

Endoscopic treatment of Gastrointestinal Neuroendocrine tumors (GI-NETs)



Apostolos Tsolakis M.D., Ph.D.

apostolos.tsolakis@ki.se or apobtsol@hotmail.com

Dept. of Oncology and Pathology, Karolinska Institute, Stockholm, Sweden

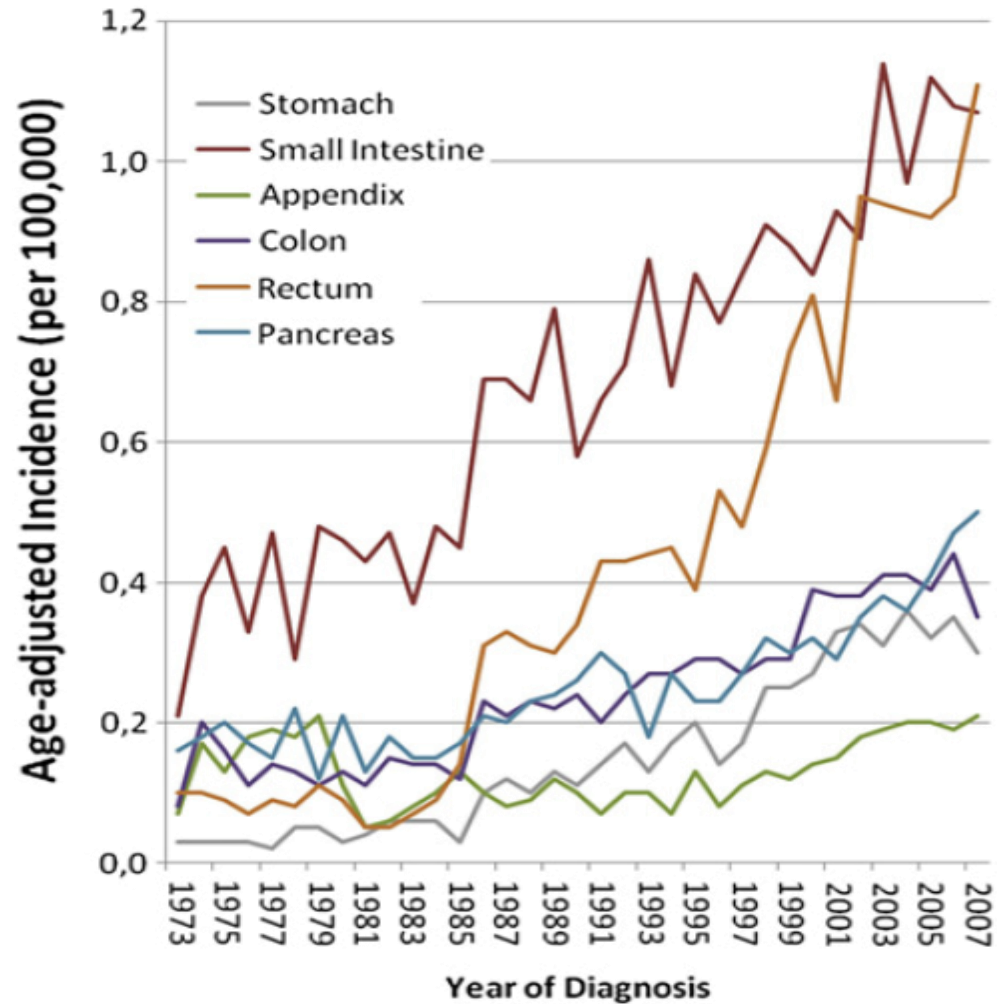
Overview

- Epidemiology/grading system of GEP NETs
- Endoscopic treatment of:
 - Esophageal NETs
 - Gastric NETs (GNETS)
 - Duodenal NETs (dNETs)
 - Rectal NETs
 - Pancreatic NETs (pNETs)



GEP, gastroenteropancreatic; NET, neuroendocrine tumor

Latest SEER, GEP NETs



Source: US SEER 9 database. Lawrence et al. *Endocrinol Metab Clin North Am.* 2011; 40(1):1-18, vii; Tsikitis VL, et al. *J Cancer.* 2012; 3: 292-302.

Grading system, incorporated by WHO 2010

Table 4 Grading proposal for foregut (neuro)endocrine tumors

Grade	Mitotic count (10 HPF) ^a	Ki-67 index (%) ^b
G1	<2	≤2
G2	2–20	3–20
G3	>20	>20

^a10 HPF: high power field=2 mm², at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density

^bMIB1 antibody; % of 2,000 tumor cells in areas of highest nuclear labeling

Table 7 Grading proposal for (neuro)endocrine tumors of ileum, appendix, colon and rectum

Grade	Mitotic count (10HPF)*	Ki-67 index (%)**
G1	<2	≤2
G2	2–20	3–20
G3	>20	>20

Esophageal NETs

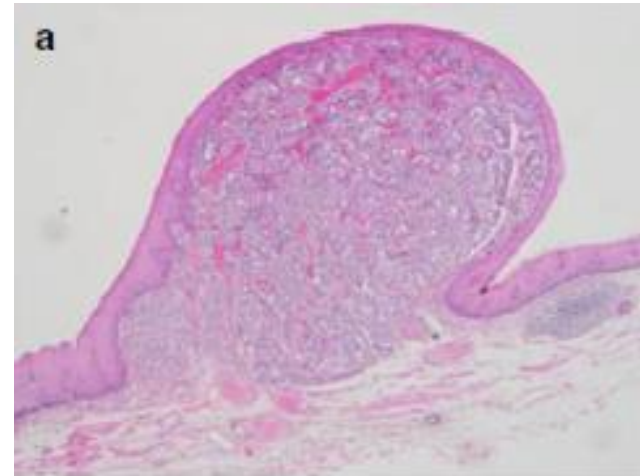
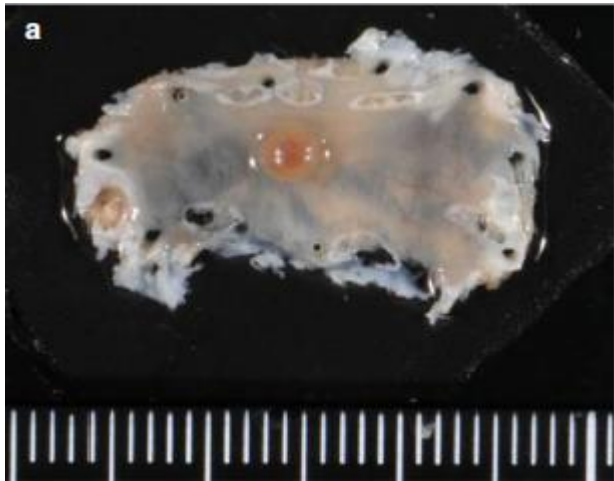
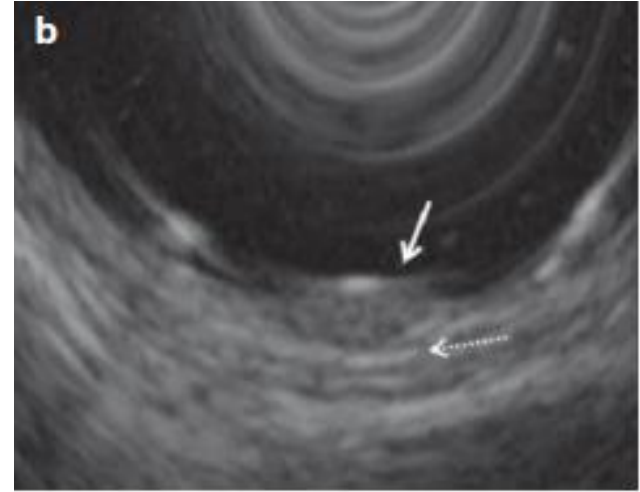
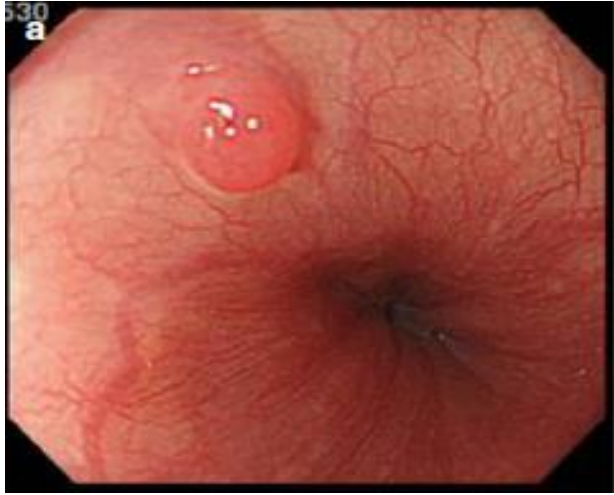


- Rare NETs that account around 1.8% of all GI NETs
- Well differentiated (NETs) and neuroendocrine carcinomas (NECs)
- Mainly located in the lower third of the esophagus
- Usually, the biochemical markers are within normal reference interval
- Mainly asymptomatic. If large may cause anemia and dysphagia

