

**GEP NEN management
Primary tumour resection in metastatic disease**

**Preceptorship on Neuroendocrine Neoplasms
ESMO**

**28-29 April 2017
Prague**

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Metastasised neuroendocrine tumours

- Symptomatic primary tumours and resectable metastases
- Symptomatic primary tumours and non-resectable metastases
- Asymptomatic primary tumours and resectable metastases
- Asymptomatic primary tumours and non-resectable metastases

Neuroendocrine tumours des GEP systems

ICL 2010-2013

161 GEP NET

	Grade 1	Grade 2	Grade 3
Metastasis	46%	78%	100%
Stage IV	28%	72%	90%
T1-4N0M0	54%	22%	0

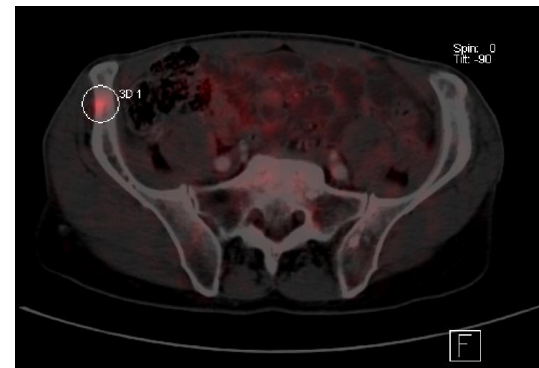
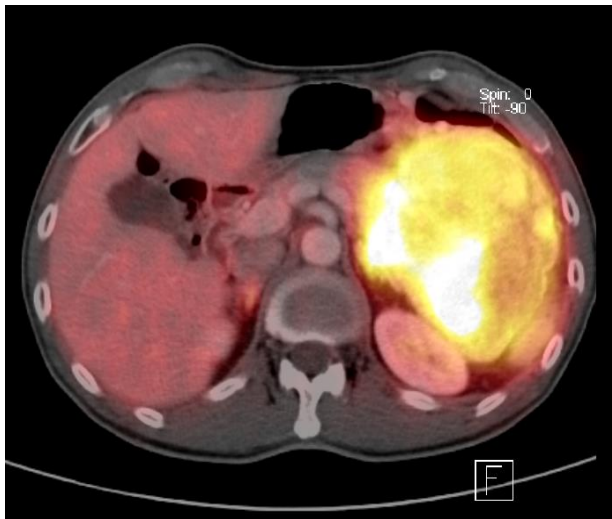
Pancreatic NET: 84, small bowel NET: 37

	PNET	SB NET
Metastasis	43%	92%
Stage IV	32%	65%

Indications for surgery in advanced PNETs

- Reduction of hormonal excess
- Avoidance of symptoms related to the mass effect / local complications
- Possible impact on progression of liver disease and survival
- Measure prior to liver transplantation
- Reduction of tumor mass to increase effectiveness of peptide receptor radionuclide treatment and targeted drugs?

The role of debulking in combination with peptide receptor radiotherapy needs to be evaluated





