

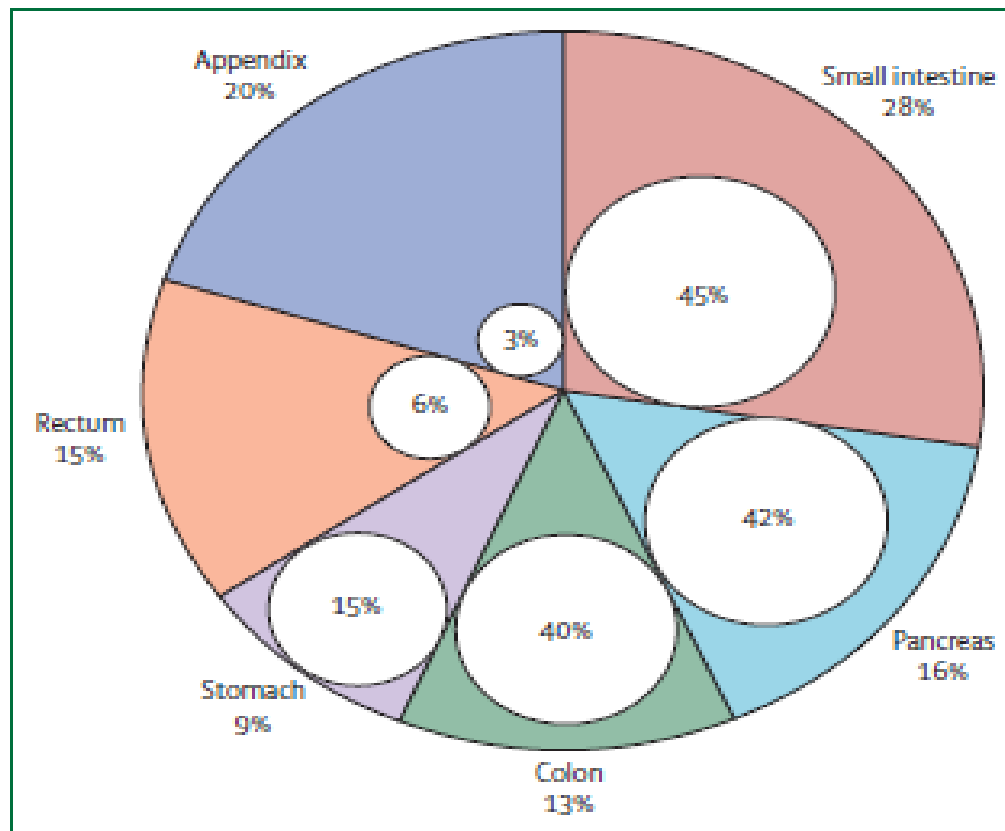
**GEP NEN management
Liver-directed treatments – Surgical approach**

**Preceptorship on Neuroendocrine Neoplasms
ESMO**

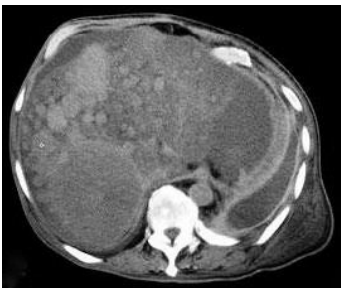
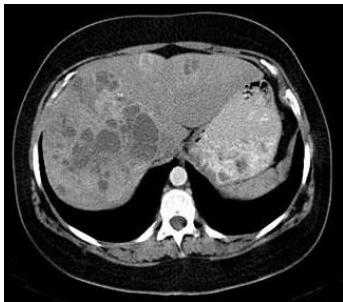
**28-29 April 2017
Prague**

