CLINICAL CASE

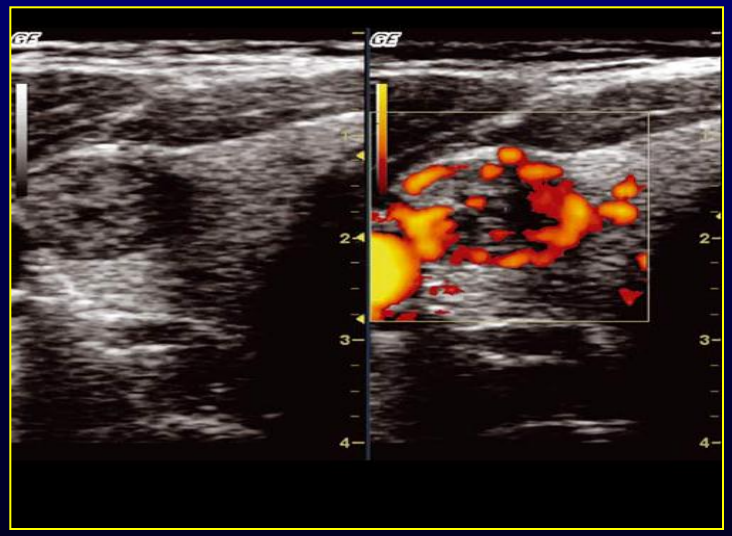
55 YEAR OLD WOMAN
PAINLESS RIGHT ANTERIOR CERVIAL ADENOPATHY

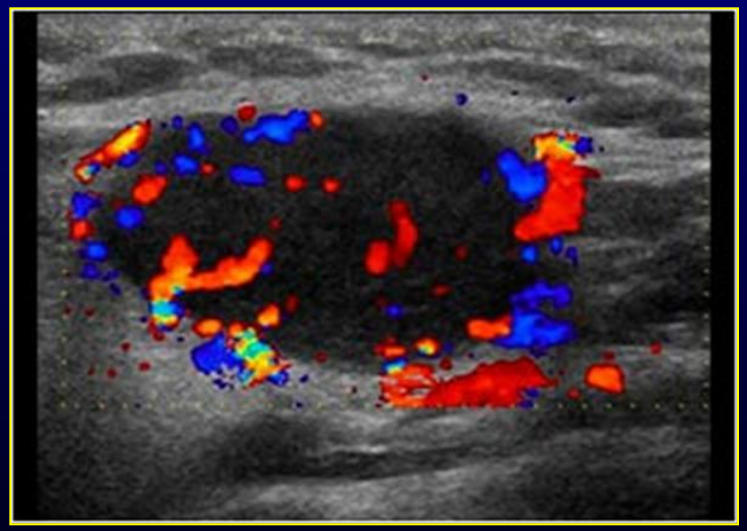
PHYSICAL EXAM

3 RIGHT ANTERIOR CERVICAL LYMPH NODES AND 1 PALPABLE NODULE IN THE UPPERPOLE OF THE RIGHT THYROID LOBE

NECK ULTRASOUND

VERY SUSPICIUOS !!!!!!!



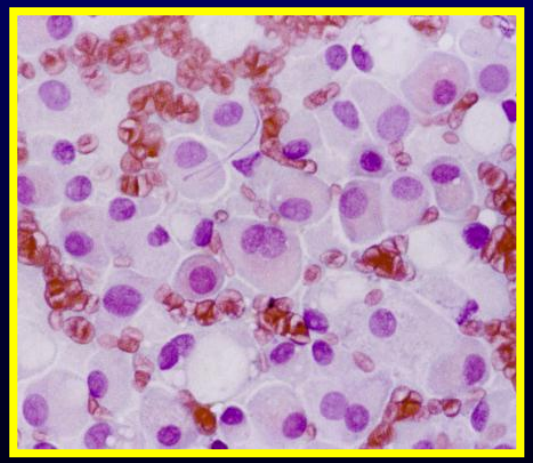


THYROID NODULE

BILATERAL NECK LYMPH NODES

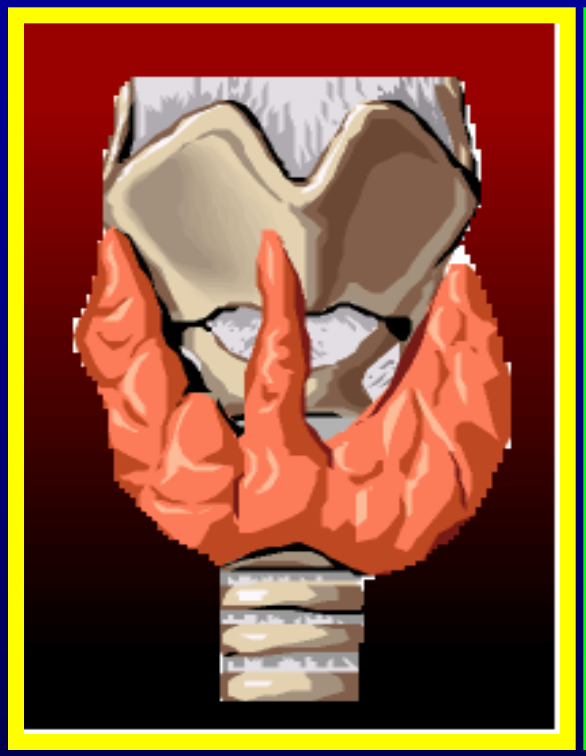
FINE NEEDLE ASPIRATION

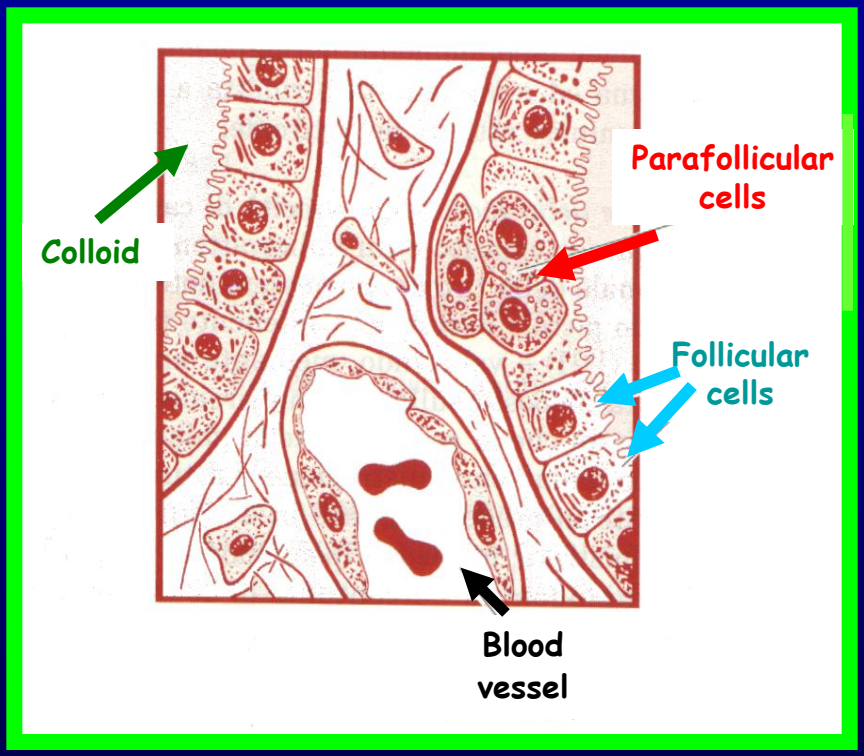
MTC CELLS FEATURES:
Binuclear cells, abundant cytoplasm, eccentric nucleus

