World NEN Lives 2020 Congress

The role of endoscopy in NEN diagnosis and treatment

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UCL

Overview of Endoscopy

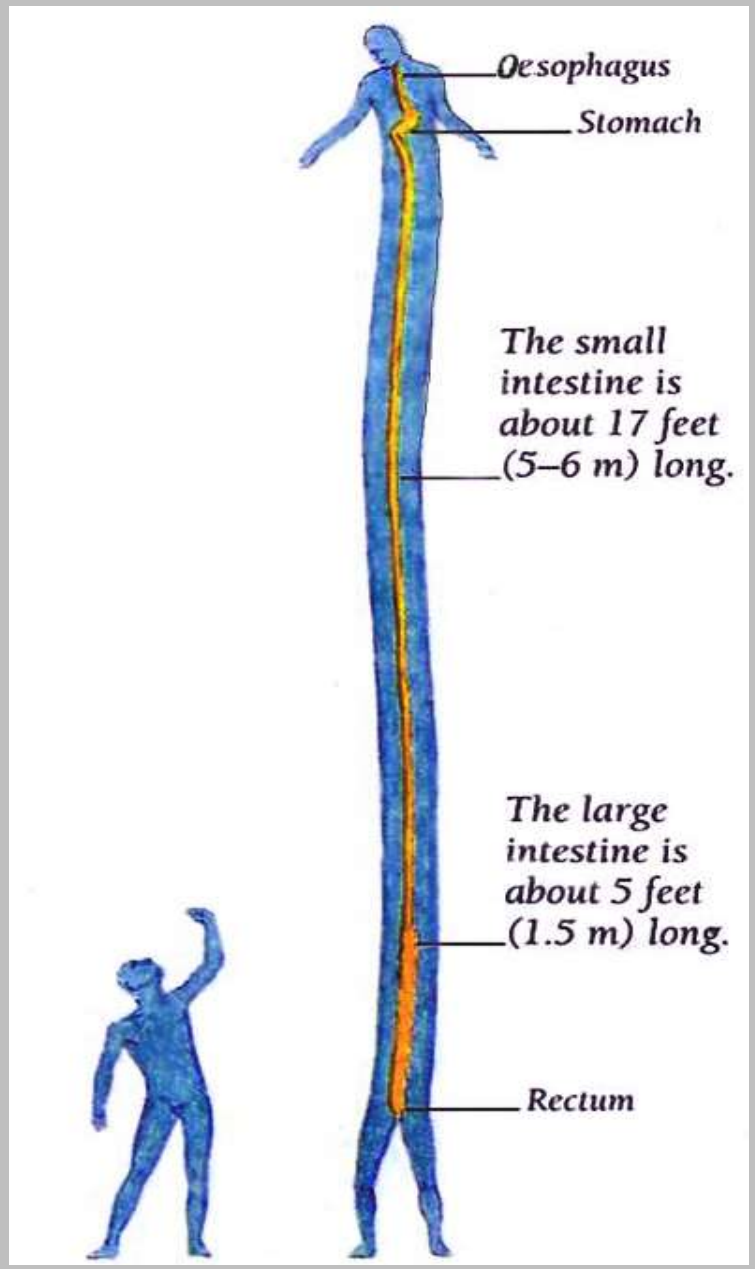
- Diagnosis and implications for management
- Endoscopic Ultrasound
- Advanced Endotherapy

Table 1 World Health Organization classification of gastrointestinal neuroendocrine tumors

Well-differentiated neuroendocrine neoplasms (NENs)		
	Ki-67 index (%)	Mitotic index/10 HPF
NET grade 1 (G1)	< 3	< 2
NET grade 2 (G2)	3-20	2-20
NET grade 3 (G3)	> 20	> 20
Poorly differentiated neuroendocrine neoplasms (NENs)		
	Ki-67 index (%)	Mitotic index/10 HPF
NEC grade 3	>20	>20
-Small cell type		
-Large cell type		
Mixed neuroendocrine neoplasms (MiNEN)		

Source: Adapted from WHO Classification of Tumors of Endocrine Organs, Fourth edition (2017)[14]

One big tube!



Oesophageal NETs

Patient	Age	Sex	KPS	ECOG	Stage	Histologic subtype	Associated neoplasm	Site	Survival (months)	Esophagec-tomy	Chemothe-rapy	Radiothe-raphy
1	79	M	50	4	Unstaged	SCCE	No	Lower	2	No	No	No
2	65	M	90	1	IIIA	SCCE	No	Middle	Alive at 26 months	Yes	No	No
3	60	M	80	1	IIIB	LCCE	No	Middle and lower	13	No	IP	30 cGy
4	65	M	30	4	IA	Carcinoid	No	Lower	7	No	No	No
5	75	F	90	1	IIA	LCCE	No	Lower	13	Yes	IP, PC	45 cGy
6	51	M	100	0	IIIC	SCCE	No	Upper and middle	Lost to follow-up at 4 months	No	EP	No
7	58	M	80	2	IV	SCCE	SCC	Middle	2	No	No	No
8	64	M	100	0	IIIA	SCCE	SCC	Middle and lower	35	Yes	IP, PT	45 cGy
9	47	M	100	0	IV	SCCE	No	Lower	10	No	IP, PT	50.4 cGy
10	78	F	70	1	IV	SCCE	SCC	Lower	13	No	IP, PT	45 cGy
11	75	M	80	1	IIIC	SCCE	No	Upper and middle	12	No	IP	45 cGy
12	80	F	50	3	IV	SCCE	SCC	Middle	6	No	No	No
13	76	M	60	3	IV	SCCE	No	Middle	5	No	IP	No
14	69	M	90	1	IIIB	LCCE	EA	Lower	18	Yes	XP (neoadjuvant), IP	No

Rare
Aggressive
Often advanced
Poor prognosis

Tustumi et al
Arch Gastro 2016

Types of Gastric NEN

Most G-NENs are incidentally diagnosed during endoscopies 0.6% to 2% of gastric polyp case

Table 2 Summary of different types of gastric neuroendocrine tumors

	Type I	Type II	Type III	Type IV
Distribution	70% to 80% of all GNETs	5% to 6% of all GNETs	15% to 20% of all GNETs	Most rare
Cell of origin; And location	ECL; Gastric body and fundus	ECL; Gastric body and fundus	ECL in most cases; Anywhere in stomach	Non-ECL; Anywhere in stomach
Gastrin status	Hypergastrinemia	Hypergastrinemia	Normogastrinemia	Hypergastrinemia -1/3rd of cases
Gastric mucosa	Atrophic	Hypertrophic	Normal	Atrophic most of the time but can be hypertrophic
Endoscopically	Multiple subcentimeter polypoid lesions	Multiple small (1 to 2 cm) polypoid lesions	Large (> 2 cm), solitary polypoid lesion	Large (> 4 cm) polypoid lesion
Treatment	Polypectomy, EMR, ESD, wedge resection of stomach, gastric antrectomy	Surgical resection of gastrinoma and aggressive gastrectomy	Partial or total gastrectomy and regional lymphadenectomy, chemotherapy	Partial or total gastrectomy with regional lymphadenectomy followed by adjuvant chemotherapy

World J Gastrointest Oncol 2020 August 15; 12(8): 850-856

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TYPE I GASTRIC CARCINOID – case history

- 52y lady of Asian origin
- Investigation of anaemia
- Multiple <1cm polyps
- Histology: low grade gastric carcinoid