Symptoms related to the local mass effect

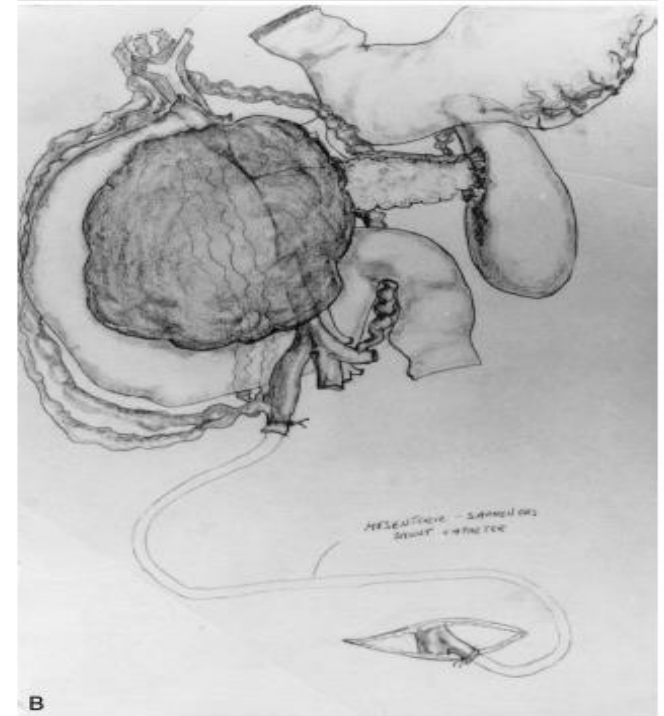
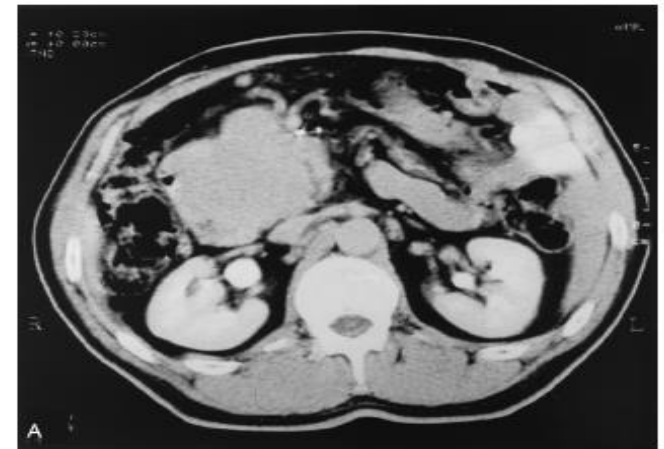
Retroperitoneal extension
48%

Intestinal obstruction
32%

Vascular encasement
14%

Hellman P et al. World J Surg 2000;34,1353

Boudreaux JP et al. Ann Surg 2005;241,839



Should primary PNET be resected in patients with unresectable liver metastases?

Table 1. Summary of the 6 studies initially considered potentially appropriate for the review

Study (first author)	Year of publication	Country	Study period accrual	Setting	Study design	PNET patients	PNETs patients' features	Patients with PNETs and unresectable liver metastases	Treatment comparison	Outcome
Solorzano [19]	2001	USA	1988–1999	single-centre	RCS	163 sporadic	163 NF	96	resected vs. unresected primary	median survival, 5-year survival
Schurr [16]	2007	Germany	1987–2004	single-centre	RCS	62 sporadic	46 NF 8 PDEC	not reported	R0/R1 resected vs. R2/non-resected	5-year survival
Nguyen [18]	2007	USA	1989–1999	single-centre	RCS	73 malignant	51 NF	51	resected vs. unresected primary	5-year survival
Fischer [17]	2008	Germany Switzerland	1994–2006	multi-centre	PCS	118	13 PDEC	23	R0 resection vs. R1/R2 resection vs. exploration	5-year survival
Bettini [15]	2009	Italy	1990–2004	single-centre	PCS	51	51 NF 5 PDEC	51	resected vs. unresected primary	mean survival, PFS
Bruzoni [11]	2009	USA	2001–2008	single-centre	RCS	35	35 NF WDEC	20	no liver metastases vs. liver metastases <50% vs. liver metastases >50%	3-year survival

