A hand wearing a blue nitrile glove holds a black magnifying glass over a red, textured model of a human thyroid gland. The model is positioned on a white surface, and the magnifying glass is held at an angle, focusing on the central part of the gland. The background is a gradient from dark grey on the left to white on the right.

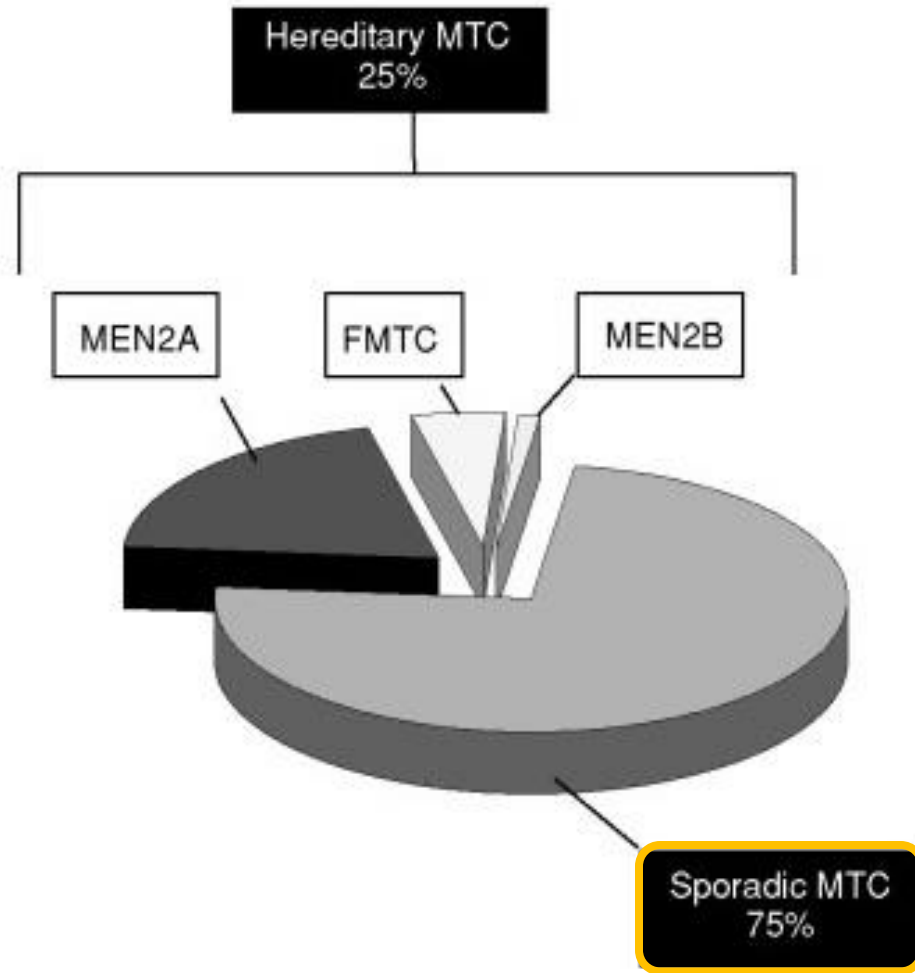
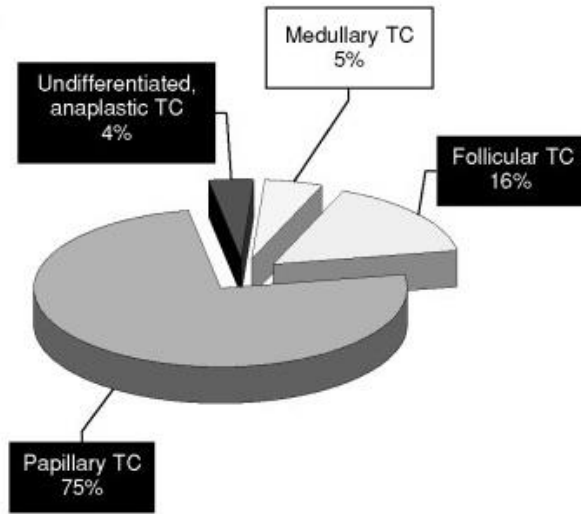
Casi clinici carcinoma midollare della tiroide

Antonio Matrone, MD, PhD

U.O. Endocrinologia

Dipartimento di Medicina Clinica e Sperimentale,
Università di Pisa

A



Medullary
Thyroid
Cancer...what
we can expect...

Objective

Cure the disease

Key factor

Disease extension at diagnosis

Thyroid disease
alone

Local lymph
nodes
involvement

Distant
metastatic
disease

Key treatments

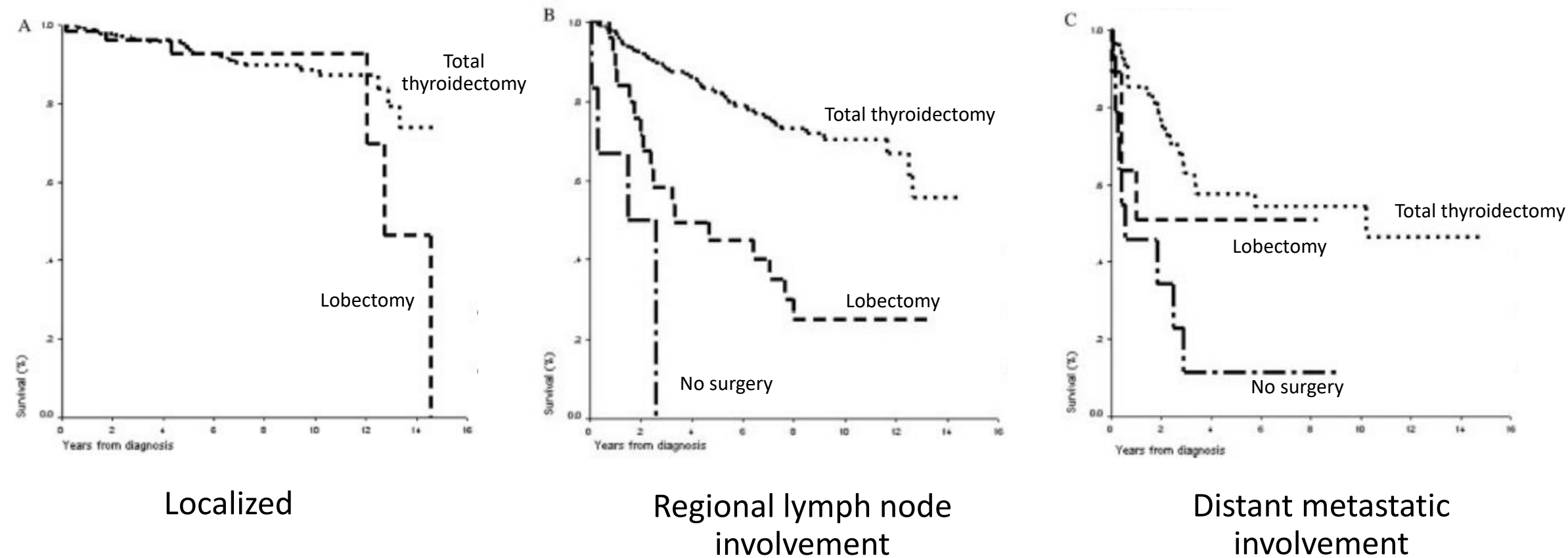
Radical surgery (if possible)

Right timing of other treatments (local or systemic)

Sporadic MTC
Clinical scenarios

Overall survival in MTC patients

SEER series n=1252 (1973-2002)



Clinical case #1



Feb 2022

Male, 65 years

Incidental finding of left thyroid nodule (1.2 cm)

Insights:

- No personal and familial history of thyroid disease
- No relevant diseases or therapies
- No symptoms
- Single nodule
- No lymph nodes involvement at US
- FNAC – TIR3B (microfollicular lesion with atypia)

How do you manage
this patient?

Surgery and
what type

Further diagnostic
tests and what type

Clinical case #1

Further diagnostic tests



May 2022

Indication for the patient was total thyroidectomy

Insights (before surgery):

- TSH 2.2, TgAb and TPOAb undetectable
- CTN 38 pg/ml (n.v. < 18.2)
- Calcium stimulation test: CTN peak 510 pg/ml
- CEA 4.2 mcg/L (n.v. <5.2)
- Total body CT scan: left thyroid nodule, no lymph nodes, no suspicious distant metastases



Surgery

Clinical case #1



June 2022

Surgical treatment of **right lobectomy** with ipsilateral central compartment lymph nodes dissection

- Histology: medullary thyroid carcinoma (1.1 cm), 1/6 metastatic lymph node of the central compartment (max dim <0.1 cm) (pT1bN1aMx)
- 3 weeks after surgery: CTN 4.4 (<18.2) and CEA 4 (<5.2)
- No surgical related adverse events (hyoparathyroidism, RLN injury)

Completion surgery

Further diagnostic tests

Follow-up

Clinical case #1



October 2022 (4 months after surgery)

Clinical evaluation

- Neck US negative for persistence/recurrence of the disease and lymph nodes metastases
- Calcium stimulation test for CTN – Basal CTN 1.2, peak CTN 6.1
- TSH 3.2
- Germline RET mutation - negative



To date, we decided to follow the patients every 8-10 months

Clinical case #1

RECOMMENDATION 24

Patients with MTC and no evidence of neck lymph node metastases by US examination and no evidence of distant metastases should have a total thyroidectomy and dissection of the lymph nodes in the central compartment (level VI). **Grade B** Recommendation

RECOMMENDATION 25

In patients with MTC and no evidence of neck metastases on US, and no distant metastases, dissection of lymph nodes in the **lateral compartments** (levels II–V) may be considered based on serum CTN levels. The Task Force did not achieve consensus on this recommendation. **Grade I** Recommendation

Clinical case #1

...some consideration about unilateral surgery in sporadic MTC...