Surgeon advised total gastrectomy

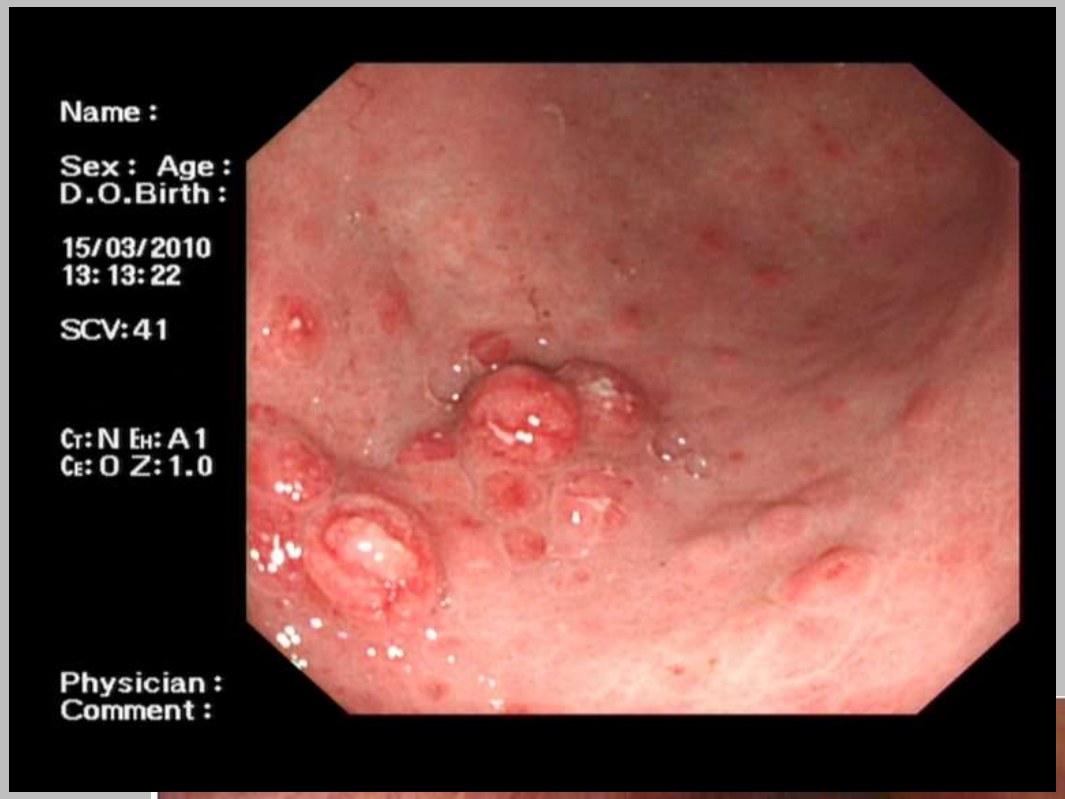
2nd opinon

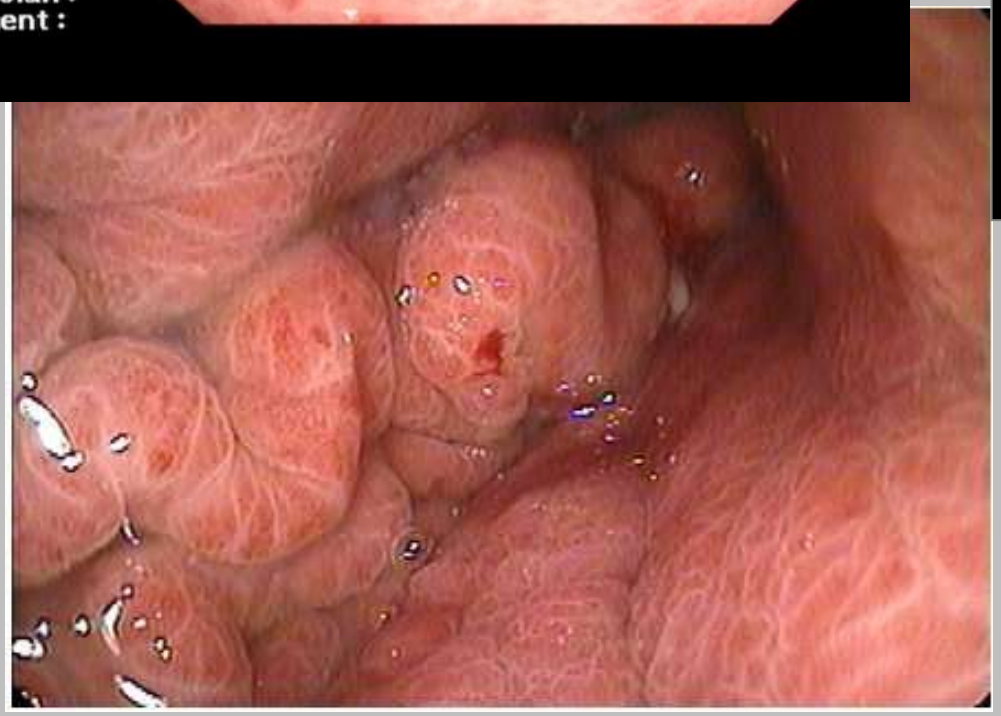
GPCA +ve = Autoimmune atrophic gastritis
Gastrin >400pmol/l
Gastric pH 7.0
Review histology = atrophic gastritis and
Type 1 Gastric Carcinoid – Low grade (Ki67 <2%)
Biology is benign >98%
Management: annual endoscopy

Understand biology

refer to specialist centres

Gastric type 2 NET





DUODENAL NENs

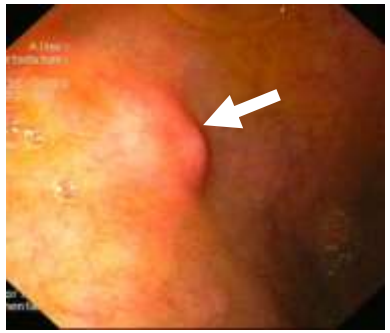
Table 3 Summary of different types of duodenal neuroendocrine tumors

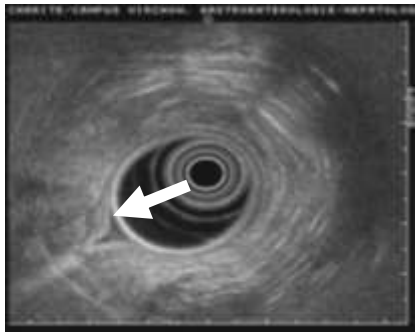
	Gastrinomas	Somatostatinoma	Gangliocytic paraganglioma	Non-functioning d-NETs	Duodenal NECs
Location	Proximal duodenum. > 80% gastrinoma triangle	Ampullary or peri-ampullary region	Peri-ampullary region	Proximal duodenum	Peri-ampullary region
Presenting symptoms	Chronic diarrhea, recurrent and refractory peptic ulcer disease, gastroesophageal reflux disease	Nausea, abdominal pain, weight loss, obstructive jaundice or very rarely somatostatinoma syndrome	Asymptomatic, gastrointestinal bleeding, anemia, abdominal pain	Asymptomatic or nausea, vomiting	Asymptomatic, nausea, vomiting, gastrointestinal bleeding
Diagnosis	BAO/MAO > 0.6, positive Secretin suppression test, EUS, somatostatin receptor scintigraphy (SRS), CT, MRI, selective angiography, Indium 111-labeled diethylenetriamine penta-acetic acid (DTPA) octreotide and (68)Ga-DOTATE PET/CT scan	CT, MRI, endoscopy, EUS-FNA	Endoscopy, EUS-FNA, CT	Endoscopy, EUS-FNA	Endoscopy, EUS-FNA
Treatment	Surgical resection or enucleation of the tumor without pancreaticoduodenectomy for nonmetastatic duodenal gastrinoma. In patients with duodenal gastrinoma with hepatic metastasis treatment options include hormonal therapy with octreotide, chemotherapy (streptozocin, doxorubicin, 5- fluorouracil), radiotherapy with yttrium 90-DOTA-lanreotide, hepatic embolization alone or with chemoembolization, cytoreductive surgery and liver transplantation	Endoscopic resection should be adequate if the NET is less than 1 cm. Transduodenal excision should be done for 1-2 cm tumor. But Whipple's surgery with local lymph node resection should be considered for more than 2 cm tumor	Endoscopic resection or radical excision including pancreaticoduodenectomy depending on the size, depth of invasion and lymph node metastasis	Transduodenal resection is indicated for d-NETs invading the muscularis propria. Radial surgery is advocated for d-NETs > 2 cm in diameter, d-NETs with lymph nodes involvement and all peri-ampullary d-NETs	radical surgery or chemotherapy

World J Gastrointest Oncol 2020 August 15; 12(8): 791-807

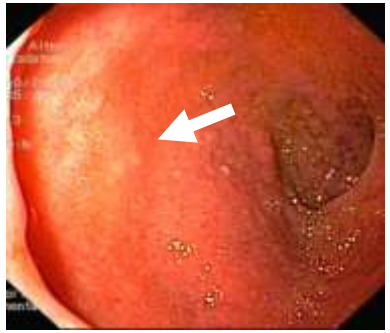
Duodenal NET: Endoscopy & Imaging

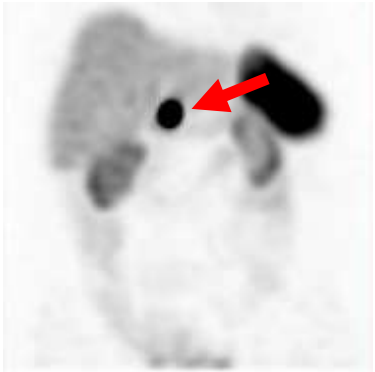
endoscopic finding 2004:

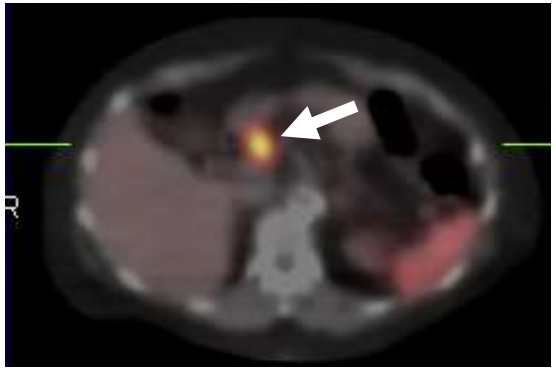




3 months after forceps biopsy:



