



Surgical strategies for patients with MEN1

Wednesday, 29 January 2025, 18:00 – 19:10 CET

Disclosure Statement

Maria Luisa BRANDI (Moderator) has the following potential conflicts of interest to disclose:

- ***Receipt of grants/research support:***
Alexion, Amgen, Amolyt, Bruno Farmaceutici, CoGeDi, Echolight, Gedeon Richter, Kyowa Kirin, Monte Rosa Therapeutics, UCB
- ***Receipt of honoraria or consultation fees:***
Amgen, Ascendis, Kyowa Kirin, Aboca, Alexion, Amolyt, Bruno Farmaceutici, Calcilytix, Echolight, Enterabio, Personal Genomics, Septerna
- ***Participation in a company-sponsored speaker's bureau:***
Alexion, Amgen, Amolyt, Bruno Farmaceutici, CoGeDi, Echolight, Gedeon Richter, Kyowa Kirin, Monte Rosa Therapeutics, UCB

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- ✓ **This webinar is intended for HCPs qualified by law to prescribe medicine.**
- ✓ UEMS accreditation: the webinar is accredited **with 1 CME point**.
 - ✓ *Participants must complete a feedback form*

Live poll question: Getting to know the audience

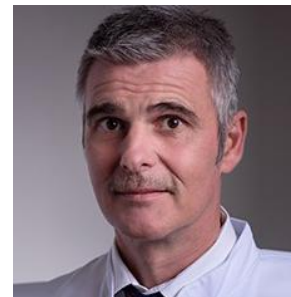
In which medical discipline are you trained or currently working?

Tonight's faculty



Maria Luisa BRANDI

Italian Foundation for Research on
Bone Diseases (FIRMO Foundation),
Italy
Endocrinology



Detlef BARTSCH

Department of Visceral, Thoracic,
and Vascular Surgery, Philipps
University Marburg, Germany
Endocrine and Pancreatic Surgery



Menno VRIENS

Department of Surgical Oncology,
University Medical Center Utrecht,
The Netherlands
Endocrine Surgery



Pier Luigi FILOSSO

Department of Thoracic Surgery,
University of Modena and Reggio
Emilia, Italy
Thoracic Surgery

Tonight's agenda

Moderator: **Maria Luisa BRANDI, ITA**

18:00 – 18:05 Opening – **Maria Luisa BRANDI, ITA**

18:05 – 18:20 Parathyroid – **Detlef BARTSCH, GER**

18:20 – 18:35 Duodenal pancreas – **Menno VRIENS, NED**

18:35 – 18:50 Thymic / lung surgery – **Pier Luigi FILOSSO, ITA**

18:50 – 19:05 Panel discussion

19:05 – 19:10 Closing – **Maria Luisa BRANDI, ITA**



MEN1-pHPT – Surgical strategies

Detlef K. Bartsch

Department of Visceral, Thoracic and Vascular Surgery

Philipps-University Marburg, Germany

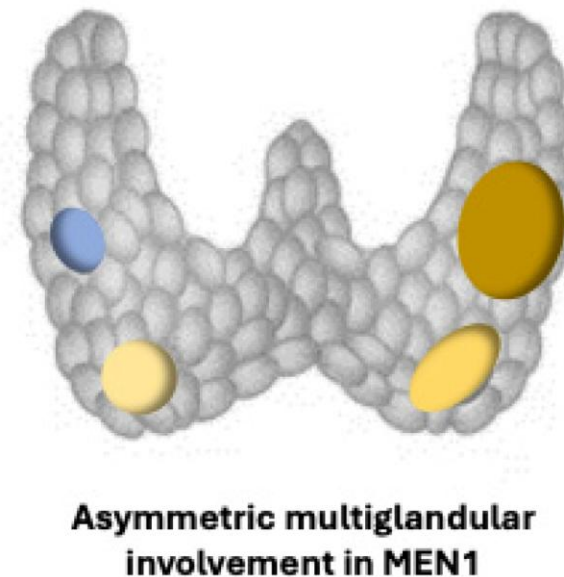
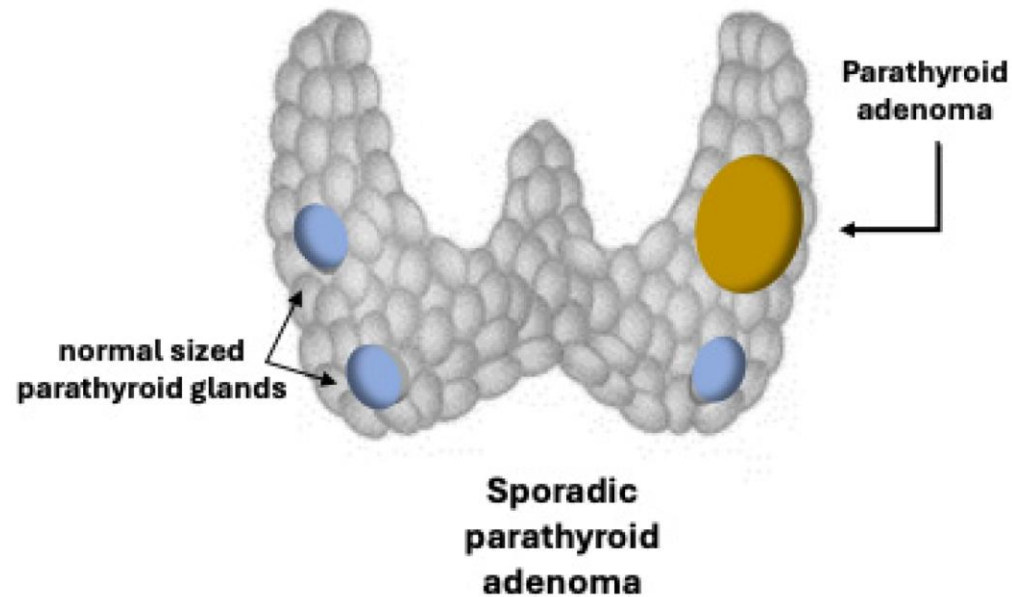
DISCLOSURES

I have no conflicts/disclosures to declare

MEN1-pHPT

characterised by:

- an asymmetric multiglandular disease
- supernumerary glands in 12-30% of patients
- early diagnosis based on screening



Goals of surgery in MEN1-pHPT

- Correct hypercalcaemia
- Avoid permanent hypoparathyroidism
- Minimise the risk for recurrence
- Avoid re-operations

Timing of index operation

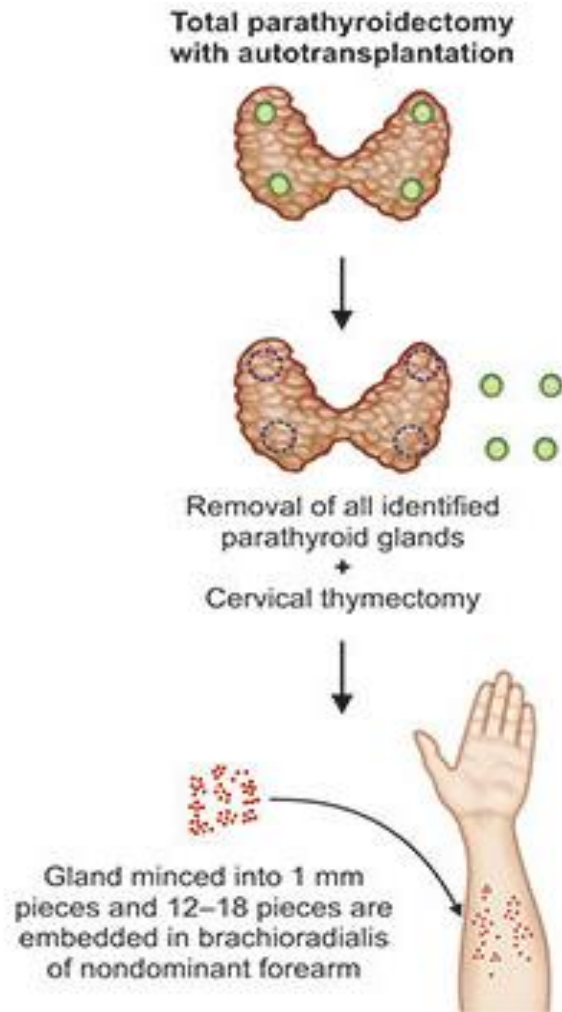
Pieterman et al., Delphi-Consensus, in preparation

- PTX can be delayed in patients without evidence of target organ involvement (e.g. low BMD, kidney stones)
- PTX is indicated in patients who are symptomatic or have evidence of target organ involvement
- PTX in asymptomatic adults is indicated, if total calcium levels are consistently above >1 mg/dl (>0.25 mmol/L) above the upper limit of the normal value

Possible index operations

- Total parathyroidectomy (TPTX)
- Subtotal parathyroidectomy (SPTX)
- Unilateral clearance
- Focused parathyroidectomy

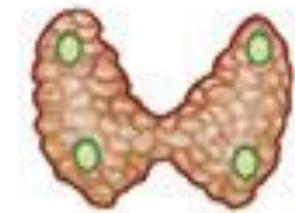
Total Parathyroidectomy (TPTX)



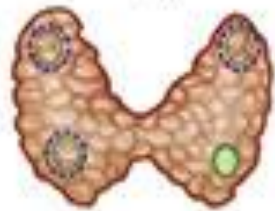
Subtotal Parathyroidectomy (SPTX)

Subtotal parathyroidectomy

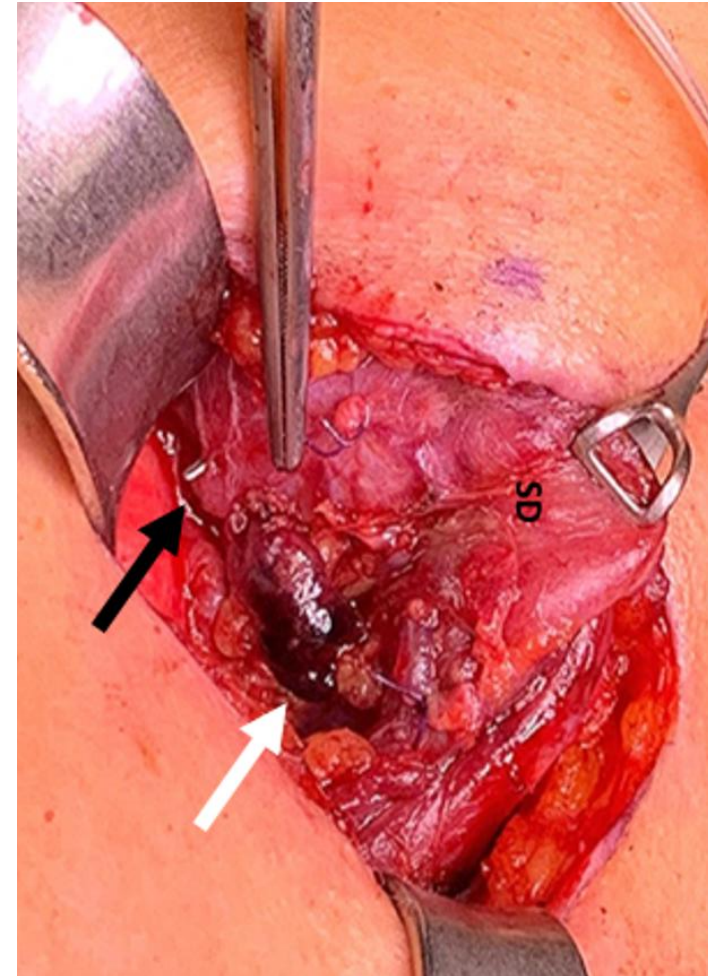
OF



Hyperplasia of
four glands



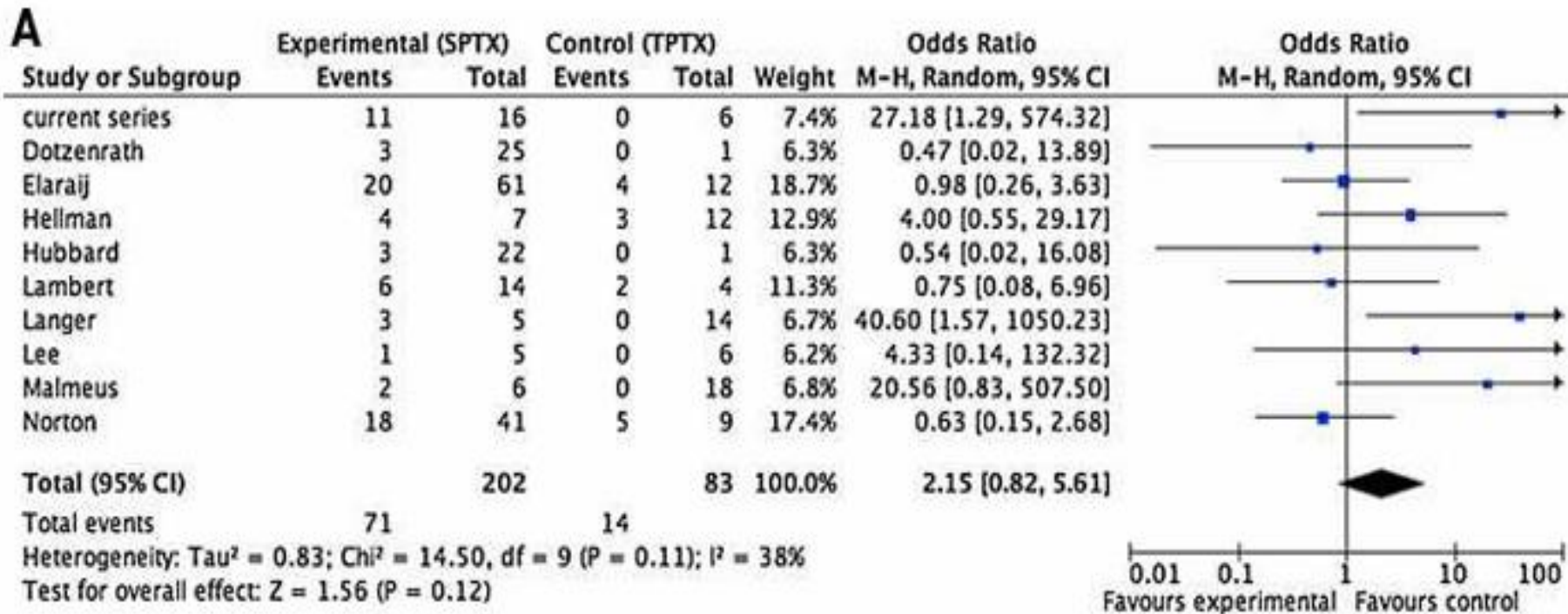
Removal of three
glands intact and
50–75% removal
of 4th gland
+
Cervical thymectomy



SPTX vs. TPTX – Recurrence

Schreinemakers et al. WJS 2011

Systematic review of 10 studies with 240 patients



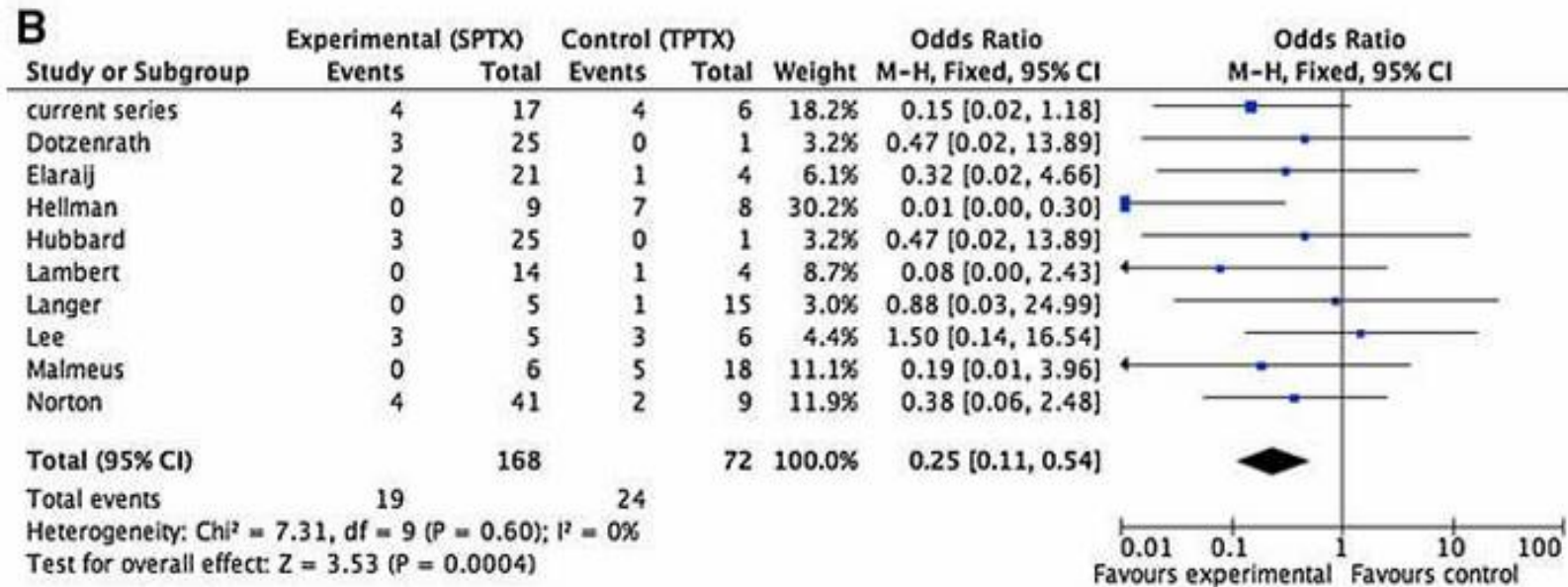
Recurrence rate TPTX 4-18% vs. SPTY 10-33%

➡ SPTX has no higher risk for recurrence (OR = 2.15, $p = 0.12$)

SPTX vs. TPTX – permanent hypoparathyroidism

Schreinemakers et al. WJS 2011

Systematic review of 10 studies with 240 patients



Hypoparathyroidism rate: SPTX 16/168 → 9.5%, TPTX 24/72 → 33.3%, $p=0.0004$

➡ SPTX has a lower risk for hypoparathyroidism than TPTX

TPTX vs. SPTX – Results

Manoharan et al., Clin. Endocrinol. 2020

Studies with more than 30 MEN1 patients

Reference	No. patients	Median follow-up (months)	Patients with persistence	Patients with recurrence	Median recurrence-free interval (months)	Patients with permanent postoperative hypoparathyroidism
Fyrsten et al ¹⁸	TPTX: 8 SPTX: 30	TPTX: 234 SPTX: 155	TPTX: 1/8 (12.5%) SPTX: 2/30 (6.7%)	TPTX: 2/8 (25%) SPTX: 8/30 (26.7%)	TPTX: ND SPTX: 100	TPTX: 5/8 (62.5%) SPTX: 0/30 (0%)
Pieterman et al ²⁸	TPTX: 32 SPTX: 23	51.6	TPTX: 6/32 (19%) SPTX: 4/23 (17%)		TPTX: 36 SPTX: 36	TPTX: 21/32 (66%) SPTX: 9/23 (39%)
Elaraj et al ¹⁷	TPTX: 13 SPTX: 58	73.2	ND	TPTX: 3/13 (23%) SPTX: 19/58 (33%)	TPTX: 130.8 SPTX: 62.4	TPTX: 6/13 (46%) SPTX: 15/58 (26%)
Tonelli et al ²¹	TPTX: 28 SPTX: 9	141.6	TPTX: 0/28 (0%) SPTX: 0/9 (0%)	TPTX: 4/28 (14%) SPTX: 2/9 (22%)	TPTX: 128 SPTX: 84	TPTX: 5/28 (18%) SPTX: 2/9 (22%)
Horiuchi et al ¹⁶	TPTX: 12 SPTX: 21	135	TPTX: 0/12 (0%) SPTX: 0/21 (0%)	TPTX: 2/12 (16.7%) SPTX: 11/21 (52.4%)	ND	TPTX: 3/12 (25%) SPTX: 1/21 (4.8%)
Montenegro et al ¹³	TPTX: 39 SPTX: 22	ND	TPTX: 2 (5.1) SPTX: 3 (13.6)	TPTX: 2 (5.1) SPTX: 1 (4.5)	ND	TPTX: 11 (28.2) SPTX: 3 (13.6)
Present study	TPTX: 38 SPTX: 23	112	TPTX: 1 (2.6%) SPTX: 0 (0%)	<u>TPTX: 4 (4.4%)</u> <u>SPTX: 9 (10.1%)</u>	TPTX: 204 SPTX: 139	<u>TPTX: 12/38 (32%)</u> <u>SPTX: 4/23 (17%)</u>

Abbreviations: ND, no data; SPTX, subtotal parathyroidectomy with bilateral cervical thymectomy; TPTX, total parathyroidectomy with autotransplantation with bilateral cervical thymectomy.

