Management of abdominal NETs

A Surgical Perspective

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CONTENTS

1. Definition of NETs
2. Anatomical distribution of NETs
3. The nature of NETs
4. Functioning vs non-functioning NETs
5. Risk factors for NETs
6. Symptoms of NETs
7. Diagnosis of NETs
8. Treatment of NETs
9. NETTER-1 clinical trial
10. Case Study

DEFINITION OF NETs

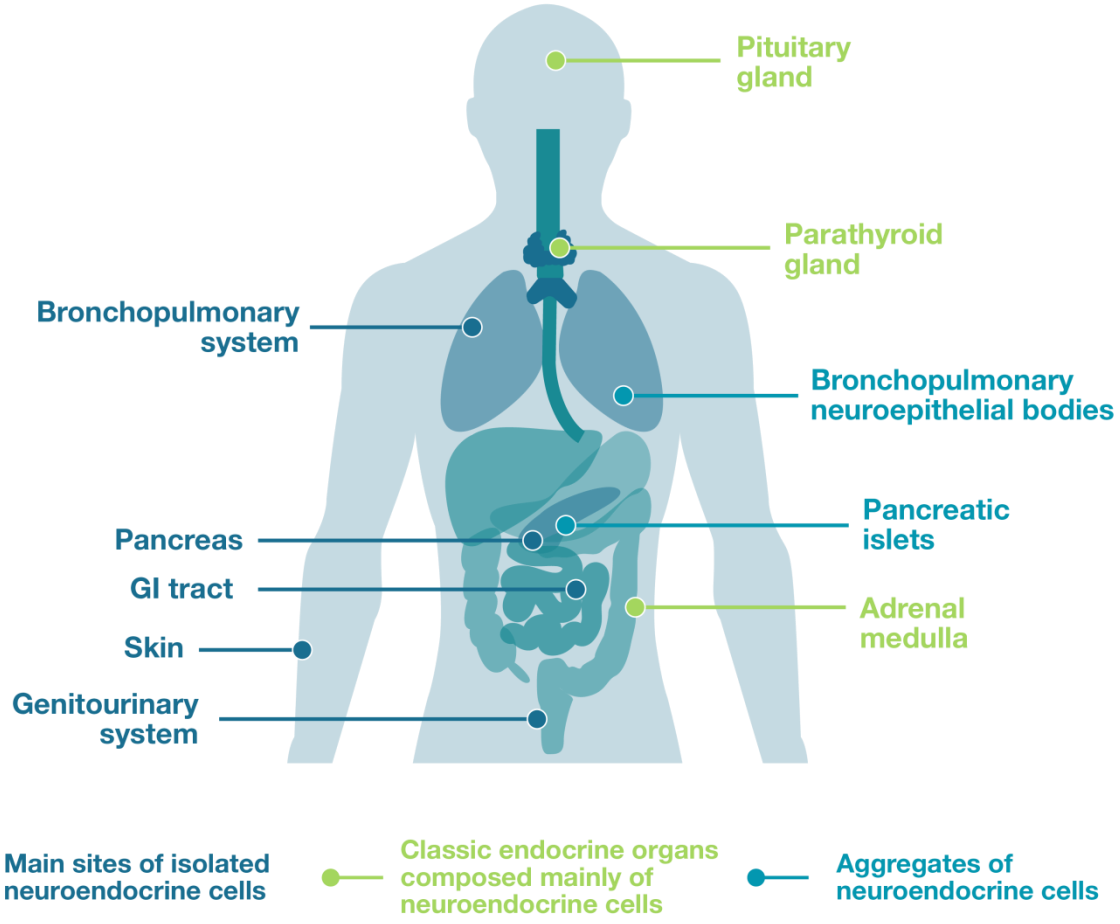
Neuroendocrine tumours (NETs) are a group of tumours that originate in cells known as neuroendocrine cells, which are distributed throughout the body.[1,2]

They are located in three broad areas:

1. **Isolated neuroendocrine cells scattered throughout most tissues.[1,3]**
2. **Aggregates of neuroendocrine cells in organs.[3]**
3. **Classic endocrine glands.[1]**

NETs were originally named 'carcinoid' (cancer-like) tumours. There have since been other terms coined to describe these lesions and the current term 'NET' was first put forward in 1995.[4,5]

The term 'carcinoid' is criticised for inaccurately implying that NETs are always benign lesions.[6]



