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GEP NEN

Principles of diagnostic work-up and therapy

Surgery

ESMO Preceptorship Programme
Neuroendocrine Neoplasms
Lugano
13 – 14 April 2018

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European ENETS Neuroendocrine Tumor Society

Disclosure

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

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Principles of surgical approach – what needs to be considered?

Site of the primary tumor

Pancreas, small bowel, bronchopulmonary system

Unknown primary tumor site

Tumor stage

Primary tumor

Extrahepatic disease +/-

Locoregional recurrence (lung, pancreas) +/-

Tumor grade

G1, G2, G3

Sporadic vs. hereditary NEN

MEN always multifocal primary tumour manifestation

Carcinoid syndrome

Perioperative octreotide treatment

Patient specific risk / surgical risk

Carcinoid heart / pancreatic fistula / bile leak / anastomotic leak

Curative vs palliatve approach

Neoadjuvant / multimodal treatment concepts

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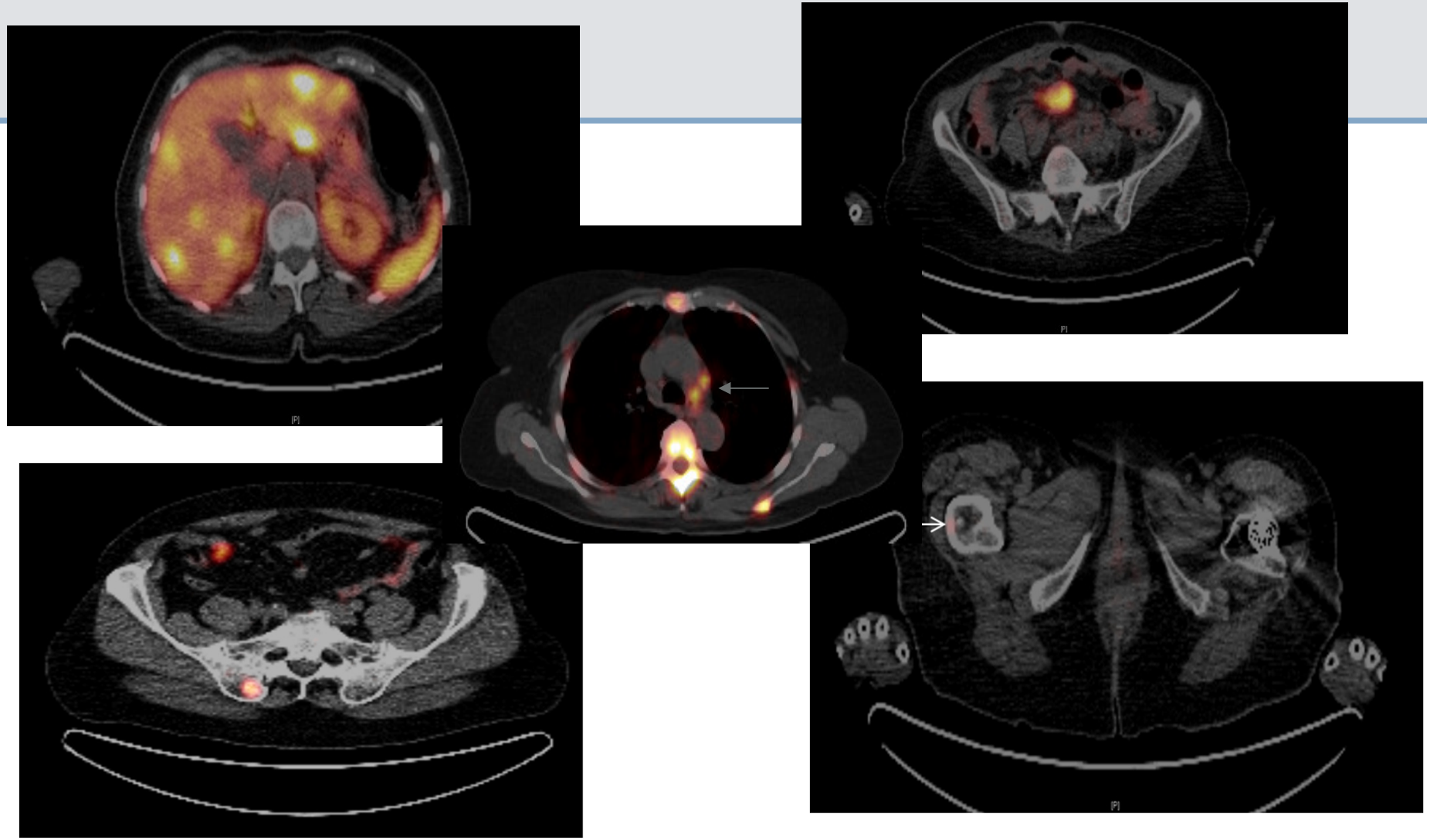
68 Ga DOTATATE PET/CT for staging of NE T

- in combination with 18F FDG PET/CT in G2/G3 NET -



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Kweekeboom DJ et al. J Nucl Med 1999;40:762

Poeppel D et al. J Nucl Med 2011;52:1864
Wild D et al. J Nucl Med 2013;54:364
Frilling A et al. Ann Surg 2010;252:850

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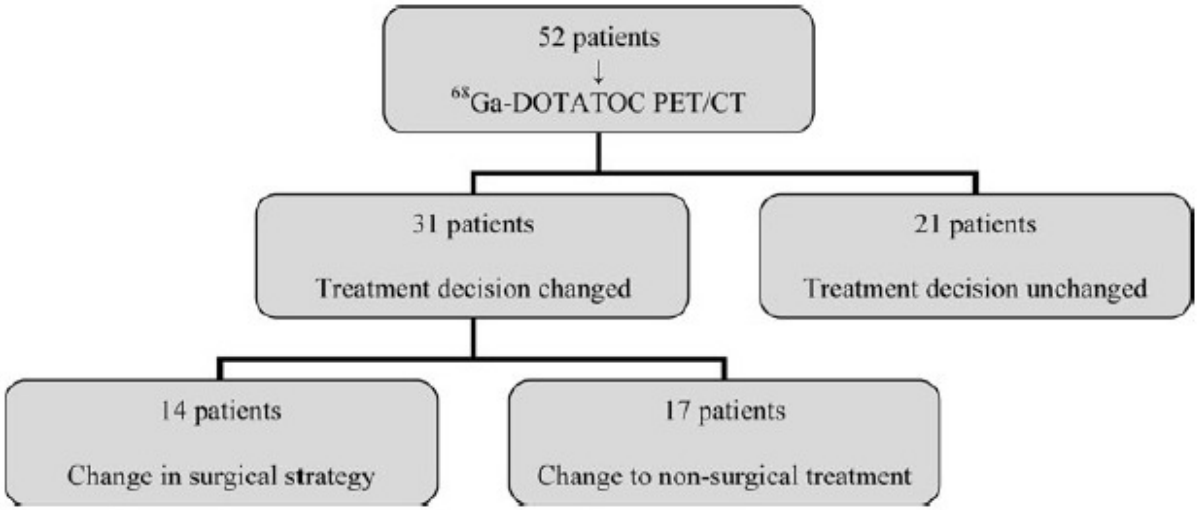
Comparison of 68Ga-DOTATOC PET/CT with Standard Imaging