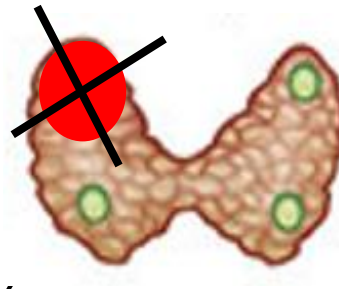
TPTX was abandoned due to the high hypopara rate (18-66%)

Less than SPTX

Preconditions:

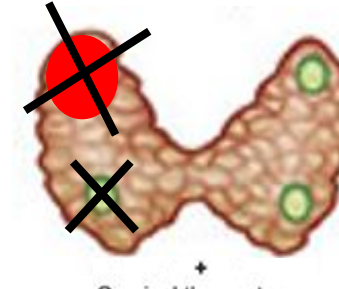
- dominant lesion identified preoperatively by imaging
- adequate drop in IOPTH after PTX

(focused PTX

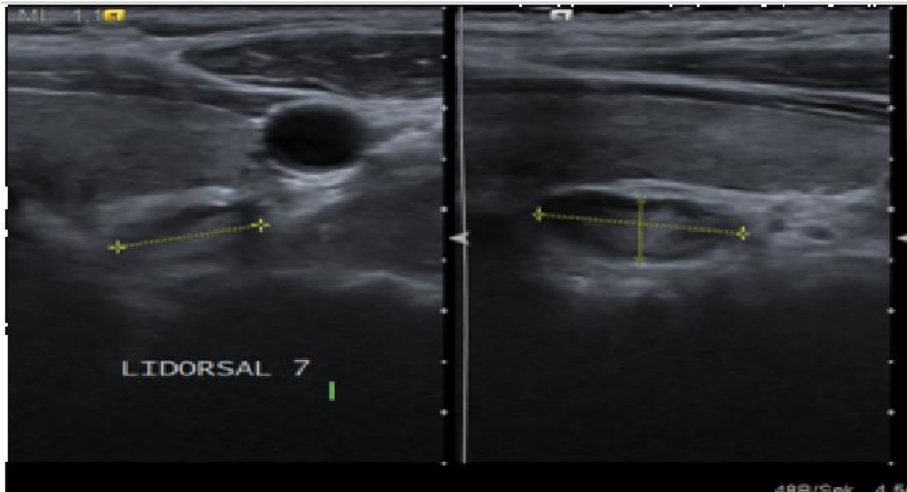


or

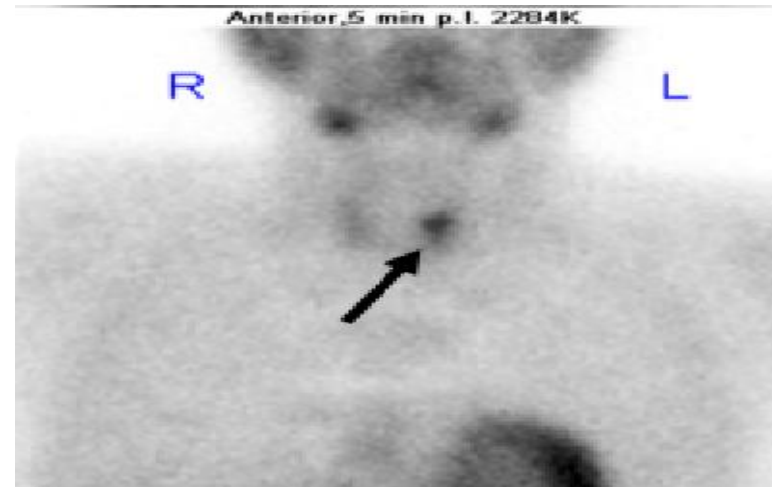
unilateral clearance)



+
Cervical thymectomy



Ultrasonography – 1 enlarged parathyroid



99Tc-MIBI-Szintigraphy – 1 positive gland

<SPTX vs. SPTX – recurrence rate

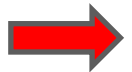
Bouriez et al., World J Surg 2022

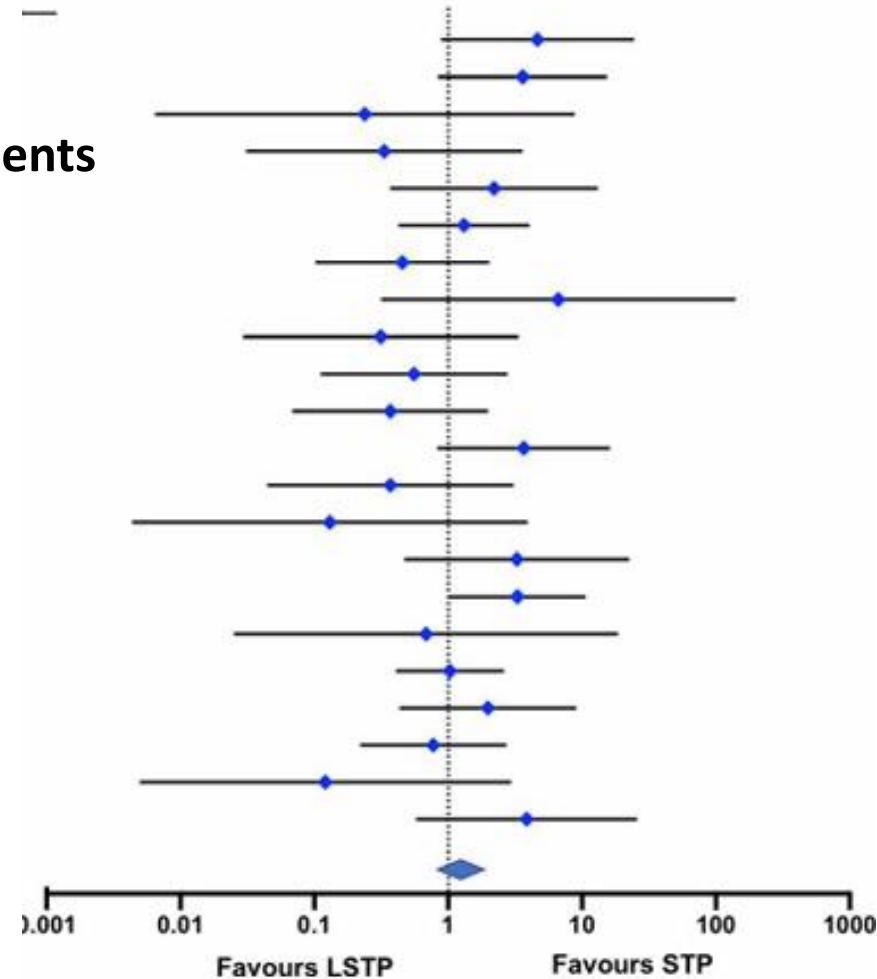
Meta-analysis of 22 studies with 814 MEN1 patients

Recurrence rate:

- <SPTX 127/342 → 37.1 %
- SPTX 124/472 → 26.3 %

OR 1.26, 95%CI 0.83–1.9, $p=0.18$

 No difference



<SPTX vs. SPTX – perm. Hypoparathyroidism

Bouriez et al., World J Surg 2022

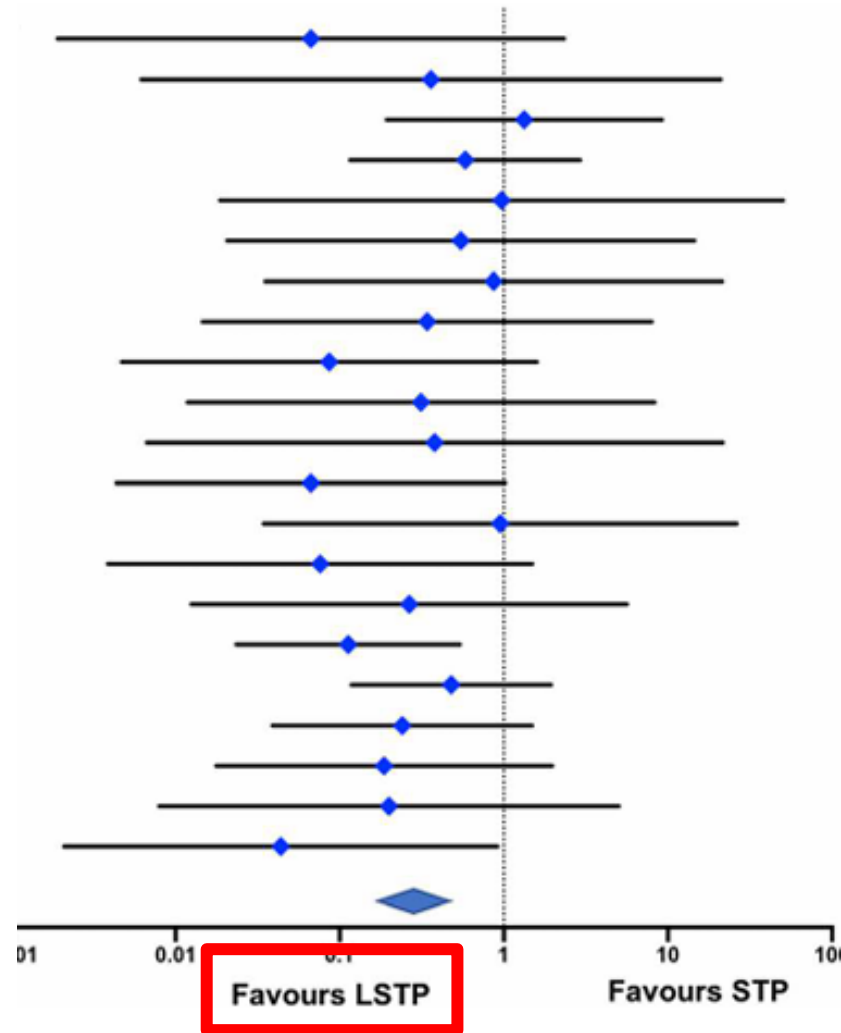
Meta-analysis of 21 studies with 747 patients

Rate perm. hypoparathyroidism

- <SPTX 15/338 → 4.4%
- SPTX 82/410 → 20%

OR 0.29, CI 95% 0.17–0.49, $p < 0.05$

 Hypopara 3x lower after <SPTX



<SPTX vs. SPTX – recurrence rate

Santucci et al., Ann Surg 2024

	Overall (n = 517); n (%)	Less Than Subtotal (n = 178); n (%)	Subtotal (n = 339); n (%)	P
Sex				
Male	230 (44.5)	77 (43)	153 (45)	0.684
Female	287 (55.5)	101 (57)	186 (55)	—
Median age at pHPT diagnosis; yr (Q1–Q3)*	36.2 (25–48)	36.4 (25–49)	36.1 (25–46)	0.743
Median age at first pHPT surgery; yr (Q1–Q3)	37.7 (27–49)	37.0 (26–50)	37.9 (28–48)	0.580
Median time between pHPT diagnosis and first pHPT surgery; mo (Q1–Q3)	6.2 (1.5–30.0)	3.5 (0.2–15.0)	8.2 (2.3–41.0)	<0.001
MEN1 diagnosis before first pHPT surgery				
Yes	370 (71.6)	103 (42)	267 (79)	<0.001
No	147 (28.4)	75 (58)	72 (21)	—
Median follow-up; mo (Q1–Q3)	113 (56–173)	103 (49–165)	119 (63–177)	0.5661
Recurrence				
Yes	275 (53.2)	122 (68.5)	153 (45)	<0.001
No	242 (46.8)	56 (31.5)	186 (55)	—
Persistent pHPT				
Yes	43 (8.3)	32 (18)	11 (3.2)	<0.001
No	474 (91.7)	146 (82)	328 (96.8)	—
Hypoparathyroidismafter 6 mo†	83 (16.0)	6 (3.4)	77 (22.7)	<0.001
Hypoparathyroidism after 12 mo†	70 (13.5)	4 (2.3)	66 (19.5)	<0.001

 Recurrence rate significantly higher after <SPTX

Selective gland excision vs. SPTX

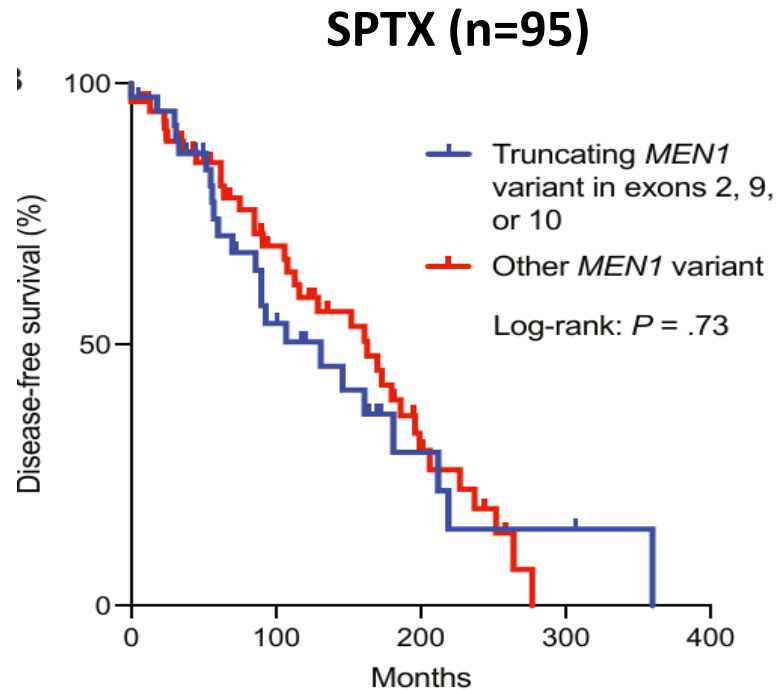
Manoharan et al., Clin. Endocrinol. 2020

Initial procedure	No. of patients	Patients with persistence (%)	Patients with recurrence (%)	Recurrence-free interval months (range)	Patients with permanent hypoparathyroidism n (%)	No. of reoperation for persistent/recurrent disease n (%)
All procedures	89	5 (5.6)	32 (36)	113.5 (0-396)	16 (18)	24 (27)
SGE	28	4 (14.2)	19 (21.3)	101 (3-301)	0 (0)	17 (60.7)
SPTX	23	0 (0)	9 (10.1)	139 (28-278)	4 (17)	4 (17)
TPTX	38	1 (2.6)	4 (4.4)	204 (75-396)	12 (32)	3 (11)

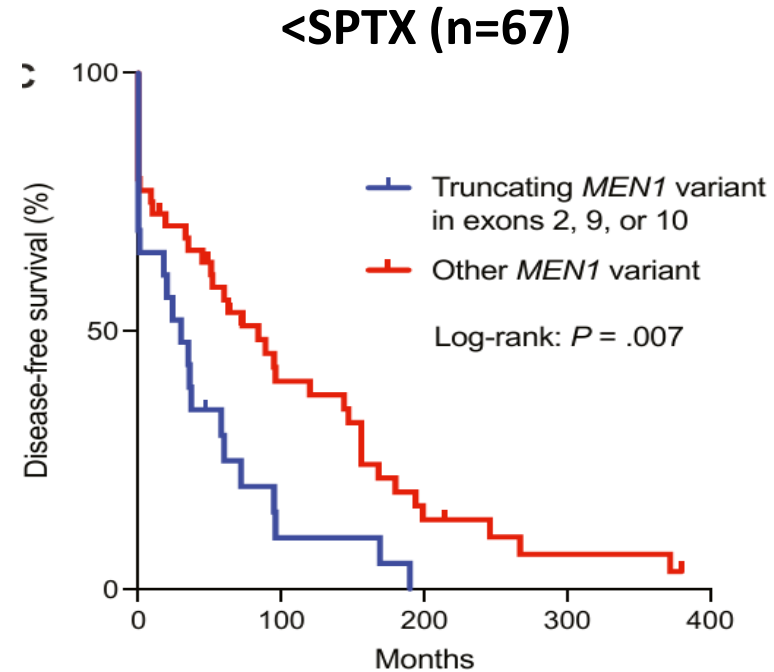
 **SGE is a valid option for selected MEN1-patients**

Genotype / Phenotype MEN1-pHPT

Shariq et al., Surgery 2024



Hypoparathyroidism 7 (7%)



6 (9%)



no <SPTX in pat. with trunc. mutations in exon 2, 9, 10

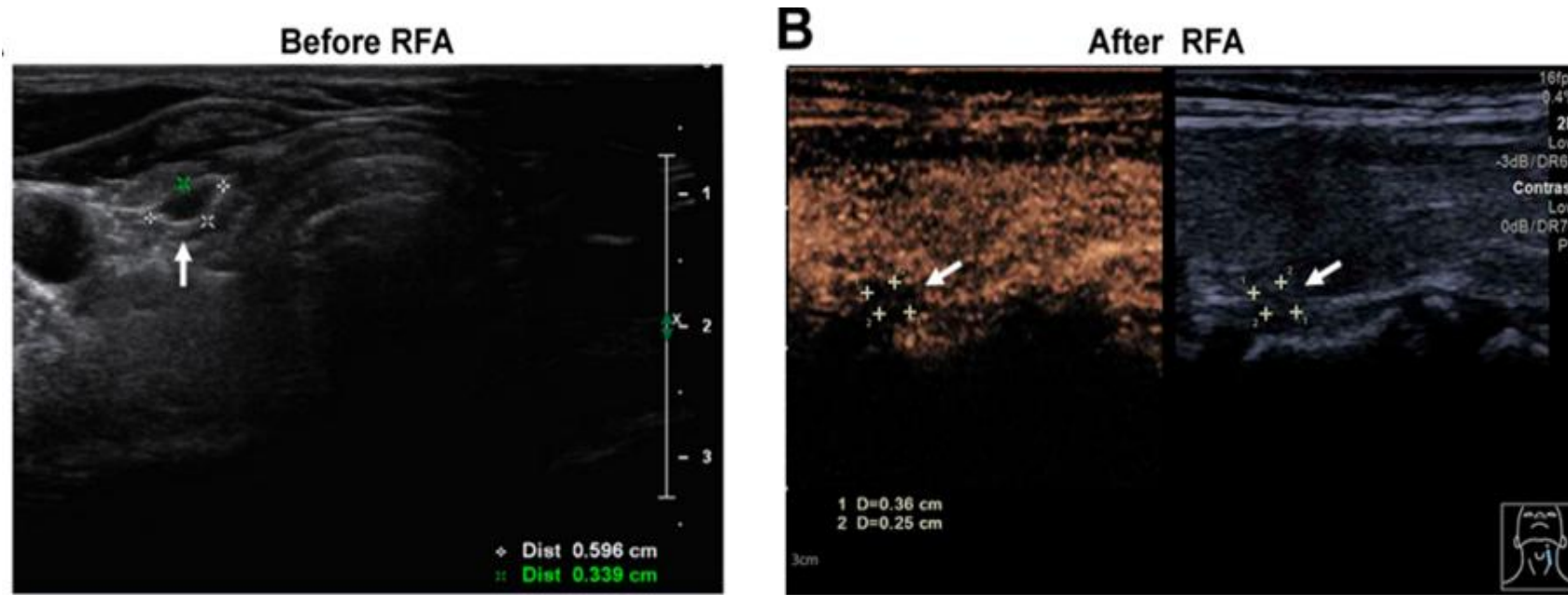
Which type of index operation?

Pieterman et al., Delphi-Consensus, in preparation

- SPTX with concomitant transcervical thymectomy is the recommended index operation
- In selected cases, unilateral clearance can be considered
- Operation should be performed by an experienced surgeon

MEN1-pHPT – Alternatives to surgery?

- Ultrasound-guided microwave ablation – only case reports
- Ultrasound-guided radiofrequency ablation – only case reports



Han et al., Diagnostics 2023

 US-guided ablation has to be considered experimental!