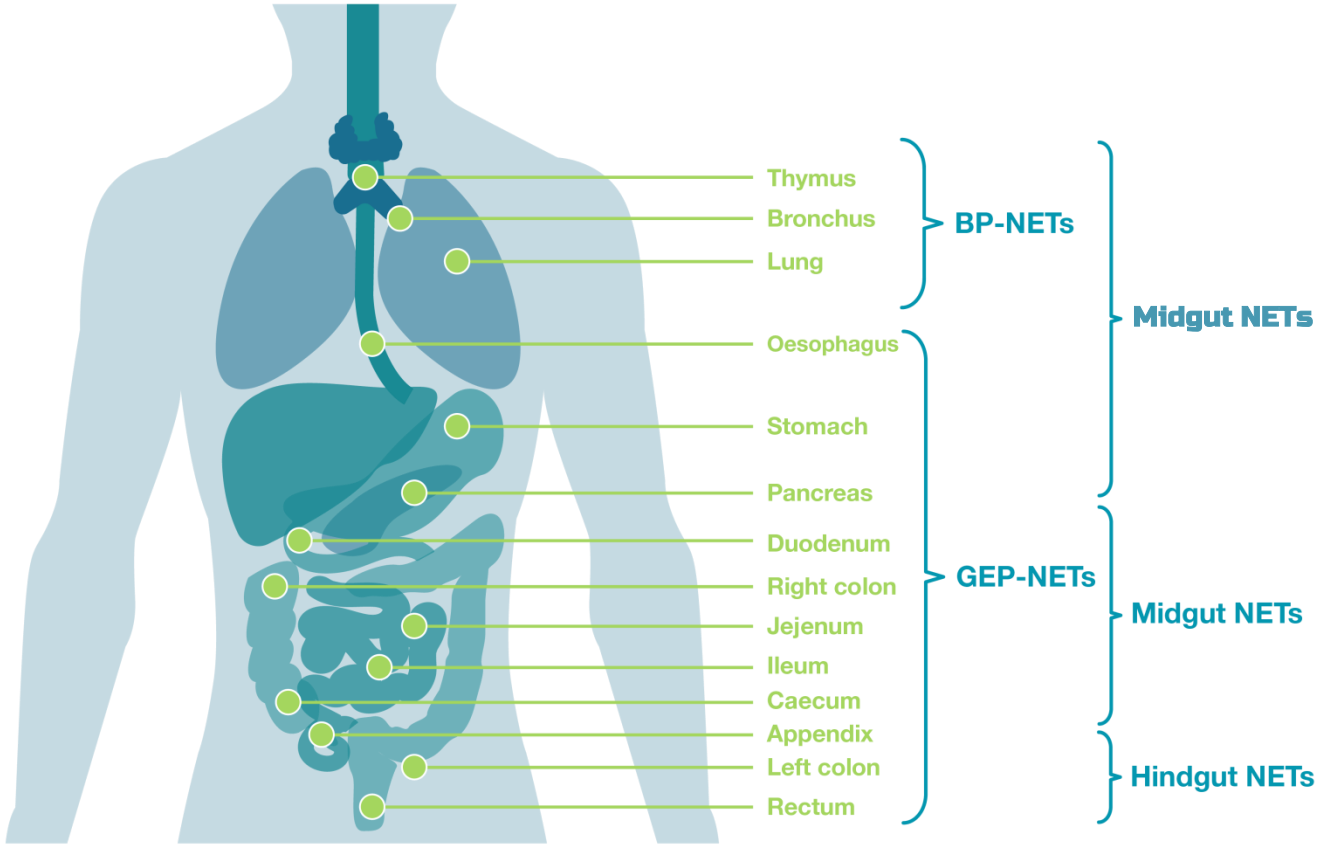
ANATOMICAL DISTRIBUTION OF NETs

NETs are classified according to their anatomical site of origin, with the vast majority arising in the GEP or BP tracts (GEP-NETs and PB-NETs, respectively).[6]

NETs are traditionally subclassified according to the embryological origin of their site:[8]

- **Foregut**
- **Midgut**
- **Hindgut**

Less common NET sites include the genitourinary tract, the adrenal medulla and the parathyroid and pituitary glands.[8,11,12]



THE NATURE OF NETs

Not only do NETs differ in their anatomical site, they also vary in their level of differentiation and 'aggressiveness' (grading).[6,13]

DIFFERENTIATION

- Refers to the extent to which tumour cells morphologically resemble healthy cells from the same tissue.[6,13]
- By definition, NETs are well differentiated.[11]
- NETs are usually organised into well-developed architectural patterns.[8,14]
- Invasive and metastatic potential of NETs is variable.[11]

GRADING

- NETs are given a histological grade which refers to the aggressiveness of the tumour; G1, G2 or G3.[6] Higher grade tumours are associated with negative patient outcomes.[14,15]
- Well-differentiated NETs are nearly always G1 or G2, poorly-differentiated NETs are G3.[6,11]

FUNCTIONING VS NON-FUNCTIONING NETs

In the case of NETs, increased proliferation of neuroendocrine cells often leads to hypersecretion of hormones.

When NETs cause clinical symptoms due to hormone hypersecretion, they are described as 'functioning'. However, most NETs do not produce biologically active hormone and are termed 'non-functioning'.[6]

Functioning NETs account for approximately:[16,6]

- **30% of GI NETs**
- **<5% of BP NETs**
- **40–55% of pancreatic NETs**

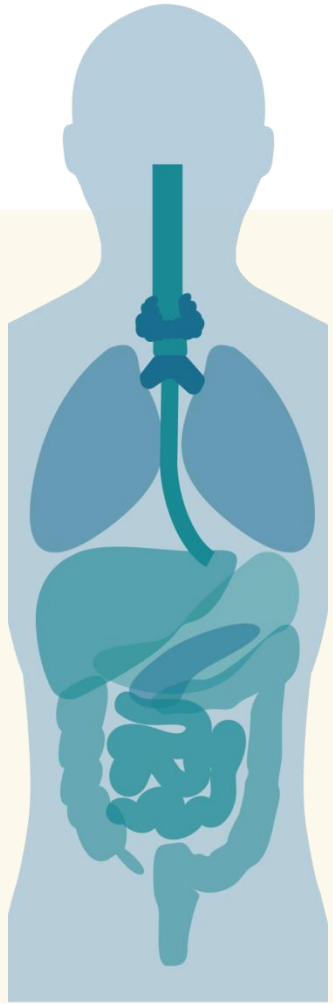
TYPE OF FUNCTIONING NET [6,2,17]	HORMONE(S) SECRETED [6,2,17]	ANATOMIC SITE [6,2,17]
Functioning carcinoid	Serotonin, tachykinin, prostaglandins, 5-HTP, histamine	Small intestine, lung or pancreas
ACTHoma	ACTH	Pancreas, bronchus, thymus
Insulinoma	Insulin	Pancreas
Gastrinoma	Gastrin	Gastrinoma triangle
Glucagonoma	Glucagon	Pancreas
PPoma	PP	Pancreas
Somatostatinoma	Somatostatin	Pancreas/duodenum
VIPoma	VIP	GEP tract, adrenal gland

SYMPTOMS OF NETs

The majority of NETs are non-functioning and symptoms, if they do occur, tend to be vague and nonspecific.[6,8]

SYMPTOMS ASSOCIATED WITH GEP-NETs

- The most prominent symptoms are abdominal pain and change in bowel habit (due to mass effects of the tumour causing intermittent bowel obstruction).[22,6,23]
- Fatigue is particularly prevalent in those with pancreatic NETs.[22]



SYMPTOMS ASSOCIATED WITH BP-NETs

- BP-NETs are associated with wheezing, coughing, haemoptysis, dyspnoea, chest pain and recurrent pneumonia.[22,8,6]
- Peripherally located lung NETs are usually asymptomatic.[8]

DIAGNOSIS OF NETs

Several tools, measures and imaging techniques are used to diagnose NETs; they often follow a logical order starting with patient presentation (although not all of the following diagnostic techniques are used in all patients).