**Professor Andrea Frilling
Department of Surgery and Cancer
Imperial College London
ENETS Center of Excellence**

Incidence of GEP NET LM in relation to the primary tumor site



Neuroendocrine liver metastases



1. Synchronous liver metastases

Primary tumor

Extrahepatic disease +/-

2. Metachronous liver metastases

Extrahepatic disease +/-

Locoregional recurrence (lung, pancreas) +/-

3. Liver metastases (NE CUP)

Unknown primary tumor site

Extrahepatic disease +/-

4. Growth type of liver metastases

Type I, II, III

5. Site of the primary tumor

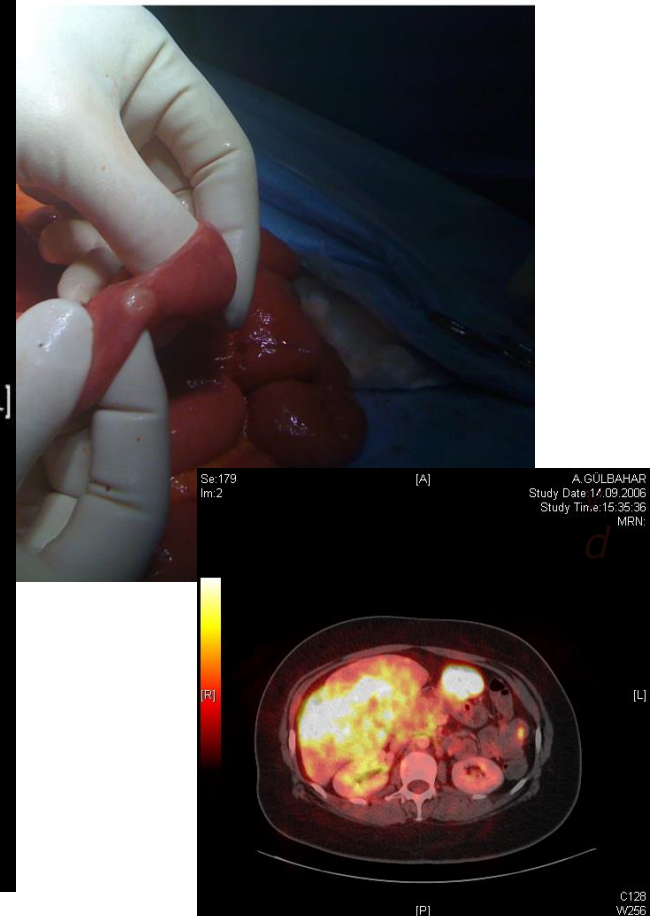
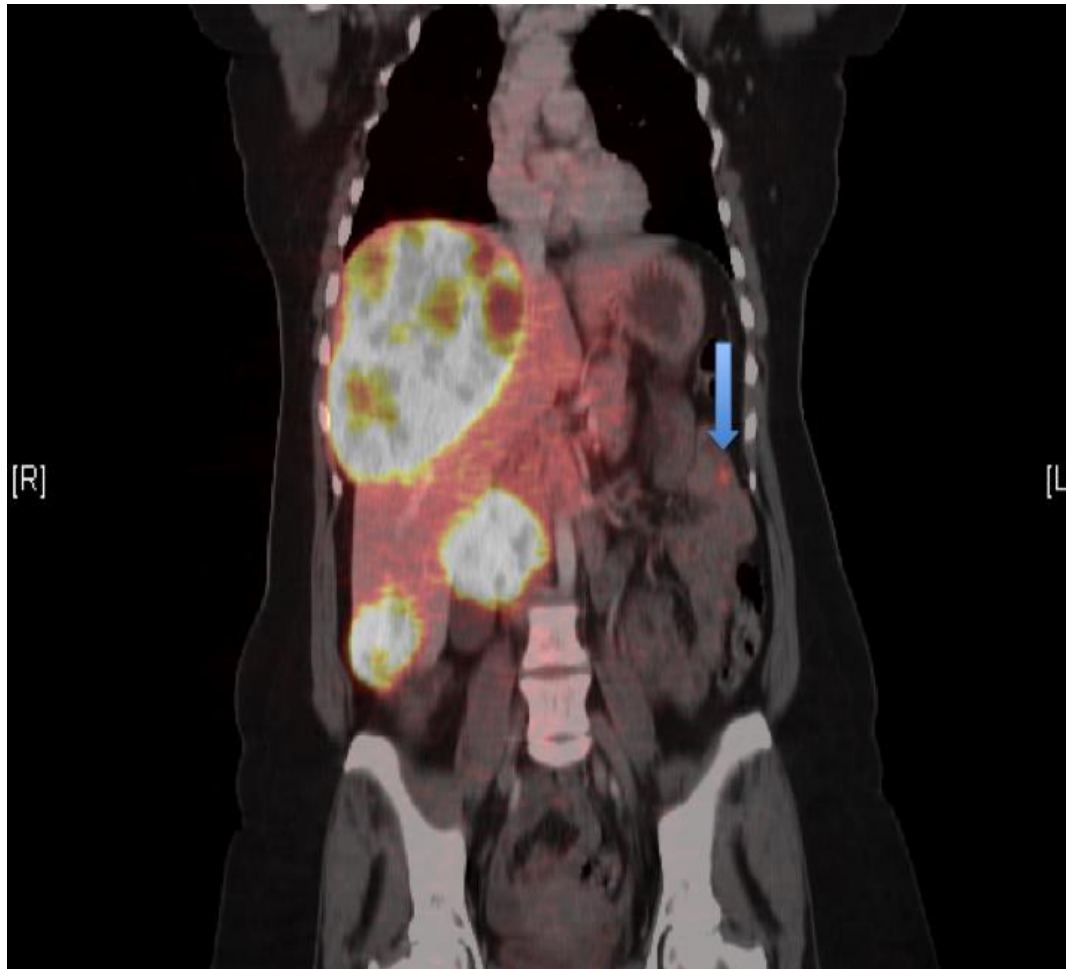
Pancreas, small bowel, bronchopulmonary system

6. Tumor grade

G1, G2, G3

7. Carcinoid syndrome / Carcinoid heart

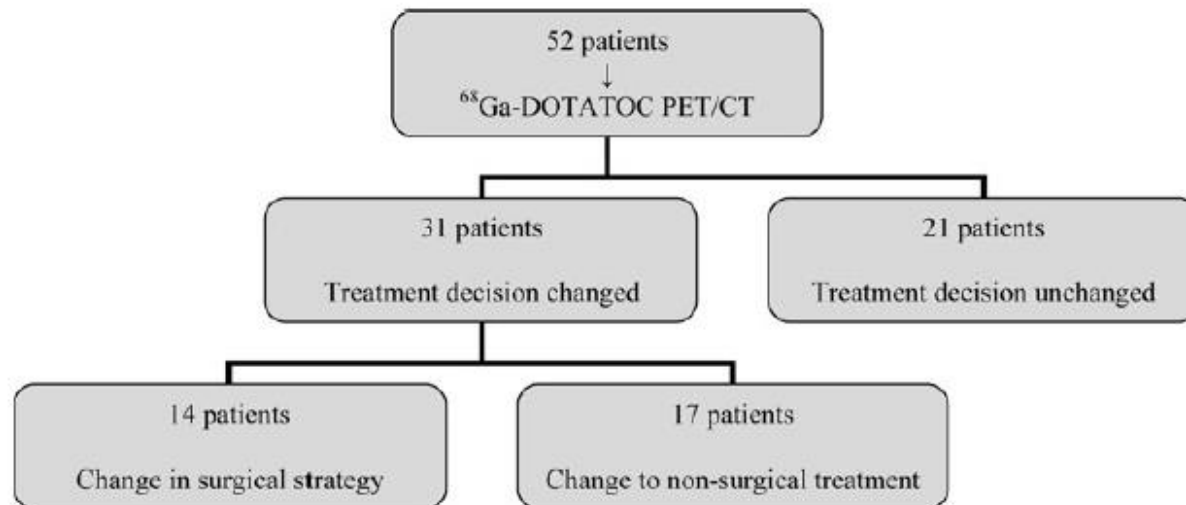
68Ga-DOTATOC PET/CT – Detection of LM and the primary tumor