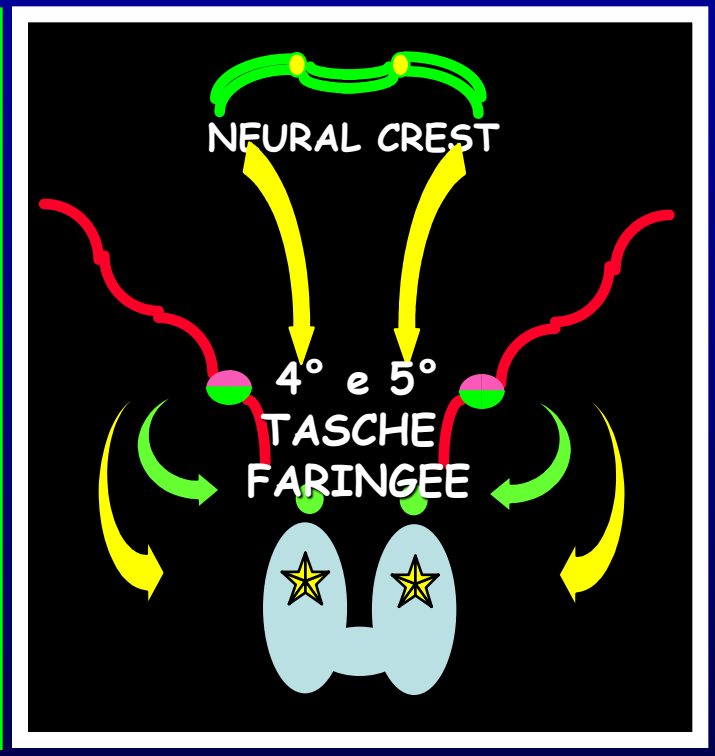


Definitive diagnosis

THYROID GLAND: 2 CELLULAR TYPES

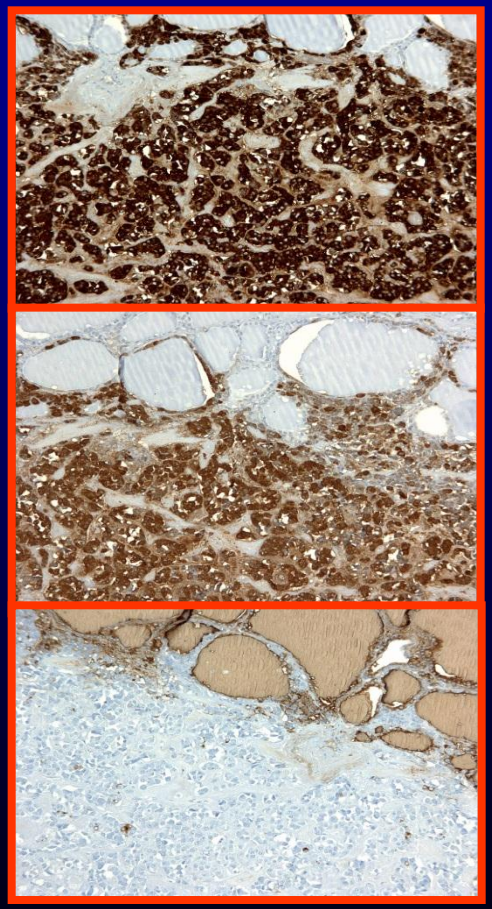






C CELL or PARAFOLLICULAR CELLS
1% THYROID CELLS
DIFFERENT EMBRYOGENESIS

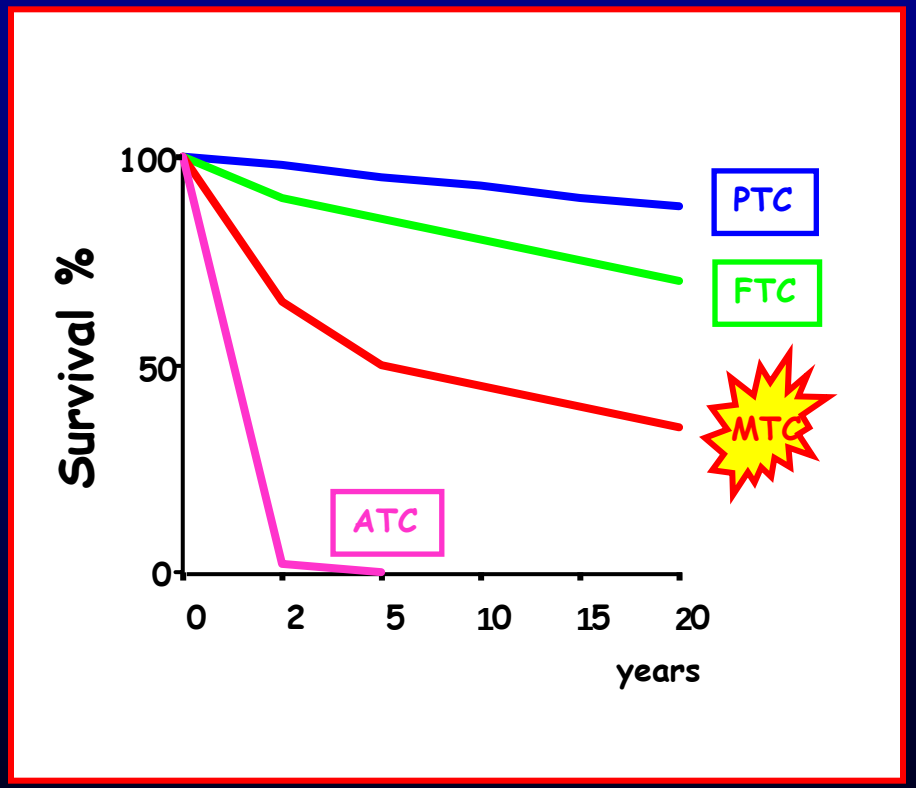
Medullary thyroid carcinoma ≠ Papillary and follicular thyroid carcinoma



CHROMOGRANIN +

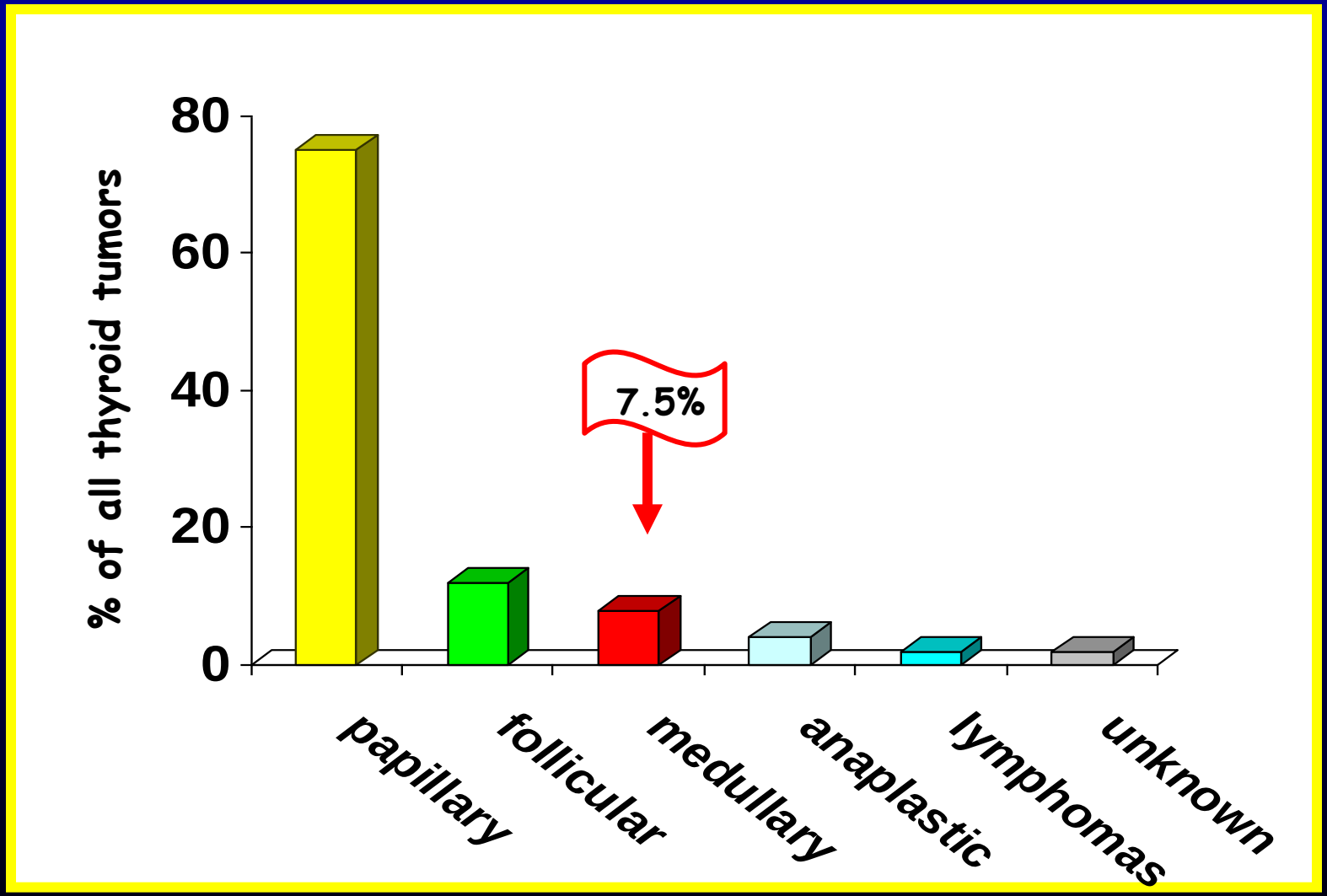
CALCITONIN +

THYROGLOBULIN -

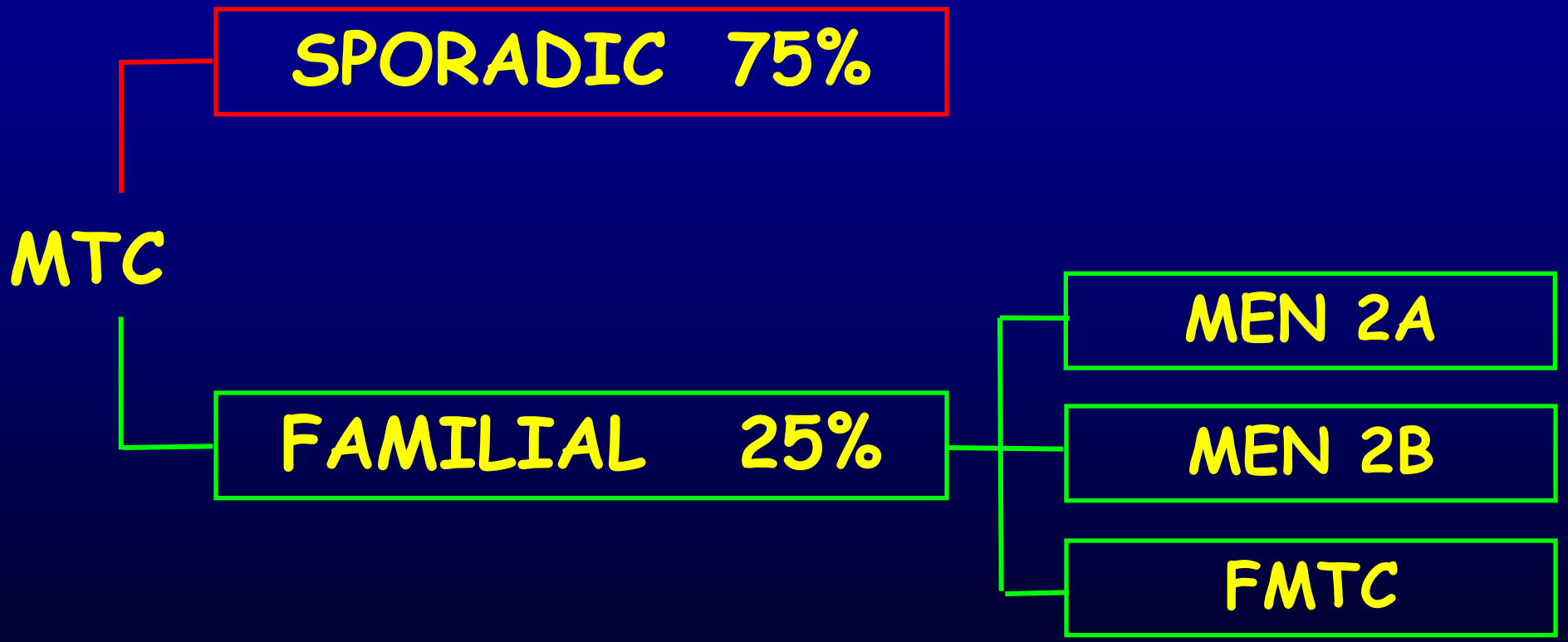


MEDULLARY THYROID CANCER (N=554)
PREVALENCE AMONG THYROID CANCERS (N=7382)

(Department of Endocrinology, Pisa, 1969-2007)