PATIENT PRESENTATION

- The diagnostic process is initiated either by **patient-reported symptoms** or **incidental findings**.[6,8,25]
- The most prominent symptoms of GEP-NETs are often **abdominal pain** and **change in bowel habit**.[22,6,23]
- If a functioning tumour is present, patients might experience **functioning syndromes**, the most common is known as **carcinoid syndrome**.[6]
    - Carcinoid syndrome presents with **watery diarrhoea**, **cutaneous flushing** and **bronchospasm**.[23]

HISTOLOGY

- **Histopathological evaluation** of biopsied tumour tissue is **mandatory for diagnosis**.[16,6]
- Tumour **differentiation** is determined by microscopic assessment using **haematoxylin/eosin (HE) staining** techniques.[26]
- If the assessment is suggestive of a NET, diagnosis can usually be confirmed by measuring two diagnostic markers called **CgA** and **synaptophysin**.[26]

DIAGNOSIS OF NETs

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BIOCHEMISTRY (BIOMARKERS)

- Diagnosis can be confirmed by assessing biomarkers that are characteristic of NETs.[26]
  - **CgA** – Produced by a wide range of GEP-, BP- and other NETs.[27-29]
  - **5-HIAA** – Midgut NETs often secrete serotonin, leading to elevation of the metabolite 5-HIAA in blood and urine.[30,32]
    Insulin and **gastrin** are two other biomarkers that can be used to aid diagnosis of NETs.[32]

ANATOMICAL IMAGING

- **CT** – CT scanning is now used in diagnosis, staging and follow-up in NET patients as the standard imaging technique.[33]
- **MRI** – MRI is increasingly being used as an initial imaging investigation in NET patients.[33-35]
- **Endoscopic ultrasonography** – has high sensitivity and specificity for diagnosis of pancreatic NETs but involves more invasive investigation than CT and MRI.[33,34]
- **Endoscopy** – is used to aid diagnosis of gastroduodenal or colorectal NETs.[33,8]

DIAGNOSIS OF NETs

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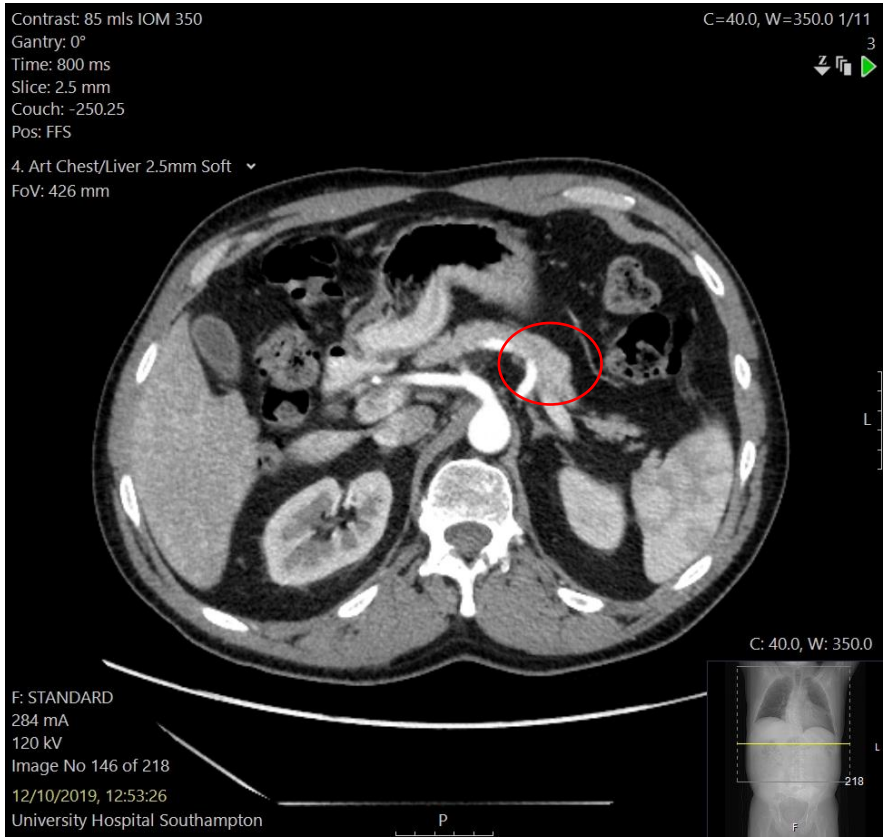
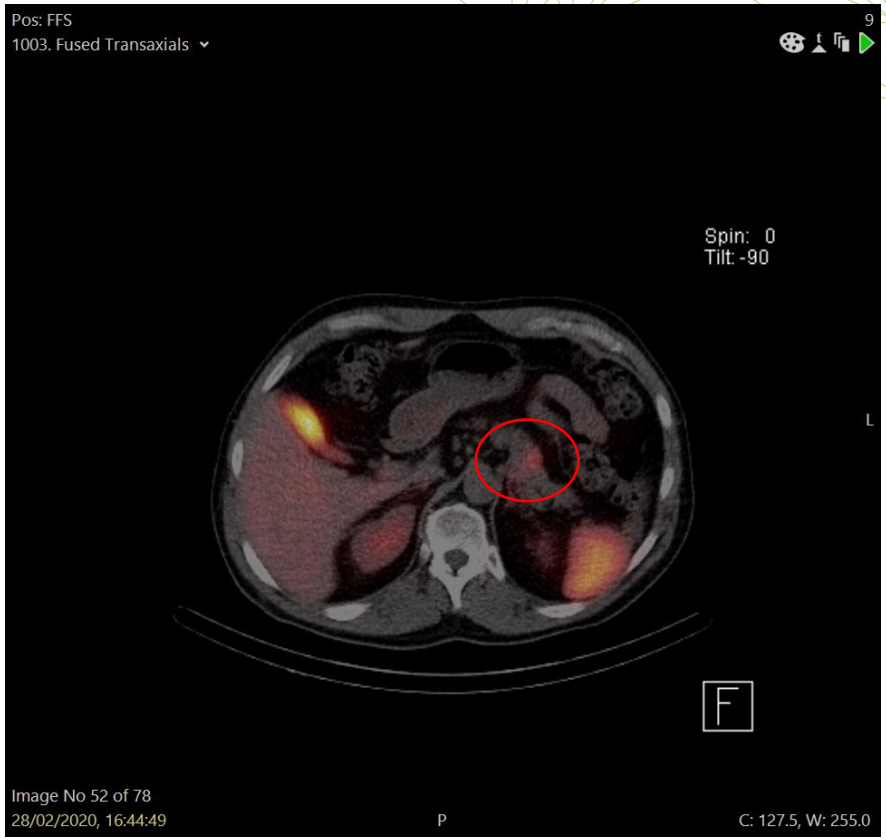
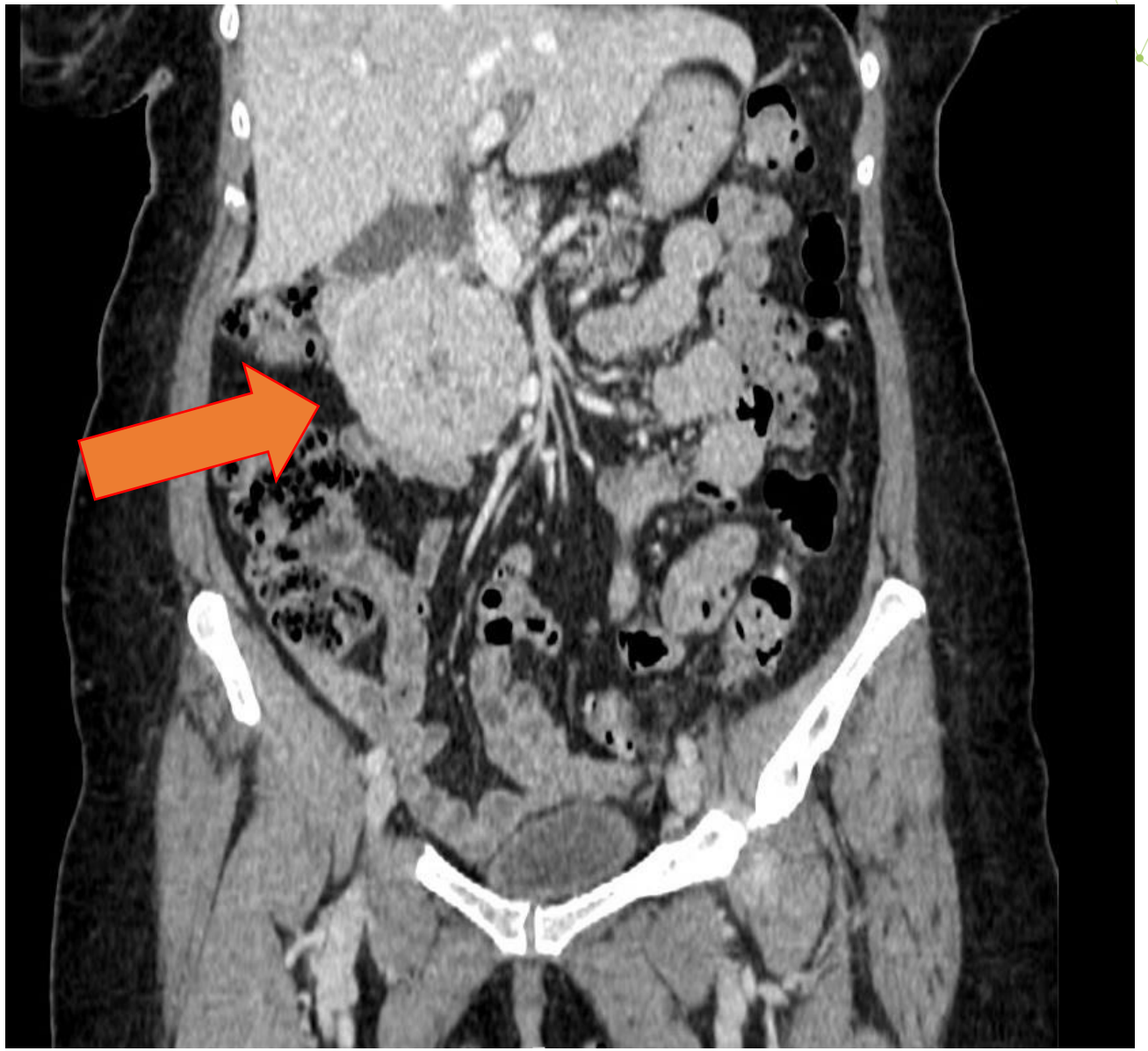
SOMATOSTATIN RECEPTOR IMAGING

