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GEP NEN

Personalised approach

Curative and Palliative Surgery

ESMO Preceptorship Programme
Neuroendocrine Neoplasms
Lugano
13 – 14 April 2018

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

European ENETS Neuroendocrine Tumor Society

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Disclosure

- Grants received:
- IPSEN
- Novartis
- AAA
- Sirtex
- Merck

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Patient tailored surgery – precision surgery

- Surgery based on patient and tumour specific features
- No more “All for One” but “One for One”
- Tumour stages III and IV frequently seen
- Multimodal treatment rather than surgery alone
- Surgery based on “omic” results

  gDNA, mRNA, miRNA, CTC, NET gene transcripts, proteomics, epigenetics, metabonomics
- Monitoring of a patient journey based on “omic” results

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Gastrinoma

- MEN 1 -

Distal pancreatectomy

Spleen saving

Resection of NE tumors

Head

Uncinate process

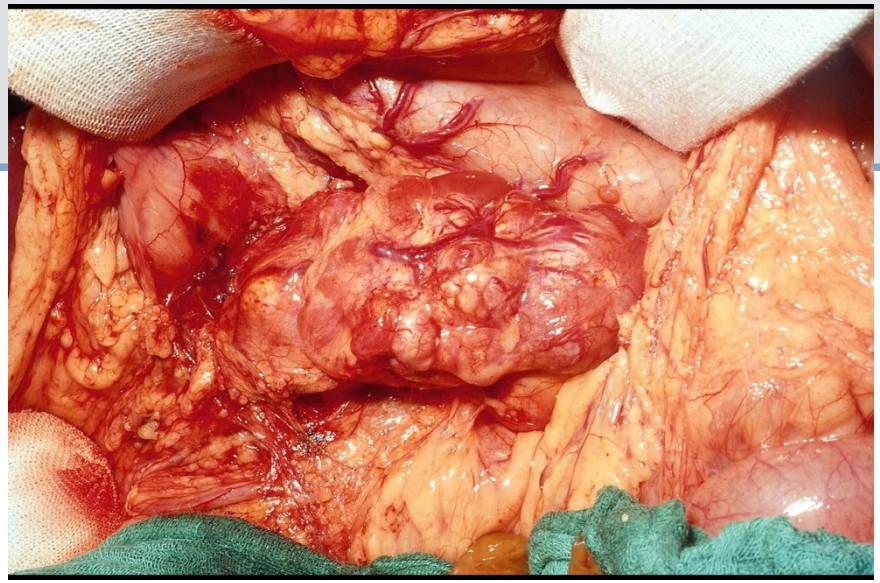
Duodenotomy

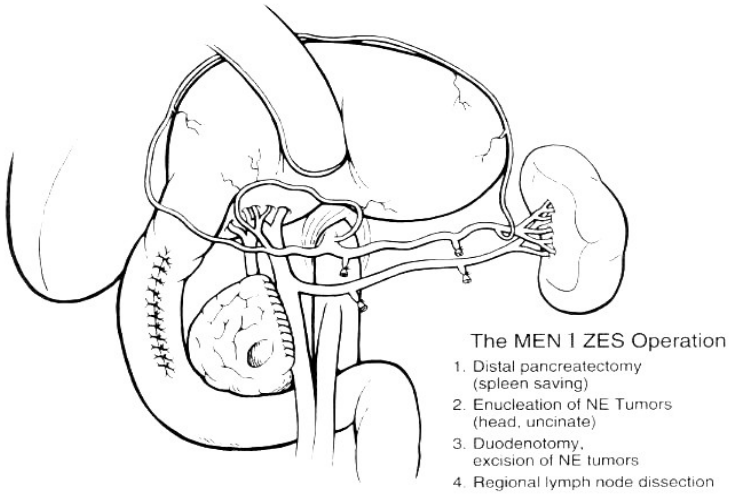
Excision of NE tumors

Regional lymph node dissection

Pancreaticoduodenectomy

Total pancreatectomy





Adapted from N. Thompson

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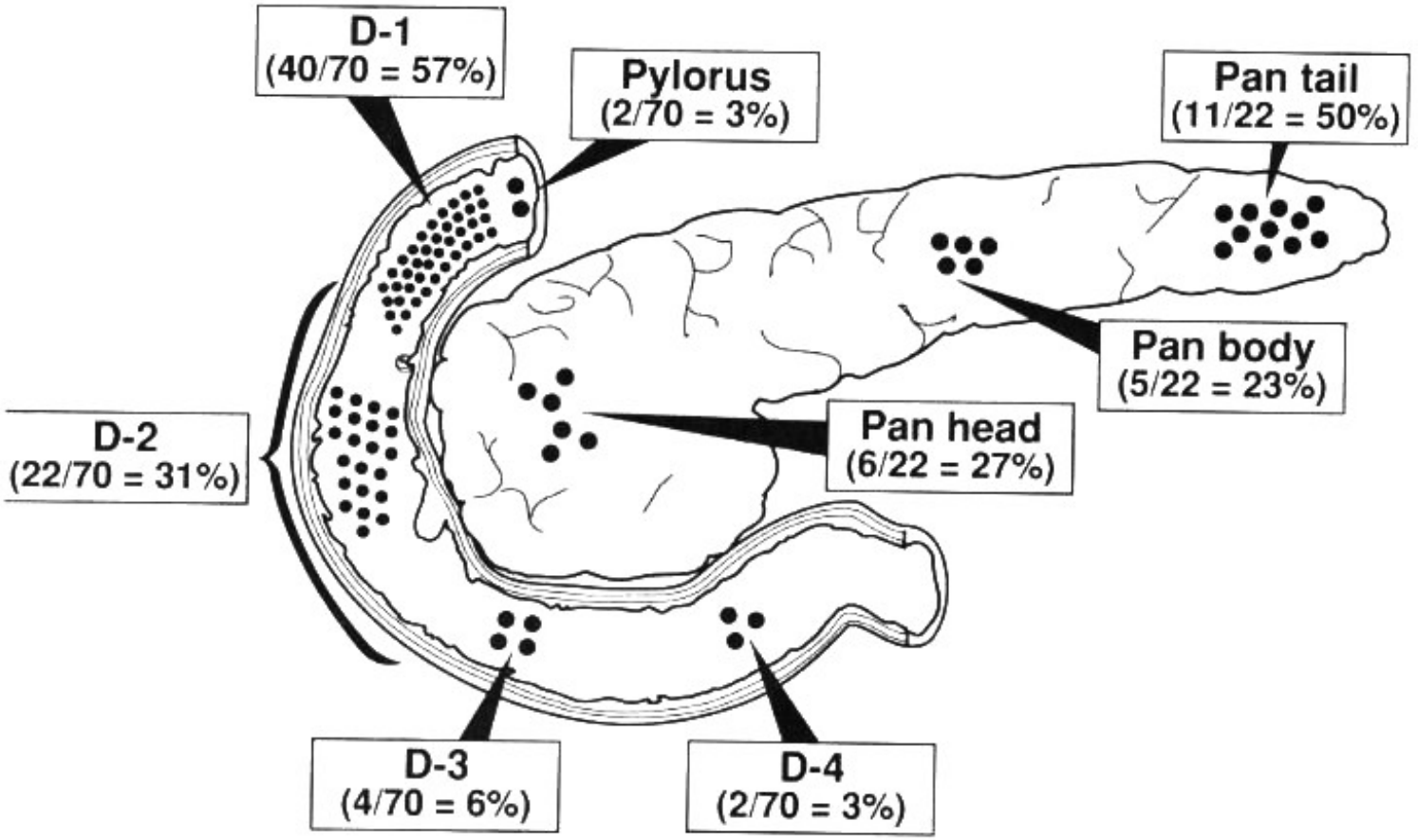
Localisation of MEN1 associated gastrinoma



Jensen R Surg Oncol 2001

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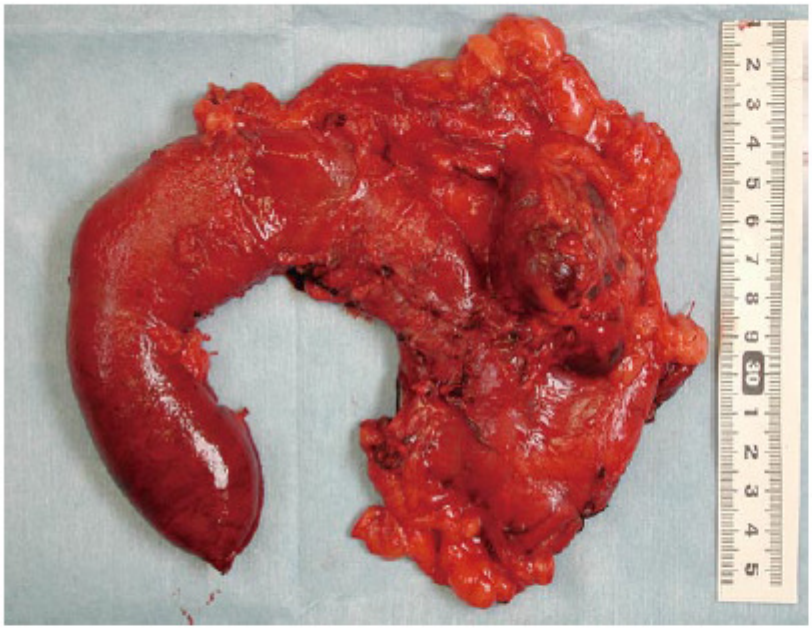