Conclusions

- Mild hypercalcaemia is more favourable than permanent hypoparathyroidism
- Tailored surgical strategies (SPTX or unilateral clearance) should be applied
- MEN1-pHPT should be treated in tertiary referral centres
- A RCT comparing SPTX vs. unilateral clearance is warranted



Thank you for your attention!

Surgical strategies for MEN1 patients with dpNETS

Menno R. Vriens, MD, PhD, FACS

Professor of Endocrine Surgical Oncology

University Medical Center Utrecht, The Netherlands

DISCLOSURES

I have no conflicts/disclosures to declare

Multiple endocrine neoplasia type 1 (MEN1)

2-3 per 100.000 persons

Autosomal dominant tumour syndrome

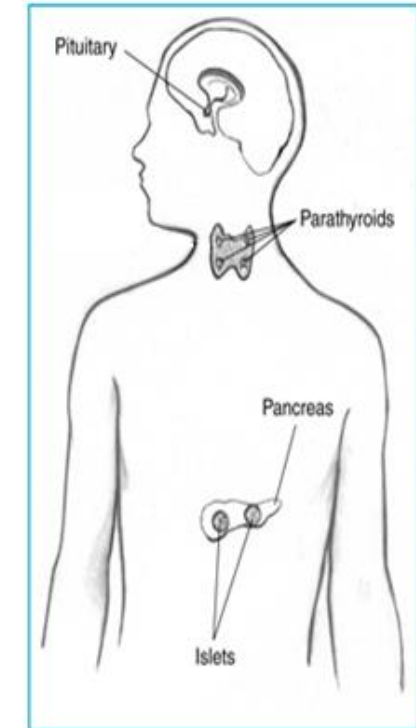
Mutation *MEN1* tumour suppressor gene

Classis triade:

Primary hyperparathyroidism (87%)

Neuro-endocrine tumours duodenum/pancreas (dpNETs) (56%)

Pituitary adenomas (44%)



Chandrasekharappa, S. C. *et al.* Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science* **276**, 404–7 (1997).

de Laat, J. M. *et al.* MEN1 redefined, a clinical comparison of mutation-positive and mutation-negative patients. *BMC Med.* **14**, 182 (2016).

Multiple endocrine neoplasia type 1 (MEN1)

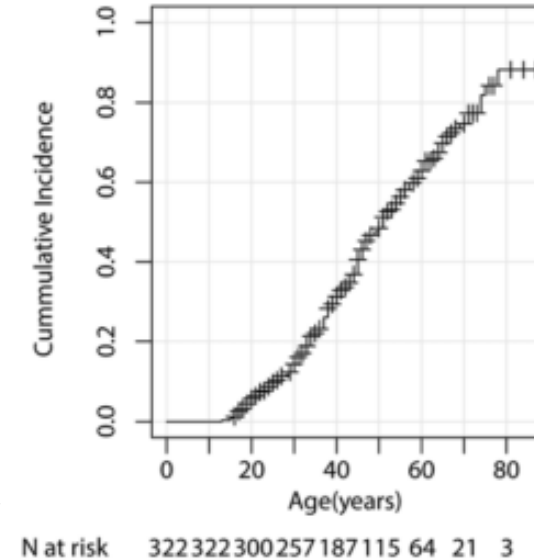
Penetrance >80% by age of 80

Multiple tumours

Major cause of death

Screenings program

Treatment indication based on size/functionality



de Laat, J. M. *et al.* MEN1 redefined, a clinical comparison of mutation-positive and mutation-negative patients. *BMC Med.* **14**, 182 (2016).

Jensen, R. T., Inherited pancreatic endocrine tumor syndromes: Advances in molecular pathogenesis, diagnosis, management, and controversies. *Cancer* **113**, 1807–1843 (2008).

Brandi, M. L. *et al.* Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J. Clin. Endocrinol. Metab.* **86**, 5658–71 (2001).

Thomas-Marques, L. *et al.* Prospective endoscopic ultrasonographic evaluation of the frequency of nonfunctioning pancreaticoduodenal endocrine tumors in patients with MEN1. *Am. J. Gastroenterol.* **101**, 266–73 (2006).



BJS, 2022, 109, 872–879

<https://doi.org/10.1093/bjs/znac006>

Advance Access Publication Date: 14 July 2022

Original Article

Life expectancy and likelihood of surgery in multiple endocrine neoplasia type 1: AFCE and GTE cohort study

Sébastien Gaujoux^{1,2,3,*} , Guillaume L. Martin^{4,5}, Eric Mirallié⁶ , Nicolas Regenet⁶, Maëlle Le Bras⁷, François Pattou⁸, Bruno Carnaille⁸, Catherine Cardot-Bauters⁹, Lionel Groussin¹⁰, Matthieu Faron¹¹, Philippe Chanson¹² , Haythem Najah¹³, Antoine Tabarin¹⁴ , Alain Sauvanet¹⁵, Philippe Ruzsiewicz¹⁶, Jean-Christophe Lifante¹⁷, Thomas Walter¹⁸, Nicolas Carrère¹⁹, Philippe Caron²⁰, Sophie Deguelte²¹, Brigitte Delemer²² , Christine Binquet^{23,24}, Anne Sophie Jannot^{4,5} and Pierre Goudet^{25,26,27}

Conclusion: Life expectancy was significantly lower among patients with MEN1 compared with the general population, and further decreased in patients with mutations affecting the *JunD* interacting domain. Almost all patients underwent at least one MEN1-specific operation during their lifetime, but there was no standardized sequence of surgery.

Dutch MEN 1 Study Group (unpublished data); lifetime probability of dpNET surgery

Results: On a total of 445 patients with MEN1, 124 resections were performed. 109 patients (24.5%) underwent at least one resection for dpNET, 13 patients underwent two resections and one patient three resections. The most frequently performed resections were a distal pancreatectomy (n=62, 50%) and in 73 patients (=58.9%), the resections were performed for NF-pNET. An incidence of 5.49 surgeries per 1000 MEN1 patients each year was calculated. The estimated probability of undergoing a resection at age 60 was 29.2% indicating that the resection free survival was estimated to be 69.8%. At 60 years the major resections make up for the biggest part of the performed resections, with a 19.2% estimated probability of undergoing a distal pancreatectomy, Whipple/PPPD 4.6% and total pancreatectomy 4.0%.

MEN 1 related PNETS

- NF-PNETS
- Gastrinomas
- Insulinomas

Recommendation for best practice

(Brandi...Thakker et al, 2025)

- MEN1-associated NF-PanNET $\leq 2\text{cm}$, surgery showed no benefit compared to active surveillance
- Imaging intervals should be individualised and based on observed growth rate and absolute size
- MRI remains the best imaging study

Metastatic Potential and Survival of Duodenal and Pancreatic Tumors in Multiple Endocrine Neoplasia Type 1

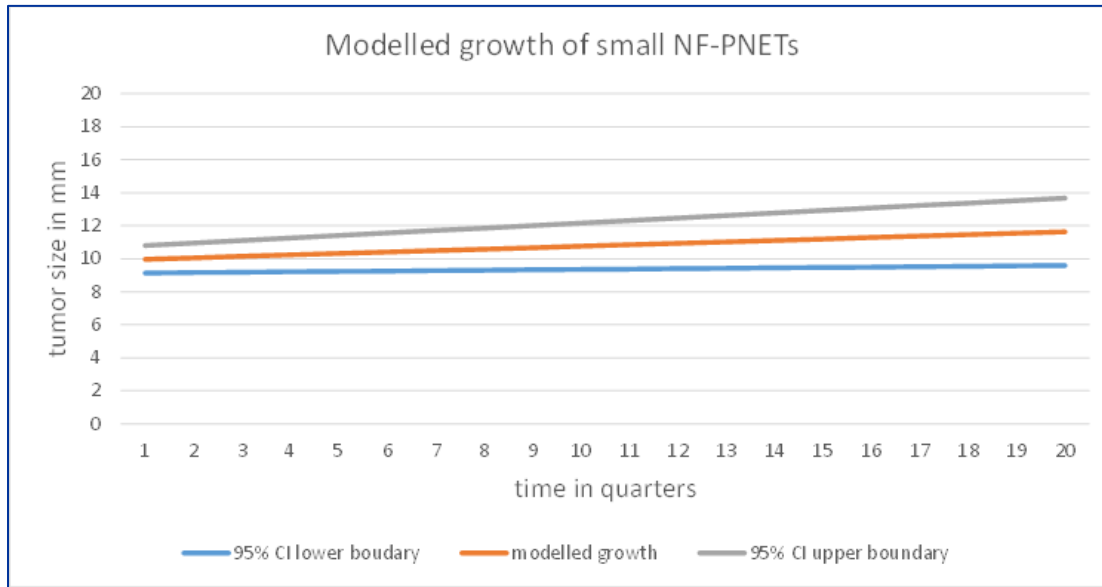
A GTE and AFCE Cohort Study (Groupe d'étude des Tumeurs Endocrines and Association Francophone de Chirurgie Endocrinienne)

Sandrine Vinault, PhD,*†‡§ Anne-Sophie Mariet, MD, PhD,*†¶ Maëlle Le Bras, MD,|| Eric Mirallié, MD,**
 Catherine Cardot-Bauters, MD,†† François Pattou, MD, PhD,†† Philippe Ruzniewski, MD, PhD,§§
 Alain Sauvanet, MD,¶¶ Philippe Chanson, MD,|||| Eric Baudin, MD, PhD,*** Dominique Elias, MD, PhD,†††
 Fabrice Menegaux, MD, PhD,††† Sébastien Gaujoux, MD, PhD,§§§ Françoise Borson-Chazot, MD, PhD,¶¶¶
 Jean-Christophe Lifante, MD, PhD,||||| Philippe Caron, MD,**** Nicolas Carrère, MD, PhD,††††
 Antoine Tabarin, MD, PhD,†††† Christophe Laurent, MD, PhD,§§§§ Marc Klein, MD, PhD,¶¶¶¶
 Laurent Brunaud, MD, PhD,||||||| Patricia Niccoli, MD, PhD,***** Frédéric Sebag, MD,†††††
 Guillaume Cadiot, MD, PhD,††††† Reza Kianmanesh, MD, PhD,§§§§§ Maxime Luu, MD,¶¶¶¶¶|||
 Christine Binquet, MD, PhD,*†‡§ and Pierre Goudet, MD, PhD†§*****

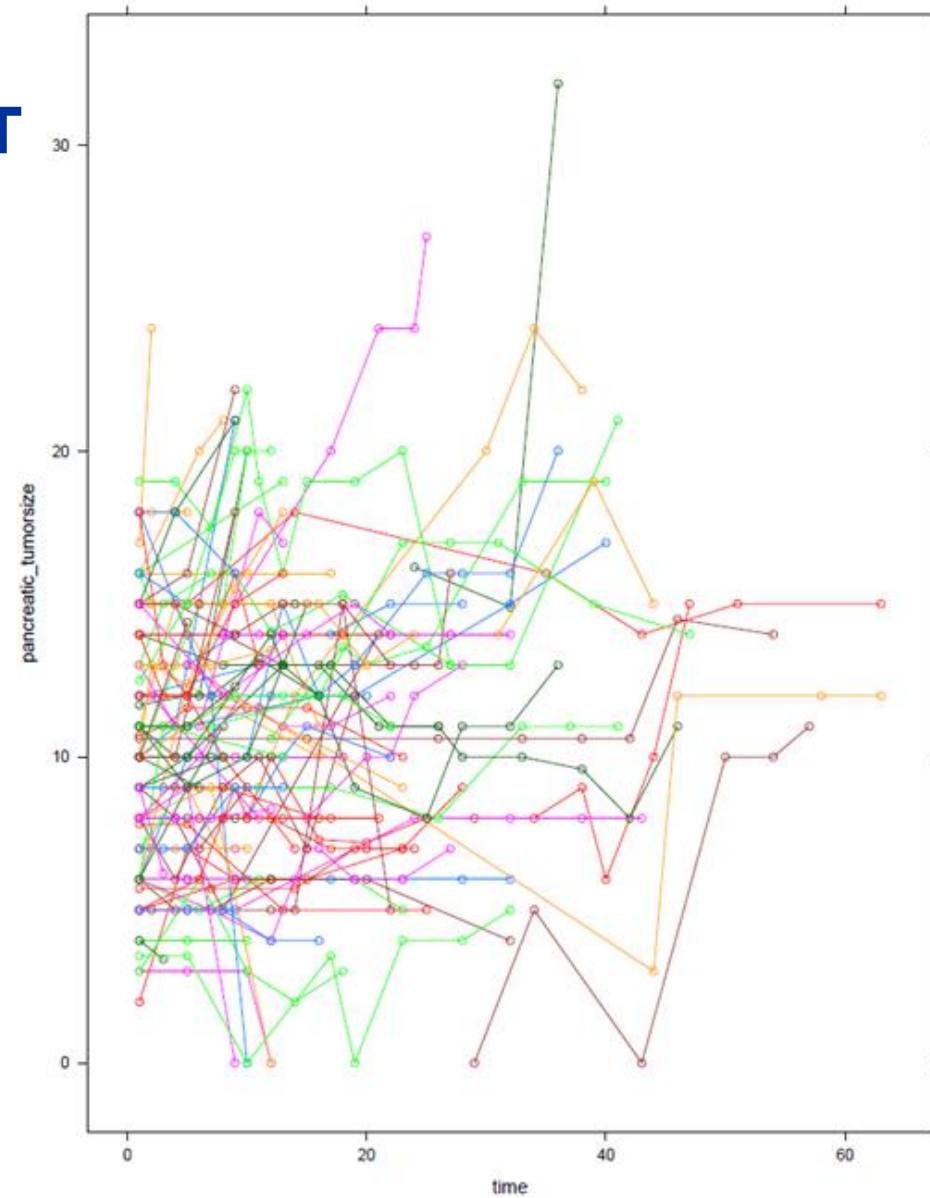
Results: Among the 603 patients included, 39 had metastasis at diagnosis of DP-NET, 50 developed metastases during follow-up, and 69 died. The Markov model showed that Zollinger-Ellison-related tumors (regardless of tumor size and thymic tumor pejorative impact), large tumors over 2 cm, and age over 40 years were independently associated with an increased risk of metastases. Men, patients over 40 years old and patients with tumors larger than 2 cm, also had an increased risk of death once metastasis appeared.

Conclusions: DP-NETs of 2 cm in size or more, regardless of the associated secretion, should be removed to prevent metastasis and increase survival. Surgery for gastrinoma remains debatable.

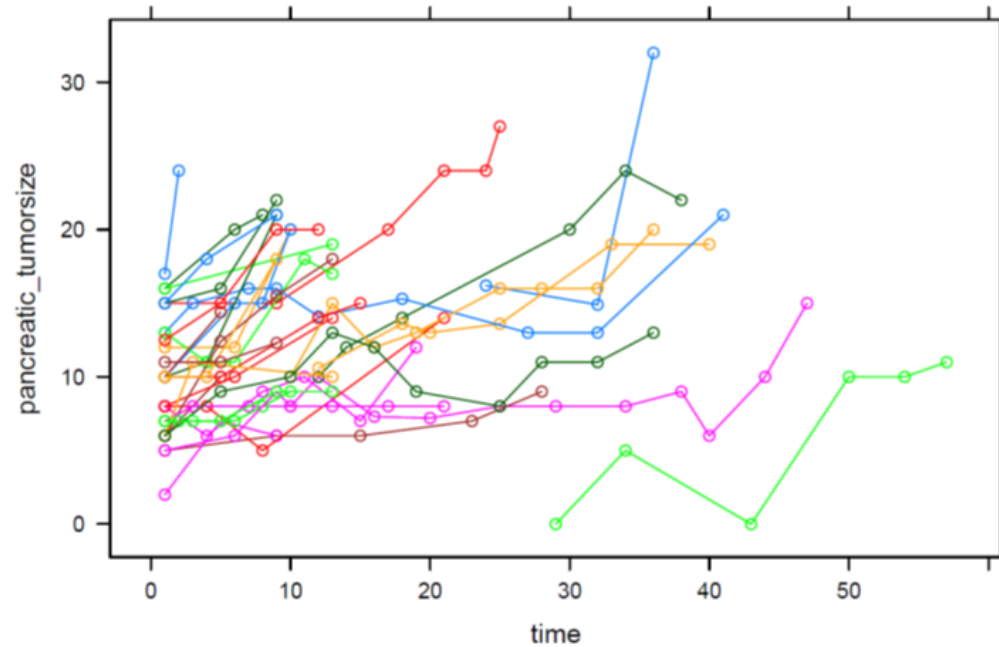
Natural course of tumours: pNET



Pieterman et al. JCEM (2017)

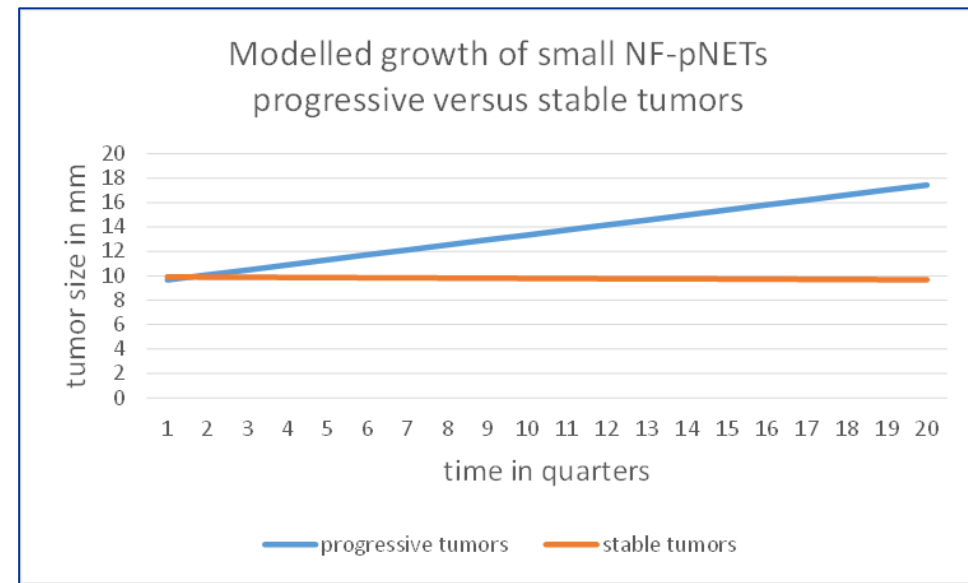


Natural course of tumours: pNET



Pieterman et al. JCEM (2017)

- Progressive tumours growth 1,6 mm/year
- Doubling time 6 years
- Genotype phenotype correlation



RESEARCH



Glucagon-Producing Pancreatic Neuroendocrine Tumors (Glucagonomas) are Enriched in Aggressive Neoplasms with ARX and PDX1 Co-expression, *DAXX/ATR*X Mutations, and ALT (Alternative Lengthening of Telomeres)

Paola Mattiolo¹ · Michele Bevere² · Andrea Mafficini^{2,3} · Anna Vera D. Verschuur⁴ · Martina Calicchia² · Wenzel M. Hackeng⁴ · Michele Simbolo¹ · Salvatore Paiella⁵ · Koen M. A. Dreijerink^{6,7} · Luca Landoni⁵ · Serena Pedron¹ · Sara Cingarlini⁸ · Roberto Salvia⁵ · Michele Milella^{3,8} · Rita T. Lawlor^{2,3} · Gerlof D. Valk⁹ · Menno R. Vriens¹⁰ · Aldo Scarpa^{1,2} · Lodewijk A. Brosens^{4,11} · Claudio Luchini^{1,2}

Pancreas



OPEN ACCESS

Original research

Non-functional pancreatic neuroendocrine tumours: ATRX/DAXX and alternative lengthening of telomeres (ALT) are prognostically independent from ARX/PDX1 expression and tumour size

Hackeng et al, *GUT* 2022

Diagnosing Nonfunctional Pancreatic NETs in MEN1: The Evidence Base

Mark J. C. van Treijen,¹ Dirk-Jan van Beek,² Rachel S. van Leeuwen,¹
Menno R. Vriens,² and Gerlof D. Valk¹

Conclusions:

- Biomarkers/blood samples of no additive value
- MRI/EUS probably best way to detect tumours
- Frequency and interval based on growth
- Best age to start screening still unknown

Reliability and Agreement of Radiological and Pathological Tumor Size in Patients with Multiple Endocrine Neoplasia Type 1-Related Pancreatic Neuroendocrine Tumors: Results from a Population-Based Cohort

Dirk-Jan van Beek^a Helena M. Verkooijen^b Sjoerd Nell^a Bert A. Bonsing^c
Casper H. van Eijck^d Harry van Goor^e Frederik J.H. Hoogwater^f
Elisabeth J.M. Nieveen van Dijkum^g Geert Kazemier^h Cornelis H.C. Dejong^{i,j}
Lodewijk A.A. Brosens^k Frank J. Wessels^l Inne H.M. Borel Rinkes^a
Gerlof D. Valk^m Menno R. Vriens^a

- 73 patients from DMSG database 2003 – 2018
- Tumour size on imaging (CT/MRI/EUS) compared to histology

Conclusion:

- In general, no over- or underestimation
- RI seems to be the best

Gastrinomas

Localisation of gastrinomas in MEN1 can also be challenging as the primary duodenal tumours are often very small (several millimeters in size) and may occur with larger and more readily visible NF-PanNETs.