NET, neuroendocrine tumor



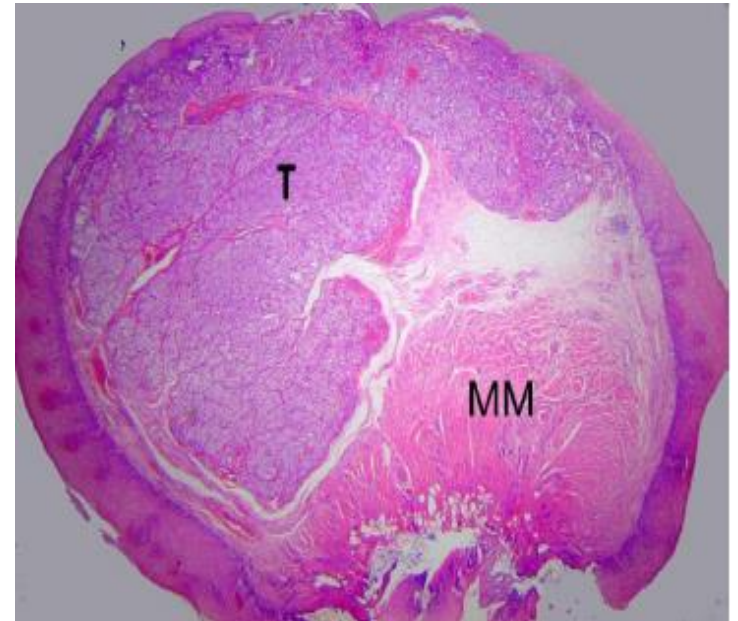
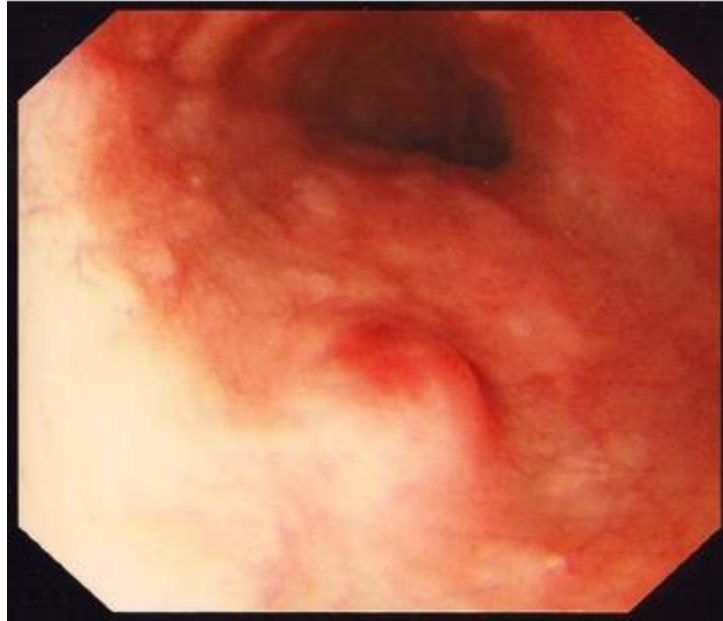
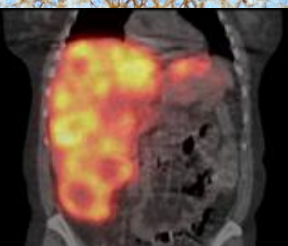
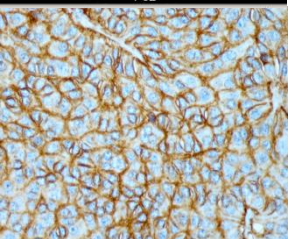
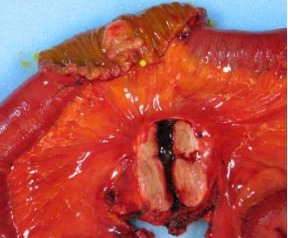
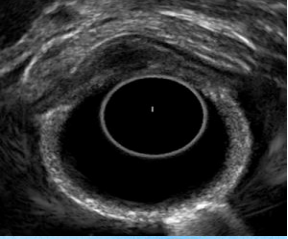
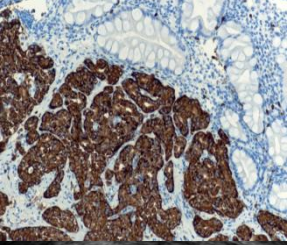
Endoscopic Submucosal Dissection (ESD) in esophageal NETs



Size <1cm, Ki67<1% (Grade 1), No lymphatic/angio-invasion

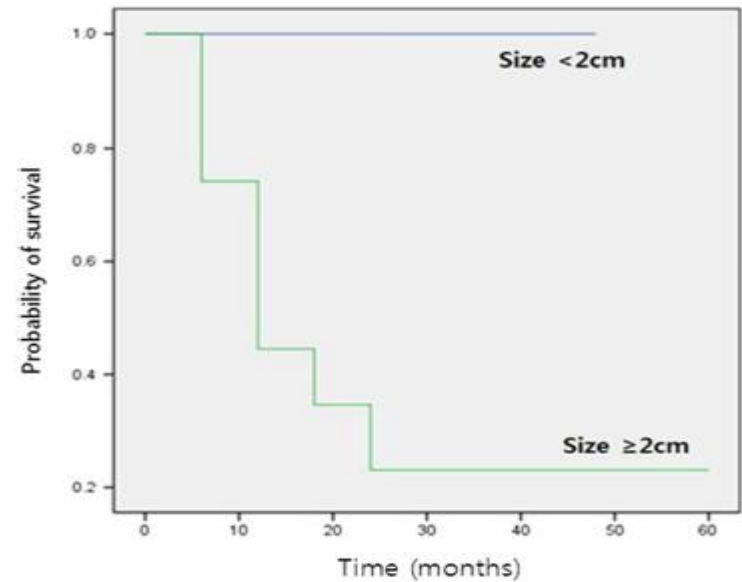
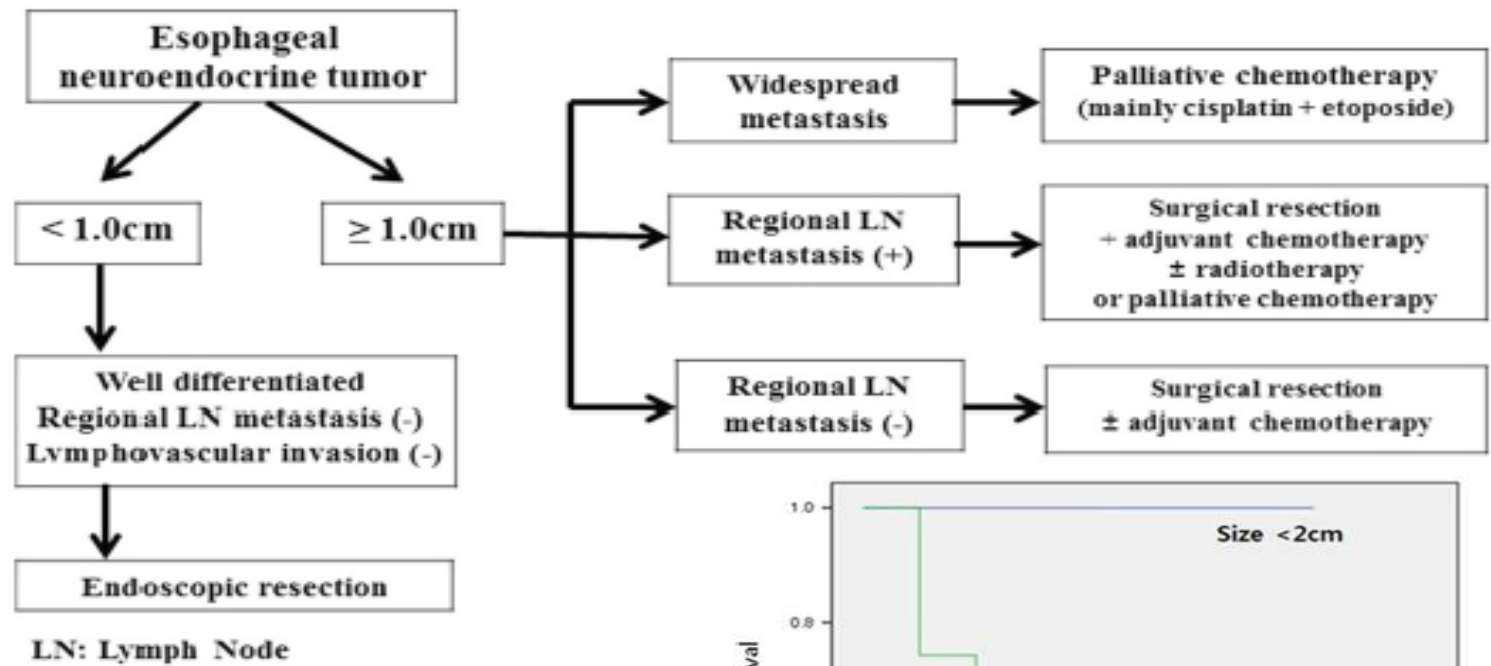
Yagi et al. Digestive Endoscopy 2015;27:527-530

Endoscopic Mucosal Resection (EMR)



Eccles JK, et al. BMJ Case Rep 2013

Guidelines for esophageal NETs



In general $\leq 1\text{cm}$ G1 lesions can be treated endoscopically

Disadvantage: Mixes NETs with NECs

Lee et al., *BMC Cancer* 2014;14:569-576

Gastric neuroendocrine tumors (GNETs)



Images courtesy of A. V. Tsolakis

Gastric NETs (GNETs) (WHO 2010 classification)

I) Neuroendocrine tumor (NET) (Ki67 G1:≤2, G2:3-20)

- Type 1 ECLomas (75-80% of all GNETs)
- Type 2 ECLomas (2-5% of all GNETs)
- Type 3 ECLomas (10-15% of all GNETs)
- Non ECLomas (ACTH-producing, EC tumors, Ghrelinomas etc.)