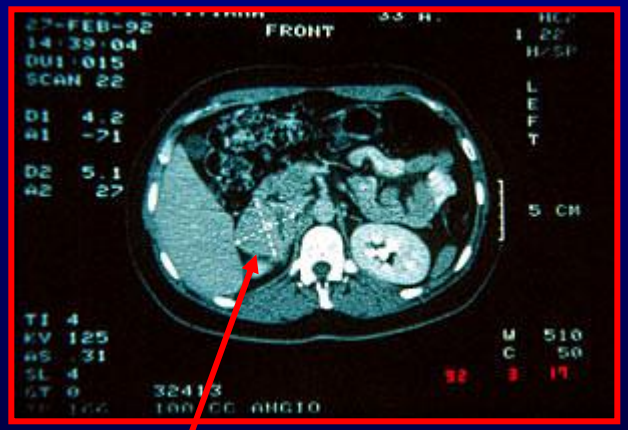


PREVALENCE OF DIFFFERENT FORMS OF MEDULLARY THYROID CARCINOMA

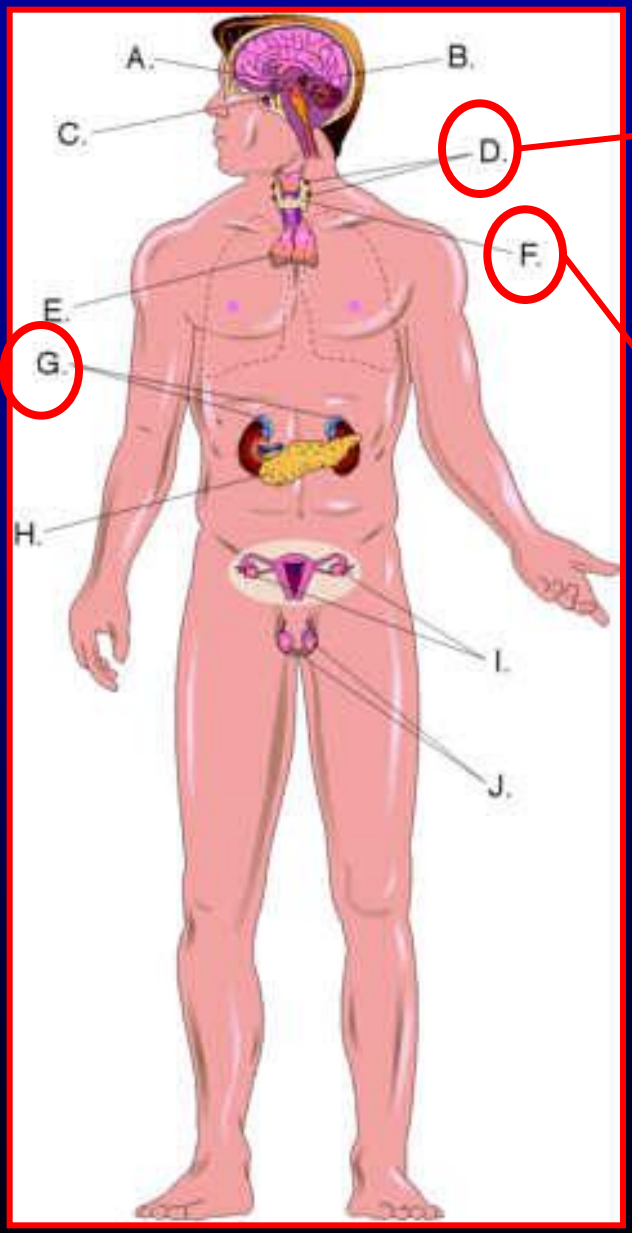


Neoplasie endocrine multiple di tipo 2

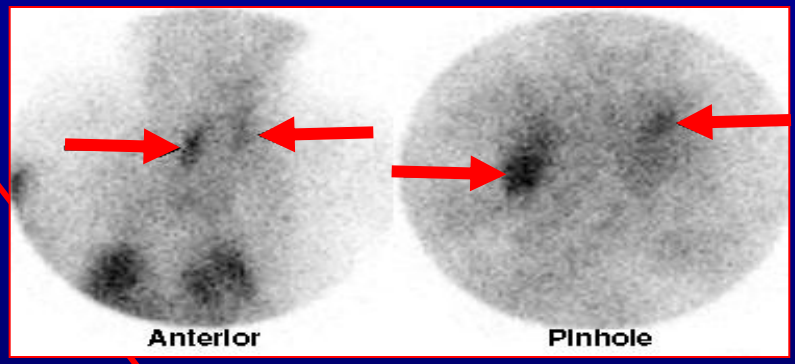
Adrenal Glands



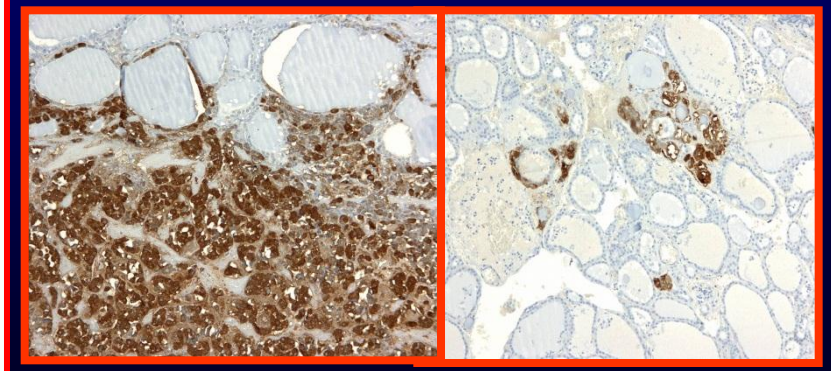
PHEO



Parathyroid

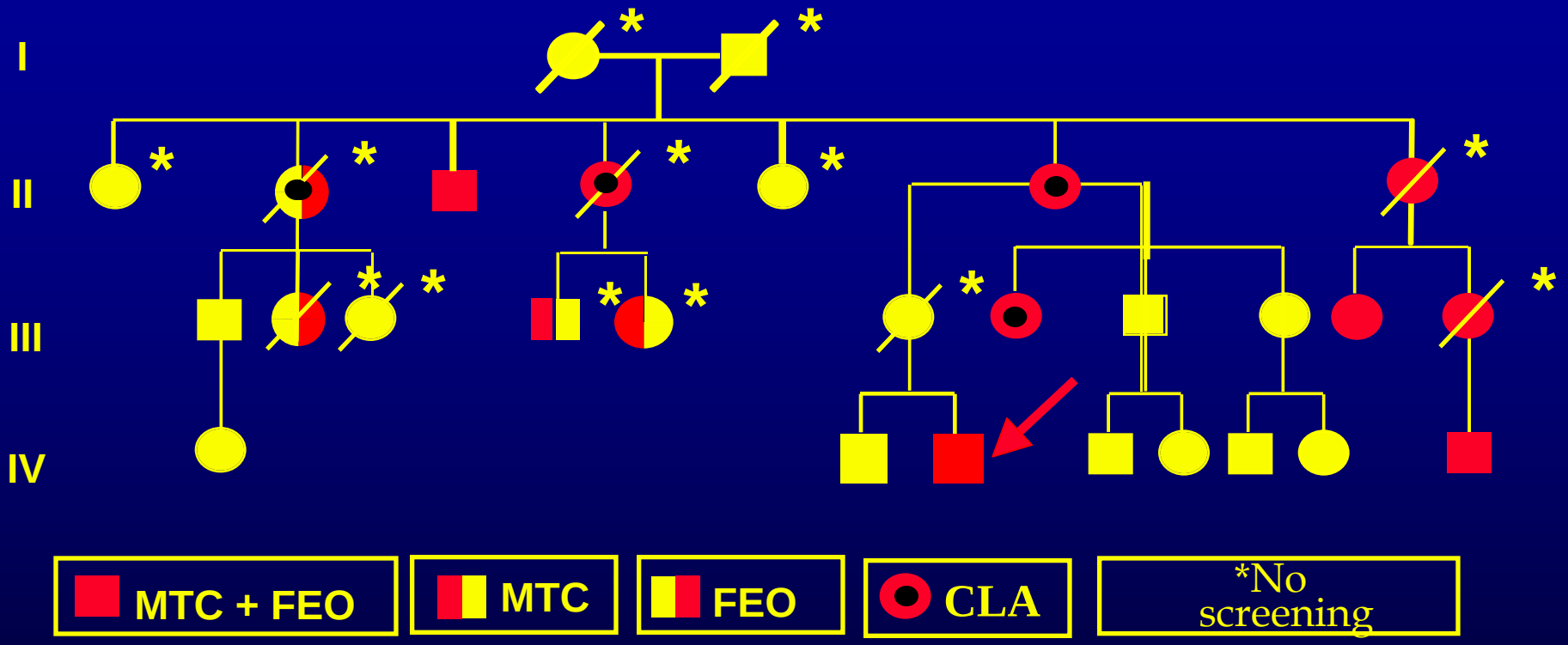


Thyroid



MTC ICC

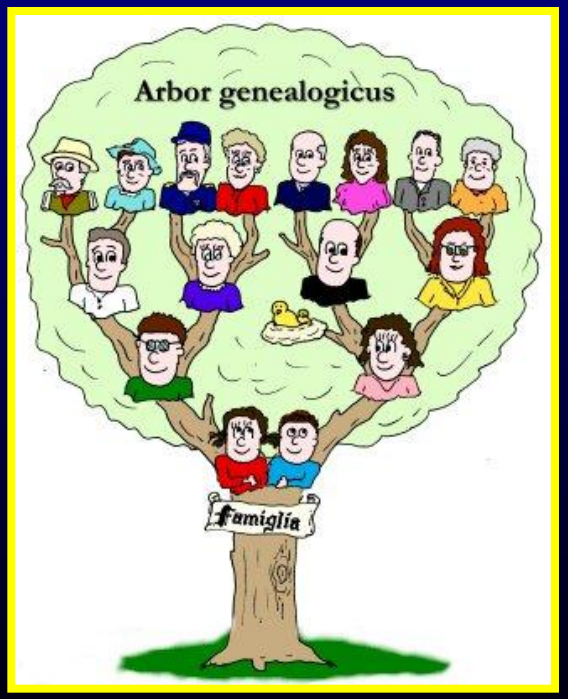
AUTOSOMINAL DOMINANT TRAIT



50% of descendants can inherit the tumoral disease

MEDICAL HISTORY

NON-SMOKER



FAMILY HISTORY NEGATIVE FOR:

THYROID CANCER
PHEOCROMOCYTOMA
HYPERPARATHYROIDISM

SPECIFIC LABORATORY TESTS IN MTC PATIENTS

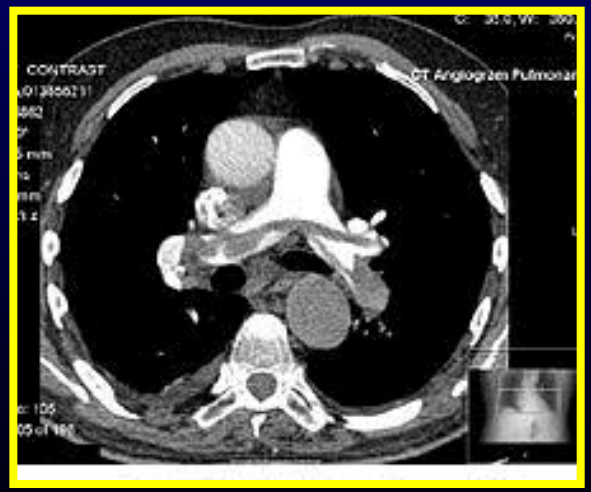
BLOOD

URINE

24 hours urine for catecholamines and total methaneprhines WNL

Calcitonin 450 pg/ml (VN < 10 pg/ml)
CEA 10 ng/ml (VN non-smoker <2.5 ng/ml)
Calcium, PTH and VitD: WNL
Fractionated plasma metanephrine: WNL

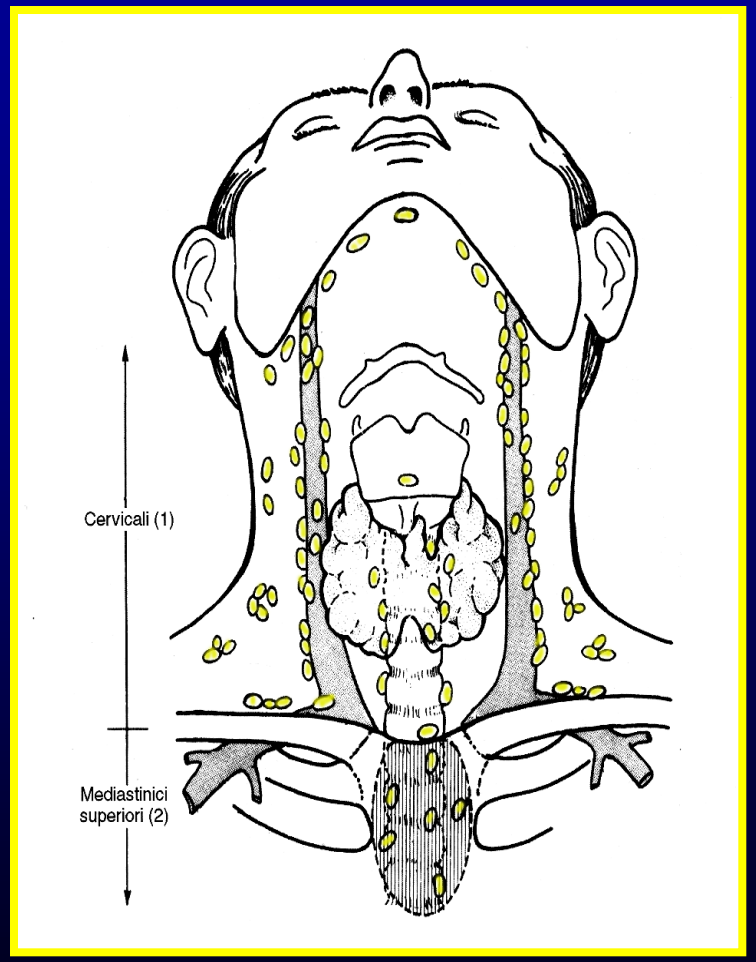
METASTATIC EVALUATION: STAGING



NECK: BILATERAL CERVICAL ADENOPATHY

CHEST AND ABDOMEN: NEGATIVE

SURGICAL TREATMENT: pathology report



TOTAL THYROIDECTOMY
+
BILATERAL CERVICAL LYMPHADENECTOMY

MTC 2.2 x1.9 cm in the right lobe
No extracapsular invasion
4/13 right and 1/9 left cervical lymph nodes with MTC metastases

T2N1M0

CLINICAL COURSE

FIRST CONTROL:

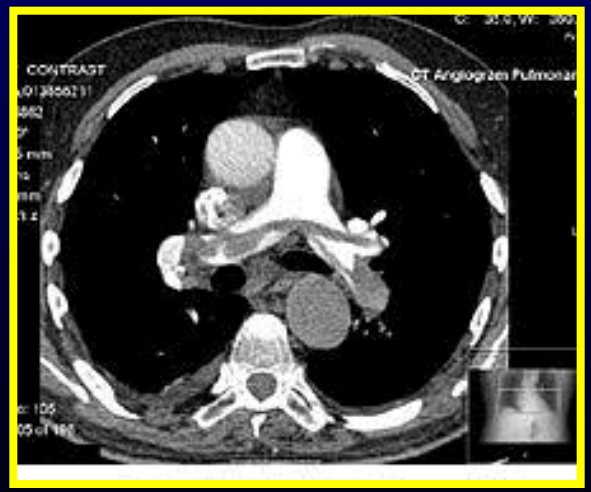
6 WEEKS AFTER TT+LNC: serum Ct and CEA → WNL

FURTHER CONTROLS EVERY 3 MONTHS

1° CONTROL (4.5 MONTHS AFTER TT+LNC):
serum Ct and CEA → WNL

2° CONTROL (7.5 MONTHS AFTER TT+LNC):
serum Ct: 125 pg/ml and CEA: 6 ng/ml

RESTAGING: TOTAL BODY CT SCAN



NEGATIVE FOR METASTATIC LESIONS

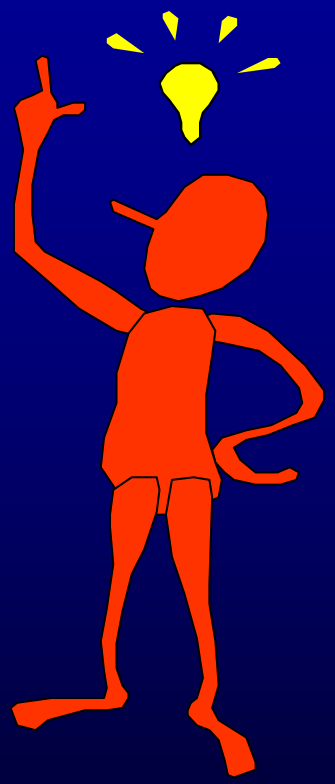
QUESTIONS

1. CONTINUED WATCHFUL WAITING WITHOUT FURTHER EVALUATION OR THERAPY

2. SURGICAL EVALUATION FOR POSSIBLE LOCOREGIONAL RECURRENCE: IF POSITIVE, CONSIDER EXTERNAL BEAM IRRADIATION

3. CONSIDER A TRIAL OF "SYSTEMIC THERAPY" USING SERUM CALCITONIN AND CEA LEVEL TO ASSESS RESPONSE

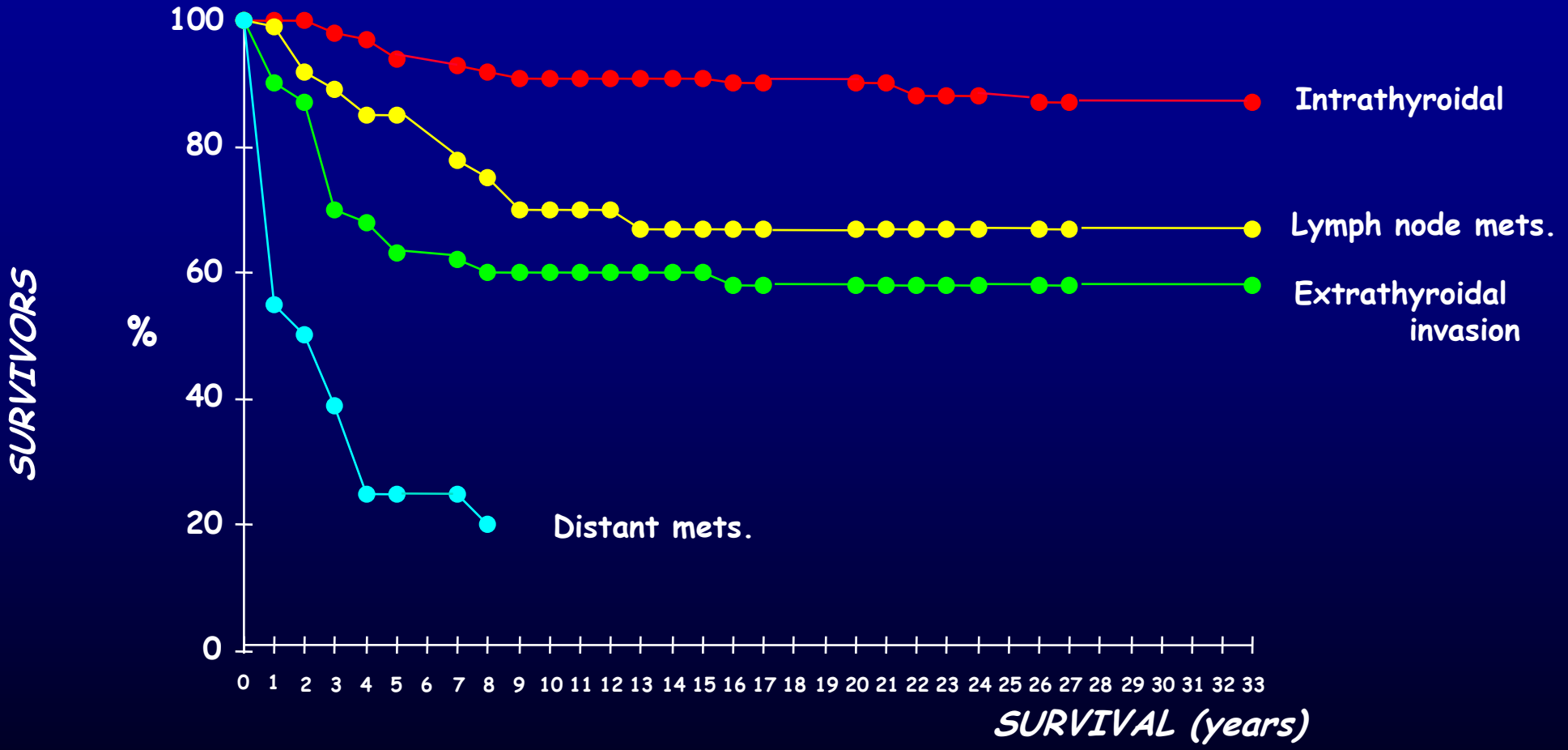
BEFORE ANSWERING



TAKE INTO ACCOUNT…

LYMPH NODES METASTASES AT DIAGNOSIS IS THE MOST IMPORTANT NEGATIVE PROGNOSTIC FACTOR

(MAYO CLINIC SERIES)

