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THE HEART OF MEDICAL EDUCATION

RECOGNISING, DIAGNOSING AND MANAGING NEUROENDOCRINE TUMOURS

MICRO LEARNING

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DEVELOPED BY NET CONNECT

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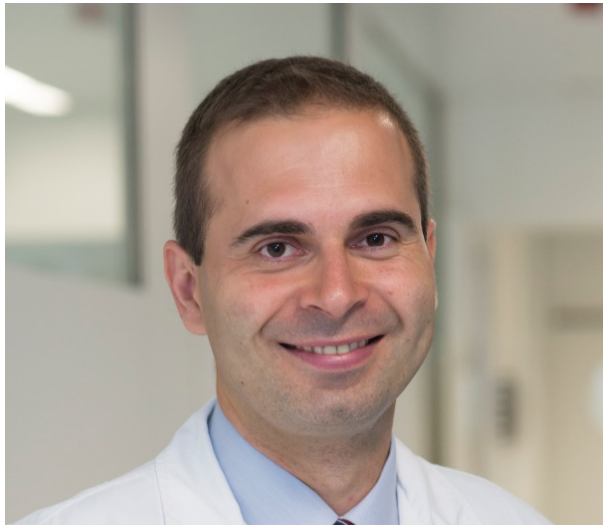

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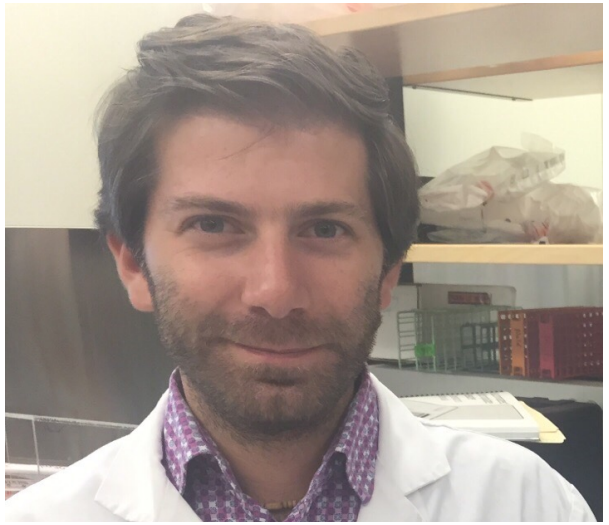


EDUCATIONAL OBJECTIVES

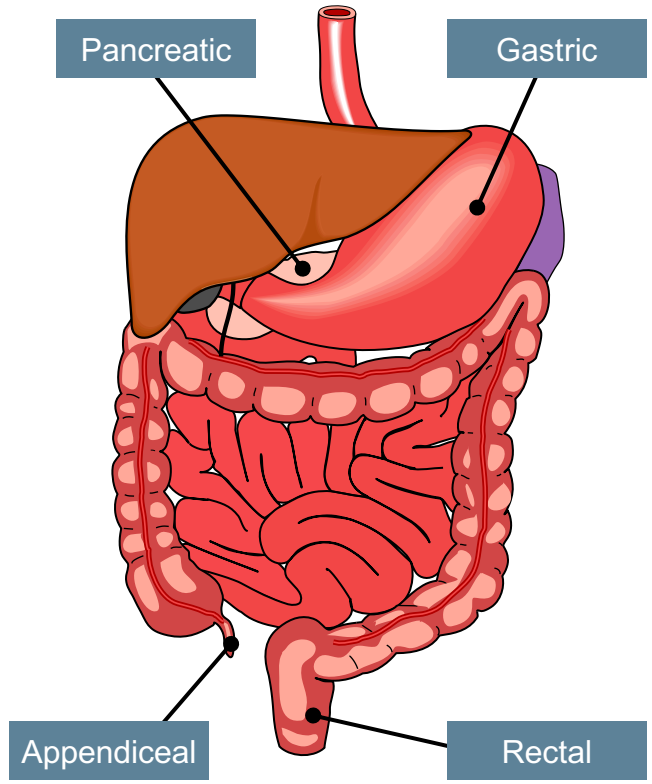
- Be able to **recognise the presenting symptoms** of potential NET patients
- Be aware of the **steps to diagnosis** and **the importance of referral to a NET centre of excellence/expertise**