- SSTR imaging has a central place in diagnosis and follow-up of NET patients.[33]
- SSTRs are expressed in high density by the majority (~80%) of GEP-NETs and BP-NETs.[33,35]
- SSTR imaging involves the administration of radiolabelled SSA tracers derived from a synthetic octapeptide named octreotide.[36]
- The SSA tracers bind to the SSTRs on the surface of NET cells.[36]
- Their location can be imaged due to the radioactive molecule (usually gallium-68), revealing the location and size of the tumour.[35,36]

40 year old patient with pancreatic body NET (pNET)







DIAGNOSIS OF NETs

Patients with NETs often experience a long delay between symptom onset (if present) and correct diagnosis. This is thought to be due to nonspecific symptomology and physician inexperience due to the relative rarity of NETs.[38,39]

9.2 YEARS

MEDIAN DIAGNOSTIC DELAY

TREATMENT OF NETs

Curative surgery is the primary aim of treatments, but this is only achievable in a minority of patients. For the remainder, goals of therapy are to control symptoms, prevent tumour growth and extend survival.[40-42]
Several classes of treatment can be used to achieve these goals, a summary of the therapies is as follows:

SURGERY

Complete resection of the tumour is the only curative treatment for NETs.[43,41]

SSAs

Bind to SSTRs expressed by tumour cells and exert anti-proliferative effects.[37,2]

LIVER DIRECTED THERAPIES

Are used to treat liver metastases, methods include heat ablation, restriction of blood supply and liver transplant.[13,41,44]

MOLECULAR-TARGETED TREATMENTS

Everolimus and Sunitinib are two kinase inhibitors used to treat NETs, most commonly of pancreatic origin.[45,46]

CHEMOTHERAPY

Alkylating agents such as Streptozocin and Temozolomide in addition with 5-fluorouracil have been used to treat inoperable NETs.[47-49]

OTHER SYSTEMIC THERAPIES

Telotristat and interferon-α are both used to treat carcinoid syndrome in those with functioning NETs.[50,51]

The concept of ‘cure’ in metastatic NETs

- Not the same as in ‘standard’ cancers
- Frequently, survival is measured in many years in slow moving disease
- May entail different treatments over a period of time
- Emphasis is on disease control and quality of life
- Surgery has a role to play along with other treatments

Treatment of GEP NETs

Patient factors

- Age
- Fitness
- Grade (Ki67)
- Local disease only: confined to the organ
- Metastatic disease (appropriate for debulking)
- Metastatic disease (symptomatic)
- Metastatic disease asymptomatic

