PANCREAS CANCER ACADEMY

Pancreatic Neuroendcrine Tumours: an overview

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Declaration of conflict of interest.

NOVARTIS : advisory board, honoraria for lectures

IPSEN : advisory board, honoraria for lectures

AAA : honoraria for lectures

Neuroendocrine cells

So where do NETs arise from?

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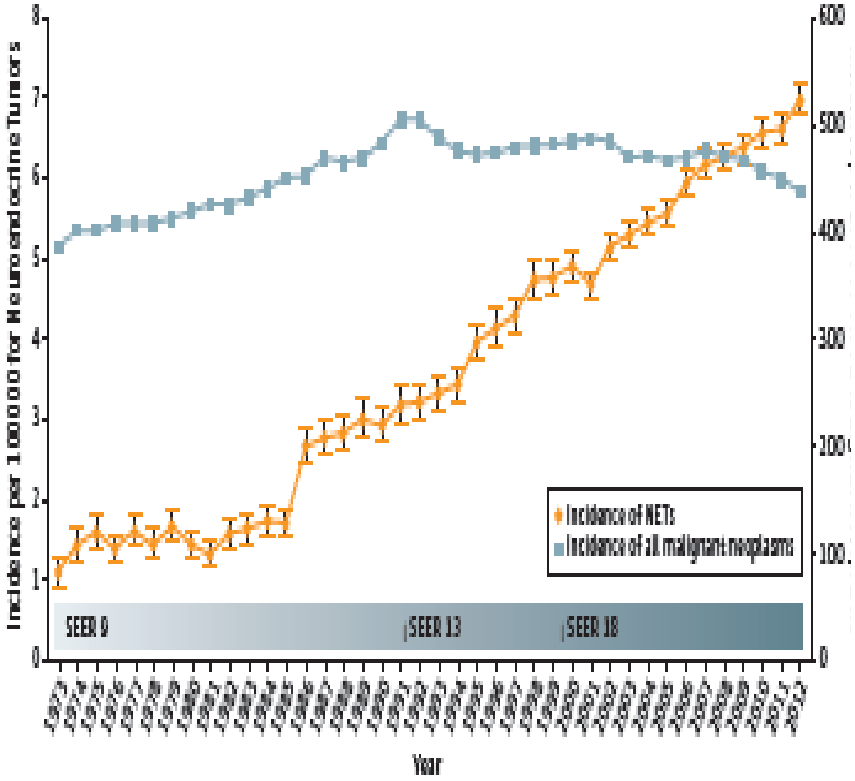
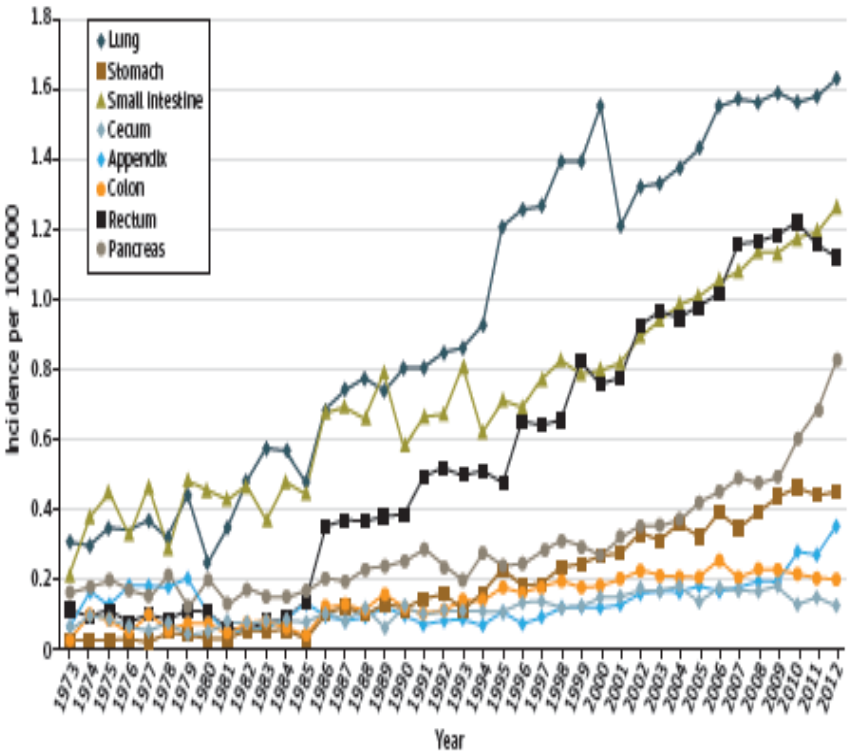
ARE NETS RARE?





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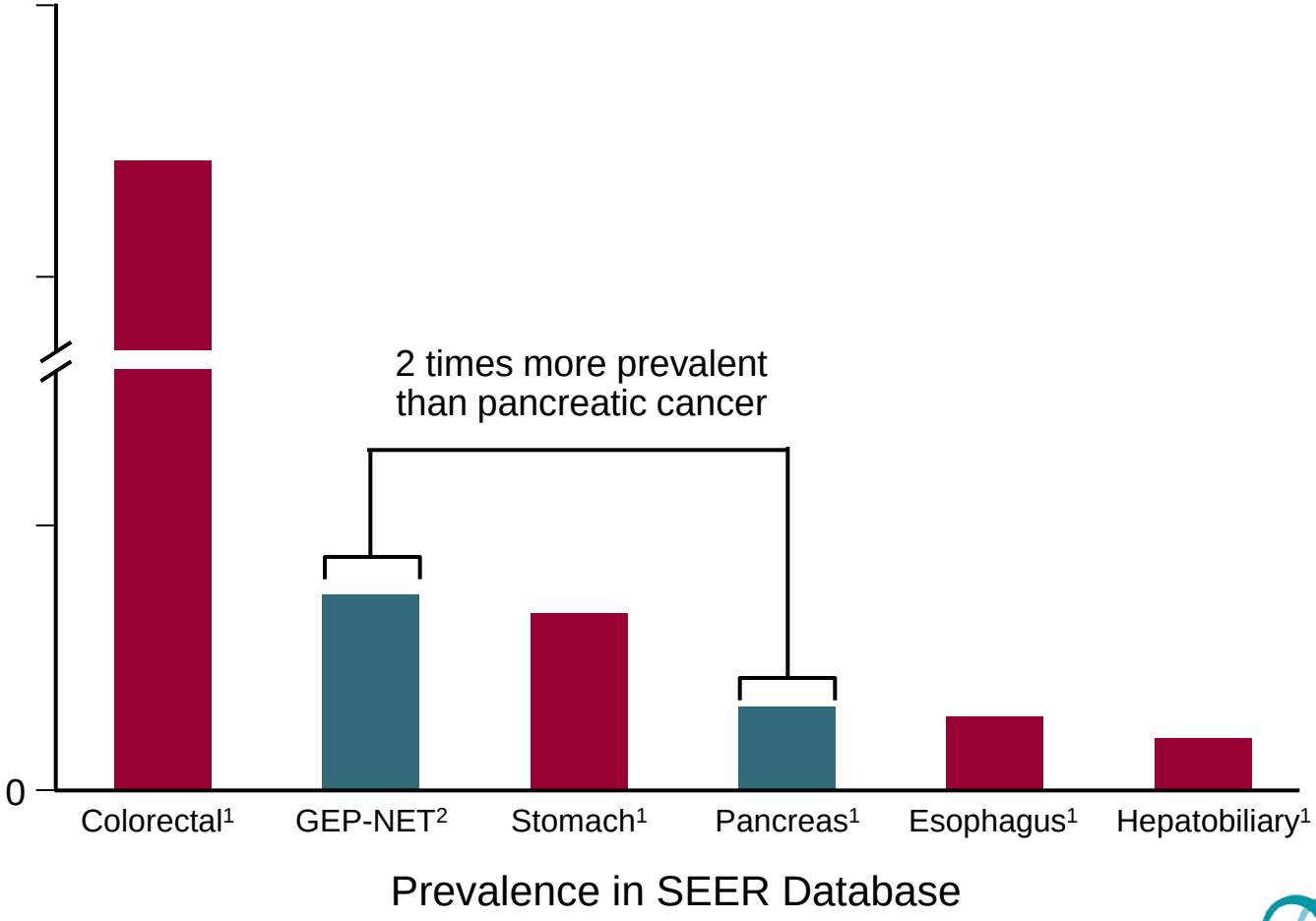
NETs Are the Second Most Prevalent Type of Gastrointestinal Malignancy