CLINICAL TAKEAWAYS

- **Recognising the symptoms of a potential NET can be challenging** as presentation may be heterogenous, dependent on hormone secretion and many patients have symptoms similar to those found in other conditions
- **Steps to diagnosis** include symptom assessment, size, grade and stage of the tumour, whether the tumour is hormone-secreting and evaluation of predisposition to an underlying hereditary syndrome
- **Referral to a NET centre of excellence is advised,** to ensure comprehensive care by a multidisciplinary team, which provides access to advanced imaging techniques and innovative treatments for the earliest possible treatment of localised and advanced tumours

INTRODUCTION

- Gastrointestinal neuroendocrine tumours covered in this module include **pancreatic**, **gastric**, **rectal** and **appendiceal** NETs. GI NETs have diverse presentations and can be mistaken for other common conditions, leading to delays in diagnosis
- Comprehensive evaluation of patients with possible NETs includes assessing symptoms, tumour characteristics, hormone secretion, and hereditary predisposition. This requires specialist investigations such as nuclear medicine scans
- Patient management and prognosis should be discussed by a fully constituted NET multidisciplinary team in a NET centre of excellence
- Localised tumours are typically considered for endoscopic or surgical resection. Early referral to a NET specialist centre can improve patient outcomes and quality of life



GI, gastrointestinal; NET, neuroendocrine tumour

Cives M, et al. CA Cancer J Clin. 2018;68:471-87

PANCREATIC NEUROENDOCRINE TUMOURS (PanNETs)

PANCREATIC NEUROENDOCRINE TUMOURS – OVERVIEW

- PanNETs are mostly sporadic but a variable portion are a result of inherited syndromes
- MEN1 is the most inherited condition followed by more uncommon conditions such as von Hippel-Lindau (VHL), von Recklinghausen's syndrome (neurofibromatosis 1), and tuberous sclerosis

Categorised as:

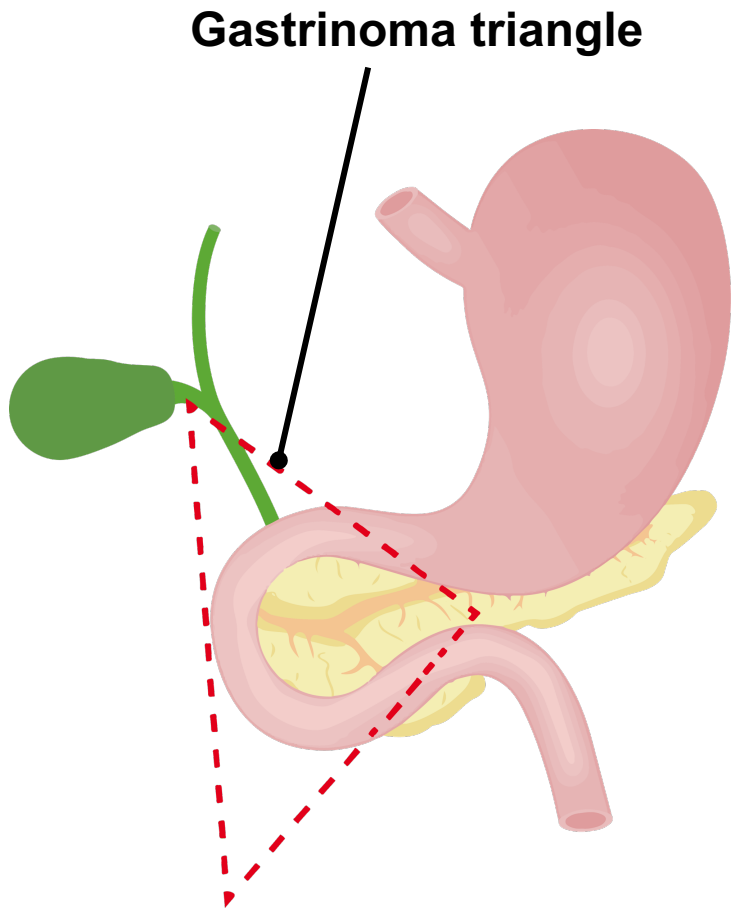
- Functional panNETs (hormone secreting)
- Non-functional panNETs (non-hormone secreting) include up to 90%
- Non-functional panNETs are asymptomatic and frequently diagnosed incidentally, leading to a delayed and challenging diagnosis