- Sporadic MTC is usually **unifocal** and only rarely multifocal (~15%) (differently from PTC)
- Dissection of the **ipsilateral central compartment** and the potential presence of lymph nodes (micro)metastases is a good indicator of the lymph node metastatic status of the disease
- **Neck US before surgery**, in expert hands, is a key tool in planning the surgical treatment
- **CTN (and CEA) values** before surgery are a good indicator of the tumor burden
- **Post operative CTN values**, both basal and stimulated, clearly reflects the persistence/recurrence of the tumor, also in patients treated with lobectomy (differently from Tg in DTC)

Clinical case #1

...some consideration about unilateral surgery in sporadic MTC...



Unilateral Surgery for Medullary Thyroid Carcinoma: Seeking for Clinical Practice Guidelines

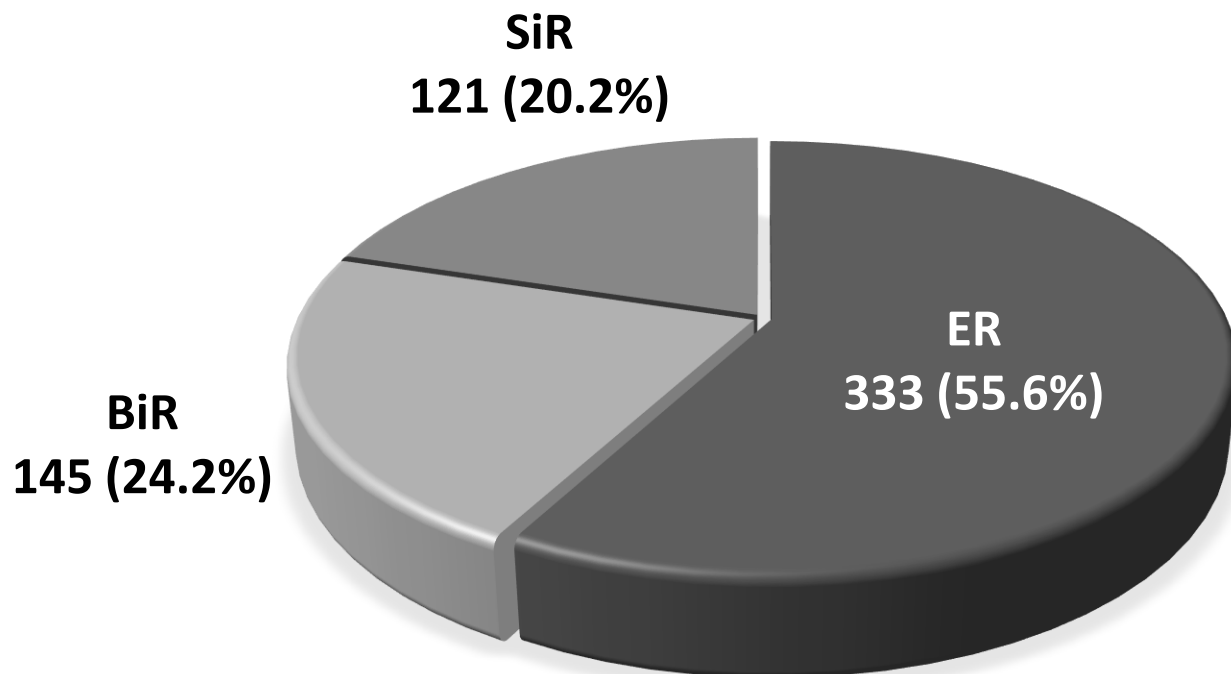
Daqi Zhang¹, Carla Colombo^{2,3}, Hui Sun^{1*}, Hoon Yub Kim⁴, Antonella Pino^{5,6}, Simone De Leo², Giacomo Gazzano⁷, Luca Persani^{2,8}, Gianlorenzo Dionigi^{3,5} and Laura Fugazzola^{2,3}*

Clinical case #1

...this is an anecdotal case...

- **To date**, the suggested surgical treatment for all sporadic MTC is represented by total thyroidectomy and prophylactic or therapeutic central compartment lymph node dissection
- Oriented latero-cervical lymph node dissection is reserved to metastatic latero-cervical lymph node diagnosed before or during surgery

Medullary Thyroid Cancer...what we can expect after surgery...



Clinical case #2



September 2007

Incidental finding of left thyroid nodule of 2.5 cm

- FNAC – Thy 4 (suspicious for papillary thyroid carcinoma)
- Neck US negative for other thyroid nodules or suspicious lymph nodes

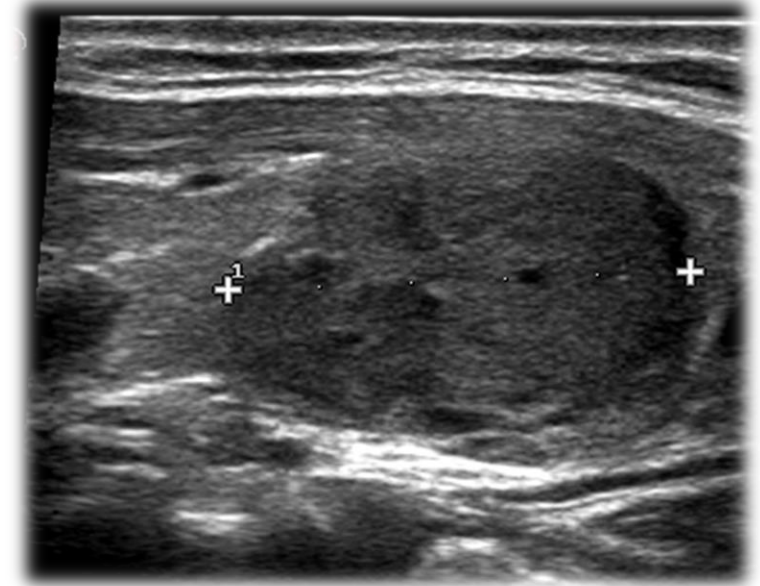
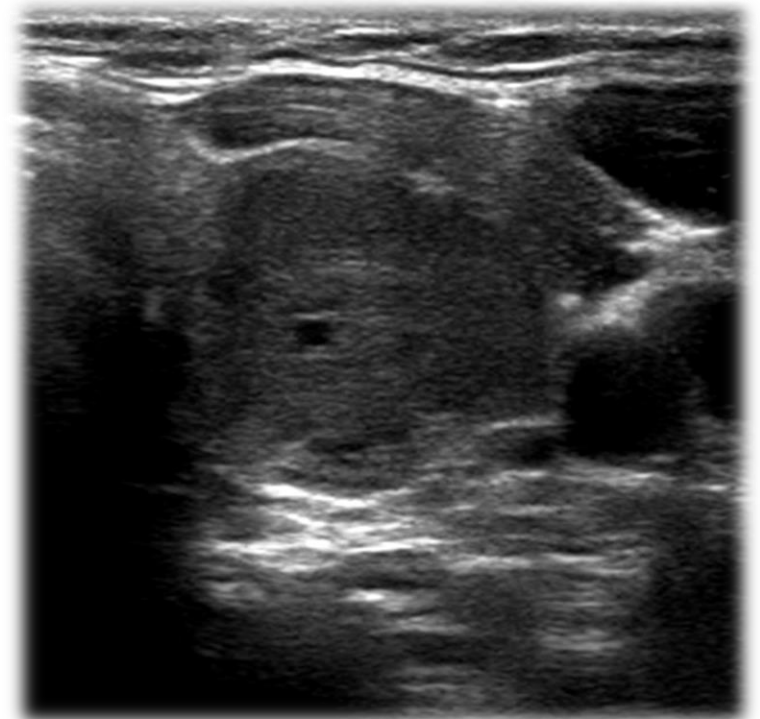
Indication for the patient was total thyroidectomy

Insights (before surgery):

- No other diagnostic tests before surgery

October 2007: Total thyroidectomy

Histology: Medullary thyroid carcinoma (2.2 cm) of the left lobe with infiltration of thyroid capsule (pT2NxMx)



Clinical case #2



December 2007

Post-operative evaluation: CTN 33 pg/ml, negative neck US, negative total body CT scan

January 2008

CTN 46 pg/ml, negative neck US

February 2008

CTN 31 pg/ml, negative neck US

April 2008

CTN 30 pg/ml, negative neck US

How do you manage this patient?

Surgery

Further
diagnostic tests

Follow-up

Clinical case #2



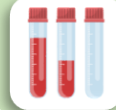
April 2008...we chose for active surveillance but...

Surgery - Central and left latero cervical compartment lymph-node dissection

Histology - 2/2 metastatic lymph nodes of the central compartment (max dim 0.6 cm) and 1/12 metastatic lymph node of the left LC compartment (max dim 0.2 cm)