Prevalence in SEER Database

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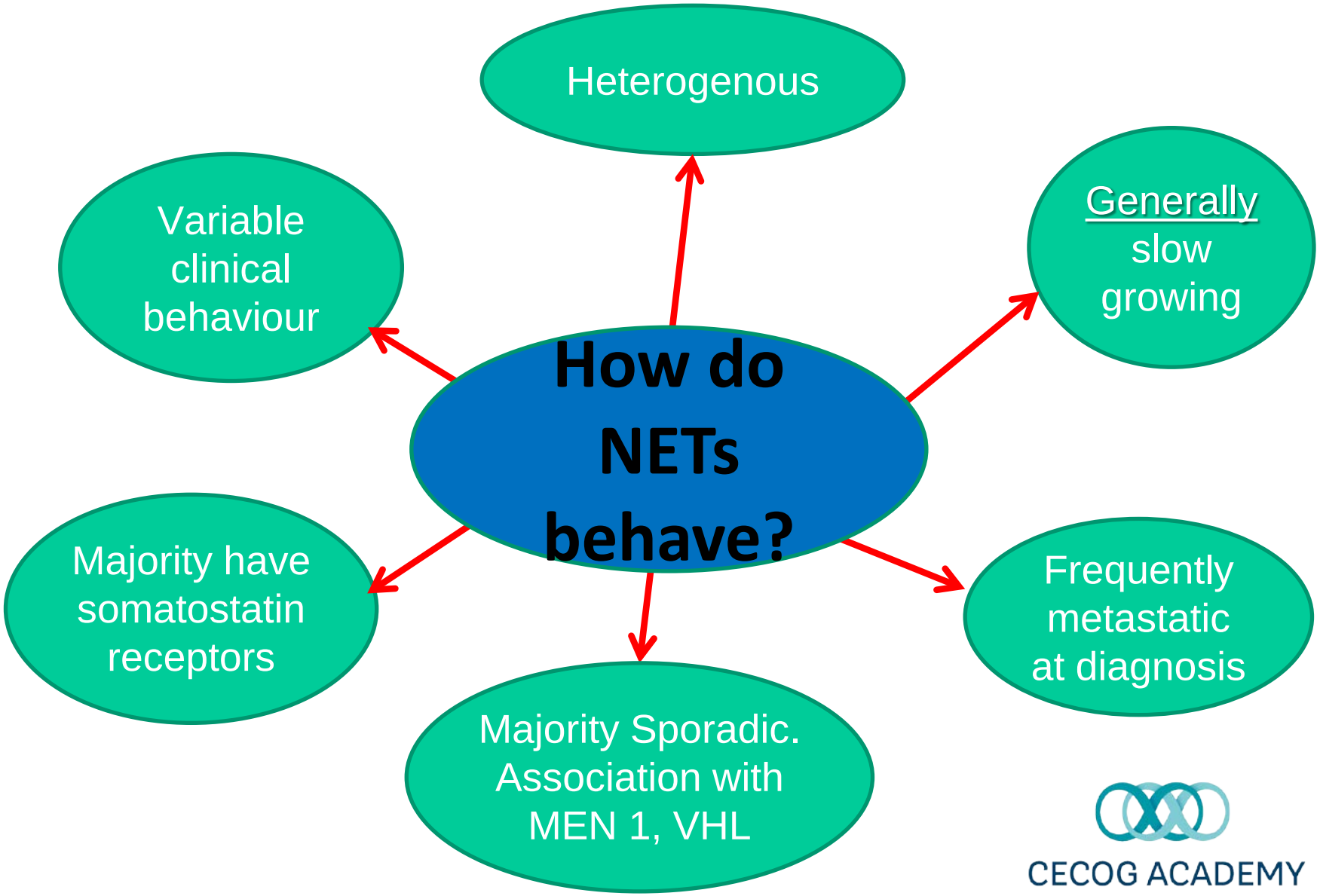

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The Classification of Pancreatic NETs

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1. Functional and non Functional

Tumour Type	Peptide	Symptoms	Incidence (per million)	Malignant
Functional Pancreatic NETs (Hormone secreting/syndrome)				
Gastrinoma	Gastrin (Z.E. Syndrome)	Resistant peptic ulcers, chronic diarrhoea responding to PPI	1-1.5	>60%
Insulinoma	Insulin	hypoglycaemia	1-2	10%
Glucagonoma	Glucagon	Wgt loss, new onset DM, necrolytic migratory erythema	0.01-1	50% +
VIPoma	VIP	Chronic diarrhoea, hypokalaemia, dehydration	<0.1	40-70%
Non-Functional	Pancreatic polyp	**Mass effect** **distur nce**	2-4	60-80%