panNET, pancreatic neuroendocrine tumour

Cives M, et al. CA Cancer J Clin. 2018;68:471-87; Jansen et al. J Cancer. 2008; 113 suppl 57: 1807-1843

FUNCTIONAL PanNETs – PRESENTING SYMPTOMS

Functional panNET type	Presenting symptoms
Gastrinomas (ZES)	• Symptoms due to gastric acid hypersecretion • If an underlying ZES, frequent multiple gastric ulcers • Abdominal pain due to ulcers, diarrhoea and heart burn • Typically located in the gastrinoma triangle
Insulinomas	• Weight gain in 20-40% of patients • Characterised by symptoms of the Whipple triad including: – Episodic hypoglycaemia – Neuroglycopenic symptoms (confusion, visual disturbances, headaches and coma) – Restoration of the symptoms after glucose intake
Rare functional panNETs	• Glucagonoma, VIPoma, somatostatinoma

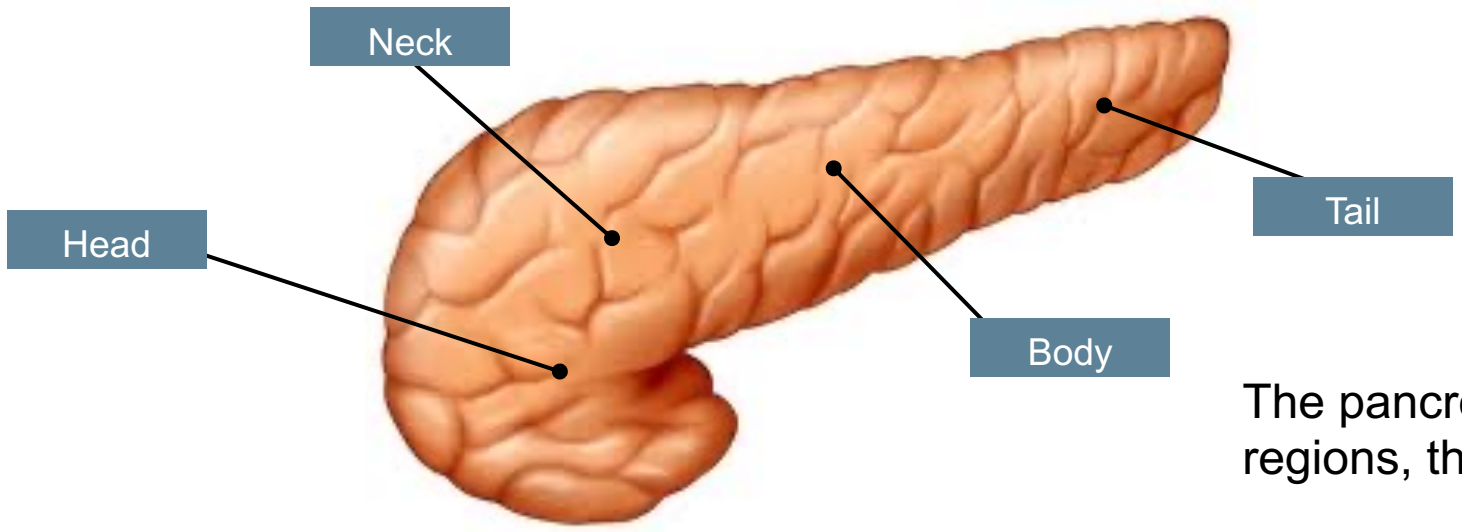


panNET, pancreatic neuroendocrine tumour; VIP, vasoactive intestinal peptide; ZES, Zollinger-Ellison syndrome

Jensen R, et al. Neuroendocrinology. 2012;95:98-119; Cives M, et al. CA Cancer J Clin. 2018;68:471-87; Dizon AM, et al. AM J Med. 1999;106 (3):307-310

NON-FUNCTIONAL PanNETs – PRESENTING SYMPTOMS

Location	Presenting symptoms
Head of pancreas	• Jaundice, pain
Body/Tail	• Diabetes, exocrine pancreatic insufficiency, pain



The pancreas is divided into four general regions, the head, neck, body and tail

panNET, pancreatic neuroendocrine tumour

Jensen R, et al. Neuroendocrinology. 2012;95:98-119; Falconi M, et al. Neuroendocrinology. 2012;95:120-34

PanNETs – STEPS TO DIAGNOSIS

Pathological diagnosis

- Preferably via EUS-FNAB done by skilled endoscopist

Laboratory test in non-functional NET

- Plasma chromogranin A (CgA) testing can be useful in diagnosing panNETs, but it is not definitive and should be used in combination with other diagnostic methods
- Peptide hormones (insulin, gastrin, glucagon, etc) can be used as tumour markers in functioning panNETs

Cross-sectional and functional imaging