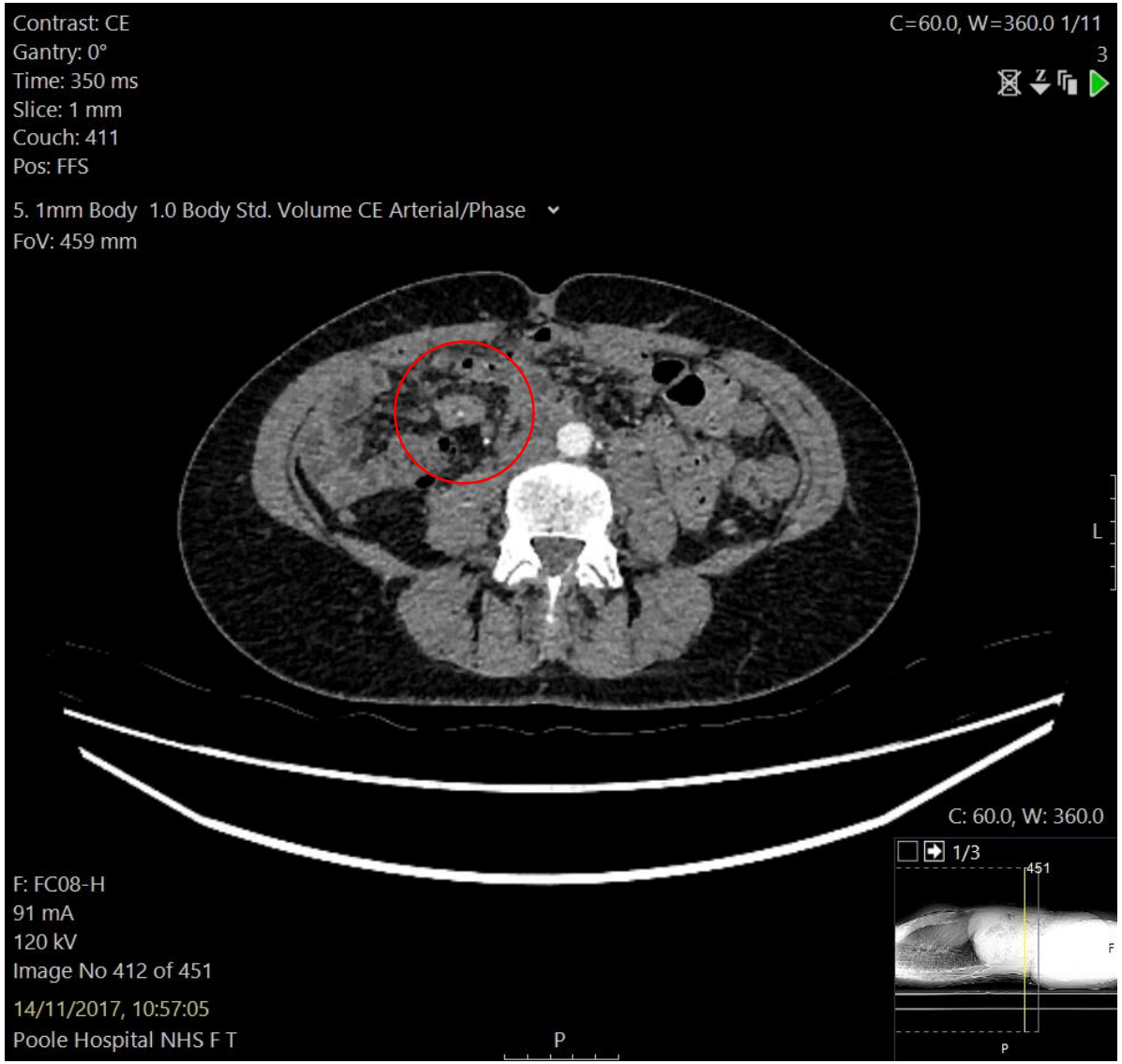
Treatment Options

- SSA (If SSTR positive on functional imaging (Tektroyd scan/ gallium dotate)
- Surgery for cure
- Surgery to debulk
- Radiological debulking (TAE/ TACE/ ablation)
- Molecular targeted therapies
- Systemic chemotherapy
- PRRT
- All of the above

Case Study

- 50 yr old lady, presented to her GP with vague abdominal symptoms and change in bowel habit
- Went on to have a CT colonoscopy as did not tolerate standard colonoscopy
- Nodal mass in small bowel mesentery picked on CT with features typical of a mid-gut NET
- No carcinoid type symptoms but had a 'funny tummy' for 'years'
- Full staging investigations with:
  - CT chest/ abdo/ pelvis
  - Liver MRI
  - Tektroyd scan
  - NET blood work including gut hormone profile, CgA+CgB and Urinary 5HIAA
  - Liver biopsy showed a well differentiated, grade 1 NET, Ki67 <1%
  - Started on SSA