July 2008

CTN <10 pg/ml, negative neck US



October 2008

Pentagastrin stimulation test for CTN

bCTN <10 pg/ml, peak CTN 42, negative neck US

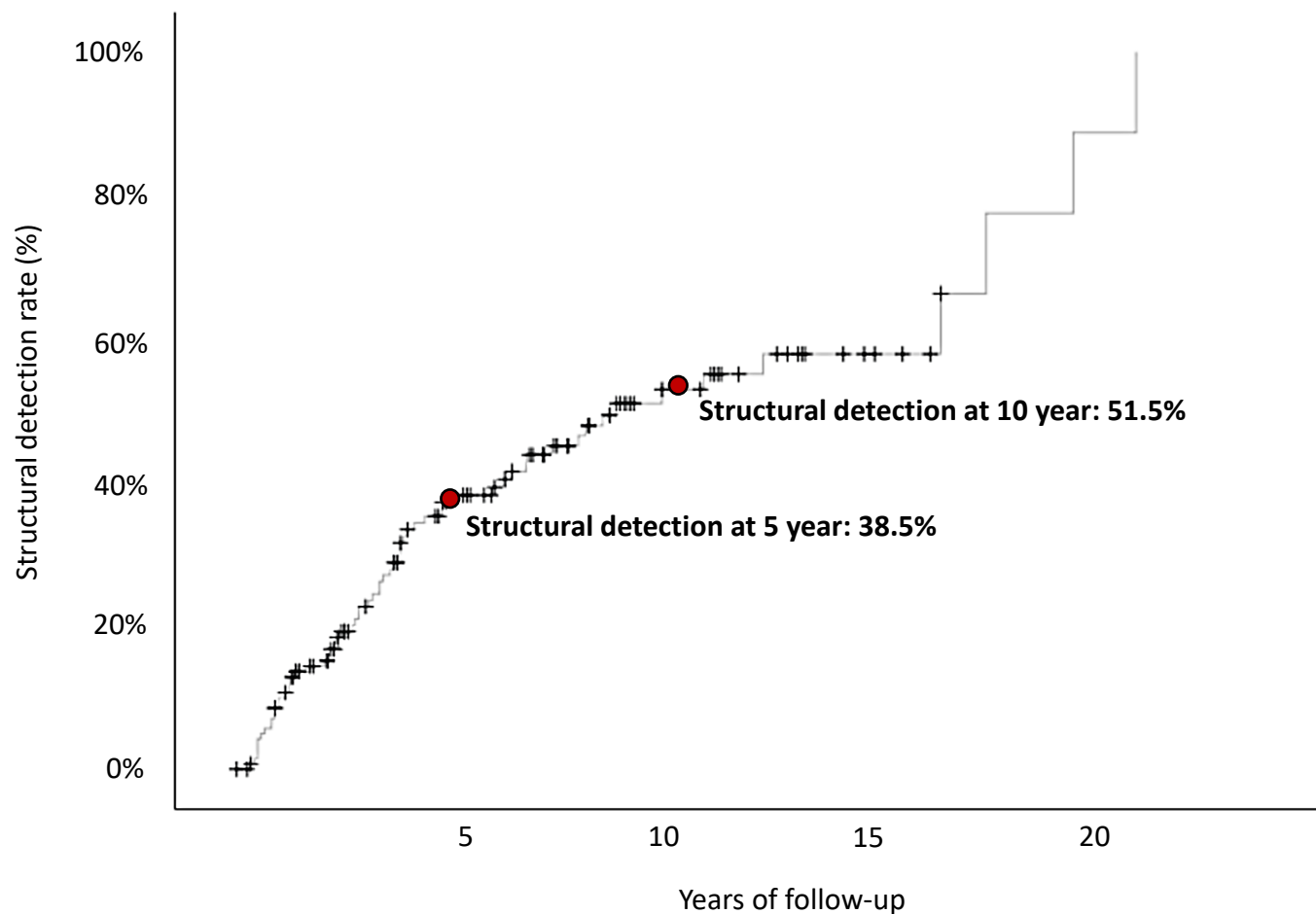
How do you define this patient?

Cured
(excellent response)

Biochemical persistence
of the disease

I don't know
(too less data
available)

Patients with biochemical disease...what we can expect over time

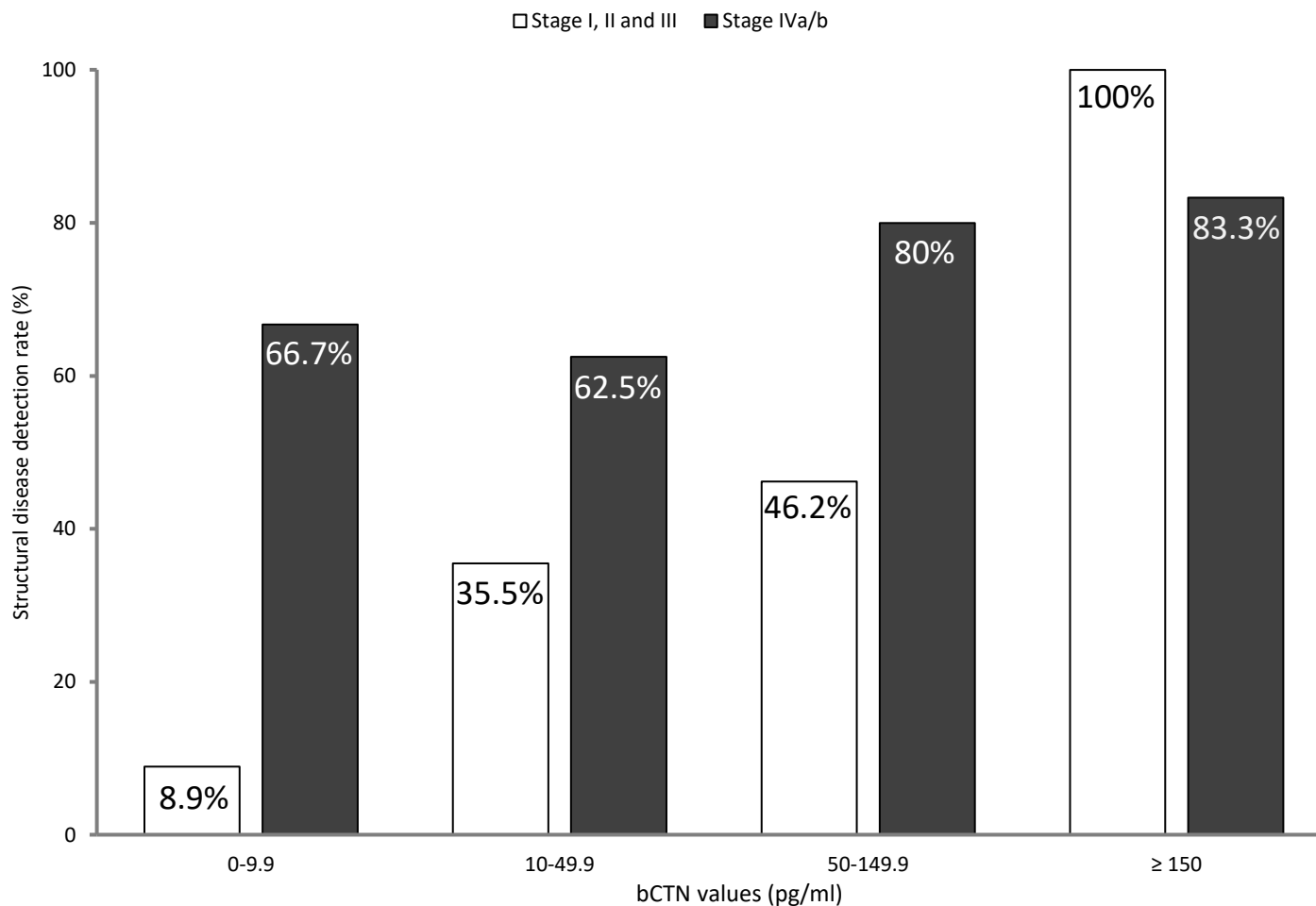


Structural disease was detected in 64/145 (**44.1%**), after a median time of **3.3 years**

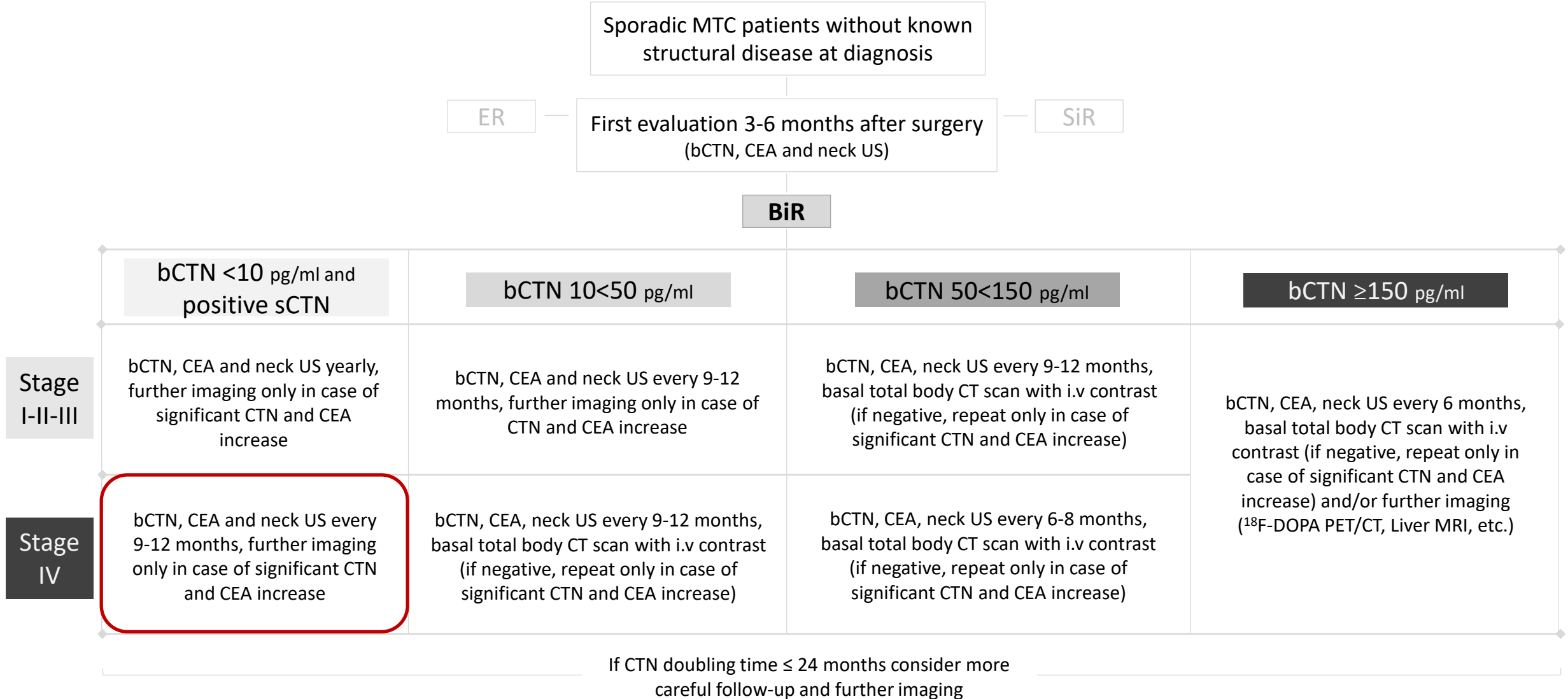
Patients with biochemical disease... factors associated with structural disease detection

