NEN PRECEPTORSHIP

LA PRATICA CLINICA NELLE NEOPLASIE NEUROENDOCRINE

5/6 Aprile 2018 | IEO, Istituto Europeo di Oncologia - Milano

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Criteri di scelta della terapia chirurgica nei NET

Milano
5 Aprile **2018**

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The role of surgery in GEP-NETs: principles

In GEP-NETs there is a clear indication for surgery, when there is the possibility to obtain macroscopic radicality which means that no visible tumor is left behind (also for liver metastases).

In GEP-NECs the role of surgery, in patients without distant metastases, should be modulated according to tumor and patient characteristics.

The role of surgery in GEP-NETs: agenda

- Gastroduodenal NENs
- PNETs
- (colo)rectal NENs
- NET liver metastases
- Primary tumor surgery in case of unresectable liver mets

- PanNENs → Dr Partelli

The role of surgery in GEP-NETs: gastric NETs

Table 1. Classification of g-NENs

	Type 1	Type 2	Type 3
Proportion among g-NENs, %	70–80	5–6	14–25
Tumor characteristics	Often small (<1–2 cm), multiple in 65% of cases, polypoid in 78% of cases	Often small (<1–2 cm) and multiple, polypoid	Unique, often large (>2 cm) polypoid and ulcerated
Associated conditions	Atrophic body gastritis	Gastrinoma/MEN-1	None
Pathology	G1–G2 NET	G1–G2 NET	G3 NEC
Serum gastrin levels	↑	↑	Normal
Gastric pH	↑↑	↓↓	Normal
Metastases, %	2–5	10–30	50–100
Tumor-related deaths, %	0	<10	25–30

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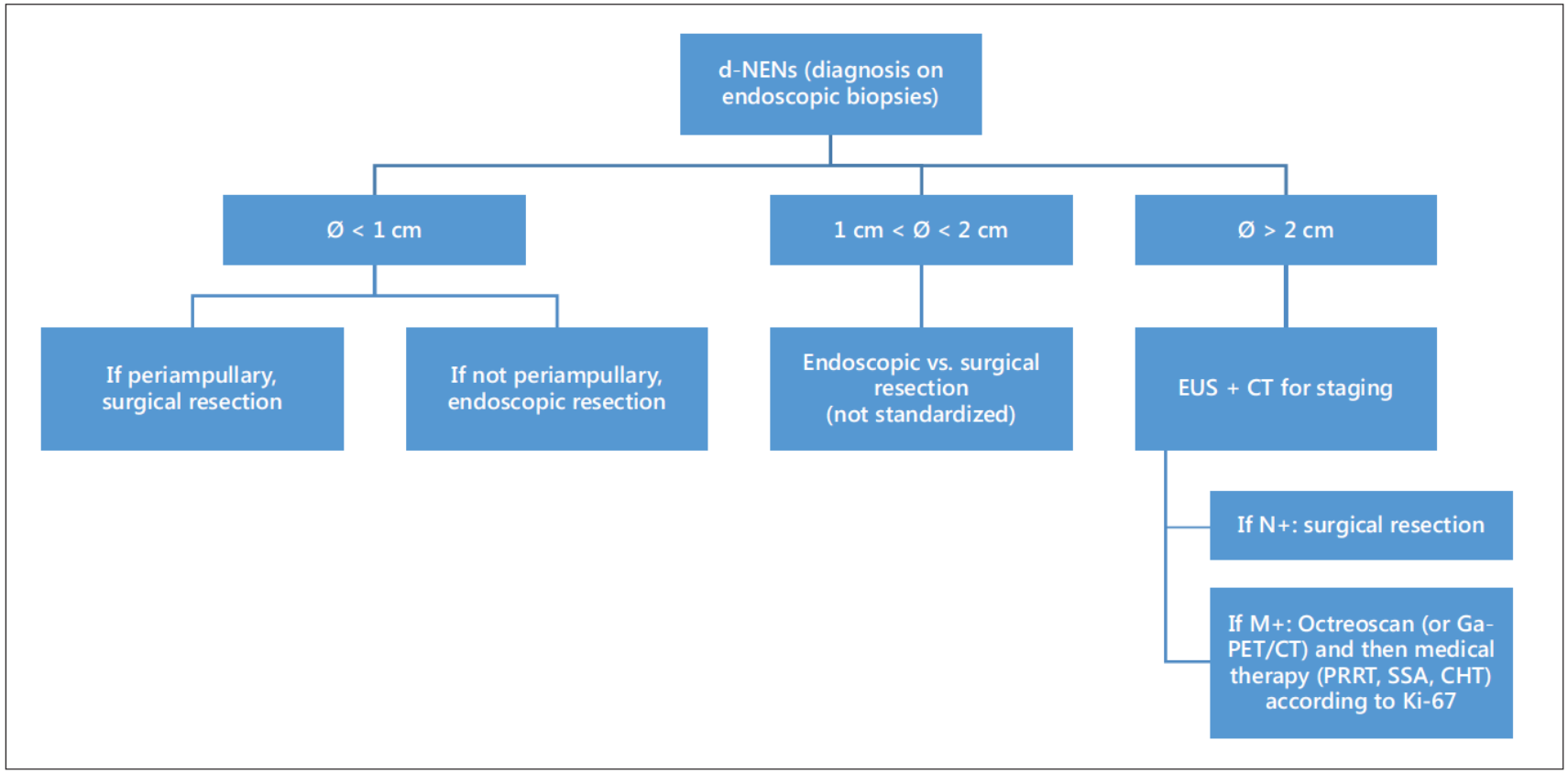
The role of surgery in GEP-NETs: gastric NETs

Type 2→The treatment depends on the concomitant duodenal or panNET as result of the underlying MEN-1 syndrome

Type 3→The same as adenocarcinoma

ENETS guidelines 2016

The role of surgery in GEP-NETs: duodenal NETs



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Rectal NENs

Colon → G3

Rectum → Smaller, G1, G2

Primary tumor site	
Lung	1.35
Thymus	0.02
Stomach	0.30
Duodenum	0.19
Jejunum/ileum	0.67
Cecum	0.16
Appendix	0.15
Colon	0.20
Rectum	0.86
Pancreas	0.32
Liver	0.04
Other/unknown	0.74

Crude incidence/year (all NENs 5.25/100.000)

VERY LAST SEER REVIEW (2018)
1.04 PER 100.000

Yao 2008

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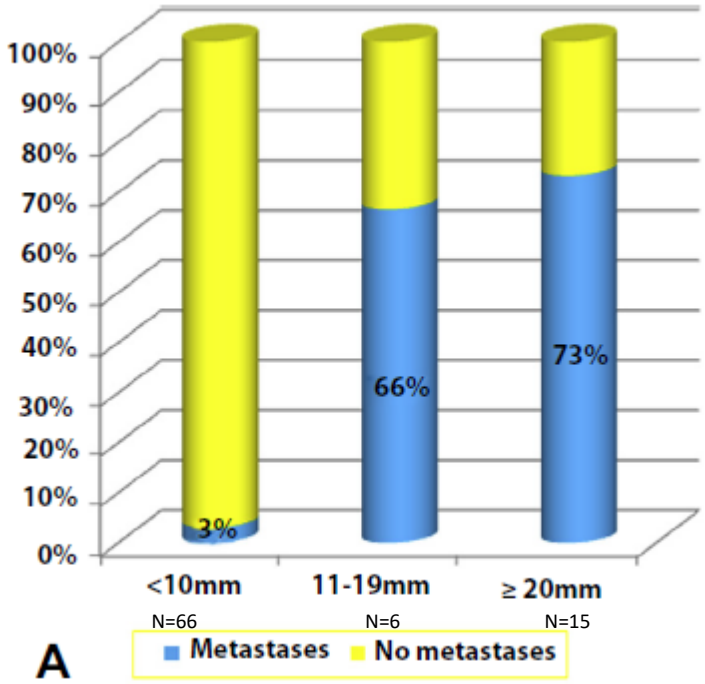
Rectal NENs: Size



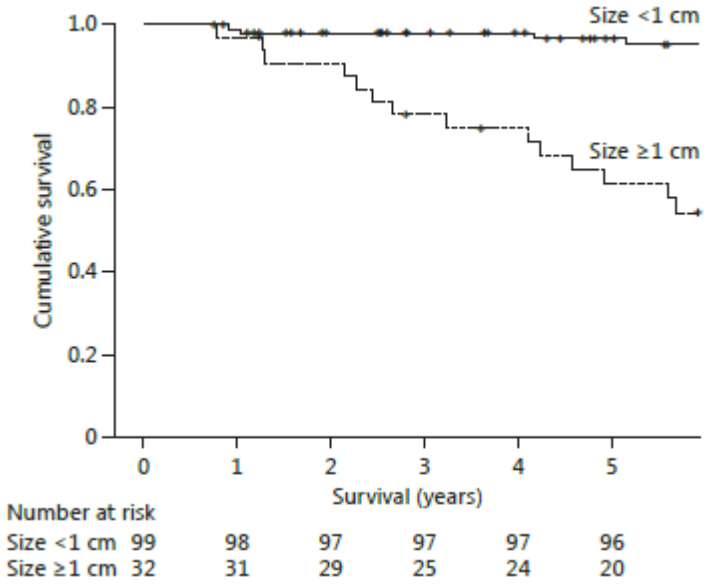


Table 1 Main factors predicting metastases in patients with rectal neuroendocrine tumors.

Predictive factor [ref]	Odds ratio	95% confidence interval
Tumor size >14 mm [16]	57.5	23.3–1002.6
Mitotic index ≥2/10 HPF [16]	56.2	2.4–1295.8
Lymphovascular invasion [16]	65.1	1.1–3846.7
Muscularis layer invasion [20]	37.9	5.0–290

HPF, high-power field.