CT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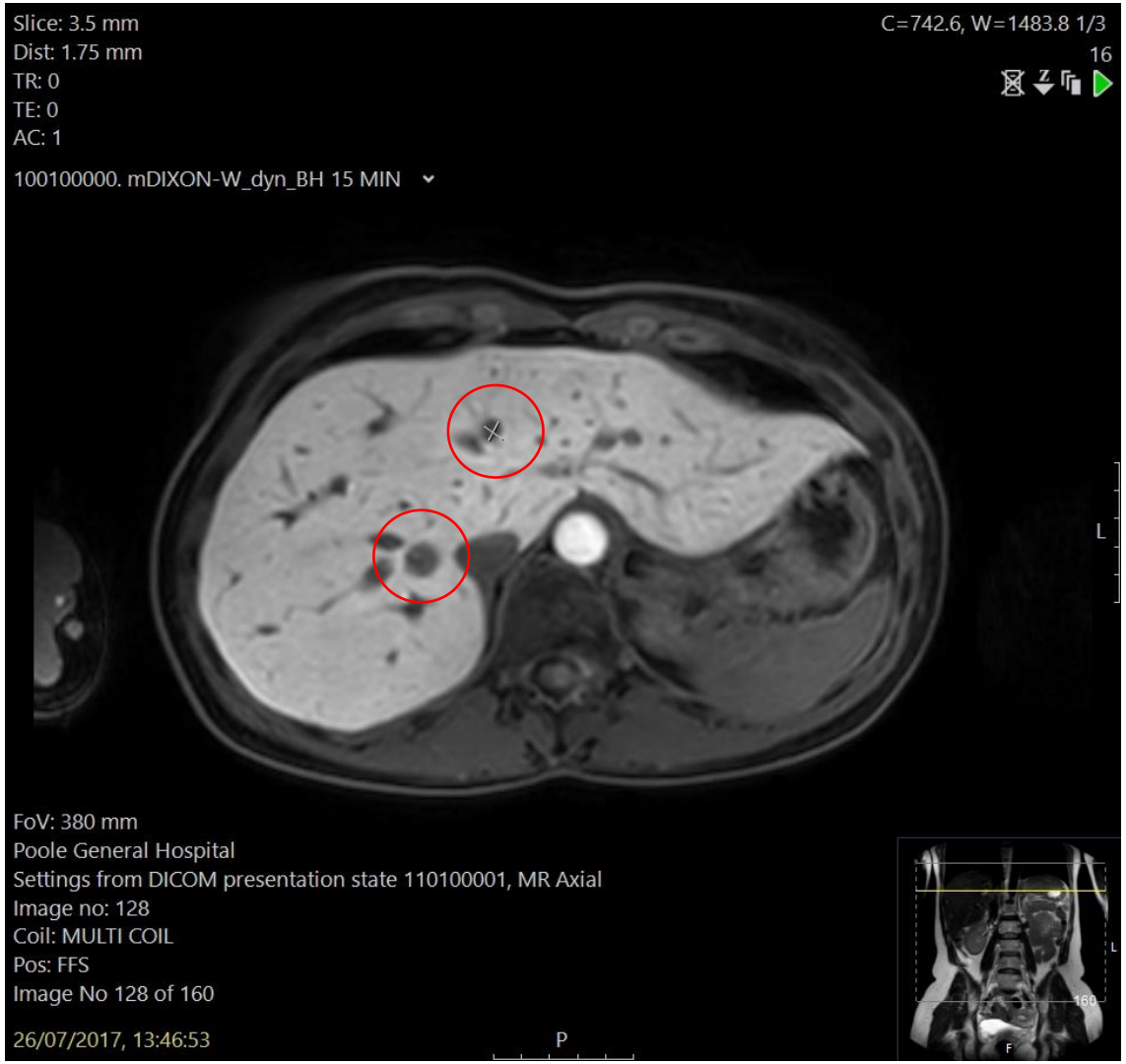
Liver MRI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