carcinoma.
Berna L et al. Eur J Nucl Med. 1998 Nov;25(11)

Stemma dell'Ospedale di S. Maria della Misericordia di Perugia
Massimo E. Dottorini
Direttore S.C. Medicina Nucleare 1
Ospedale "Santa Maria della Misericordia" Perugia

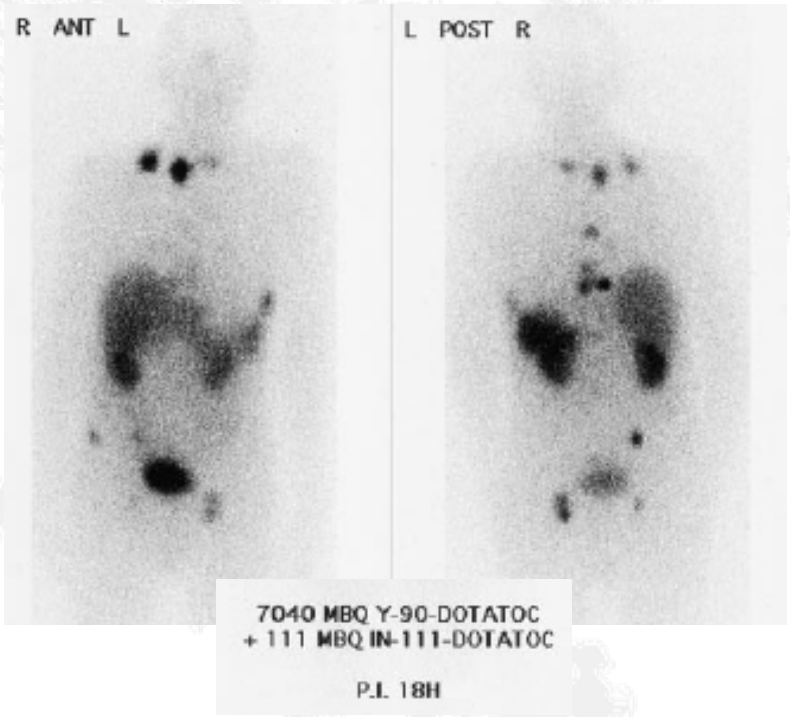
Nuclear medicine treatments of MTC

- ^{131}I-mIBG
- anti-carcinoembryonic-antigen radioimmunotherapy
- radioreceptor treatment:
  - somatostatine analogues (^{90}Y-DOTATOC)
  - CCK
- ^{131}I after human sodium iodide symporter (hNIS) gene transfer

Stemma dell'Ospedale di S. Maria della Misericordia di Perugia

Massimo E. Dottorini
Direttore S.C. Medicina Nucleare 1
Ospedale "Santa Maria della Misericordia" Perugia

12 MTC pts (PD) treated with ^{90}Y-DOTATOC (02-98/09-02)
Cumulative activity 1.7-14 GBq in 1-4 cycles
Infusion of positively charged amino acids for renal protection



	Objective response
CR	-
PR	-
SD	41.7 %
PD	58.3 %

Radiopeptide transmitted internal irradiation of non-iodophil thyroid cancer and conventionally untreatable medullary thyroid cancer using [90Y]-DOTA-$_D$-Phe^1-Tyr^3-octreotide: a pilot study.
Waldherr C et al. Nucl Med Commun. 2001 Jun;22(6):673-8.

Massimo E. Dottorini
Direttore S.C. Medicina Nucleare 1
Ospedale "Santa Maria della Misericordia" Perugia

The chosen approach in thyroid cancer
does not seem to be suitable
for obtaining a significant tumour response.

Radiopeptide transmitted internal irradiation of non-iodophil thyroid cancer and conventionally untreatable medullary thyroid cancer using [90Y]-DOTA-$_D$-Phe^1-Tyr^3-octreotide: a pilot study.
Waldherr C et al. Nucl Med Commun. 2001 Jun;22(6):673-8.

Stemma dell'Ospedale di S. Maria della Misericordia di Perugia

Massimo E. Dottorini
Direttore S.C. Medicina Nucleare 1
Ospedale "Santa Maria della Misericordia" Perugia

21 MTC pts (PD) treated with ^{90}Y-DOTATOC (02-98/09-02)
Cumulative activity: 7.5-19.2 GBq in 2-8 cycles
Infusion of positively charged amino acids for renal protection

	Objective response	Biochemical response
CR	2 (9.5 %)	1 (4.8 %)
PR	-	5 (23.8 %)
SD	12 (57.1 %)	3 (14.3 %)
PD	7 (33.4 %)	12 (57.1 %)

Receptor radionuclide therapy with 90Y-DOTATOC in patients with medullary thyroid carcinomas.
Bodei L et al. Cancer Biother Radiopharm. 2004 Feb;19(1):65-71.