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	*P*
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



Frilling A et al. Ann Surg 2010;252:850

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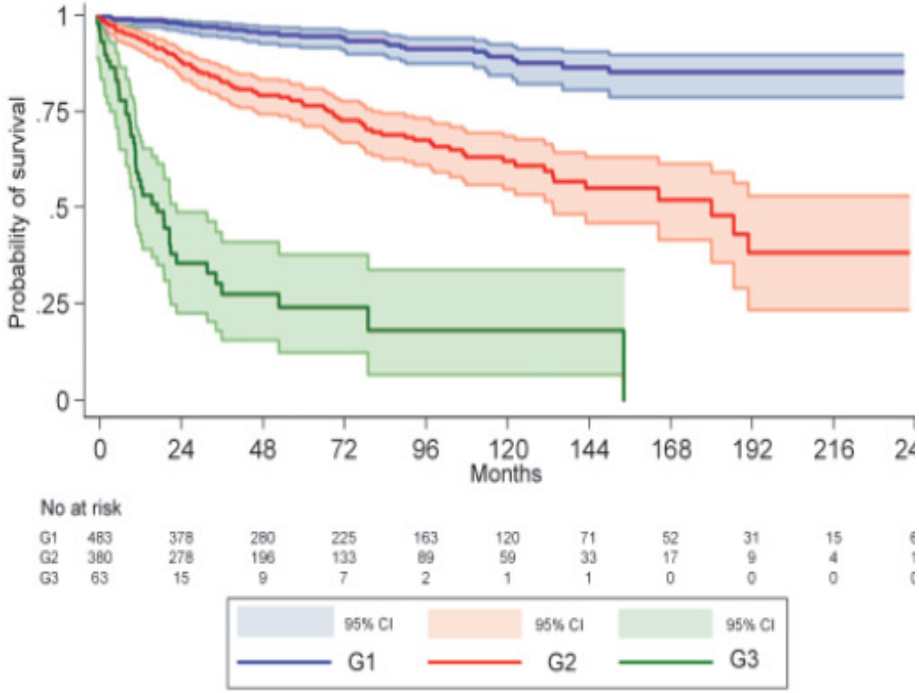
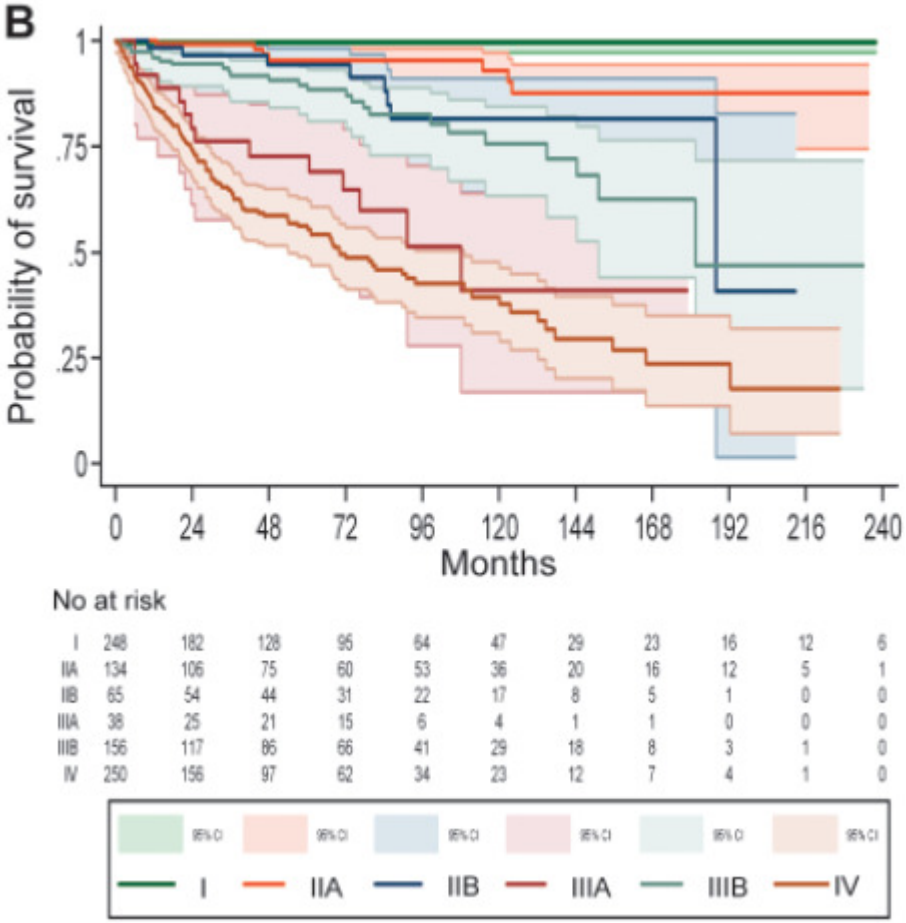
Survival according to the grade and stage of PNET





Rindi G et al. J Natl Cancer Inst 2012;104:764

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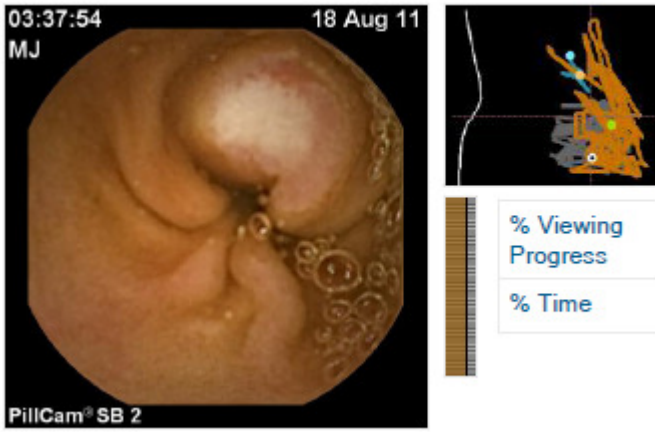
Neuroendocrine tumors of small bowel

Video capsule endoscopy



Comments
? Submucosal Lesion

	N
Patients	11
Median age (years)	65 (range 30–81)
Symptoms	
Asymptomatic	3
Bleeding	3
Carcinoid syndrome	6
Median serum CgA level (pmol/L)	153 (range 26–4122)
Median serum CgB level (pmol/L)	132 (range 47–405)
5-HIAA in 24 h urine (μmol/24 h)	33.7 (range 6.5–850.1)
Metastases on CT/MRI	
Liver	6
LN	8
Bone	1
Lung	1
Metastases on ^{68}Ga-DOTATATE PET/CT	
Liver	5
LN	6
Bone	3
Lung	1
Site of lesions on VCE	
Proximal ileum	2/8
Mid ileum	3/8
Terminal ileum	3/8
Surgery	6/11
Median primary tumour size (mm)	11.5 (range 8–25)
Tumour stage	
$T_2N_1M_0$	1
$T_3N_1M_0$	1
$T_1N_2M_1$	2
$T_2N_1M_1$	1
$T_3N_1M_1$	1