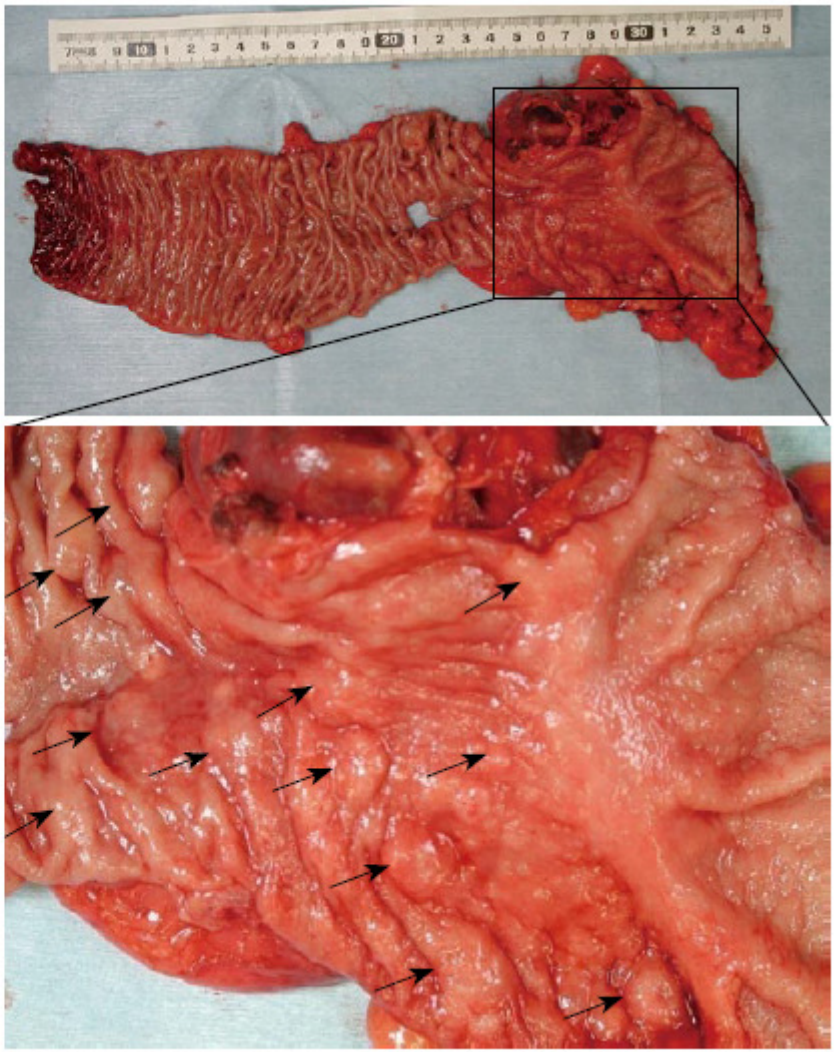

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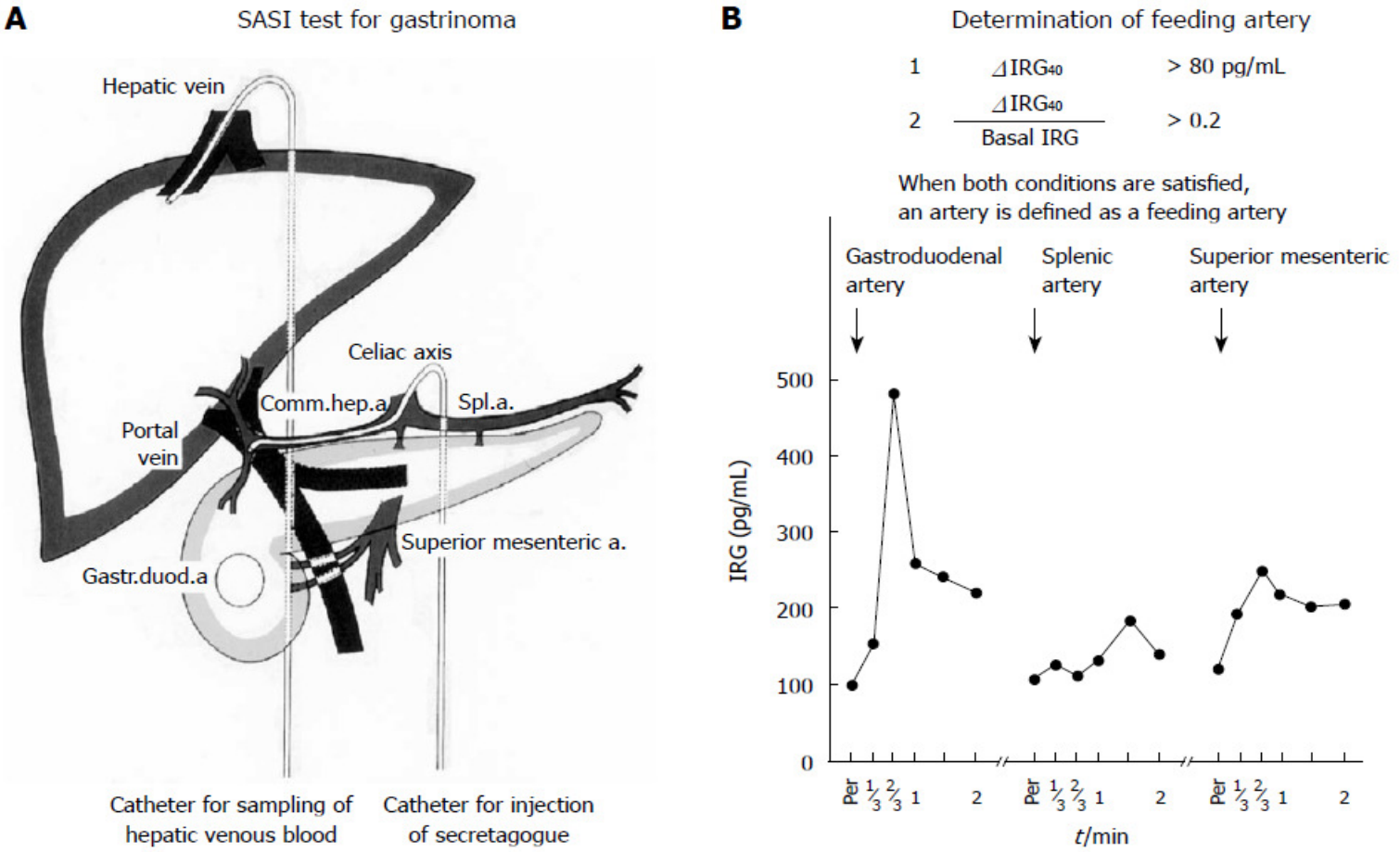
Selective arterial secretagogue injection (SASI test) for localisation of functional PNET and determination of extent of pancreatic resection



Imamura M World J Gastroenterol 2010:16:4519-4525

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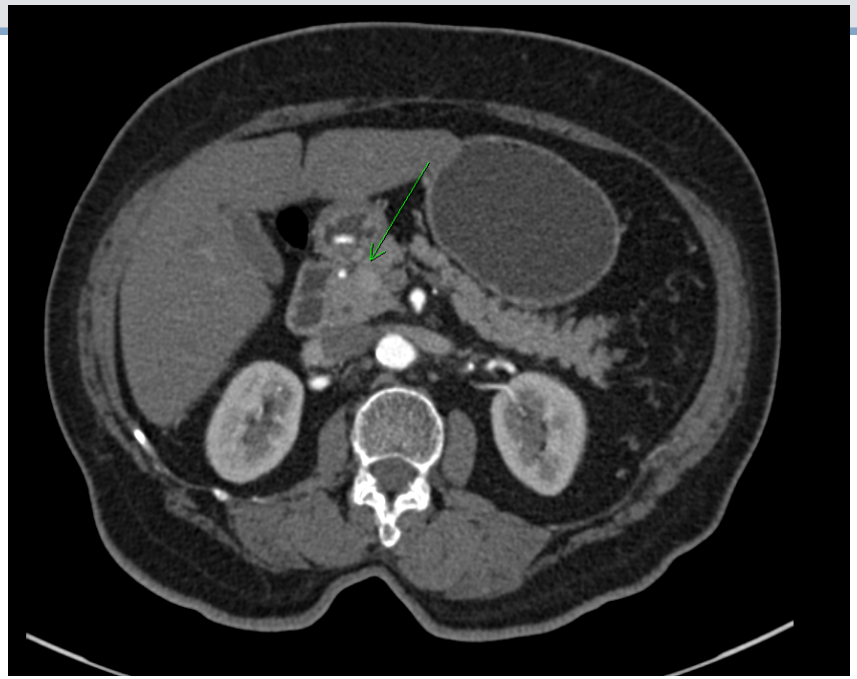
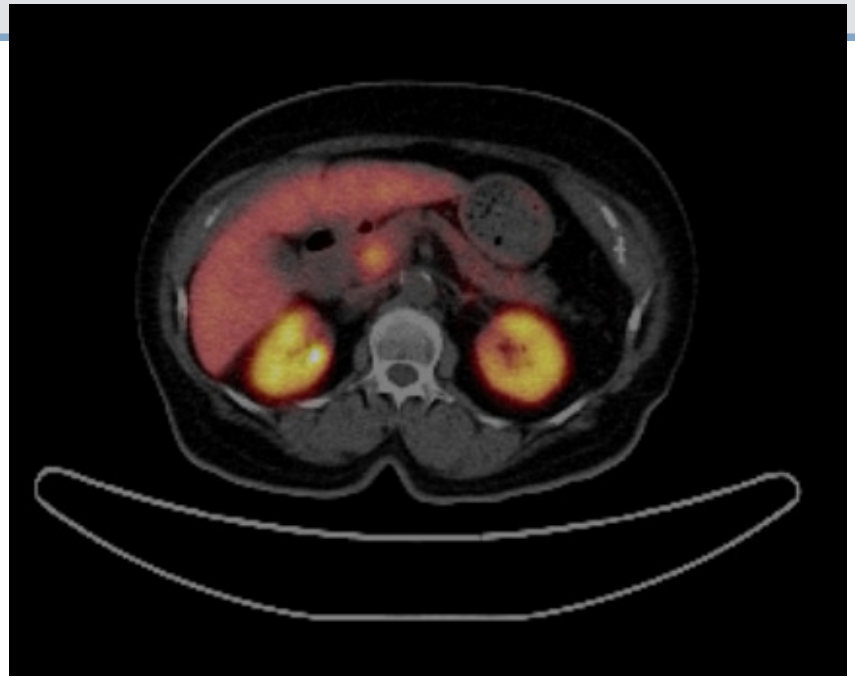
Incidentally detected <2cm in size non-functional PNET (T1)





To resect a T1 NF PNET?

Haynes AB et al. Arch Surg 2011;146:534-8
Kuo EJ et al. Ann Surg Oncol 2013:20:2815-21
Mills L et al. Endocrine Connections 2017;8:876-881

To observe a T1 NF PNET?