- MTC less radiosensitive
- sst_2 receptor expression in MTC is generally not very high
- maximum cumulative activity may not be sufficient to deliver a curative absorbed dose to the tumor
- sst_2 receptor may not be the optimal target to deliver radiation doses to the tumor

- CCK and bombesin receptors are extensively expressed in MTC
- Lutetium-177 and alfa-emitters could be more effective in small sized lesions
- ^{90}Y-DOTATOC therapy could be more useful in the early phases of the disease

Receptor radionuclide therapy with 90Y-DOTATOC in patients with medullary thyroid carcinomas.
Bodei L et al. Cancer Biother Radiopharm. 2004 Feb;19(1):65-71.

64 MTC pts treated with ^{90}Y-DOTATOC
Cumulative activity: 0.8-22.3 GBq in 1-16 cycles
All 3 CR were stage III

	Objective response
CR	5 %
PR	3 %
SD	36 %
PD	56 %

Bodei L et al. Personal communication 2006

Nuclear medicine treatments of MTC

- ^{131}I-mIBG
- anti-carcinoembryonic-antigen radioimmunotherapy
- radioreceptor treatment:
  - somatostatine analogues (^{90}Y-DOTATOC)
  - CCK2/gastrin-R
- ^{131}I after human sodium iodide symporter (hNIS) gene transfer

Stemma dell'Ospedale di S. Maria della Misericordia di Perugia

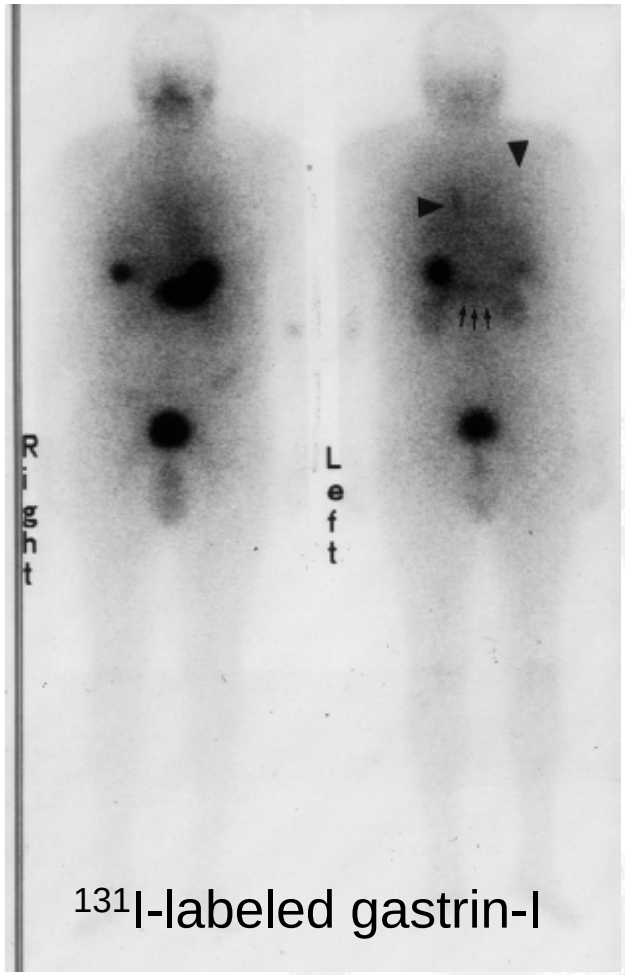
Massimo E. Dottorini
Direttore S.C. Medicina Nucleare 1
Ospedale "Santa Maria della Misericordia" Perugia

Radioreceptors treatment of MTC

- high incidence (90%) and high-density expression of CCK-2/gastrin receptors in human medullary thyroid cancer (MTC)

- independence of CCK-2/gastrin-R status on the degree of tumor differentiation in human MTCs

Cholecystokinin(CCK)-A and CCK-B/gastrin receptors in human tumors.
Reubi JC et al. Cancer Res. 1997 Apr 1;57(7):1377-86.



^{131}I-labeled gastrin-I

Table 1. Radiation dosimetry of ^{131}I-labeled gastrin-I in subcutaneous TT-xenograft-bearing nude mice

	Dose (cGy/mCi)	Tumour/non-tumour ratio	Dose at 3 mCi (Gy)
Tumor	175	–	5.3
Lung	53	3.3	1.6
Liver	39	4.5	1.2
Gallbladder	1458	0.1	43.7
Pancreas	159	1.1	4.8
Spleen	34	5.1	1.0
Stomach	332	0.5	10.0
Intestine	95	1.8	2.9
Kidney	1040	0.2	31.2
Brain	5	35.0	0.2
Muscle	21	8.3	0.6
Bone	27	6.5	0.8
Blood	67	2.6	2.0
Whole-body	146	1.2	4.4

Targeting of cholecystokinin-B/gastrin receptors in vivo: preclinical and initial clinical evaluation of the diagnostic and therapeutic potential of radiolabeled gastrin. Behr TM et al. Eur J Nucl Med. 1998;25:424–430.