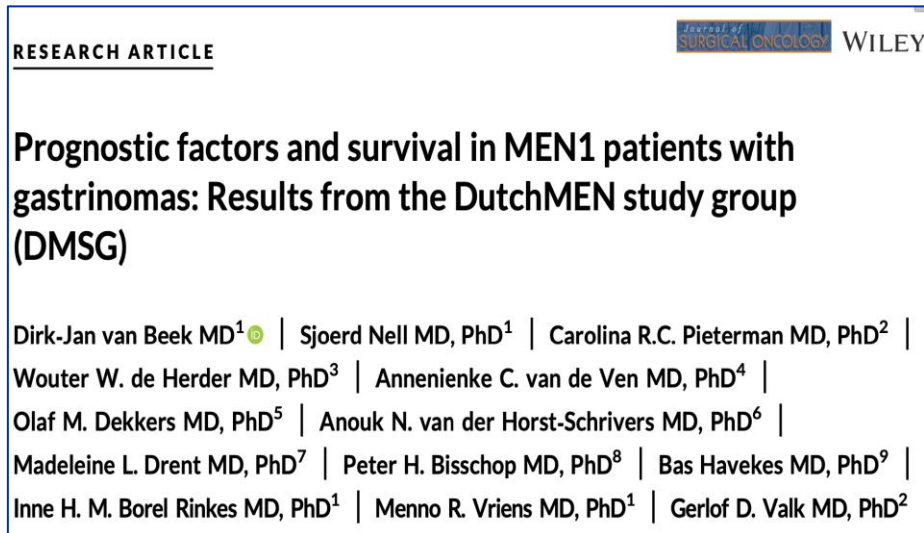
Brandi/Thakker 2025

Metastatic Patterns of Duodenopancreatic Neuroendocrine Tumors in Patients With Multiple Endocrine Neoplasia Type 1

Wenzel M. Hackeng, MD, Dirk-Jan van Beek, MD,† Aranxa S.M. Kok, BS,*
Madelon van Emst, BS,* Folkert H.M. Morsink, BS,* Mark J.C. van Treijen, MD,‡
Inne H.M. Borel Rinkes, MD, PhD,† Koen M.A. Dreijerink, MD, PhD,§
G. Johan A. Offerhaus, MD, PhD,* Gerlof D. Valk, MD, PhD,‡
Menno R. Vriens, MD, PhD,† and Lodewijk A.A. Brosens, MD, PhD**

In conclusion, for patients with MEN1-related hypergastrinemia and PanNETs, a duodenal origin of periduodenopancreatic lymph node metastases should be considered, even when current conventional and functional imaging studies do not reveal duodenal tumours preoperatively.

Am J Surg Pathol, 2022



Methods:

- 63 patients from DMSG database 1990 – 2014
- Factors associated with prognosis

Conclusion:

High gastrin levels (FSG) and pancreatic tumour size are strong prognosticators

Personalised work-up and therapy are based on FSG

Insulinomas

Original article

Surgery for multiple endocrine neoplasia type 1-related insulinoma: long-term outcomes in a large international cohort

D. J. van Beek¹, S. Nell^{1,2}, H. M. Verkooijen³, I. H. M. Borel Rinkes¹, G. D. Valk² (on behalf of the DutchMEN study group) and M. R. Vriens¹, on behalf of the International MEN1 Insulinoma Study Group*

Background:

- 10-15% of patients with MEN1
- Optimal surgical strategy still unknown

Methods:

- DMSG + 38 centres around the world 1990 – 2016
- 96 patients
- Resolution of hyperglycaemia and recurrence

Conclusion:

- Surgery more successful than previously thought
- Less is more (if possible enucleation)



Philipps



Universität
Marburg



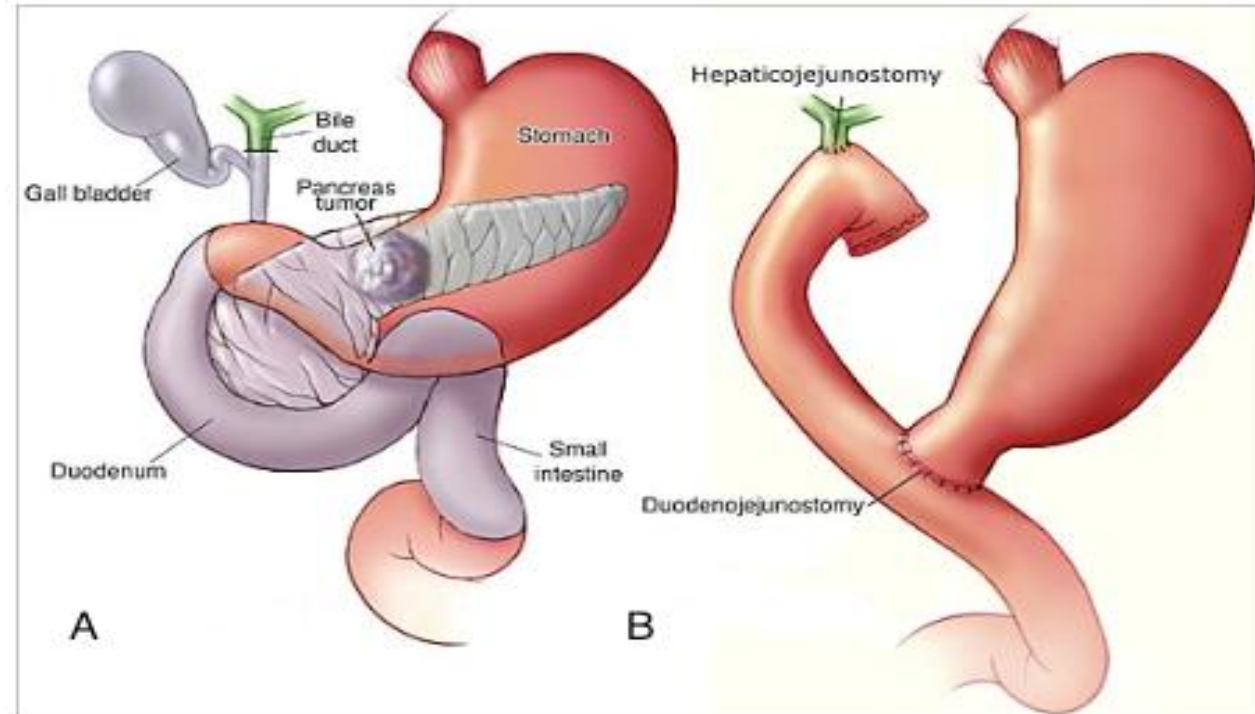
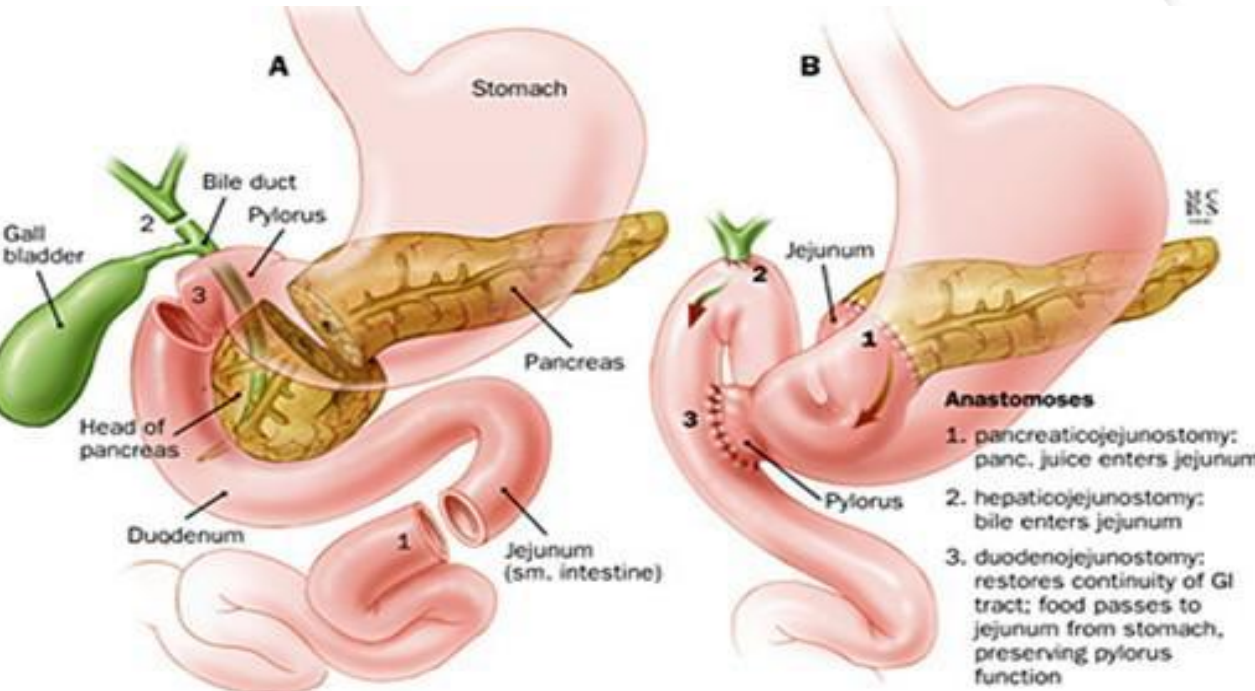
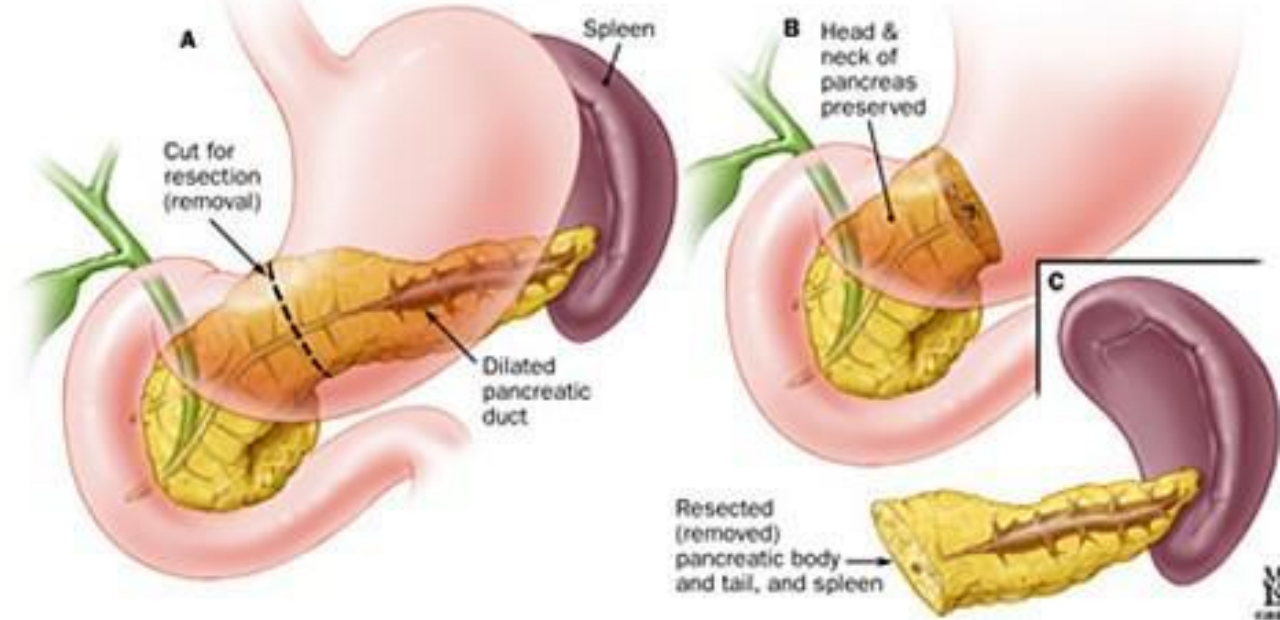
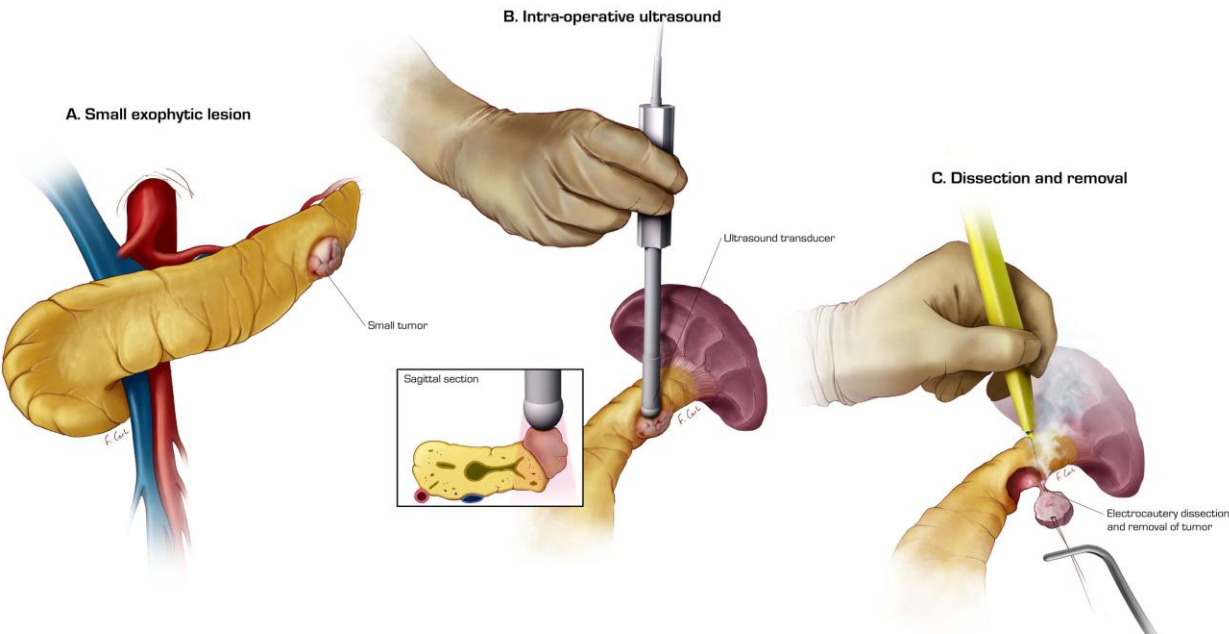
THE UNIVERSITY OF
CHICAGO
MEDICINE



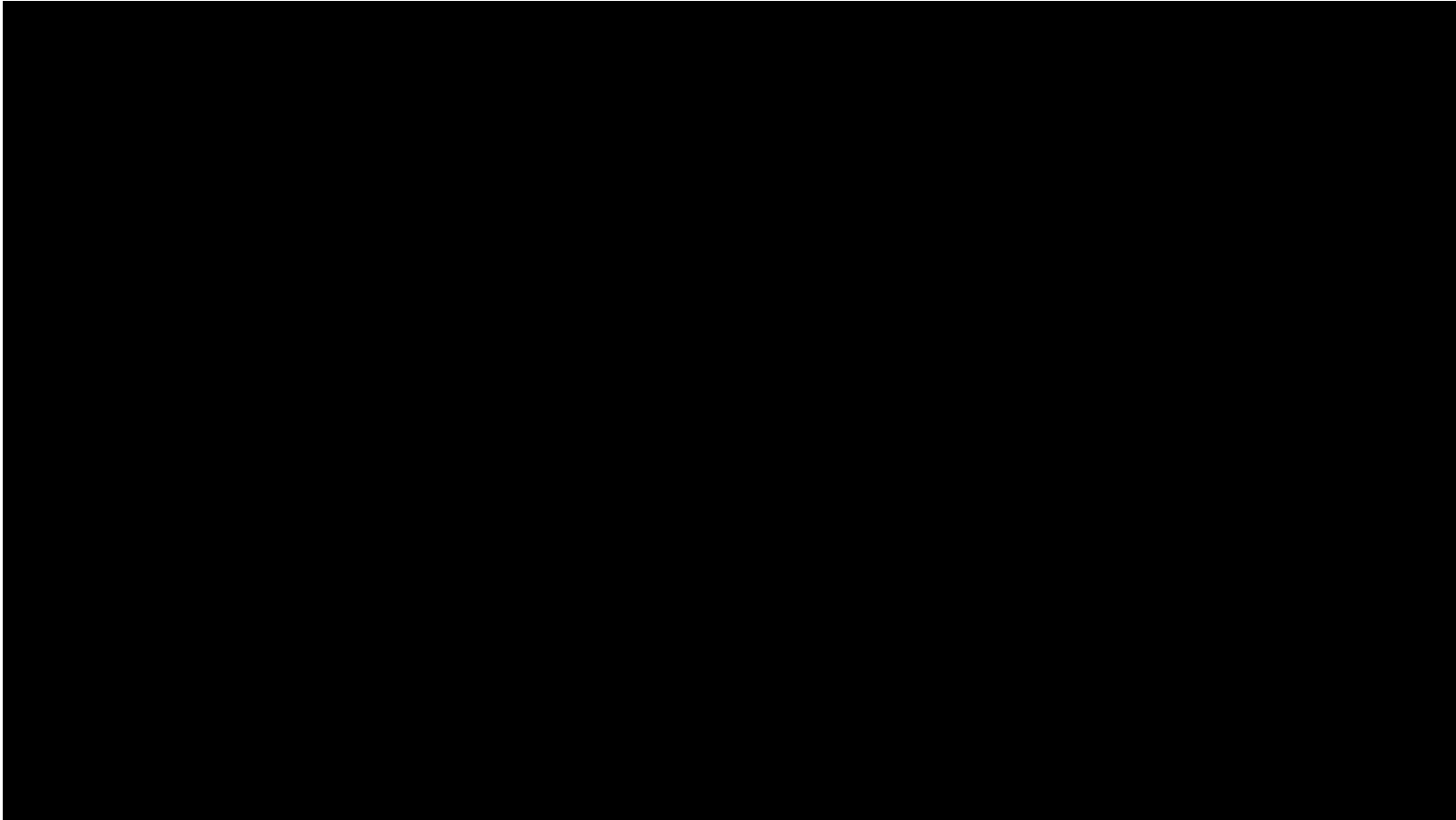
National Institutes
of Health



Enucleation Procedure



Robot assisted enucleation and distal pancreatectomy



Surgery

Early and Late Complications After Surgery For MEN1-related Nonfunctioning Pancreatic Neuroendocrine Tumors

Sjoerd Nell, MD, Inne H. M. Borel Rinkes, MD, PhD,† Helena M. Verkooijen, MD, PhD,‡
Bert A. Bonsing, MD, PhD,§ Casper H. van Eijck, MD, PhD,¶ Harry van Goor, MD, PhD,||
Ruben H. J. de Kleine, MD,** Geert Kazemier, MD, PhD,†† Elisabeth J. Nieveen van Dijkum, MD, PhD,‡‡
Cornelis H. C. Dejong, MD, PhD,§§ Gerlof D. Valk, MD, PhD,¶¶, On behalf of the DMSG, and
Menno R. Vriens, MD, PhD||||*

Dutch MEN 1 Study Group:

61 operations:

- Mainly 'limited' surgery (distal pancs and enucleations)
- 1/3 had a severe complication
- Severe complications mainly after major surgery
 - Pancreatoduodenectomy
 - Total pancreatectomy

Ann Surg 2018

Surgery

Background:

Incidence and severity of complications after major surgery for MEN1-related dpNETs were assessed.
(Whipple / total panc)