Gleeson 2014
Weinstock 2013
De Mestier 2013
Park 2011

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Rectal NENs: Ki-67

Table 4 Independent risk factors for metastasis in the multivariate logistic regression analysis

	OR for metastasis (95 % CI) univariate analysis	OR for metastasis (95 % CI) multivariate analysis	*P* value
Endoscopic tumor size >10 mm	9.84 (2.18–44.4)	0.48 (0–3290)	0.86
Central depression (+)	5.7 (1.39–23.4)	0.19 (0.008–4.6)	0.31
Depth of SM invasion >4000 μm	6.8 (1.6–29.6)	0.51 (0.02–13)	0.69
Ki-67 LI > 3.0 %	120 (11.1–1302.9)	88 (2.7–2888)	0.012
Lymphatic or venous permeation (+)	67.6 (10.2–446.8)	111 (3.8–3284)	0.006

CI confidence interval; *LI* labeling index; *OR* odds ratio; *SM* submucosal

Sugimoto 2015

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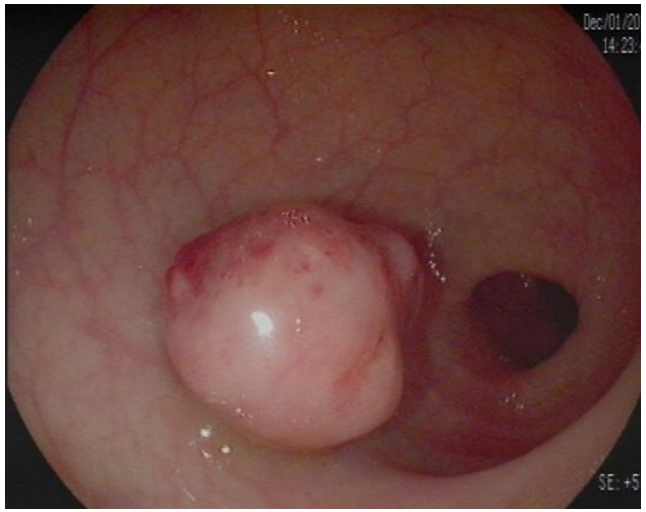
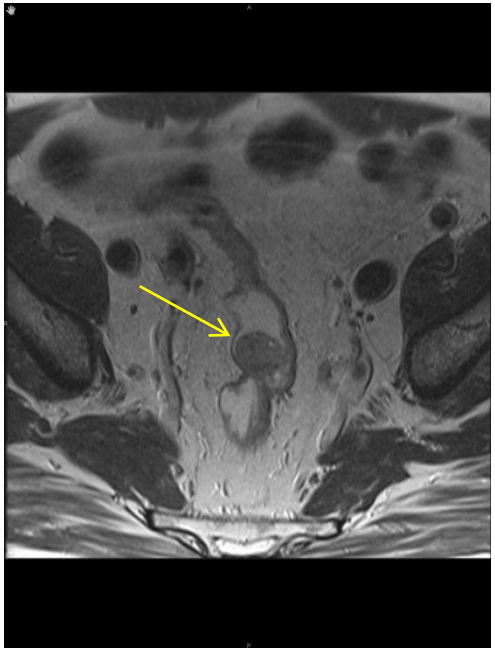
Rectal NENs: clinical case





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Rectal NENs: from endoscopy to surgery

Endoscopy (<1.5 cm):

EMR 59.1% complete

EMR-C 72.4%

ESMR-L 94.8%

ESD 93.9%

Surgery: (LN or muscolaris involvement; mitotic index ≥2/10HPF)

TEMS

Laparoscopic LAR

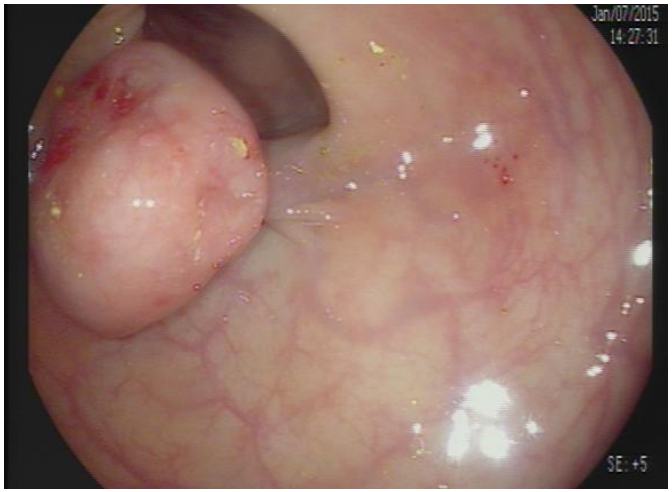
Robotic LAR

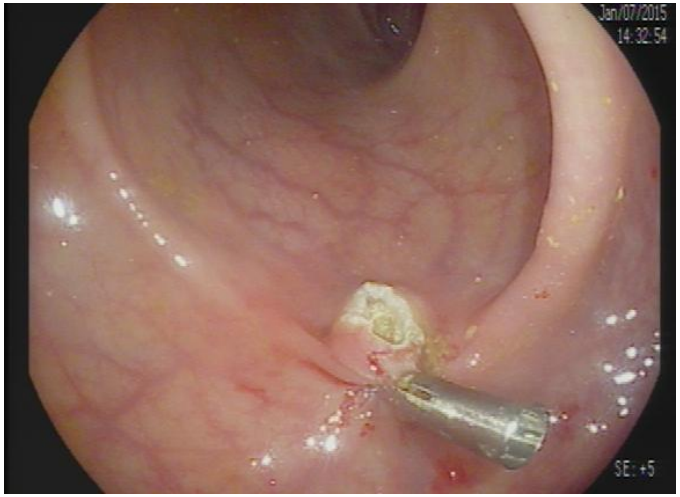
TME

De Mestier 2013

IEO Istituto Europeo di Oncologia

Rectal NENs: clinical case





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Rectal NENs: 5 yrs survival

Localized (ENETS, WHO stage I-II-IIIa)	94-100%
LN Mets (ENETS, WHO stage IIIb)	54-74%
Distant Mets (ENETS, WHO stage IV)	15-37%

Yao 2008
Tsikitis 2012
Scherübl 2011

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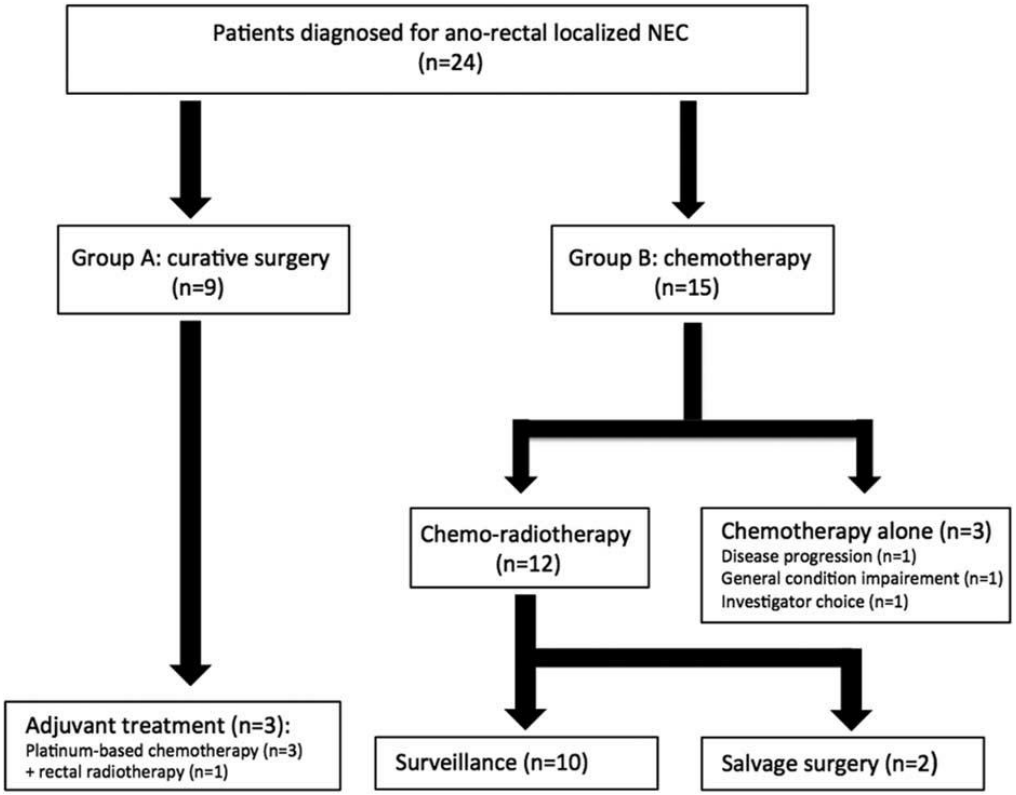
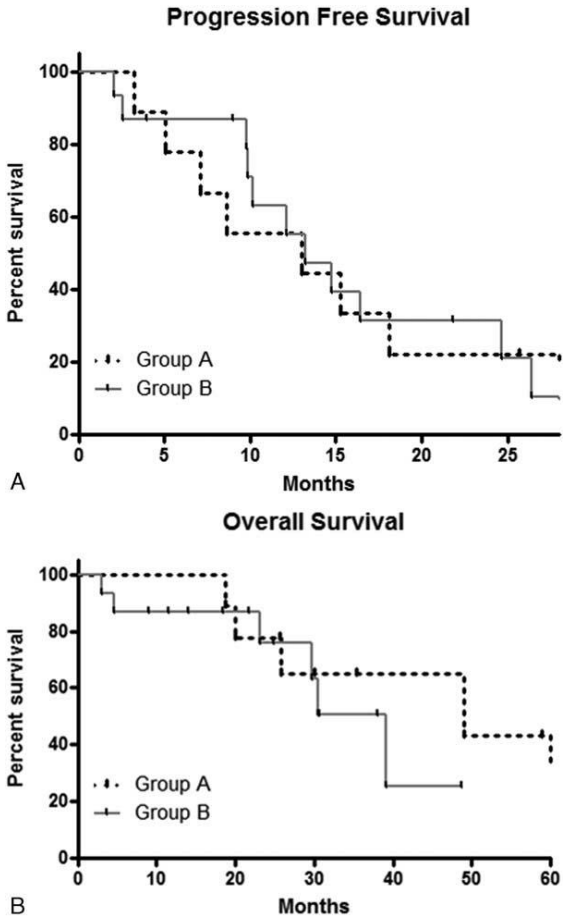
Rectal NEC