68Ga-DOTATOC PET/CT changes initial treatment decision in up to 60% of patients with NE liver metastases

TABLE 1. Comparison of ^{68}Ga -DOTATOC PET/CT and Standard Imaging With CT and/or MRI in Detection of Lesion Site

Lesion Site	^{68}Ga -DOTATOC PET/CT, No. Patients	Standard imaging, No. Patients	<i>P</i>
Primary tumor	11/12	8/12	1.00
Primary tumor recurrence	8/40	2/40	<0.001
Liver	40/52	33/52	0.251
Lymph nodes	21/52	7/52	<0.001
Skeletal system	7/52	2/52	<0.001
Lung	2/52	0/52	<0.001



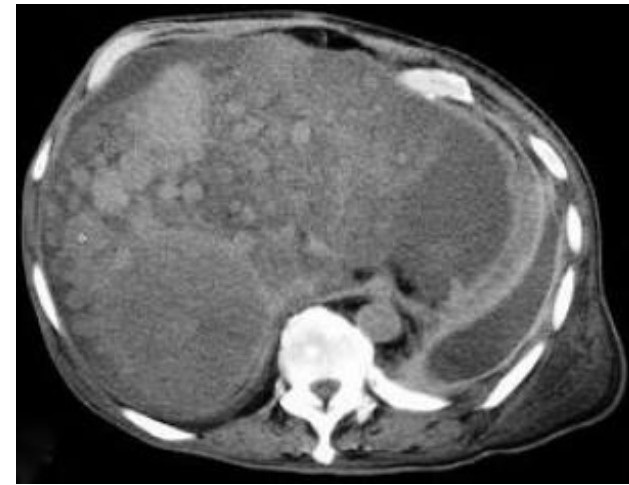
Neuroendocrine liver metastasis – morphologic growth types



Type I: Single metastasis



Type II: isolated metastatic bulk accompanied with smaller deposits



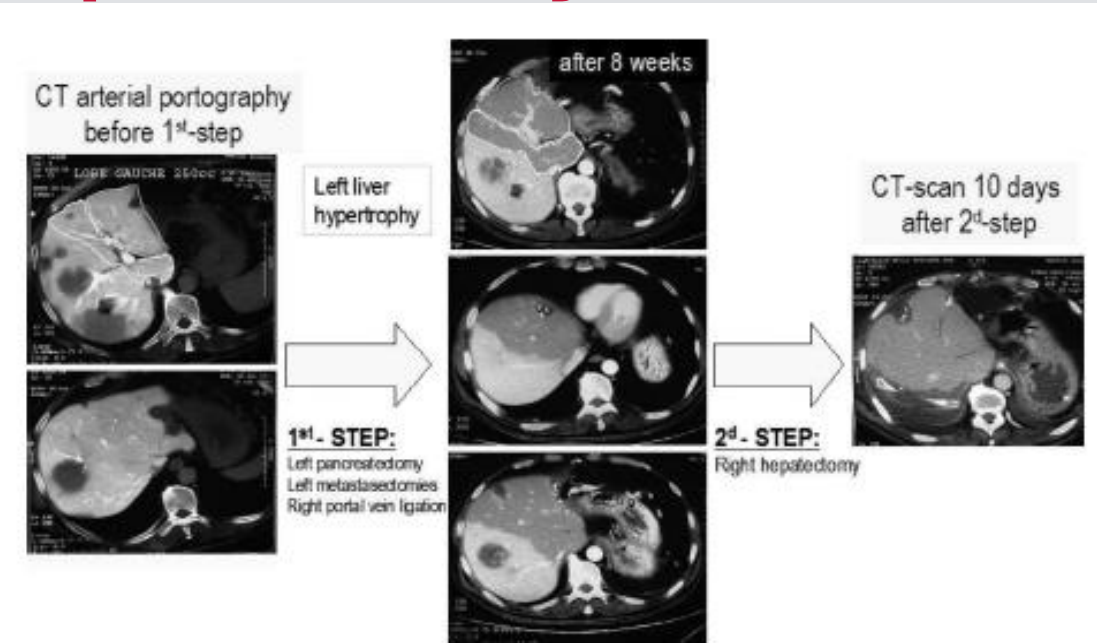
Type III: disseminated metastatic spread

20-30% of the patients with NE LM are potential candidates for surgery with radical (“curative”) intent