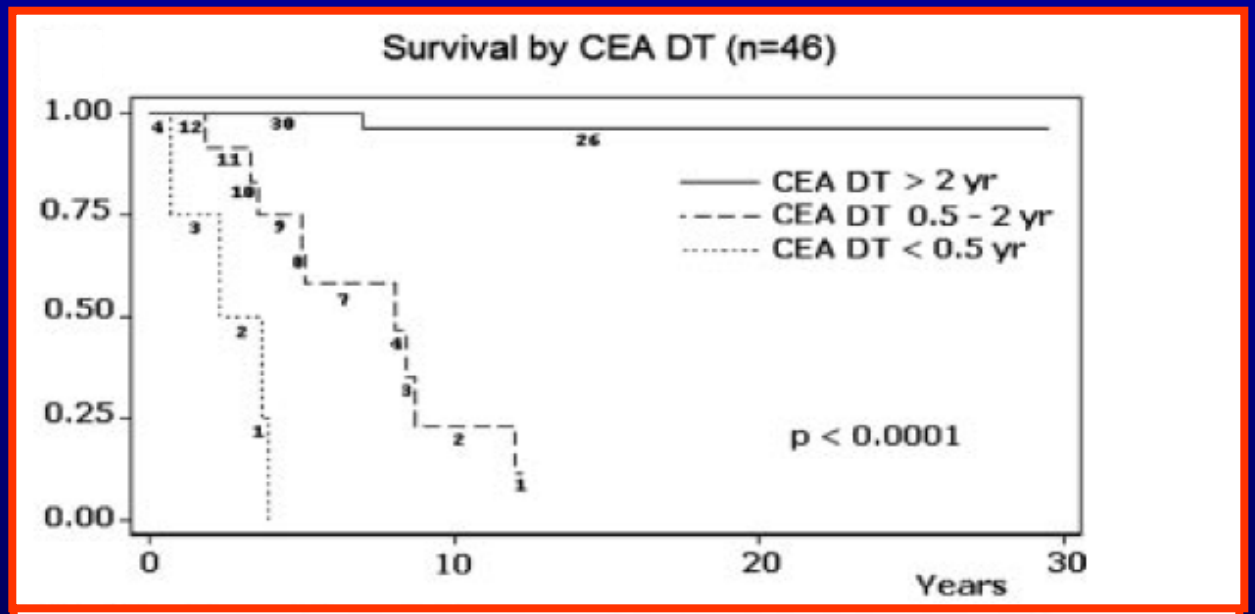


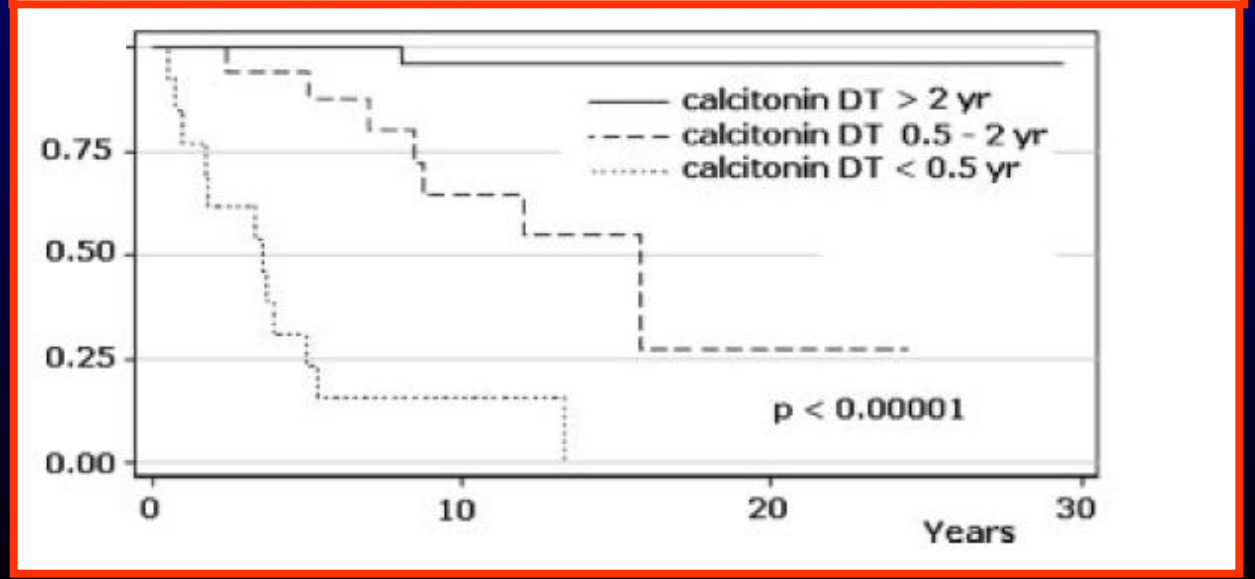
Gharib H et al, Mayo Clin Proc 67:934, 1992

Prognostic Impact of Serum CT and CEA Doubling-Times in Patients with Medullary Thyroid Carcinoma