- Cross-sectional imaging is mandatory before functional imaging
- 70% of tumours express high levels of somatostatin receptors mainly SSTR2 and SSTR5 and can be imaged with a radio-labelled somatostatin analogue
- Ga^{68}-PET/CT provides imaging of whole body and functional information about somatostatin expression

Genetic testing and counselling

- Should be performed in case of suspected familial predisposition and suggestive clinical scenarios (i.e., co-occurrence of parathyroid adenoma, pituitary adenoma and panNET is highly suspicious for MEN1 syndrome)

- Upon confirmation of histopathological diagnosis: advisable to refer patient to NET centre of excellence
- Patient survival is usually long and treatment centres closer to home are deemed more favourable

CT, computed tomography; EUS-FNAB, endoscopic ultrasound fine needle aspiration biopsy; Ga^{68}, gallium-68; GI, gastrointestinal; NET, neuroendocrine tumour; panNET, pancreatic NET; PET, positron emission tomography; SSTR2, somatostatin receptor 2; SSTR2. somatostatin receptor 5

Jensen R, et al. Neuroendocrinology. 2012;95:98-119; Falconi M, et al. Neuroendocrinology. 2012;95:120-34

PanNETs – MANAGEMENT BASED ON TUMOUR FUNCTIONALITY AND SIZE

Functionality	Tumour management
Functional	• Surgery is the main treatment for localised disease • SSAs might be administered to palliate hormonal symptoms before surgery • PPIs are the treatment of choice for the palliation of Zollinger-Ellison syndrome
Non-functional	• Treatment should be tailored according to tumour size for G1 • Surgery is the mainstay for G2 and G3

Size	Tumour management
<1 cm	• Watch and Wait (W&W) is recommended for G1 panNETs
1–2 cm	• W&W or surgical resection should be discussed with the patient • Results of the ASPEN study will highlight if any difference exists between the two management modalities
>2 cm	• Surgical resection + regional lymph node dissection should be performed