Multicentric French study (11 centers)



Mean Ki-67 72%

75% of tumors Ki-67 > 50%



Brieau 2015

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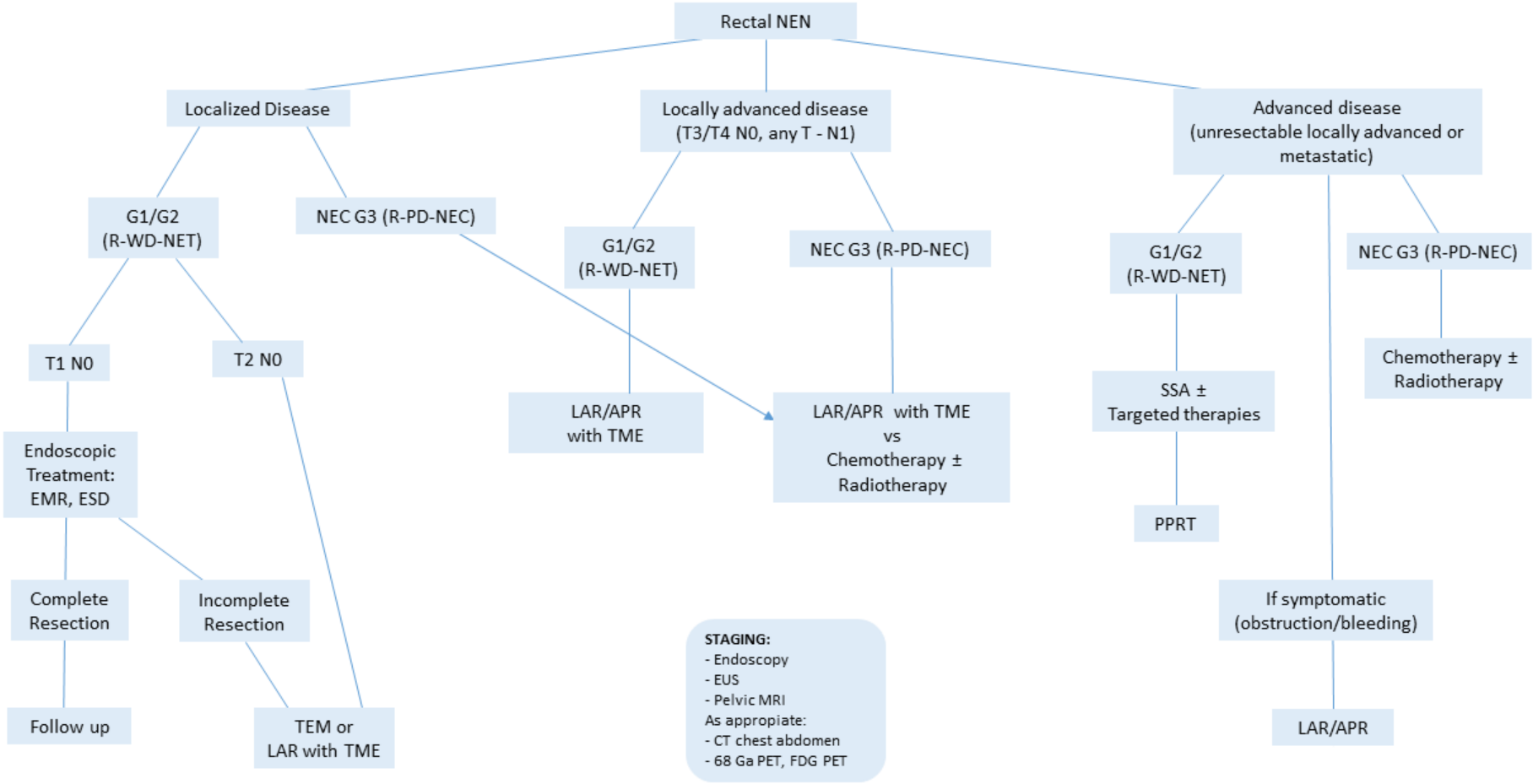
Rectal NENs



Bertani et al. *CTR in press*

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Surgery for GEP-NET liver metastases an open issue

Surgery has been proposed as the only potential curative treatment for metastatic PNETs, although few case series have been published

Survival outcomes from liver resection for NET metastases since the year 2000 range from 74% to 100% at 5 years after surgery, with disease-free survival spanning from 29% to 96%

However, it is possible that good results for surgery represent selection bias. The Cochrane systematic reviews which were conducted did not identify any benefit of liver resection, either in terms of complete resection (R0 or R1) or cytoreduction (R2)

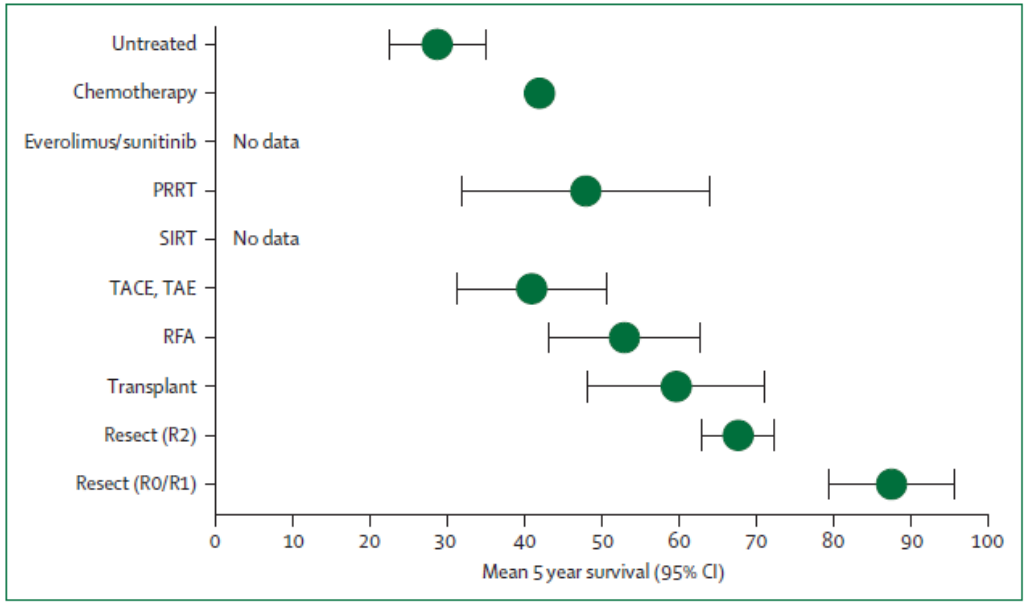
Treatment approaches to GEP NEN liver metastases

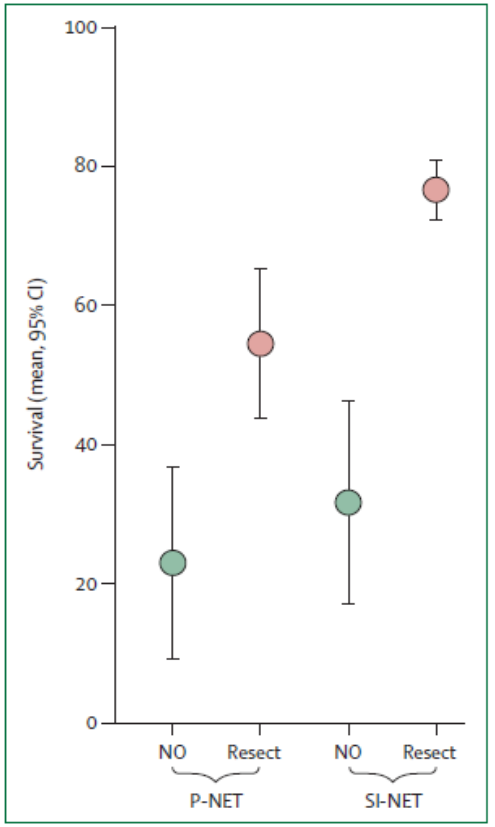
- Evidence-based best practice strategies are scarce

- Different clinical patterns according to the local practice and experience

- Many treatments are available

Treatment outcomes of GEP NEN liver metastases





Frilling A et al. *Lancet Oncol* 2014

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What is missing?

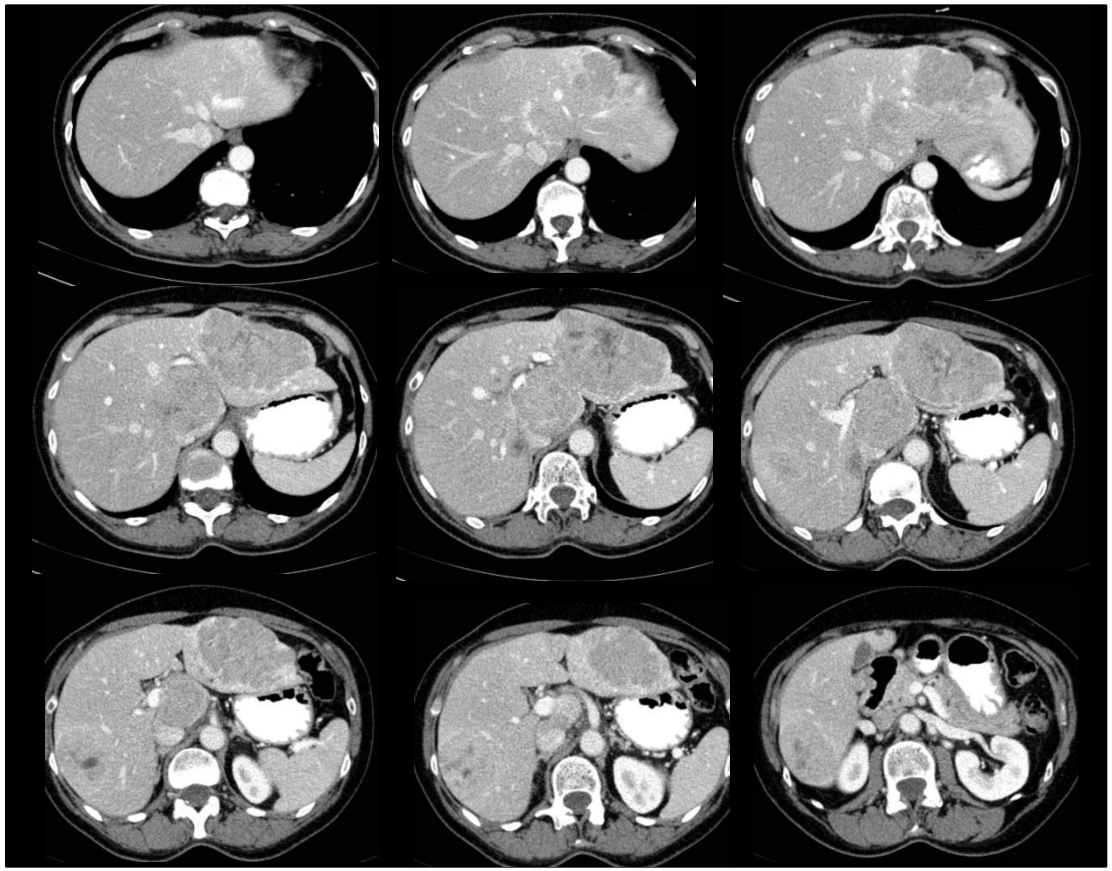
Resectable → Resect

Are we doing right?