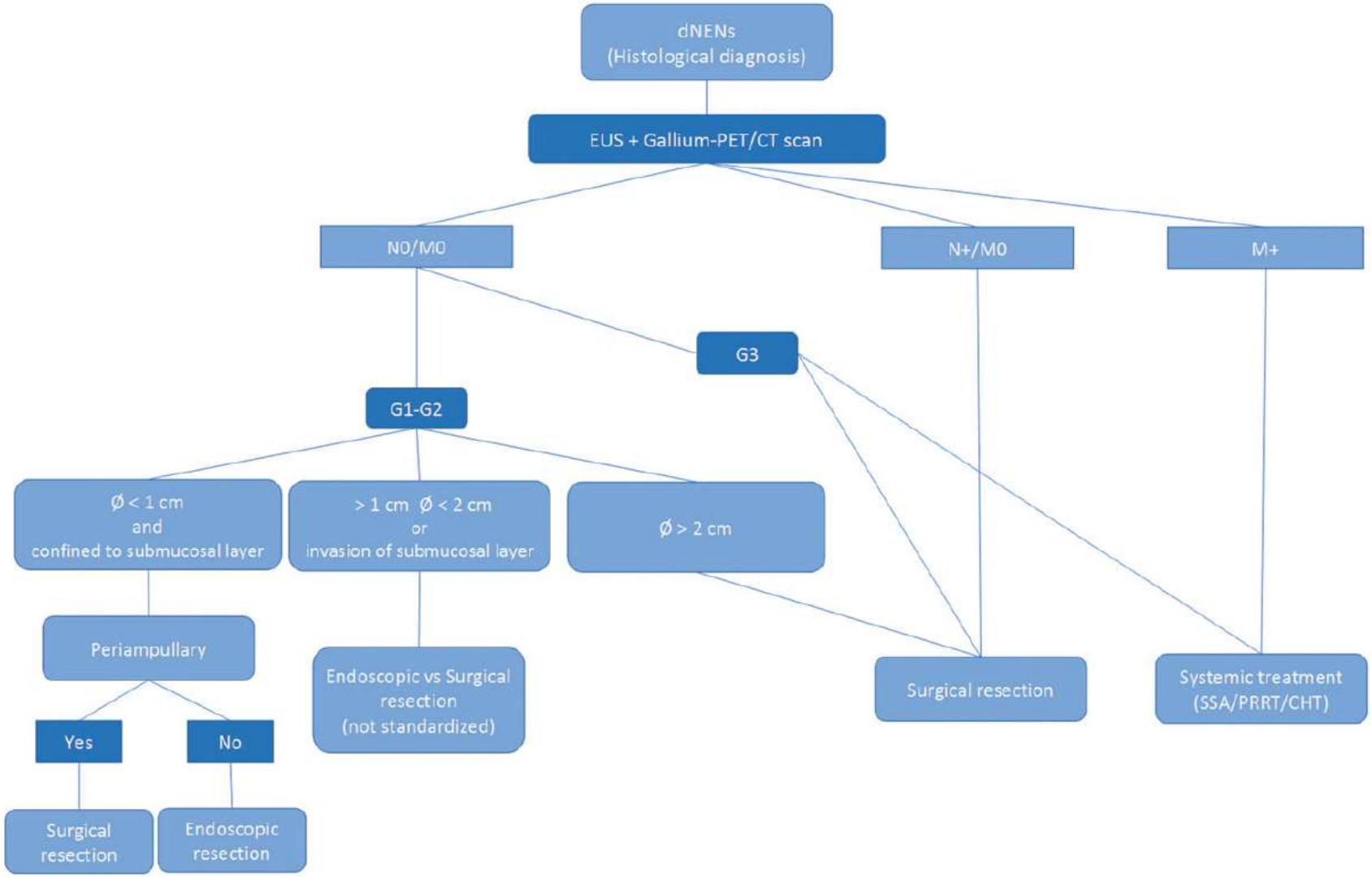




pT1 cN1 cM0 G1 Rx

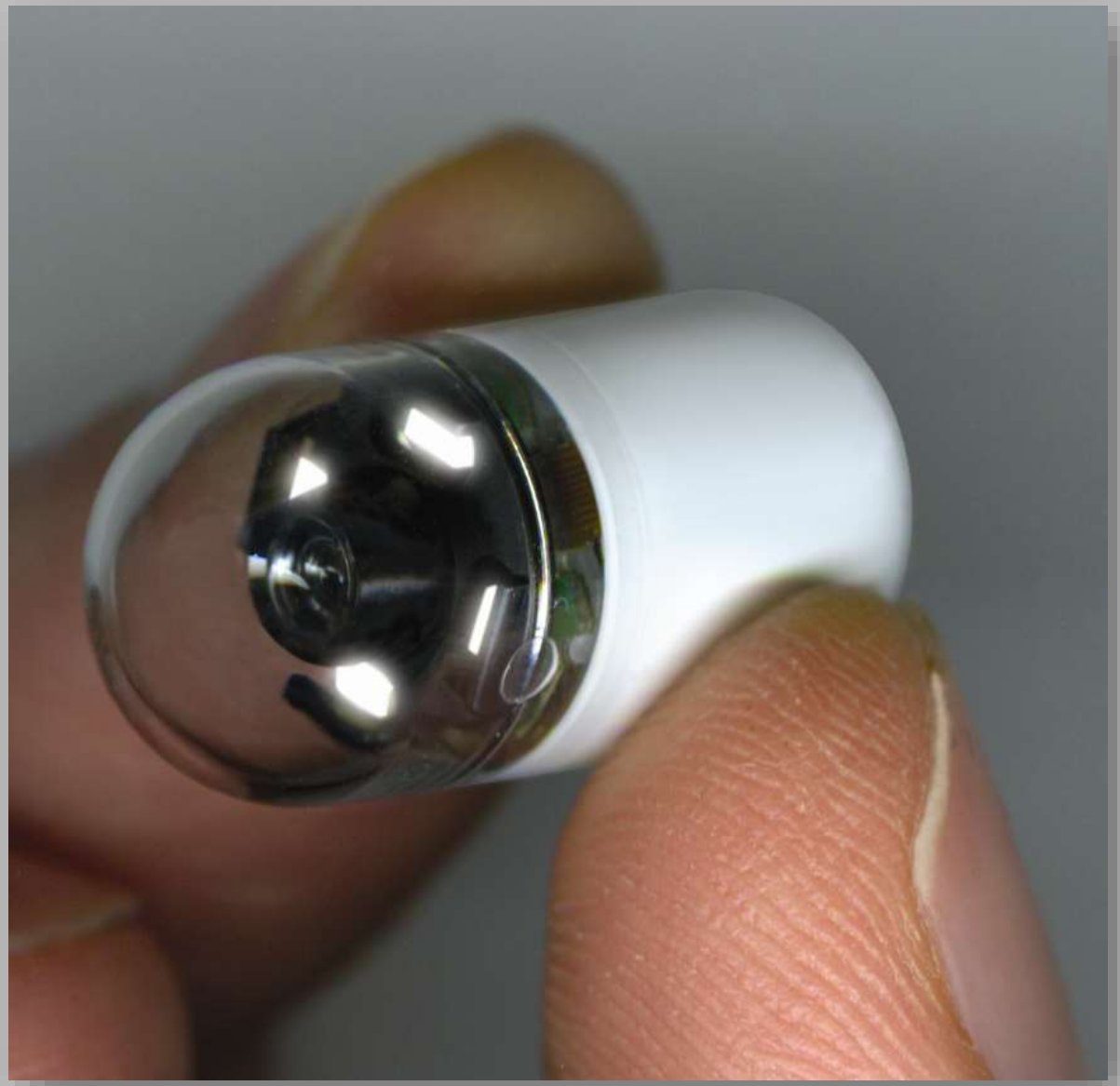
Pape Charite Berlin 2013

Duodenal NETs



What about surveillance <1cm?