Barbet J, Campion L, Kraeber-Bodéré F, Chatal J and the GTE Study Group

PROGNOSTIC FACTORS IN THE FOLLOW UP

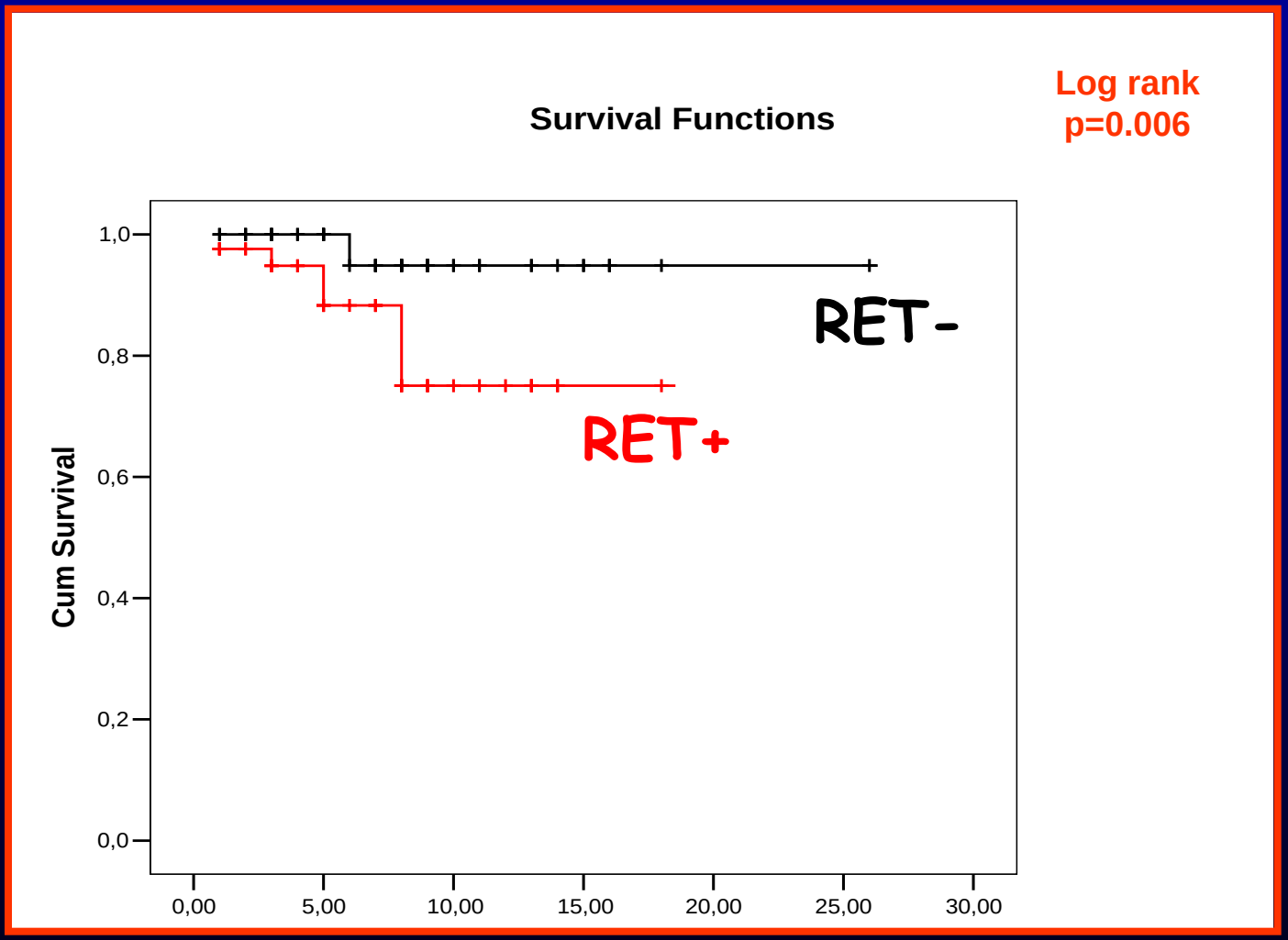




J Clin Endoc Metab, 2005

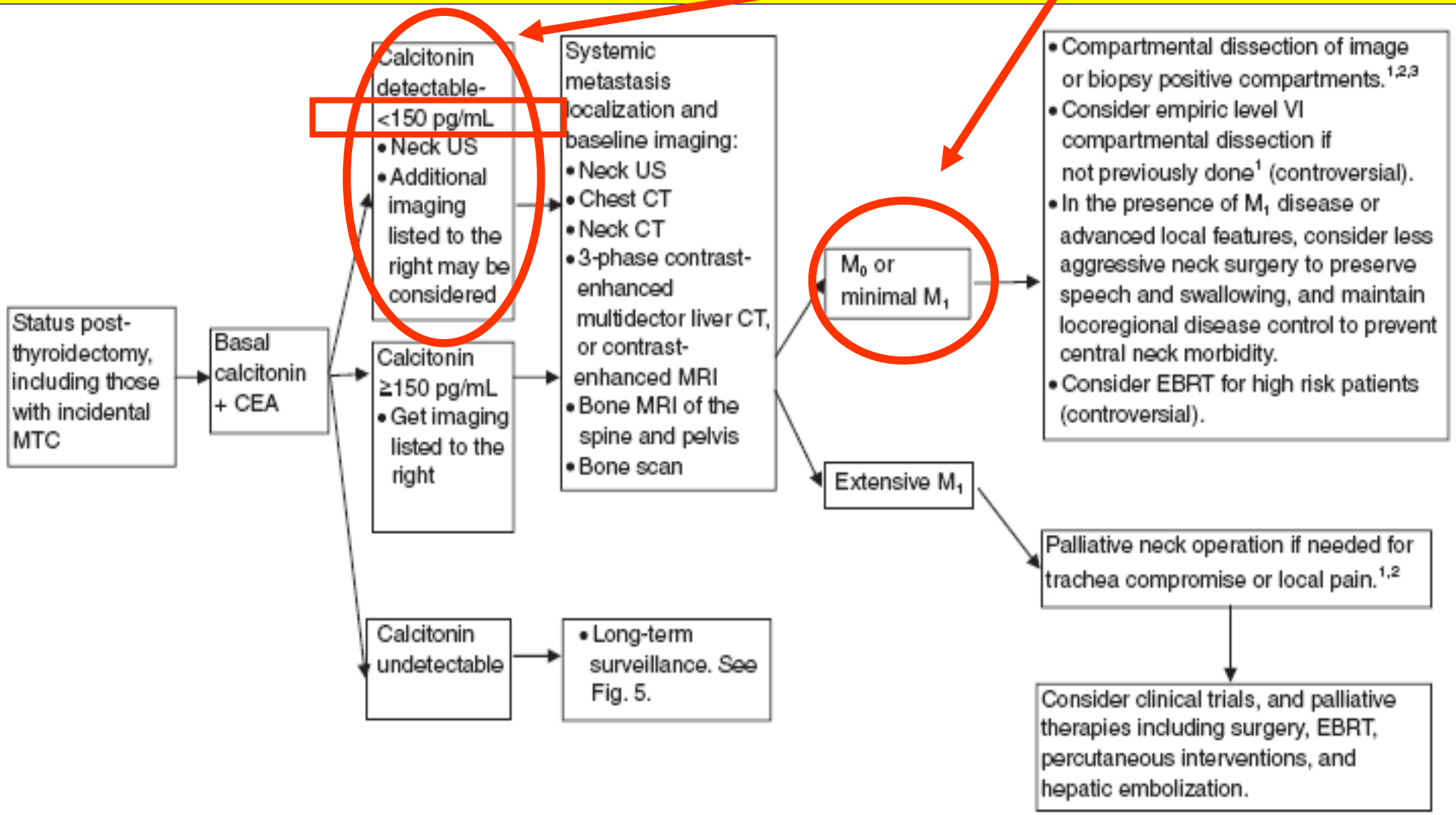
SURVIVAL CURVE IN MTC PATIENTS WITH AND WITHOUT RET SOMATIC MUTATIONS

n= 100, mean follow-up 10 years



Elisei R et al, J Clin Endocrinol Metab. 2008, 93:6827

ATA-ETA GUIDELINES: we are here



CLINICAL COURSE our MTC CASE

No evidence of locoregional recurrence and or distant metastases

Thus…

Waiting and see program

14 months after TT+LNC…

Serum Ct: 800 pg/ml
(it was 125 pg/ml 6.5 months before)

TB CT scan:

1) mediastinal adenopathy in the upper retrosternal area, with no evidence of superior vena caval obstruction **but** <u>persistent retrosternal pain</u>

2) multiple pulmonary nodules (biggest: 1.5 cm)

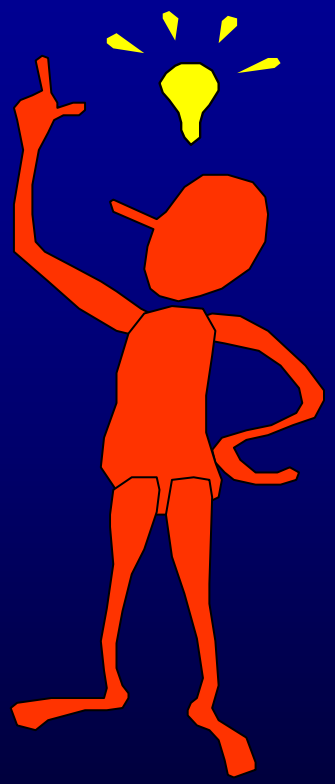
3) no liver metastases

QUESTION

WHAT DO YOU RECOMMEND FOR THIS SYMPTOMATIC PATIENT WITH AN ECOG PERFORMANCE STATUS OF 1?

1. EBRT
2. CHEMOTHERAPY
3. TKI TARGETED THERAPY

BEFORE ANSWERING



TAKE INTO ACCOUNT…

1. EXTERNAL BEAM IRRADIATION (EBRT)

Update on External Beam Radiation Therapy in Thyroid Cancer

James D. Brierley

Department of Radiation Oncology, University of Toronto, Princess Margaret Hospital, Toronto, Ontario, Canada M5G 2M9

(*J Clin Endocrinol Metab* 96: 2289–2295, 2011)

Summary

Further single institutional data supports the use of EBRT in improving local control in highly selected patients with MTC. However, given the natural history of the disease, survival is not improved; therefore, EBRT should be reserved only in patients at high risk of devastating cervical recurrence requiring extensive ablative surgery.

1.EXTERNAL BEAM IRRADIATION (EBRT)

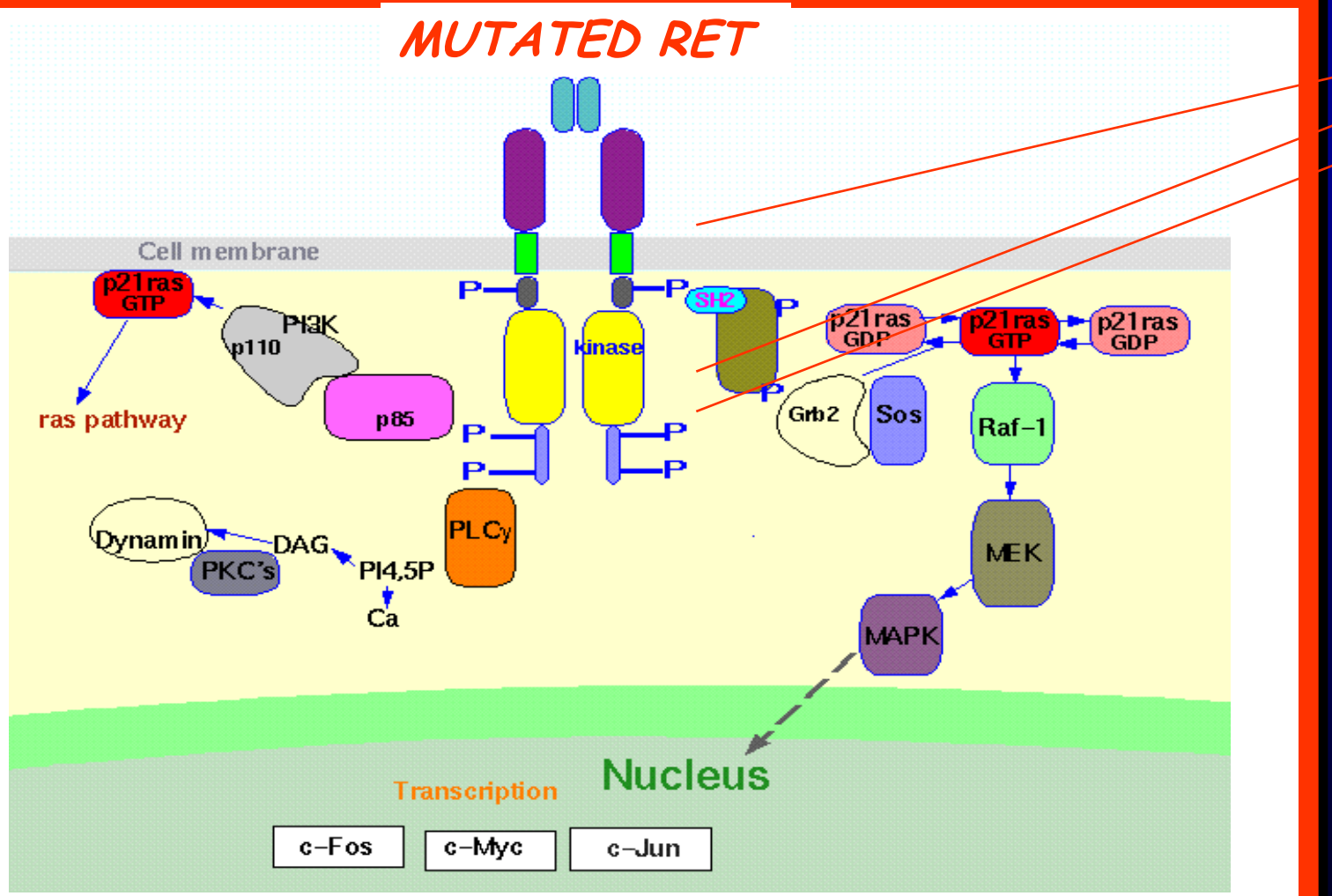
J Exp Clin Cancer Res 2003, 22(4 Suppl):65-70.
Locoregional pain treatment. Troubles and prospectives: antalgic radiotherapy.
Mantini G et al.

Pain control in patients with cancer represents a significant aspect of radiation therapy practice. Radiation therapy is one of the most effective, and often the only, therapeutic option to relieve pain caused by nerve compression or infiltration by malignant tumor, pain from liver and bony metastases and it provides also successful palliation of dysphagia caused by oesophageal carcinoma and of pain due to pancreatic cancer.

CONVENTIONAL CHEMOTERAPY IN MTC

DRUGS	REFERENCES	PAZ	CR	PR	SD	PD
duxorubicin	Burgess 1978	6	--	3	3	--
duxorubicin	Leight 1980	7	--	1	--	6
duxorubicin	Droz 1984	13	1	2	4	6
doxo+cisplat	Shimaoka 1985	6	--	2	--	4
doxo+cisplat	Droz 1984	14	1	2	4	7
dox+cisp+bleo	De Besi 1991	8	--	4	4	--
cisplatinum	Leight 1980	3	--	--	--	3
etoposide	Fiore 1984	2	--	1	--	1
methotrexate	Hoskin 1987	1	--	1	--	--
doxo+cisp+ vindesine	Scherubl 1990	10	--	1	6	3
dacarbaz+5FU	Orlandi 1994	7	--	3	2	2
5FU+decarbaz/s treptoz.	Schlumberger 1995	20	--	3	11	6
rubidazone	Stepanas 1979	1	--	--	--	1

TYROSINE-KINASE INHIBITORS: RATIONALE



ACTION

Stop Phosphorylation

Stop signal trasmission

Inhibition cellular growth

RATIONALE TKI THERAPY: COSTITUTIVE ACTIVATION OF RET !