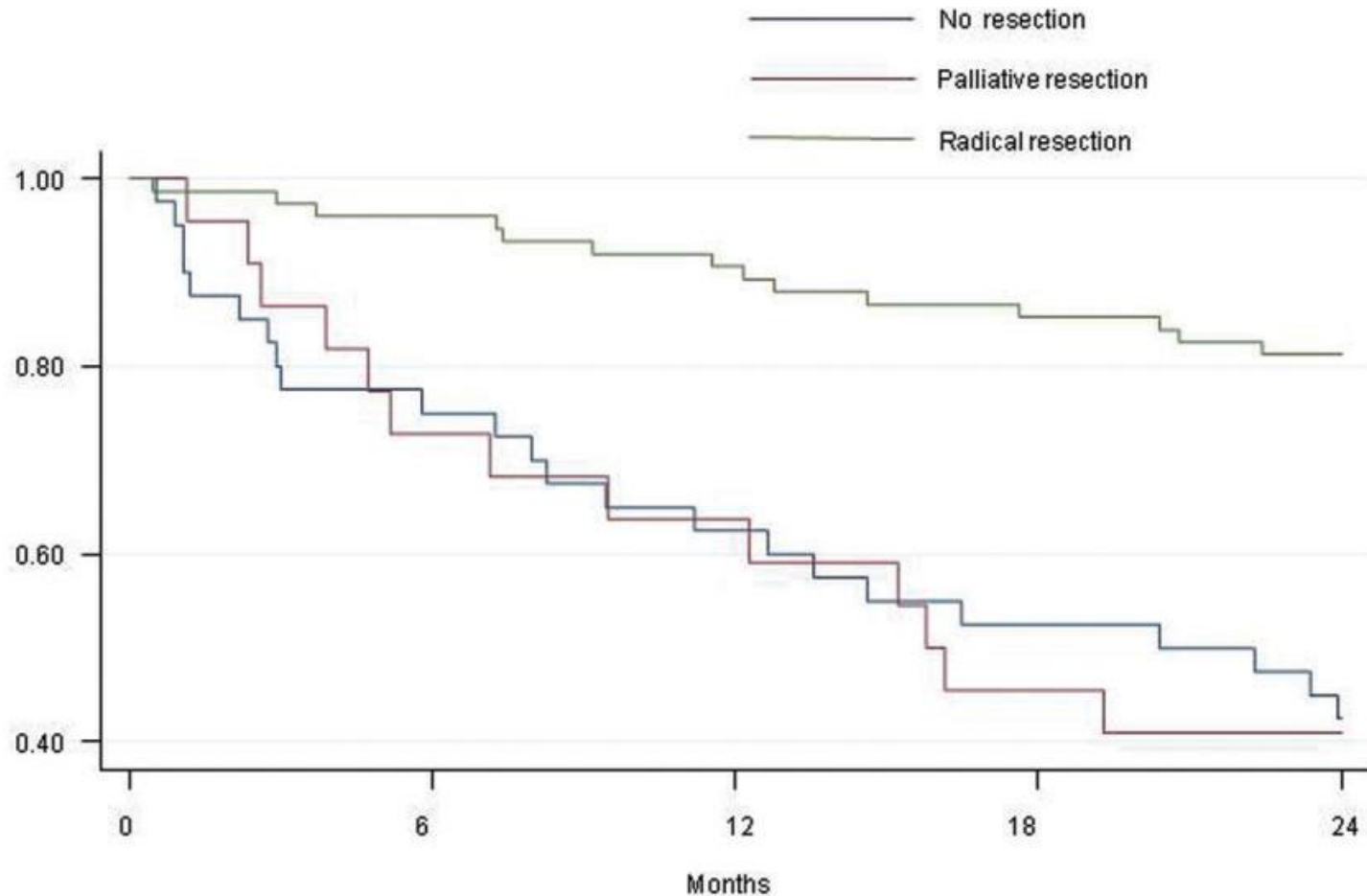
RCS = Retrospective cohort study; PCS = prospective cohort study; PFS = progression-free survival; NF = no-functioning; WDEC = well-differentiated endocrine carcinoma; PDEC = poorly differentiated endocrine carcinoma.

Should primary PNET be resected in patients with unresectable liver metastases?