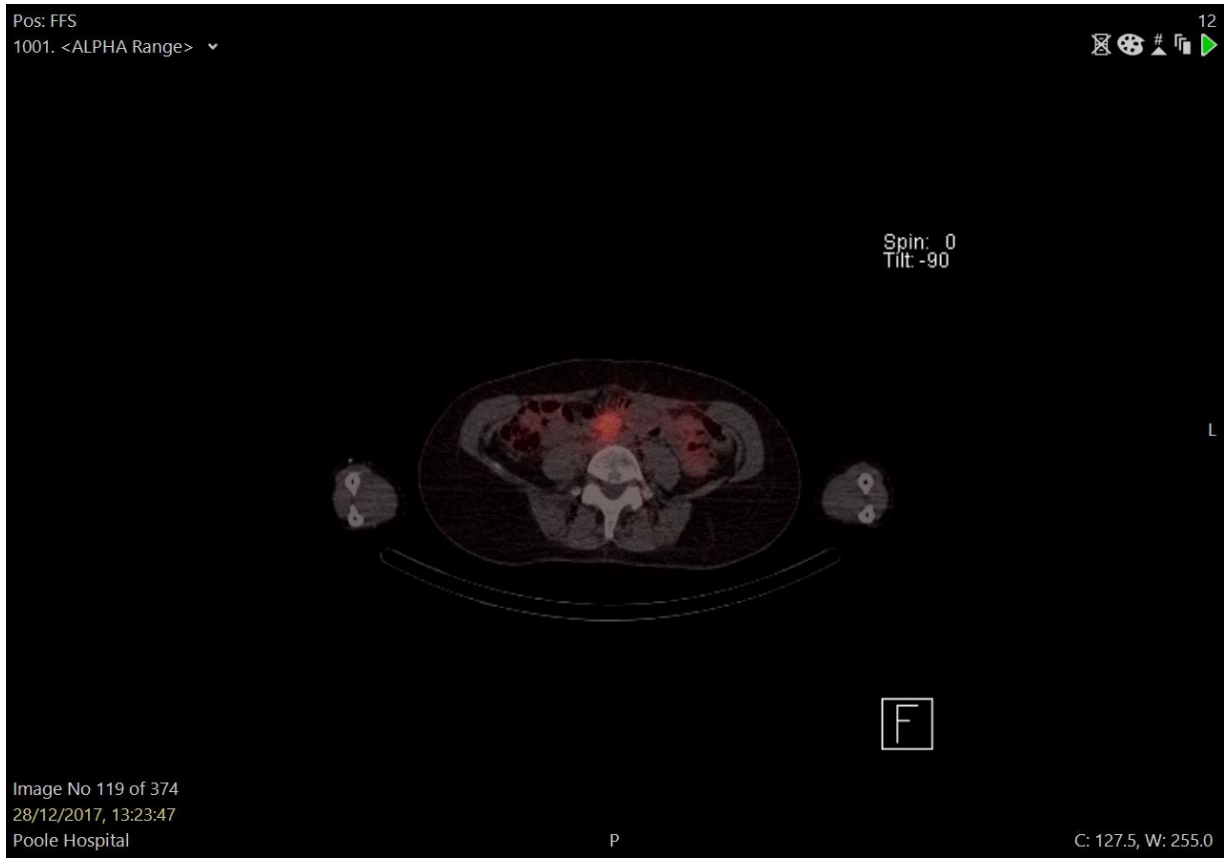
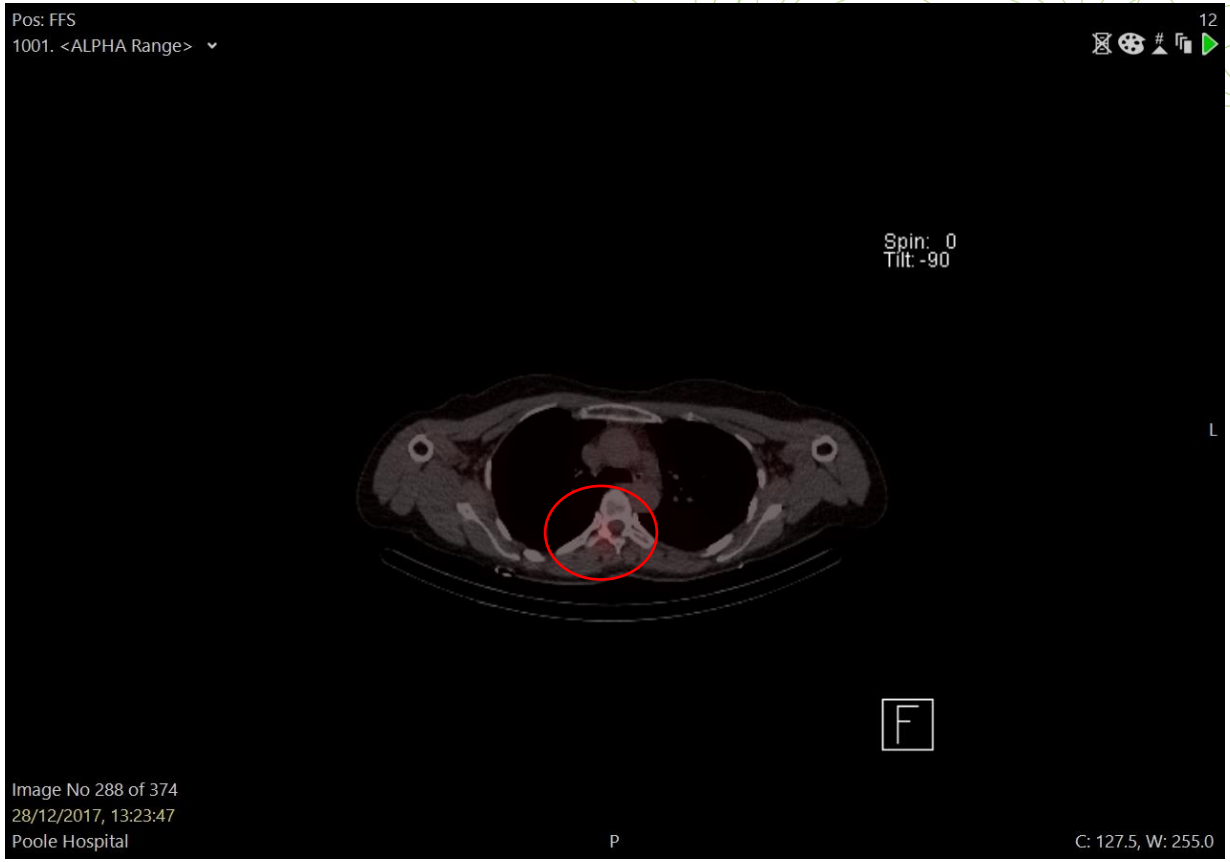
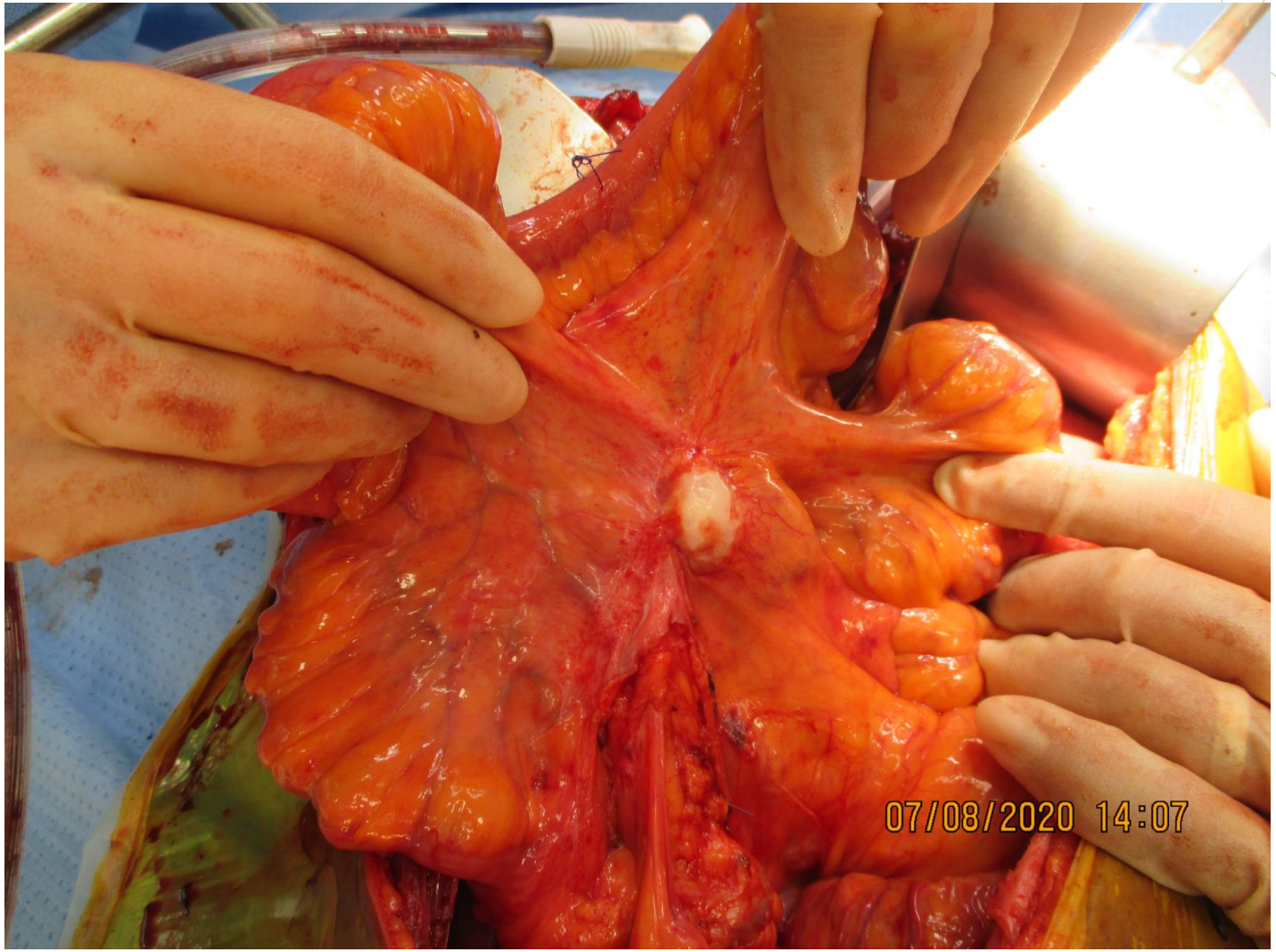
Tektroyd scan