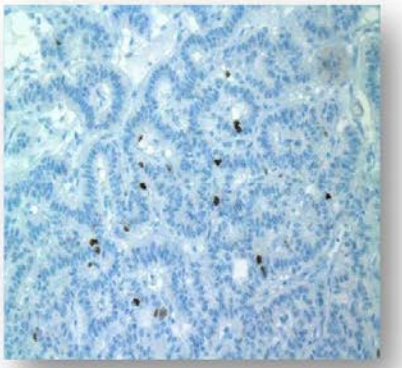
Often diagnosed late as no syndrome

2. Grading

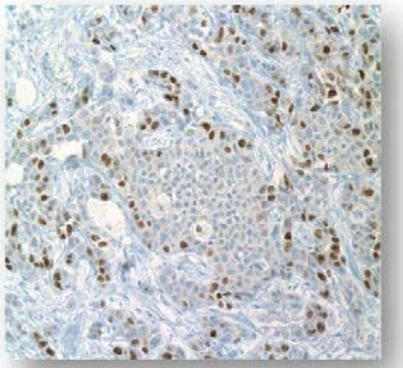
WHO 2017	Mitoses/10 HPF*	Ki-67 Index*
Well-differentiated NENs		
NET grade 1		< 3
NET grade 2		3–20
NET grade 3		> 20
Poorly differentiated NENs		
NEC grade 3		> 20
Small-cell type		
Large-cell type		

Majority are panNET G1 and 2.

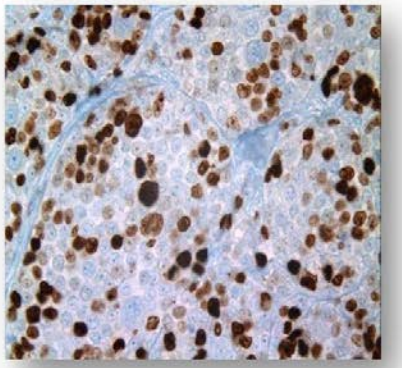
Focus of talk on these



G1



G2



G3

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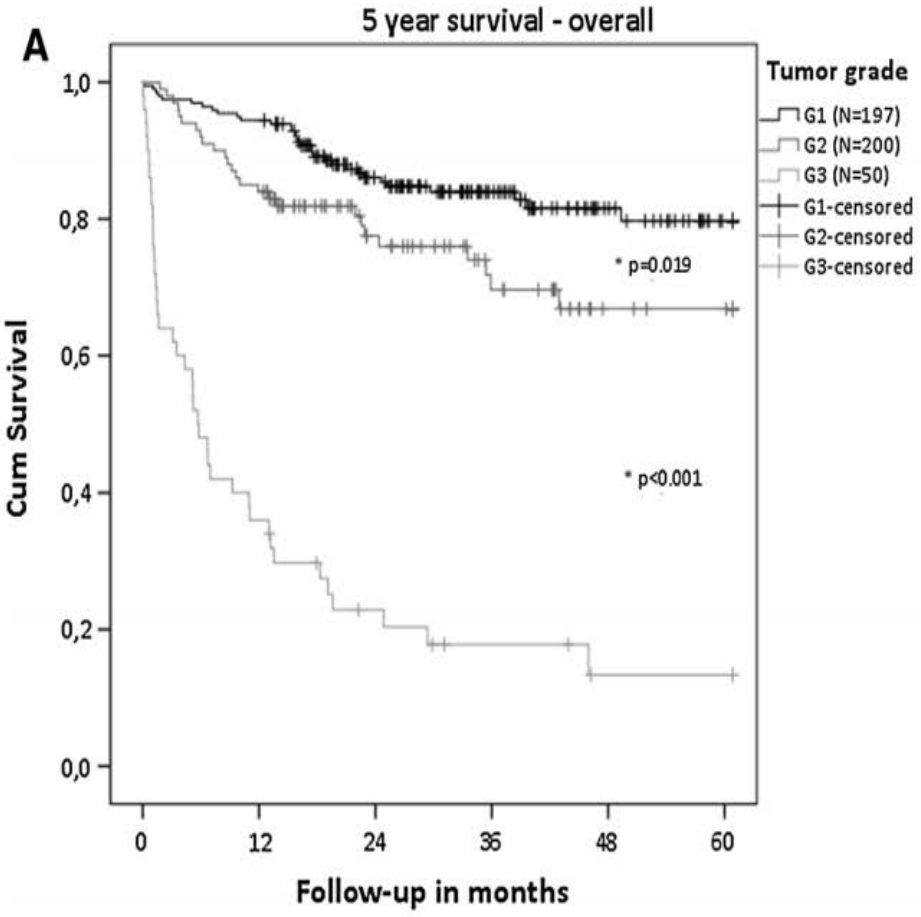
Survival by Grade, both overall and metastatic



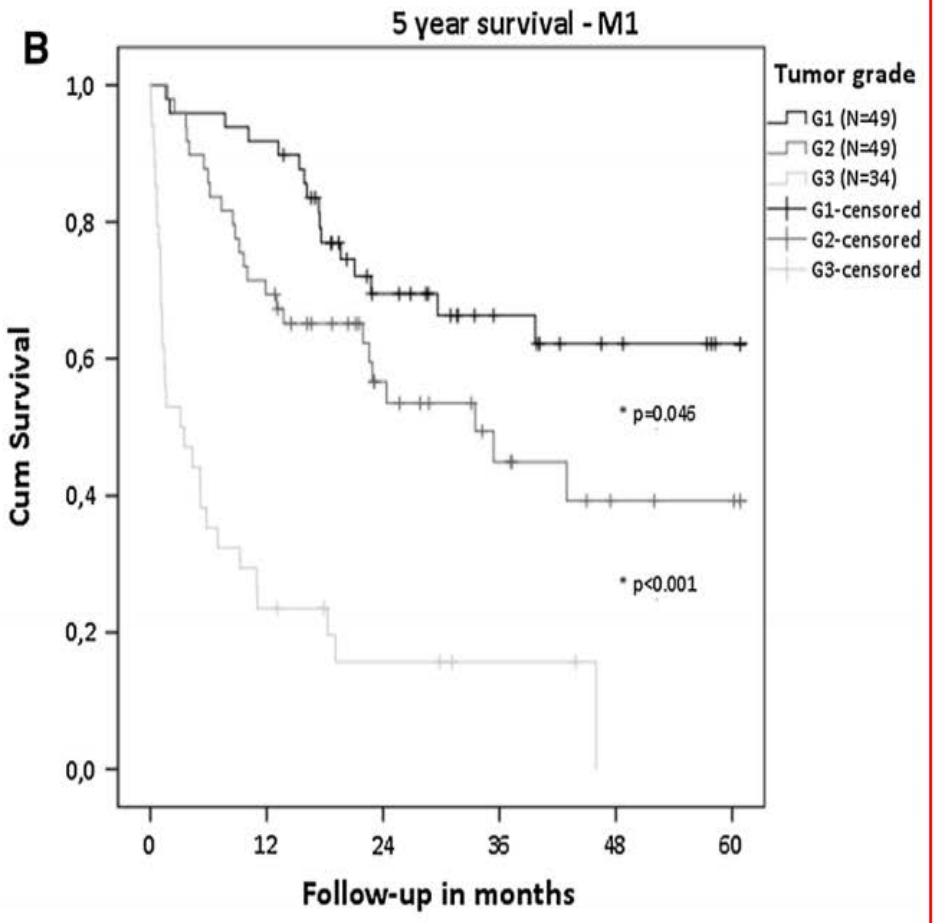


Fig. 1 Overall survival of patients with different tumor grades. **a** Overall patient population. **b** Patient with metastatic disease