Case 2

V.V. ♀ 57 yrs

Biopsy-proven NEN LM (3 lesions max diameter 9,7 cm) ; primary duodenum



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Timing of surgery

- Which is the role of SSA?

- Which is the role of preoperative TAE?

- How aggressive should we be?

Case 2

V.V. ♀ 57 yrs

Biopsy-proven NEN LM (3 lesions max diameter 9,7 cm) ; primary duodenum

PET with ^{68}Ga SSA

Start SSA

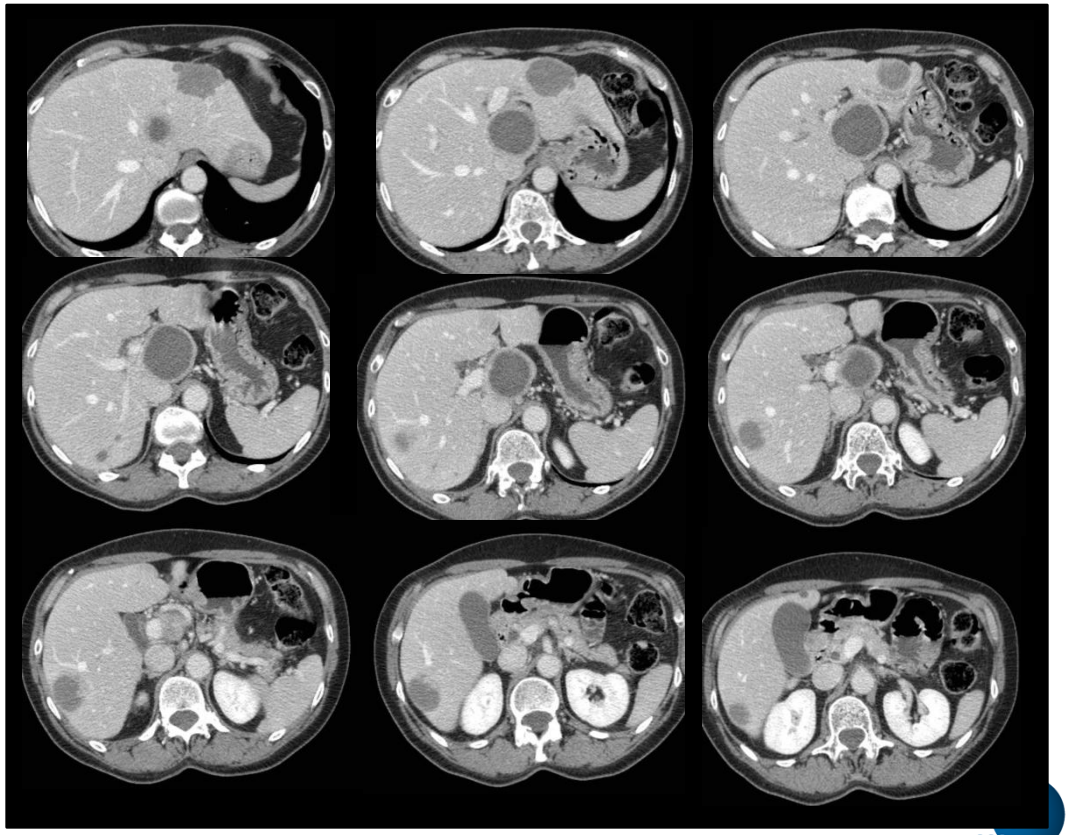
After 3 monts TAE (followed after 2 months by a second and a third TAE)

Case 2

V.V. ♀ 57 yrs

Biopsy-proven NEN LM (3 lesions max diameter 9,7 cm) ; primary duodenum

3 months after TAE



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Case 2

V.V. ♀ 57 yrs

Biopsy-proven NEN LM (3 lesions max diameter 9,7 cm) ; primary duodenum

PET with ^{68}Ga SSA with a reduction of the liver uptake and an increase of the duodenum uptake

↓

Liver resection af all lesions + duodenal resection

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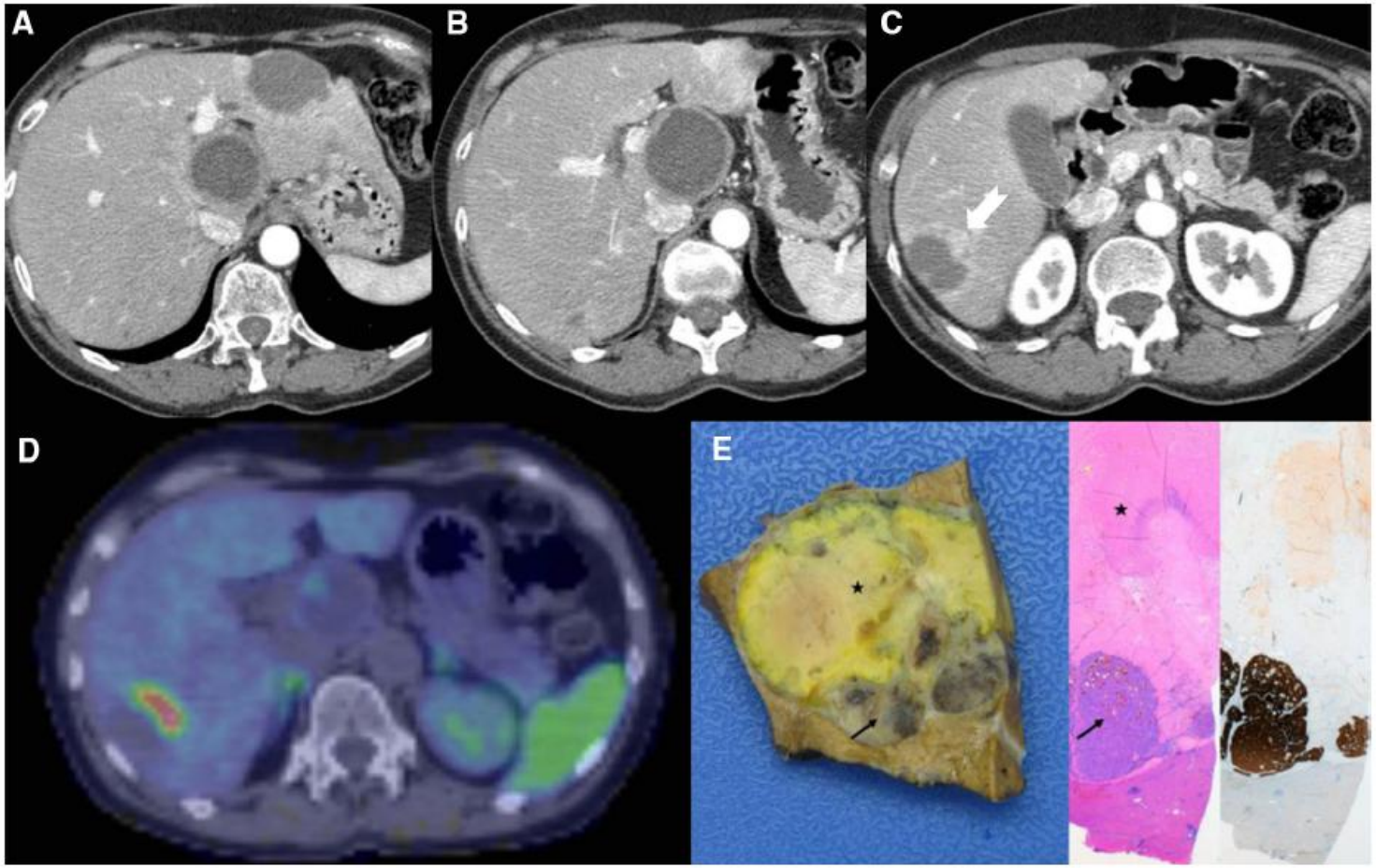
GEP-NET surgery for liver metastases an open issue



Liver mets from duodenal NET

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Surgery for GEP-NET liver metastases

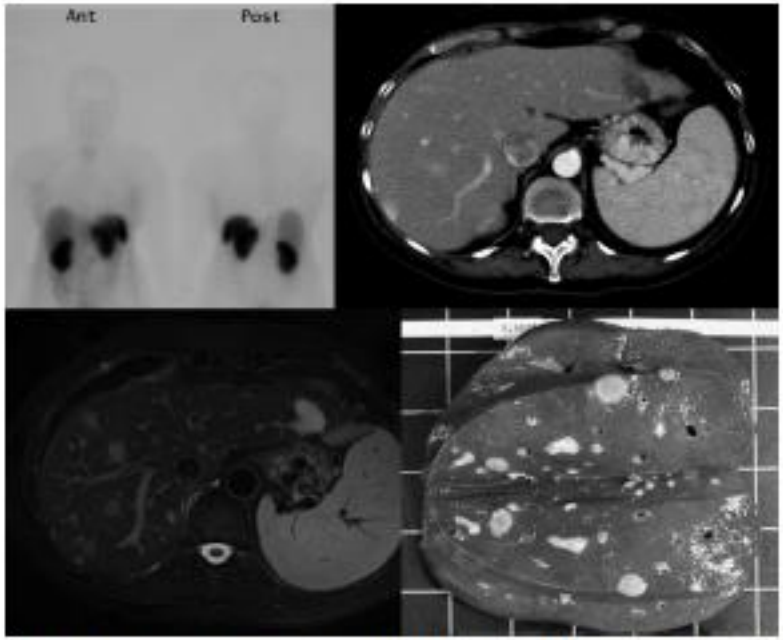

FIGURE 1. Preoperative Somatostatin receptor scintigraphy, CT-scan, MRI of a patient with liver metastasis of neuroendocrine origin and the first histologic slices.