Frilling A et al. Dig Liver Dis 2014;46:1038-42

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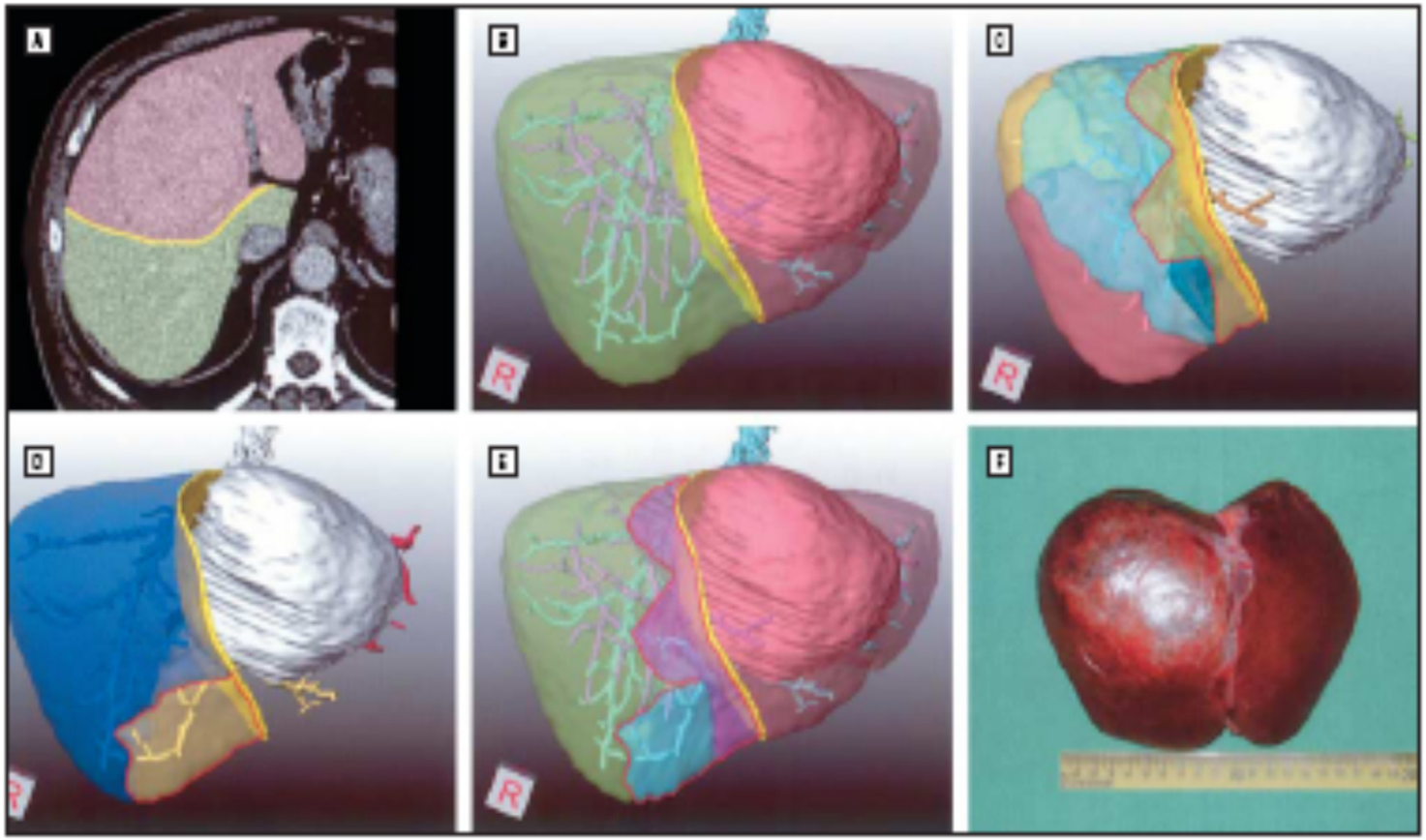
Virtual tumor resection and 3D- computer assisted surgical planning



Lang H et al. Arch Surg 2005;140;629

Neuroendocrine tumors of the pancreas

- Pancreatic NET - functional and non-functional
- Pancreatic non-functional NET (NF PNET) are defined by the absence of a hormone hypersecretion syndrome
- NF PNET account for 45% -90% of all PNET
- Associated with MEN1 syndrome in ~20%
- Associated with VHL syndrome in ~5%
- Small NF PNET are more frequently detected
- Grading and staging

Treatment decision
Prognosis

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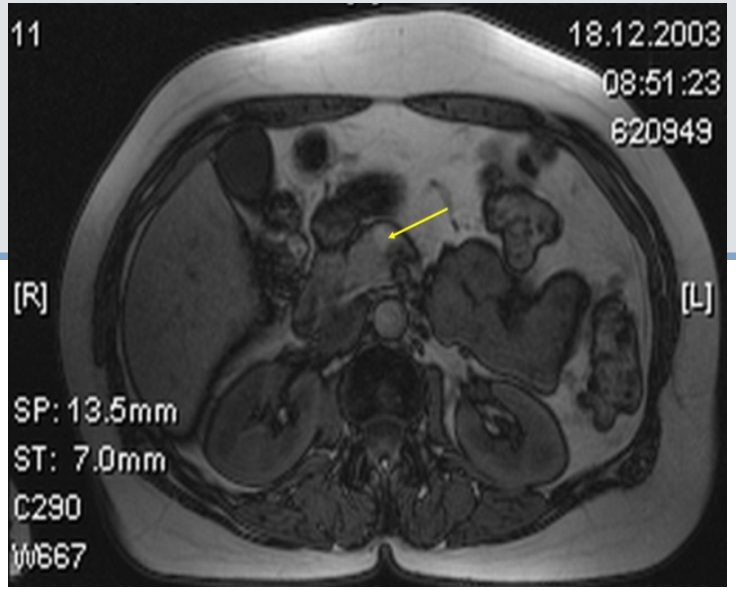
Insulinoma

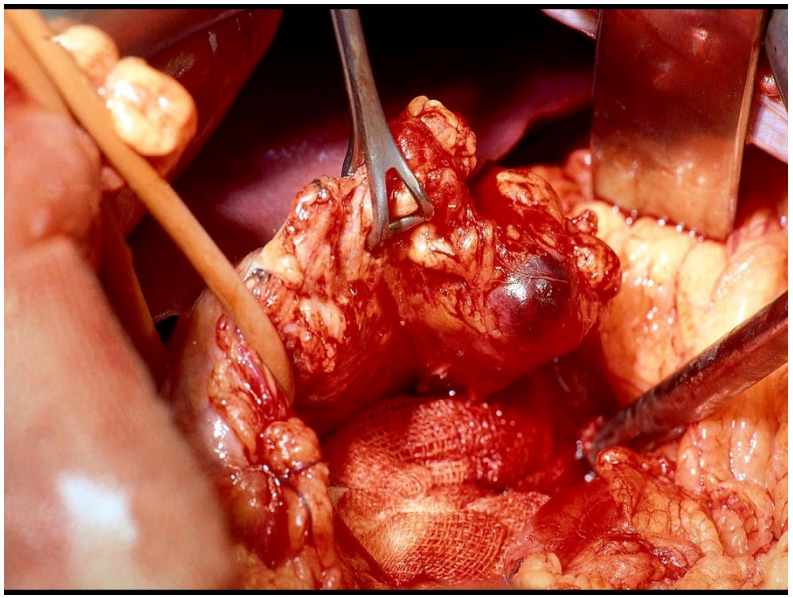


Hypoglycemia
Tumor size <2 cm in 80 %
Benign tumors in 90 %

Enucleation
- Blunt dissection
- Prevention of fistulas (up to 45%)
- IOUS tumor / pancreatic duct