Methods:

- 27 patients from national cohort 2003 – 2017
- Complications, severity, cumulative complication index (CCI)

Ann Surg Oncol
<https://doi.org/10.1245/s10434-020-09496-1>

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

Check for updates

ORIGINAL ARTICLE – ENDOCRINE TUMORS

Complications After Major Surgery for Duodenopancreatic Neuroendocrine Tumors in Patients with MEN1: Results from a Nationwide Cohort

Dirk-Jan van Beek, MD, MSc¹ , Sjoerd Nell, MD, PhD¹, Wessel M. C. M. Vorselaars, MD, PhD¹, Bert A. Bonsing, MD, PhD², Casper H. J. van Eijck, MD, PhD³, Harry van Goor, MD, PhD⁴, Elisabeth J. Nieveen van Dijkum, MD, PhD⁵, Cornelis H. C. Dejong, MD, PhD^{6,7}, Gerlof D. Valk, MD, PhD⁸, Inne H. M. Borel Rinkes, MD, PhD¹, and Menno R. Vriens, MD, PhD¹ on behalf of the DutchMEN Study Group (DMSG)

Conclusion:

- High risk of severe complications
- Patient selection of utter importance

Surgery MEN 1 vs sporadic

Background:

Little is known about the risks of complications after surgery for PNETS in MEN1 patients versus sporadic, non-MEN1 patients

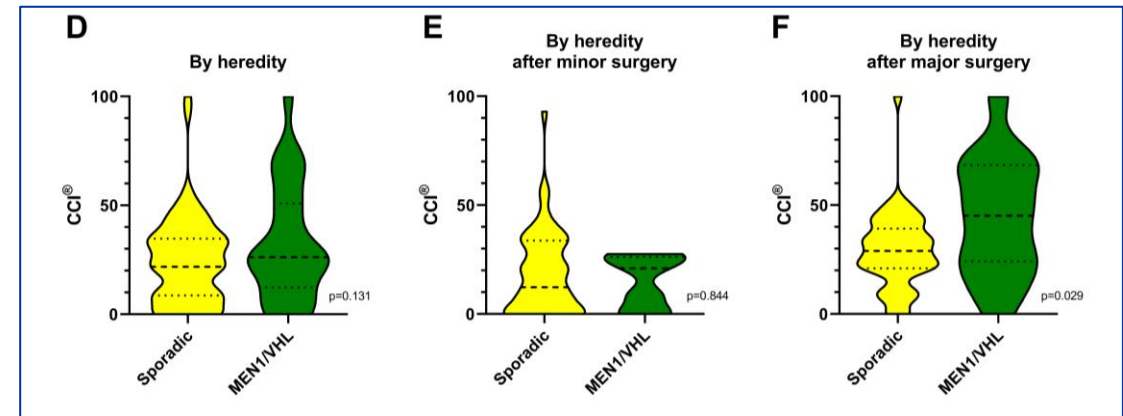
Methods:

UMC Utrecht + UMC Groningen 2008 – 2018

- Complications, severity, cumulative complication index (CCI)
- Factors associated with complications

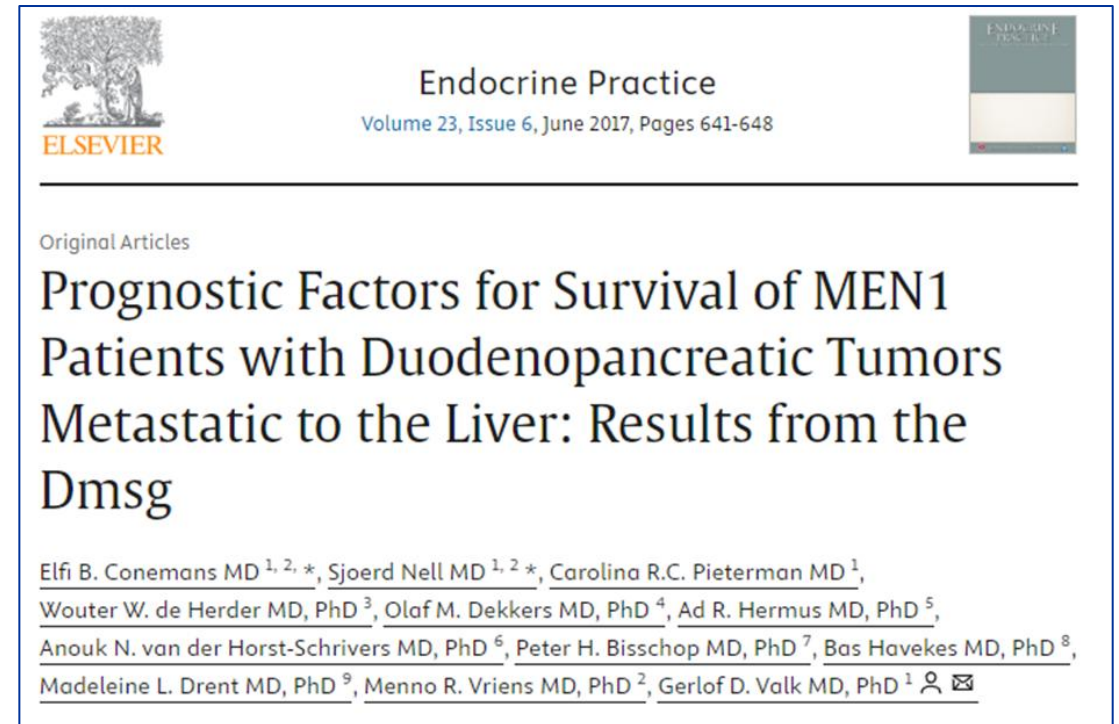
Conclusions:

- Complications mainly related to extension of surgery
- In specialised centres less failure to rescue
- MEN1 patients have more complications after major surgery and should be treated in centers of excellence



Conclusions (continued):

- 14% of MEN1 patients with a dpNET developed liver metastases
 - median age of 53 years
- A combination of various strategies led to
 - a 10-year overall survival of 50%
 - a 5-year progression free survival of 24%
- A minority underwent surgical resection



(Near) future.....Now!

A better risk stratification for each MEN 1 patient

Tumour related characteristics

Better patient selection for major surgery

Reduction of complications

Further centralisation of MEN1 care

National working group

More education

INTERNATIONAL COLLABORATION

Thymic/lung surgery

Pier Luigi Filosso, MD

Associate Professor of Thoracic Surgery

Chief Thoracic Surgery Unit

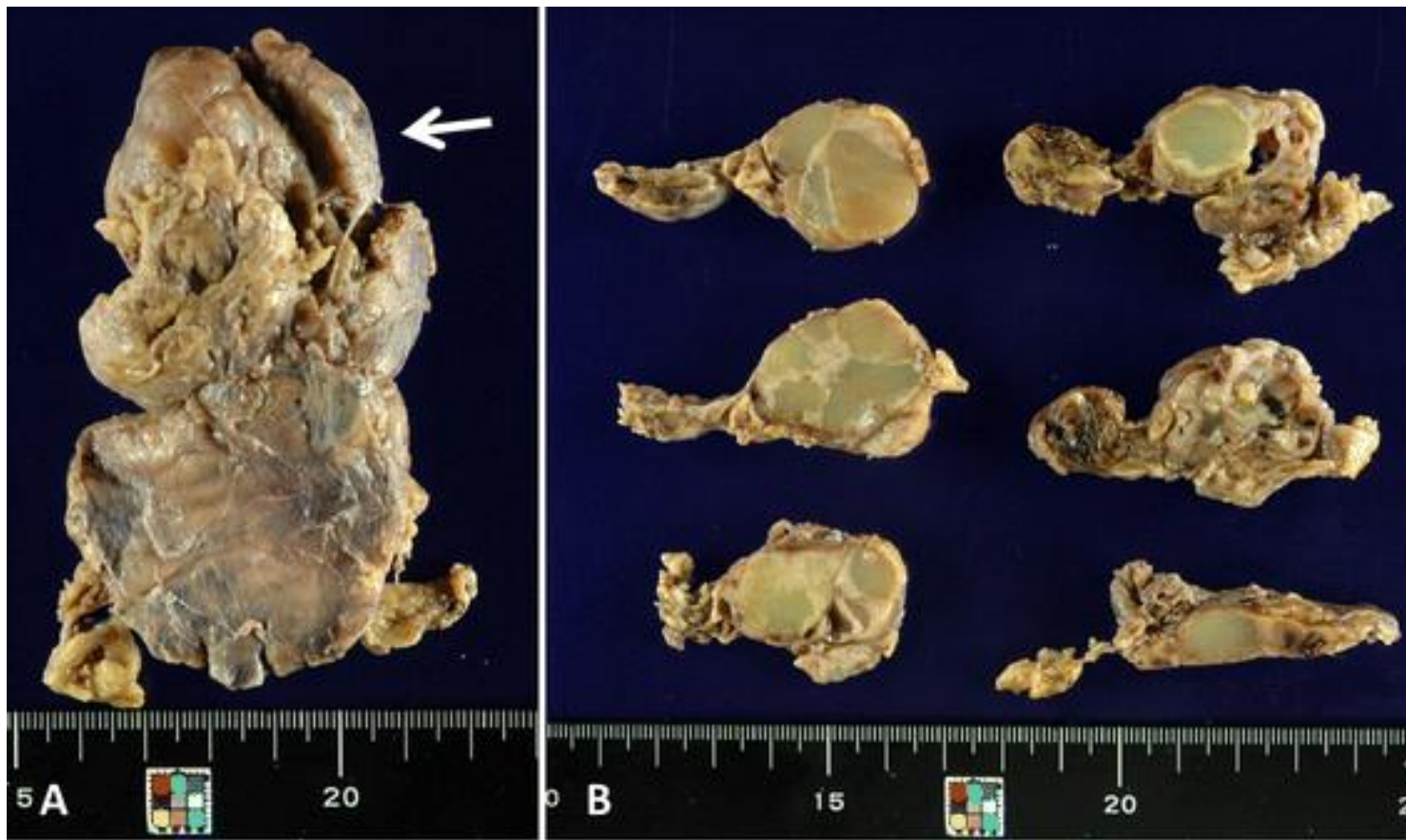
University of Modena – Reggio Emilia Italy

pierluigi.filosso@unimore.it

DISCLOSURE INFORMATION

No conflicts of interest to declare

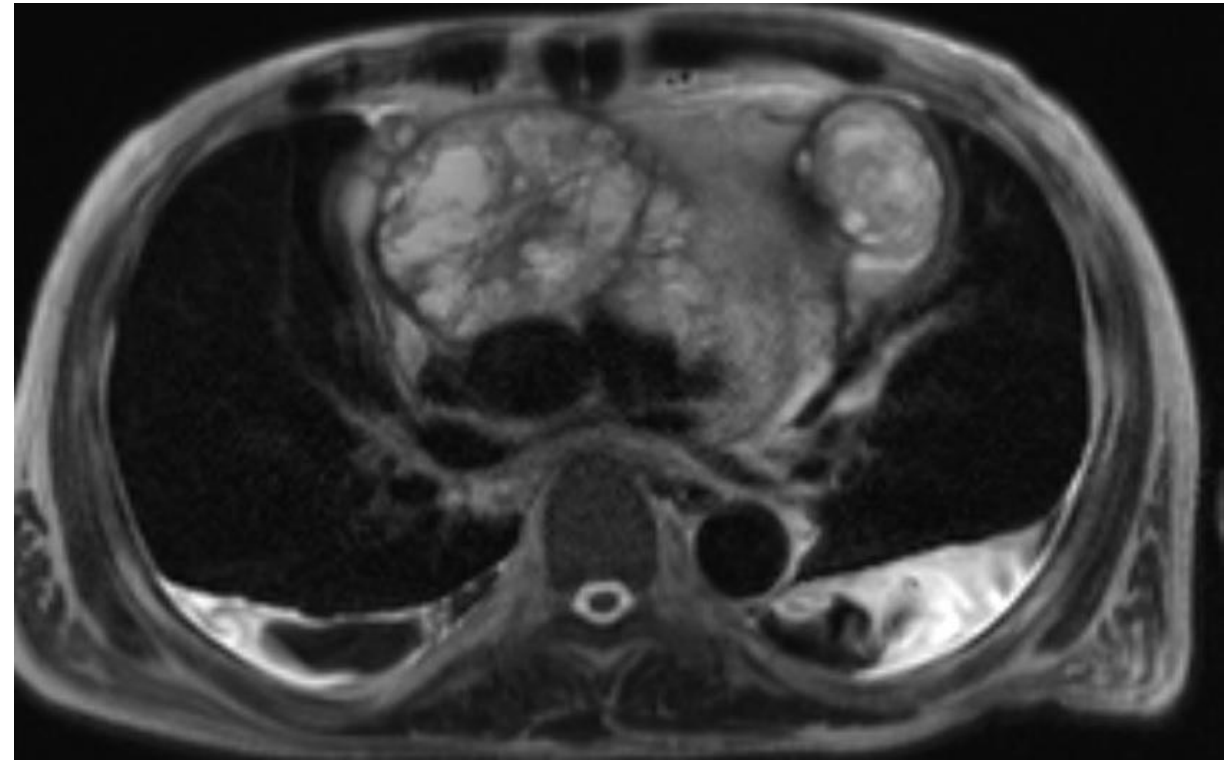


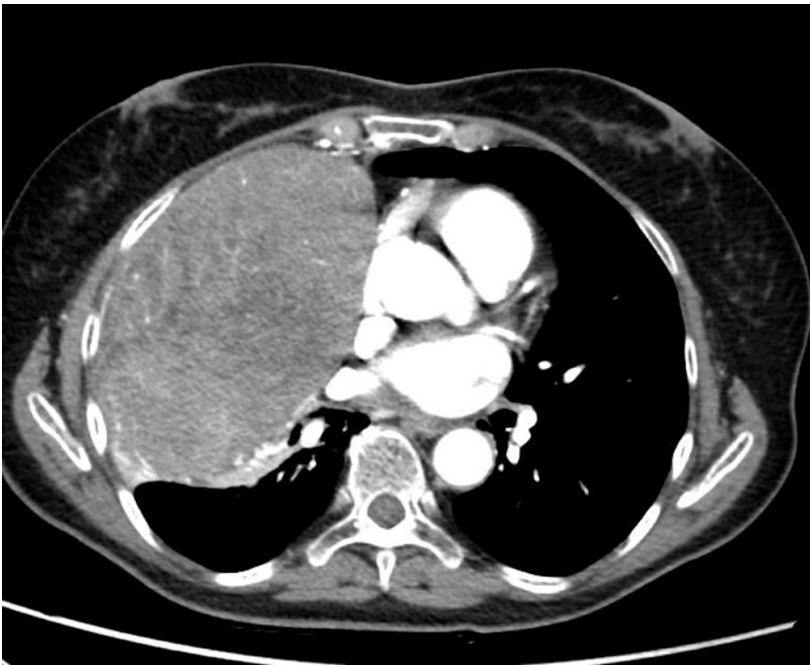


Thymic Neuroendocrine Tumour (TNET)



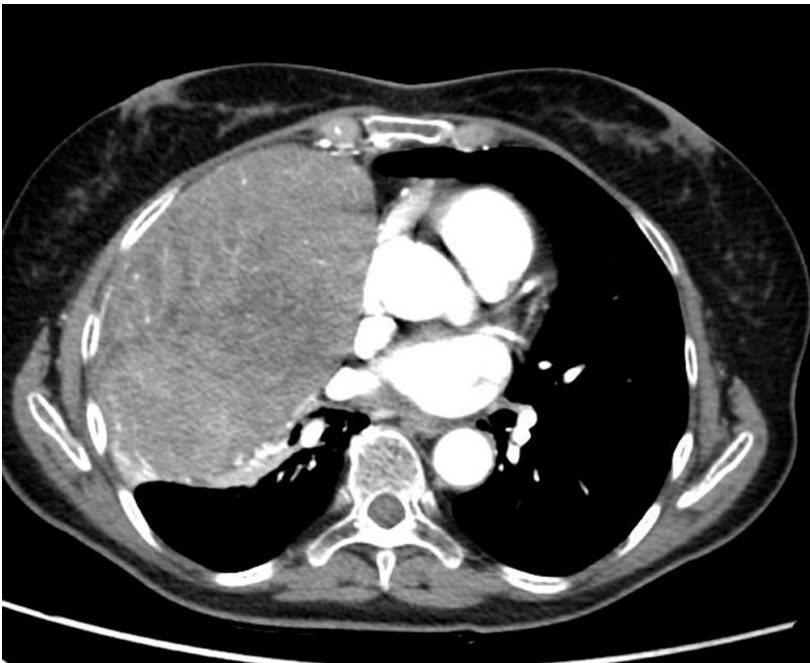
Thymic Neuroendocrine Tumour (TNET)





TNETs: Facts

- ✓ Usually sporadic
- ✓ 25% in MEN 1 patients



TNETs in MEN 1 patients: Facts

- ✓ Predominantly in males
- ✓ Smokers
- ✓ Prevalence: 2% - 8%
- ✓ Age: > 40 years
- ✓ Generally symptomatic
- ✓ Locally aggressive
- ✓ Ectopic hormonal syndrome(s) very rare if compared to sporadic TNETs



TNETs in MEN 1 patients: Facts

- ✓ Extremely malignant
- ✓ They have become more significant in determining MEN 1 pts' survival
- ✓ MEN 1 high risk mortality (HR:16.1;95%CI:1.4-17.9;P<0.0001)

Clin Endocrinol 2017

Clinical Features and Prognosis of Thymic Neuroendocrine Tumors Associated with Multiple Endocrine Neoplasia Type 1: A Single Center Study, Systematic Review, and Meta-analysis

Lei Ye^{1*}, MD, Weixi Wang^{1*}, MD, Naykky Singh Ospina^{2*}, MD, Lei Jiang^{1*}, MD, Ioannis Christakis³, MD, Jieli Lu¹, MD, Yulin Zhou¹, MD, Wei Zhu¹, MD, Yanan Cao¹, MD, Shu Wang¹, MD, Nancy D. Perrier³, MD, William F. Jr. Young², MD, Guang Ning^{1,4}, MD, Weiqing Wang^{1†}, MD

Lei Ye^{1*}, MD, Weixi Wang^{1*}, MD, Naykky Singh Ospina^{2*}, MD, Lei Jiang^{1*}, MD, Ioannis Christakis³,
MD, Jieli Lu¹, MD, Yulin Zhou¹, MD, Wei Zhu¹, MD, Yanan Cao¹, MD, Shu Wang¹, MD, Nancy D.
Perrier³, MD, William F. Jr. Young², MD, Guang Ning^{1,4}, MD, Weiqing Wang^{1†}, MD

TNETs in MEN 1 patients: meta-analysis

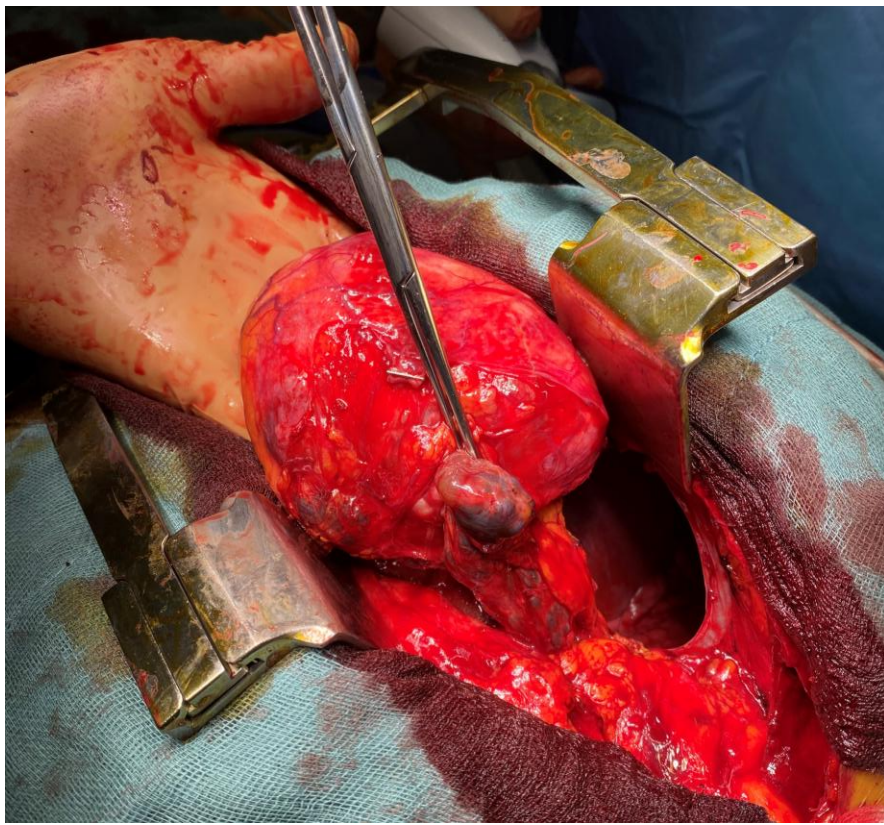
- ✓ 2710 MEN 1 pts 99 TNETs
 - ✓ pool estimated prevalence: 3.7%
- ✓ 40 TNETs died median survival: 8 years
 - ✓ 69.5% 5y OS 33.3% 10y OS
- ✓ Older age (>40 years)
- ✓ Larger tumours (>5 cm diameter)
- ✓ MTS presence