G, grade; panNET, pancreatic neuroendocrine tumour; SSA, somatostatin analogue

Jensen R, et al. Neuroendocrinology. 2012;95:98-119; Cives M, et al. CA Cancer J Clin. 2018;68:471-87

GASTRIC NEUROENDOCRINE TUMOURS (GNETs)

GASTRIC NEUROENDOCRINE TUMOURS – OVERVIEW

- GNETs represent about 8.7% of all NETs
- Categorised as types 1, 2 and 3
- Tumour markers include CgA but elevation of this marker alone does not necessarily indicate presence of GNET, particularly in the context of atrophic gastritis

CgA, chromogranin A; GNET, gastric NET; NET, neuroendocrine tumour

Li TT. World J Gastroenterol. 2014;20(1):118-125; Cives M, et al. CA Cancer J Clin. 2018;68:471-87

GNETs – PRESENTING SYMPTOMS

GNET type	Presenting symptoms & frequency
1	• Occurs in patients with chronic gastritis and accounts for 80% of GNETs • Benign behaviour
2	• Occurs in patients with underlying gastrinoma primarily in patients with MEN1 • Symptoms of Zollinger-Ellison syndrome including diarrhoea, heartburn and peptic ulceration
3	• Sporadic (less than 15% of all GNETs) • Higher malignancy potential

GNET, gastric neuroendocrine tumour; MEN1, multiple endocrine neoplasia type 1

Li TT. World J Gastroenterol. 2014;20:118-25; Cives M, et al. CA Cancer J Clin. 2018;68:471-87

GNETs – STEPS TO DIAGNOSIS

GNET type 1

- Elevated serum gastrin level
- Gastric pH >4
- CgA elevation
- Evidence of chronic atrophic gastritis on biopsy

GNET type 2

- Elevated serum gastrin level
- Low gastric pH
- In case of underlying gastrinoma, painful abdominal point in the choledocho-pancreatic area of Chauffard-Rivet

GNET type 3

- Not associated with gastrin overproduction
- Ki-67 index of >20%

CgA, chromogranin A; GNET, gastric neuroendocrine tumour

Basuroy R, et al. Aliment Pharmacol Ther. 2014; 39:1071-84; Cives M, et al. CA Cancer J Clin. 2018;68:471-87

GNETs – MANAGEMENT

GNET type	Management
1	• Endoscopic surveillance every 6-12 months is appropriate in the vast majority of cases • In selected cases, netazepide, an oral antagonist of gastrin/cholecystokinin receptors can be useful • There is no indication for gastrectomy • Patient should be referred to the nearest NET centre of excellence for consultation and surveillance
2	• Treatment for underlying gastrinoma in NET centre of excellence
3	• Surgical resection • Patient should be referred to NET centre of excellence

GNET, gastric NET; NET, neuroendocrine tumour

Basuroy R, et al. Aliment Pharmacol Ther. 2014; 39:1071-84; Cives M, et al. CA Cancer J Clin. 2018;68:471-87

RECTAL NEUROENDOCRINE TUMOURS (RNETs)

RECTAL NEUROENDOCRINE TUMOURS – OVERVIEW AND PRESENTING SYMPTOMS

Prevalence/incidence

- RNETs: 12% to 27% of all NETs
- Higher incidence and prevalence in both African American and Asian populations vs Caucasians

Classification

- Low grade (G1)
- Intermediate grade (G2)
- High grade (G3)