Distal pancreatectomy
- Large lesion
- Malignancy

No „blind resections“



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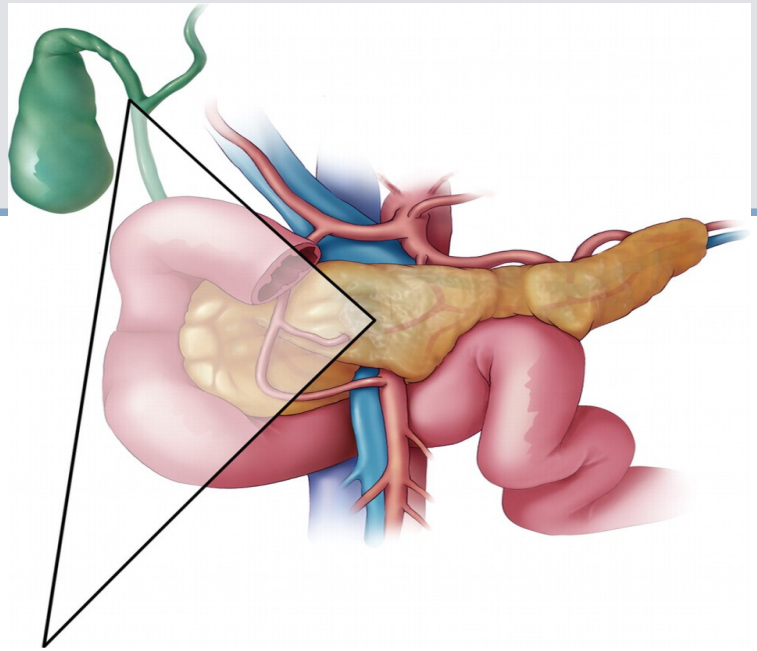
Gastrinoma



Zollinger - Ellison syndrome

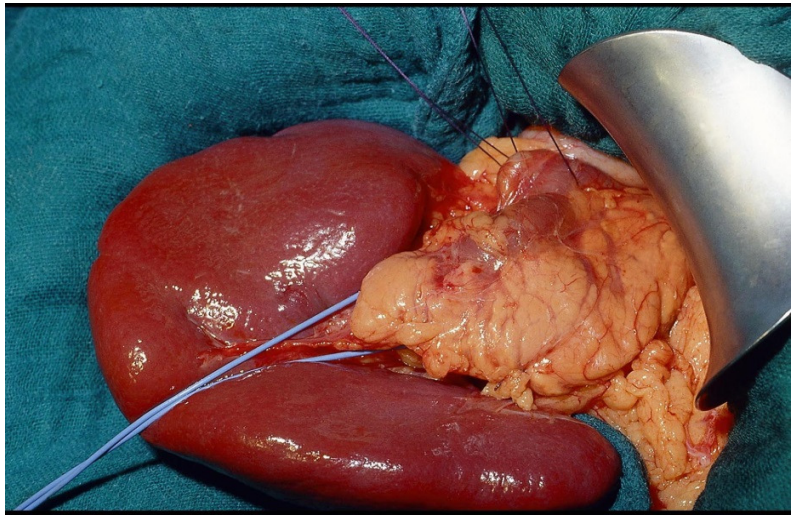
Malignant potential

Gastrinoma triangle

Duodenal wall tumors

Resection rather than enucleation

Lymphadenectomy



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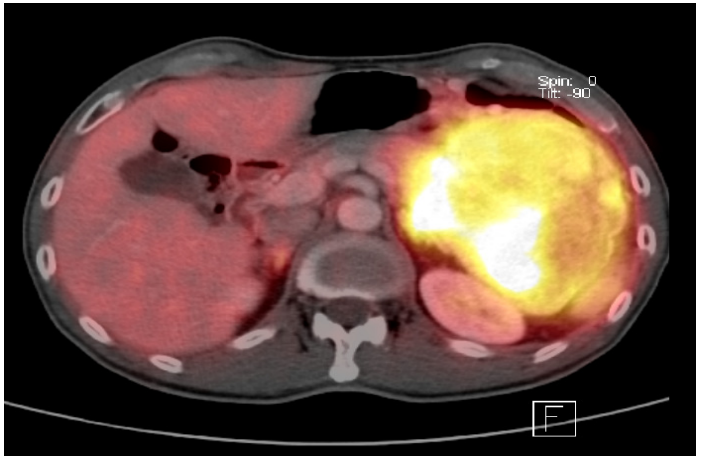
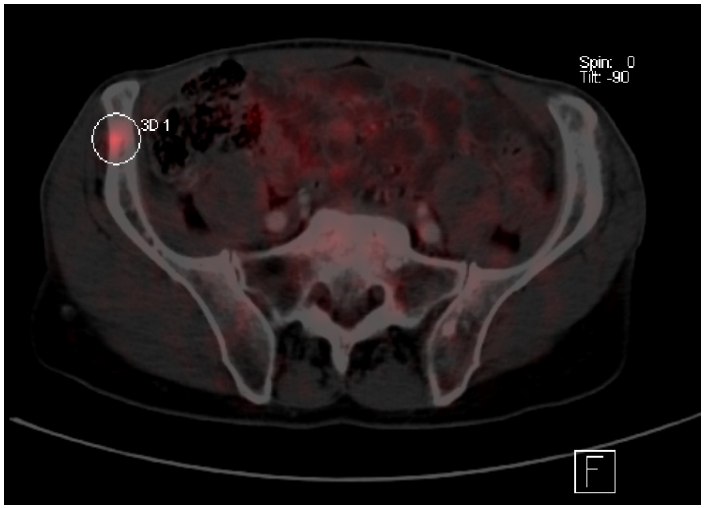
Non-functional pancreatic NET – Resection if feasible