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C. G. Genc et al 2018 World J Surg **2018** 42:490–497

Staging

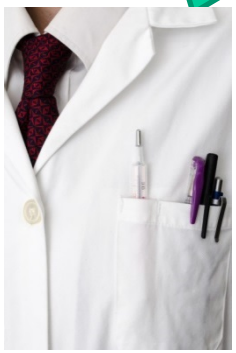
- Similar process to other cancers, using AJCC/TNM system
- Survival by stage: Variable in different databases and study reports.
- Nodal and distant mets poor prognostic factors.

Median Survival in months (all grades combined)		
Localised	Regional	Distant Mets
136	**77**	**24**
James C. Yao, et al 2008 J Clin Oncol. **2008** Jun 20;26(18):3063-72		

5 year survival (all grades combined)		
Primary (no nodes)	Nodal disease	Distant Mets
78%	**44%**	**27%**
C. G. Genc et al 2018 World J Surg **2018** 42:490–497		

Being diagnosed…

You've got the best type of cancer that there is



What patients are told….

They're not even really malignant

Gosh, you're really interesting. I've not seen one of these since medical school

…sometimes

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Delays in Diagnosis

- Delays in diagnosis- possibly 5-7 years from initial symptoms[1]
- Multiple GP visits, inconclusive investigations
- Wrongly diagnosed; commonly IBS, gastritis IBD
- Heightened feelings of anxiety and frustration

1. Modlin et al 2008. Lancet oncology 2008; 9(1);61-72

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Diagnostic tests

- History and clinical examination
- Specialist biochemical tests
- Imaging studies
  - CT/MRI
  - Octreoscan /Ga68 PET Dotatate
- Histology - “gold standard”
- Insulinoma
  - MRI Pancreas, 72 hour fast, EUS/Bx, calcium stimulation study.

Can lead to even longer time to diagnosis and treatment. Should have referral to specialist centre

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Specific Biochemical Tests

- Chromogranin A.
  - Sensitivity : 60-90%. Poor specificity; raised PPIs, Atrophic gastritis, IBD, Renal failure. Not raised in Insulinomas
  - Correlates with tumour burden
  - Early decrease of its levels may predict PFS and OS
- Fasting gut hormones
  - functioning pancreatic NETs
  - gastrin, VIP, somatostatin, glucagon
- Screening for MEN-1 in pNETs
  - Ca, PTH

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Somatostatin Receptors in NETs

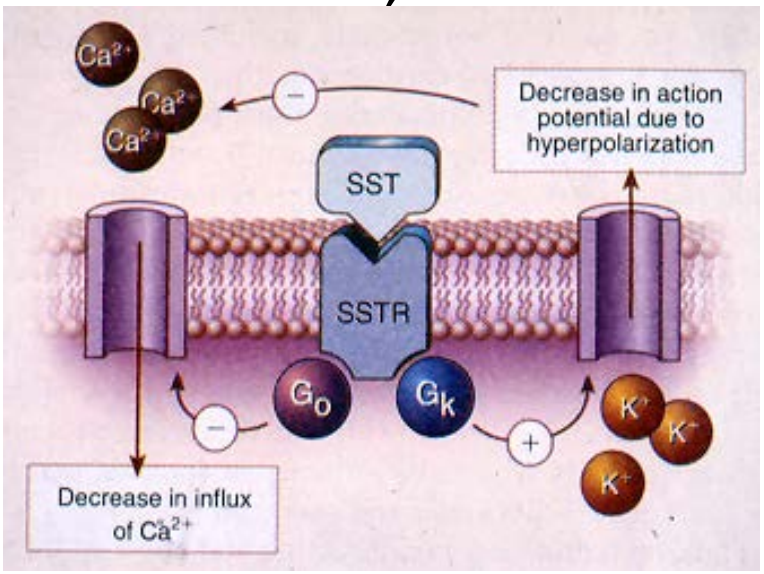
Expressed in majority of NETs

- SSTR2 -95% pNET, lower in insulinomas
- Role in proliferation, hormone secretion, induction of apoptosis

Target for

- Somatostatin Analogues
- Octreoscan/Dotatate scan
- Peptide Receptor

Radionuclide Therapy (PRRT)



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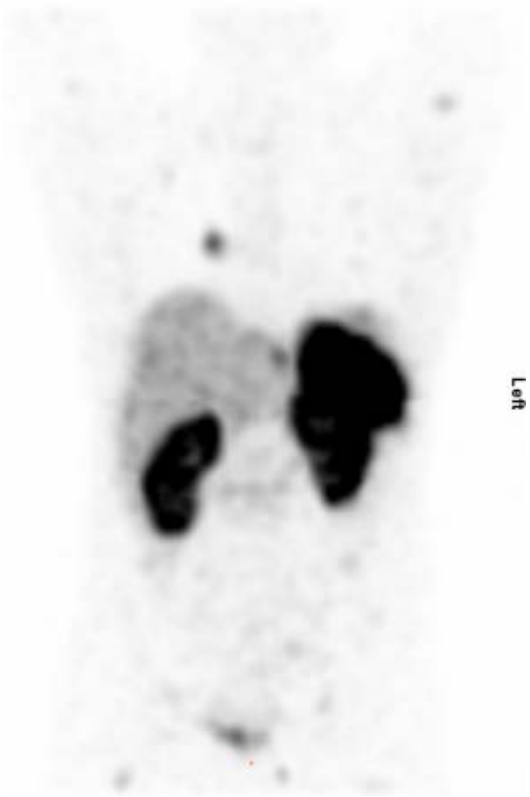
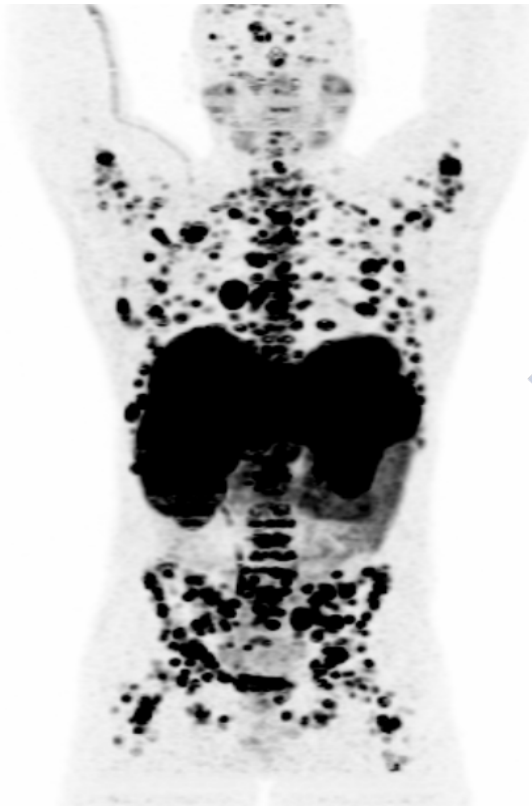
Scintigraphy- SSR based imaging