II) Neuroendocrine carcinoma (NEC) (~5%) (G3:Ki67>20)

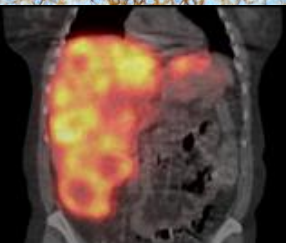
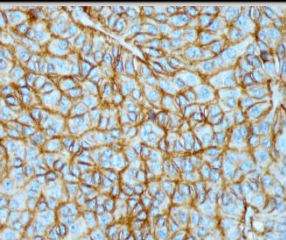
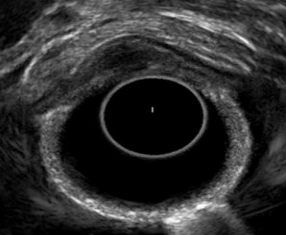
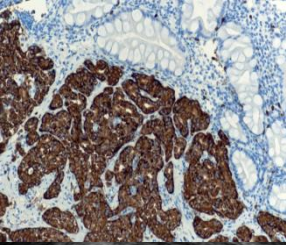
- Small-cell NECs (SC-NECs)
- Large-cell NECs (LC-NECs)

III) MANEC (Mixed adenoneuroendocrine carcinoma)

ACTH, adrenocorticotropic hormone; ECLoma, enterochromaffin-like (ECL) cell carcinoids

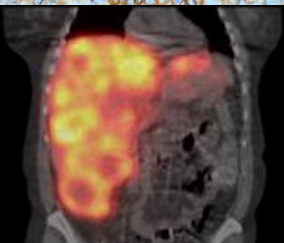
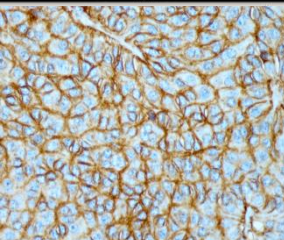
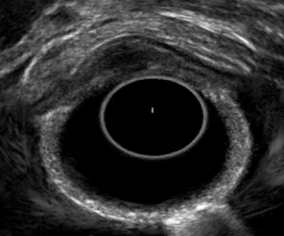
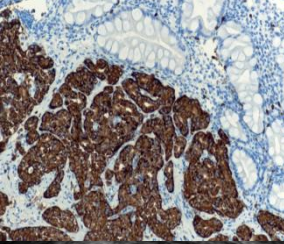
Rindi G. et al. In: *WHO Classification of Tumours of the Digestive System*, 4th ed, International Agency for Research on cancer (IARC), Lyon 2010. p.13.

Tsolakis AV et al., *JCEM* 2004;89(8):3739-44.



Characteristics of ECLomas

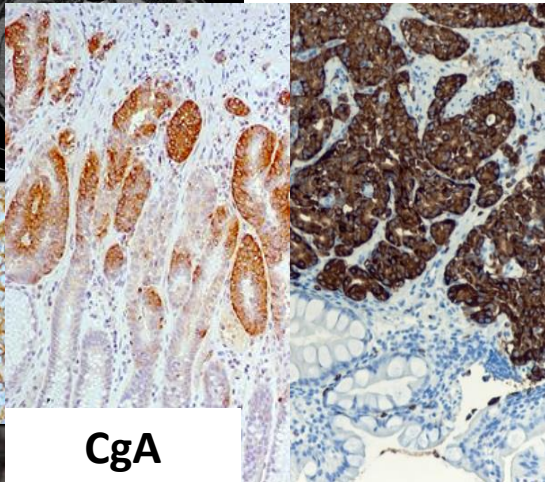
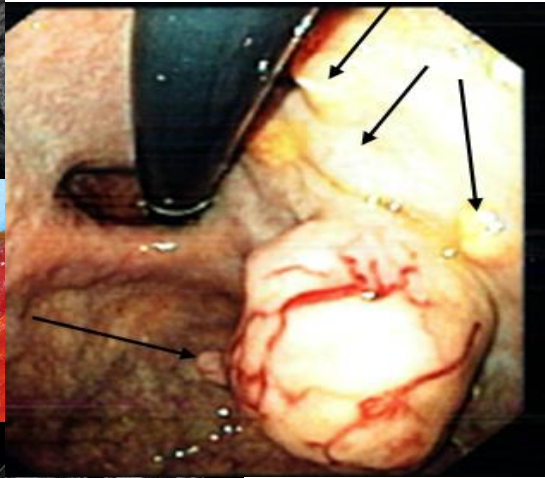
Characteristics of ECLomas			
	Type 1	Type 2	Type 3
Localization	Oxyntic mucosa	Oxyntic mucosa, (antrum)	Oxyntic mucosa, antrum
Tumor characteristics	Usually multiple	Usually multiple	Almost always solitary
Tumor size	<1-2cm	<1-2cm	>2cm
Histopathology	Hyperplasia, dysplasia, neoplasia	Hyperplasia, dysplasia, neoplasia	Normal adjacent mucosa
Endocrine-cell hyperplasia	ECL-, ghrelin-, gastrin-cells	ECL-, ghrelin-cells	Rarely ghrelin-cells
Biological behavior	Slow growth, rarely metastasizes	Slow growth, may metastasize	Aggressive
Gastrin levels	↑-↑↑	↑-↑↑-↑↑↑	Normal
Gastric acid output	Low or absent	High	Normal
Secretin test	Negative	Positive	Negative



GNETs (well differentiated)

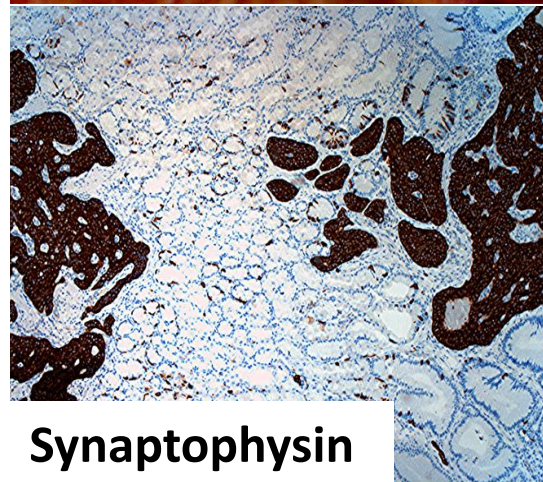
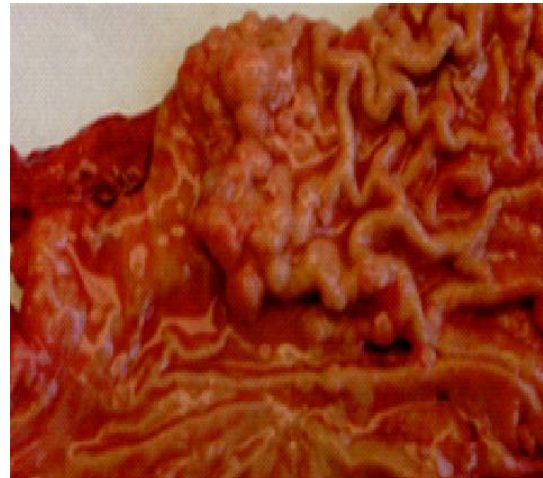
Types 1-3 ECLomas

Type 1 ECLoma (CAG-A)



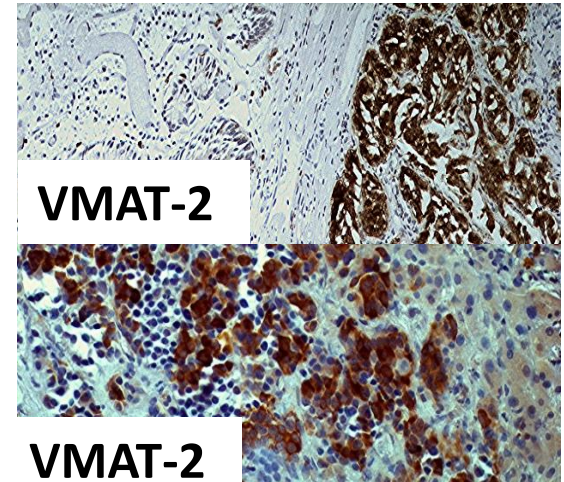
CgA

Type 2 ECLoma (MEN1/ZES)



Synaptophysin

Type 3 ECLoma (solitary)