Rossi Scan J Gastro 2018



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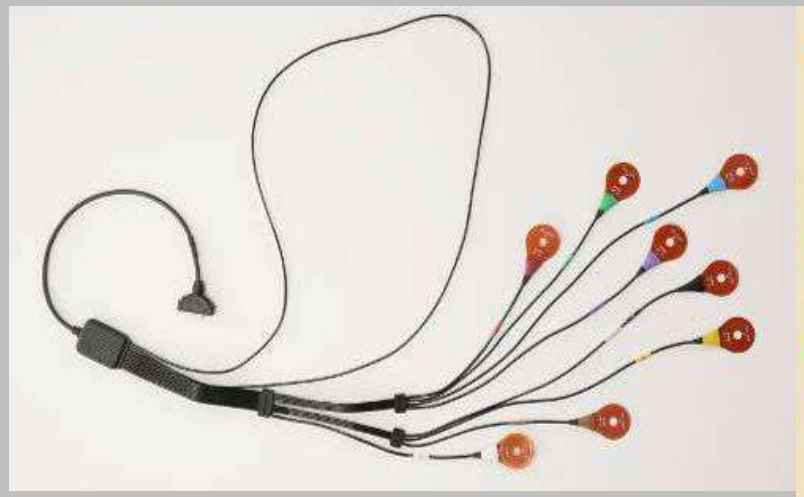

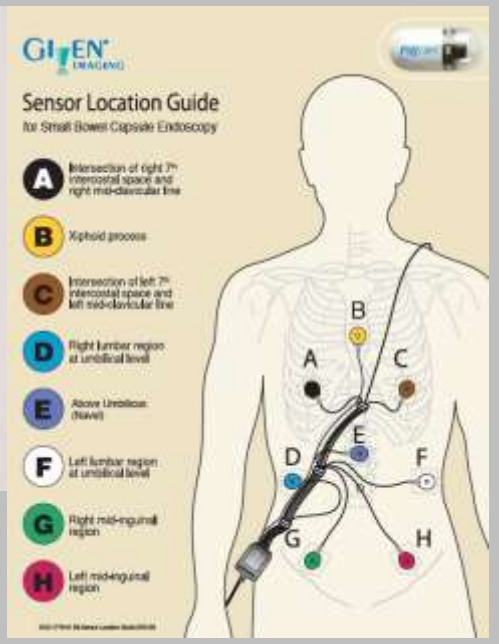

Image: courtesy of NC Carolyn Davison, South Tyneside NHS FT

Lumley Castle & London, European Capsule Endoscopy Course

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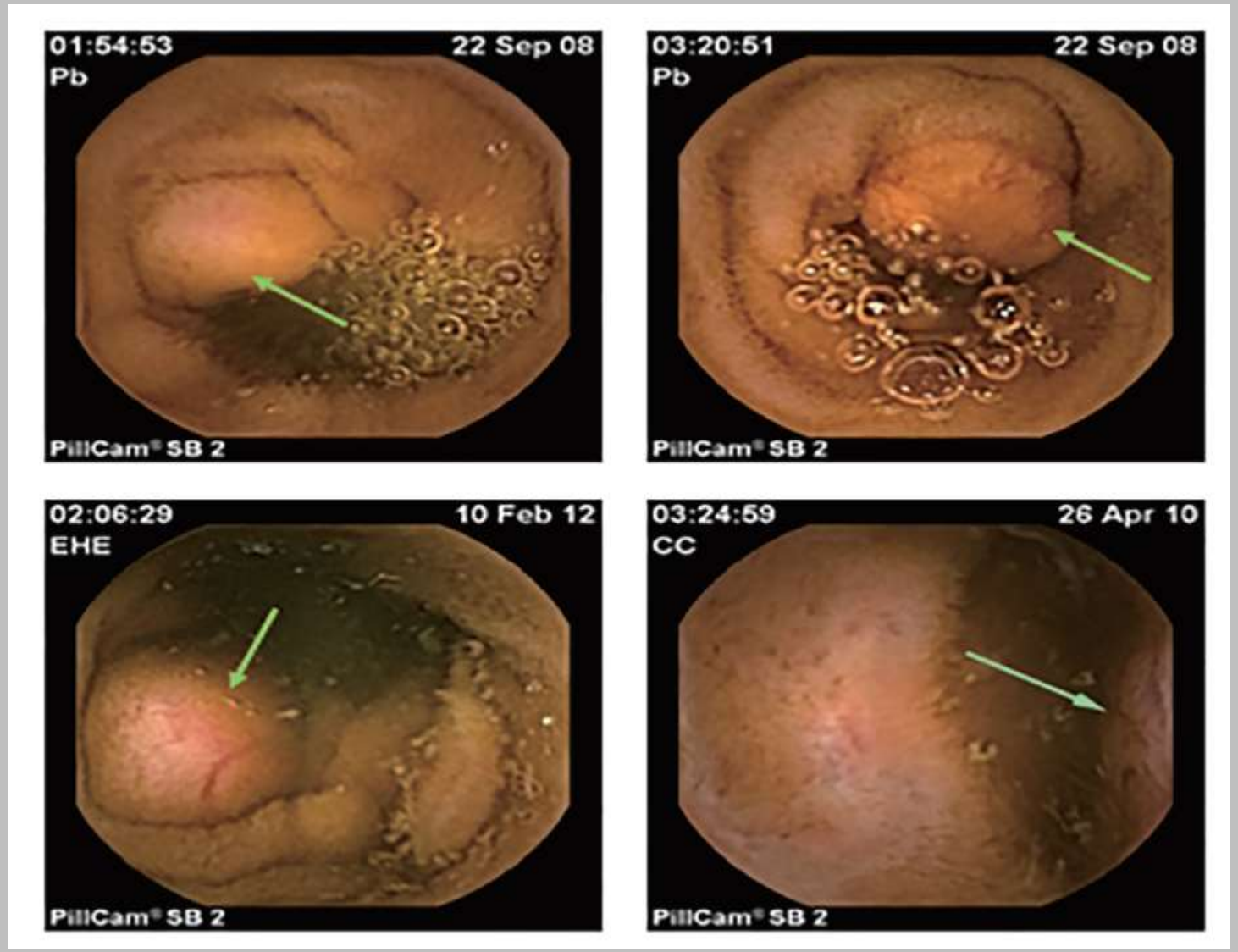
PillCam SB3™ (Given Imaging Ltd, Israel)
CMOS; 26 x 11 mm; view-angle: **156°**; 2fps;
max recording time: 11 hours.

Endocapsule™ (Olympus, Japan)
CCD; 24 x 11 mm; view-angle: 145°; 2fps;
max recording time: 8 hours.

OMOM Capsule Endoscope™ (Jinshan Group, China)
CMOS; 27.9 x 13 mm; view-angle: 140°; 0.5-2fps;
max recording time: 7 hours.

Mirocam™ (Intromedic, Seoul, Korea)
CMOS; 24 x 11 mm; view-angle: 150°; 3fps;
max recording time: 11 hours.

Small bowel NETs detected on capsule endoscopy



Gastroenterol Res. 2017;10(6):347-351

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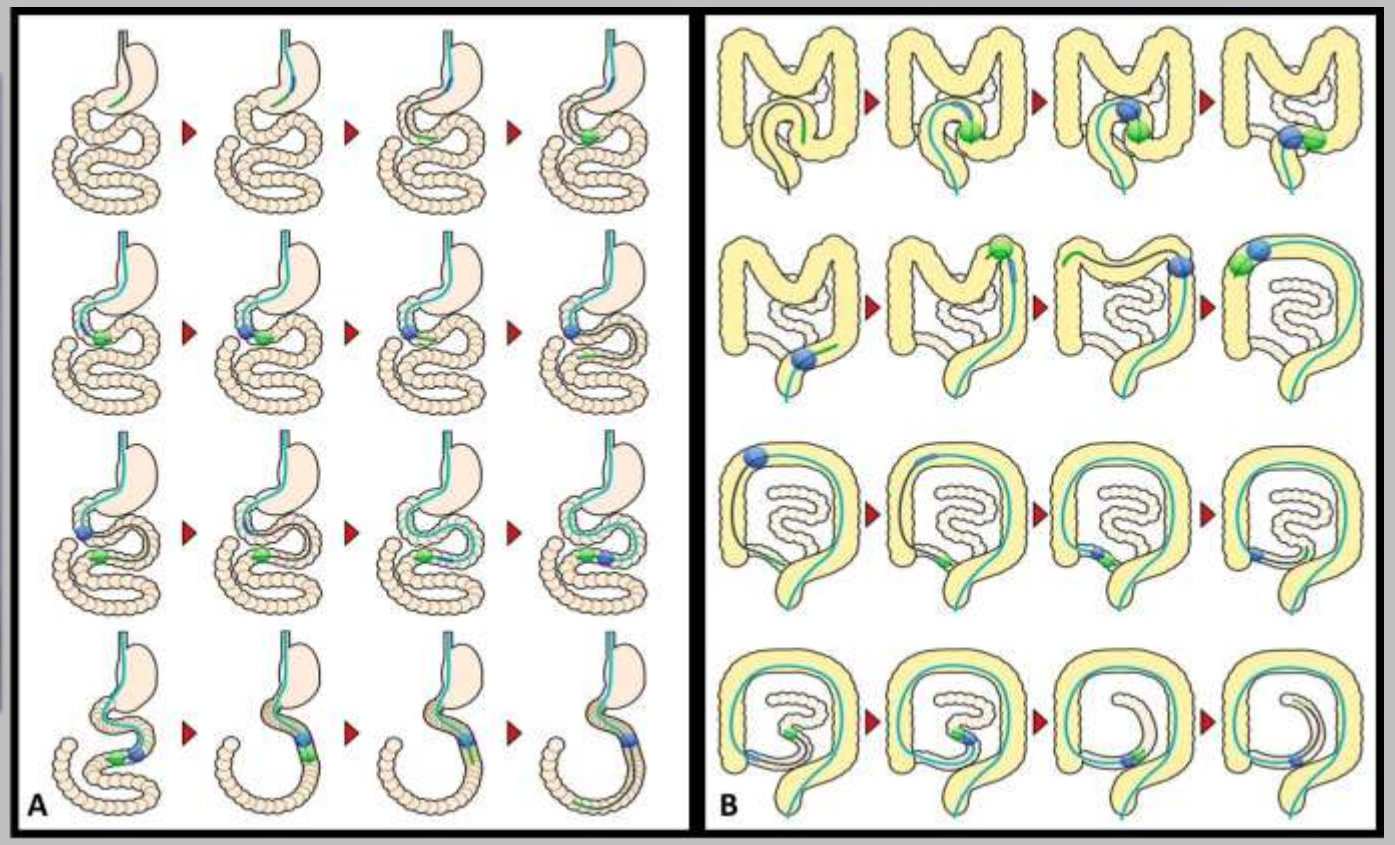
Double Balloon Enteroscopy (DBE)