Lee LC et al. Surgery 2013;154:785-91
Fernandez-Cruz L et al. HPB 2012;14:171-6
Gaujoux S et al. J Clini Endocrinol Metab 2013;98:4784-9

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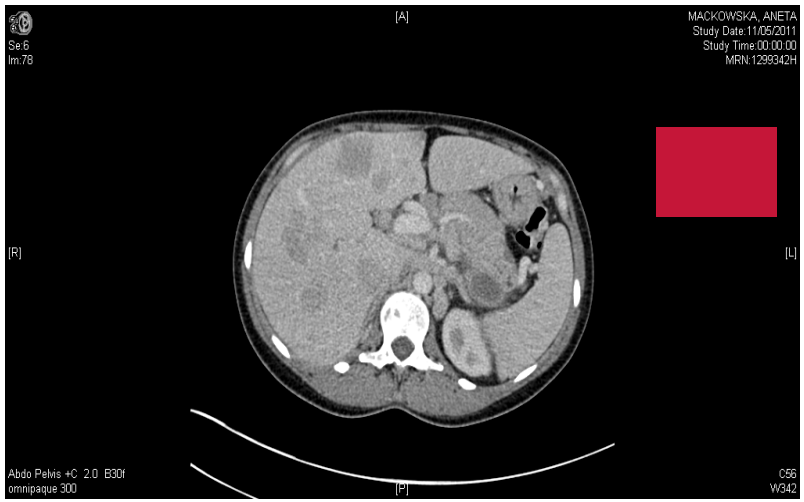
Role of resection of the primary PNET in presence of unresectable LM

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



Capurso G et al. Neuroendocrinology 2011;93:223-9

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Small bowel neuroendocrine tumors

n=84 patients
ICL, UKE, UKH

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 ≤2%)	65 (83.3)
G2 (Ki67 3-20%)	11 (14.1)
G3 (Ki67 >20%)	2 (2.6)

Tumour Stage	N (%)
$T_{1-4}N_0M_0$	9 (10.7)
$T_{1-4}N_1M_0$	24 (28.6)
$T_{1-4}N_0M_1$	1 (1.2)
$T_{1-4}N_1M_1$	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)

Clift AK et al. J Surg Gastroenterol 2015,

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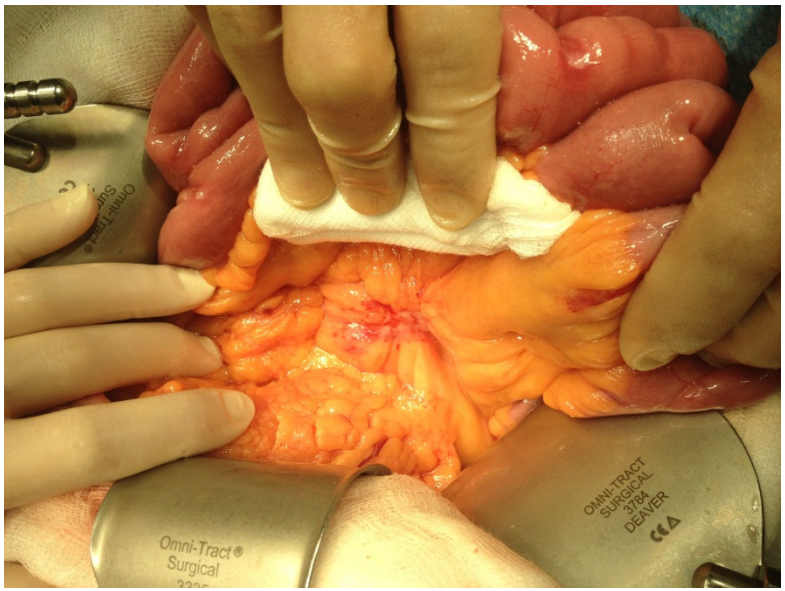
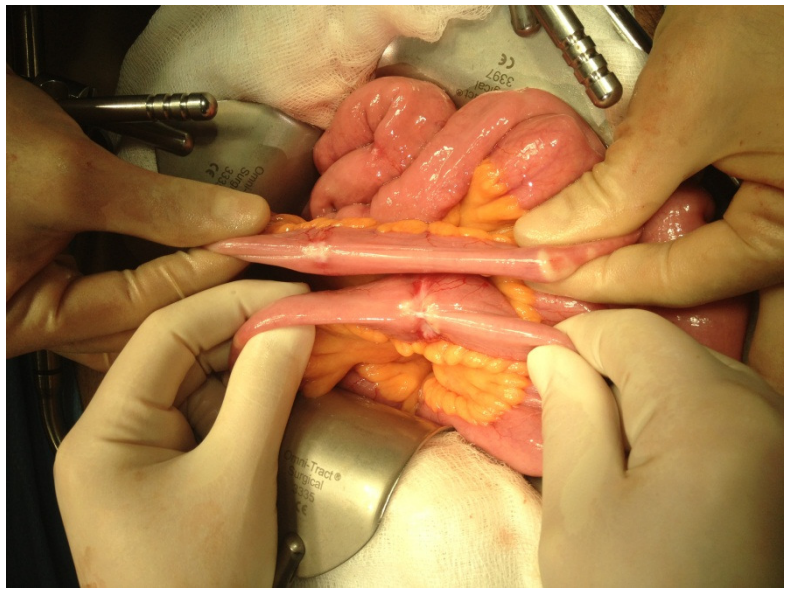
Multifocal small bowel NET, level IV LN metastases





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Comparision of imaging with intraoperative findings in SB NET - ~30% more lesions detected intraoperatively

Patient	CT/MRI			68Ga DOTATATE PET/CT			VCE	Colonoscopy	Enteroscopy	Additional intra-operative findings#		
	T	N	M	T	N	M	T	T	T	T	N	M
1	0	0	1	1	0	1	NP	1	NP	0	1	1m
2	0	0	1	0	0	1	NP	0	NP	1m	0	1m
3	0	0	0	0	0	0	1	1	NP	0	0	0
4	1	0	0 *	NP			NP	NP	NP	0	0	0
5	0	0	0	1	0	0	1	1	NP	0	1	0
6	0	0	0	1	0	0	NP	1	NP	0	1	0
7	0	0	1	0	0	1	1	1	NP	0	1	1m
8	0	1	0	0	1	0	NP	0	NP	1m	0	0
9	1	0	0	1	0	0	NP	1	NP	0	1	0
10	1	0	0	0	1	0	NP	0	NP	0	1	0
11	1	1	1	0	1	1	NP	NP	NP	0	0	0
12	1	0	0	1	0	0	NP	0	NP	0	0	0
13	0	1	0	1	1	0	NP	1	NP	0	0	0
14	1	1	0 *	NP			NP	NP	NP	0	0	0
15	1	1	1	0	1	1	1	0	NP	1m	0	1m
16	0	1	0	0	1	0	1	0	NP	1m	1m	0
17	1	0	0	1	0	0	NP	1	NP	0	1	0
18	0	0	0	1	1	0	NP	0	NP	1m	0	0
19	1	0	0	1	0	0	NP	NP	1	1m	1	0
20	1	0	0	1	0	0	1	0	NP	1m	0	0

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Langenbecks Arch Surg (2010) 395:185–192
DOI 10.1007/s00423-009-0520-x

CASE MANAGEMENT AND CLINICAL CONSEQUENCES

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

ELSEVIER

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]

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[b] The University of Melbourne, Melbourne, Victoria 3010, Australia
[c] Department of Surgical Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria 3002, Australia

Accepted 21 August 2011
Available online 8 September 2011

Neoadjuvant Treatment of Nonfunctioning Pancreatic Neuroendocrine Tumors with [^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate

Esther I. van Vliet[1], Casper H. van Eijck[2], Ronald R. de Krijger[3], Elisabeth J. Nieveen van Dijkum[4], Jaap J. Teunissen[1], Boen L. Kam[1], Wouter W. de Herder[5], Richard A. Feelders[5], Bert A. Bonsing[6], Tessa Brabander[1], Eric P. Krenning[1], and Dik J. Kwekkeboom[1]

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

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Neoadjuvant peptide receptor radionuclide therapy for an inoperable neuroendocrine pancreatic tumor