		OR	95% CI	p
Sex	Female	1	--	--
	Male	1.624	0.625-4.222	0.484
Stage according to 8 th edition AJCC	I, II and III	1	--	--
	IVa/b	3.311	1.260-8.701	0.015
bCTN (pg/ml)	0-9.9	1	--	--
	10-49.9	2.084	0.705-6.158	0.184
	50-149.9	3.989	1.015-16.153	0.049
	≥ 150	8.612	1.331-55.735	0.024
CTN doubling time	> 24 months	1	--	--
	≤ 24 months	4.131	1.408-12.123	0.010

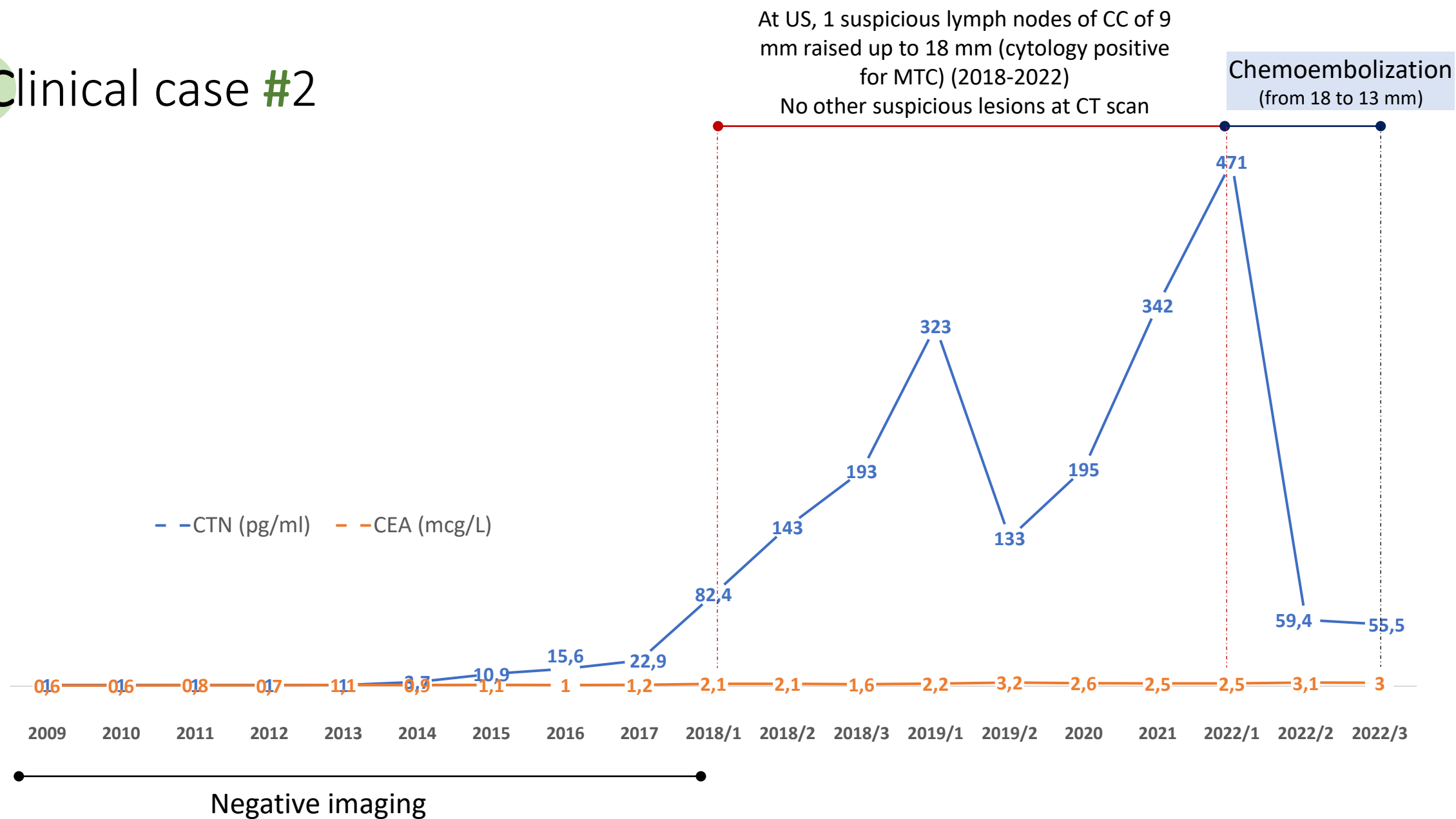
Patients with biochemical disease... factors associated with structural disease detection



Patients with biochemical disease... how to manage...



Clinical case #2



Clinical case #3



Male, 43 years old



March 2011: Morning diarrhea for 1 months, worsened up to 8 times/daily



March 2011: Colonoscopy (negative)

Gastroenterological visit (negative), but at physical examination, occasional finding of a thyroid nodule



Thyroid US: Left thyroid nodule 3.5 cm and multiple homolateral suspicious neck lymph nodes (IV level)



CT scan: Left thyroid nodule 3.5 cm, multiple homolateral neck lymph nodes (IV level).
Lung micronodules highly suspicious for metastases (max diam 0.7 cm)



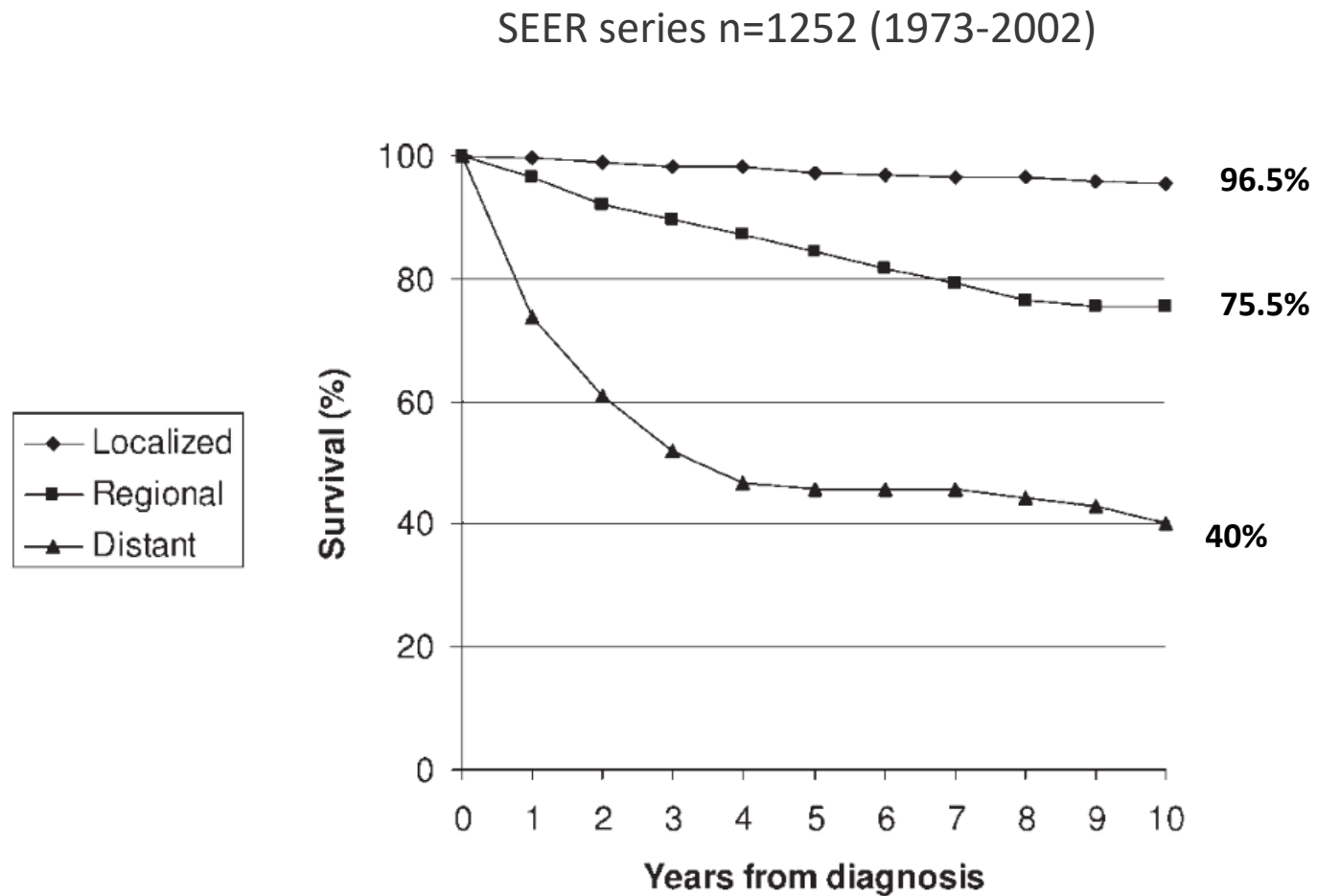
Calcitonin: 1149 pg/ml (< 18.2)