Techniques to improve resectability

Downstaging

Chemotherapy
TACE
PRRT
Radioembolization



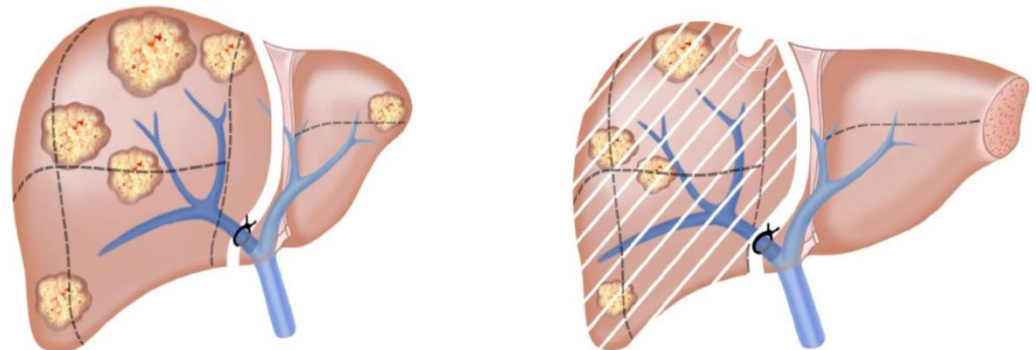
Improvement of resectability

PVE
Resection + RFA

Two stage hepatectomy

ALPPS

Kianmanesh R et al. Ann Surg 2008;247:659



Schadde E et al. World J Surg. 2014 Jun;38(6):1510-9

Ablative treatment of neuroendocrine liver metastases

RFA, LITT, microwave, cryoablation

Overall 5-year survival 37-53%

Limited hepatic tumor burden

Predominant lesion < 5cm

Post-ablation margin >1cm

Median overall survival 6 years

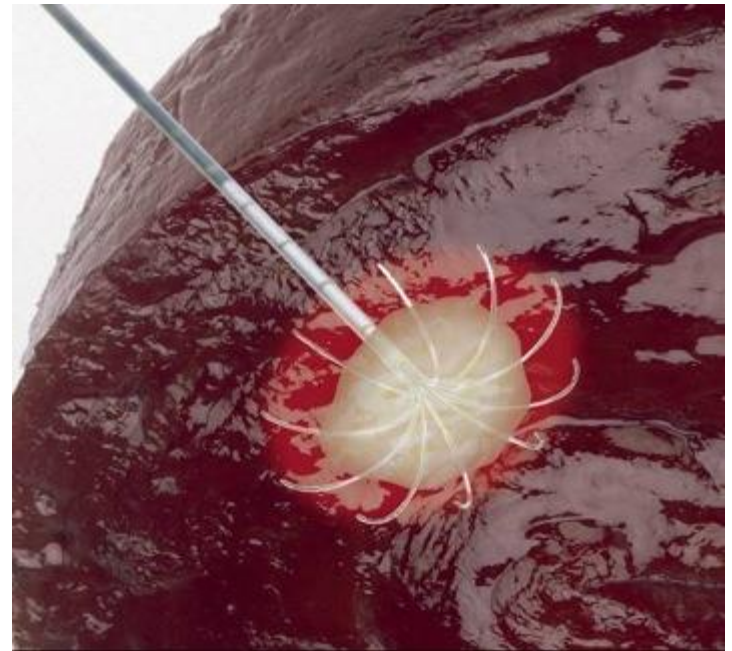
Median disease-free survival 1.3 years

At median follow-up of 30 months

23% local recurrence

63% new lesions

53% extrahepatic disease



Outcomes from liver resection for NE LM

Reference	No. of Patients Undergoing Resection	No. of R0 Resections	5-Year OS, %	5-Year DFS, %	Other Survival Data After R0 Resection	30-Day Morbidity and Mortality
Saxena 2011 ³⁰	74	28	NR	NR	Median OS, 73 mo	Mortality, 1.3% (4% at 60 d)
Scigliano 2009 ³¹	41	26	88	31		Morbidity, 14%; mortality, 0%
Frilling 2009 ²¹	27	23	100	96		Morbidity, 7.4%; mortality, 0%
Gomez 2007 ³²	18	15	86	90		Morbidity, 22%; mortality, 5.6%
Elias 2003 ³³	47	25	74	66		Morbidity, 45%; mortality, 5%
Sarmiento 2003 ³⁴	170	75		76		Morbidity, 14%; mortality, 1.2%
Norton 2003 ³⁵	16	16	82			Morbidity, 19%; mortality, 0%
Nave 2001 ³⁶	31	10	86		Median survival, 70 mo	Morbidity, 13%
Coppa 2001 ³⁷	20	20	67	29		NR
Yao 2001 ³⁸	16	16	70			Morbidity, 12%; mortality, 0%
Chamberlain 2000 ³⁹	34	15	85			Mortality, 6%
Pascher 2000 ⁴⁰	26	13	NR	NR		Mortality, 0%

Abbreviations: DFS, disease-free survival; NR, not reported; OS, overall survival; R0, resection with negative margins.