Kaemmerer D et al. World J Gastroenterol 2009,15;5867-5870

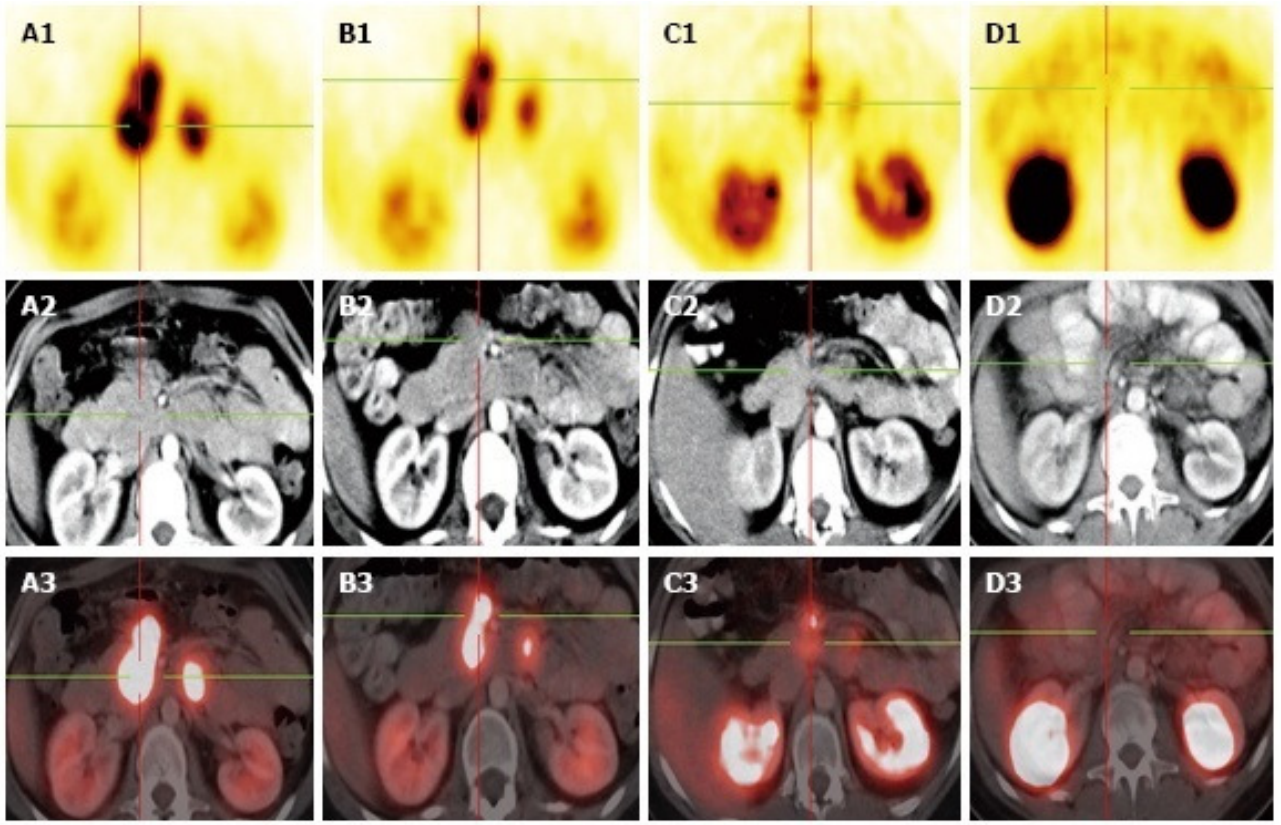

Figure 2 Gallium-68 DOTA-NOC PET-CT in the follow up. A: Octreotide scan prior to PRRT-1, Gallium-68 DOTA NOC PET-CT and prior operation, showing multiple paraaortal lymph nodes next to the pancreas head; B: 3 mo after PRRT-1; C: 5 mo after PRRT-2 showing consistently decreasing mesenterial lymph nodes metastases with a decreasing SUV; D: Octreotide scan as follow up 18 mo after operation-complete remission.

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Multimodal treatment of a malignant insulinoma

- 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
- Symptom control, but no reduction of tumor mass

- High uptake on 68Ga-DOTATOC PET/CT
- 6 cycles of 177Lu-PRRT
- No side effects

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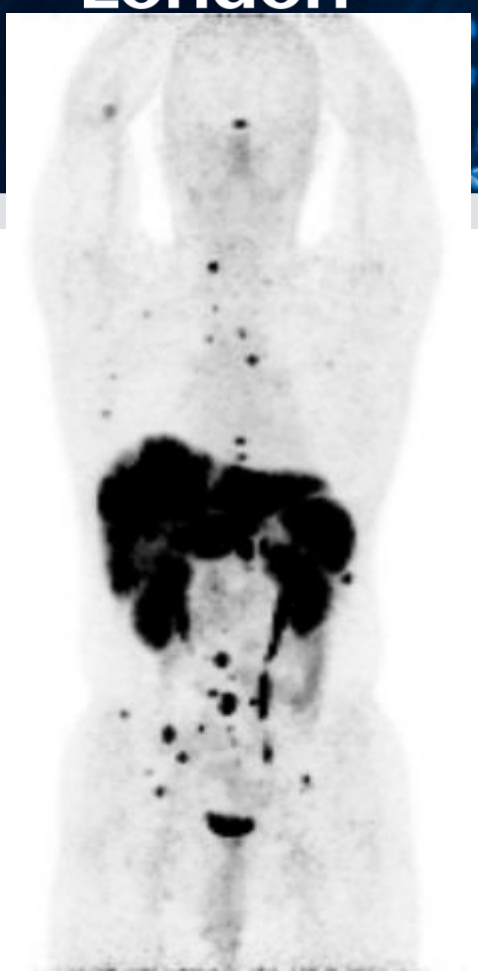

Before PRRT (2012))

After 4 Doses (2013)

After 6 Doses (2014)

Malignant insulinoma

Decision for surgical debulking + RFA after downstaging with PRRT

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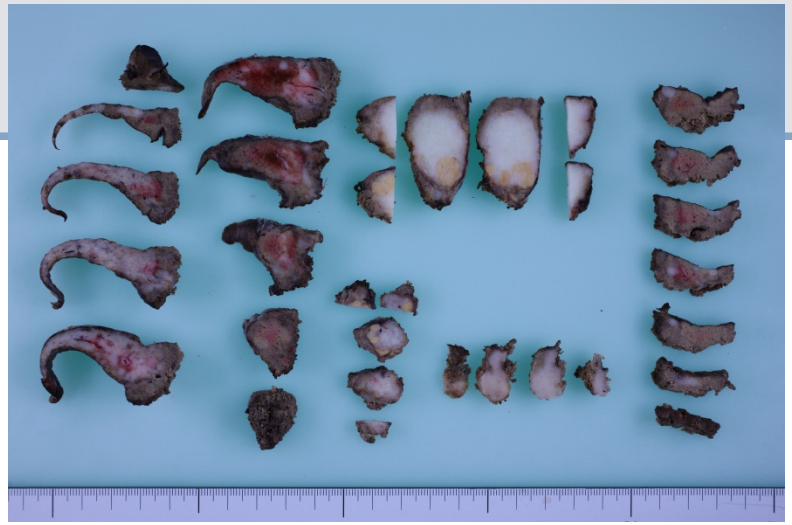

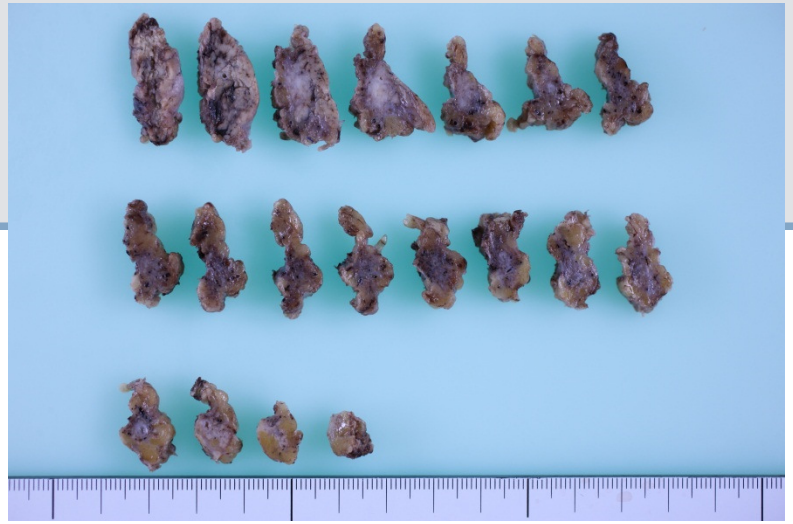

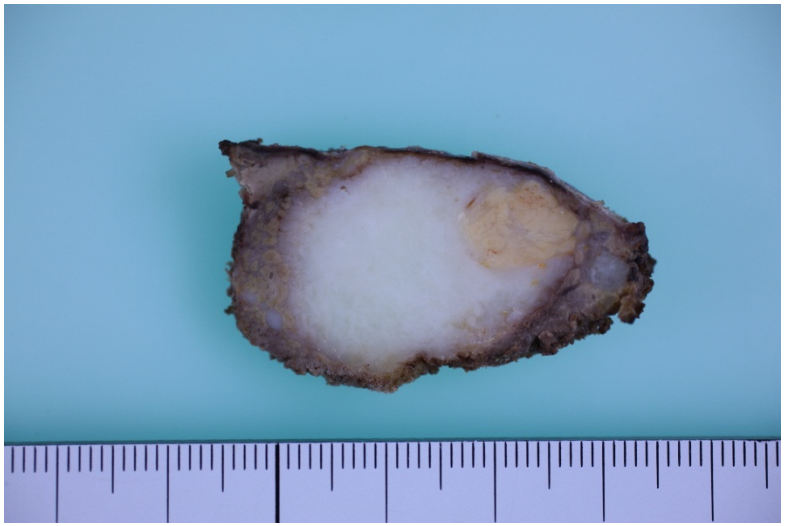

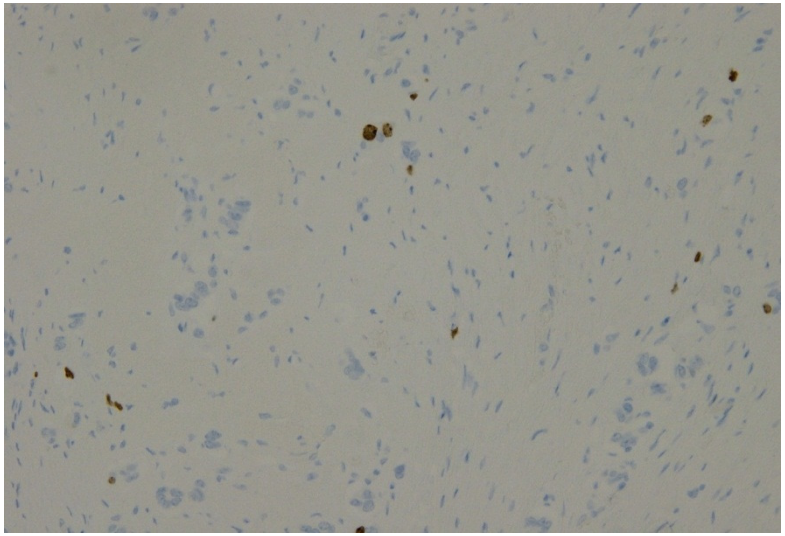

Ki67 <2%, G1 tumor

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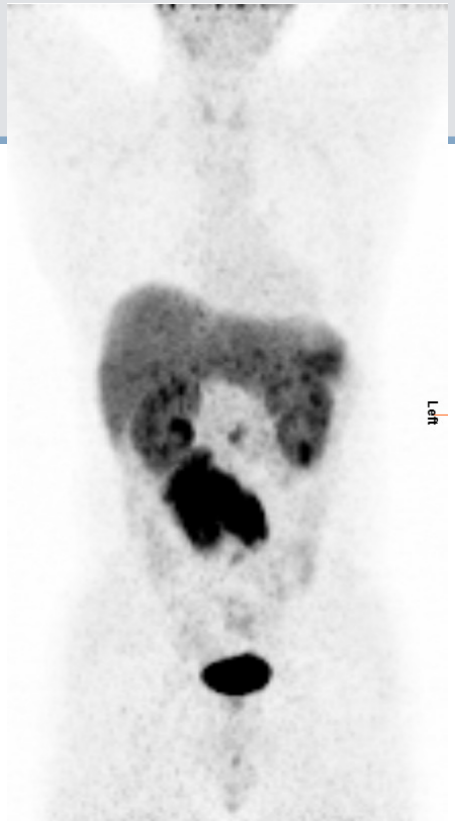