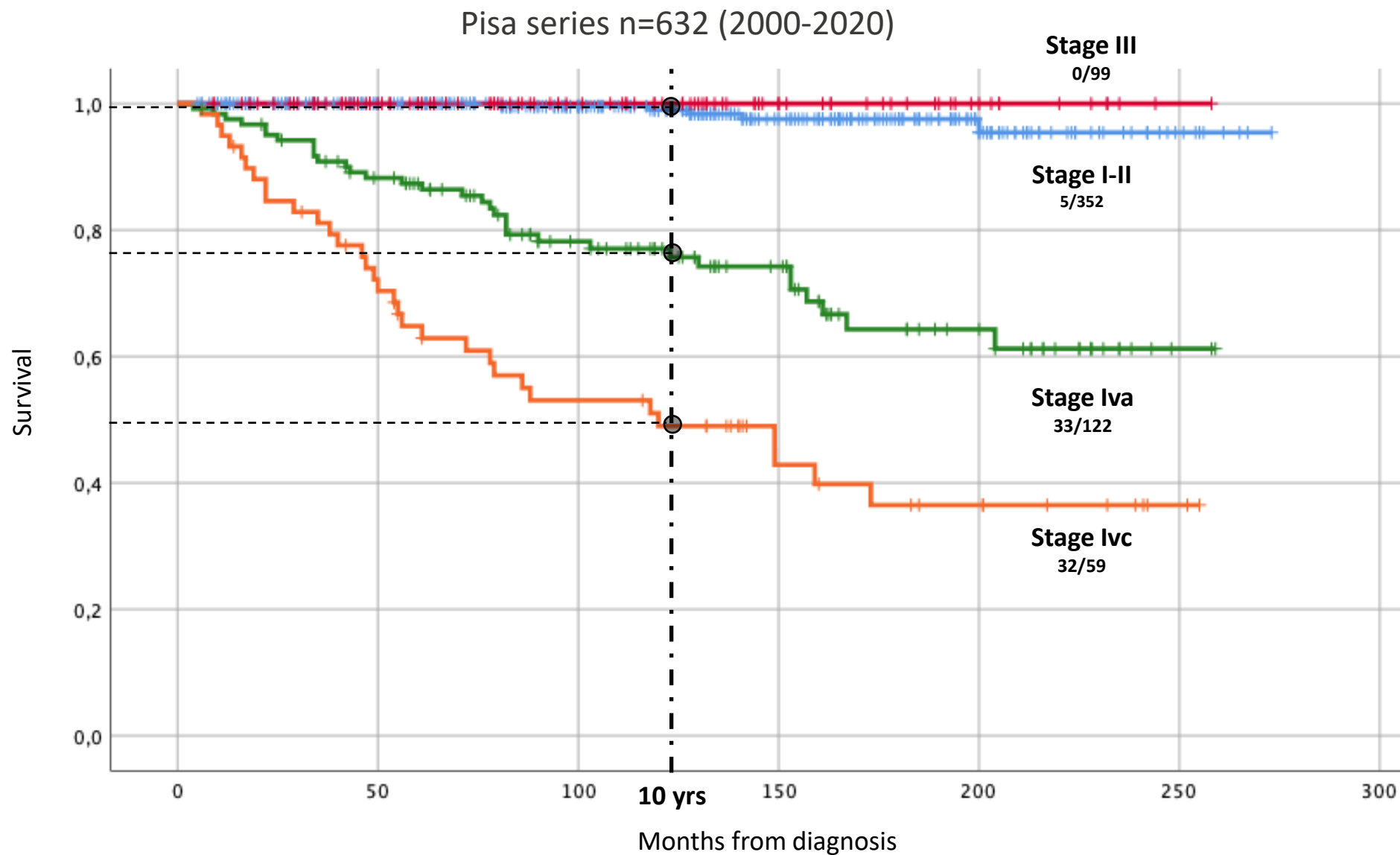
June 2011: Total thyroidectomy plus type II left modified radical neck dissection:

- MTC (3.5 cm), lympho-vascular perineural invasion, soft tissue involvement
- Stage pT4 (for RLN infiltration) pN1b (15/32 metastatic lymph nodes – max diam 3 cm)

Disease specific survival in MTC



Disease specific survival in sporadic MTC



Clinical case #3



July 2011

Post-operative left vocal cord impairment

Tumor markers:

- Calcitonin: 477 pg/mL
- CEA: not performed
- Germline RET mutation: negative



July 2011

Total body CT scan with contrast: Lymph node metastasis (2.5 cm) between common subclavian and carotid artery, in contact with the esophagus.

Mediastinal lymph nodes (max diam 2 cm)



October 2011

Left lymphadenopathy confirmed at neck US (3 cm) and at FNAC (MTC metastasis; CT on washing fluid 20160 pg/ml)

- Calcitonin 360 pg/ml



January 2012

Total body CT scan: Increase of all lymph nodes in the neck and mediastinum (max diam 3.8 cm)

Bronchoscopy: left vocal cord palsy. Compression and submucosal infiltration of the trachea (extension: 2.5 cm)

Esophagoscopy: compression of the right part of the esophagus

Clinical case #3



February 2012

Thoracic surgery with removal of neck and mediastinal lymph nodes through sternal split (10/23 metastatic lymph nodes – max diam 4 cm with ENE)



May 2012

CT scan of the neck and thorax:

- Persistence of lymph nodes metastases in the neck and mediastinum (max diam 4.8 cm) with appearance of liver lesions (max diam 0.9 cm)
- Calcitonin 442 pg/ml; CEA 41.9 ng/ml

How do you manage this patient?

Surgery *a/o* local
therapies

Systemic therapies

Follow-up

Clinical case #3



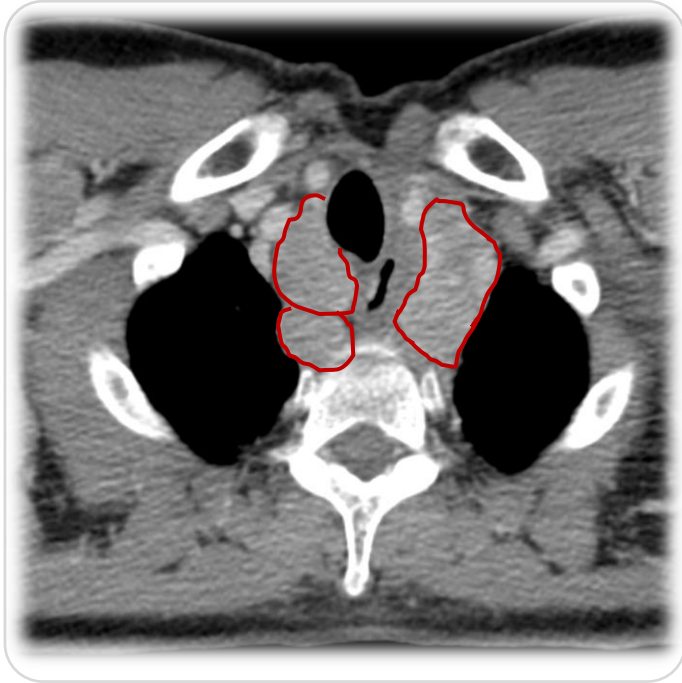
July 2012

RET somatic mutation testing: M918T

Patient was enrolled in the international, randomized, double blind study (NCT01496313) to evaluate the safety and efficacy of two starting doses of vandetanib (150 vs 300 mg/daily) in advanced medullary thyroid cancer patients

Efficacy of the treatment (mediastinal lymph nodes) – Vandetanib 300 mg/daily

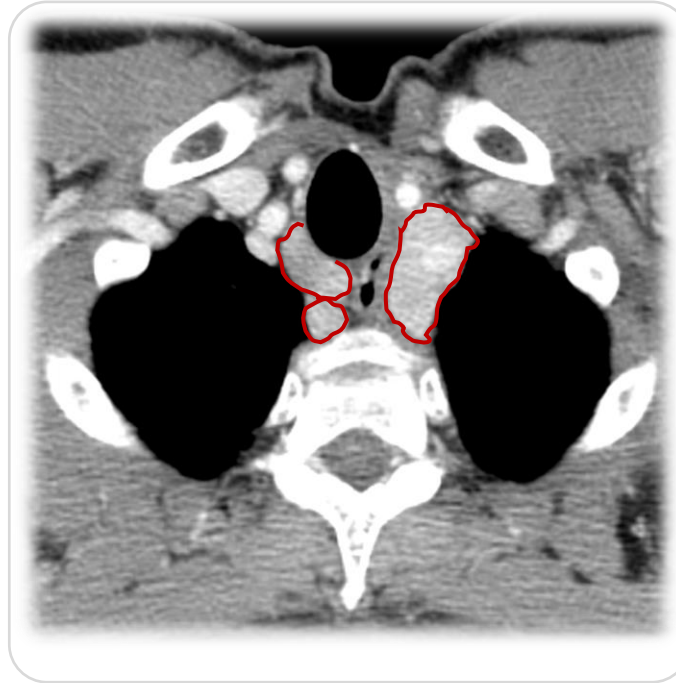
July 2012



Before treatment

CT 560 pg/ml and CEA 48.3 mcg/L

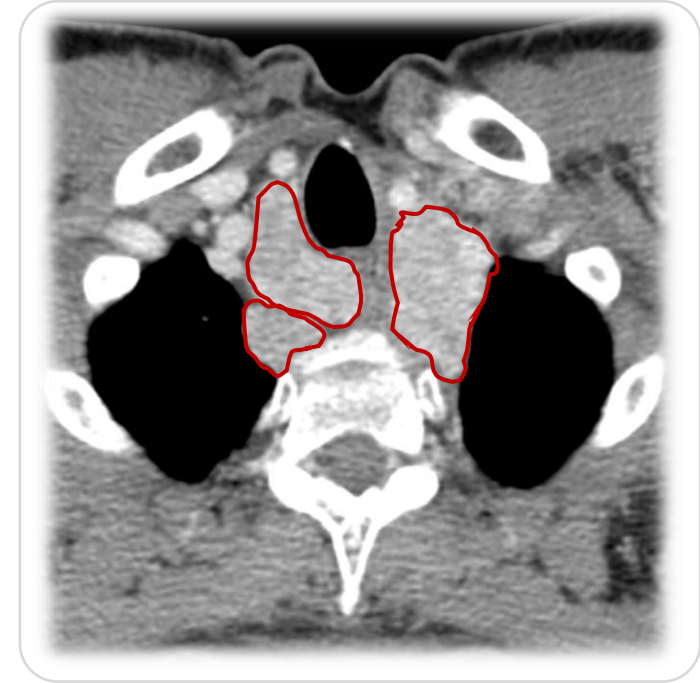
March 2014



Best Response: Partial Response

CT 203 pg/ml and CEA 50.3 mcg/L

October 2016



Progressive Disease

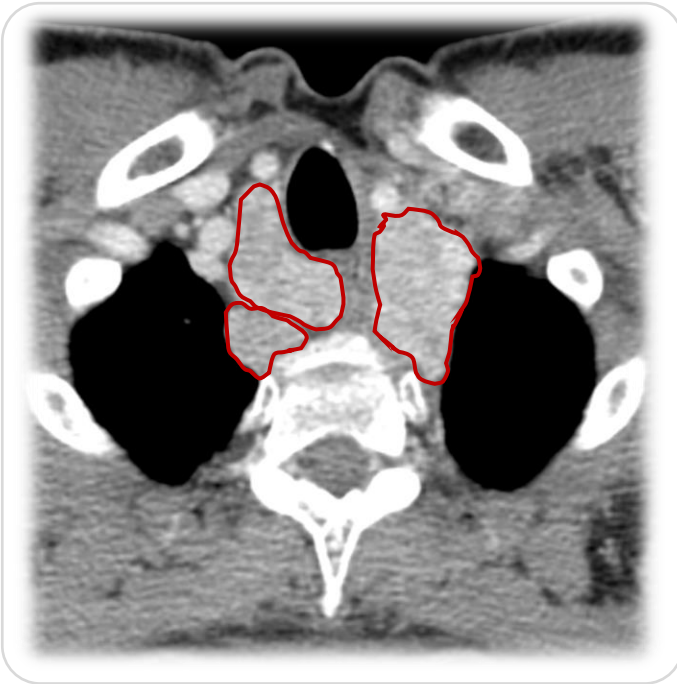
CT 808 pg/ml and CEA 56.1 mcg/L

Manageable AE of Grade 1 and 2

(cutaneous rash, hypertension, increase in AST and ALT, hypothyroidism) – no dose reduction

Clinical case #3

October 2016



Progressive Disease

CT 808 pg/ml and CEA 56.1 mcg/L

How do you manage this patient?