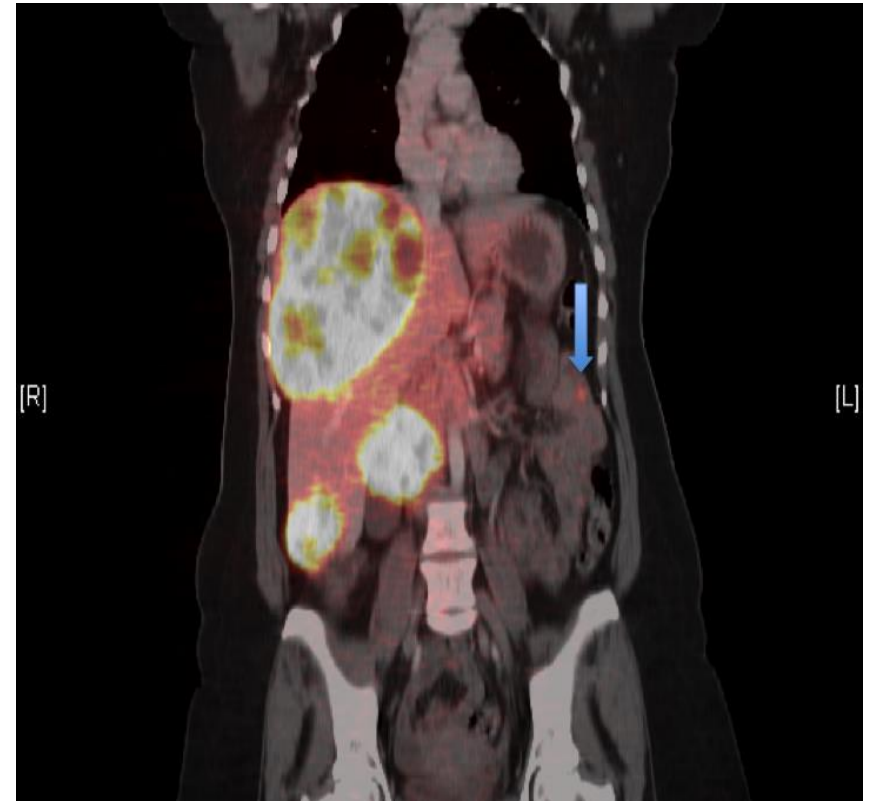
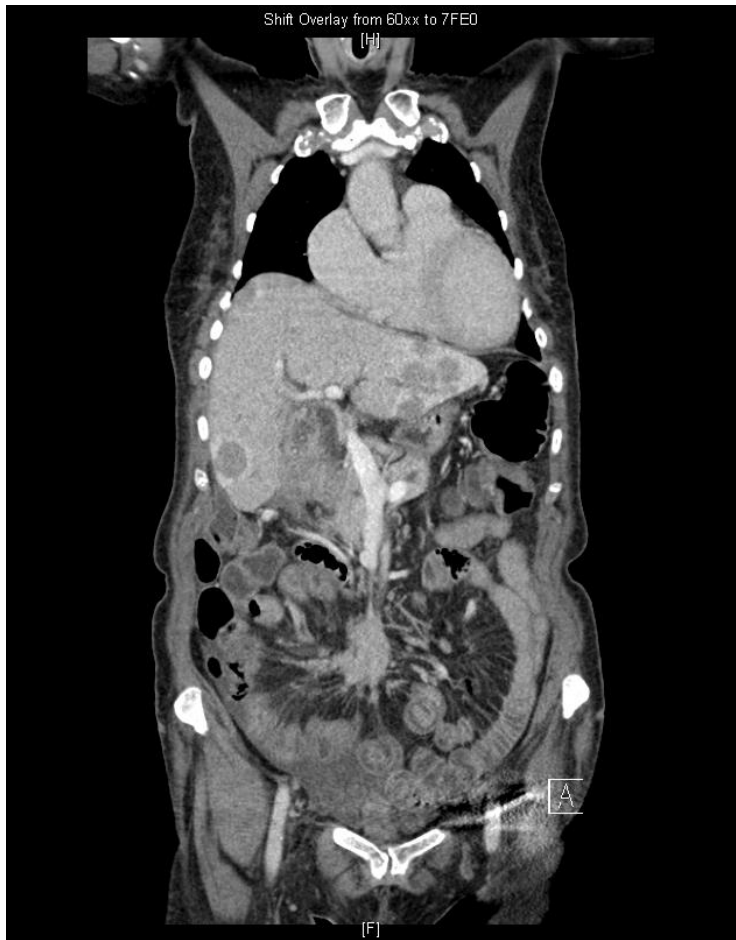
Study (first author)	Median overall survival, months	5-Year survival, %	Median PFS months	Symptom improvement
Bettini [15]				
Resected	54.3 (95% CI 25–86)	40.4	7.6 (95% CI 0.5–14.7)	88%
Unresected	39.5 (95% CI 5.4–73.6)	41.8	12 (95% CI 3.7–20.3)	31%
Nguyen [18]				
Resected	not reported	60	not reported	not reported
Unresected	not reported	30	not reported	not reported
Solorzano [19]				
Resected	36 (95% CI 26.4–96)	49	not reported	not reported
Unresected	21.6 (95% CI 16.8–32.4)	16	not reported	not reported