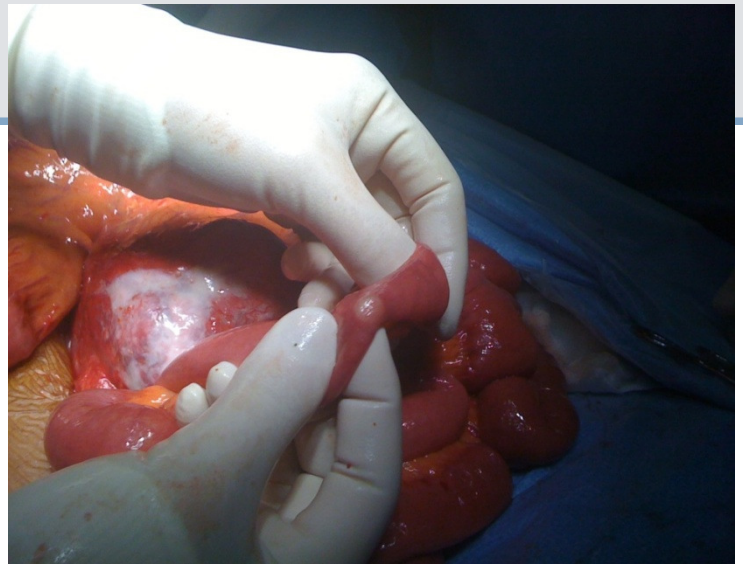

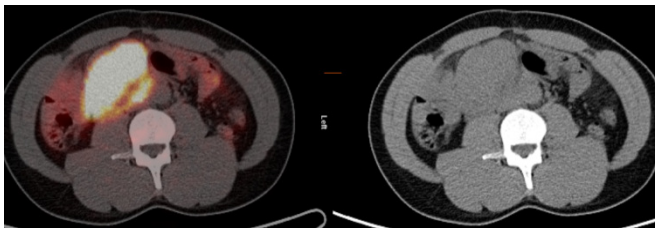

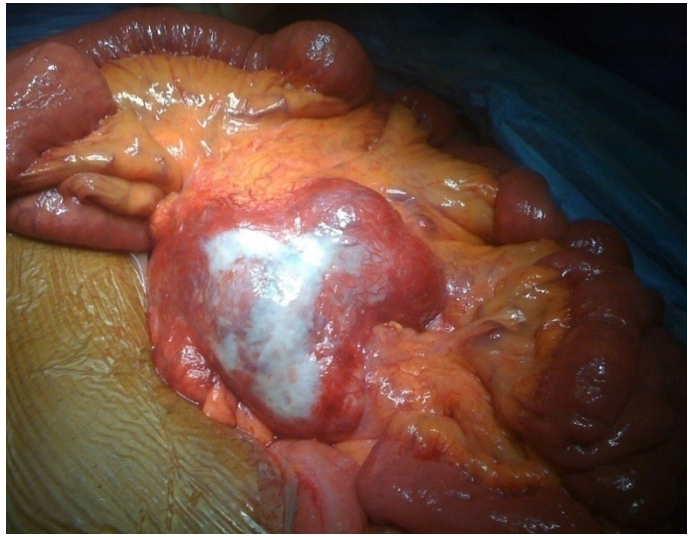

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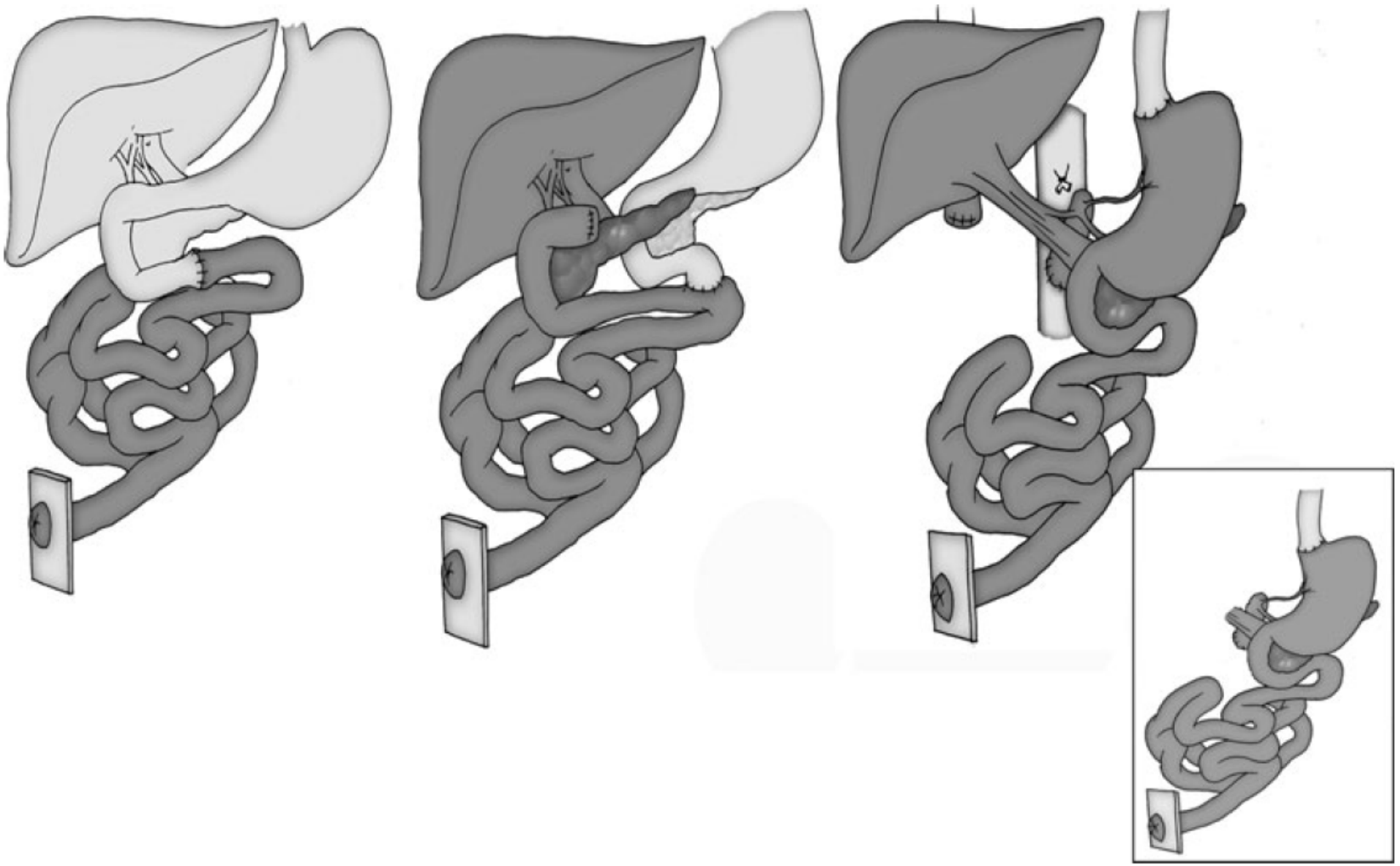
Different types of multivisceral transplantations



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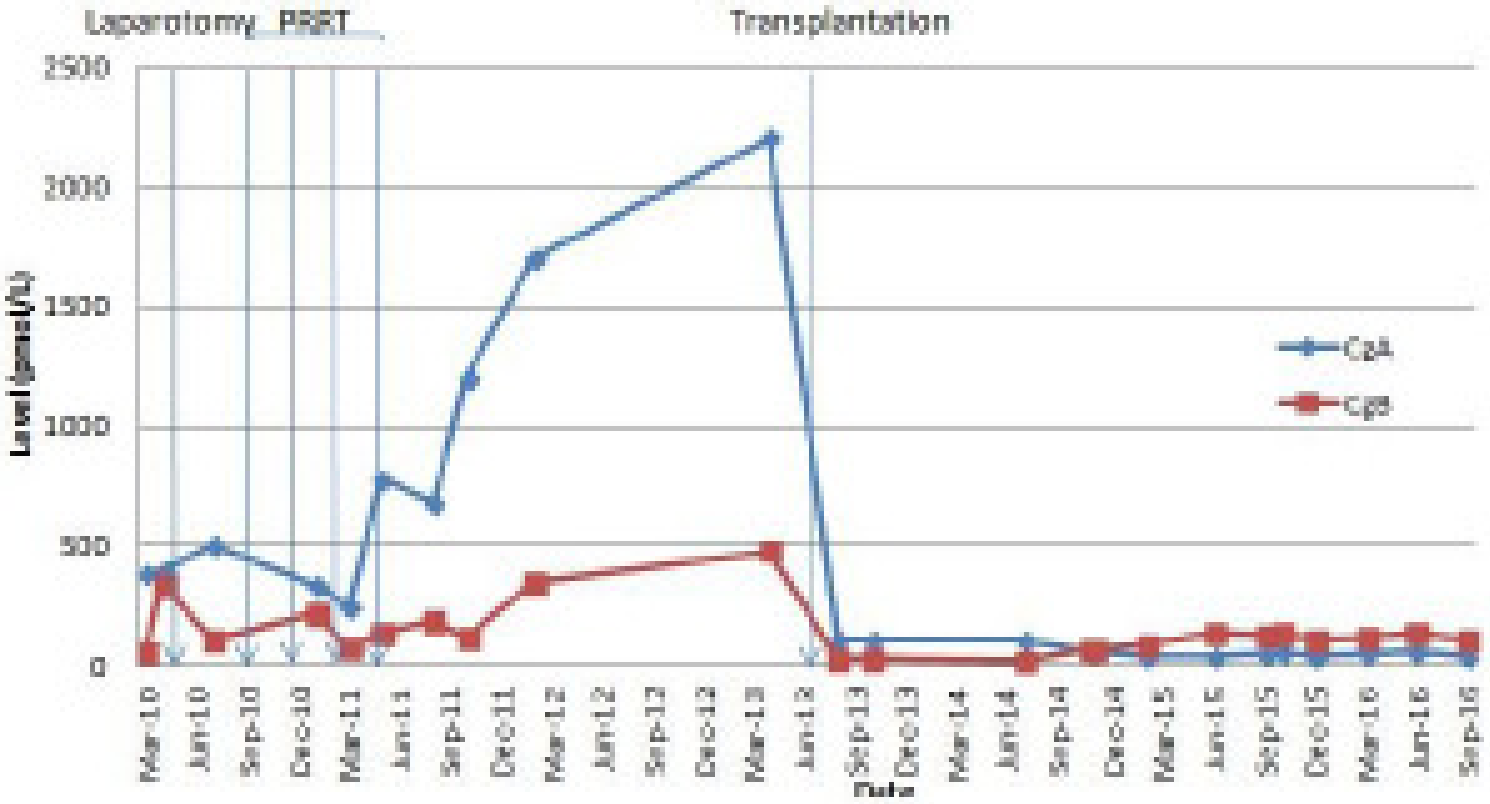
Multivisceral liver-free transplantation for metastasised small bowel NET
Downstaging with Lu-177 PRRT



Frilling A et al. Transplant Proc 2015;47:858

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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			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	Median survival, 70 mo	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%

Frilling A and Cliff AK Cancer 2014, doi:10.1002/cncr.28760

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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

					No. LM Preoperatively Identified on Imaging					
			Pathologic Findings		Ultrasound Examination					
Patient	Primary Tumor	Type of Hepatectomy	No. LM	Size cm (min-max)	Normal	Contrast Enhanced	CT-Scan	MRI	Somatostatin Receptor Scintigraphy	Intraoperative Findings
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.