Stemma dell'Ospedale di S. Maria della Misericordia di Perugia

Massimo E. Dottorini
Direttore S.C. Medicina Nucleare 1
Ospedale "Santa Maria della Misericordia" Perugia

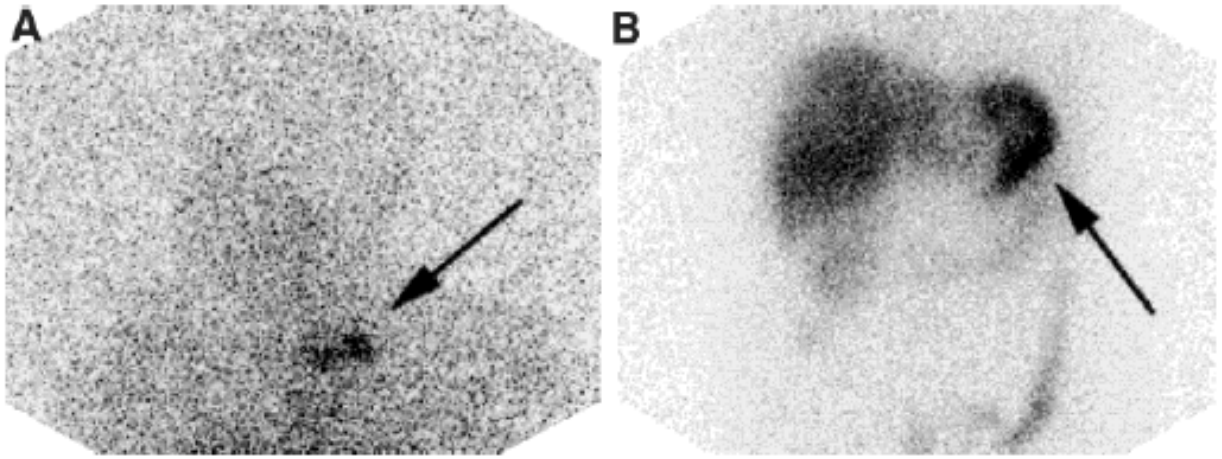


FIGURE 6. Visualization of CCK-B receptors in 45-y-old woman with MTC after intravenous administration of 222 MBq [^{111}In-DTPA^{0}]CCK$_8$ (10 μg peptide). Scans at 48 h after injection show uptake in lymph node metastases in neck region (A, arrow) and in receptor-positive stomach (B, arrow).

Preclinical and Initial Clinical Evaluation of ^{111}In-Labeled Nonsulfated CCK$_8$ Analog: A Peptide for CCK-B Receptor-Targeted Scintigraphy and Radionuclide Therapy. de Jong M et al. M J Nucl Med 1999; 40:2081–7

Stemma dell'Ospedale di S. Maria della Misericordia di Perugia

Massimo E. Dottorini
Direttore S.C. Medicina Nucleare 1
Ospedale "Santa Maria della Misericordia" Perugia

- receptor-specific, time- and temperature-dependent internalization of [^{111}In- DOTA$_0$]CCK8
- tumor-to background ratio for [111In-DOTA0]CCK8 already was significantly higher than that for 125I-CCK10 at 4 h after injection,
- a tumor-to-blood ratio of 16 was reached 24 h after injection,
- low kidney uptake

Preclinical and Initial Clinical Evaluation of ^{111}In-Labeled Nonsulfated CCK$_8$ Analog: A Peptide for CCK-B Receptor-Targeted Scintigraphy and Radionuclide Therapy. de Jong M et al. M J Nucl Med 1999; 40:2081–7