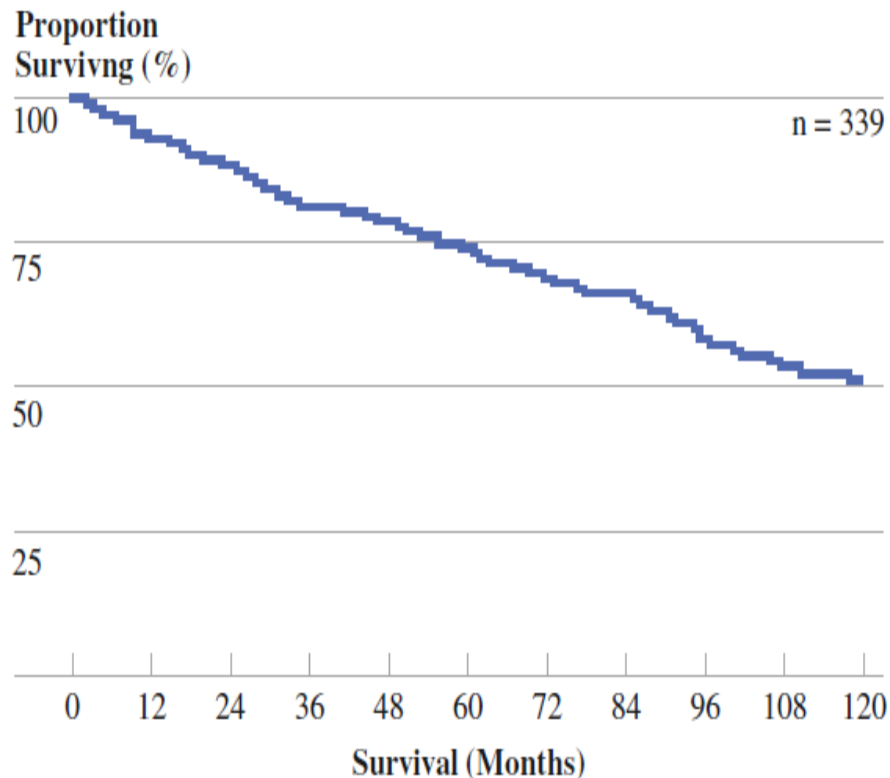
5-year survival: 67 – 100%

5-year disease-free survival: 29 – 96%

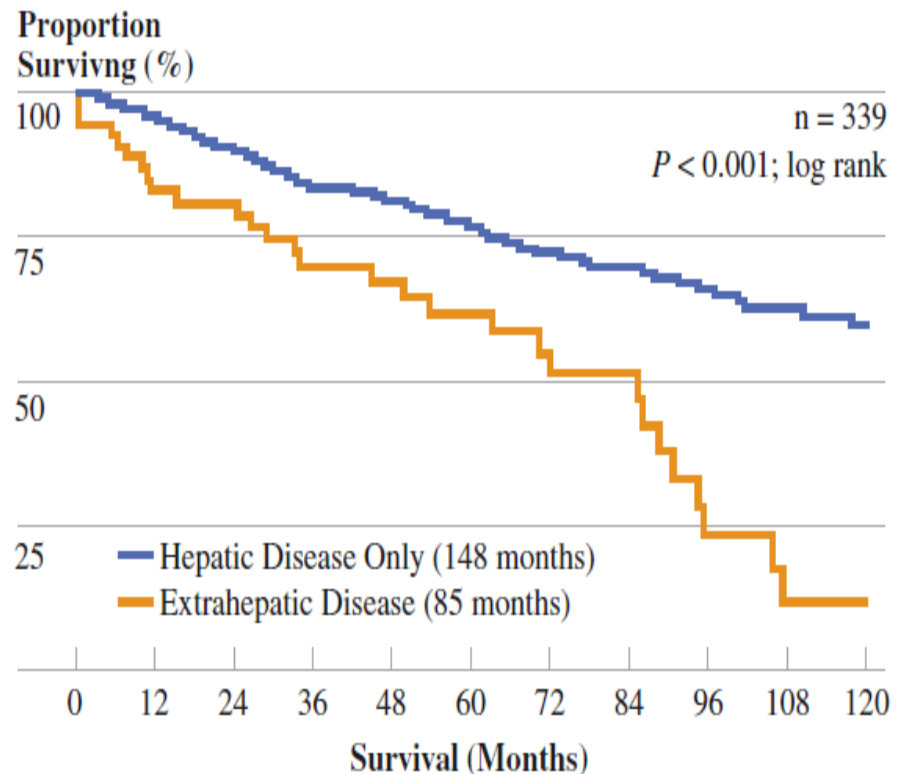
30-day mortality: 0 – 6%

Surgical management of NE LM

- International multi-institutional analysis -



5-year survival 74%
10-year survival 51%



5%-year disease recurrence 94%

Hepatic Metastases From Neuroendocrine Tumors With a “Thin Slice” Pathological Examination

They are Many More Than You Think . . .

Elias D et al. Ann Surg 2010;251:307-310

TABLE 1. Histological, Preoperative Examinations, and Peroperative Exploration Results of 11 Hepatectomies for Neuroendocrine Tumor

Patient	Primary Tumor	Type of Hepatectomy	No. LM Preoperatively Identified on Imaging							
			Pathologic Findings		Ultrasound Examination		CT-Scan	MRI	Somatostatin Receptor Scintigraphy	Intraoperative Findings
			No. LM	Size cm (min-max)	Normal	Contrast Enhanced				
1	Not identified	Right	13	(0.6–7)	8	8	6	7	0	9
2	Stomach	Left	5	(0.25–1.2)	4	4	4	3	2	5
3	Insulinoma	Right	22	(0.1–2.5)	7	8	5	10	3	10
4	Glucagonoma	Left	59	(0.1–3.5)	4	7	6	13	3	18
5	Insulinoma	Left	9	(0.7–5.5)	4	NA	5	9	0	6
6	Small bowel	Right	16	(0.5–3.5)	7	7	4	7	3	4
7	Small bowel	Right	13	(0.5–5)	6	NA	7	7	10	10
8	Small bowel	Left	12	(0.1–1.4)	2	3	3	2	0	3
9	Lung carcinoma	Right	8	(0.2–5)	3	NA	4	5	3	5
10	Zollinger-Ellison	Left	88	(0.1–5)	0	8	2	6	3	8
11	Glucagonoma	Right	28	(0.2–5)	15	NA	12	20	7	17
Total			273		60	45	58	89	34	95
Mean			24.8 ± 25.7		5.4 ± 3.9	6.4 ± 2.1	5.3 ± 2.7	8.1 ± 5.0	3.1 ± 3.0	8.6 ± 5.0
Median			13		4	7	5	7	3	8

NA indicates non applicable.