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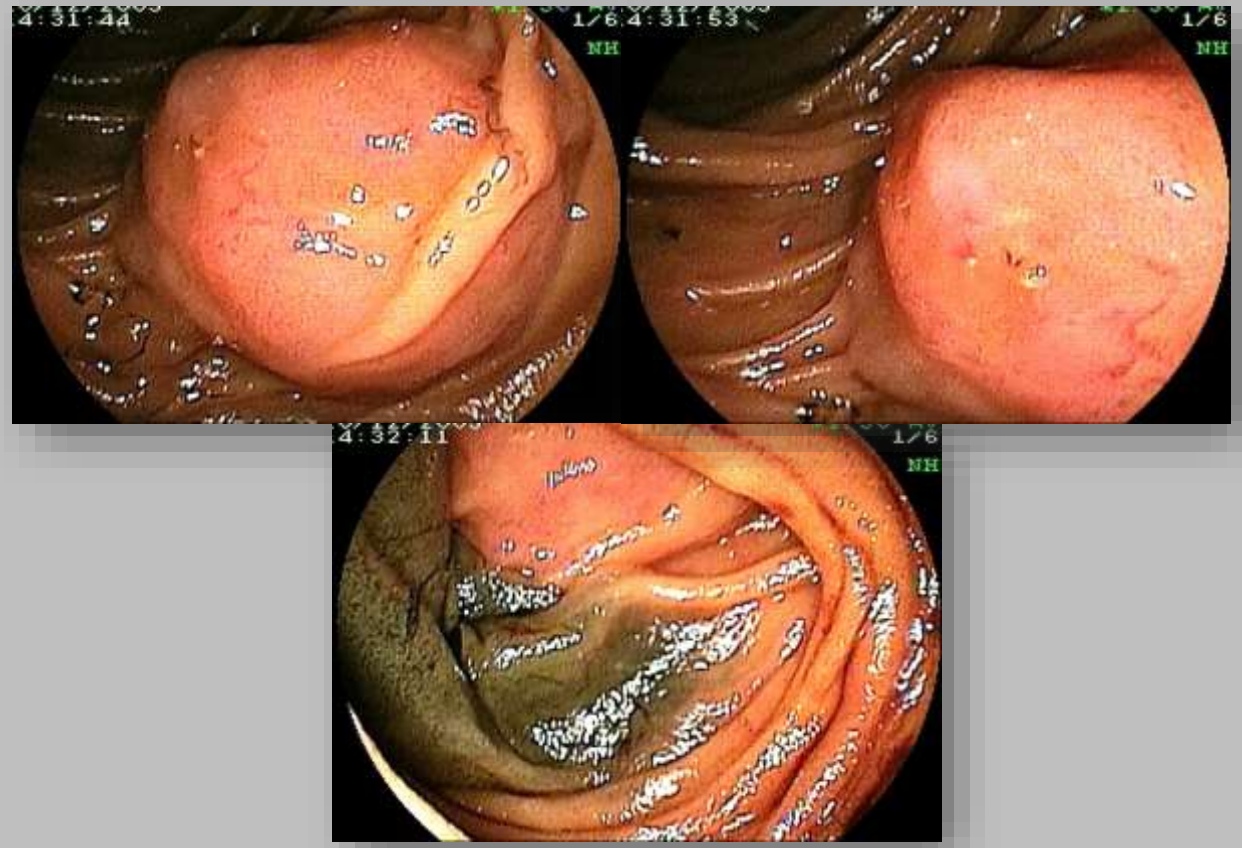
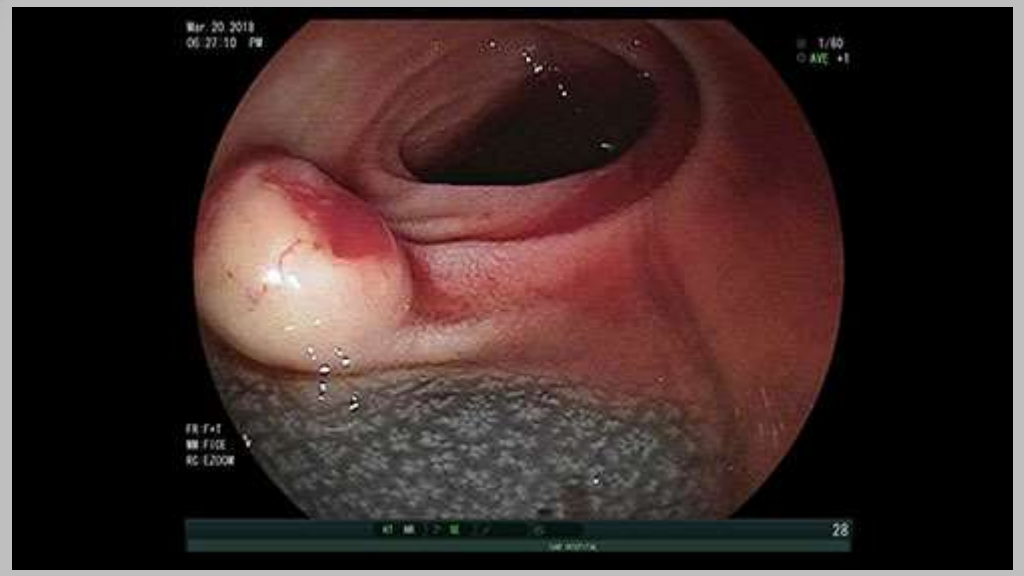
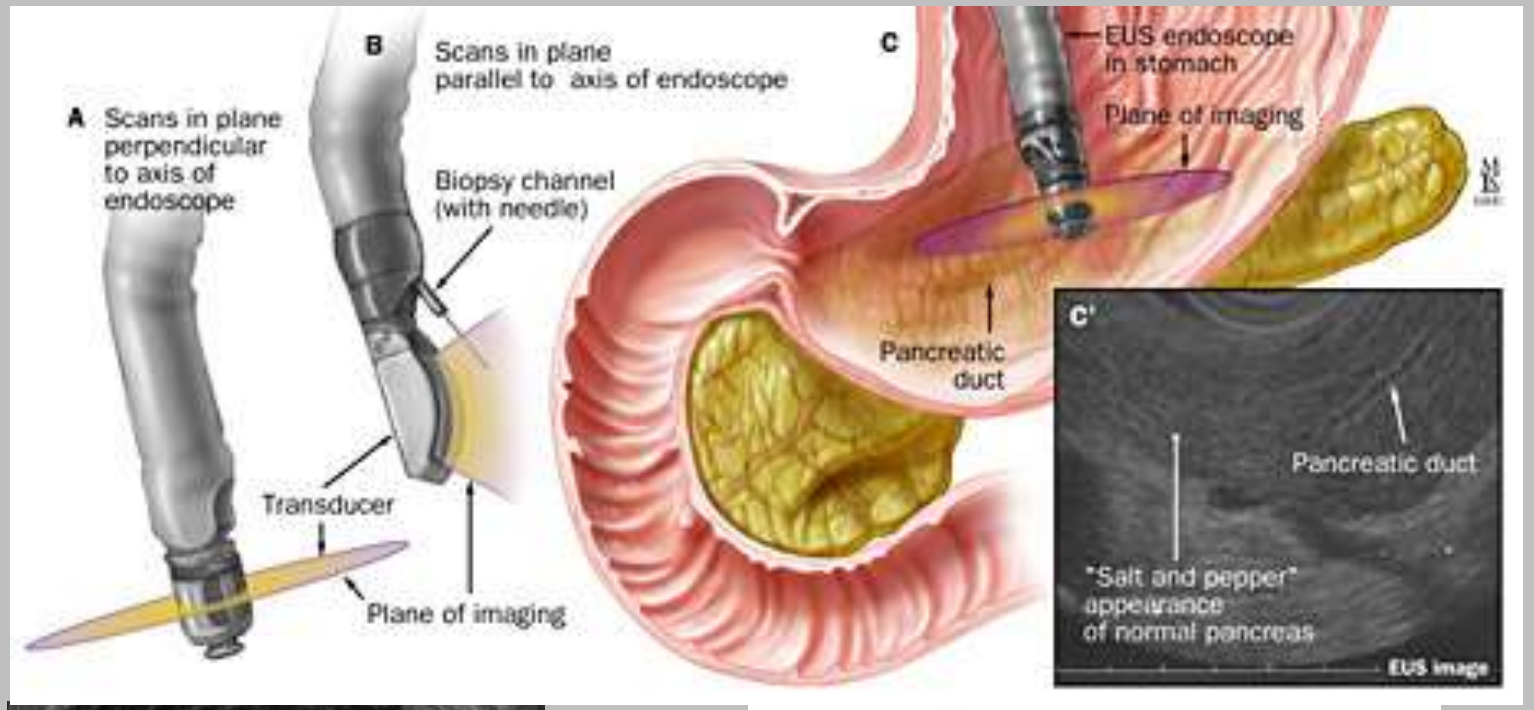
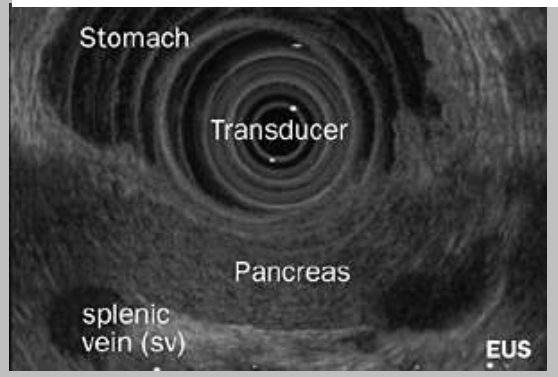
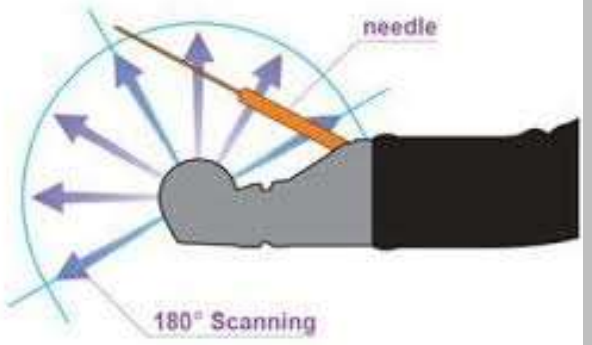