Pancreatic NET – outcome according to extent of surgical treatment



Metastasised small bowel neuroendocrine tumors



Small bowel neuroendocrine tumors

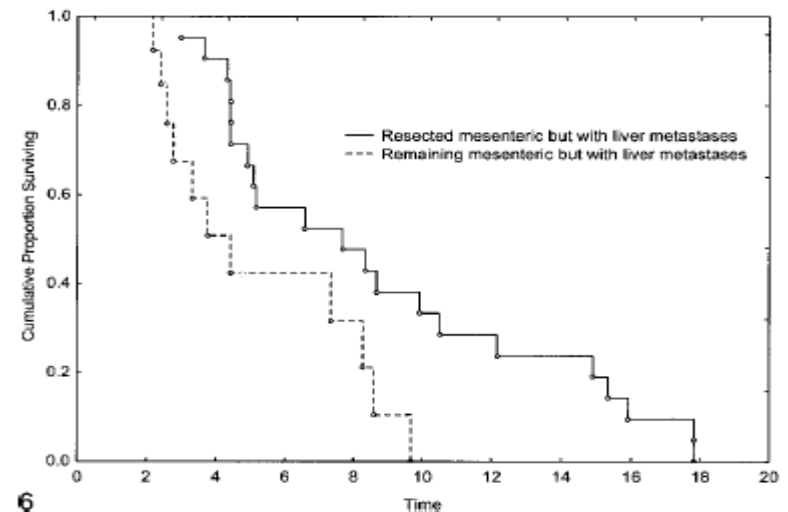
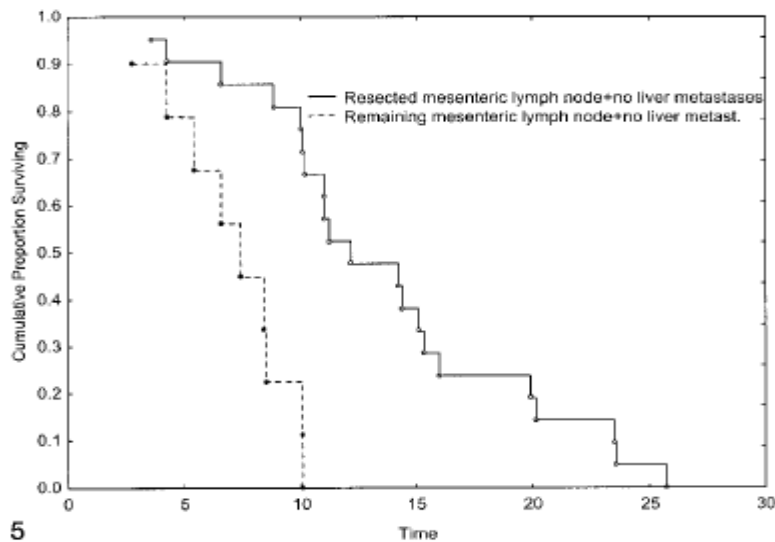
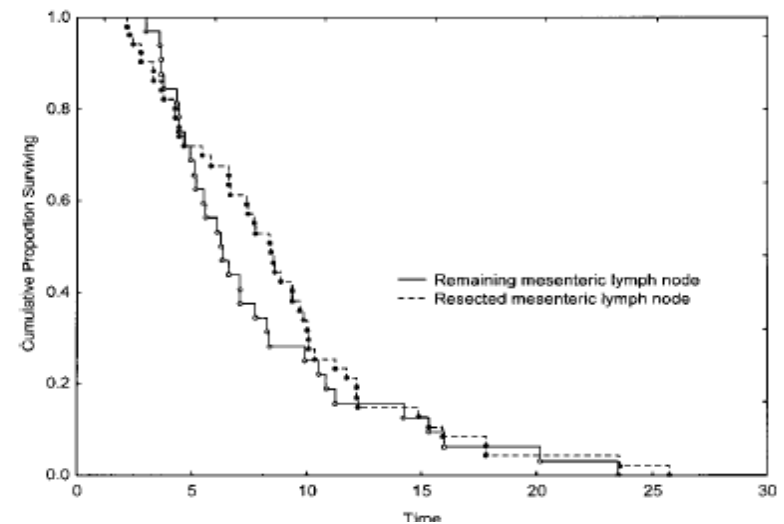
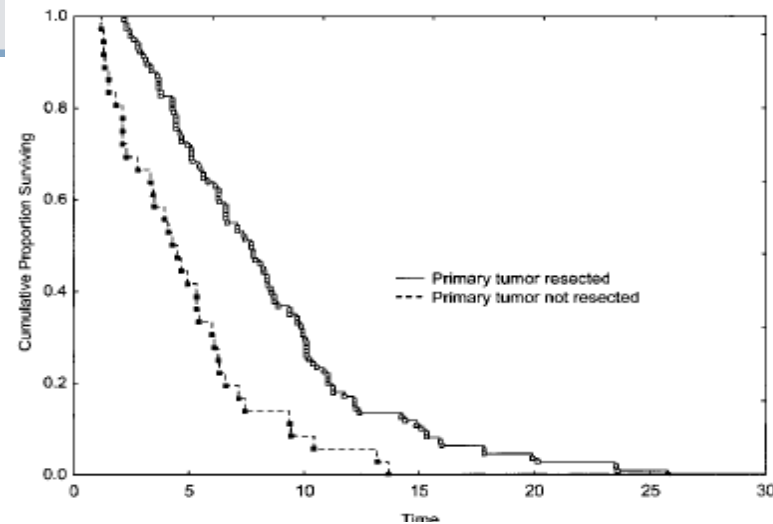
n=84 patients