- Liver specimens were systematically sliced 3-4 mm of thickness
- Preop imaging detected less than 50% of lesions 849% for MRI)
- The size of the smallest lesion was no greater than 2 mm in 54% of pts

Elias et al Ann Surg 2010

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GEP-NET unresectable liver metastases

Primary tumor resection

YES ?

NO ?

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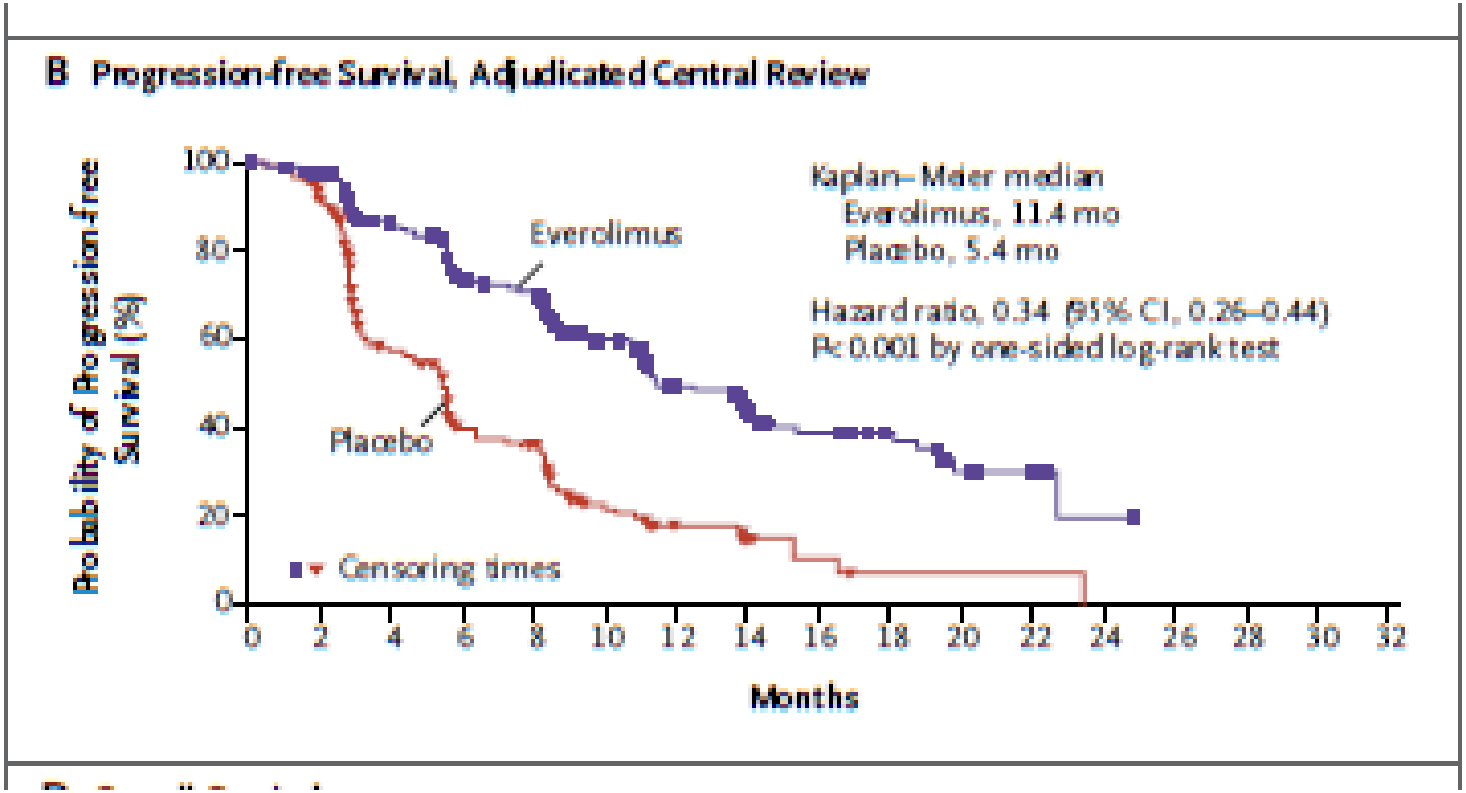
PNETs-Everolimus



Yao NEJM 2011: previous surgery?

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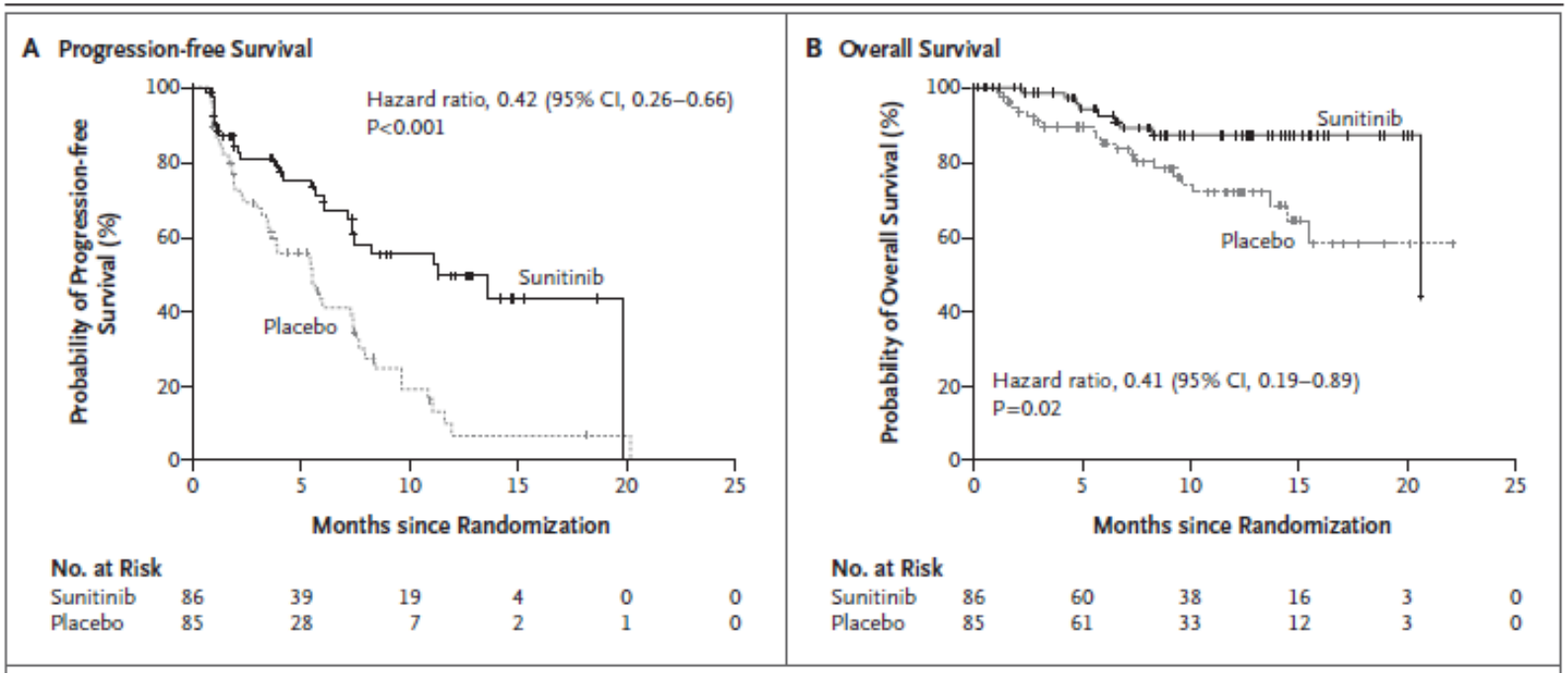
PNETs-Sunitinib

The NEW ENGLAND JOURNAL of MEDICINE



Raymond NEJM 2011: previous surgery→88% vs 91%

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Systematic review

Systematic review of resection of primary midgut carcinoid tumour in patients with unresectable liver metastases

G. Capurso[1], M. Rinzivillo[1], R. Bettini[2], L. Boninsegna[2], G. Delle Fave[1] and M. Falconi[2,3]

[1]Digestive and Liver Disease Unit, II Medical School, University 'Sapienza', S. Andrea Hospital, Rome, and Departments of Surgery, [2]Ospedale Sacro Cuore–Don Calabria, Negrar, and [3]University of Verona, Verona, Italy

Correspondence to: Dr M. Falconi, Department of Surgery, University of Verona, Division of General Surgery, Ospedale 'Sacro Cuore – Don Calabria', Via Don Sempreboni, 5, Negrar, Italy (e-mail: massimo.falconi@univr.it)