Upper GI Endoscopic Ultrasound







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ENDOSCOPIC ULTRASOUND (EUS)

EUS appearance of pancreatic neck gastrinoma 1.5x2.4cm

Anderson *Am J Gastro* 2000

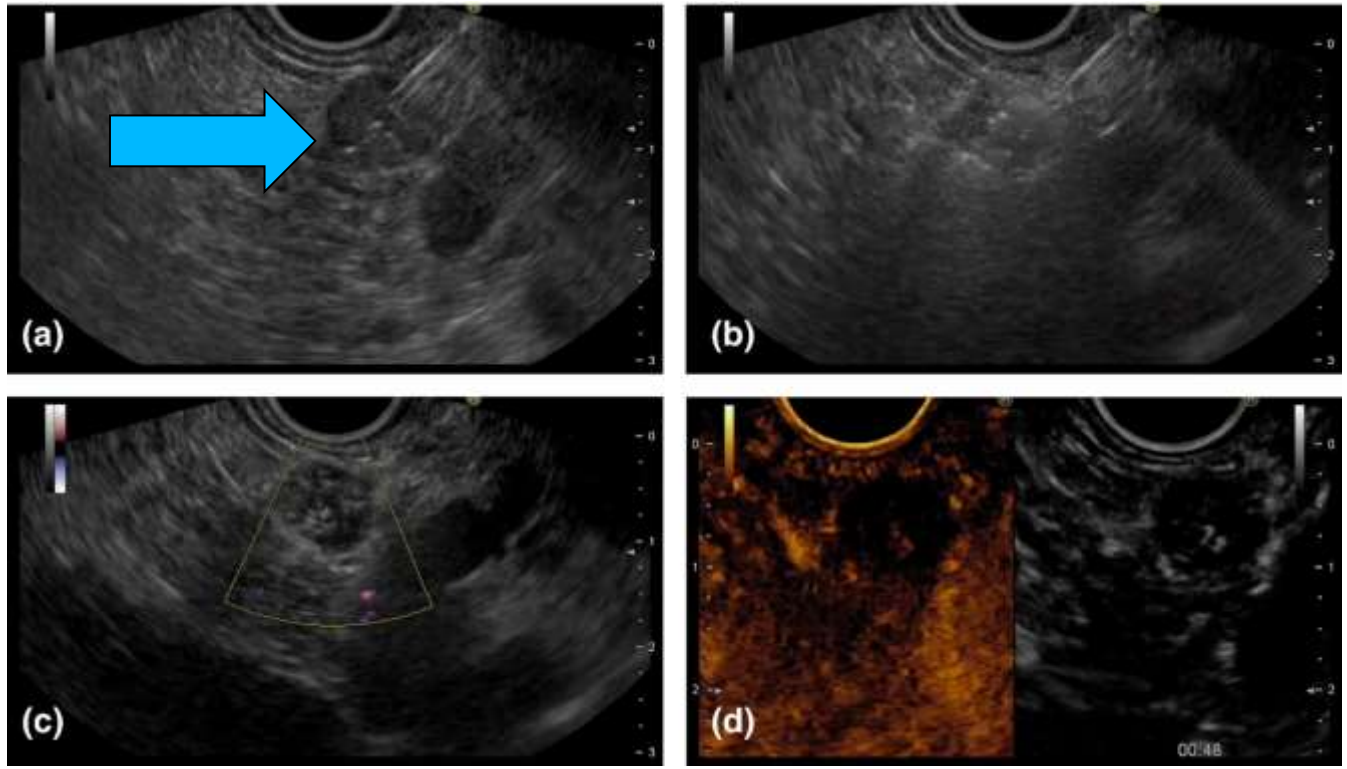
EUS

Gastric carcinoids – depth of invasion

Pancreatic NETs – location/biopsy/staging – contrast studies for insulinoma (Sonovue™ microbubbles)

Rectal carcinoid – depth of invasion and local LNs - staging

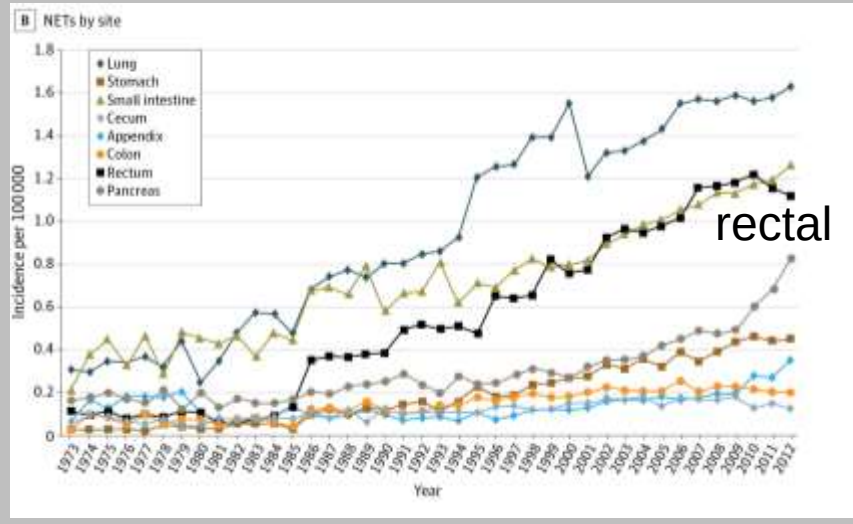
Interventional endoscopic ultrasound for pancreatic neuroendocrine neoplasms



Endoscopic ultrasound (EUS)-guided RFA ablation of a small pancreatic insulinoma:
(A) the EUSRA 19G needle is inserted into the lesion;
(B) after RFA application there is a hyperechoic area extending to the borders of the lesion;
(C) post-treatment Power Doppler examination during EUS showing lack of vascular signal;
(D) contrast-enhanced EUS demonstrating lack of enhancement suggestive of a successful of treatment, 1 month after radiofrequency ablation ablation.