Parameter	N (%)
Total number of patients	84
Mean age (range)	59.6 years (32 to 88)
Gender	
Male	46 (54.8)
Female	38 (45.2)
Tumor functionality	
Functioning	27 (32.1)
Non-functioning	57 (67.9)
Tumor grade	
G1 (Ki67 \leq 2%)	65 (83.3)
G2 (Ki67 3-20%)	11 (14.1)
G3 (Ki67 >20%)	2 (2.6)

Tumour Stage	N (%)
T ₁₋₄ N ₀ M ₀	9 (10.7)
T ₁₋₄ N ₁ M ₀	24 (28.6)
T ₁₋₄ N ₀ M ₁	1 (1.2)
T ₁₋₄ N ₁ M ₁	50 (59.5)

Locations of distant metastases	N (%)
Liver	45 (53.6)
Bone	1 (1.2)
Peritoneum	2 (2.4)
Liver and bone	2 (2.4)
Liver and peritoneum	1 (1.2)

Long term results of surgery for small intestinal NET



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Should primary midgut NETs be resected in patients with unresectable liver metastases?

Table 1 Summary of the six studies considered for the review

Reference	Year	Country	Study accrual period	Setting and design	Proportion of patients with SI-NETs*	Male sex (%)	Age (years)†	Treatment(s) compared	Outcome
Givi <i>et al.</i> ¹⁸	2006	Oregon, USA	1995–2006	Single RCS	76 of 84 (90)	51	NR	Resected <i>versus</i> unresected	PFS, median OS, 5-year survival
Strosberg <i>et al.</i> ¹⁹	2009	Florida, USA	1999–2003	Single RCS	146 of 146 (100)	44.6	60 (14–84)	Resected <i>versus</i> unresected	Median OS, 5-year survival
Ahmed <i>et al.</i> ²⁰	2009	UK	1973–2007	Multicentre RCS	319 of 360 (88.6)	52.5	61.5 (16–86)	Resected <i>versus</i> unresected	Median OS, 5-year survival
Søreide <i>et al.</i> ²¹	1992	Norway	1960–1989	Single RCS	65 of 75 (87)	NR	61 (18–80)	Resected <i>versus</i> unresected and resection <i>versus</i> no resection of metastases	Median OS
Norlén <i>et al.</i> ²²	2012	Sweden	1985–2010	Single RCS	603 of 603 (100)	53.9	63.1(11.3)‡	Resected <i>versus</i> unresected	5-year survival
van der Horst-Schrivers <i>et al.</i> ²³	2007	The Netherlands	1992–2003	Single RCS	47 of 76 (62)	NR	59.4‡	Resected <i>versus</i> unresected	Median OS, 5-year survival