VMAT-2

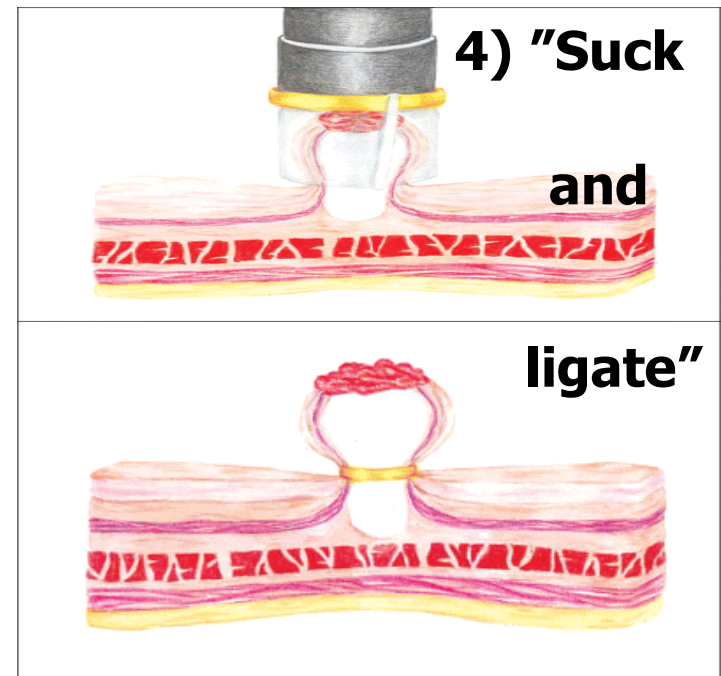
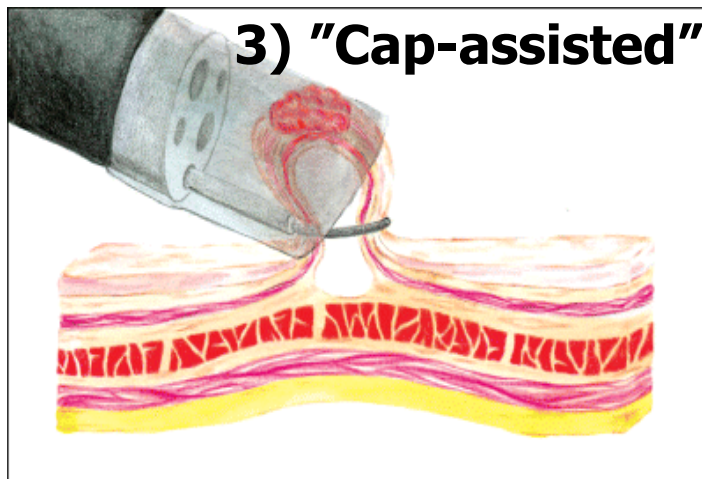
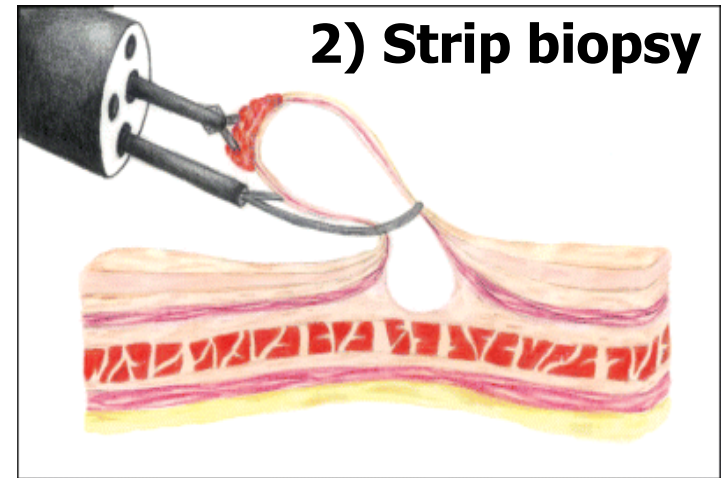
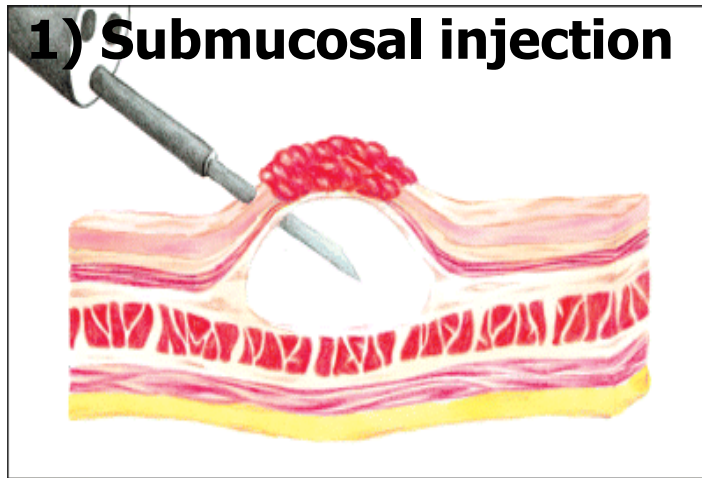
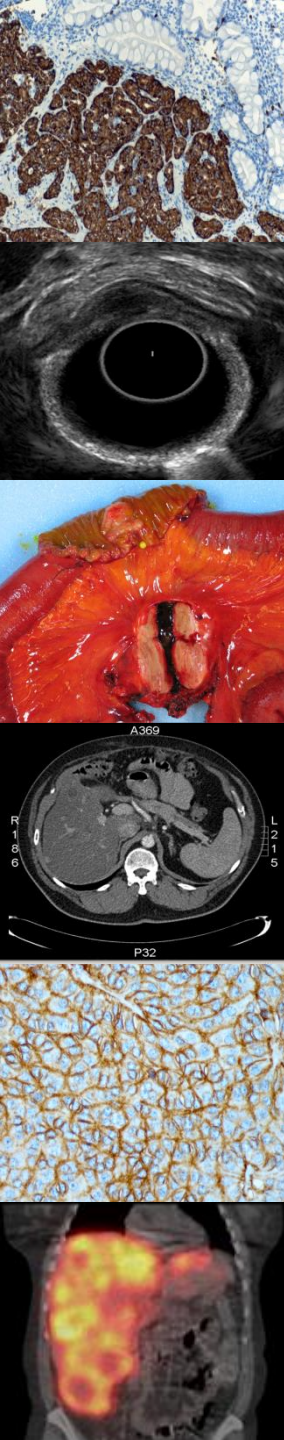
VMAT-2

CAG-A, Chronic atrophic gastritis type A; MEN1, Multiple Endocrine Neoplasia 1; ZES, Zollinger Ellison syndrome; CgA, Chromogranin A; VMAT-2, vesicular monoamine transporter-2.

Suggestion for gastroscopy for GNETs

- Describe the macroscopy of the mucosa.
- Include at least 2 biopsies from tumor-free antrum mucosa.
- Include around 4 biopsies from tumor-free corpus mucosa.
- Include biopsies from the polyps.
- Consider to obtain gastric juice for PH-levels.

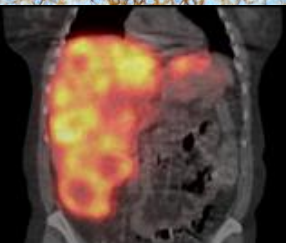
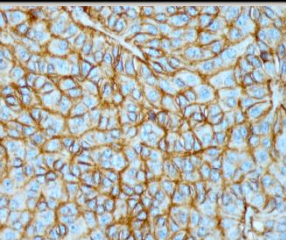
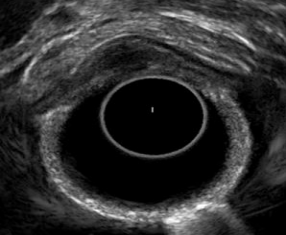
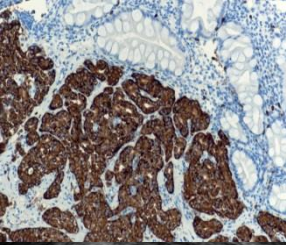
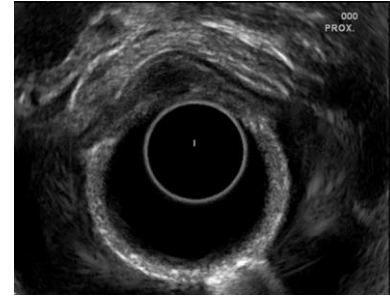
Endoscopic Submucosal Resection (ESMR)



Conio et al. *Am. J of Gastroenterology* 101:653-663 (2006)

Guidelines for ESMR/ESD

- If possible perform EUS.
- Perform ESMR/ESD if type 1 ECLomas with up to 6 tumors measuring ~1 cm (≥ 1 cm metastatic cases reported) that do not invade muscularis propria.
- After ESMR/ESD thorough histopathological assessment.
- Recommend additional surgery if high Ki67, invasion of muscularis propria, high vascular invasion or residual tumor.

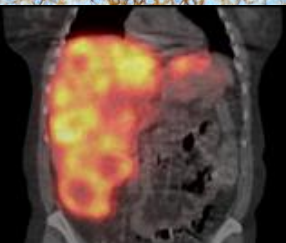
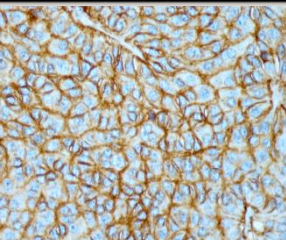
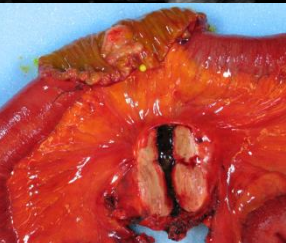
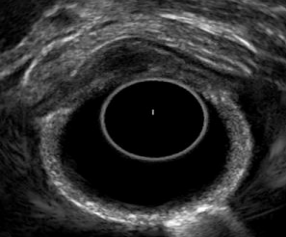
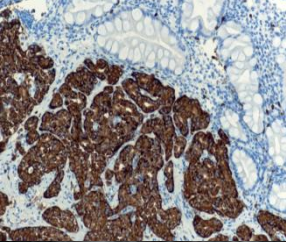


ESMR, endoscopic submucosal resection; ESD, Endoscopic submucosal dissection

Ruszniewski P. et al., *Neuroendocrinology*. 2006; 84:158-164.