Neuro-endocrinology

Neuroendocrinology 2011;93:223–229
DOI: 10.1159/000324770

Received:
Accepted
Published

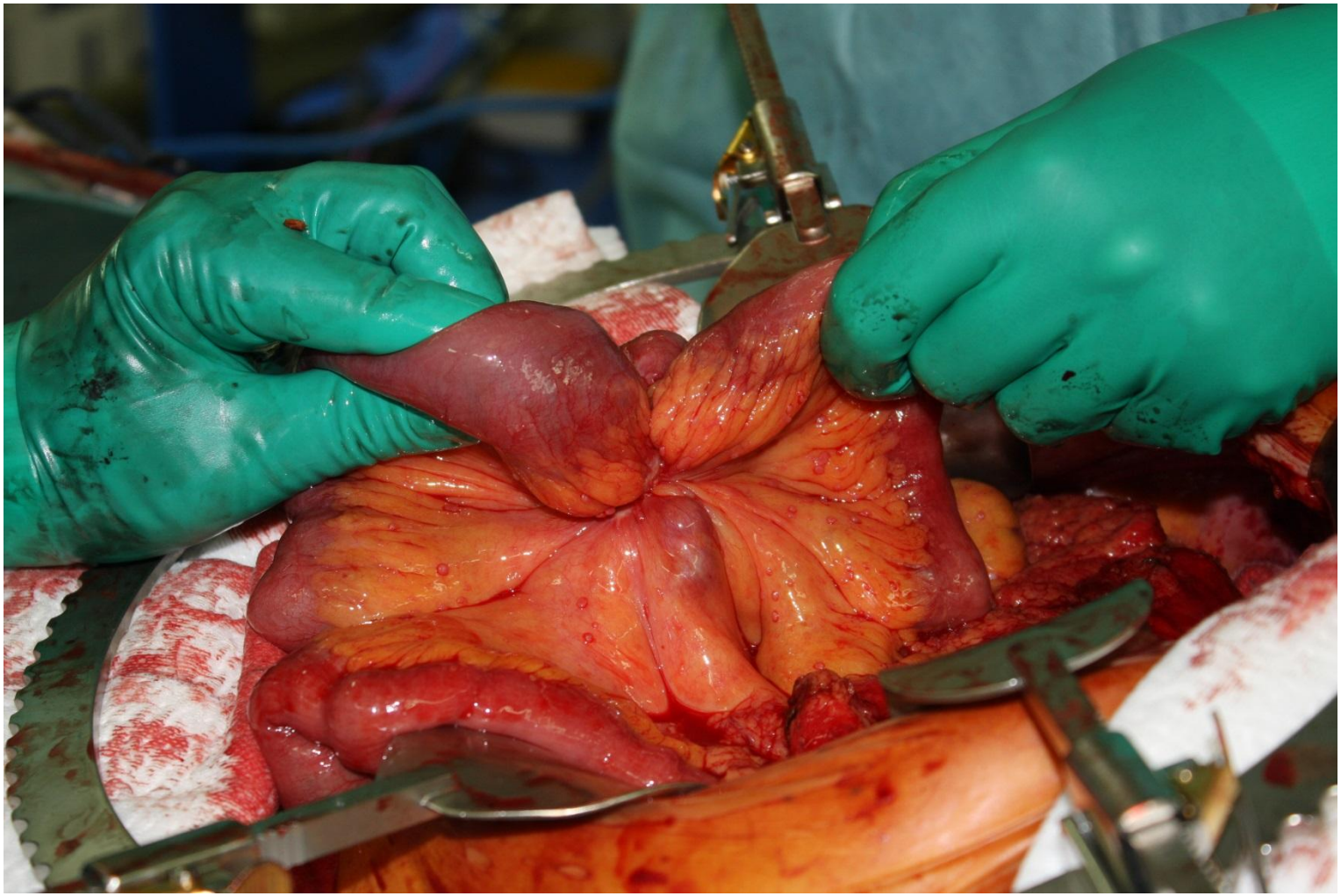
Role of Resection of the Primary Pancreatic Neuroendocrine Tumour Only in Patients with Unresectable Metastatic Liver Disease: A Systematic Review

Gabriele Capurso[a] Rossella Bettini[b] Maria Rinzivillo[a] Letizia Boninsegna[b, c]
Gianfranco Delle Fave[a] Massimo Falconi[b]

[a]Digestive and Liver Disease Unit, II School of Medicine, 'Sapienza' University of Rome, Rome, [b]Department of Surgery, Ospedale Sacro Cuore-Don Calabria, Negrar, and [c]Department of Surgery, University of Verona, Verona, Italy

ENETS guidelines:
Suggested SI-NET
Not recommended
PNETs

Resectable



Need for preoperative classification

- Inspired from **intraoperative** schema of Ohrvall et al. 2000 (Upsala)

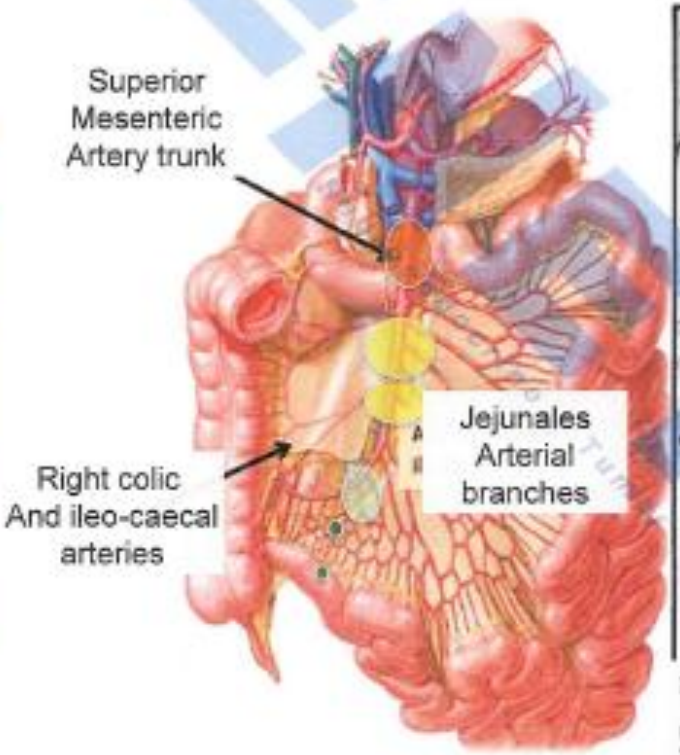
Stage 4

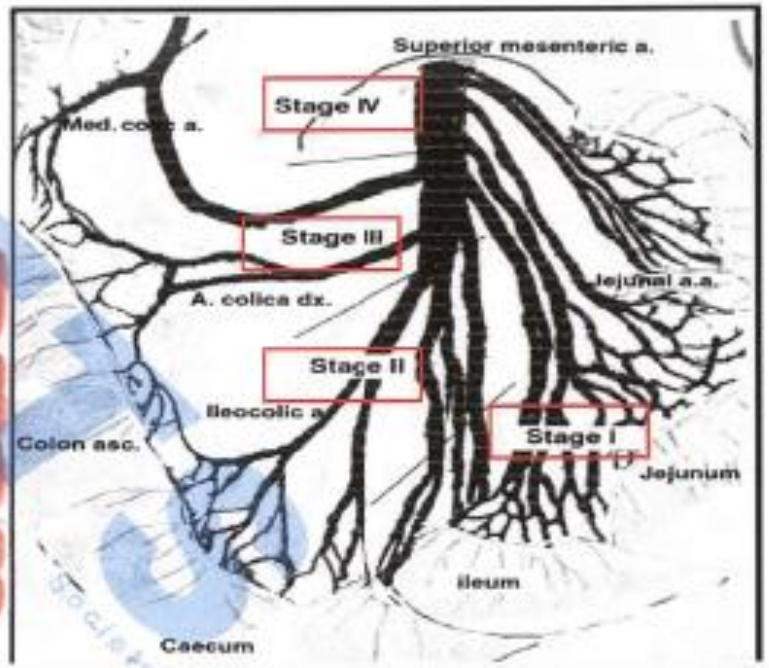
Stage 3

Stage 2

Stage 1

Stage 0





Method for Dissection of Mesenteric Metastases in Mid-gut Carci

Ulf Ohrvall, M.D., Ph.D.,[1] Barbro Eriksson, M.D., Ph.D.,[2] Claes Juhlin, M.D., Ph.D.,[1] Sederin Kärnegil, M.D., Ph.D.,[1] Jonas Rastad, M.D., Ph.D.,[2] Per Hellman, M.D., Ph.D.,[1] Göran Åkerström, M.D., Ph.D.[1]

[1]Department of Surgery, University Hospital, S-751 85 Uppsala, Sweden
[2]Department of Medicine, University Hospital, S-751 85 Uppsala, Sweden

2000

ENETS 2014 Abstract N° =03, Degulete et al.