Active surveillance

Surgery a/o
local therapies

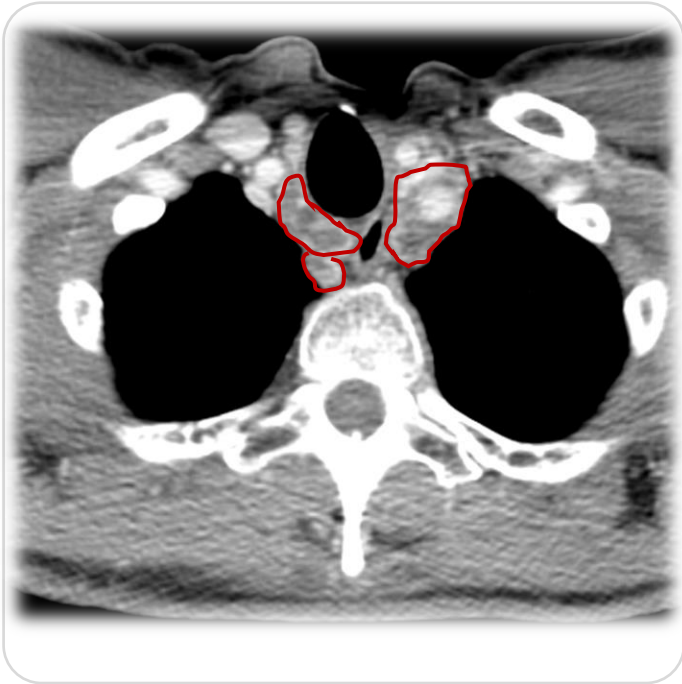
Switch to another
systemic therapies

Second line treatment – Lenvatinib (off-label) 24 mg/daily (starting dose)

February 2017

Lenvatinib 24 mg/daily
after 1 month decreased to 20 mg/daily due
to AEs Asthenia G3, Hypertension G2

April 2017 – CT 448 pg/ml

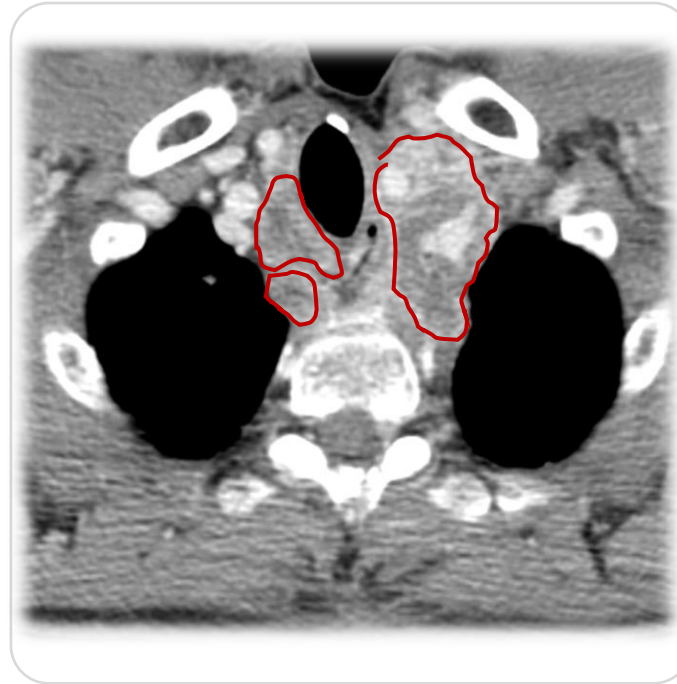


After 2 months of Lenvatinib
Partial Response

October 2018

Lenvatinib 20 mg/daily
Asthenia G1, Hyperthension G1,
Anorexia G1, Diarrhea G2

October 2018 – CT 1054 pg/ml



After 18 months of Lenvatinib
Progressive disease according to RECIST 1.1
in neck lymph nodes

October 2019

Lenvatinib 20 mg/daily
decreased to 14 mg/daily due to
Asthenia G3, Anorexia G2, Diarrhea G2

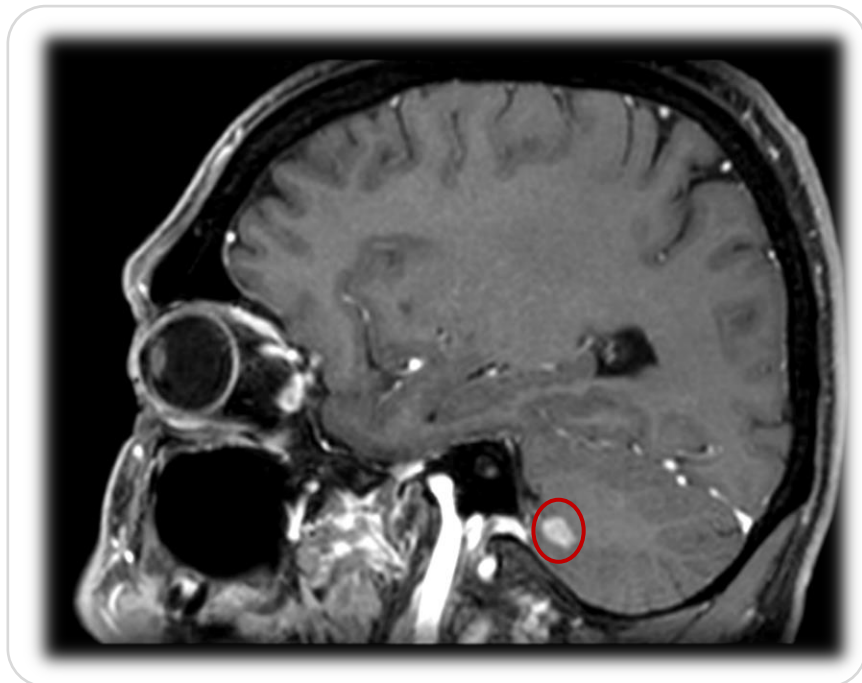
April 2020 – CT 7967 pg/ml



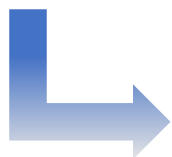
After 36 months of Lenvatinib
Progressive disease according to RECIST 1.1
in lymph nodes, lung, liver and...

And...