- ✓ 98% of familial cases show a germinal RET mutation
- ✓ 40-45% of sporadic cases show a somatic RET mutation
- ✓ RET mutation is correlated with an advanced stage at diagnosis and a lower survival

TYROSINE KINASE INHIBITORS (TKI)

The majority of TKI inhibit several receptors with different degree of inhibition

DRUG	IC_{50}(nm)							
	VEGFR1	VEGFR2	VEGFR3	RET	MET	KIT	BRAF	OTHER
IMATINIB	19.500	10.700	5.700	-	>100.000	410	-	ABL (38)
AXITINIB	1.2	0.25	0.29	-	-	-	-	-
VANDETANIB	1.600	40	108	130	-	-	-	EGFR (500)
MOTESANIB	2	3	6	59	-	8	-	PDGFR (84)
SUNITINIB	15	38	30	224	-	1-10	-	FLT3 (21)
GEFITINIB	-	-	-	-	3.200	-	-	EGFR (14)
SORAFENIB	-	90	20	5.9	-	68	22	CRAF (6)
E7080	22	4	-	35	-	-	-	FGFR1 (25)
CABOZANTINIB (XL-184)	-	0.035	-	4.5	1.8	-	-	-

RATIONALE TKI THERAPY: NOT ONLY RET !

✓ Microvessels, expression of **neo-angiogenesis**, are more represented in MTC than in other thyroid tumors (Fontanini G et al, Mod Pathol, 1996)

✓ **VEGFR-1, and VEGFR-2** are <u>overexpressed</u> in MTC (Capp C, et al, Thyroid, 2010)

✓ **MET** is <u>overexpressed</u> in a subgroup of MTC (Papotti M et al, Endoc Pathol 2000, Trovato M et al, Thyroid 1998)

✓ **EGFR** is <u>overexpressed</u> in MTC (Wang W et al, Acta Oncol, 1997) and in particular in its metastasis (Rodriguez-Antona C et al, Endoc Rel Cancer 2010)

ZETA Study Design

PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED OR METASTATIC MTC (N=331)

2:1 RANDOMIZATION

VANDETANIB 300 MG/DAY
N=231

PLACEBO
N=100

Follow for progression

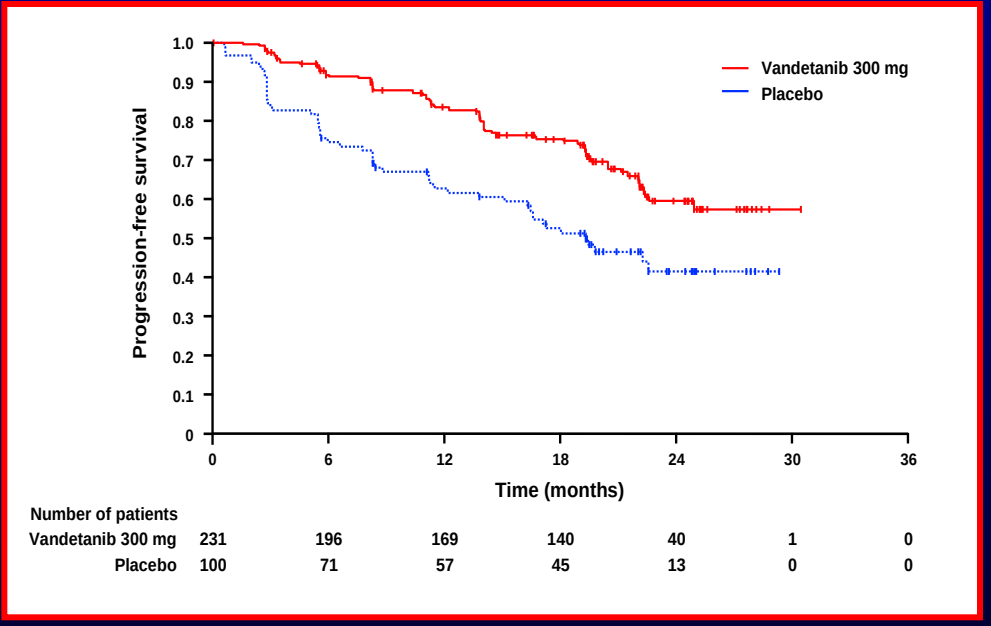
Follow for progression

Discontinue blinded treatment at progression:
cross over placebo vs drug

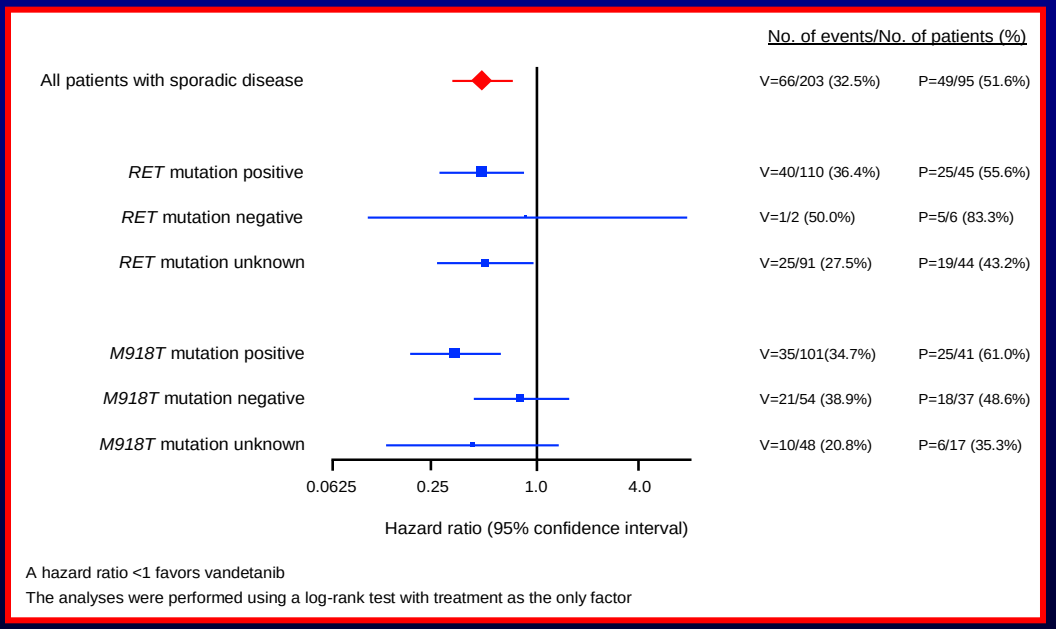
FOLLOW FOR SURVIVAL

Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial (ZETA)

Samuel A Wells,[1] Bruce G Robinson,[2] Robert F Gagel,[3] Henning Dralle,[4] James A Fagin,[5] Massimo Santoro,[6] Eric Baudin,[7] Rossella Elisei,[8] Barbara Jarzab,[9] James Vasselli,[10] Jessica Read,[11] Peter Langmuir[10] Anderson J Ryan[12] and Martin Schlumberger[7], for the ZETA investigators*



Significant increase of progression free survival



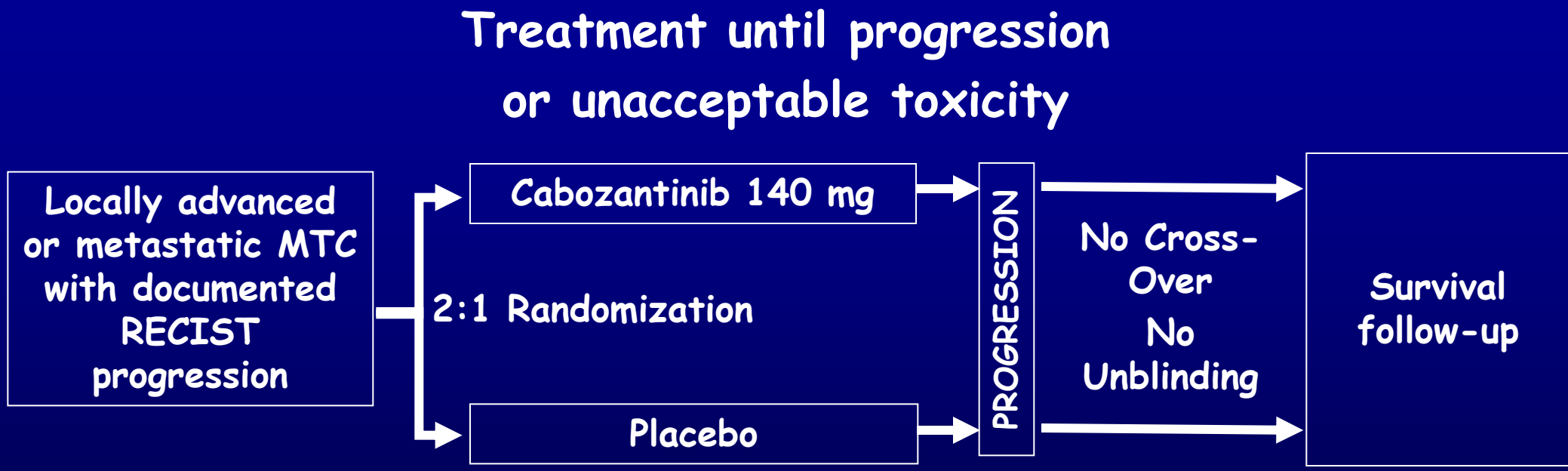
RET negative MTC are responsive to Vandetanib BUT Ret positive cases are more responsive

J Clin Oncol, 2012

VANDETANIB ALREADY COMMERCIALLY AVAILABLE IN USA: APPROVED BY EMA IN FEBRUARY 2012

CAPRELSA

Phase 3 Study Design (EXAM)