*Values in parentheses are percentages. †Values are median (range) unless indicated otherwise; ‡values are mean(s.d.). SI-NET, small intestinal neuroendocrine tumour; RCS, retrospective cohort study; PFS, progression-free survival; OS, overall survival; NR, not reported.

Should primary midgut NETs be resected in patients with unresectable liver metastases?

Reference	No. of patients	Median overall survival (months)	5-year survival (%)	Median progression-free survival (months)
Givi <i>et al.</i> ^{18*}	Resected 66	108	81	54
	Unresected 18	50	21	27
Strosberg <i>et al.</i> ¹⁹	Resected 100	110	NR	NR
	Unresected 35	88	NR	NR
Ahmed <i>et al.</i> ²⁰	Resected 209	119 (89, 149)	74	NR
	Unresected 76	57 (32, 81)	46	NR
Søreide <i>et al.</i> ²¹	Resected 53	139	NR	NR
	Unresected 12	69	NR	NR
Norlén <i>et al.</i> ²²	Resected 493	NR	75	NR
	Unresected 86	NR	28	NR
Van der Horst-Schrivers <i>et al.</i> ²³	Resected 27	75 (44, 107)	57	NR
	Unresected 49	52 (37, 68)	44	NR



The potential for induction peptide receptor chemoradionuclide therapy to render inoperable pancreatic and duodenal neuroendocrine tumours resectable

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Neoadjuvant Treatment of Nonfunctioning Pancreatic Neuroendocrine Tumors with [¹⁷⁷Lu-DOTA⁰,Tyr³]Octreotate

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Eur J Nucl Med Mol Imaging (2011) 38:1669–1674
DOI 10.1007/s00259-011-1835-8

ORIGINAL ARTICLE

Peptide receptor radionuclide therapy as a potential tool for neoadjuvant therapy in patients with inoperable neuroendocrine tumours (NETs)

Anna Sowa-Staszczak • Dorota Pach • Robert Chrzan • Małgorzata Trofimiuk •
Agnieszka Stefańska • Monika Tomaszuk • Maciej Kołodziej • Renata Mikołajczak •
Dariusz Pawlak • Alicja Hubalewska-Dydejczyk

- 36-year old male diagnosed with malignant insulinoma (G2 PNET, pancreatic tail tumor, bilobar LM, LN and bone metastases), severe hypoglycaemia in 2012
- Glucose 41 mg/dl, chromogranin A >300 pmol/L
- Not suitable for resection or LTX + resection
- Treatment with Diazoxide, Everolimus, Sandostatin LAR, TACE of the right liver lobe
- Ineffective symptom control, no reduction of tumor mass