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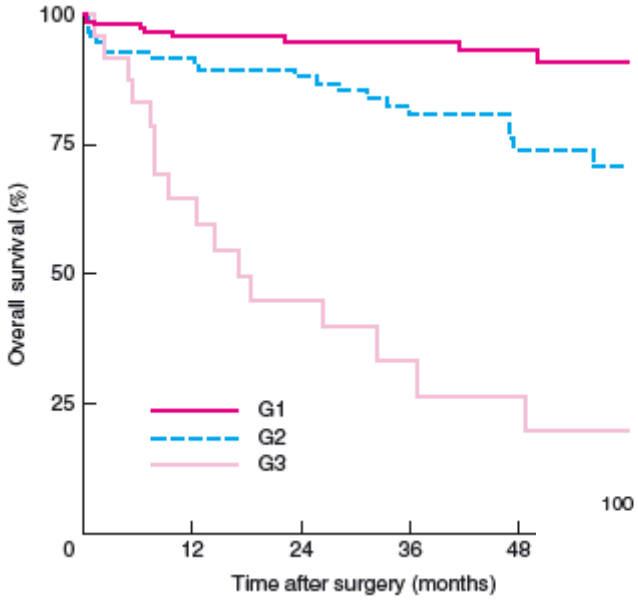
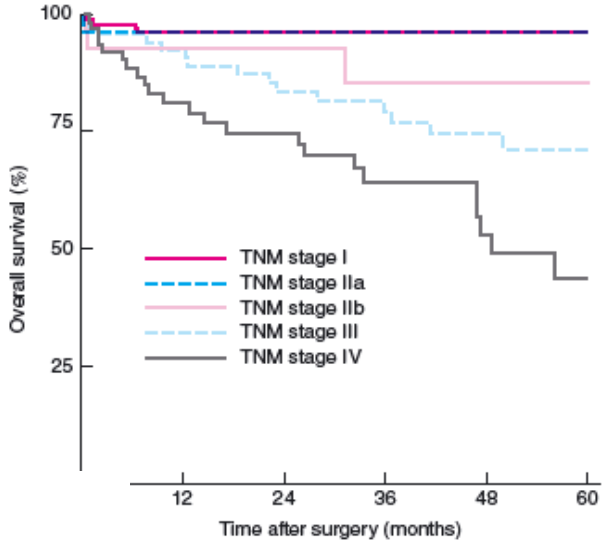
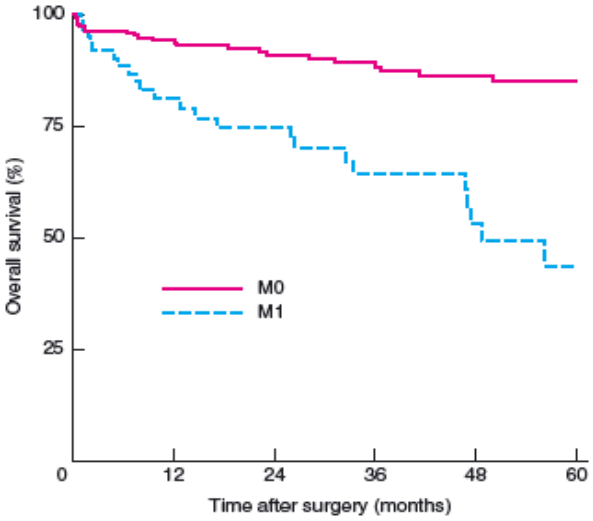
Pancreatic NEN – predictors of survival following surgery







Fischer L et al. Brit J Surg 2014, DOI: 10.1002/bjs.9603

Treatment of gastric NEN

Type	Function	Treatment
Well diff. type 1	Inactive	Endoscopic ablation or Excision, size < 1cm, multiple
Well diff. type 2	Inactive	Endoscopic ablation or Excision, size < 1cm, multiple Resection Association with MEN 1 / ZES
Well diff. type 3	Inactive	Subtotal gastric resection Size > 2 cm, solitary Gastrectomy and lymphadenectomy
Poorly diff. type 4	Inactive	Gastrectomy and lymphadenectomy Size > 2 cm, solitary

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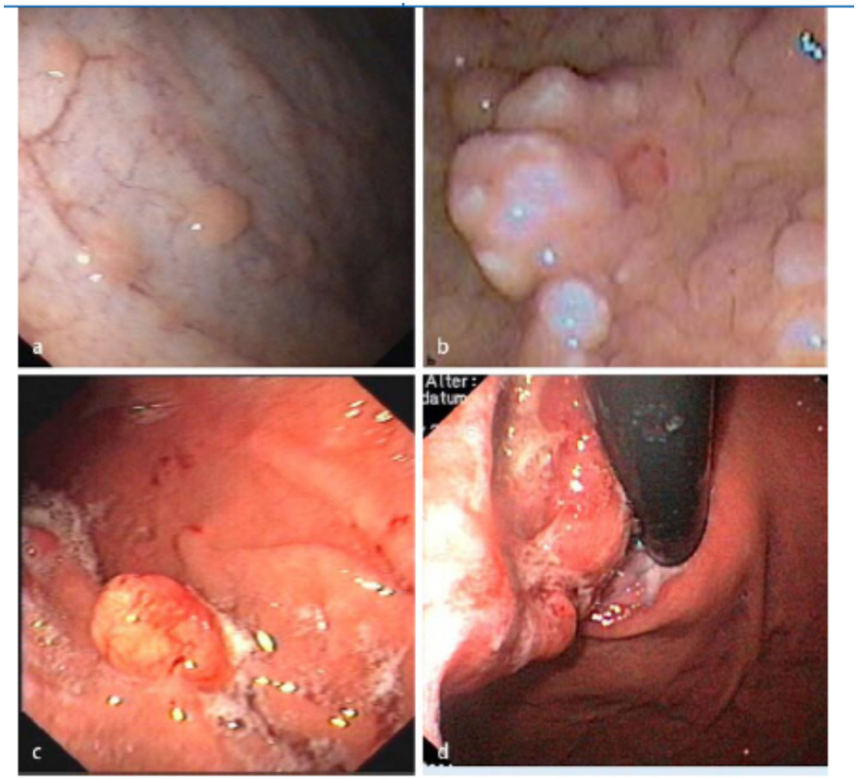
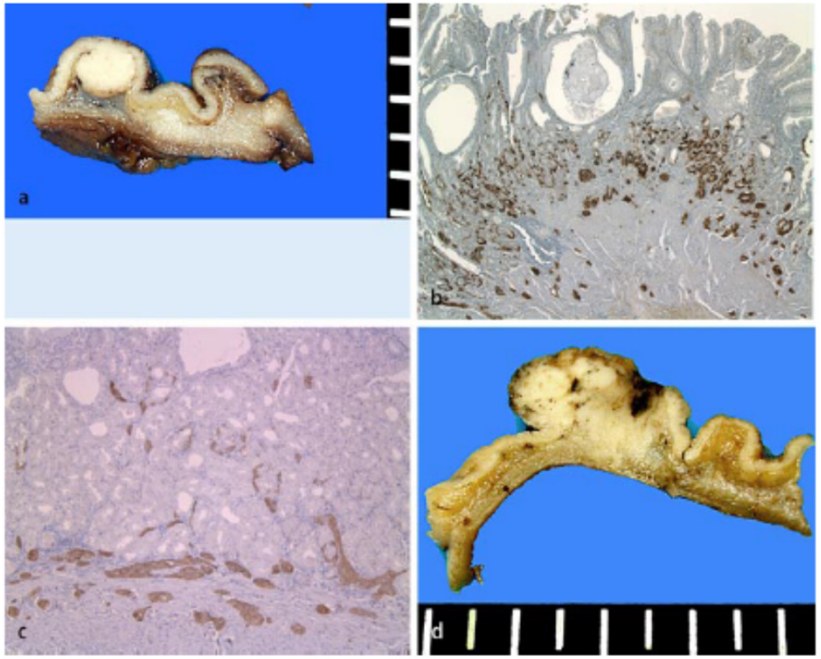
Gastric NEN - type adapted management endoscopic ablation / surgery