Delle Fave et al., *Neuroendocrinology*. 2016; 103:119–124.

Endoscopic Submucosal Resection (ESMR) for type 1 ECLomas



- Ichikawa J et al. Endoscopy 2003
 - Strip biopsy and cap assisted, 5 cases, 3-12 mm, 6-66m f/u
 - No recurrence
- Hopper AD et al. J Gastro and Hep, 2009
 - Duette kit, 34 GNETs (8 pts), 0.6-10 mm, 30d f/u
 - R0, No complications

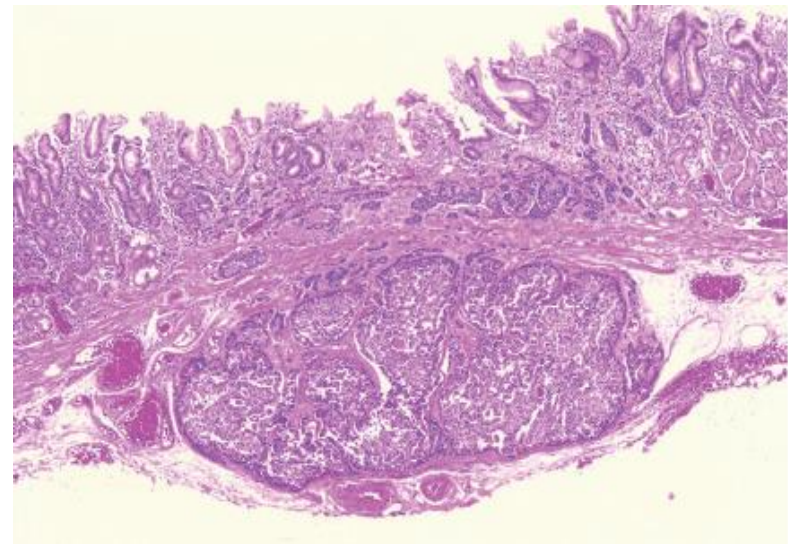
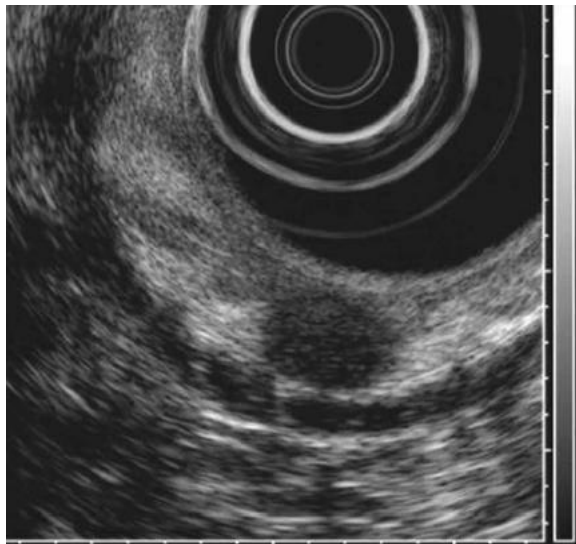
Endoscopic Submucosal Dissection (ESD) for GNETs



- Li QL et al. 2012 WJG
 - 19 pts with 24 GNETs (16 type 1 in 11 pts and 8 type 3)
 - Hook or IT knife, 2-30mm all confined to SM
 - Complete resection rate 100%
 - Complications: Delayed bleeding in 1 case
 - Mean f/u 24.4m (range 12-48m), 1 recurrence 7m after
- Suzuki et al. 2012 Surg Endosc
 - Flex knife, 2 type 1 GNETs
 - 100% en bloc, R0, no perforations
 - Mean f/u 37m, no recurrence

EMR vs ESD in type 1 ECLomas

- Kim HH et al. 2014 Gastro Research and Practice
 - 62 pts, 87 GNETs, <10mm, No invasion beyond SM layer
 - Lower vertical margin involvement rate at ESD vs EMR 2.6% vs 16.7% $p=0.038$
 - Complete resection rate ESD=94.9% vs EMR=83.3%, $p=0.174$
 - Similar complications



EMR, Endoscopic mucosal resection; ESD, Endoscopic submucosal dissection

EMR or ESD in type 3 ECLomas

- Kwon YH et al 2013 WJG
 - 50 type 3 GNETs, 41 excised with EMR and 9 with ESD
 - 33 lesions $\leq 10\text{mm}$, 17 lesions $>10\text{mm}$. Mucosal or SM.
 - Incomplete resection EMR:ESD 6 (14.6%) : 1 (11.1%)
 - Mean f/u 43.73m, range 13-60m, 20 pts $>60\text{m}$ f/u
 - No recurrence. ESD is good for type 3 GNETs $<20\text{mm}$

Main disadvantage: no grading score used, no Ki67-IR results

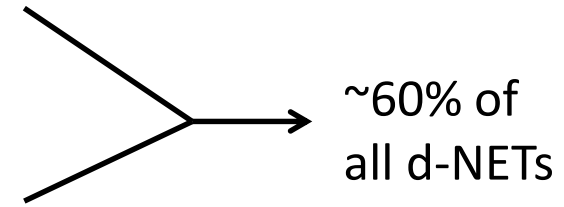
Duodenal NETs (d-NETs)



Image courtesy of A. V. Tsolakis

WHO 2010 classification

- Functioning: gastrinomas
- Nonfunctioning (NF)
 - gastrin-immunoreactive (-IR),
 - SS-IR ~20% of all d-NETs
 - Undefined/Other hormones-IR (serotonin, PP, calcitonin) ~10% of all d-NETs
- Gangliocytic paraganglioma <9% of all d-NETs
- NECs ~2% of all d-NETs

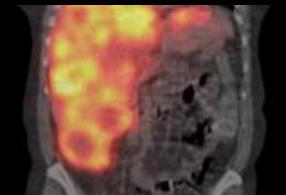
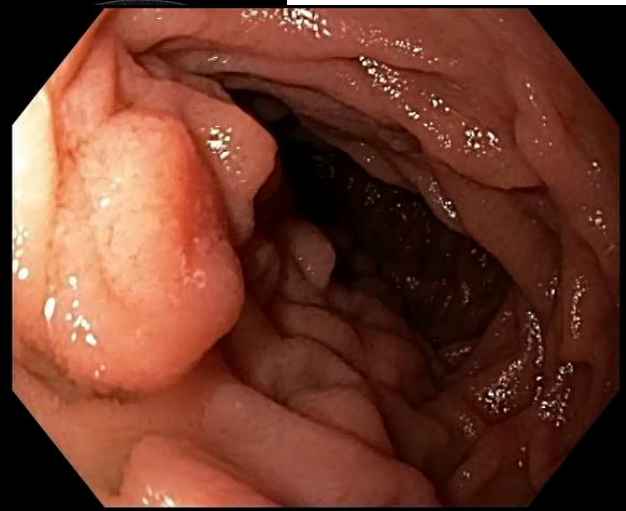
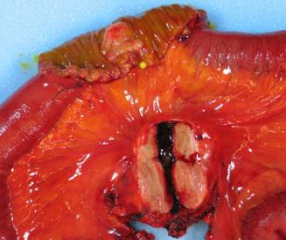
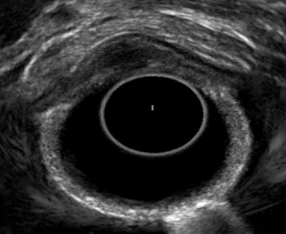
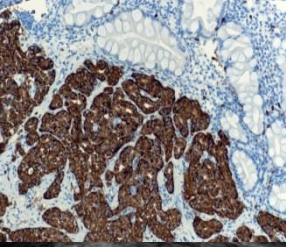


Most duodenal NETs are nonfunctioning (with biochemical markers within reference interval) and are located in the 1st or 2nd part, rarely in 3rd or 4th.

Multiple lesions in ~10% of all d-NETs. Should lead to suspicion of MEN-1.