Surgery



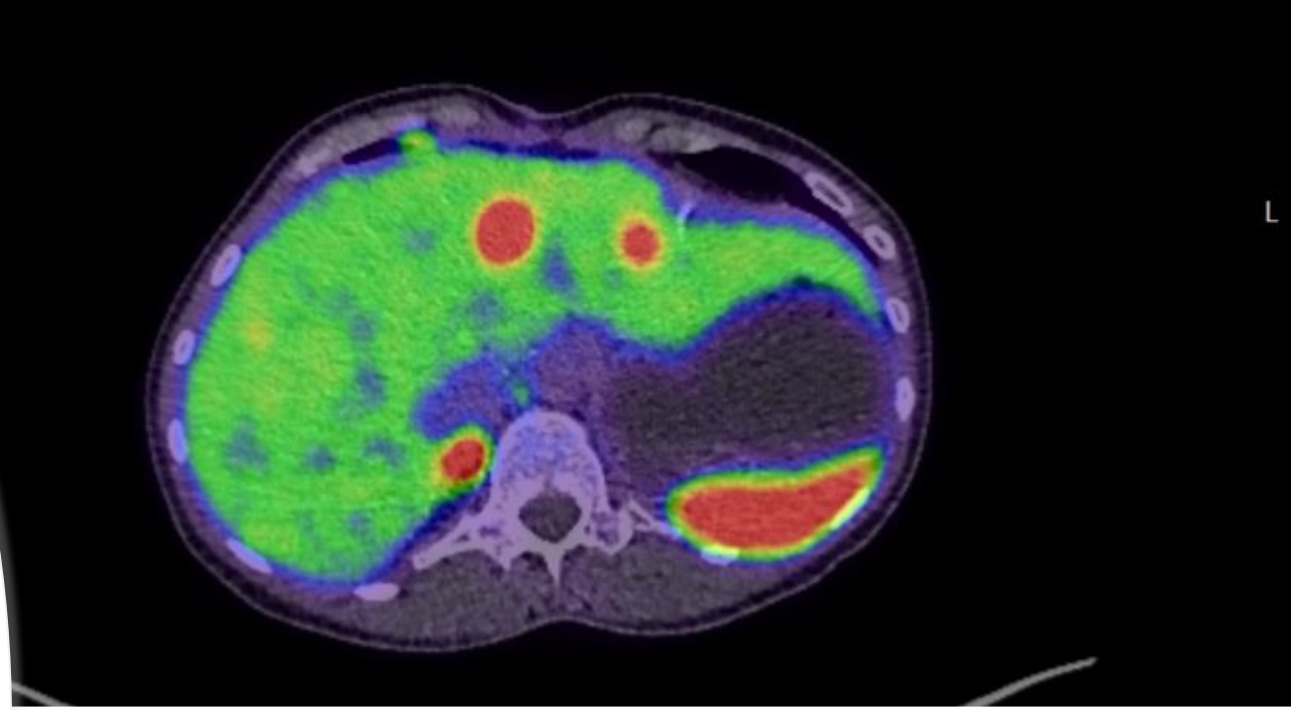
Surgery

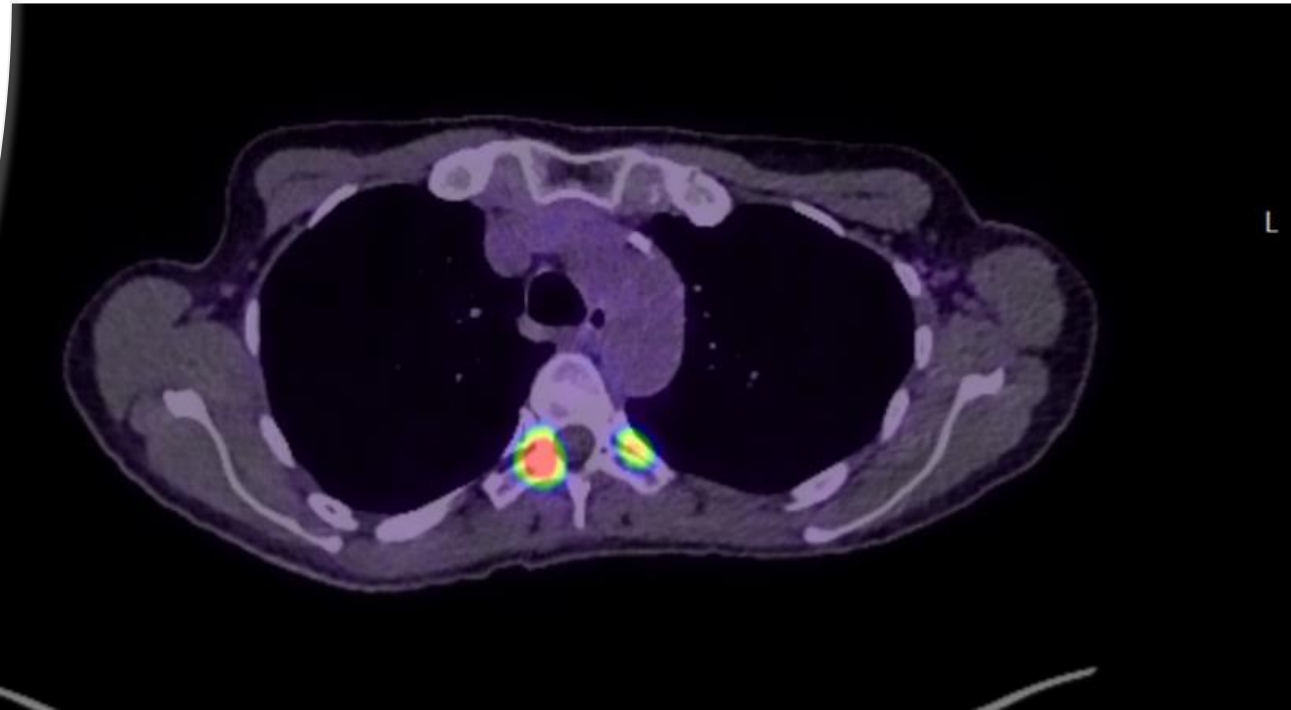
- 15 liver metastases resected
- 5 small tumours in the ileum (small bowel) resected
- Small volume peritoneal peritoneal disease resected
- All visible disease resected

8 months post op: Gallium 68 scan

Currently undergoing PRRT

Training to be a healthcare assistant!





Conclusion

- GEP NETs require a multi-disciplinary approach
- Due to heterogeneity of disease and variable patterns of tumour burden, a bespoke approach is required. One that is tailored to each patient
- A patient with metastatic disease may be treated with a multimodal approach across the course of their illness. This may include:
  - Surgery for debulking/ symptom control
  - TAE/ TACE
  - SSAs
  - Molecular targeted therapy
  - PRRT

Acknowledgements

- Mark Southern
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?Questions?