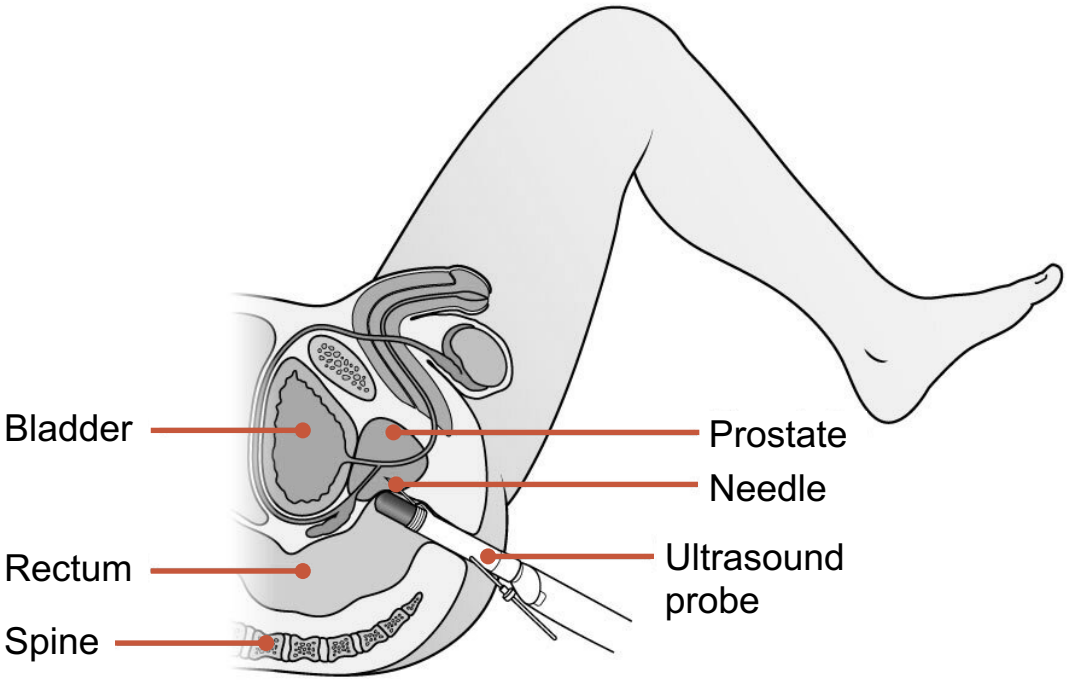
Symptoms

- Often asymptomatic
- 50% present with:
  - Rectal tenesmus
  - Changes in bowel habits

NET, neuroendocrine tumour; RNET, rectal NET

Volante M, et al. Pathologica. 2021.DOI: 10.32074/1591-951X-230; Caplin M, et al. Neuroendocrinology. 2012;95:88-97; Cives M, et al. CA Cancer J Clin. 2018;68:471-87

RNETs – STEPS TO DIAGNOSIS



Endoscopy

- Most rectal tumours are discovered endoscopically and receive a confirmed diagnosis after histological assessment
- Full colonoscopy is used to rule out other colonic diseases
- **Gold standard of diagnosing RNETs**

Imaging

- Endoanal/rectal ultrasound (EUS) highly useful for pre-operative assessment. EUS can assess tumour size, depth of invasion and presence of pararectal lymph node metastases

RNET, rectal neuroendocrine tumour

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

RNETs – MANAGEMENT

Tumour size	Tumour management
<1 cm	• Endoscopic removal
1–2 cm	• Mostly removed endoscopically if there is a low mitotic index and no invasion of muscularis propria
>2 cm	• Surgical resection
It is important to note that localised rectal NETs should not be treated as typical rectal cancers by treating patients with chemoradiotherapy	