Liver transplantation for neuroendocrine liver metastases

First Author	Year	Patients	Overall Survival					Disease-Free Survival			
			1-year (%)	2-year (%)	3-year (%)	5-year (%)	10-year (%)	1-year (%)	3-year (%)	5-year (%)	10-year (%)
Bonaccorsi-Riani[17]	2010	9	88		77	33		67	33	11	
Olausson[13]	2007	15 ^a				90			70	20	
Marin[18]	2007	10	86		57				38		
Mazzaferro[12]	2007	24				90				77	
van Vilsteren[19]	2006	19	88					80			
Frilling[20]	2006	15	78.3			67.2		69.4		48.3	
Florman[21]	2004	11	73			36					
Cahlin[22]	2003	7		80							
Rosenau[11]	2002	19	89			80	50	56		21	21
Coppa[23]	2001	9				70				53	

a = includes 5 patients undergoing multivisceral transplantation.

Liver Transplantation for Neuroendocrine Tumors in Europe—Results and Trends in Patient Selection

A 213-Case European Liver Transplant Registry Study

5-year OS 52% and DFS 30%

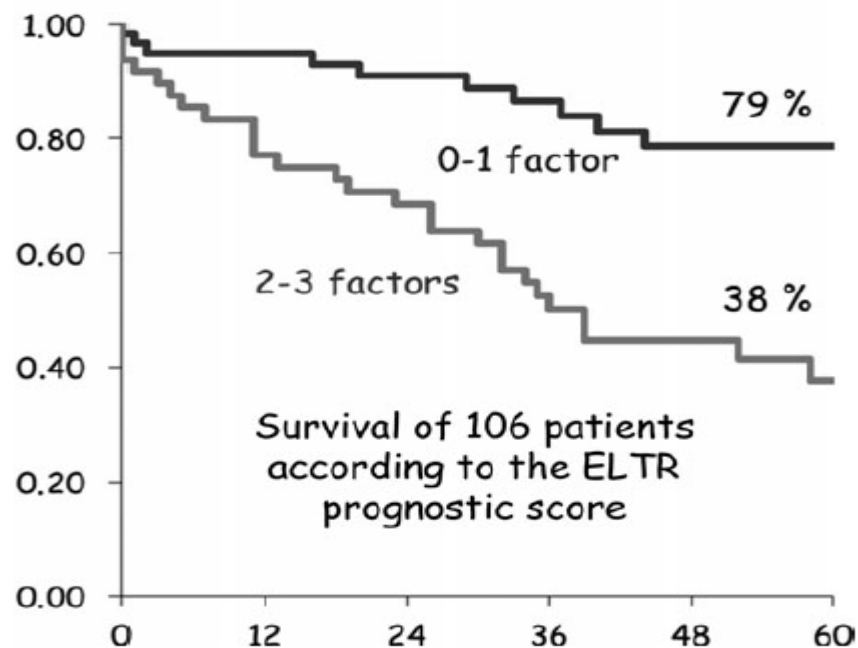


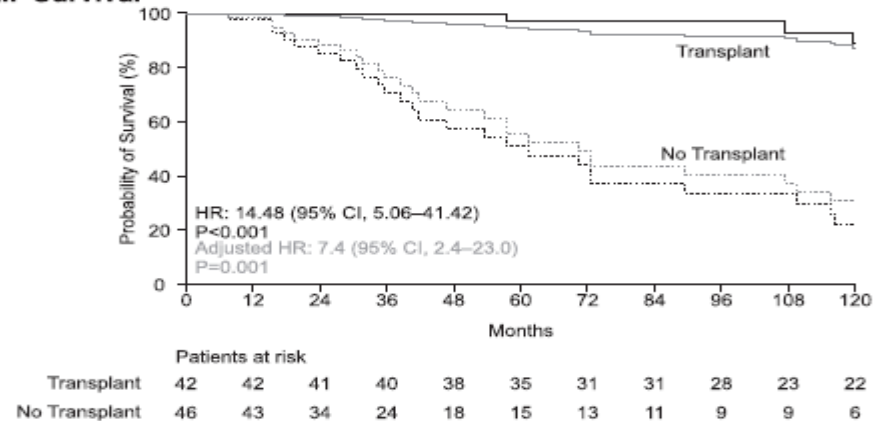
FIGURE 2. Overall survival of 106 patients according to the number of adverse prognostic factors: hepatomegaly, resection in addition to LT, and age more than 45 years. Top: 5-year survival rates: 77%, 79%, 39%, and 33% for 0, 1, 2, or 3 factors, respectively. Bottom: after gathering in 2 groups. 0–1 factors ($n = 58$) and 2–3 factors ($n = 48$). $P < 0.0001$.