Digestive Endoscopy, First published: 29 January 2020, DOI: (10.1111/den.13635)

Rectal NETs



Rectal NETs represent 1.8% of all rectal neoplasms (*Yamagishi et al 2012)*

Based on US-based SEER database reporting, the incidence is 1–2 per 100,000 population per year (1988–2012), (*McConnell et al, 2016)*

Rectal NETs make up 35% of GEP-NETs overall, but >70% of all GEP-NETs in Japanese/South Asian populations; also more prevalent black afro-carribean origin

>50% of rectal NETs are found incidentally

Bowel Cancer screening has found Incidence of 0.2% (*Jung et al Cancer 2014)*

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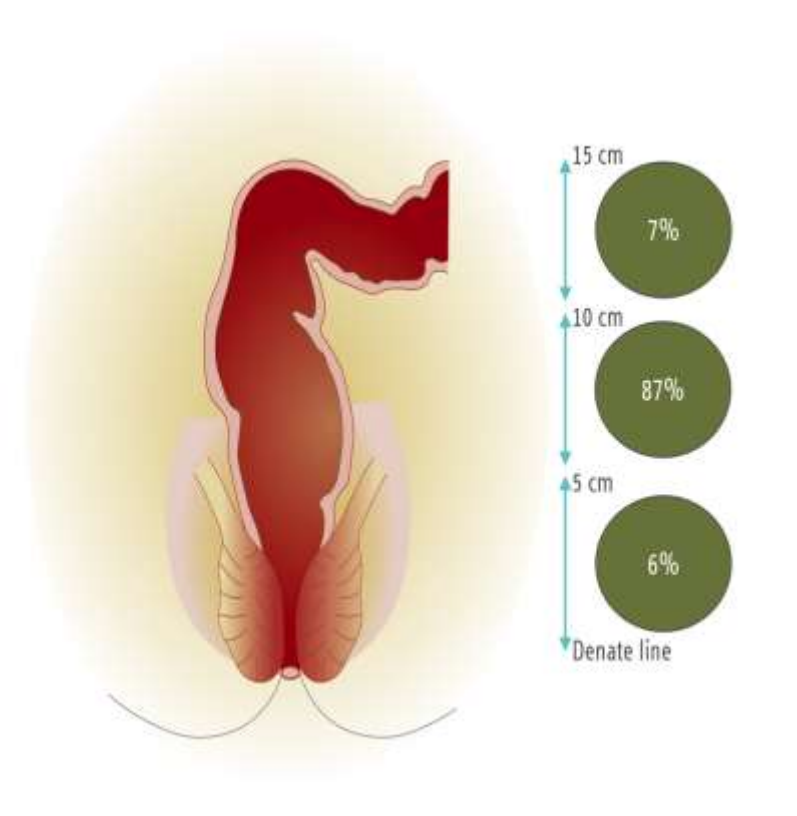
Location and Size



Size	Incidence
<1cm Lymph-node metastases Distant metastases	80–85% 2% (at diagnosis) 0.2% (lifetime)
1–2cm Lymph-node metastases Distant metastases	10–12% 19% (at diagnosis) 25% (lifetime)
>2cm Lymph-node metastases Distant metastases	6–8% 20% (at diagnosis) 60% (lifetime)

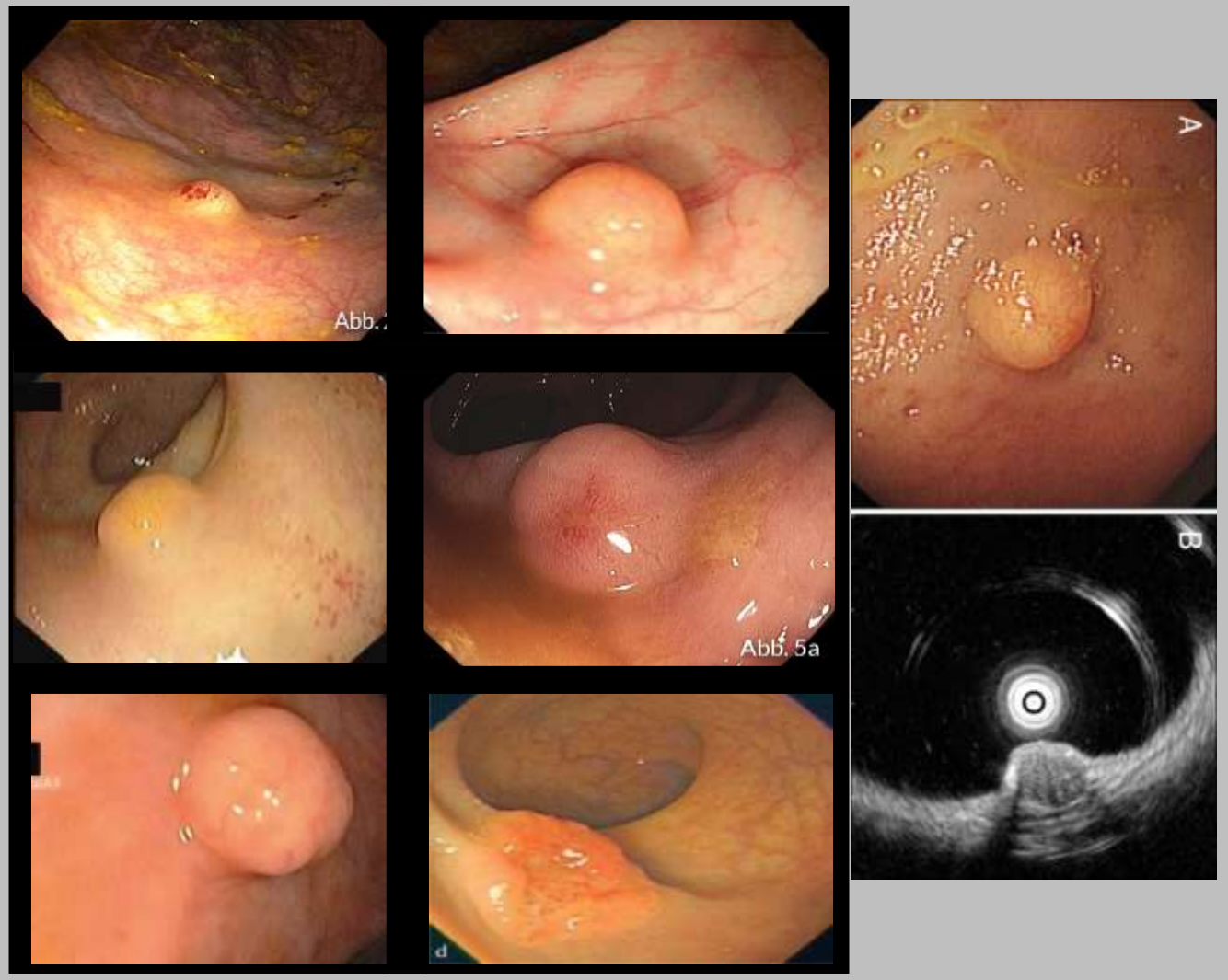
Adverse features

- Several features increase the risk of lymph-node involvement and the lifetime risk of distant metastases, which in turn has a bearing on survival

Endoscopy	Histology
Size > 1cm	Grade more than G1
Atypical appearance	Invasion of muscularis
Ulceration	Lympho-vascular or peri-neural invasion

Endoscopic appearance

- Typical
  - Yellowish submucosal lesion with reddish tinge
  - Smooth, round and mobile
  - Central punctum
  - Significant micro-vessel density
- Atypical
  - Ulceration
  - Bleeding
  - Associated with more-aggressive disease
- Appearance
  - 78% Typical
  - 10% Semi-pedunculated
  - 6% Ulcerated
  - 8% Erosive