In111 Octreotide scan



Ga68 PET Dotatate Scan



- Improved sensitivity, resolution of PET
- Increased tumoural affinity (10x to SSR-2)
- Reduced radiation dose (less than ½: 4-5 vs. 12 mSv)
- Study duration 2-3 hours (vs. 24-48 hours)

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Treatment of NETs

- Improvement and maintenance of patient's quality of life.
- Medical control of patient's symptoms.
- Resection of tumor primary and if possible, metastatic lesions.
- Control of tumor growth in cases of advanced disease.

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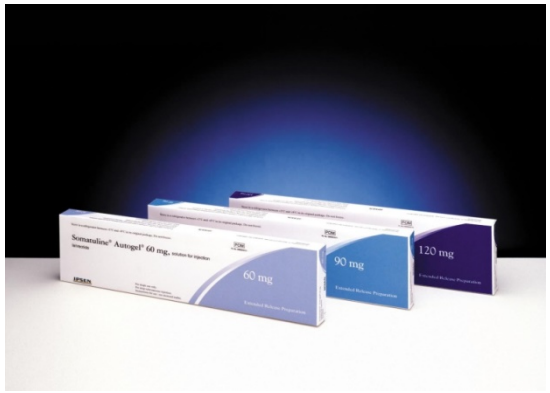
Somatostatin Analogues



Inhibit hormone production by NETs

1st line if functional and non-resectable

Proven antiproliferative and disease stabilising effects

May be 1st line in NF-pNETS
Improved PFS
Tumour shrinkage in 2-8% of patients?

Appropriate 1st line in <u>most low grade NETs</u>

Low prolif> high prolif
(? Ki 67 < 5%)
Low vol > high vol?
Slow growing > fast growing

Surgery: Localised Disease

- Resection: large survival benefits.
  - Functioning tumours: best chance to cure syndrome and increase oncological outcome
  - Large Non-functioning tumours: as above
- What about non functioning small pNETs <2cm

Risk of Overtreatment (unnecessary surgery for indolent lesion)

VS

Risk of Under treatment (missing chance to cure more aggressive disease)

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Localised disease continued

- Most NF-pNETs follow a fairly indolent course
- NF pNETs largest cause of early death in MEN 1
- Watchful waiting- annual imaging , is recognised approach
  - Dutch study-1% NET related mortality in 7.2 years median follow up[1]

Possible criteria for surgery

Criteria for surgery
Size (>1cm or >2cm)
Change of Size > 0.5cm annually
Proliferation index G2

Decision Making Issues

Patient Preference
Comorbidities
Surgeons Preference
Position of tumour

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1. Sjoerd Nell 2018. Annals of Surgery Volume 267, Number 6, June 2018

Case Study 1- indolent NF NETs in MEN 1

- 63 year old lady- MEN 1- diagnosed insulinoma 50 years ago- excised
- Non-Function pNET-distal pancreatectomy 1984
- Multiple pancreatic lesions slowly growing since 2000- annual MRI scan
  - Non functioning, largest 19mm in 2018 (5.5mm in 2005)
  - Remains well- keen to avoid surgery as long as possible. Next operation would be total pancreatectomy
  - Continues annual surveillance

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Case Study 2: Surgery in setting of MEN 1

- 23 year old woman. MEN 1- annual screening
- Growing lesions age 13;
  - distal pancreatectomy- clinically well 3 years
- Aged 16- gastrinomas with ZE syndrome. Not medically wellcontrolled
  - Pancreas sparing duodenectomy- confirmed Grade 2 WD NET
- Aged 18- night hunger and sweating, 72 hour fast confirmed insulinoma
  - Not controlled medically
  - MRI showed several lesions-specialist scan confirmed central lesion insulin secreting.
  - Completion pancreatectomy- confirmed 7 NETs, largest of which was insulinoma.

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Case 2: Surgery in setting of MEN 1

18 months post surgery; in clinic in tears.

Described to Nurse the trauma of whole disease experience.

- Recurrent nightmares about surgery. Depressed and anxious.
- Fear and uncertainty regarding ongoing symptoms and possible recurrence,
- Ongoing issues with Gastric symptoms and diabetic control

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Case 2: Surgery in setting of MEN 1

- Required extensive input from gastroenterology and specialist diabetic services
- Teenage/Young Adult cancer psychologist referral made
  - Focused counselling reduced anxiety significantly and nightmares stopped
  - Ongoing support-living with fear of recurrence, annual surveillance, concerns about future relationships, having children.

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Regional and metastatic Disease

- Locally Advanced disease- aggressive surgical a
  survival advantage if no macroscopic dis
- Metastatic:
  - if potential curati resection
  - Primar lative techniques
    election bias and heterogeneous trials)
  - g liver mets
    - ? 70% of disease sufficient for benefit[1]

Lack of robust Health related QoL data

1. Morgan et al 2018. Surgery 163(2018);218-225

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Treatments for advanced inoperable GEP-NETs

- Medical therapy
  - Somatostatin analogues (SSAs)
- Molecular targeted therapies
  - Everolimus
  - Sunitinib
- Systemic chemotherapy
- Loco-regional therapy
  - Radiofrequency ablation (RFA)
  - Embolization/chemoembolization/ radioembolizatio
- PRRT using 177 Lu – DOTATATE
- External radiation (for bone/brain metastases)