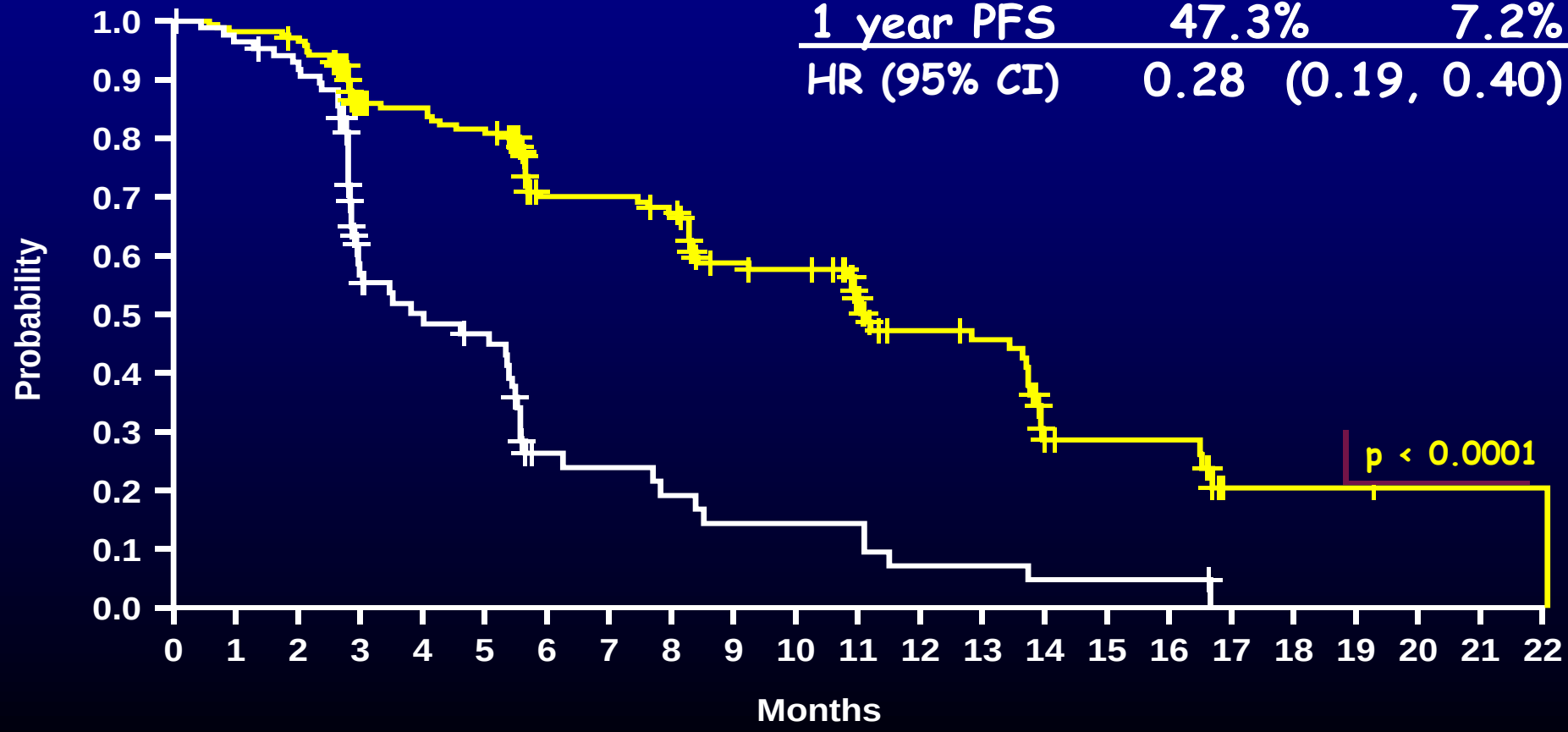


330 subjects randomized across 90 sites in 23 countries:

55.8% in Europe
30.9% in North America
13.3% in the rest of the world

Progression Free Survival by IRC (Primary Endpoint)

	Cabozantinib	Placebo
Median PFS (months)	11.2	4.0
1 year PFS	47.3%	7.2%
HR (95% CI)	0.28 (0.19, 0.40)	



What we did???

We first explored the possibility of a surgical excision of mediastinal lymph nodes

Yes and complete

Yes, big debulking but not complete, + adjuvant EBRT

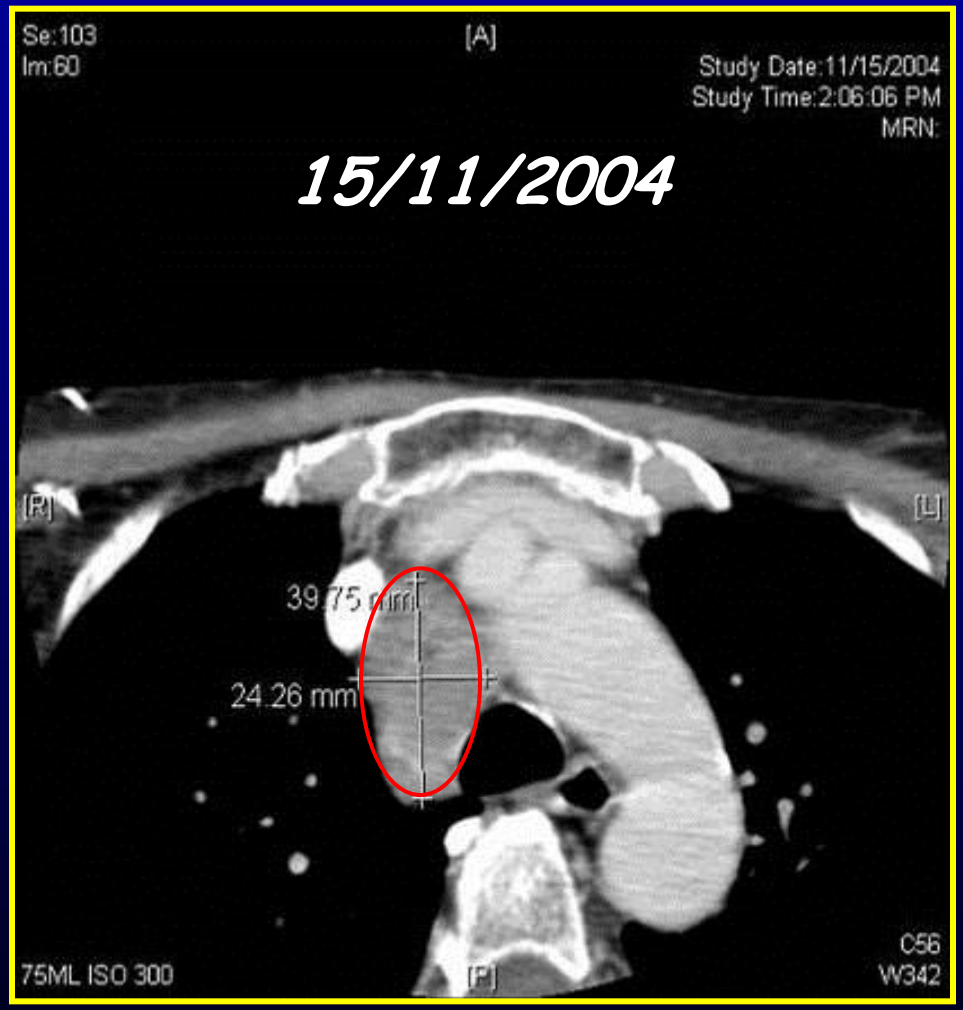
Not possible

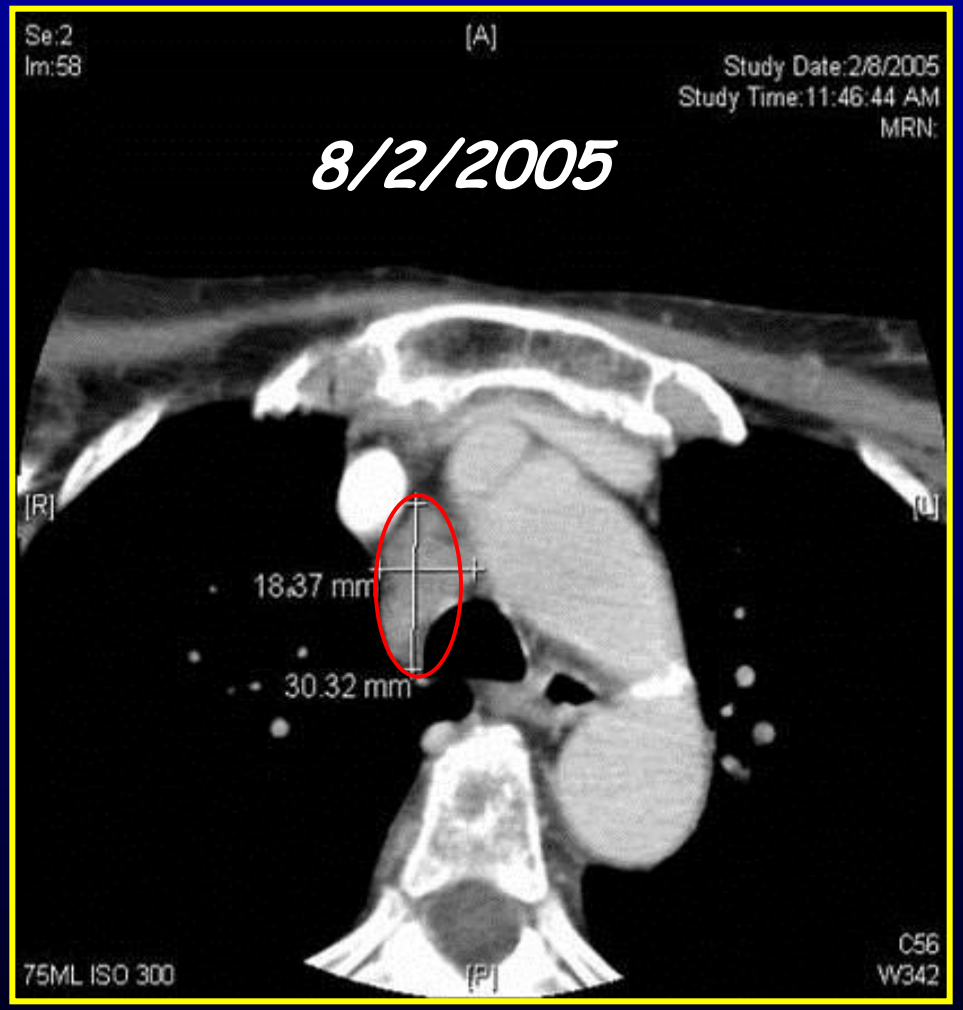
CT scan and Ct measurement 3-4 months later

If new disease and/or lung progression

Vandetanib

2. VANDETANIB AND MEDIASTINAL LYMPH NODE METASTASES





She is still «on» vandetanib: stable disease, stable Ct and CEA

THANK YOU FOR YOUR ATTENTION!!!