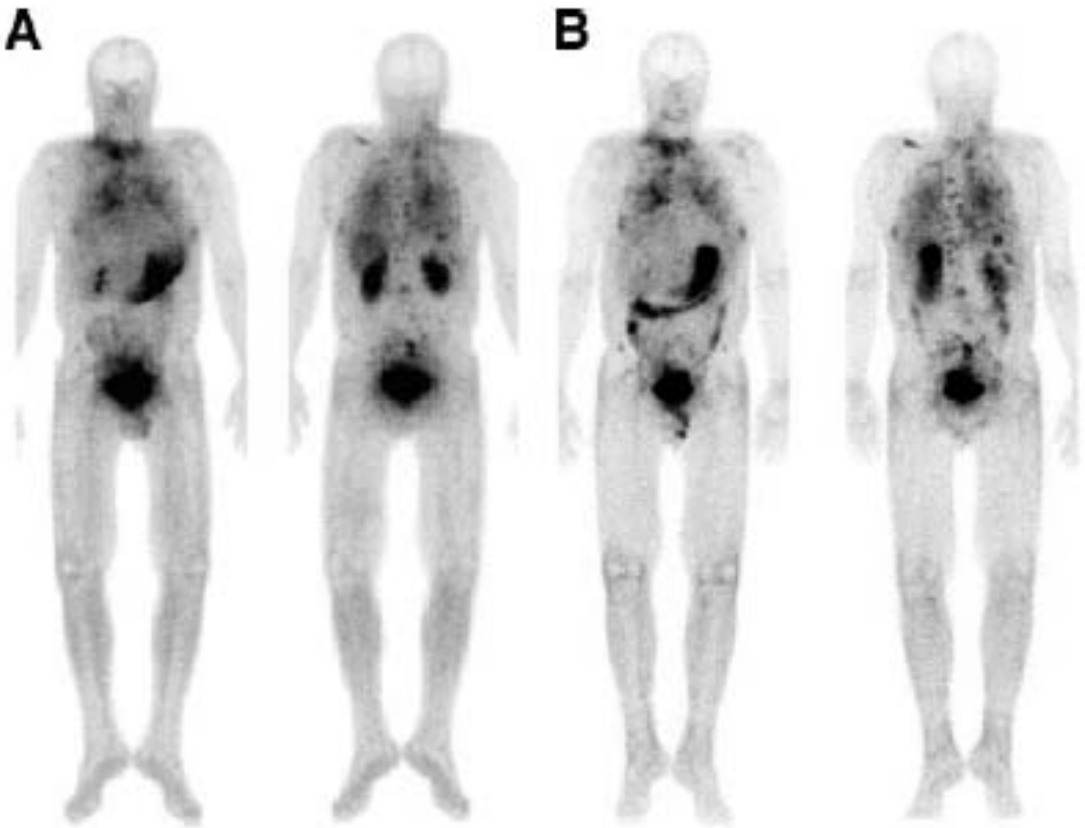


FIGURE 7. Whole-body images of patient with metastatic MTC 90 min (A) and 240 min (B) after intravenous injection of 740 MBq [^{99m}Tc]Demogastrin 2.

… exciting possibility to eventually develop the respective ^{188}Re-based therapeutic agents

CCK-2/Gastrin Receptor–Targeted Tumor Imaging with 99mTc-Labeled Minigastrin Analogs. Nock BA J Nucl Med 2005; 46:1727–1736

Massimo E. Dottorini
Direttore S.C. Medicina Nucleare 1
Ospedale "Santa Maria della Misericordia" Perugia

Radio-receptor treatment in advanced medullary thyroid carcinoma

- not yet ready for clinical practice
- an interesting model for nuclear medicine treatments of solid tumors
- an exciting possibility for the future

Stemma dell'Ospedale di S. Maria della Misericordia di Perugia

Massimo E. Dottorini
Direttore S.C. Medicina Nucleare 1
Ospedale "Santa Maria della Misericordia" Perugia

Nuclear medicine treatments of MTC

- ^{131}I-mIBG
- anti-carcinoembryonic-antigen radioimmunotherapy
- radioreceptor treatment:
  - somatostatine analogues (^{90}Y-DOTATOC)
  - CCK2/gastrin-R
- ^{131}I after human sodium iodide symporter (hNIS) gene transfer

Stemma dell'Ospedale di S. Maria della Misericordia di Perugia

Massimo E. Dottorini
Direttore S.C. Medicina Nucleare 1
Ospedale "Santa Maria della Misericordia" Perugia

- pretargeted radioimmunotherapy (pRAIT) with bispecific monoclonal antibody (BsMAb) and a iodine-131 (131I) -labeled bivalent hapten
- retrospective comparison of survival of 34 patients treated with pRAIT with 39 patients not treated
- median follow-up 121 months (34-354)

Survival improvement in patients with medullary thyroid carcinoma who undergo pretargeted anti-carcinoembryonic-antigen radioimmunotherapy: a collaborative study with the French Endocrine Tumor Group.
Chatal JF al. J Clin Oncol. 2006 Apr 10;24(11):1705-11.

- 10-year overall survival of patients with Ct DT < 2 yrs: treated 110 not treated 61 (p <0.03)
- 47% of high-risk patients biologic responders.
10-year OS: 89% (responders) vs 15% (nonresponders) vs 24% (untreated)
- high-grade hematologic toxicity in 9/34 pts (frequent bone/bone marrow uptake)

Survival improvement in patients with medullary thyroid carcinoma who undergo pretargeted anti-carcinoembryonic-antigen radioimmunotherapy: a collaborative study with the French Endocrine Tumor Group.
Chatal JF al. J Clin Oncol. 2006 Apr 10;24(11):1705-11.