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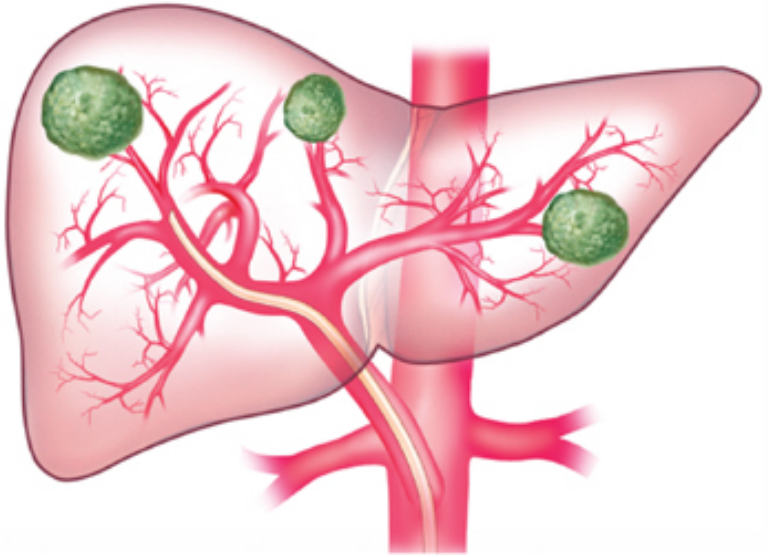
Liver metastases without extrahepatic disease (or bulk of disease in liver in functional NET)

- Ablation:
  - RFA, Microwave
- Embolisation
  - TAE, TACE, SIRT
- Diffuse liver mets
  - Systemic drug therapies / PRRT
- Rarely- liver transplantation



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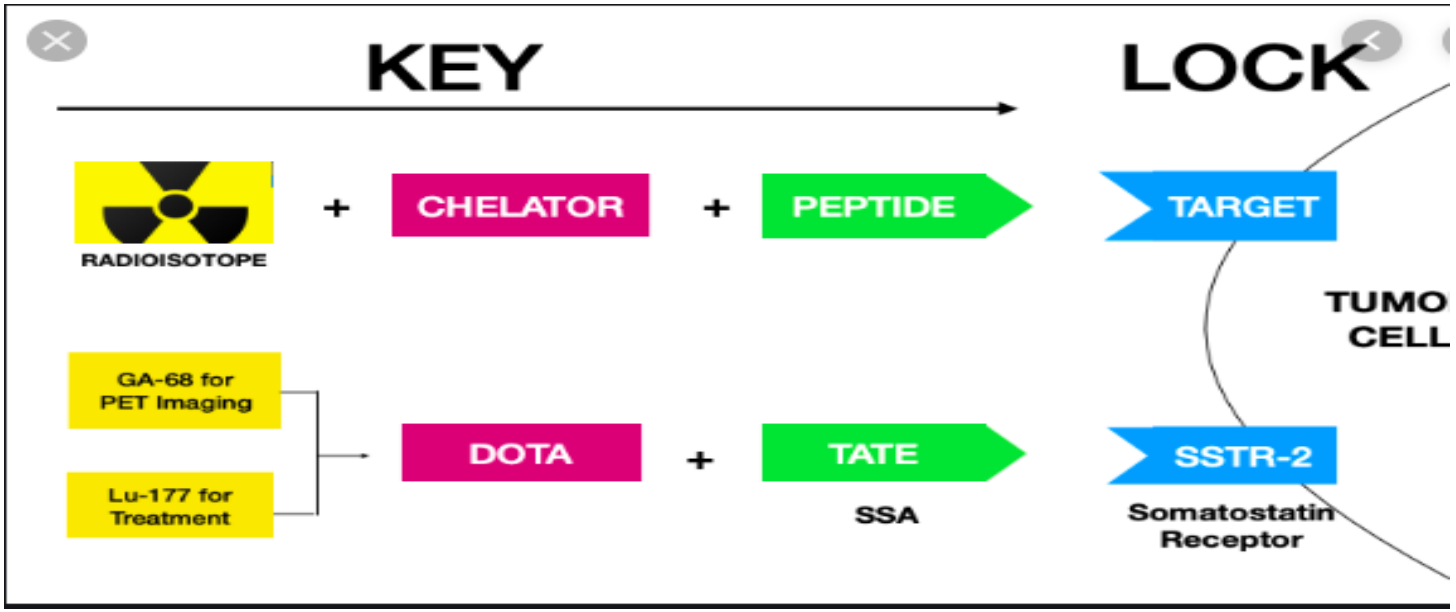
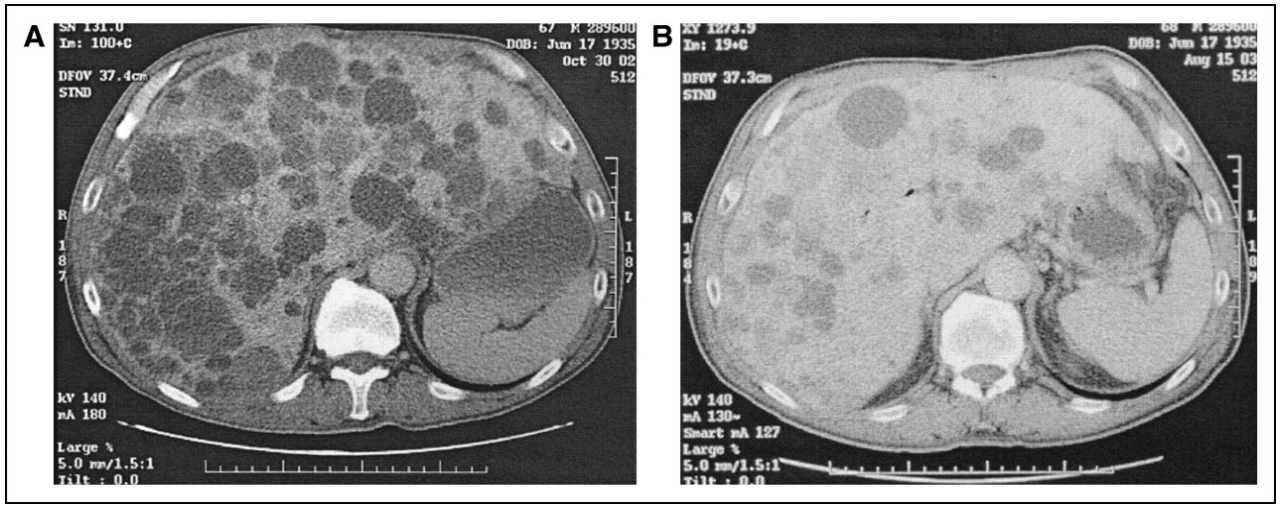
1st line therapeutic options for unresectable metastatic pNET

Drug	Grading	SSR status	Special consideration
Lanreotide	G1 (low G2)	+	Low tumour burden
Strep/Cape chemotherapy	G1/G2		Progressive in short term or higher tumour burden or symptomatic
Everolimus	G1/G2		Insulinoma or contraindication for chemotherapy
Sunitinib	G1/G2		Contraindication for chemotherapy
PRRT	G1/G2	+	Extended disease, extrahepatic disease