Long-Term Benefit of Liver Transplantation for Hepatic Metastases From Neuroendocrine Tumors

at 5 and 10 years in survival (97.2% and 88.8% vs. 50.9% and 22.4%, respectively; $p < 0.001$) and time-to-progression (13.1% and 13.1% vs. 83.5% and 89%;

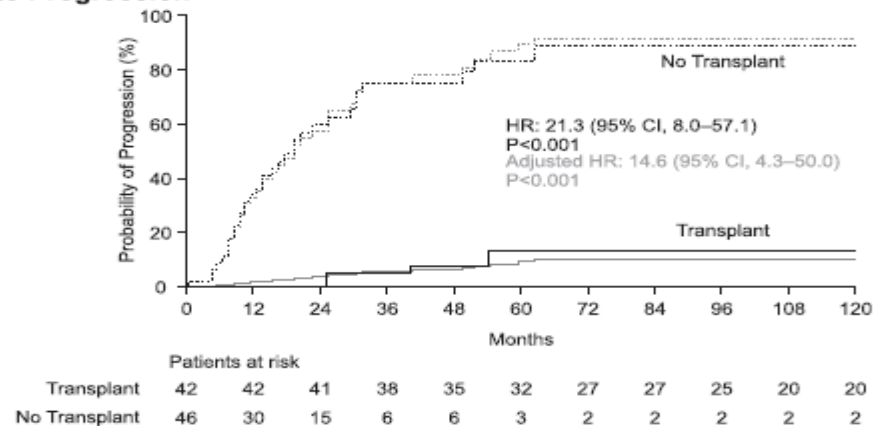
A

Overall Survival



B

Time to Progression

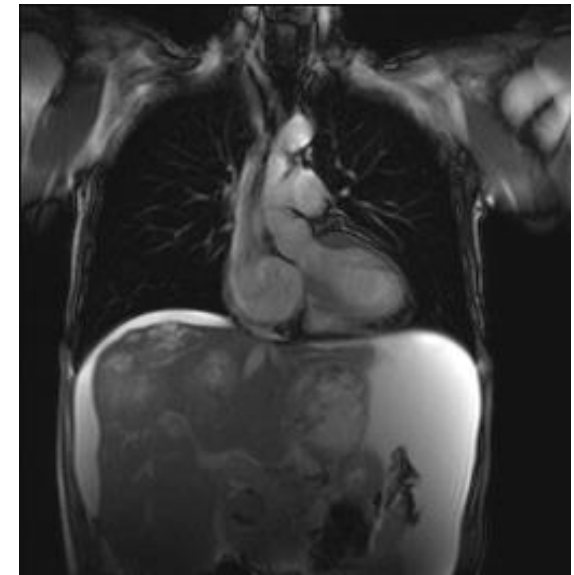
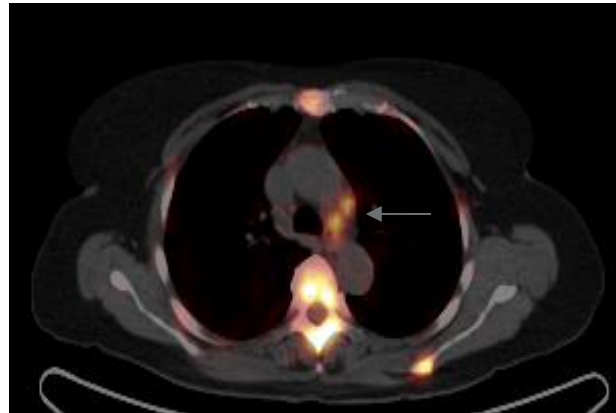
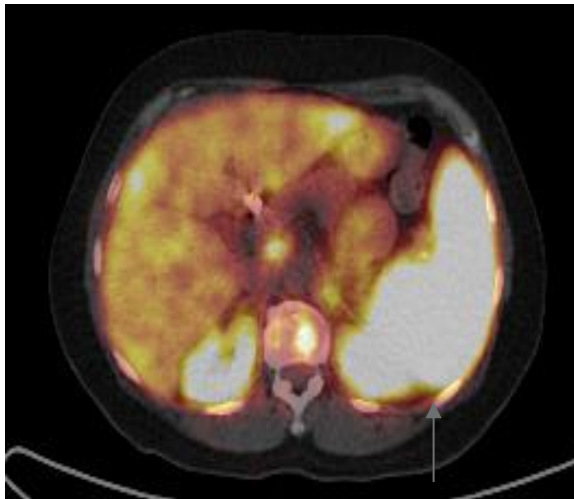


Exclusion criteria for liver transplantation in NET patients

[HPB \(Oxford\)](#). 2015 Jan;17(1):23-8. doi: 10.1111/hpb.12308. Epub 2014 Jul 3.

Liver transplantation for neuroendocrine tumour liver metastases.

[Fan ST¹](#), [Le Treut YP](#), [Mazzaferro V](#), [Burroughs AK](#), [Olausson M](#), [Breitenstein S](#), [Frilling A](#).