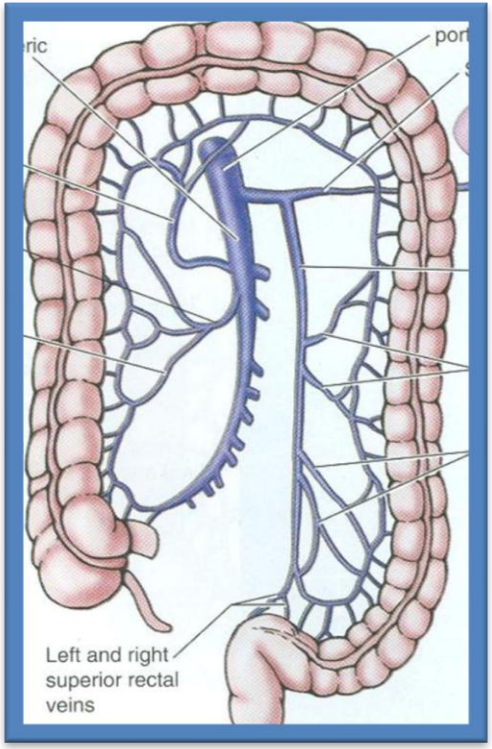
Degree of venous involvement

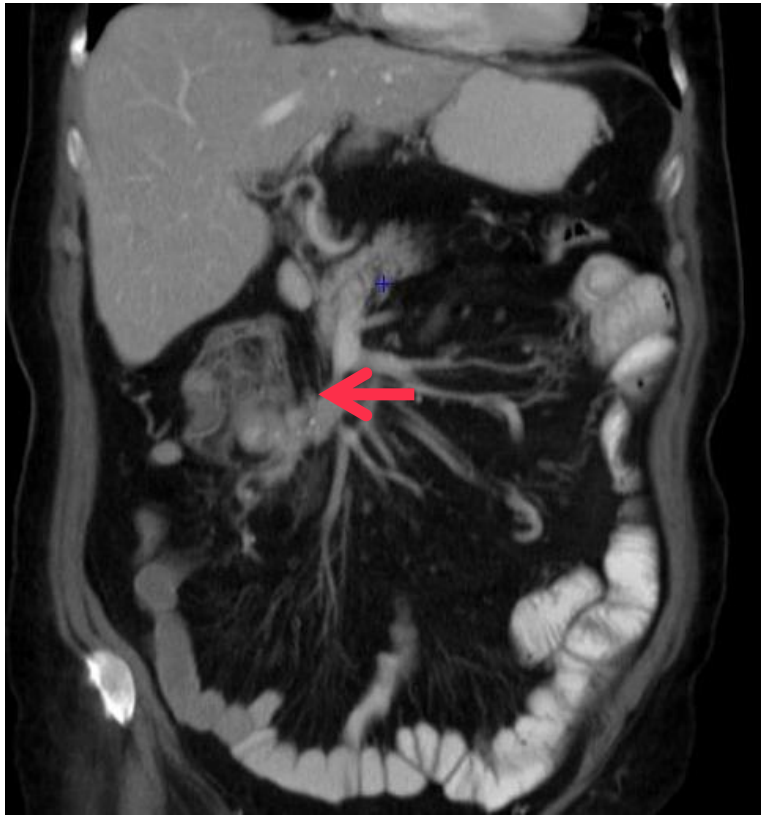
PERIPHERAL

- Distal to the first 3 collateral
- Origin of the middle colic vein is preserved

PROXIMAL

- Infiltration of the origin middle colic vein or SMV collateral above its level





Piccioli et al. *ENETS 2018 Abstract*

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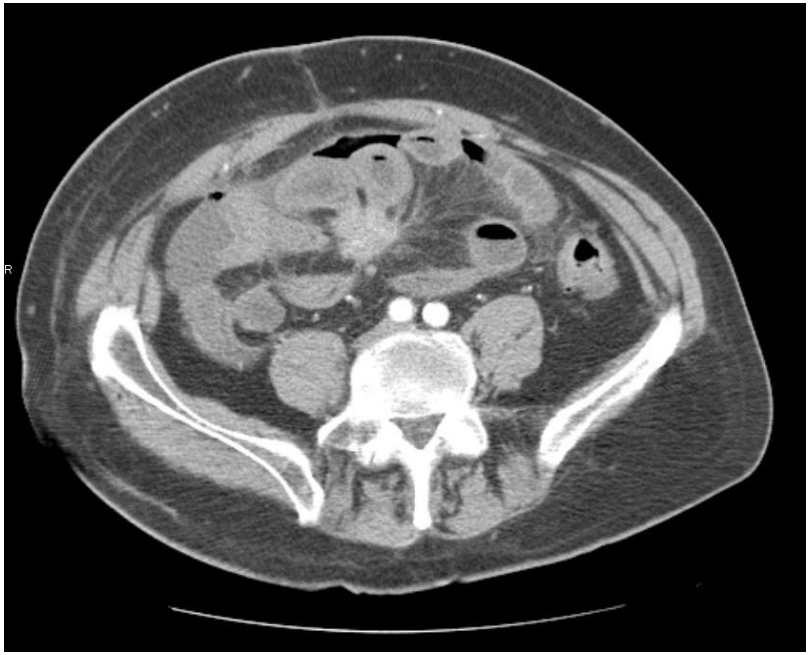
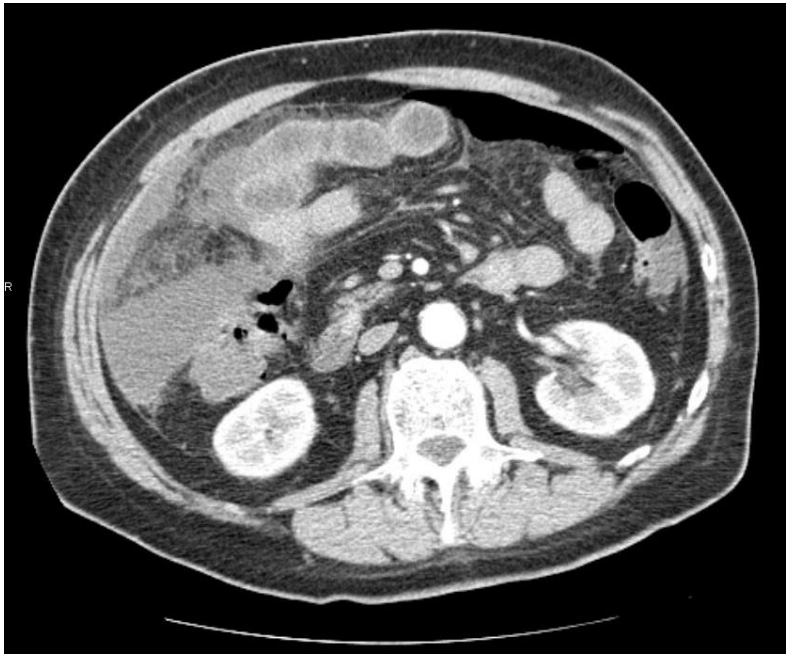
Mesenteric retraction





Piccioli et al. *ENETS 2018 Abstract*

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Results

	Univariate analysis			Multivariate analysis		
	Complete PT and LN resection (n=26)	Uncomplete resection/by-pass/not resected (n=10)	p	HR	95% CI	p
L-D stage						
LN stage 0-I	10 (39)	0	**0.03**	0,474	0.08-0.319	**0.002**
LN stage II	6 (23)	1				
LN stage III	9 (35)	4				
LN stage IV	1 (0,04)	5				
MV involvement						
absent	14	2	**0.008**			
peripheral	12	5				
proximal	0	3				
Mesenteric fibrosis retraction						
absent	24	6	**0.039**	0,344	0.103-0.723	**0.011**
present	2	4				

Piccioli et al. *ENETS 2018 Abstract*

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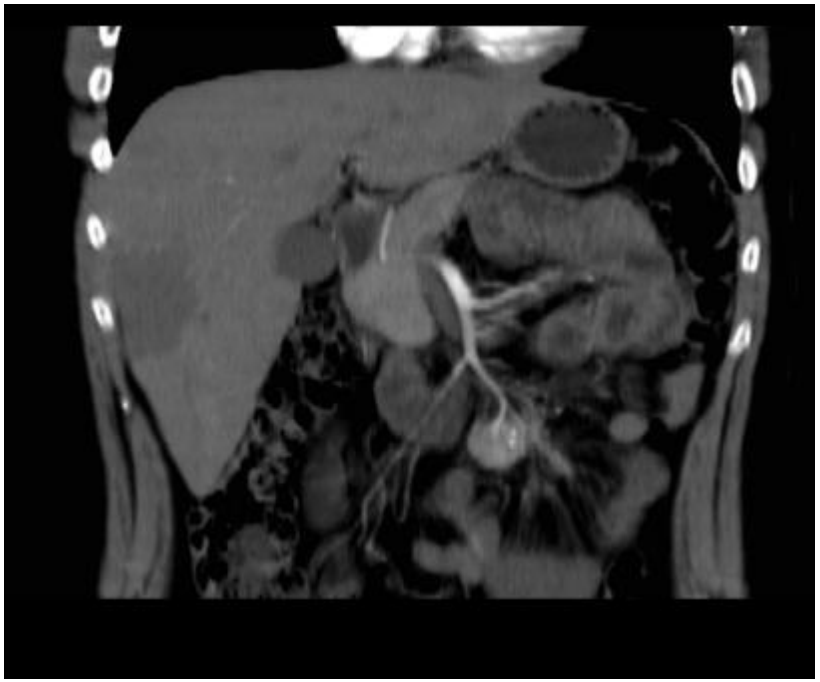
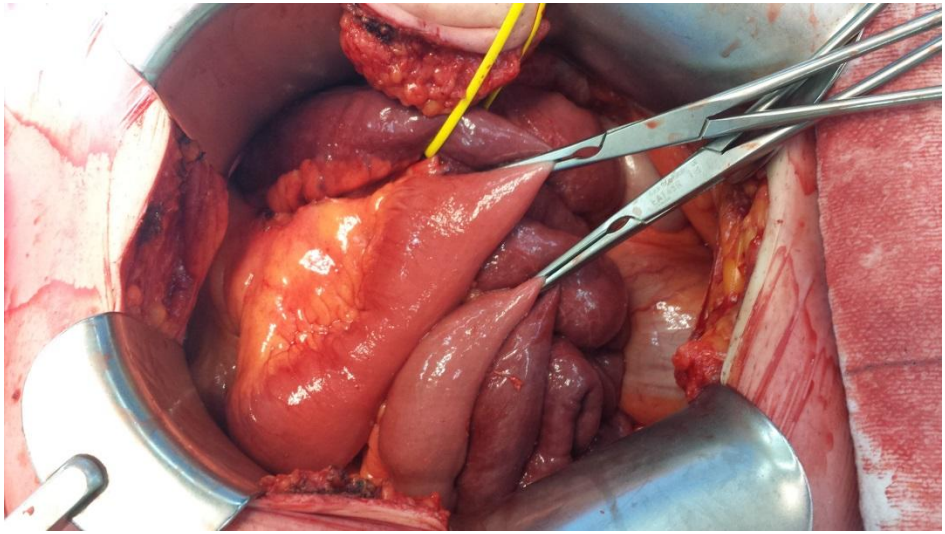
Resectable