Endoscopical and echoendoscopical features of dNETs

- Submucosal mass or firm yellow sessile nodule
- Intraluminal polypoid mass \pm ulceration
- Single or multiple, vary in size
- Irregularity or deformity of overlying mucosa
- Homogenous, isoechoic, 2nd layer mass



Risk factors for metastases in:

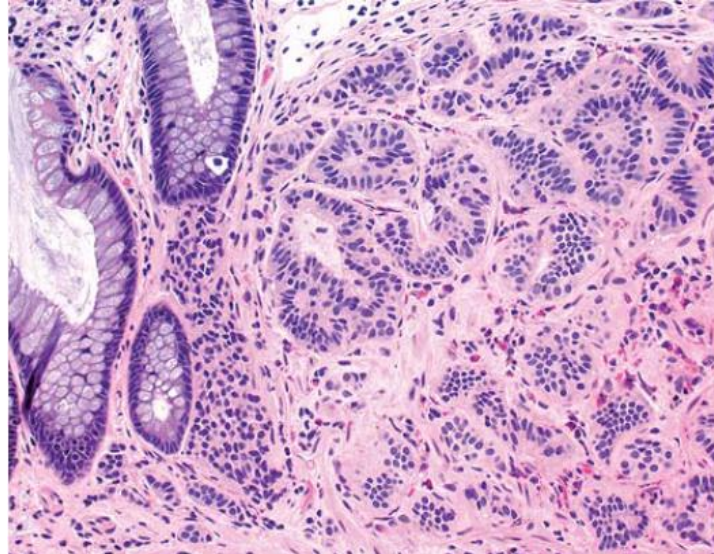
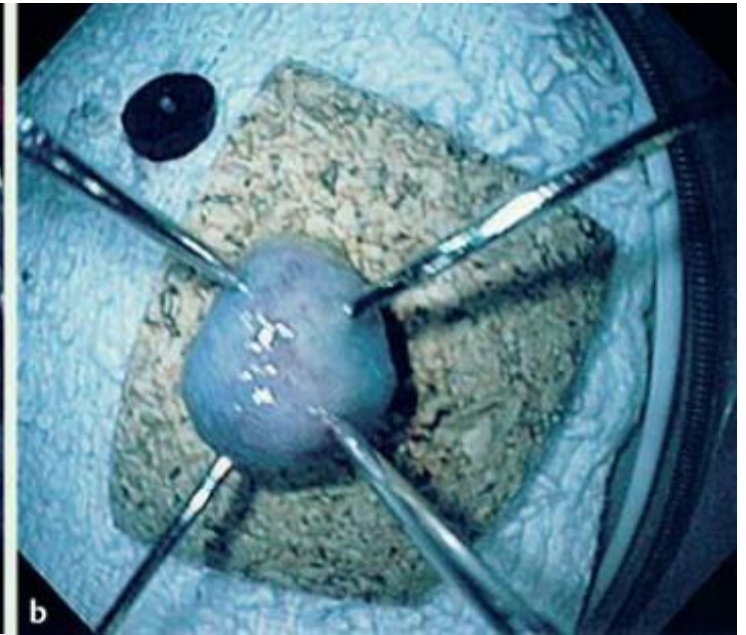
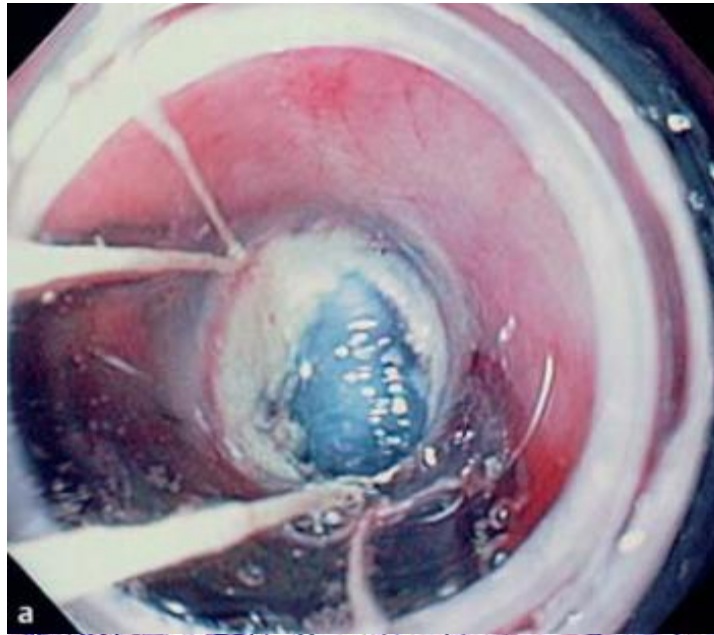
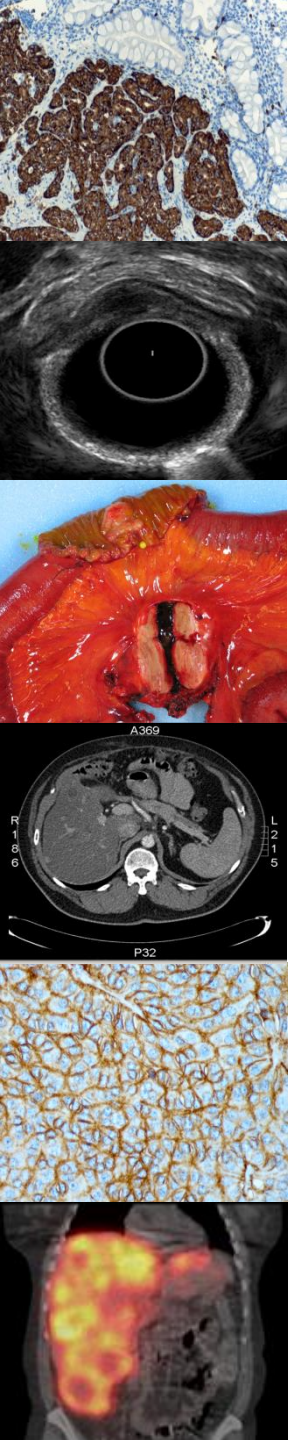
1) Non-ampullary dNETs

- G2
- ≥ 11 mm
- Multiple tumors
- Functioning tumors (gastrinomas, SSomas)

2) Ampullary dNETs

- Subcentimeter lesions reported to be metastatic (individualize before making a decision if < 2 cm)
- If > 2 cm, $> 48\%$ risk for mets (Whipple's indicated)

ESMR-Duette kit and dNETs



2 lesions in the duodenal bulb
12X9mm and 8X7mm
R0, no complications

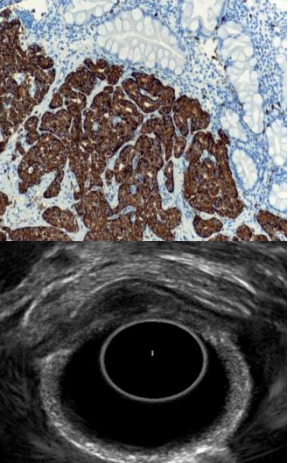
Neumann H et al Endoscopy 2013;45:E365-366

ESMR, Endoscopic submucosal resection

ESD and dNETs

- Li et al. 2012 WJG
 - IT or hook knife, 4 dNETs, size 5-15mm
 - 100% en bloc, no complications
 - F/u 10-30m, no recurrence
- Suzuki et al. 2012 Surg Endosc
 - Flex knife, 3 dNETs (duodenal bulb), < 1cm, all SM lesions
 - 100% en bloc, 2/3 perforations
 - Mean f/u 37m, no recurrence
- Matsumoto et al. 2011 GIE
 - 5 dNETs, size 3-8mm, duodenal bulb
 - 4/5 en bloc (1 aborted due to difficulty), 1/5 M and 4/5 SM2
 - 2/5 perforations

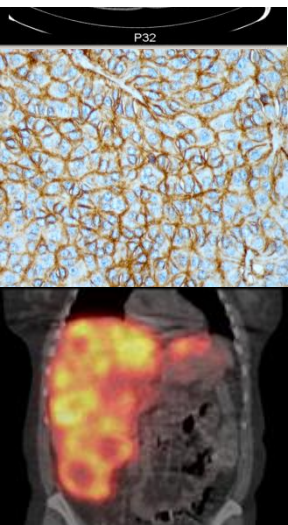
EMR vs EMR-L/hybrid vs ESD



- 41 dNETs, ~1 cm (2-12mm), G1, confined in SM, without mets
18 treated with EMR, 16 with EMR-L, 2 with hybrid technique and 4 with ESD
- Mean follow up 17 m (1-53 m)

Table 2 Treatment outcomes after endoscopic resection for duodenal carcinoid tumors according to treatment methods

	EMR (n = 18)	EMR-L (n = 16)	EMR-P (n = 3)	ESD (n = 4)
Mean procedure time (range, min)	13 (4-39)	14 (10-35)	18 (12-26)	33 (12-48)*
Mean resection size (range, mm)	7 (2-18)	7 (5-12)	12 (8-17)*	12 (10-5)*
Mean lesion size (range, mm)	6 (2-12)	5 (2-8)	6 (3-8)	6 (4-9)
Endoscopic complete resection	16 (89%)	16 (100%)	3 (100%)	4 (100%)
Pathological complete resection	10 (56%)	4 (25%)	1 (33%)	4 (100%)**
Bleeding	1 (6%)	0 (0%)	1 (33%)	3 (75%)***



Laparoscopic Endoscopic Co-operative Surgery (LECS)

- Non-ampullary d-NETs of bulb, >20 mm or 2nd/3rd, >10mm

Kim et al., *J Gastro and Hep* 2014;29:318-324

Ichikawa D et al., *WJG* 2016; 22(47): 10424-10431

Rectal Neuroendocrine Tumors (NETs)