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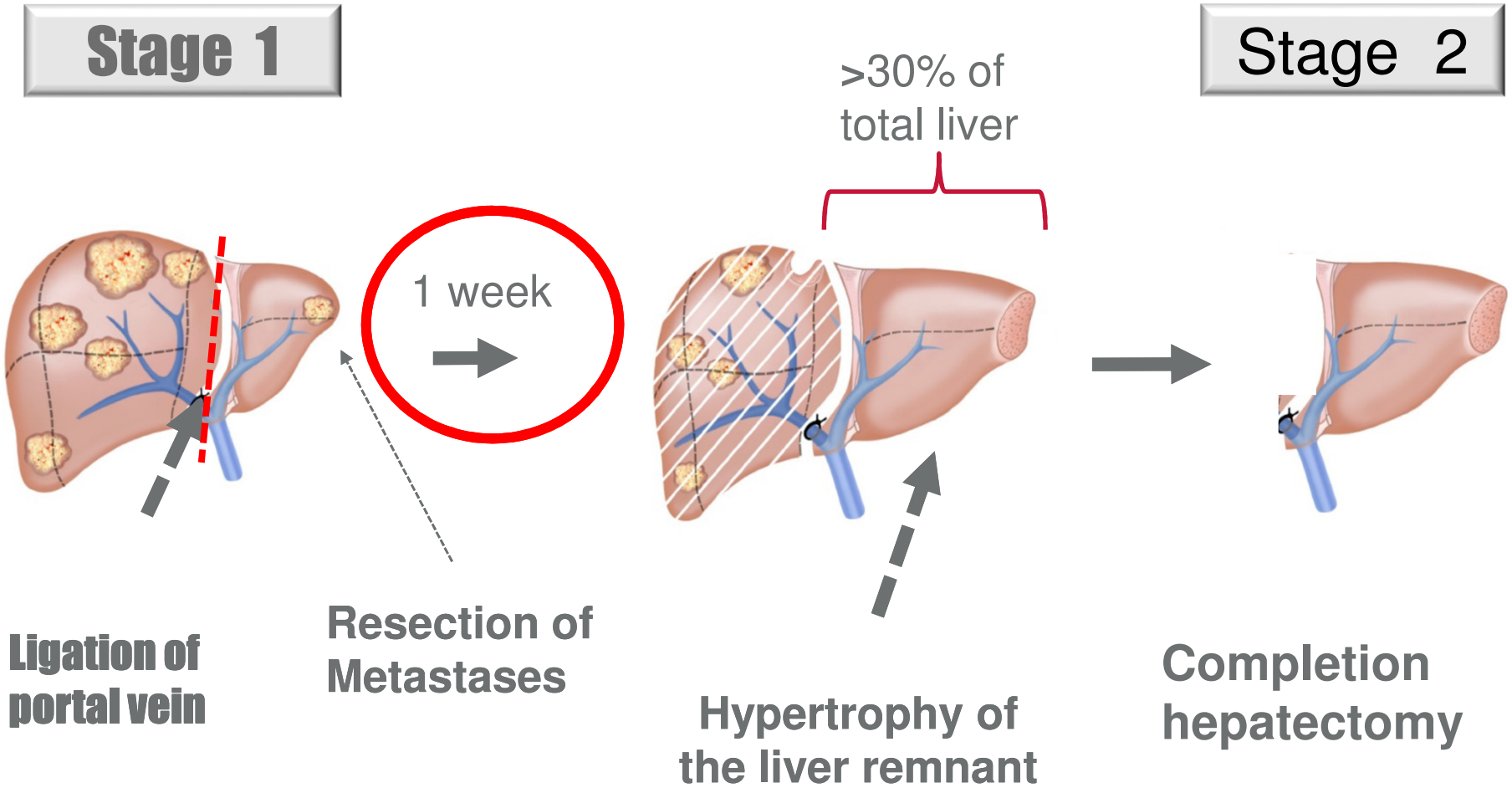
Associating Liver Partition with Portal vein ligation for Staged hepatectomy



Second operation: 90% of the patients

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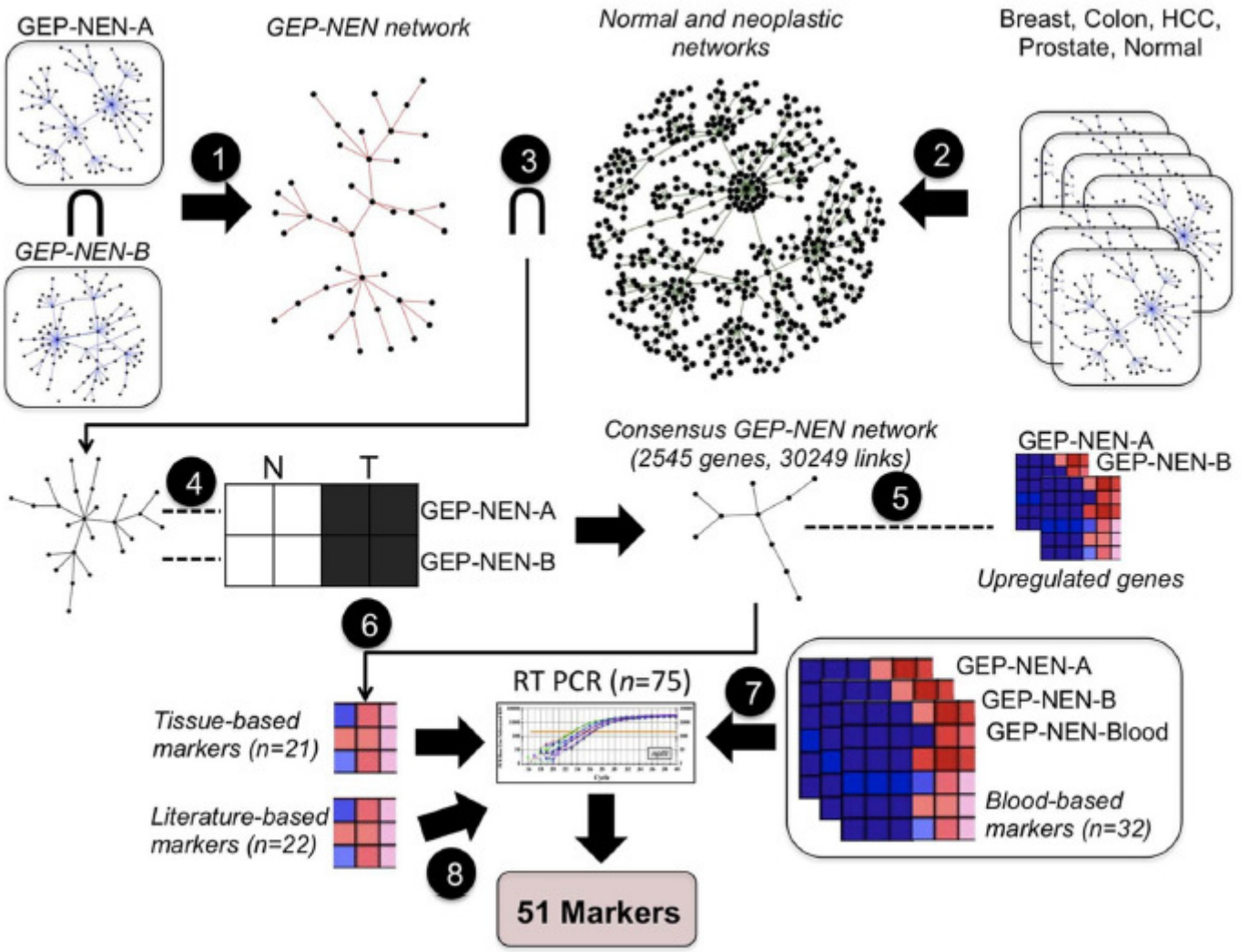
NETest

Multiple synchronous transcripts analysis allows identification of intestinal NET