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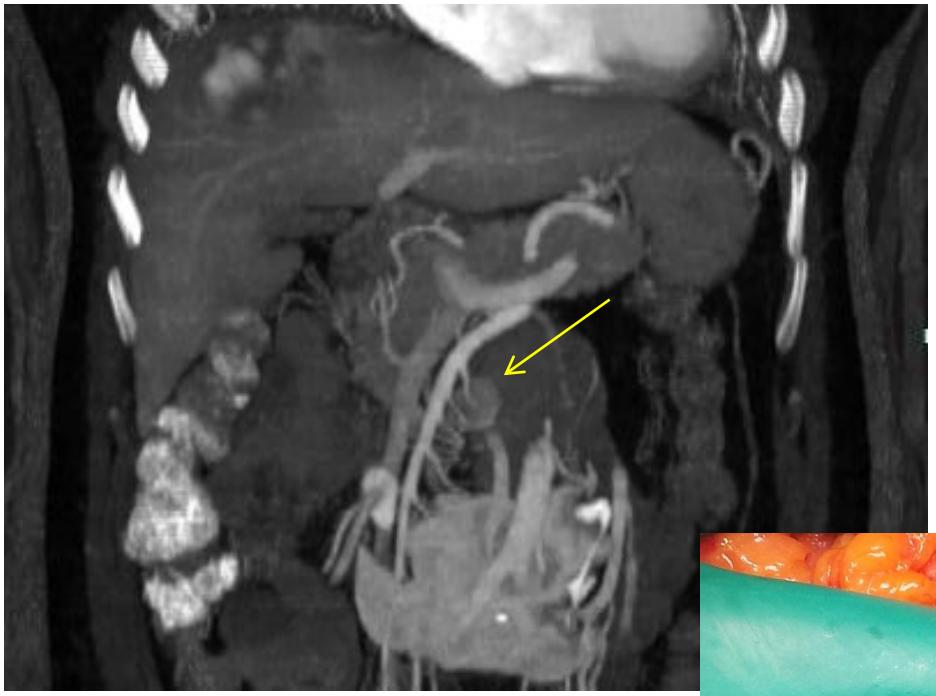
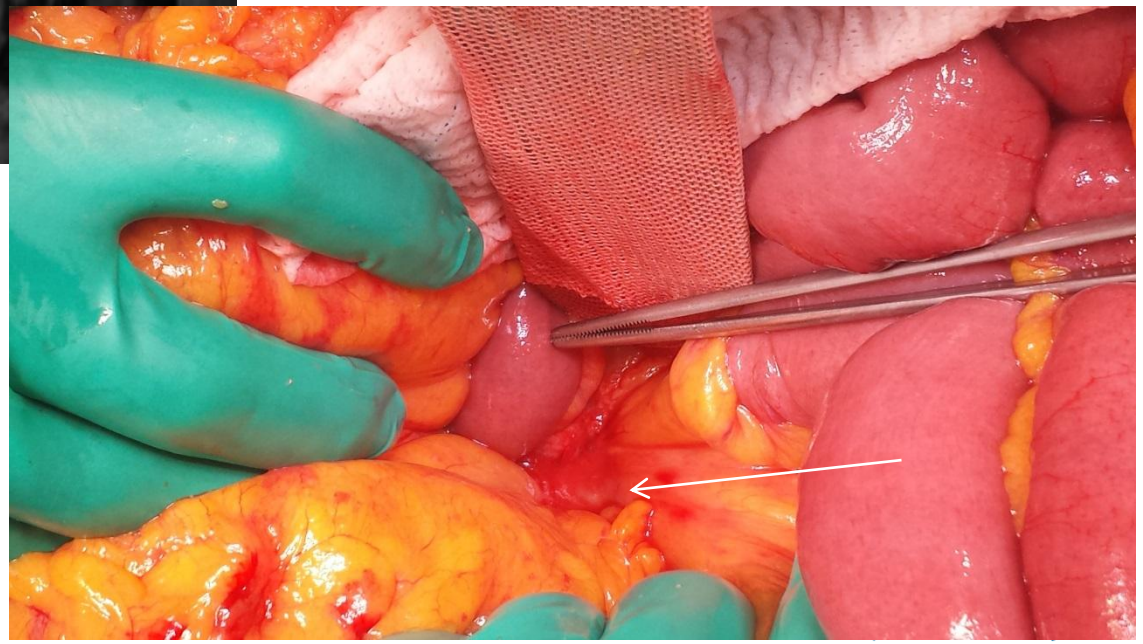
Unresectable





SI-NET: prognostic factors after debulking surgery

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Original research

Small intestinal neuroendocrine tumors with liver metastases and resection of the primary: Prognostic factors for decision making

Emilio Bertani [a,*], Massimo Falconi [b], Chiara Grana [c], Edoardo Botteri [d], Antonio Chiappa [e], Pasquale Misitano [f], Francesca Spada [g], Davide Ravizza [h], Barbara Bazolli [d], Nicola Fazio [g]

Bertani et al Int J Surg 2015

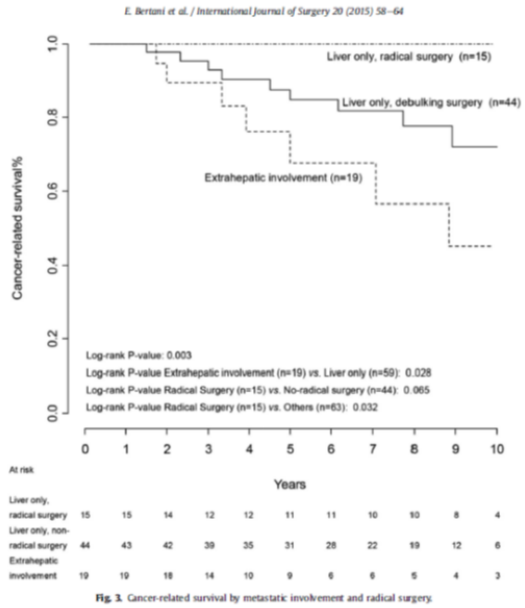


Fig. 3. Cancer-related survival by metastatic involvement and radical surgery.

Table 3
Multivariable analysis for cancer-related survival in patients who underwent radical and debulking surgery (A) or debulking surgery alone (B).

Variable	Comparison	HR (95% C.I.)	P
A			
Extrahepatic involvement	Yes *vs.* No	3.10 (1.12–8.59)	0.030
Liver tumor burden	25–50% *vs.* <25%	3.21 (0.95–10.8)	0.036
	>50% *vs.* <25%	8.88 (1.53–51.4)	
Ki-67	1 unit increase	1.14 (1.02–1.26)	0.021
B			
Extrahepatic involvement	Yes *vs.* No	2.45 (0.89–6.76)	0.030
Liver tumor burden	25–50% *vs.* <25%	2.93 (0.85–10.1)	0.016
	>50% *vs.* <25%	7.19 (1.27–40.8)	
Ki-67	1 unit increase	1.12 (1.00-1.25)	0.081

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The question

JAMA Oncology | Original Investigation

Association of a Prophylactic Surgical Approach to Stage IV Small Intestinal Neuroendocrine Tumors With Survival

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Figure 1. Study Flow Diagram

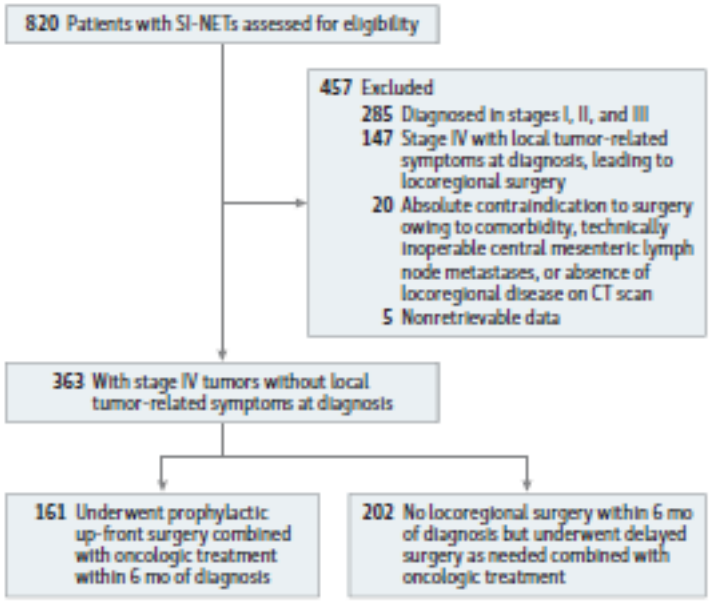
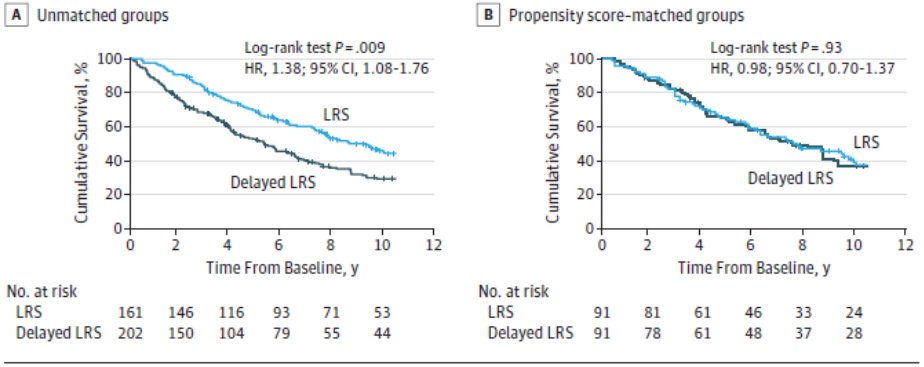


Figure 2. Kaplan-Meier Survival Analyses



53 out 91 in the «non operated» matched group underwent surgery after 6 months from diagnosis because of symptoms (n=20) or not

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The question

Primary tumor resection

WHEN ?

The role of surgery in GEP-NENs: which aspects are you interested in?

- Gastroduodenal NENs →type 3 (g) →size and N matter (d)
- PanNENs→size matter
- Small bowel NETs →always!
- (colo)rectal NENs →maybe…
- Liver metastases →G1-G2 WD-NETs
- Primary tumor surgery in case of unresectable liver mets (small bowel and pancreas) → I don't know

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Thank you

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