Lei Ye^{1*}, MD, Weixi Wang^{1*}, MD, Naykky Singh Ospina^{2*}, MD, Lei Jiang^{1*}, MD, Ioannis Christakis³,
MD, Jieli Lu¹, MD, Yulin Zhou¹, MD, Wei Zhu¹, MD, Yanan Cao¹, MD, Shu Wang¹, MD, Nancy D.
Perrier³, MD, William F. Jr. Young², MD, Guang Ning^{1,4}, MD, Weiqing Wang^{1†}, MD

Clin Endocrinol 2017

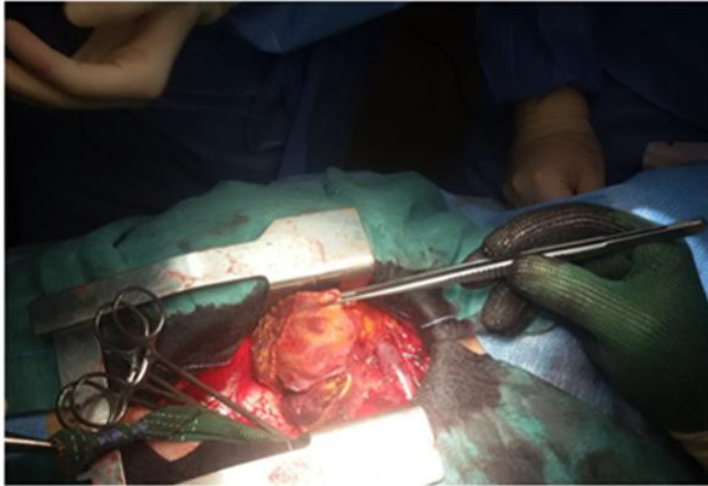
TNETs in MEN 1 patients: Europe/America vs Asia pts comparison

- ✓ Prevalence slightly > Asia
- ✓ Male & smoker > Europe/America
- ✓ Overall survival longer in Europe/America
- ✓ Surgery + CT-RT adjuvant > Europe/America

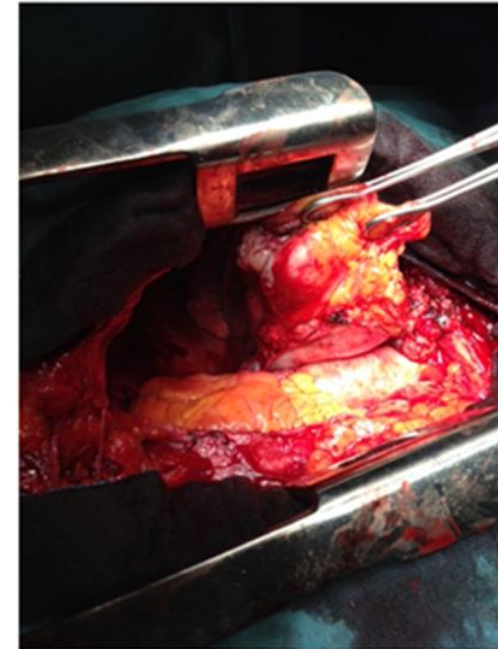


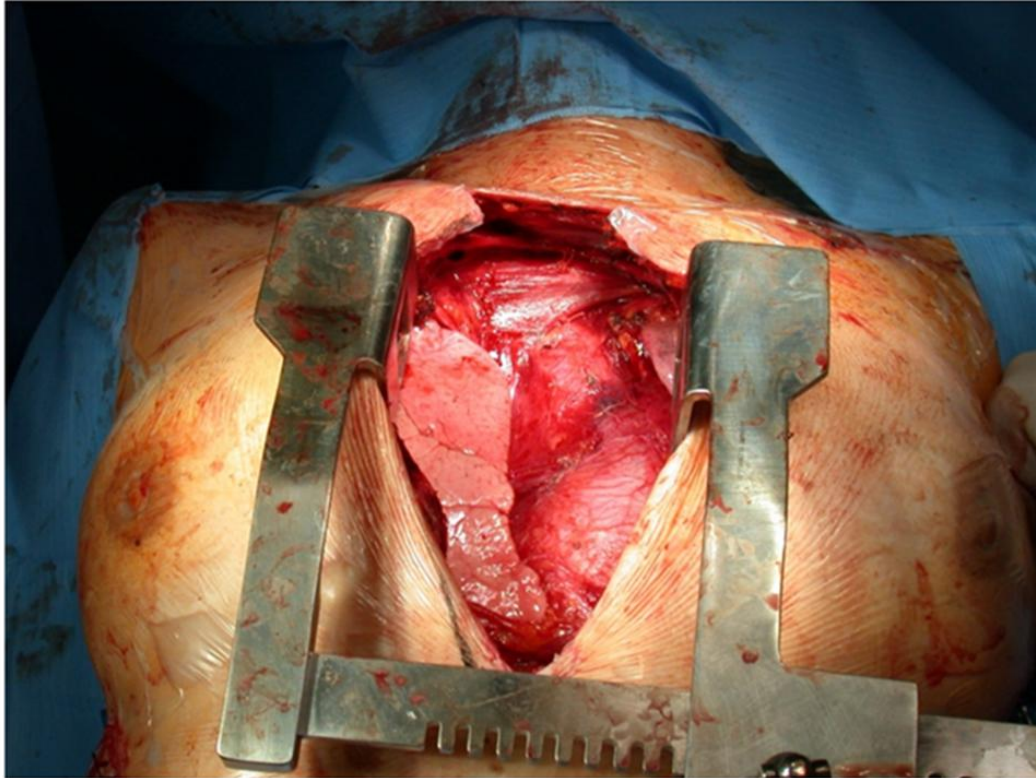
TNET: Surgical issues

Complete Surgical Resection (R0) Gold Standard for cure in any Stage



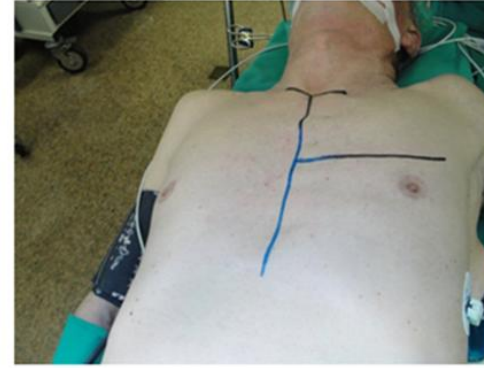
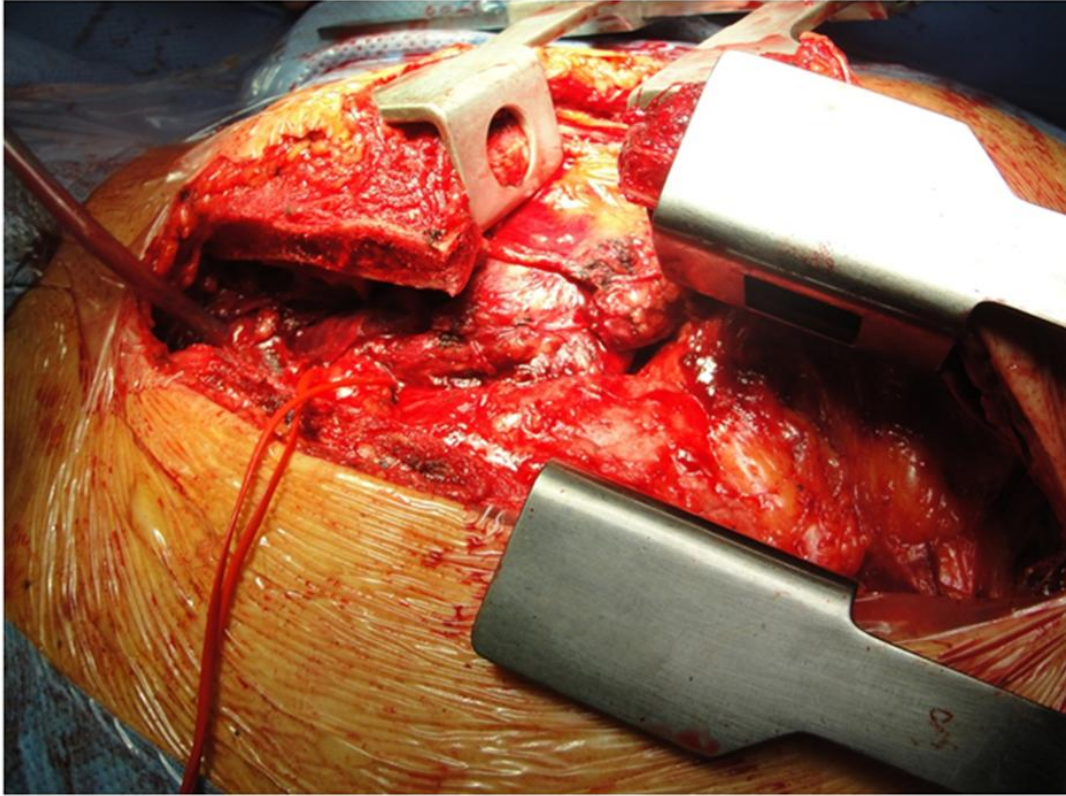
Resectability rate
28% to 90% (mean 86%)





Median sternotomy:

- ✓ The standard surgical approach
- ✓ Optimal access to the anterior mediastinum, pleura, pericardium, great vessels, lung



Combined approaches

- ✓ Invasive or large lesions
- ✓ Major involvement of the lung, pleura, diaphragm, great vessels

Clinicopathological features and current treatment outcomes of neuroendocrine thymic tumours

Wentao Fang ^{a,*†}, Pier Luigi Filosso ^{b,†}, Anja C. Roden ^{c,†}, Zhitao Gu ^a, Yuan Liu ^d, John Agzarian ^e, Robert K. Shen ^f and Enrico Ruffini ^b

European Journal of Cardio-Thoracic Surgery 59 1004–1013

Surgical approach (137 patients, missing data = 5)			
Open surgery	Sternotomy	91	68.9
	Lateral thoracotomy	19	14.4
	Clam-shell	7	5.3
	Combined	4	3.0
Minimally invasive	Thoracoscopic	8	6.1
	Robot-assisted	2	1.5
	Trans-cervical	1	0.8
Resection status (137 patients)			
Resection status (137 patients)	R0	103	75.1
	R1	4	2.9
	R2	30	21.9

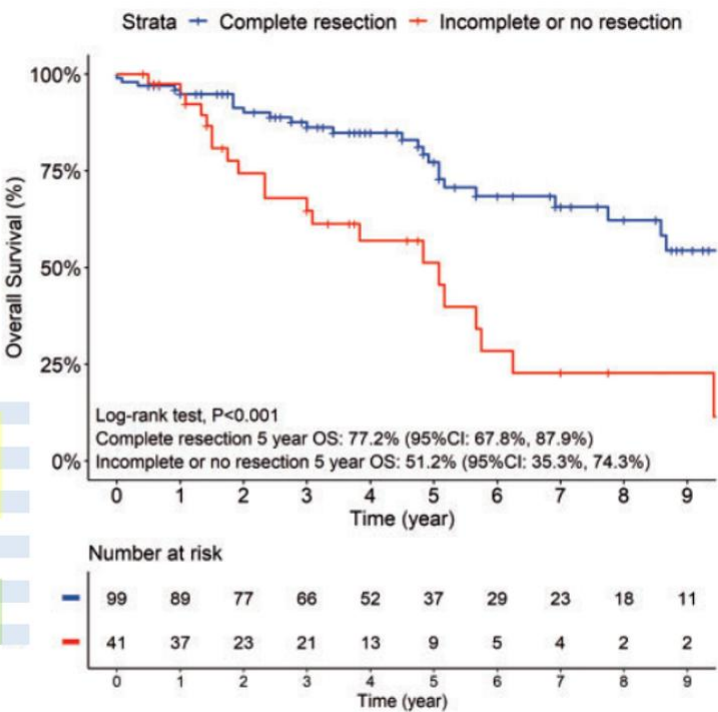
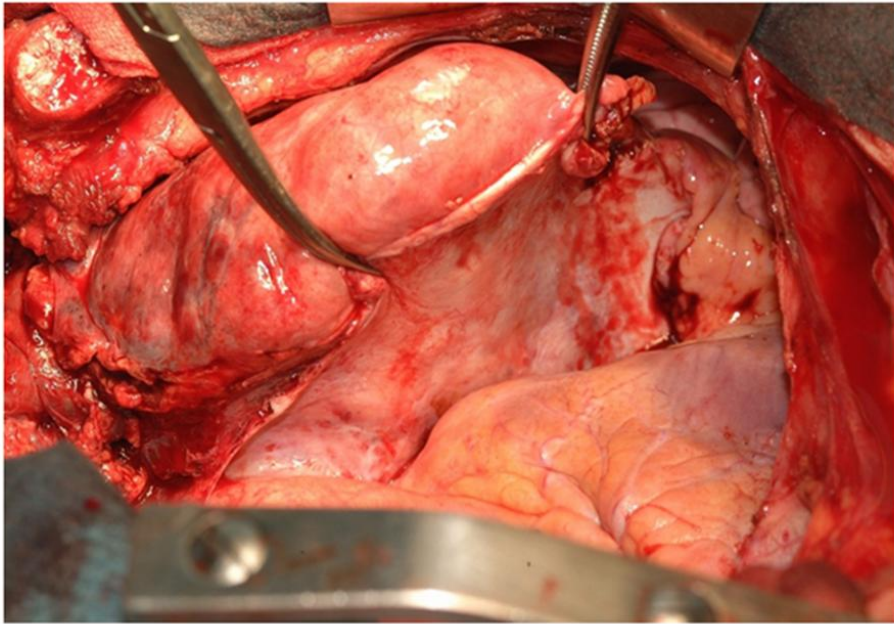
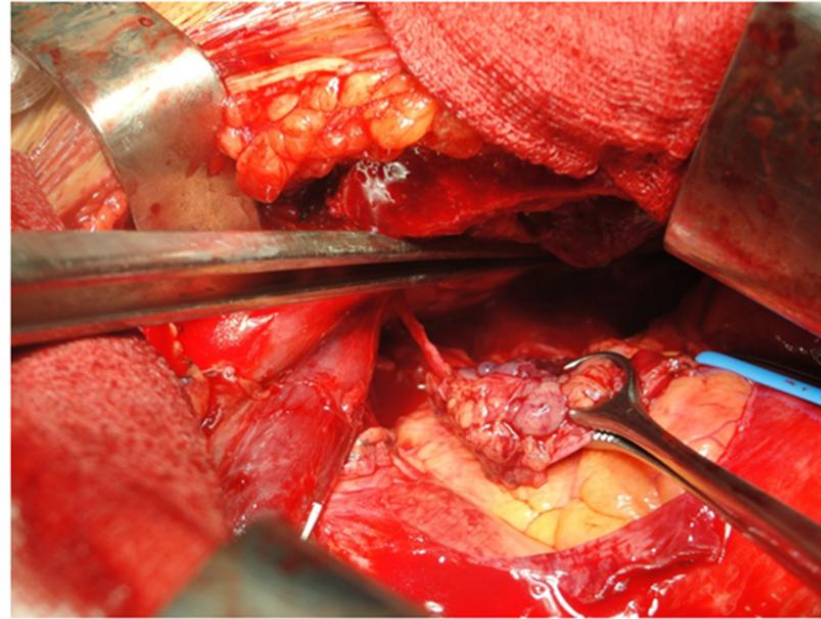


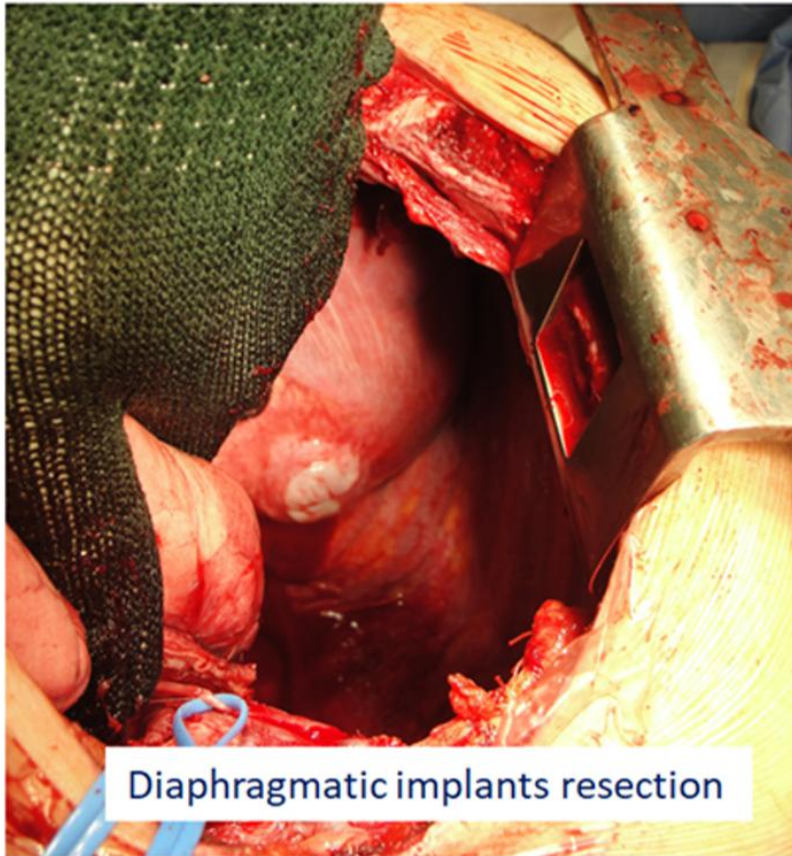
Figure 1: Overall survival of patients with neuroendocrine thymic tumours according to resection status. CI: confidence interval; OS: overall survival.