Ki67 >20%

No portal venous drainage

Liver involvement ?%

Mazzaferro < 25% - 50%

Staged surgery with neoadjuvant ^{90}Y -DOTATOC therapy for down-sizing synchronous bilobular hepatic metastases from a neuroendocrine pancreatic tumor

Oliver Stoeltzing • Martin Loss • Elisabeth Huber •
Volker Gross • Christoph Eilles • Jan Mueller-Brand •
Hans J. Schlitt



Available online at www.sciencedirect.com
SciVerse ScienceDirect

EJSO 38 (2012) 64–71

EJSO
the Journal of Cancer Surgery
www.ejso.com

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

T.W. Barber ^{a,*,1}, M.S. Hofman ^{a,b,1}, B.N.J. Thomson ^{b,c,2}, R.J. Hicks ^{a,b,1}

^a Centre for Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, Victoria 3002, Australia

^b The University of Melbourne, Melbourne, Victoria 3010, Australia

^c Department of Surgical Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria 3002, Australia

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Available online 8 September 2011

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

Esther I. van Vliet¹, Casper H. van Eijck², Ronald R. de Krijger³, Elisabeth J. Nieveen van Dijkum⁴, Jaap J. Teunissen¹, Boen L. Kam¹, Wouter W. de Herder⁵, Richard A. Feelders⁵, Bert A. Bonsing⁶, Tessa Brabander¹, Eric P. Krenning¹, and Dik J. Kwekkeboom¹

¹Department of Nuclear Medicine, Erasmus MC, University Medical Center, Rotterdam, The Netherlands; ²Department of Surgery, Erasmus Michoacande Ocampo, University Medical Center, Rotterdam, The Netherlands; ³Department of Pathology, Erasmus Michoacande Ocampo, University Medical Center, Rotterdam, The Netherlands; ⁴Department of Surgery, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; ⁵Department of Internal Medicine, Erasmus MC, University Medical Center, Rotterdam, The Netherlands; and ⁶Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands.

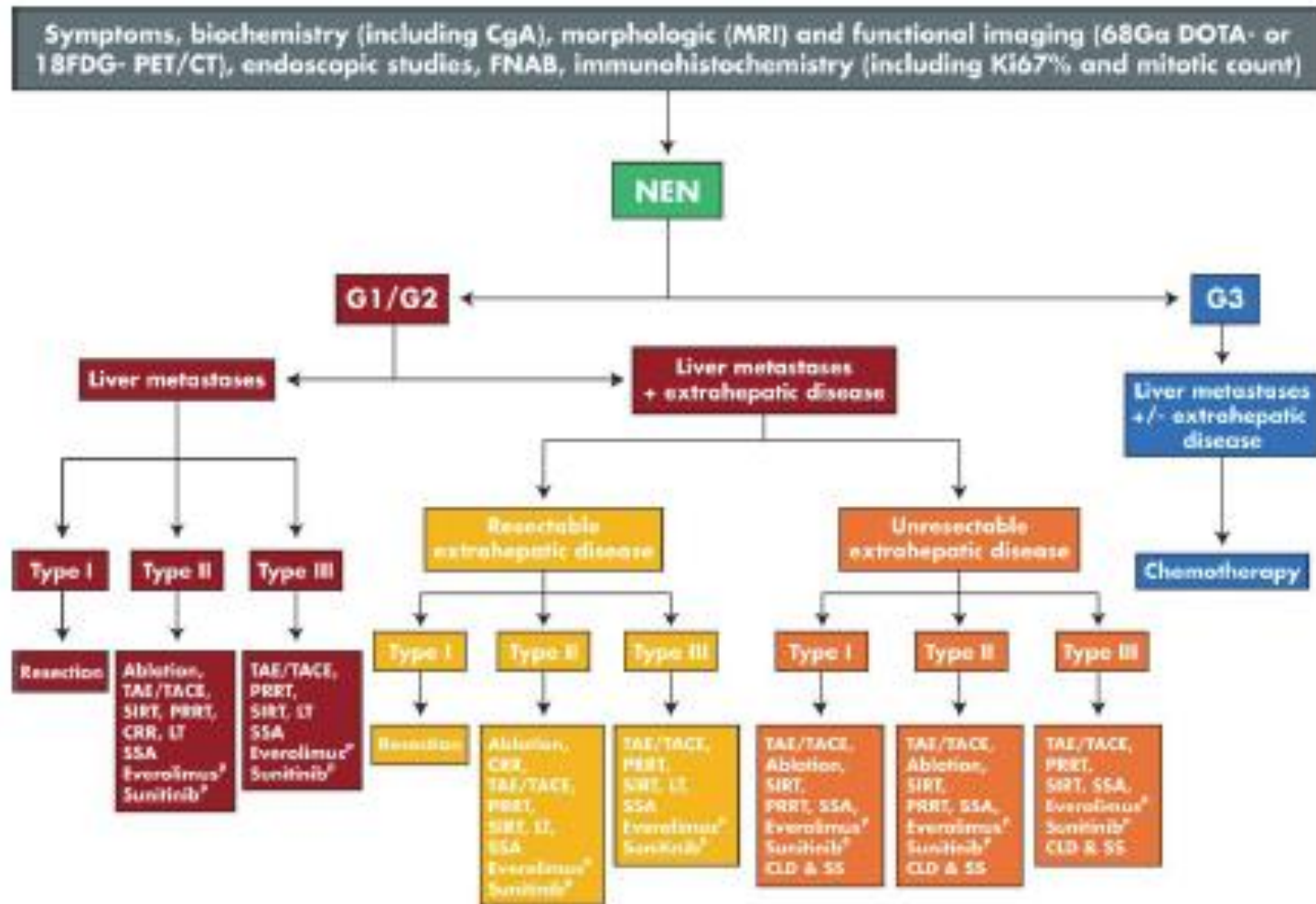
Eur J Nucl Med Mol Imaging (2011) 38:1669–1674
DOI 10.1007/s00259-011-1835-8

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

Management of neuroendocrine liver metastases



Survival following surgery of NE LM compared to other treatment modalities – systematic review