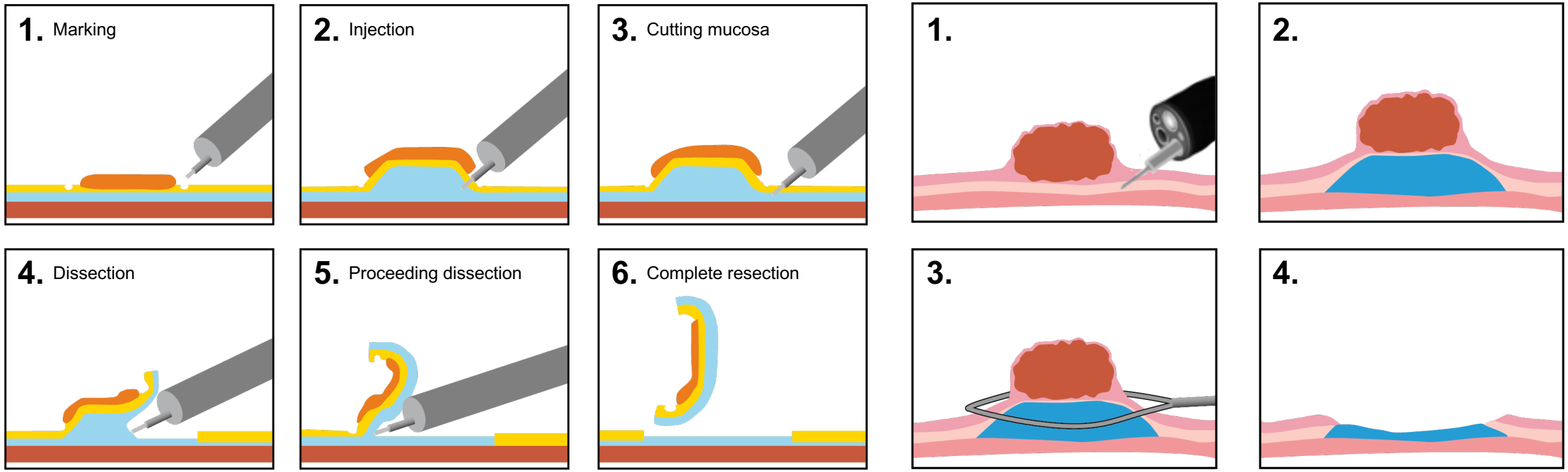
Endoscopic removal methods

- Endoscopic submucosal dissection (ESD) – high complete and *en-bloc* resection rates, but also an increased risk of complications including perforation
- Endoscopic mucosal resection (EMR) – first line for resection of small rectal NETs due to safety and effectiveness. EMR-L is a variation that includes a ligation band and is commonly used
- Due to highly specialised nature of procedure, referral of patients to NET centres of excellence is advisable

EMR-L, EMR with a ligation device; NET, neuroendocrine tumour; RNET, rectal NET

Chablaney S, et al. Clin Endosc. 2017;50:530-36; Maione F, et al. Diagnostics. 2021;11:771; Caplin M, et al. Neuroendocrinology. 2012;95:88-97

ESD AND EMR ENDOSCOPIC TECHNIQUES



EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection

https://www.adventhealth.com/sites/default/files/assets/cie-understanding-endoscopic-mucosal-resection_0.pdf (accessed March 2023)

APPENDICEAL NEUROENDOCRINE TUMOURS (ANETs)

APPENDICEAL NEUROENDOCRINE TUMOURS – OVERVIEW AND DIAGNOSIS

- The **prognosis of lower stage appendiceal NETs is excellent** with more than 90% survival probability at 10 years and an overall risk of metastases of <10%
- No characteristic tumour specific symptoms
- In most cases incidentally found during surgery for appendicitis
- Histopathologically confirmed patients can be referred to NET centres of excellence for a multidisciplinary approach and treatment

NET, neuroendocrine tumour

Volante M, et al. Pathologica. 2021;113:19-27; Pape U-F, et al. Neuroendocrinology. 2016;103:144-152

ANETs – MANAGEMENT AND RECENT DEVELOPMENTS

Tumour size	Intervention
<2 cm	• Simple appendectomy
>2 cm	• Simple appendectomy with right-sided hemicolectomy

The SurvivApp trial found evidence that right-sided hemicolectomy is not indicated in patients with 1-2 cm tumours who had complete resection, via appendectomy