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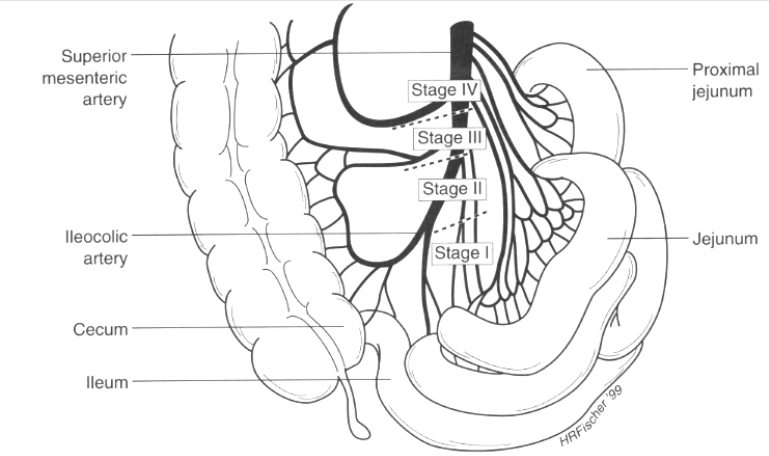
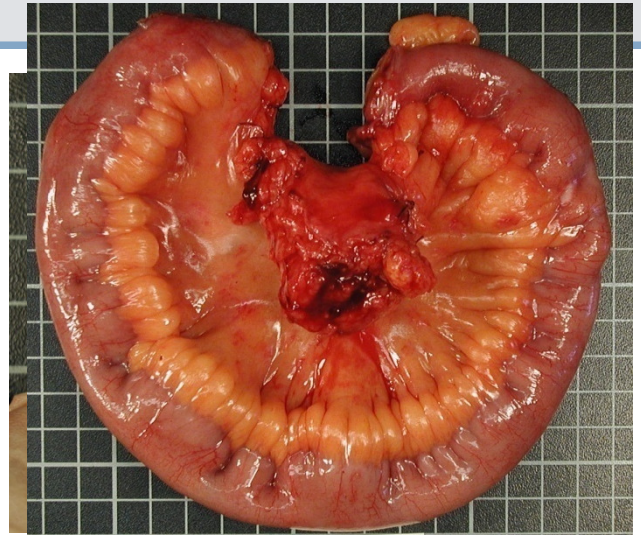
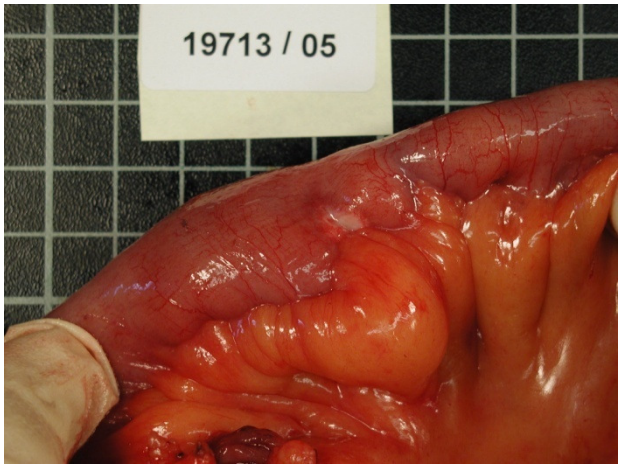
Neuroendocrine tumors of the midgut

– lymph node metastases-







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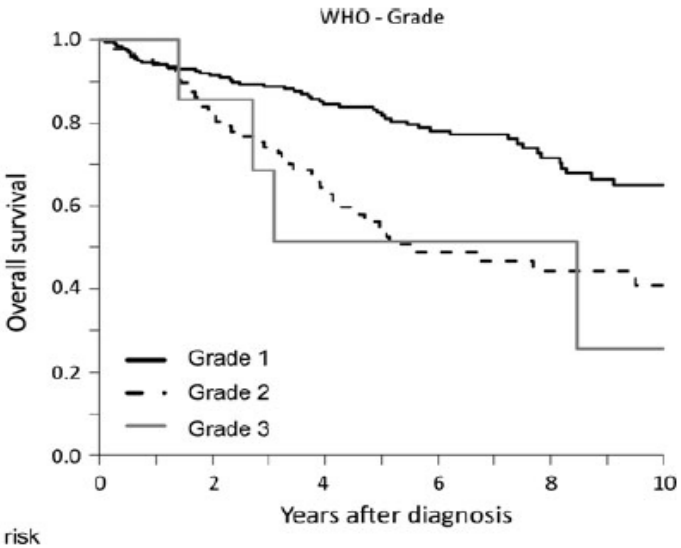
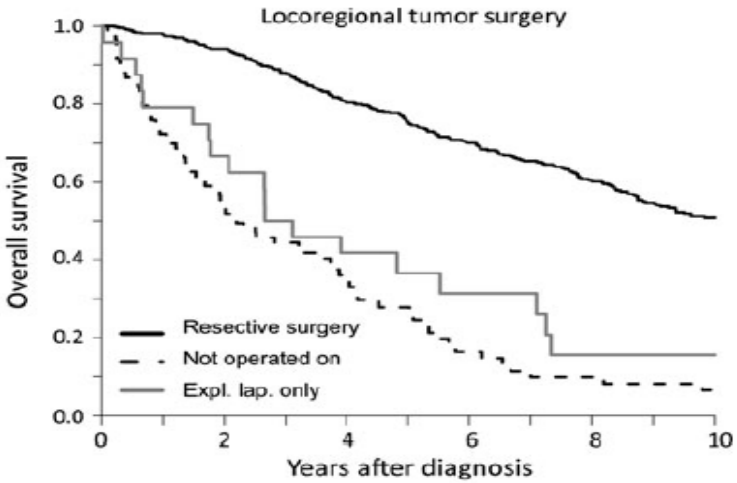
Long term results of surgery for small intestinal NEN

603 patients
1985-2010
Median OS 8.4 years, 5-year survival 67%



No. At risk						
Grade 1	203	176	133	96	59	32
Grade 2	89	68	42	24	17	11
Grade 3	7	6	3	2	2	1



No. At risk						
Resective surgery	493	448	349	268	194	132
Not operated on	86	44	22	10	6	4
Expl. lap. only	24	16	9	6	3	3

Norlen O et al World J Surg 2012;36:1419-1431

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Appendiceal NET

Original Paper

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Surgical Management of Patients with Neuroendocrine Neoplasms of the Appendix: Appendectomy or More?