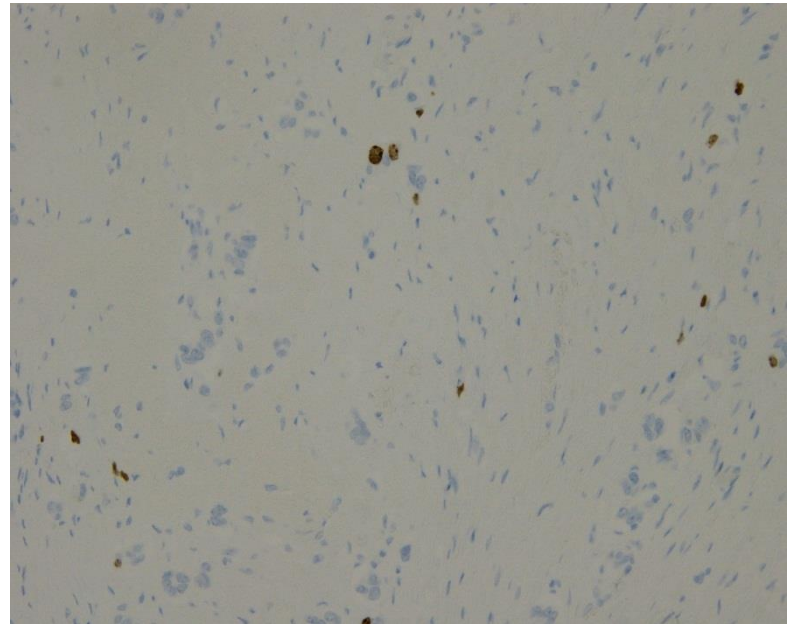
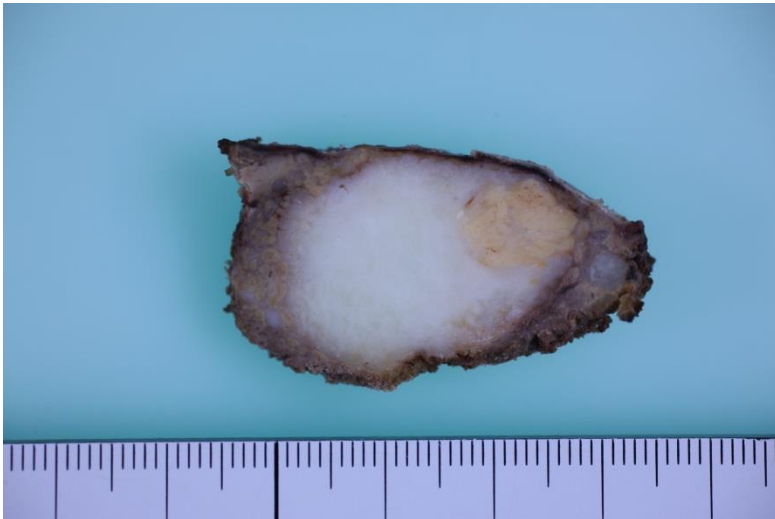
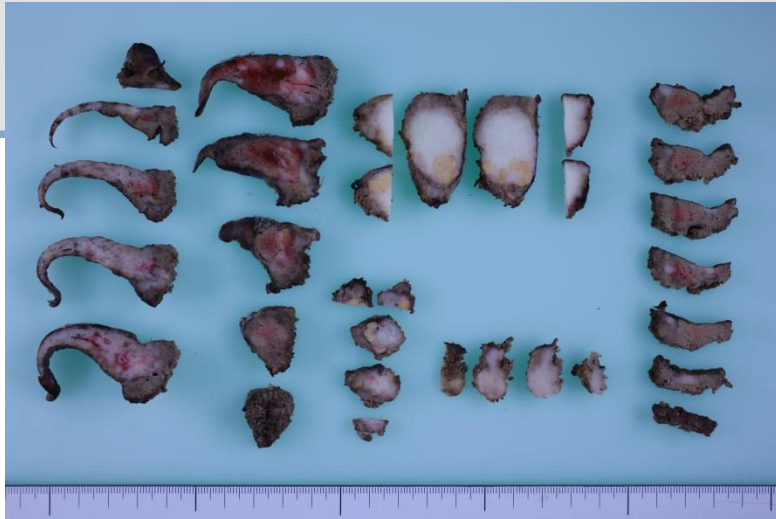
*BEFORE ^{177}Lu PRRT
(2012))*



After 4 Doses (2013)



After 6 Doses (2014)



12-month follow-up

- Patient asymptomatic
- Back to work as a cardiologist
- Glucose, insulin, C-peptide, CgA – normal
- No evidence of progression on CT and MRI liver
- 68 Ga DOTATATE PET/CT no uptake
- On Lanreotide 120 mg 4-weekly