Peptide Receptor Radionuclide Therapy (PRRT)





CT of NF pNET before treatment (left)

3 months after the last treatment (right)

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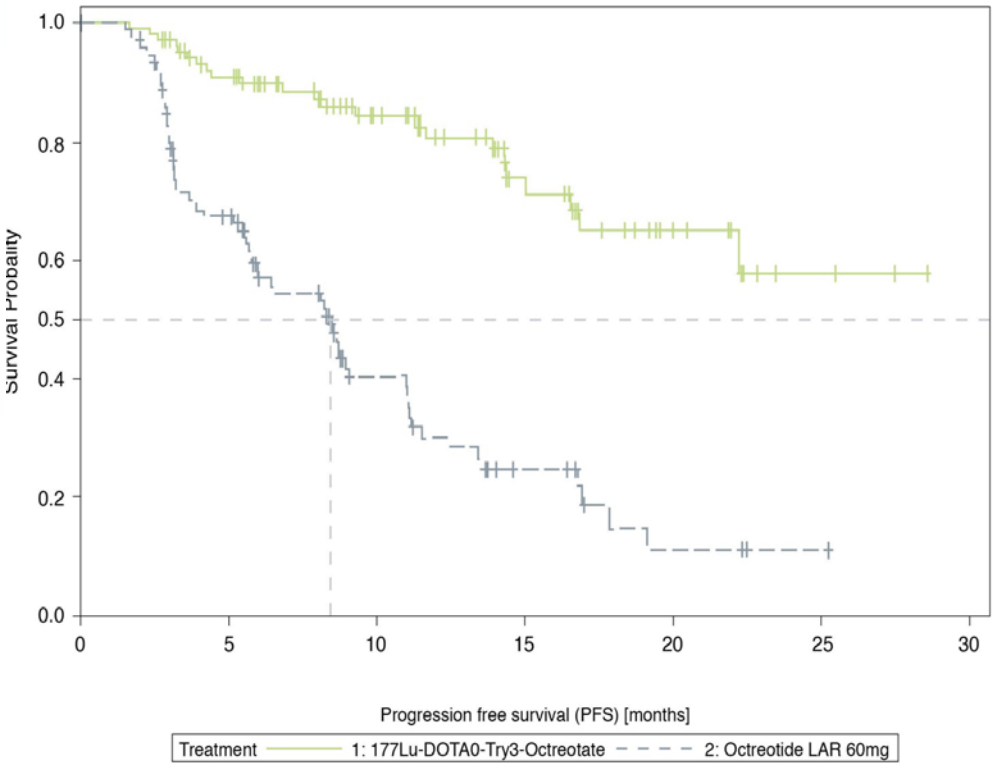
PRRT: Improved Progression Free Survival-NETTER 1 Study

	177-Lu-Dotatate (n=101)*	Sandostatin LAR 60 mg (n=100)*
Complete Response (n)	1	0
Partial Response (n)	17	3
Objective Response Rate (*)	18%	3%
Confidence Interval (95%)	10% - 25%	0% - 6%
Statistical Significance	p = 0.00043	
All patients	**(n=116)**	**(n=113)**
Progressive Disease	6 (5%)	27 (24%)
Stable Disease	77 (66%)	70 (62%)



Strosberg et al 2017 N Engl J Med 2017 Jan 12; 376(2): 125-135

79% reduction in the risk of disease progression/death

Estimated Median PFS in the ^{177}Lu-Dotatate arm
≈ 40 months

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Issues in treating NETs patients

Range of active therapies

Limited evidence on sequencing of treatments

Limited phase 3 data

Access to therapies is variable

Access to expert MDT / Specialist centre and Patient involvement in decision making crucial

When to change therapy

Progressive disease- how to define

? Change in symptoms

? Radiological progression

? Biochemical progression

When to use active surveillance vs treatment

Low volume / symptomatology/ grade / patient choice

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Case study 3

- 45 year old man Sep 2008-weight loss, abnormal LFTS, onset of diabetes. CT scan and OPA- palpable central abdominal mass.
  - CT scan: “Locally advanced panc mass”.
  - Oncologist- “presumed pancreatic ductal adenocarcinoma”- bleak picture. Plan: palliative chemotherapy. Referred to specialist pall care services

Patient informed 2 days later that Bx confirmed

WDNET, G2, Ki 67 3%

Oct 2008: Octreoscan (avid mass- no distant disease).

Refer to HPB surgeons

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Operative period

Jan 2009: total pancreatectomy.

- Post op- steatorrhoea.
- Increased PPIs, diet advice, specialist diabetic team input.

May 2009- no residual disease on Octreoscan

- Energy increasing, diabetes better controlled. Gastric symptoms managed on PPIs, Creon,

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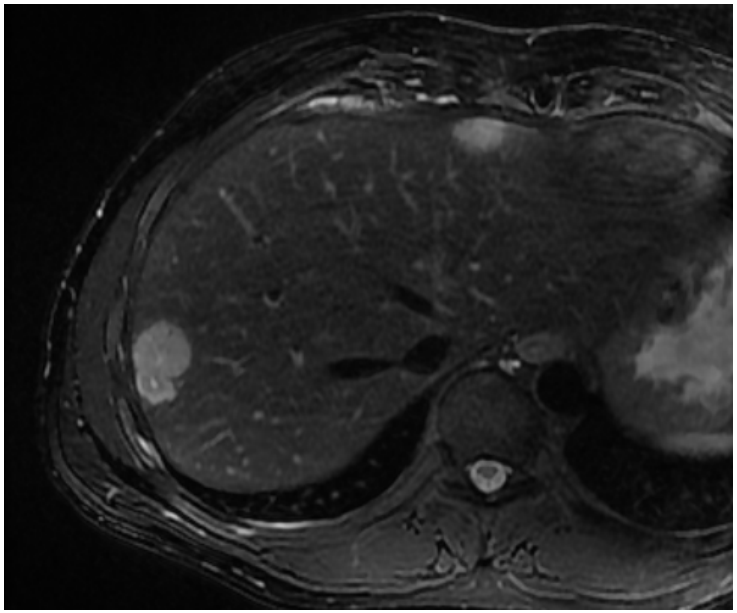
2011-2012

- Jan 2011-2 x Liver metastases found on MRI.
  - Resected- grade 2
  - metastatic NET-Ki67 3%
- Aug 2012-MRI progressive disease-bilobar liver mets
  - Commenced Streptozocin/Capecitabine chemotherapy Sep 2012