Advanced Endotherapy

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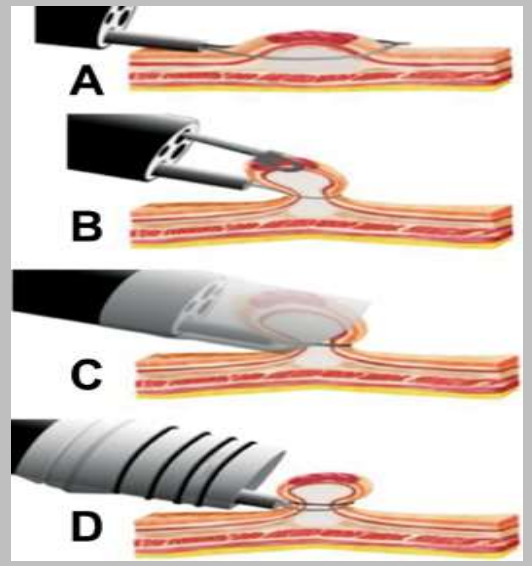
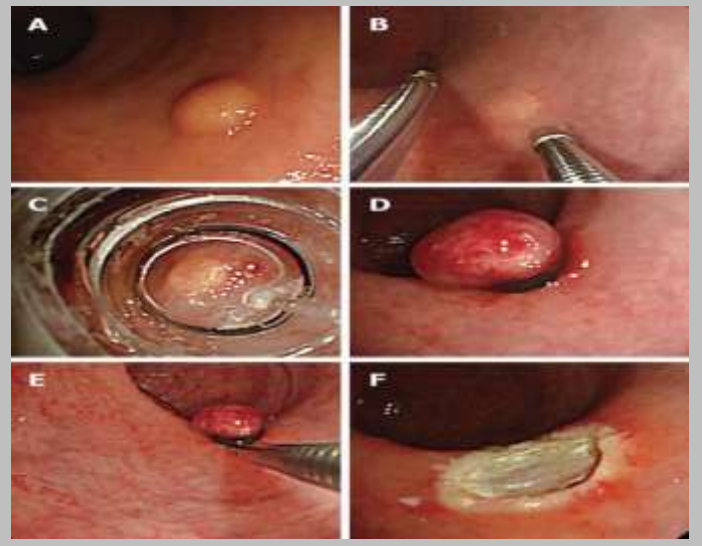
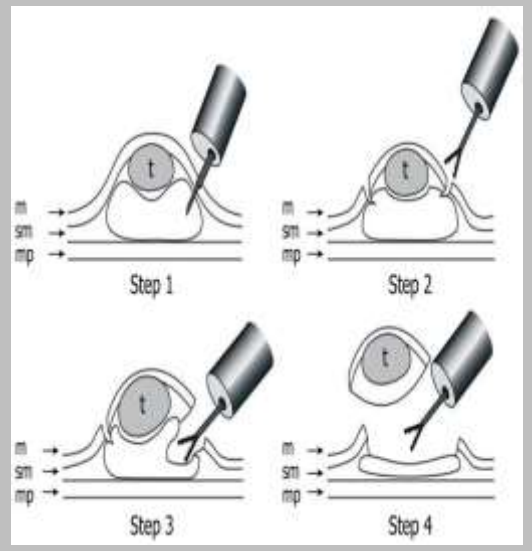
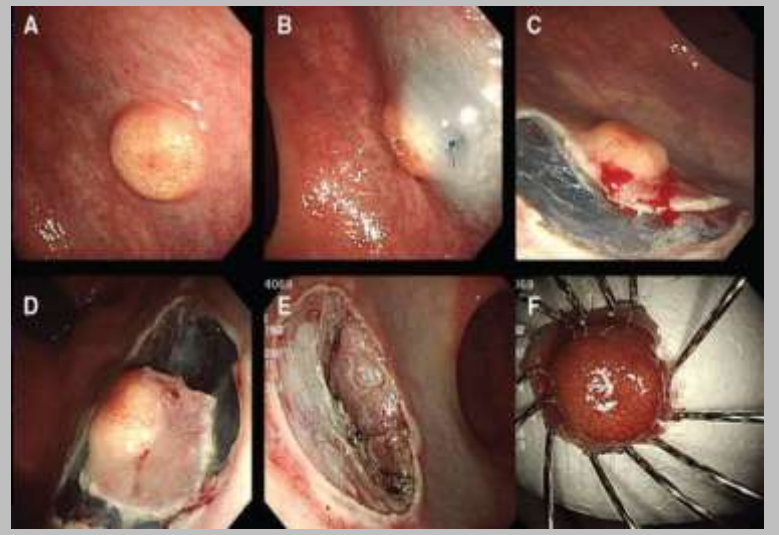
Endoscopic Mucosal Resection vs Endoscopic Submucosal Dissection









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EMR V ESD

Table 2 Clinical outcomes by endoscopic treatment modality *n* (%)

	EMR-C (*n* = 65)	ESD (*n* = 51)	*P* value
Procedure time (min), mean ± SD,	3.83 ± 1.17	14.43 ± 7.26	< 0.001
Complication	0 (0.0)	4 (7.8)	0.044
Bleeding	0	4 (7.8)	
Perforation	0	0	
Endoscopic complete resection	65/65 (100)	51/51 (100)	
Histologic complete resection	60/65 (92.3)	40/51 (78.4)	0.042
Vertical margin involvement	1 (1.5)	1 (2.0)	0.864
Lateral margin involvement	1 (1.5)	2 (3.9)	0.710
Vertical and Lateral margin involvement	0 (0.0)	2 (3.9)	0.159
Indeterminate margin	3 (4.6)	6 (11.8)	0.178
Vertical:Lateral:Vertical and Lateral, *n*	2:1:0	1:3:2	
Lymphovascular invasion	0	1	0.322

World J Gastroenterol 2015 August 21; 21(31): 9387-9393

Also
Transanal Endoscopic Microsurgery TEMs

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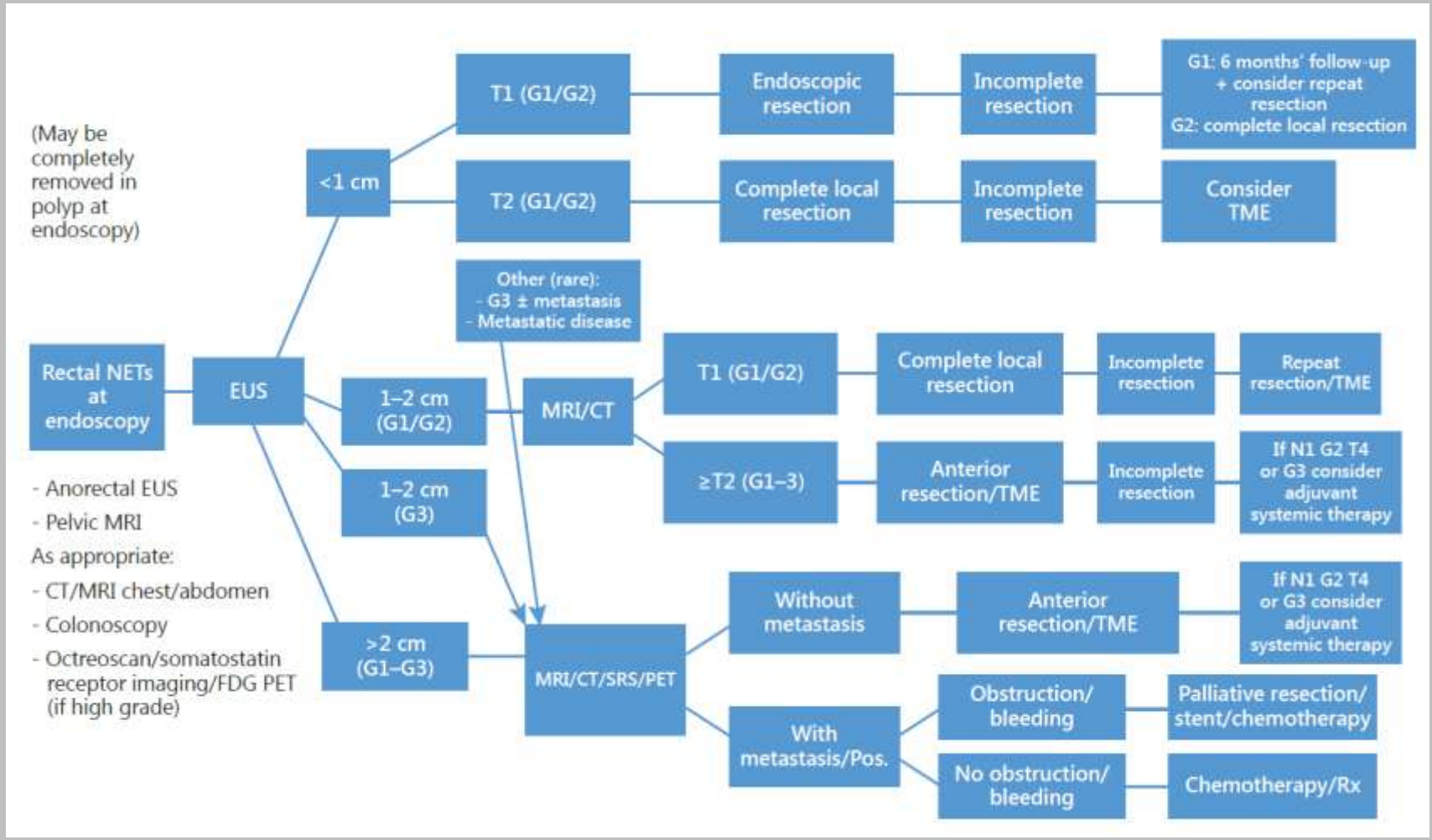
Summary: Management



Reproduced from Ramage JK, et al. Neuroendocrinology 2016; 103: 139–143. © (2016) Karger AG.

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Summary

- All cases should be reviewed by a NET pathologist and discussed in a NET MDT
- NETs often require staging with EUS (except those <0.5 cm in diameter)
- Lesions with adverse features cross-sectional imaging for metastases +/- Ga68 DOTATATE PET
- SURVEILLANCE may be appropriate for sub-cm G1 Duodenal NET
- Endoscopic resection: EMR V ESD
  - Depends on size and any adverse features
- Rectum: TEMs should be considered where endoscopic resection is incomplete or not possible
- Surgical Resection dependent on size and grade
- Follow-up tailored to each patient based on size and presence of adverse features at diagnosis

Neuroendocrine Tumour Unit

ENETS

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