- Detection of mRNA of 51 genes in the Blood -



Modlin IM et al. PLOS ONE 2013;5:1-12

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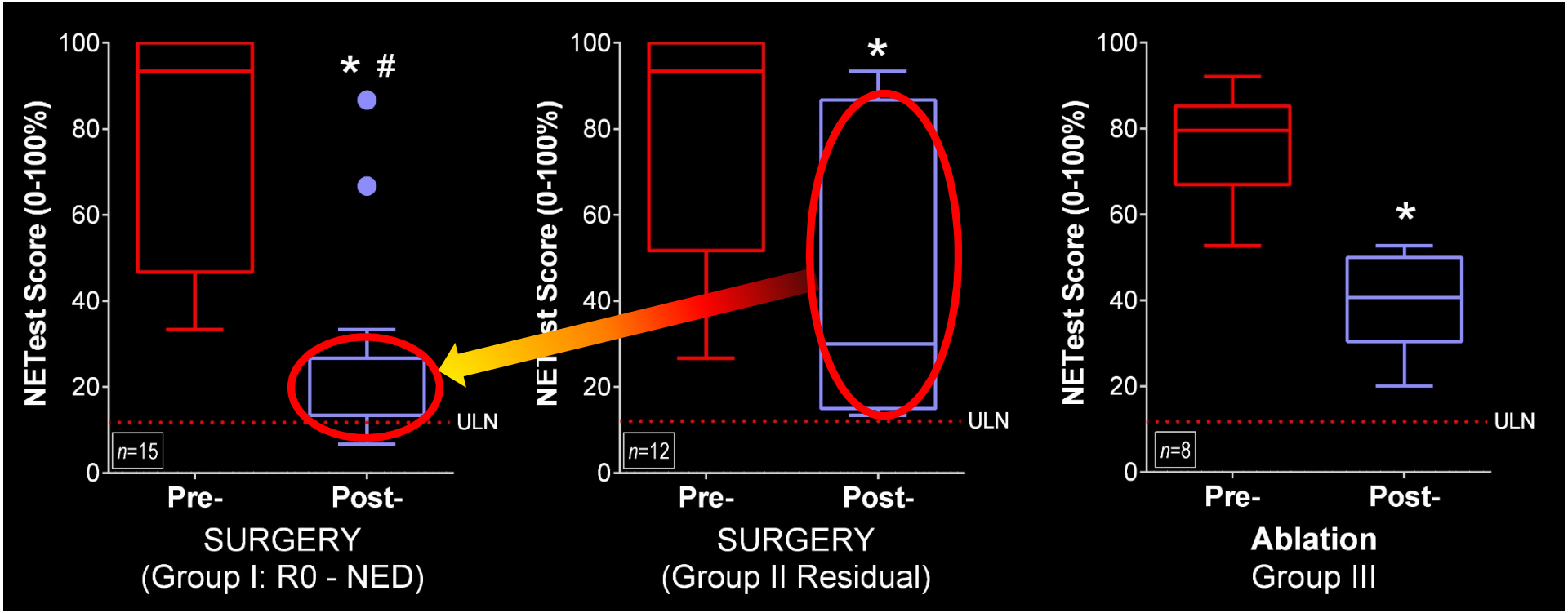
NETest – tumour transcripts in blood

- Assessment of efficacy of surgery -



Surgery decreases the circulating NETest signature

R0 does not always decrease the circulating NETest signature to normal

*p=0.001 vs Pre-
#p<0.05 vs. Residual

Modlin IM, Frilling A et al. Surgery 2016;159:336-47

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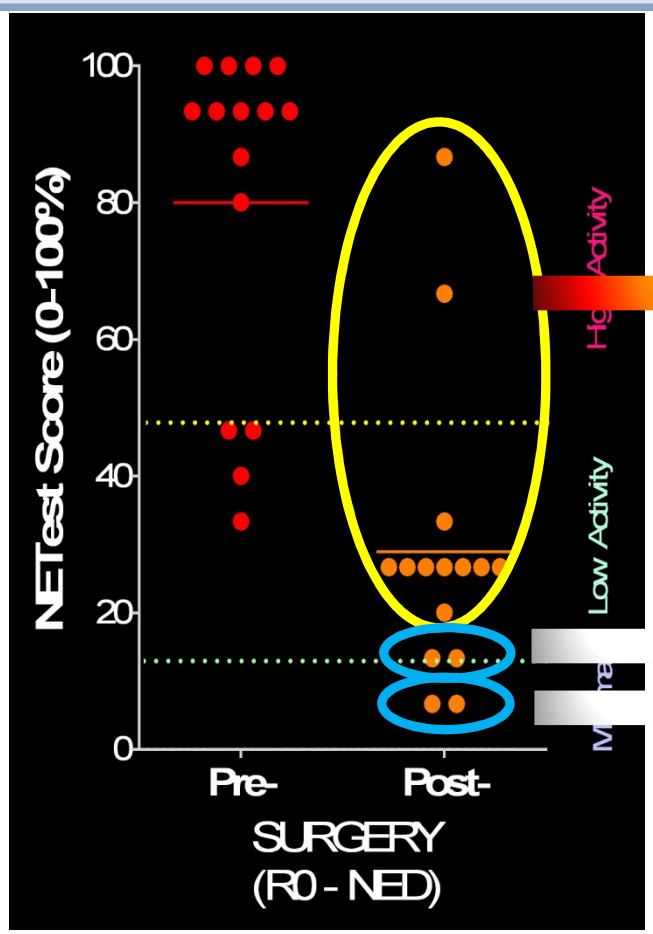
Disease Recurrence and the NETest

Group I (R0) (*n*=15 patients)



73% = biochemical evidence of disease

4 (36%) image-positive recurrence (6 months)

Sensitivity = 100%

No evidence of disease (6 months post op.)

No evidence of disease (36, 42 months post op.)

NETest is predictive of disease recurrence

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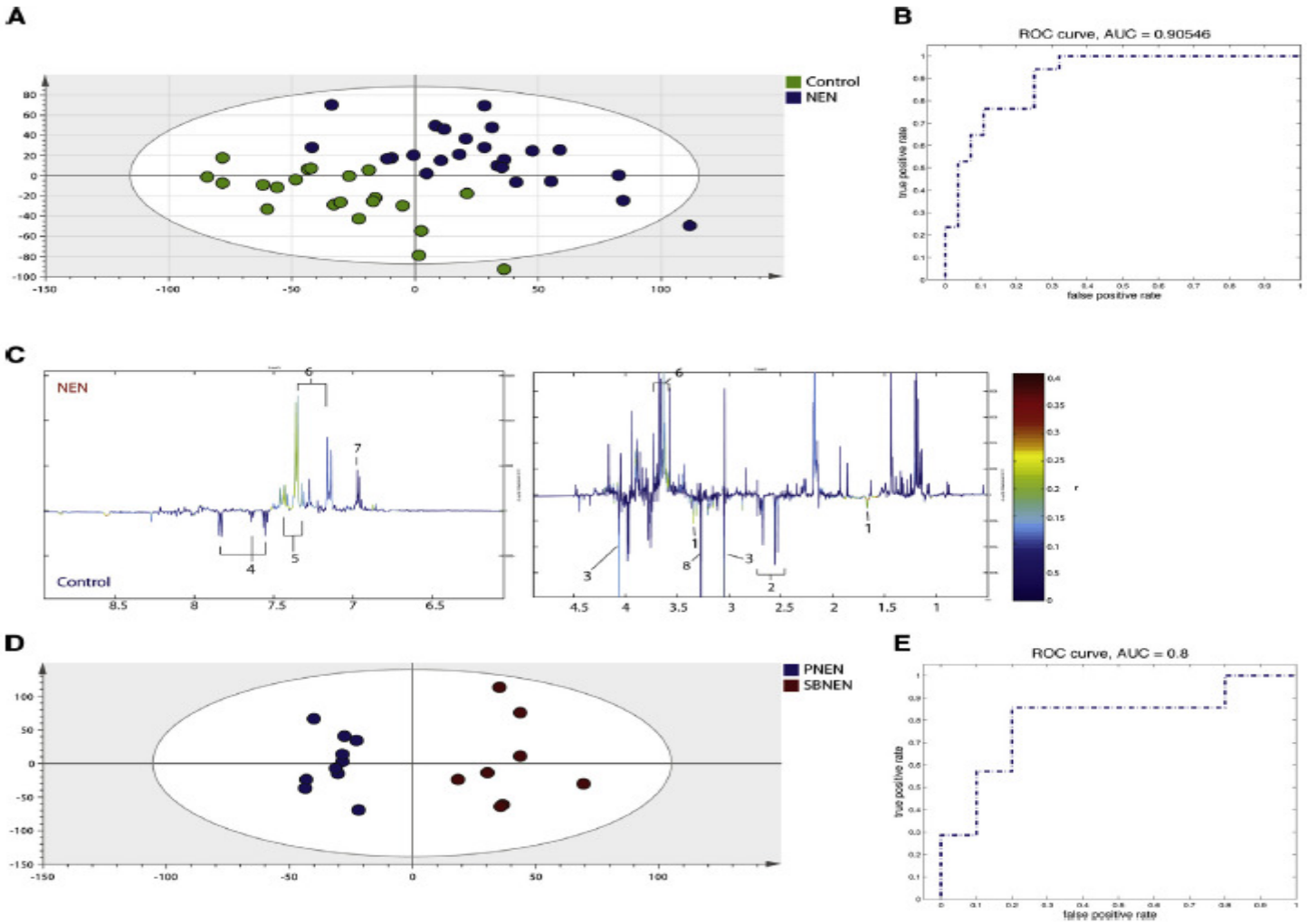
Metabolic profiling in NET by 1H nuclear magnetic resonance (NMR) spectrometry