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Appendiceal NET

Table 3. Clinicopathological characteristics of the patients diagnosed with appendiceal neuroendocrine neoplasms in the study cohort ($n = 215$)

Total number of patients	215
Mean age (range), years	33.2 (9–79)
Gender	
Male	85 (39.5%)
Female	130 (60.5%)
Index operation performed	
Simple appendectomy	193 (89.8%)
Right hemicolectomy	16 (7.4%)
Subtotal colectomy	1 (0.5%)
Panproctocolectomy	2 (0.9%)
Other	3 (1.4%)
Tumour size	
<1 cm	95 (44.2%)
1–2 cm	69 (32.1%)
>2 cm	51 (23.7%)
Depth of invasion	
Serosal	32 (14.9%)
Periappendicular fat	17 (7.9%)
Vascular invasion	14 (6.5%)
Involved margin	25 (11.6%)
ENETS stage[1]	
I (T1N0M0)	96 (44.7%)
IIa (T2N0M0)	52 (24.2%)
IIb (T3N0M0)	38 (17.7%)
IIIa (T4N0M0)	10 (4.7%)
IIIb (T1–4N1M0)	17 (7.9%)
IV (T1–4N0–1M1)	2 (0.9%)
ENETS tumour grade[2]	
G1	200 (93%)
G2	9 (4.2%)
G3	1 (0.5%)

ENETS, European Neuroendocrine Tumor Society. [1] At initial diagnosis. [2] Available for 210 patients.

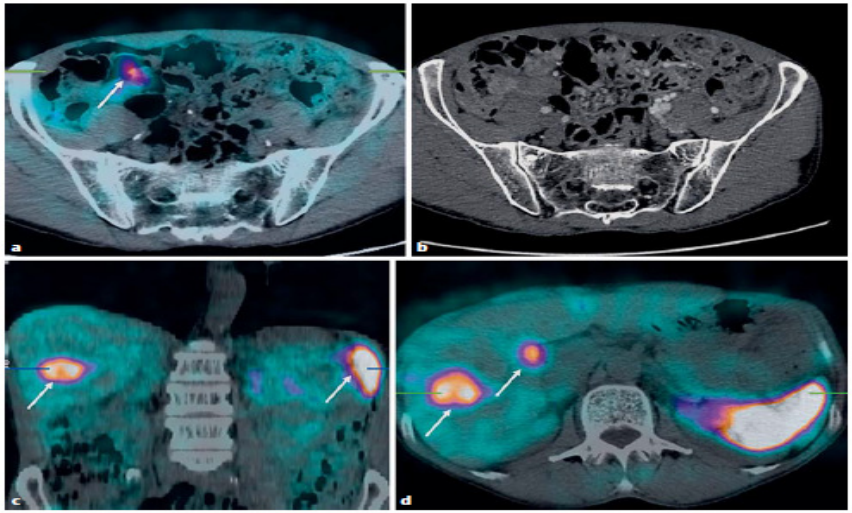

Fig. 1. Findings on CT and Tektrotyd® whole-body SPECT/CT in a 64-year-old male patient with liver metastases from an appendiceal neuroendocrine tumour (G2, Ki-67 index 8%). **a** Increased radiotracer uptake corresponding to a 23-mm appendiceal tumour is evident (arrow). **b** CT showing no clear abnormality in the same region. **c, d** Foci of increased radiotracer uptake corresponding to hepatic metastases (arrows). The uptake in the spleen is within physiological range.

7.9% of patients had +LN at appendectomy
24.5% of patients had + LN at completion RHC

5-and 10-years survival was both 99.05%

? Biological relevance of +LN in appendiceal NETs

RHC might be an overtreatment for a substantial number of appendiceal NETs

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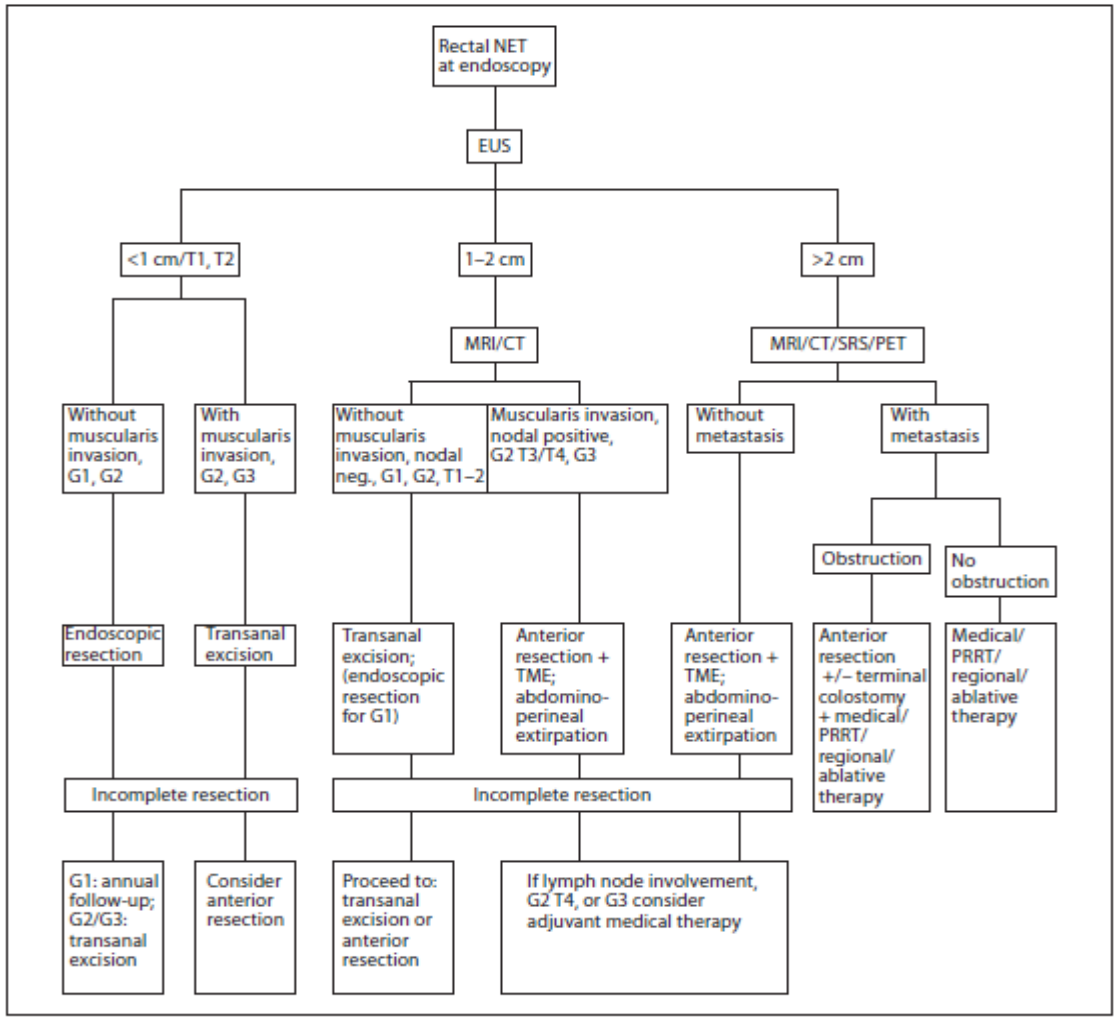
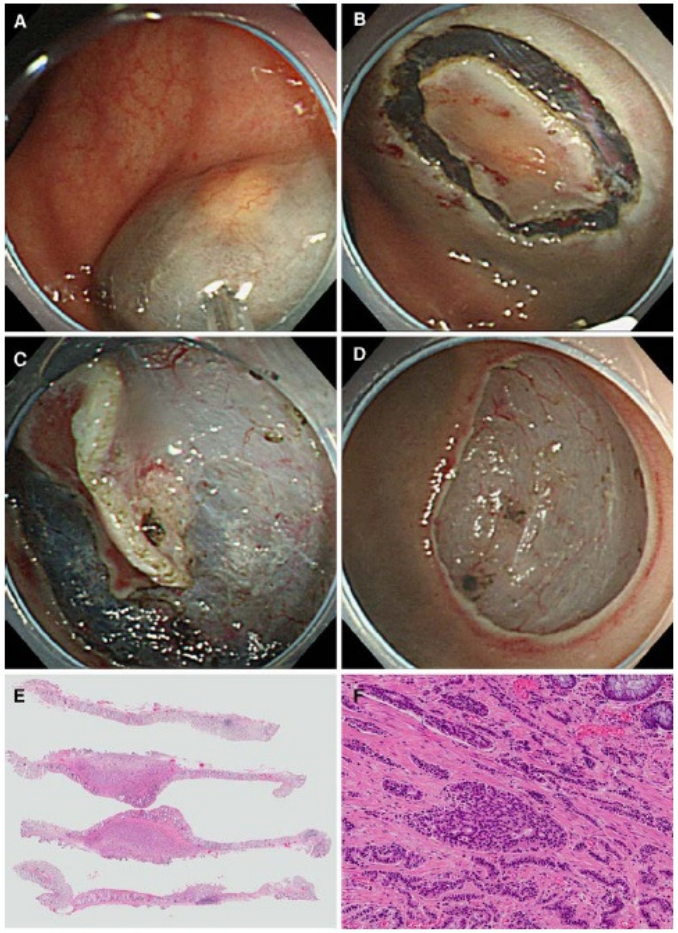
Rectal NEN