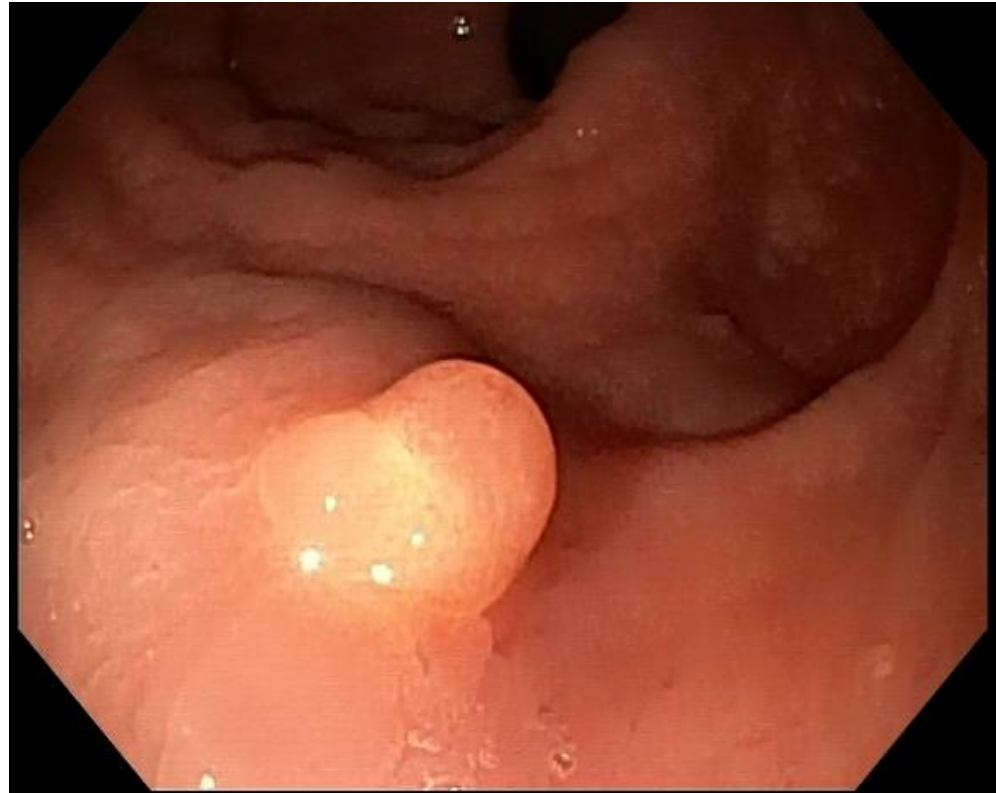
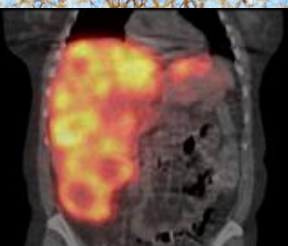
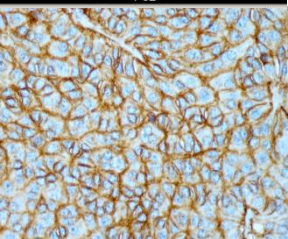
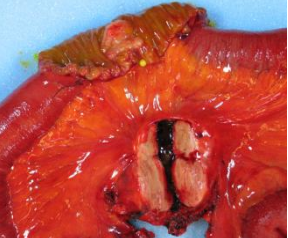
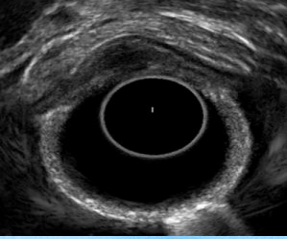
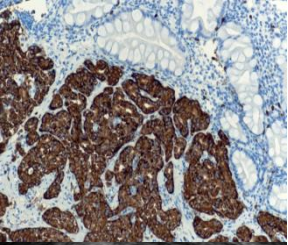


Image courtesy of A. V. Tsolakis

Rectal NETs (WHO 2010 classification)

I) Well differentiated neuroendocrine tumors (G1-2)

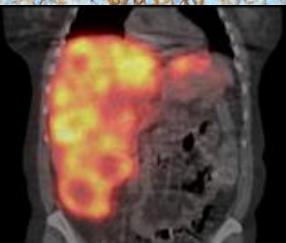
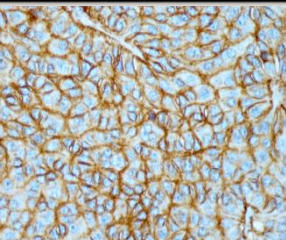
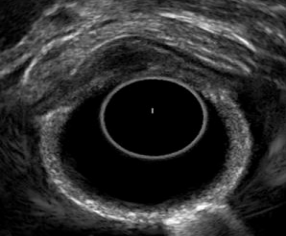
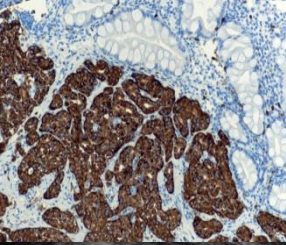
- L-cell type (60% of the cases)
- EC-cell type (30% of the cases)
- Other rare cases (e.g. SSomas, ectopic Cushing etc.)

II) Neuroendocrine carcinoma (NECs)

- Small-cell NECs (SC-NECs)
- Large-cell NECs (LC-NECs)

III) Mixed adenoneuroendocrine carcinoma (MANEC)

- African-Americans:Americans ratio 2.30 while 0.46 for non-NETs of rectum
- Asian:Non Asian ratio = 4.99
- Hindguts are related to IBD. 15 times higher risk in Crohn's

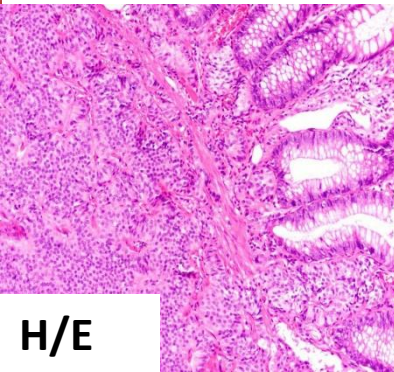
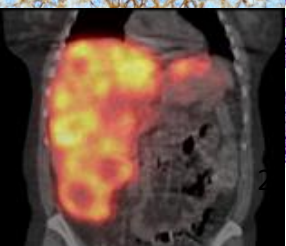
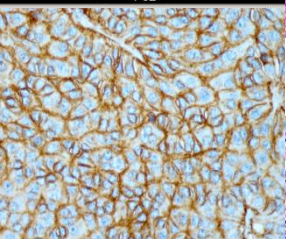
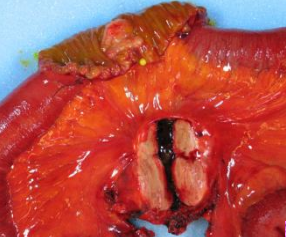
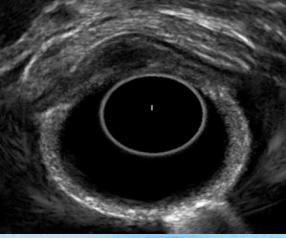
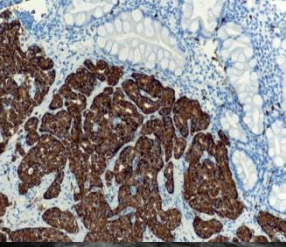


Rectal NETs (well differentiated)

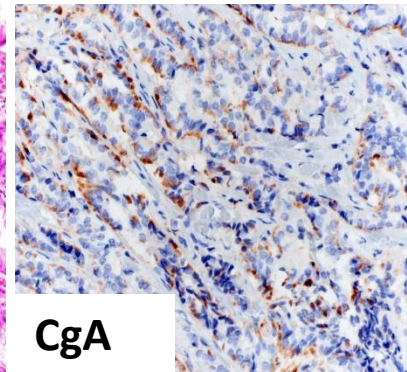
L-cell and EC-cell type

- Low malignant. Confined in mucosa or submucosa. Usually G1.
- Usually solitary, rarely multiple and familial. Usually asymptomatic.
- M:F ratio 1.05:1.11. Average age at diagnosis 48-52 years.
- Increasing incidence, most common type of NETs.