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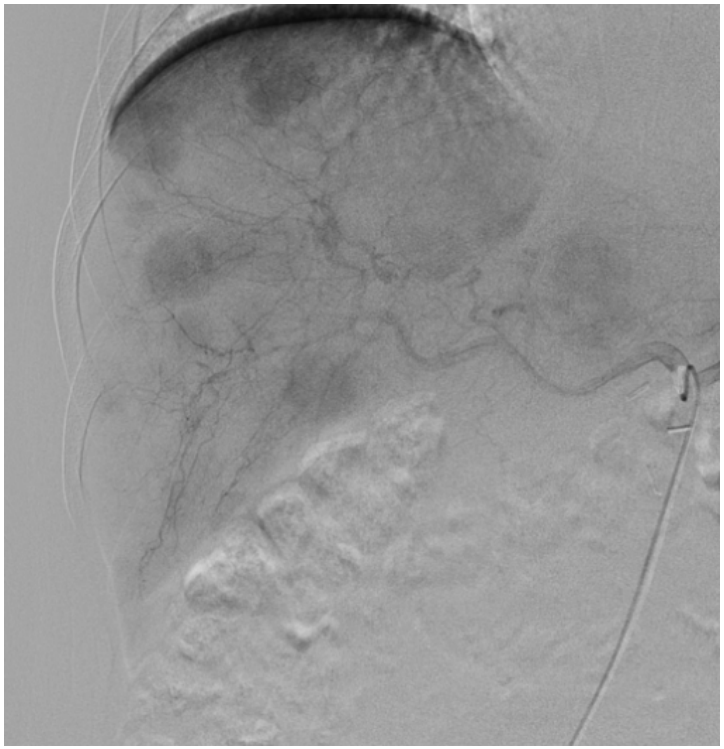
2013-2014

- 2013- Further metastatic progression in liver. Commenced Everolimus
  - Rash, mild mucositis, high blood sugars. Stopped after 3 cycles
  - Post treatment scan – further progression of liver mets and slowly growing upper abdominal lymphadenopathy
- Treated with Selective internal Radiation therapy (SIRT) April 2014
  - Scan Oct 2014-Extensive reduction of liver metastases



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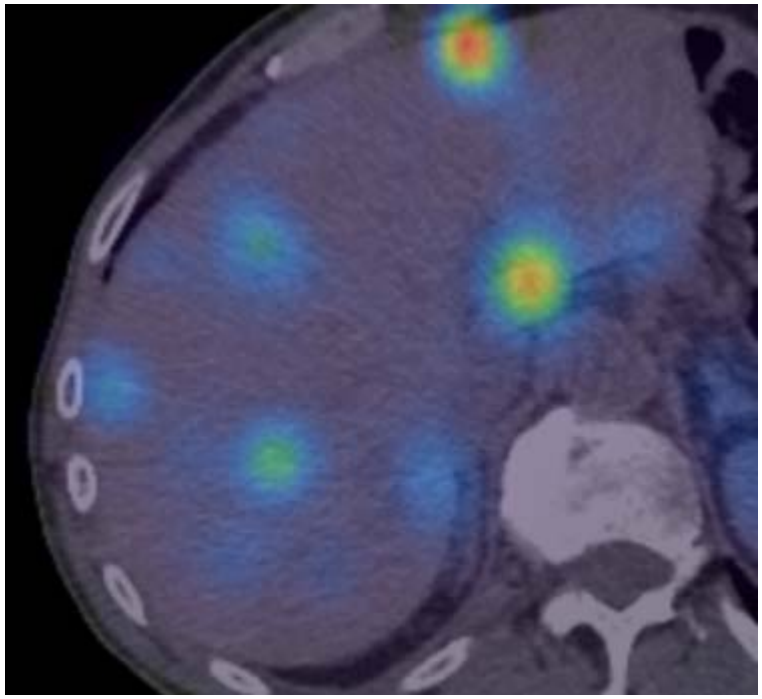
2014-2016

Slowly enlarging metastases:

commenced on Somatuline Autogel

- intolerable steatorrhea despite increased Creon.
- Patient preference; discontinued

- 2016: Octreoscan Scan- progressive avid abdominal lymphadenopathy and liver mets, new bone mets



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2016-2017

- 2 x PRRT therapy
- Post treatment CT/MRI: >50% reduction in liver mets and reduction in lymphadenopathy

- Isolation extremely stressful
- Intensive support from specialist team to enable him to complete treatment
- Wished to stop at 2 cycles

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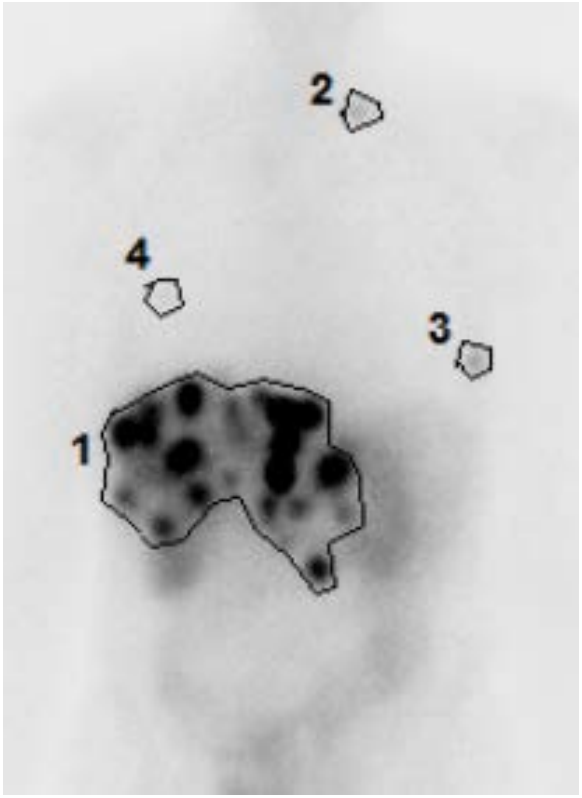
2018

- Further progression
- Rechallenged with PRRT x 2 cycles
- Further excellent response



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Summary

- Repeat treatments with period of remission of many years
  - Continues on Annual surveillance
- Main physical symptoms
  - Insulin controlled diabetic (struggles with control), frequency of stool and steatorrhea, fatigue
- Psychologically:
  - Anxiety, fear of progression, inability to plan for future
- Requires ongoing nursing and psychological team support

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Take home messages

- Most NETs are slow growing tumours, with multiple treatment option
- Each case has to be considered at each stage on its individual merits by specialist MDT
- There is a lack of clear evidence to support the specific sequencing of treatments
- The impact of delays in diagnosis and long-term chronic symptoms can have a massive impact on HRQoL
- Key work needs carried out to explore the long term HRQoL issues facing patients with pNETs.

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Thank you on behalf of Oxford NET Specialist team, The Oxford NET Natter Group and the NET Patient Foundation