Caplin M et al. Neuroendocrinology 2012;95:88-97

Yamaguchi et al. Surg Endosc 2010;24:504-508

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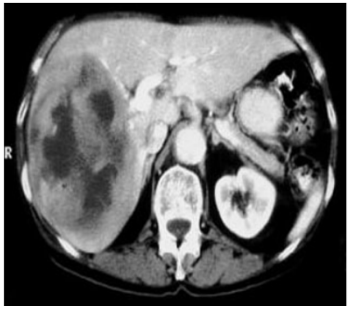
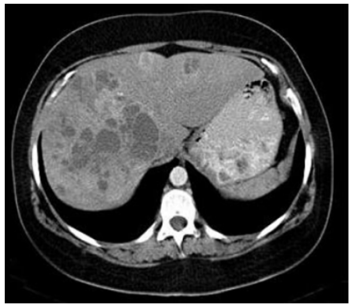
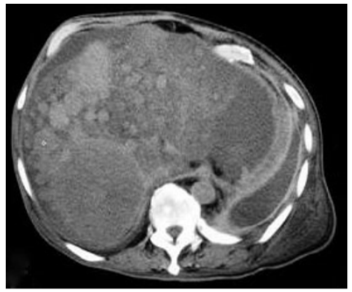
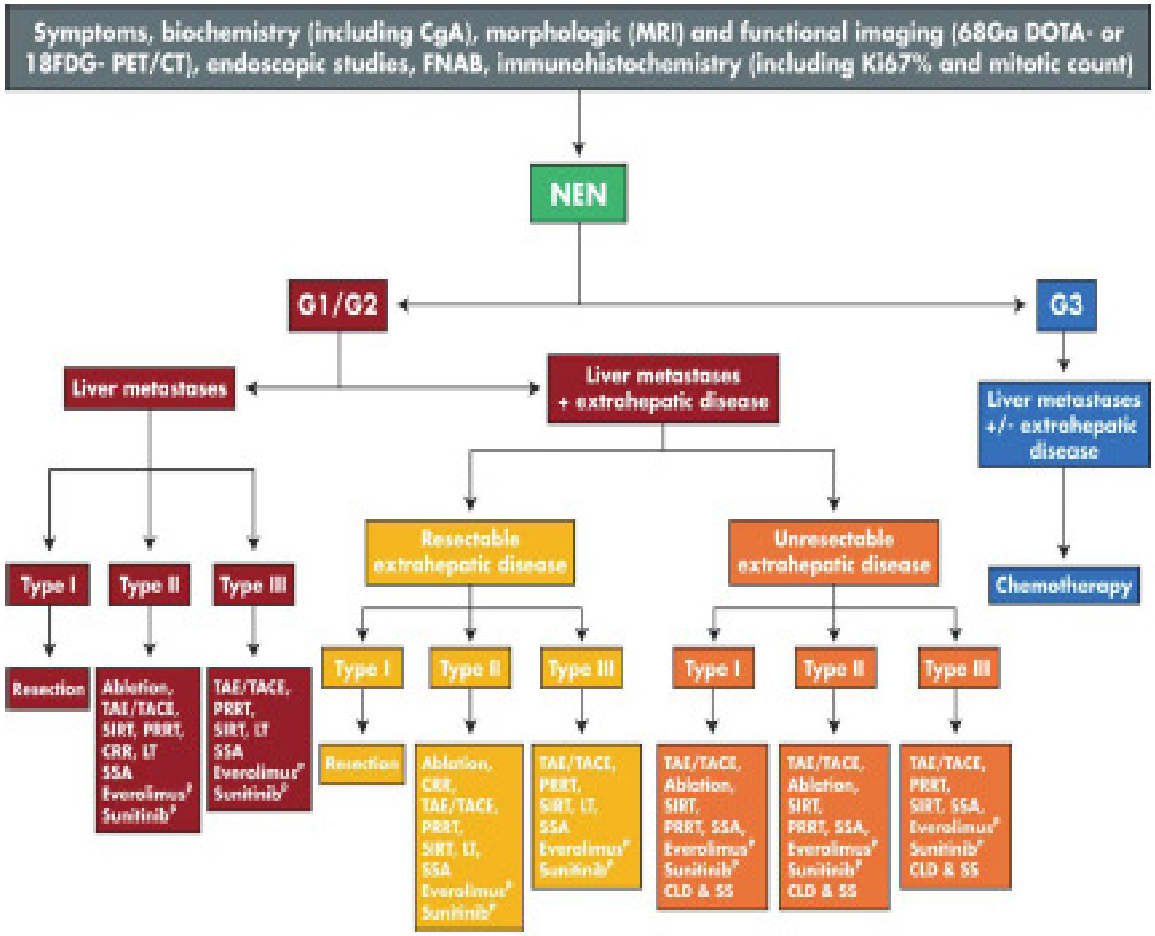
Personalised management of patients with neuroendocrine liver metastases









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