April 2020

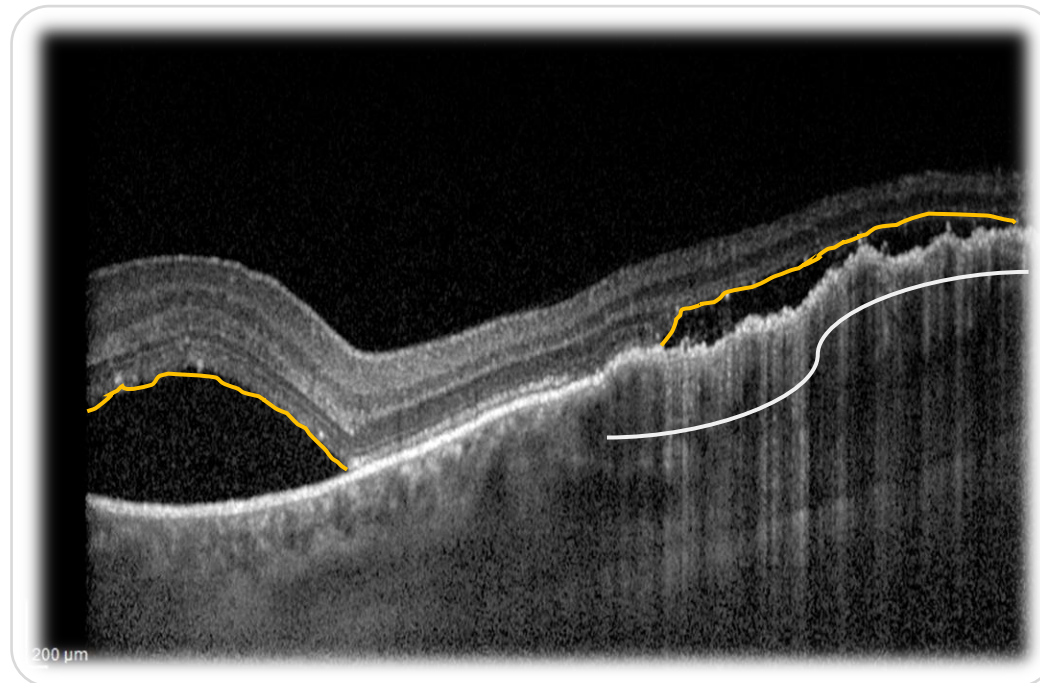


Cerebellar metastases



Radiotherapy

May 2020

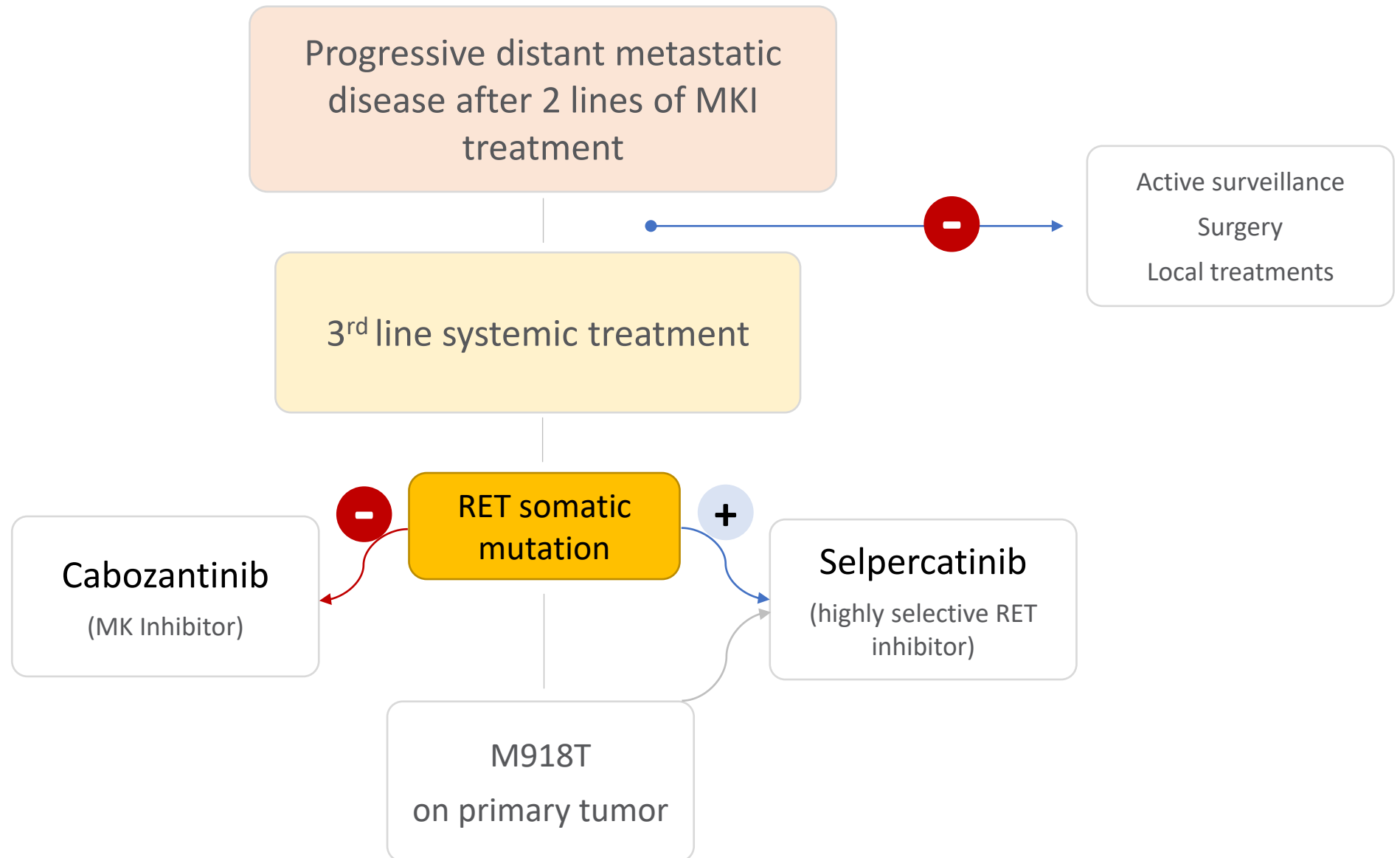


Choroidal metastases with complete visual loss in left eye



No effective therapies
available

Clinical case #3



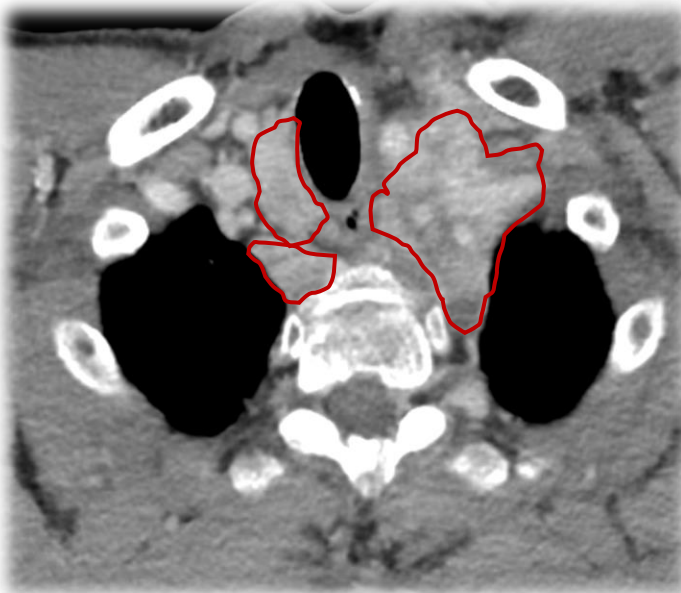
Expanded access program (EAP), Libretto-201 – Selpercatinib 160 mg/BID EFFICACY

June 2020

Selpercatinib at 160 mg BID (EAP)

- Calcitonin: 5191 pg/mL
- CEA: 103.5 ng/mL

August 2020 CT 882 pg/ml



October 2020

C3D1 selpercatinib 160 mg BID

July 2021 – CT 236 pg/ml

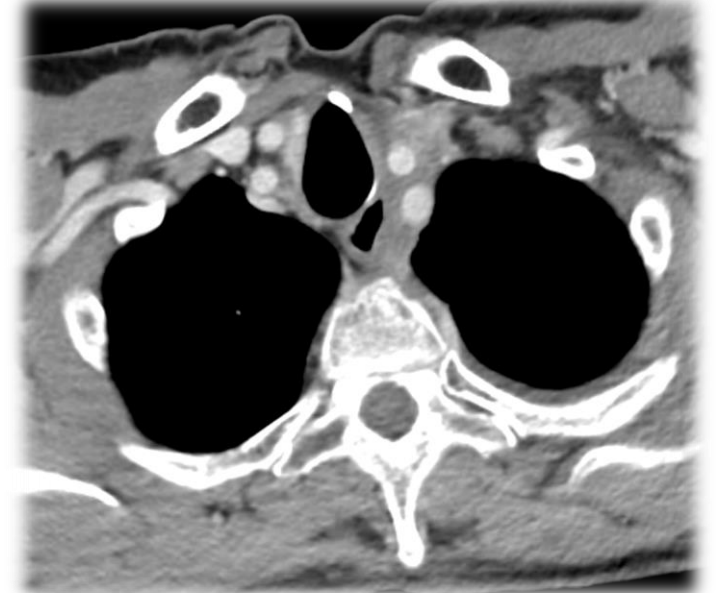


Partial Response

November 2020

Total body CT scan: Partial response in mediastinal lymph nodes and liver lesions

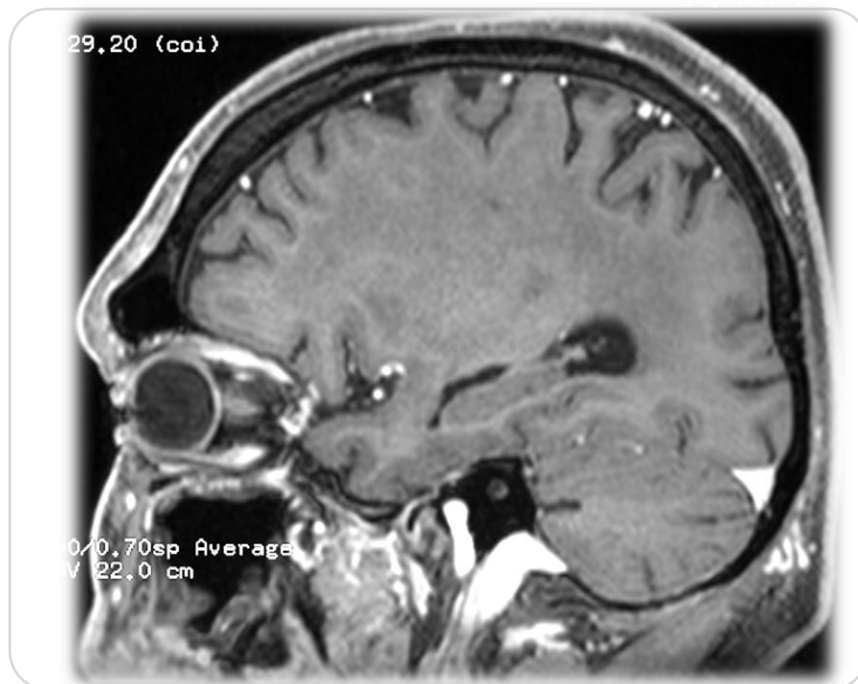
March 2022 – CT 279 pg/ml



Partial response

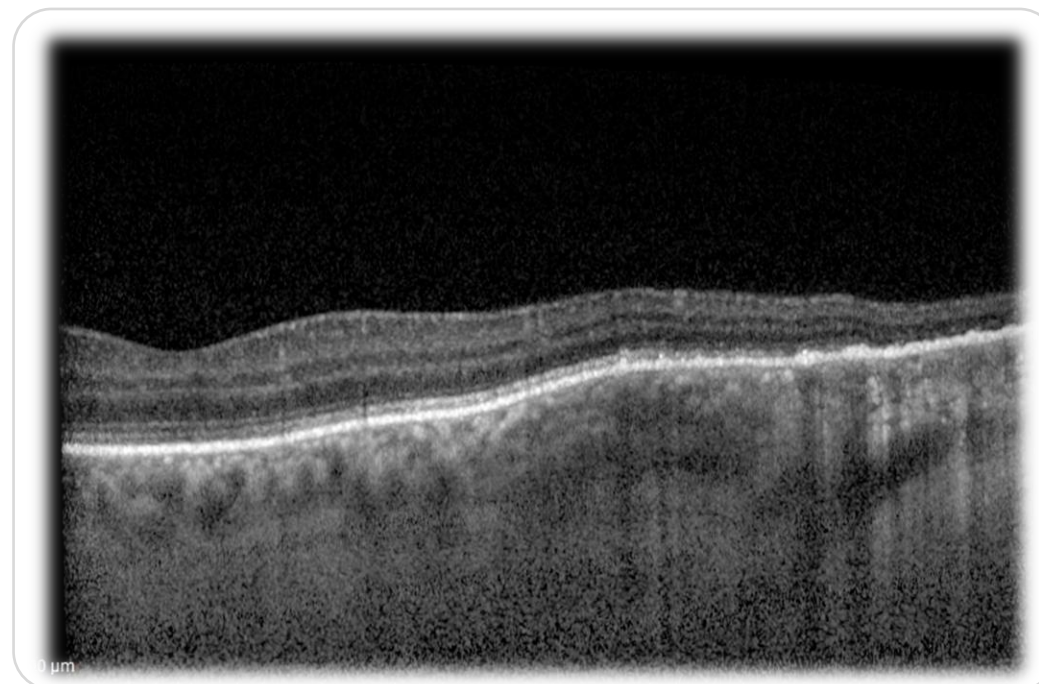
And...