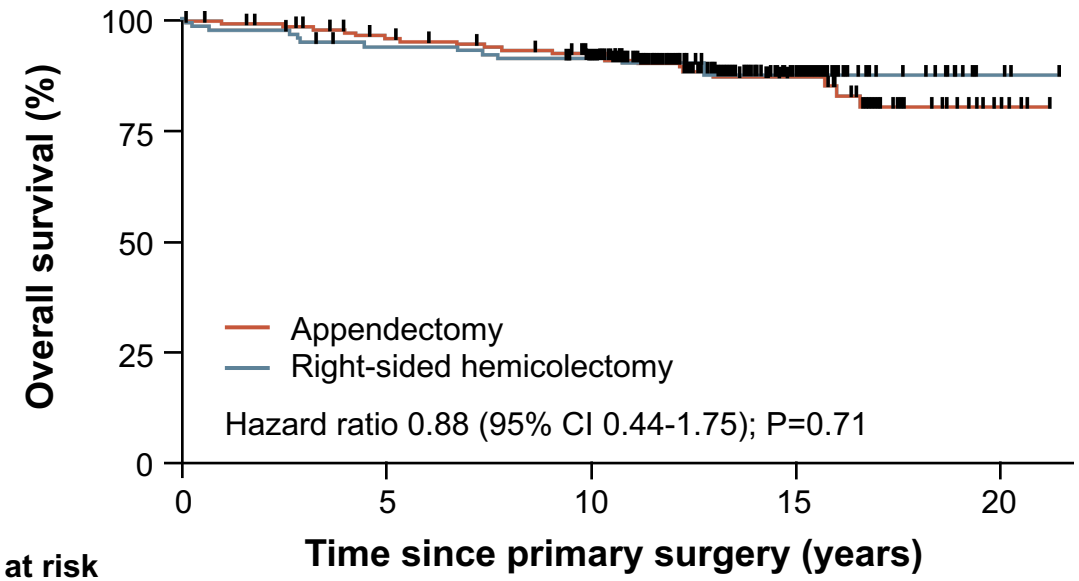
- Retrospective cohort study
- Pooled data from 40 hospitals in 15 European countries
- Patients of any age and ECOG PS
- Histopathologically confirmed ANETs sized 1-2 cm

ANET, appendiceal NET; ECOG PS, Eastern Cooperative Oncology Group performance status; NET, neuroendocrine tumour

Nesti C, et al. Lancet Oncol. 2023. 24:187-94

SurvivApp – RESULTS AND DISCUSSION

OS from the time of primary surgery



Number at risk (number censored)					
Appendectomy	163 (0)	147 (9)	134 (16)	50 (95)	4 (141)
Right-sided hemicolectomy	115 (0)	105 (3)	96 (9)	38 (65)	3 (101)

Two main findings:

- Right-sided hemicolectomy has no benefit on long-term survival after complete resection of the primary 1-2 cm tumours by appendectomy
- Regional lymph node metastases of appendiceal NETs of 1-2 cm in size are clinically not relevant and not associated with reduced tumour-specific survival

However, the follow-up duration from this study has been too short to confirm that remnant lymph nodes have no impact on OS and more data is required

CI, confidence interval; NET, neuroendocrine tumour; OS, overall survival

Nesti C, et al. Lancet Oncol. 2023. 24:187-94

SUMMARY

- Recognising pancreatic, gastric, rectal and appendiceal NETs can be challenging and patients may experience no symptoms or symptoms found in other diseases. At the **localised stage**, symptoms also depend on **size** and the **hormones produced by the tumour**
- Steps to diagnosis of a potential NET include assessing all symptoms, size, grade, and stage of the tumour. In **panNET diagnosis**, hereditary syndromes may play a key role and **genetic counselling** is **advised**
- Referral to a NET centre of excellence with a multidisciplinary team is recommended for comprehensive care, specialised expertise, access to advanced diagnostic techniques and personalised support for patients with neuroendocrine tumours

NET, neuroendocrine tumour; panNET, pancreatic NET

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