Kinross J M et al. Surgery 2013;153:1185

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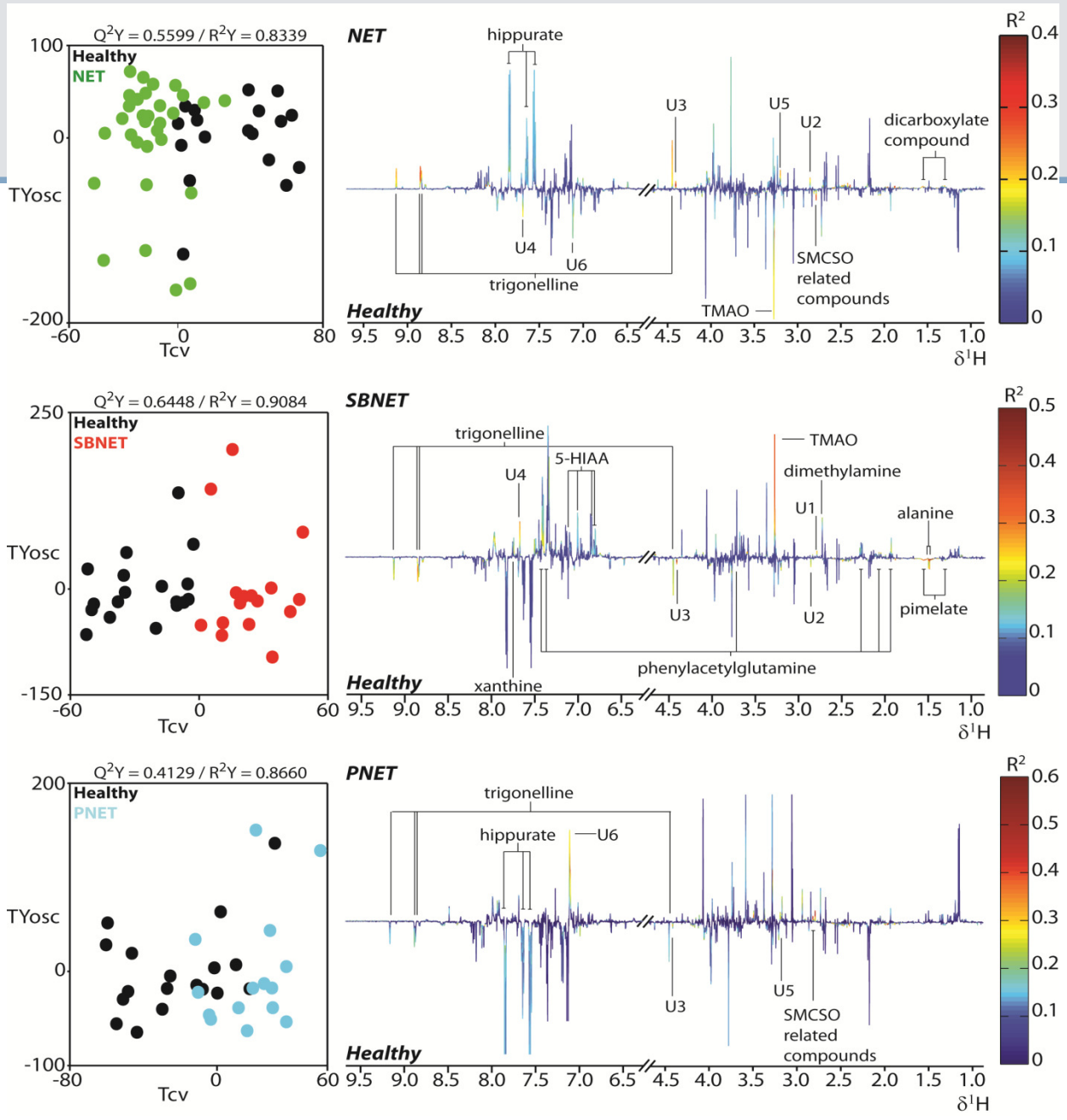

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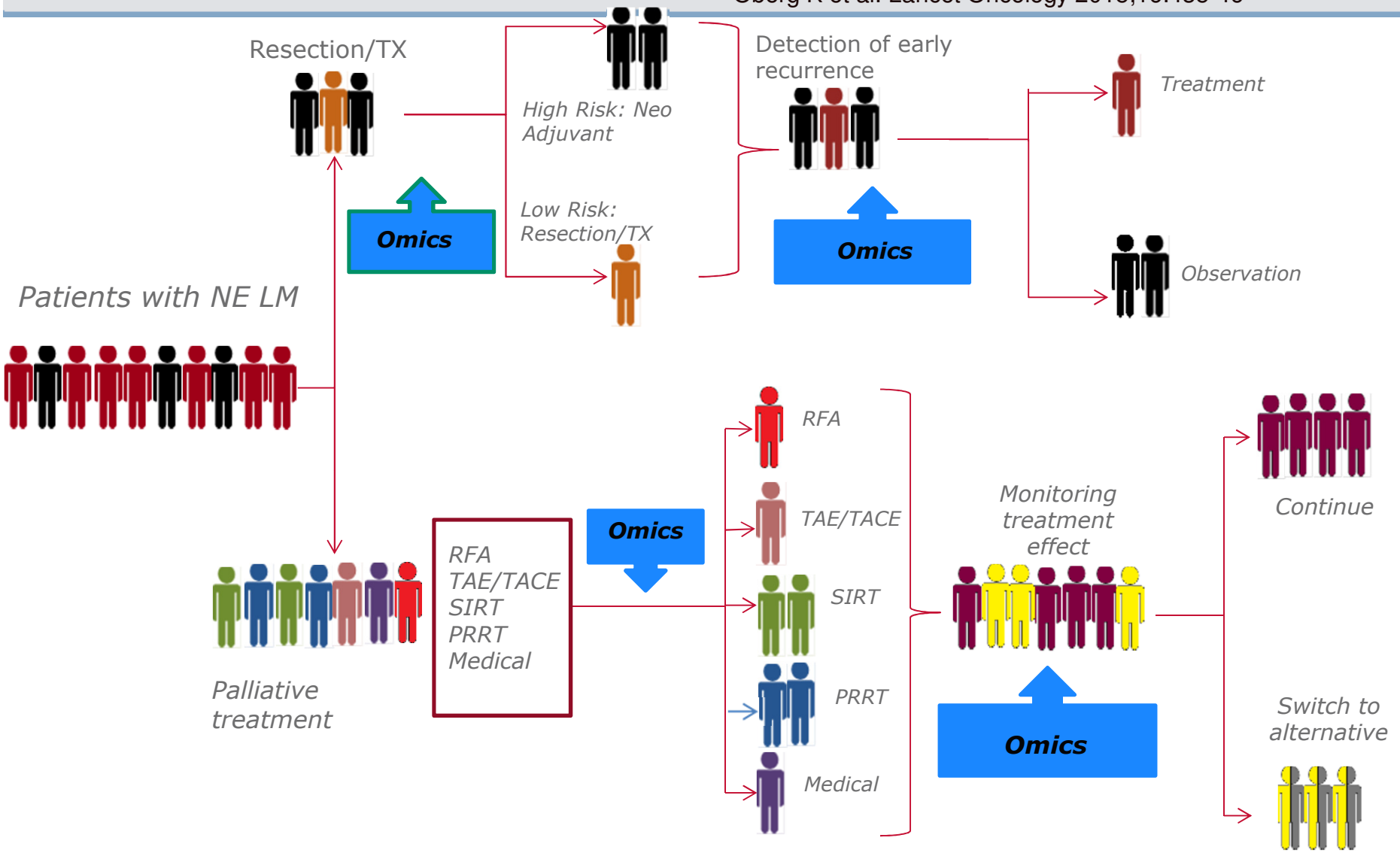
Personalised treatment of NET

Need for novel multidimensional tumor markers

Frilling A et al. , Lancet Oncology, 2014;15:8-21

Oberg K et al. Lancet Oncology 2015;16:435-46



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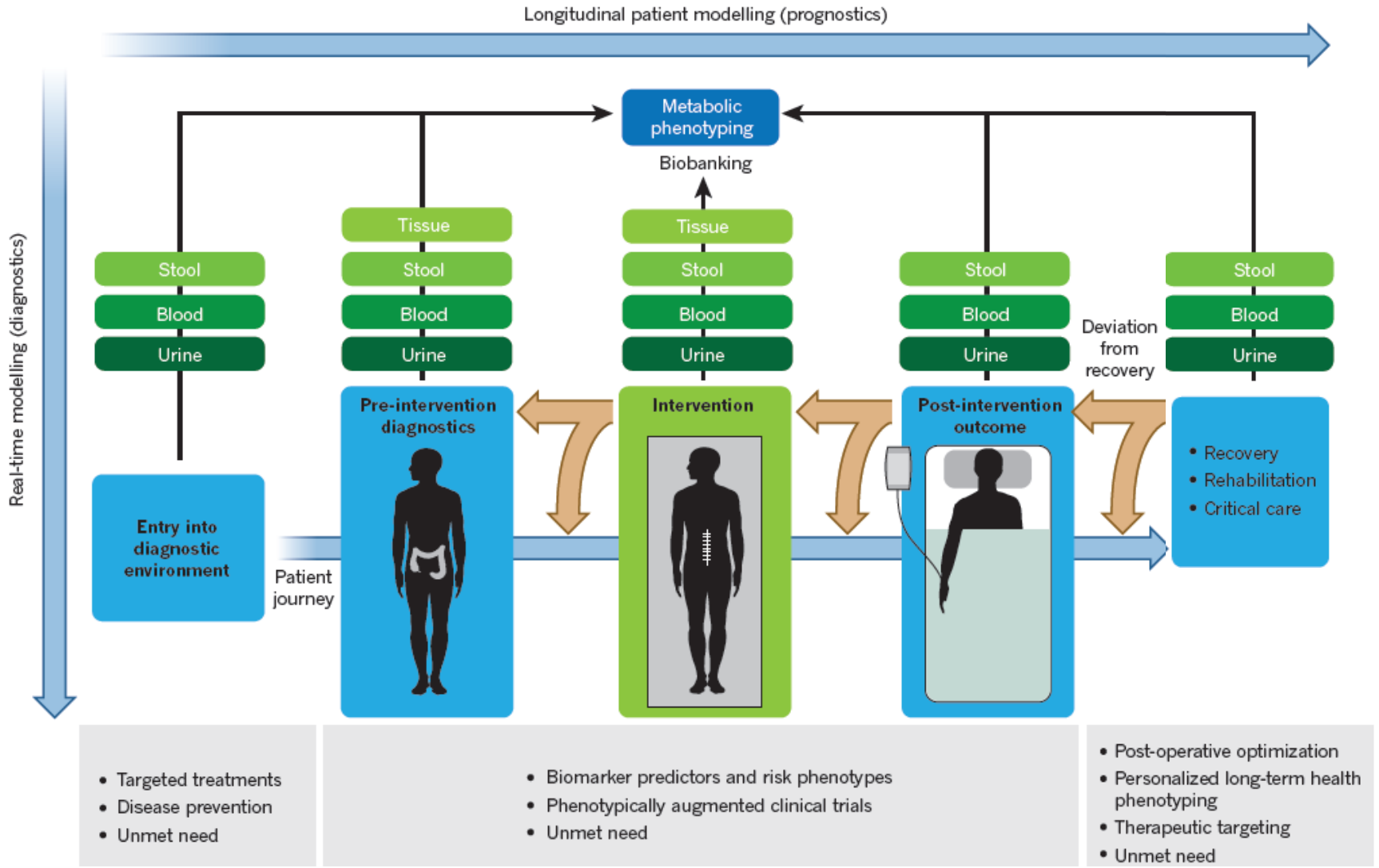
Metabonomics during the patient journey



Nicholson J et al, Nature, 491, 384-92, 2012