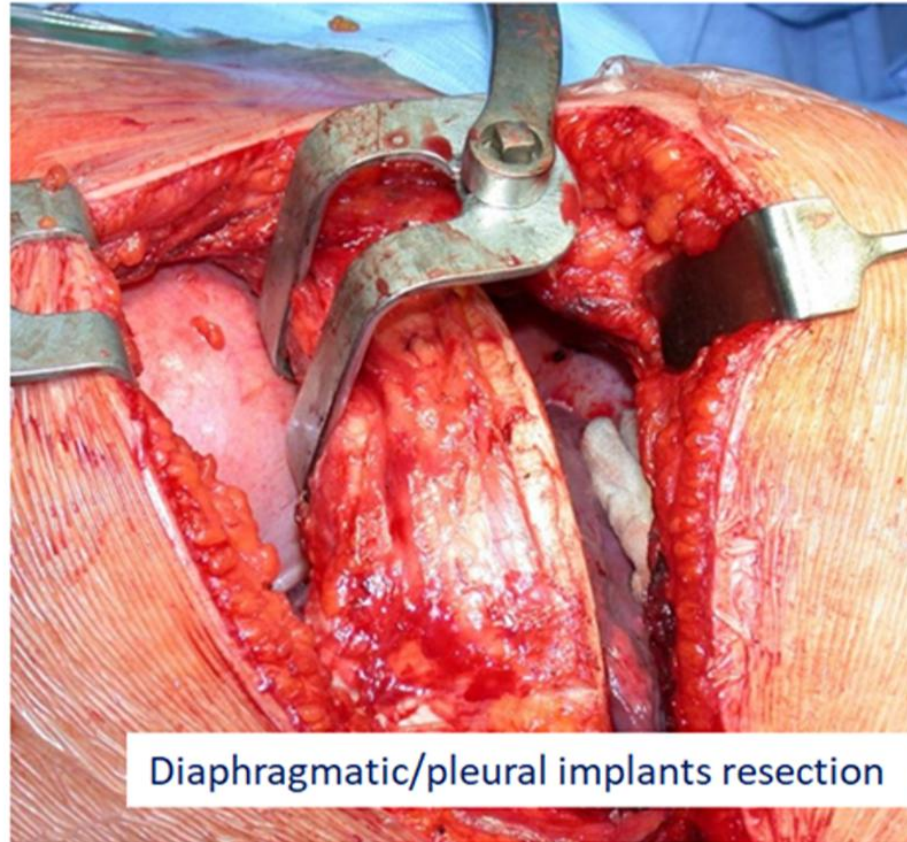
Large pericardial resection



Phrenic nerve resection

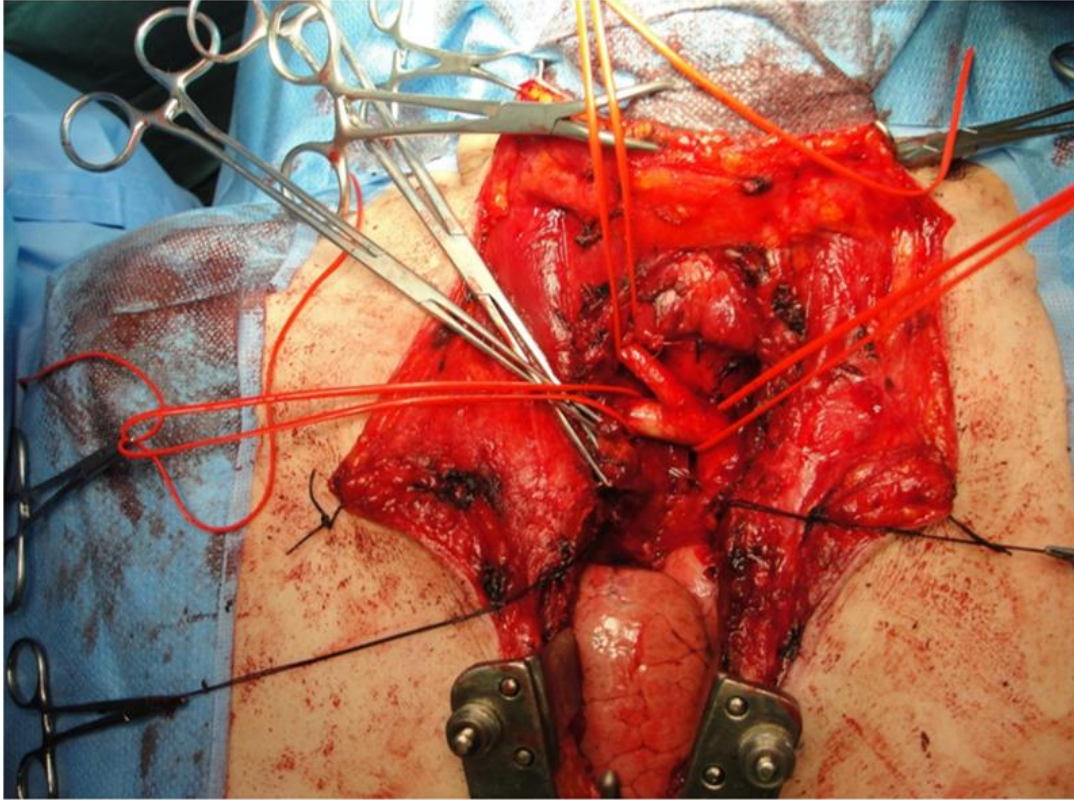


Diaphragmatic implants resection

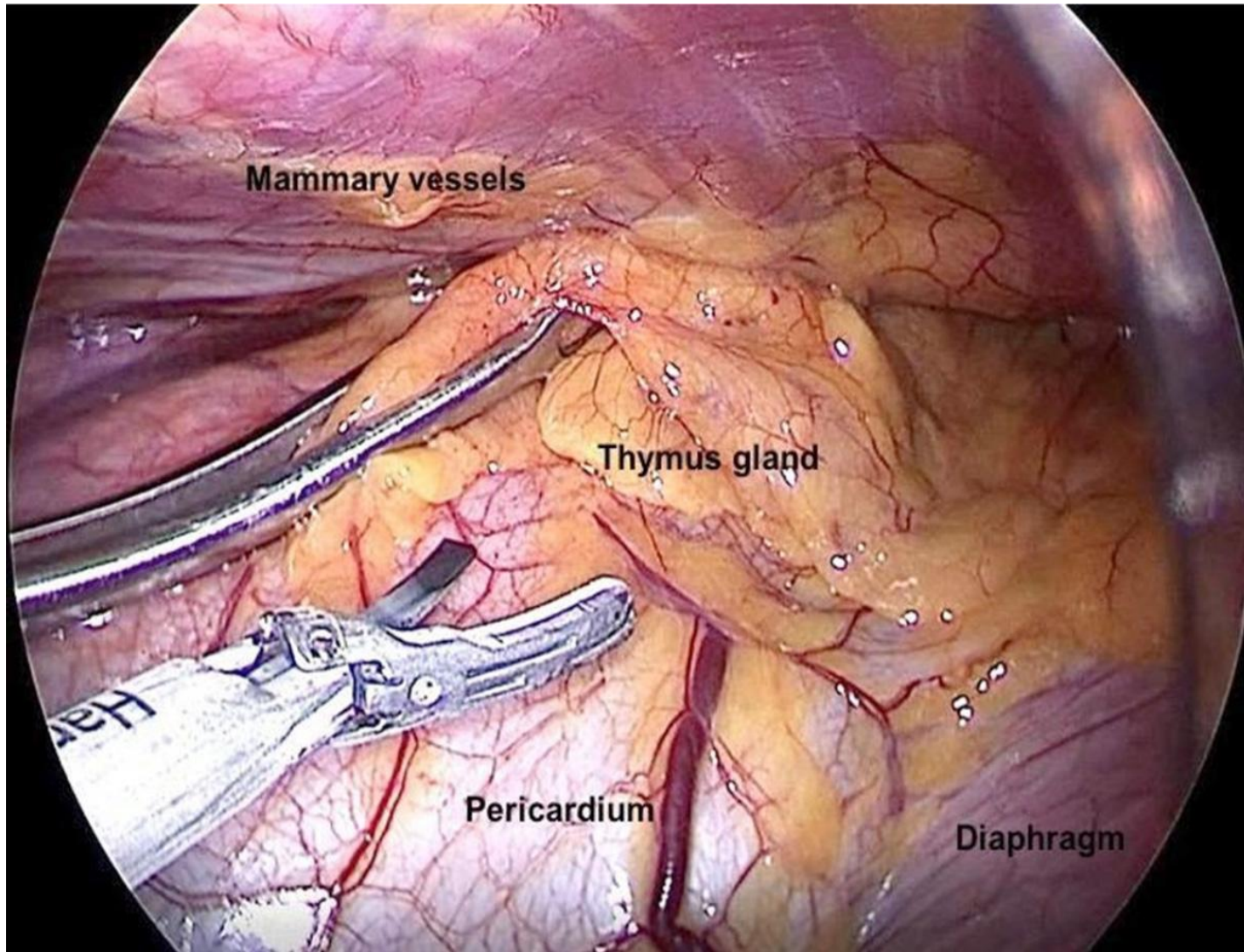


Diaphragmatic/pleural implants resection

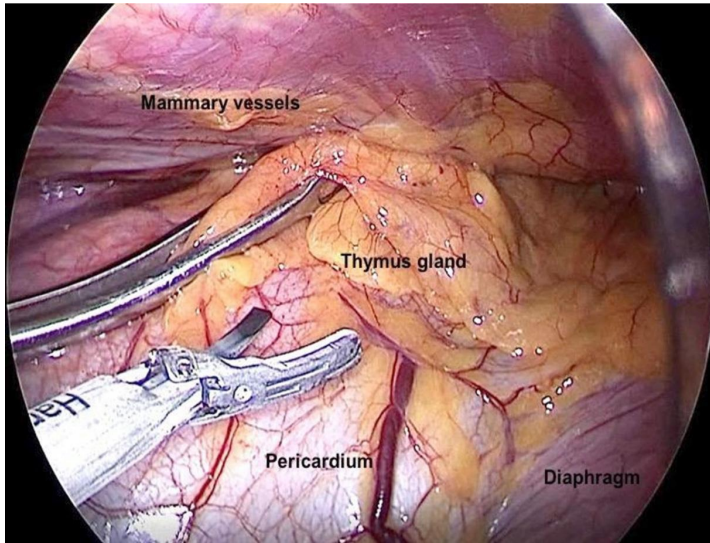
Prognostic factors



- ✓ Completeness of resection
- ✓ Masaoka Stage



Prophylactic thymectomy: Does it still have a role?

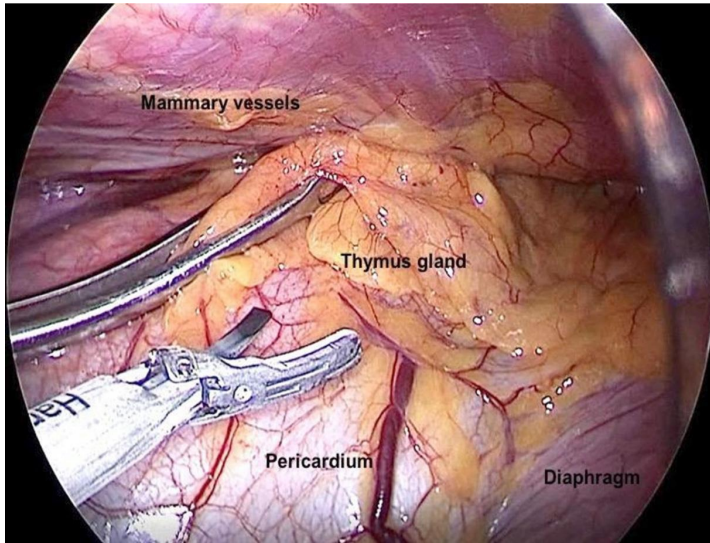


Prophylactic thymectomy: Does it still have a role?

YES:

Males, smokers, age > 40 years MEN 1 pts

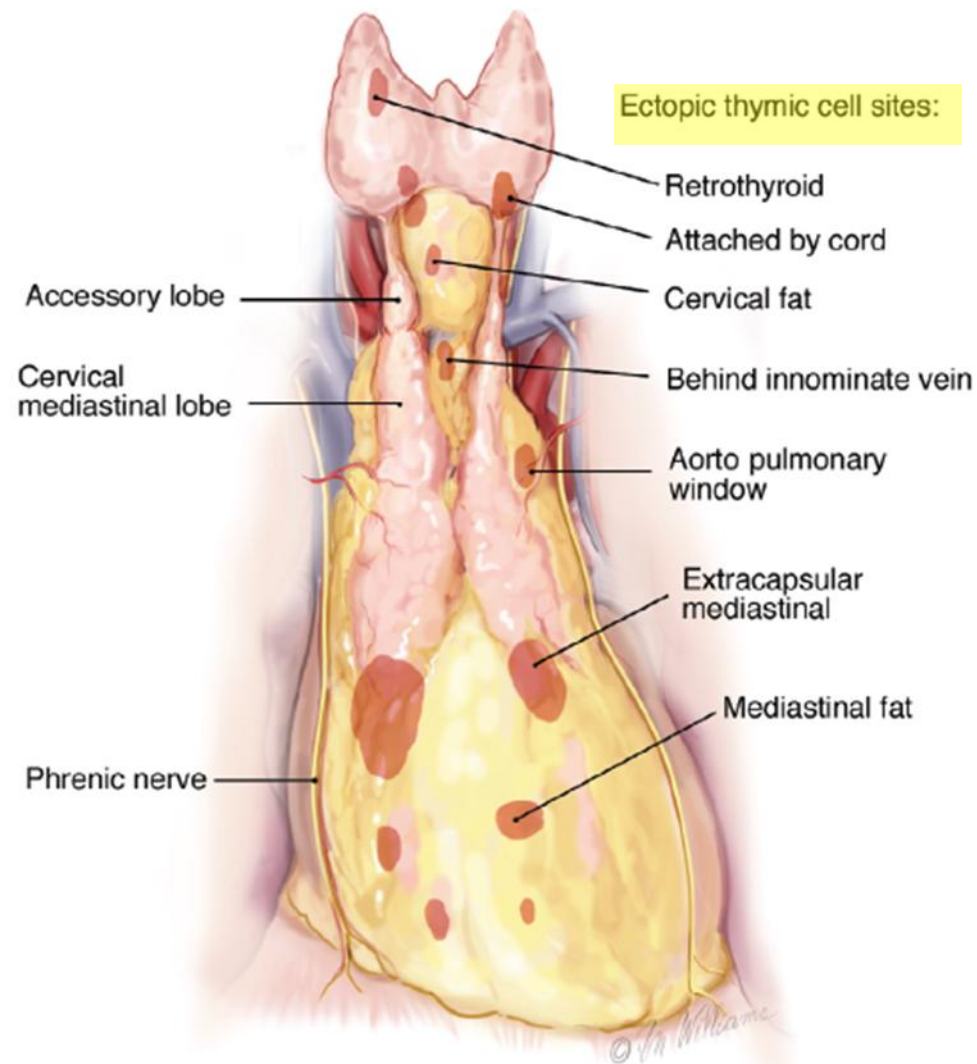
At the time of parathyroidectomy (cervical/neck exploration)



Prophylactic thymectomy: Does it still have a role?

NO:

It's better to improve the programs of screening/follow-up
Thoracic CT-MRI scans every 1-2 years



The problem of ectopic thymic cell sites in the mediastinum

Revisiting the Evidence for Routine Transcervical Thymectomy for the Prevention of Thymic Carcinoid Tumours in MEN-1 Patients

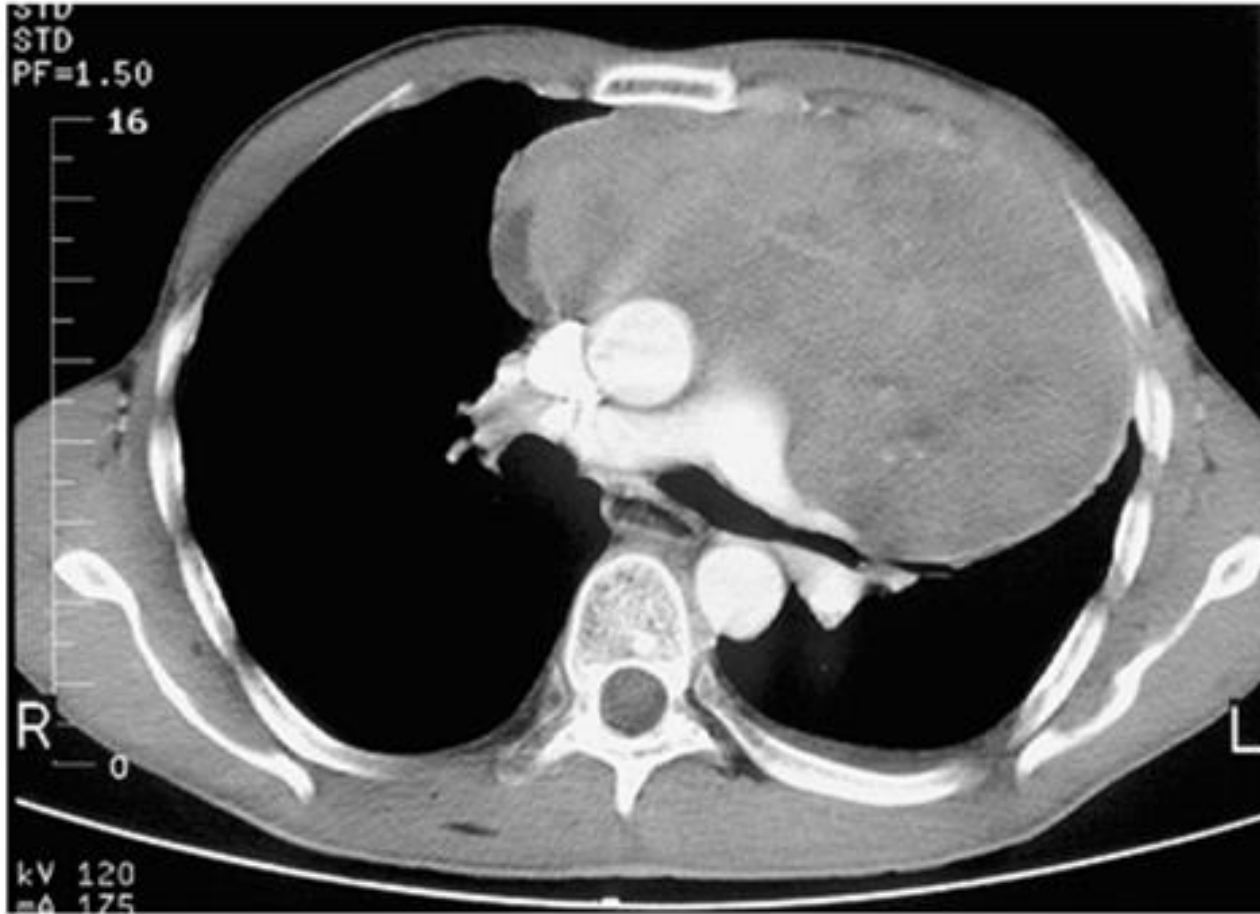
Mechteld Christine De Jong^a Rajeev Parameswaran^{a, b}

^aDepartment of Endocrine Surgery, National University Hospital, Singapore, Singapore; ^bDepartment of Surgery, Yong Loo Lin School of Medicine, Singapore, Singapore

Oncology, 2022

TCT in MEN 1 pts: meta-analysis

- ✓ 122 total cohort of pts among 7 articles
 - ✓ 1 incidental TNET found during TCT
 - ✓ 9 TNETs diagnosed during FU
 - ✓ Median overall TNET development: 36 months



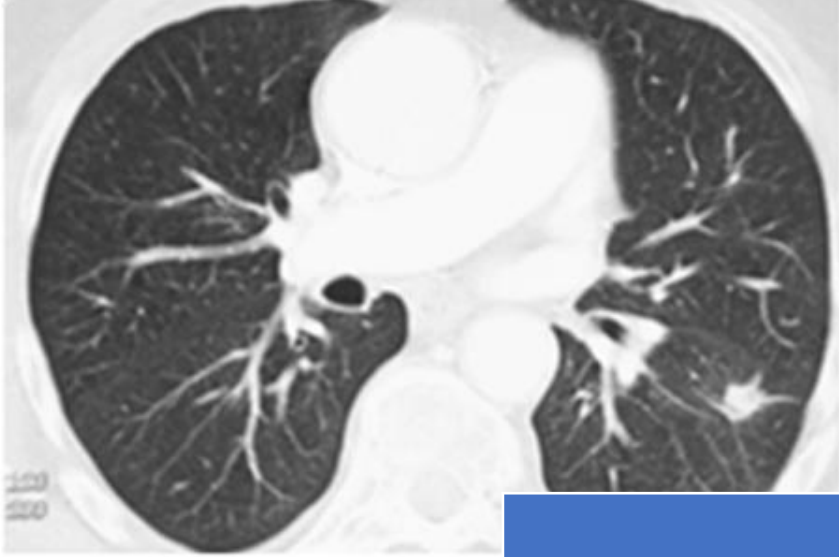
TNET conclusions

Conclusions 1/1

- ✓ 25% TNETs are observed in MEN 1 pts (usually males, smokers and age > 40 years). Compared to sporadic TNET they are symptomatic
- ✓ Pt. age, TNET's diameter and presence of MTS are negative prognostic factors
- ✓ Completeness of resection, tumour stage and adjuvant treatment are positive prognostic factors
- ✓ The indication for prophylactic thymectomy to prevent TNET development is still debated
- ✓ Very important is routine FU with chest CT/MRI every 1-2 years