November 2020



Disappearance of cerebellar metastases
confirmed up to March 2022

July 2020



Complete sight rescue and disappearance of choroidal metastases after only 1
month of treatment confirmed up to January 2023

Expanded access program (EAP), Libretto-201 – Selpercatinib 160 mg/BID SAFETY

C1D15

Lymphocyte count decreased (G2), after 1-month → G1
GGT and ALP increased (G1), after 2 months → resolved
Periorbital edema (G1) → ongoing
Localized edema of the ankles (G1) → ongoing

C13D1 (12 months of treatment)

Pleural effusion (G1) → ongoing

C20D1 (19 months of treatment)

Cholecystitis (G2) → ongoing and managed with medical treatment

C22D1 (21 months of treatment)

Selpercatinib 160 mg/BID
Total body CT scan: stable disease but appearance of **chylous ascites (G2)**



Grade 3/4 TRAEs occurring in ≥1%*, n (%) ¹	All patient enrolled (n=746)	
	Grade 3	Grade 4
Patients with ≥1 AE	222 (30)	17 (2)
Hypertension	92 (12)	1 (0.1)
Increased ALT	54 (7)	6 (0.8)
Increased AST	42 (6)	5 (0.7)
Prolonged QT interval	21 (3)	0 (0)
Diarrhea	12 (2)	0 (0)
Fatigue	8 (1)	0 (0)

AE number: IT202204003936

The AE on this slide has been reported to PV via Lilly processes and/or the products complaints organization

¹Modified from: Sherman E, et al. Presented at: 2021 ASCO Annual Meeting (virtual); June 4-8, 2021. Abstract: 6073

Chylous effusions in advanced medullary thyroid cancer patients treated with selpercatinib

*European Journal of
Endocrinology*
(2022) **187**, 905–915

Alessandro Prete¹, Carla Gambale¹, Virginia Cappagli¹, Valeria Bottici¹, Piercarlo Rossi², Marco Caciagli³, Piermarco Papini³, Donatella Taddei⁴, Simona Ortori², Luciano Gabbriellini⁵, Alessandro Celi⁵, Gabriele Materazzi³, Rossella Elisei¹ and Antonio Matrone¹

Table 2 TEAEs (rate $\geq 30\%$) and SAEs reported in the study population.

	CTCAE G1	CTCAE G2	CTCAE G3	CTCAE G4
TEAEs (%)	Lymphopenia (60) Hypoglycaemia (60) Effusions (50) Leukopenia (50) Hyperphosphatemia (40) Hypoalbuminemia (40) Hypocalcaemia (40) Increased bilirubin (40) Periorbital oedema (40) Anaemia (30) Fatigue (30) Neutropenia (30) Transient hyperglycaemia (30)	Lymphopenia (70) Erectile dysfunction (42)* Leukopenia (40) Hypocalcaemia (40) Effusions (30) Hypoalbuminemia (30)	Lymphopenia (40)	Lymphopenia (10)**
SAEs (%)	Bone fracture (20), neoplastic cachexia (20), respiratory insufficiency (20), acute acalculous cholecystitis (10), acute kidney failure (10), bilateral inguinal hernioplasty (10), deep venous thrombosis (10), dyspnoea (10), intestinal ischaemia (10), pericardial effusion (10), pneumonia (10), pulmonary embolism (10), QT prolongation (10).			

*Reported rate is only for males; **Reported rate is $<30\%$ as it is the only grade 4 TEAE.

SAEs, serious adverse events; TEAEs, treatment emergent adverse events.

Selpercatinib

Chylous effusions



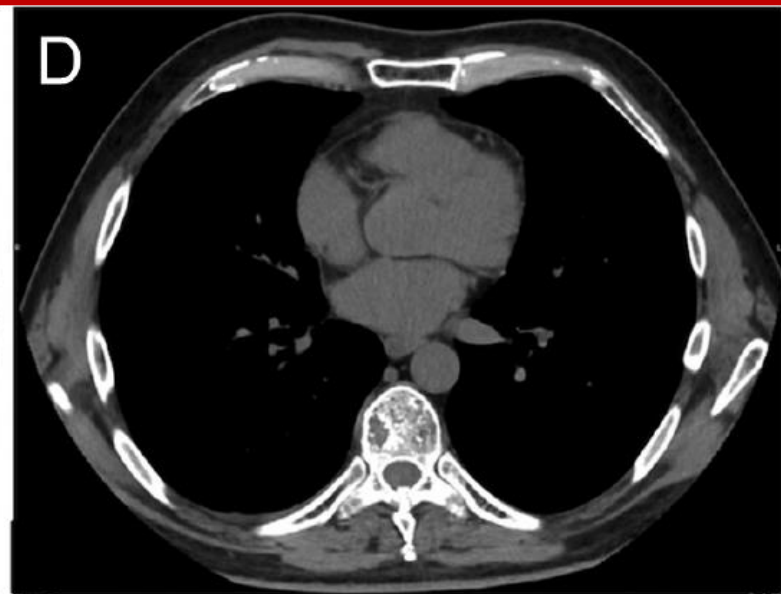
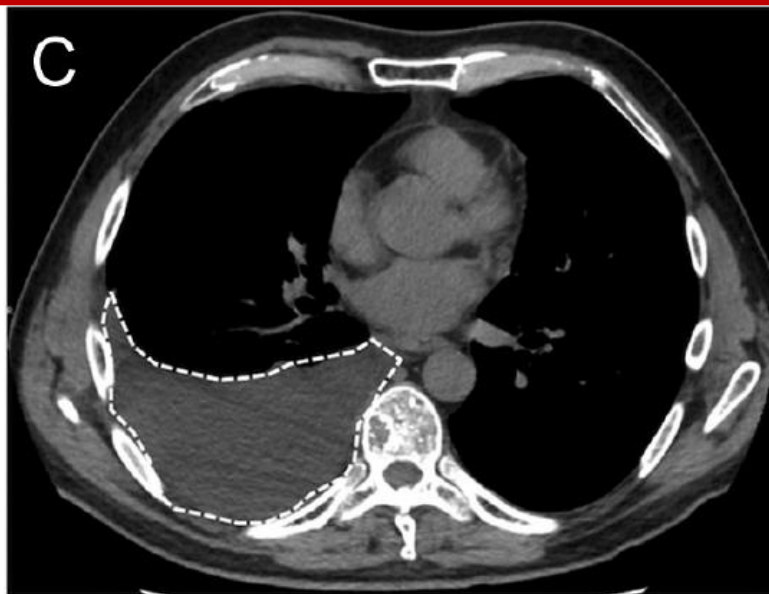
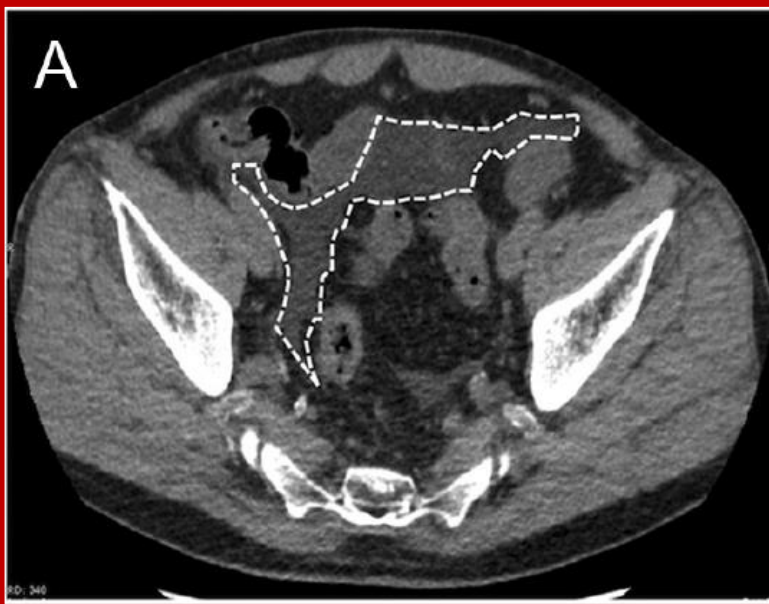
C25D1 (24 months of treatment)

Selpercatinib 120 mg/BID
Total body CT scan: stable disease,
disappearance of chylous ascites
Absence of new TEAEs



C32D1 (31 months of treatment)

Selpercatinib 120 mg/BID
Total body CT scan: stable disease
Absence of new TEAEs



160 mg/BID (full dosage)

120 mg/BID (dose -1)

Conclusions



New
diagnostic
tools



Rethinking
surgical treatment
in low risk cases



Several drugs
for the
advanced cases



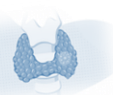
New highly
selective
inhibitors



Improving the
knowledge and
moving forward



Development of
new and more
selective drugs



Neo-adjuvant
treatments

Cure the disease

Thank you
for your
attention

- anto.matrone@yahoo.com
- antonio.matrone@med.unipi.it