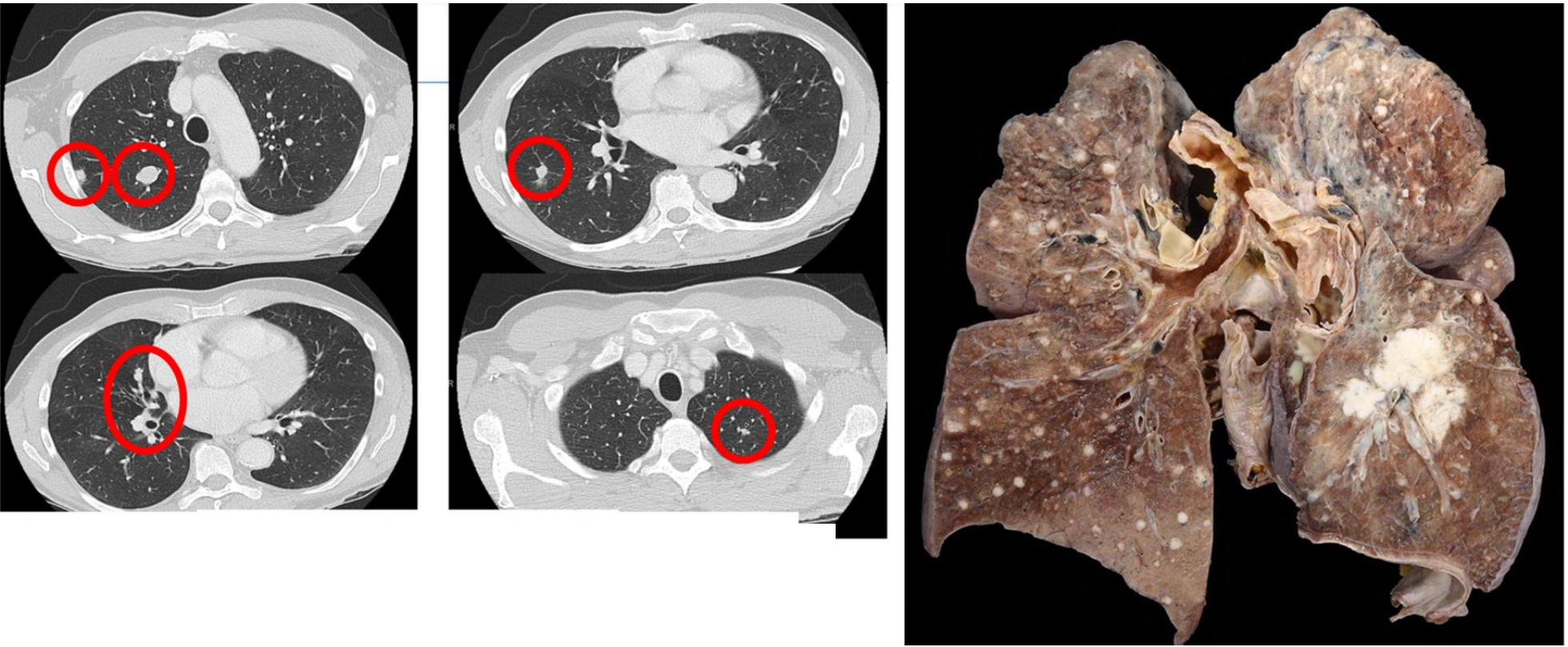


Bronchial carcinoid (BC)

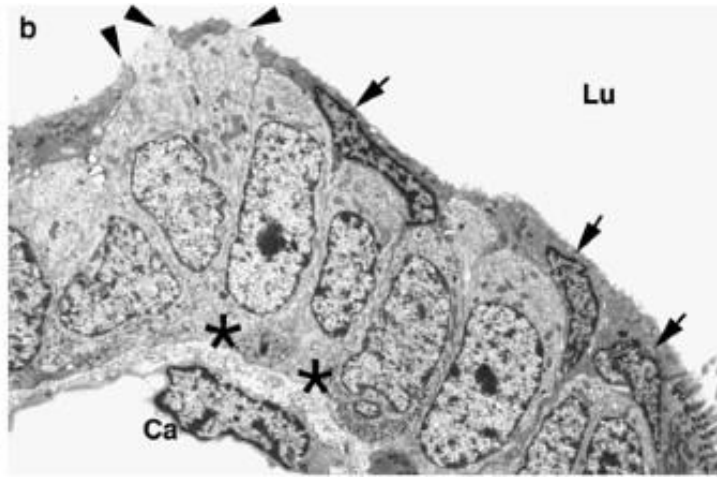
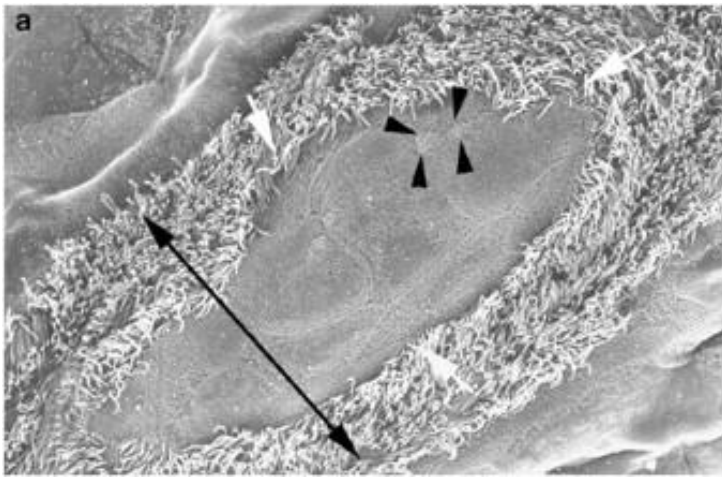


BCs in MEN 1 patients: Facts

- ✓ Prevalence: 5% - 31% in MEN 1 pts
- ✓ Usually small size nodule(s) in peripheral location, asymptomatic
- ✓ BCs have a much more indolent clinical behaviour (do not increase mortality)
- ✓ Hypergastrinemia is significantly common in such pts
- ✓ Occur more frequently in female



In MEN 1 pts BCs may be multicentric,
developing both synchronously and/or
metachronously



Hypergastrinemia (HG), BCs and MEN 1

- ✓ Hypergastrinemia is a potent stimulus for neuroendocrine cells proliferation
- ✓ **HG may therefore play a role in the transformation of lung neuroendocrine precursor cells to become carcinoids**
- ✓ Lung neuroendocrine precursor cells are in fact BCs progenitors



BCs: surgical issues



Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids

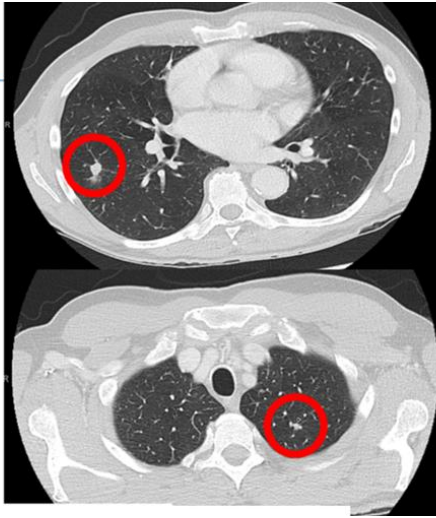
M. E. Caplin^{1*}, E. Baudin², P. Ferolla³, P. Filosso⁴, M. Garcia-Yuste⁵, E. Lim⁶, K. Oberg⁷, G. Pelosi⁸,
A. Perren⁹, R. E. Rossi^{1,10} & W. D. Travis¹¹ the ENETS consensus conference participants[†]

Ann Oncol 2015;26:1604

The purpose of surgery is to
conserve as much of the normal
lung tissue as possible, while
performing a **wide tumor-free
margins resection**

surgery: recommendations for the best practice

- In the case of localized disease, the surgical techniques of choice are lobectomy or sleeve resection (*Level of evidence 5, Grade of recommendation A*).
- Complete anatomic resection and systematic nodal dissection are recommended as the resection extent of choice of patients with peripheral tumors (*Level of Evidence 5, Grade of recommendation D*).
- For patients with localized disease, the extent of resection should be determined by the extent of the tumor and the location of the tumor.



Multiple BCs in MEN 1 pts

- ✓ Small size, multifocality (even bilaterality), apparently indolent natural history of BCs in MEN 1 pts, oblige the surgeon **to use surgical therapy judiciously**

Thymic and Bronchial Carcinoid Tumors in Multiple Endocrine Neoplasia Type 1: The Mayo Clinic Experience from 1977 to 2013

Naykky Singh Ospina¹ • Geoffrey B. Thompson² • Francis C. Nichols III³ •
Stephen D. Cassivi³ • William F. Young Jr¹

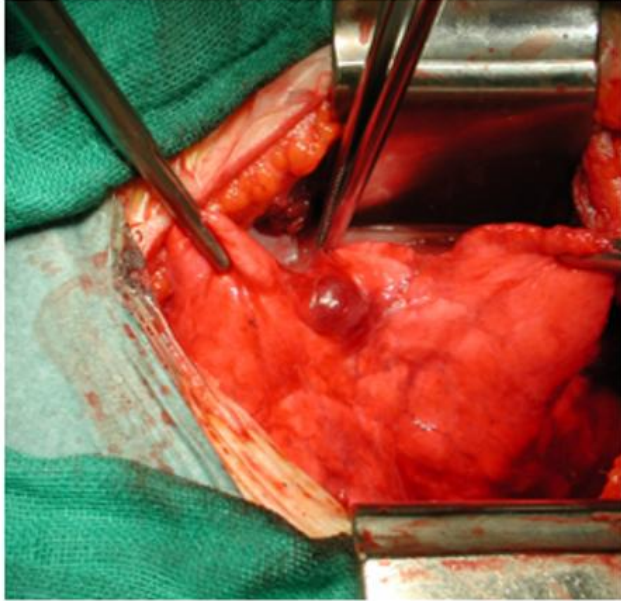
Horm Cancer, 2015

BCs in MEN 1 pts

- ✓ 17 cases of BCs in MEN 1 pts
- ✓ The majority of the pts were diagnosed on routine radiological screening
- ✓ All pts underwent surgical resection (wedge res or lobectomy)
- ✓ None of the pts developed distant MTS at FU

Peripherally-located tumors

- ✓ Wide wedge resection*
- ✓ Segmentectomy
- ✓ Lymphadenectomy



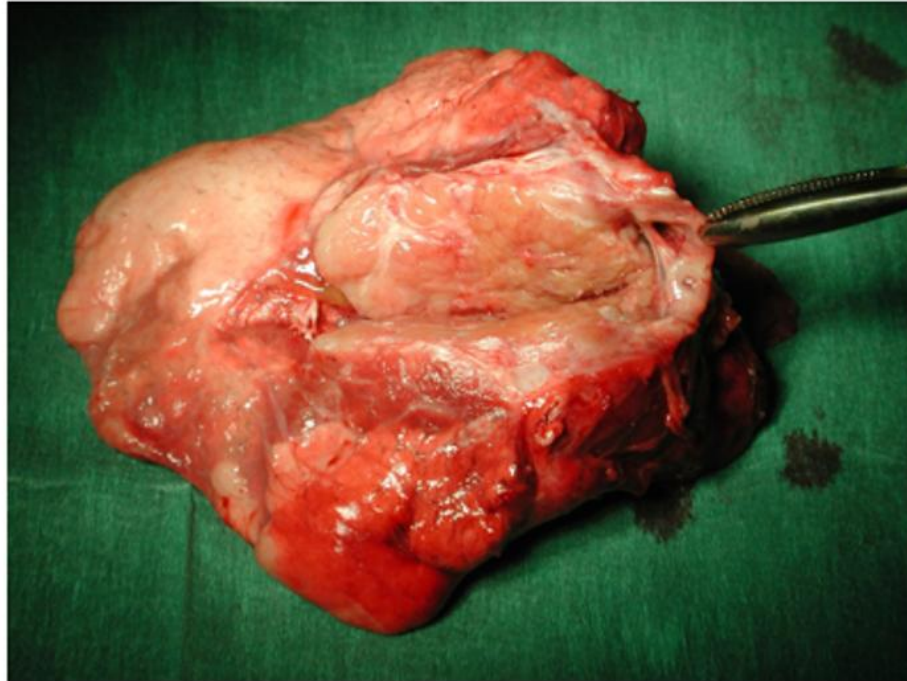
*Final pathology report should confirm TC

BCs' surgical options in MEN 1 patients (1/2)

Peripherally-located tumors



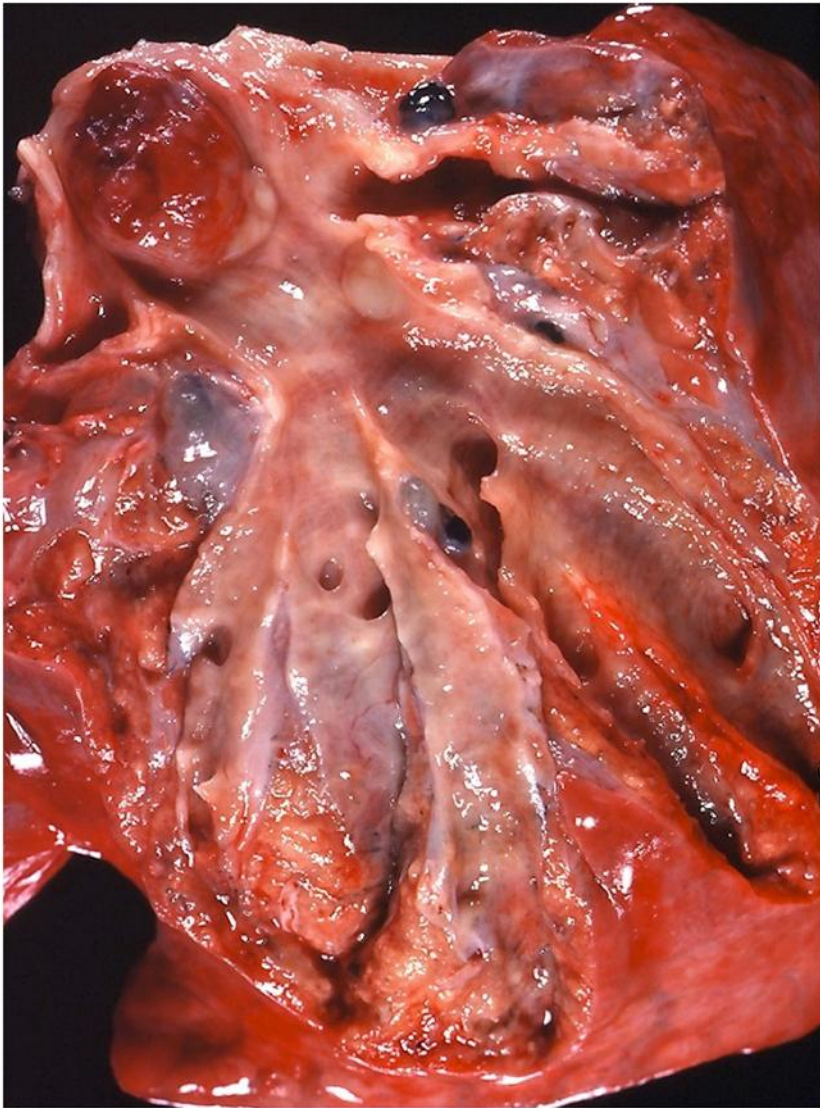
- ✓ Lobectomy
- ✓ Lymphadenectomy



BCs' surgical options in MEN 1 patients (2/2)



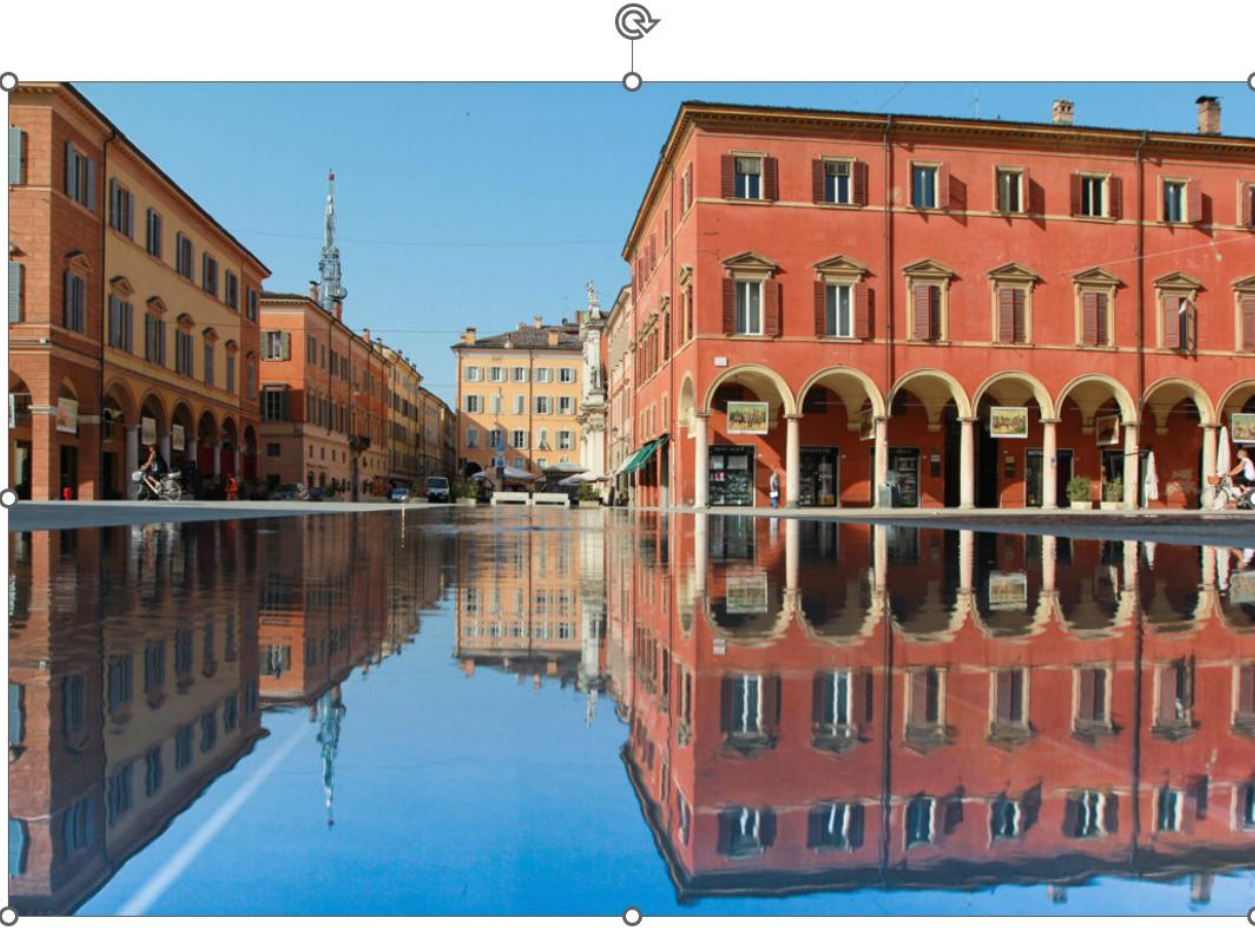
Minimally-invasive surgery is presently the best approach for early-Stage peripheral BCs



BCs conclusions

Conclusions 1/1

- ✓ Approximately 5%-30% BCs are observed in MEN 1 pts (typically females)
- ✓ Usually diagnosed during radiological screening; generally asymptomatic
- ✓ May be multicentric, developing both synchronously and metachronously
- ✓ Unlike TNETs, which have an aggressive clinical course, BCs in MEN 1 pts behave indolently, and radical surgery is the treatment of choice



Modena

Thank you very
much for your
attention

pierluigi.filosso@unimore.it



Discussion



Closing comments

Take-home messages

A BIG "Thank You" to:

- ✓ Our speakers and moderators
- ✓ The ENETS Office team: Leah MATTHEWS, Ulrike KNELL, and Martina FLESCHEN
- ✓ The ENETS Education Group
- ✓ YOU, our valued participants

The ENETS Education Group

- Eric BAUDIN | Endocrinology | France
- Emanuel CHRIST | Endocrinology | Switzerland
- Timm DENECKE | Radiology | Germany
- Antongiulio FAGGIANO | Endocrinology | Italy
- Gregory KALTSAS | Endocrinology | Greece
- Anna KOUMARIANOU | Oncology | Greece
- Francesco PANZUTO | Gastroenterology | Italy
- Margot TESSELAAR | Oncology | The Netherlands

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