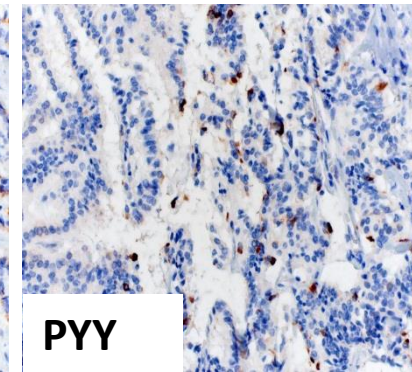
Images courtesy of A. V. Tsolakis



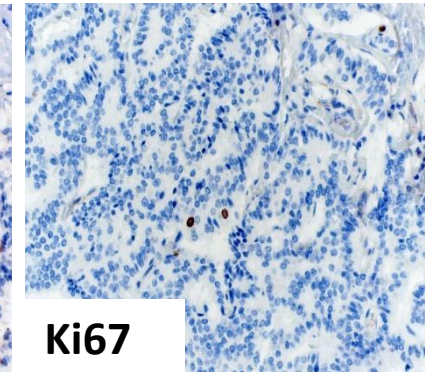
H/E



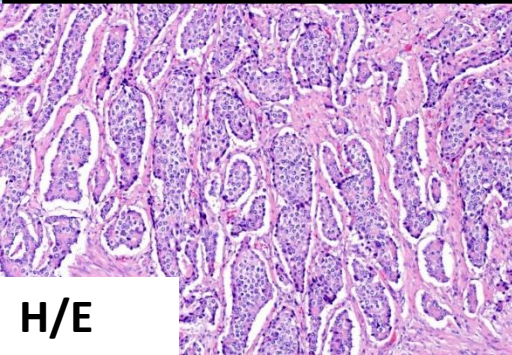
CgA



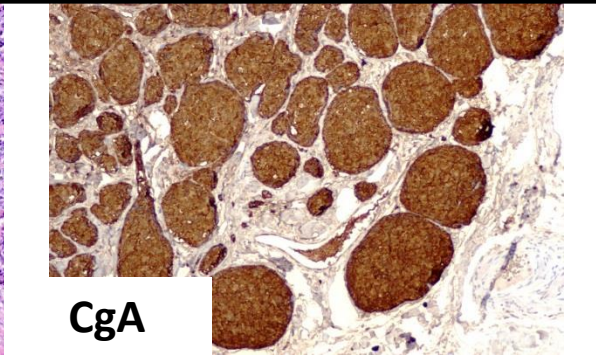
PYY



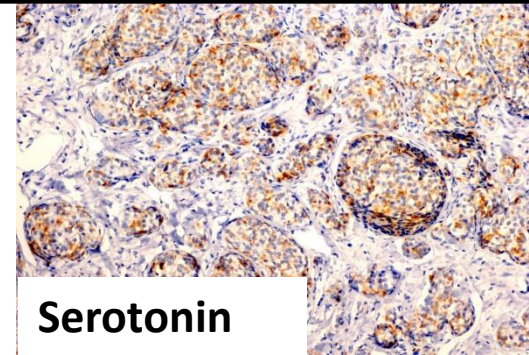
Ki67



H/E

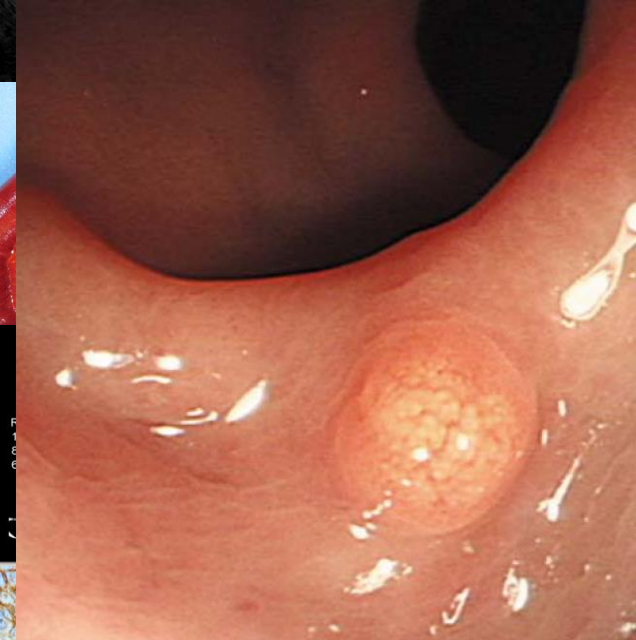
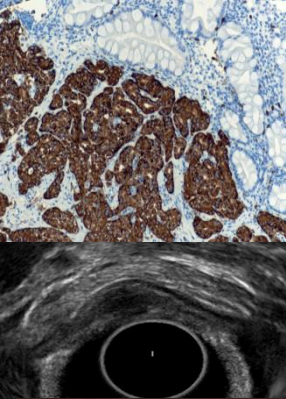


CgA



Serotonin

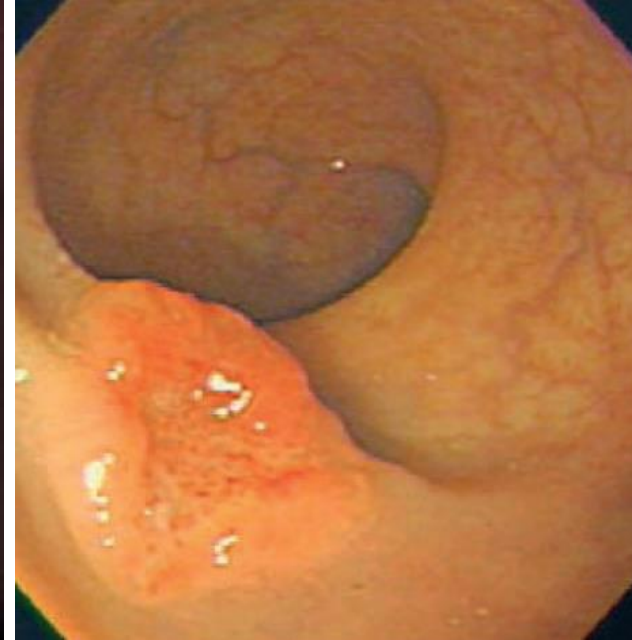
Endoscopical findings of rectal NETs



Typical pattern

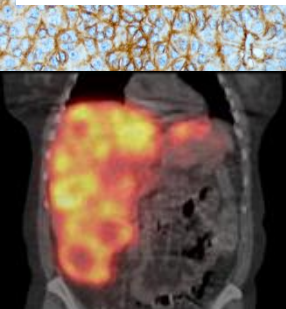


Central depression



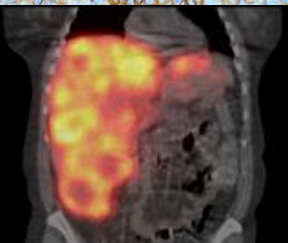
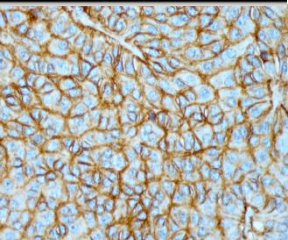
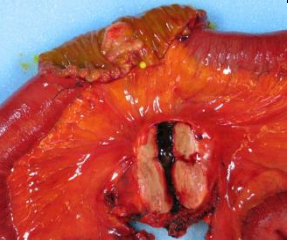
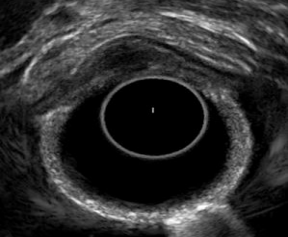
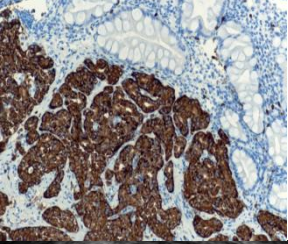
Ulcerated

Typical endoscopic feature: Smooth round and sessile elevation
Submucosal lesion
Normal appearing or yellow-discolored mucosa
Central depression and ulcerated have worse prognosis



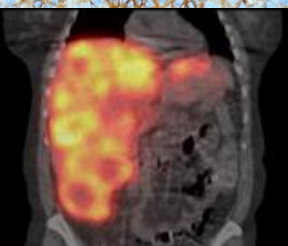
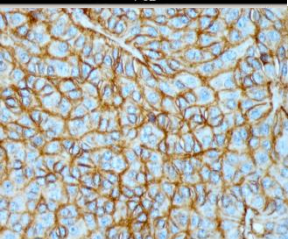
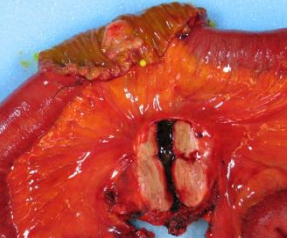
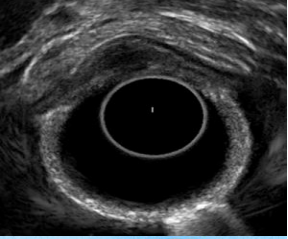
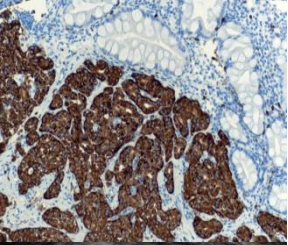
Prognostic factors - Size

- <1 cm (80% of the cases)
3%-4% have metastasized at diagnosis
- 1-2 cm (15% of the cases)
10-15% have metastasized at diagnosis. Especially for lesions >16mm should be operated and not endoscopically removed
- >2 cm at diagnosis (5% of the cases)
60-80% have metastasized at diagnosis



EUS and rectal NETS

Defines the depth of lesion and detects possible local metastases



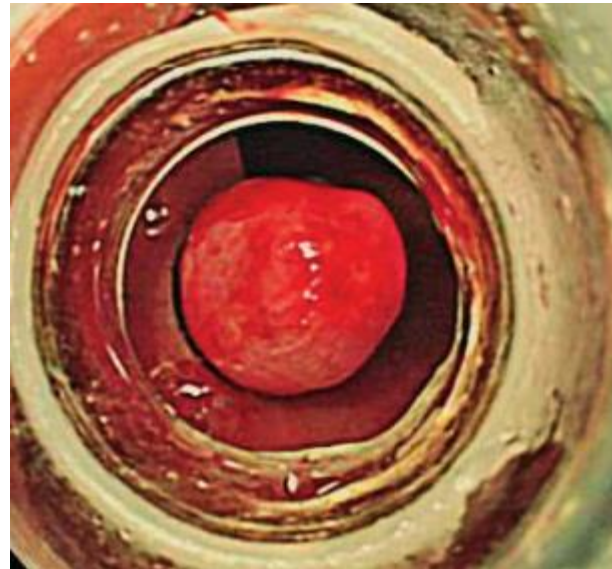
Rectal NETs: 2nd or 3rd layer lesions

Ramage J.K. et al. *Neuroendocrinology* 2016;103:139–143

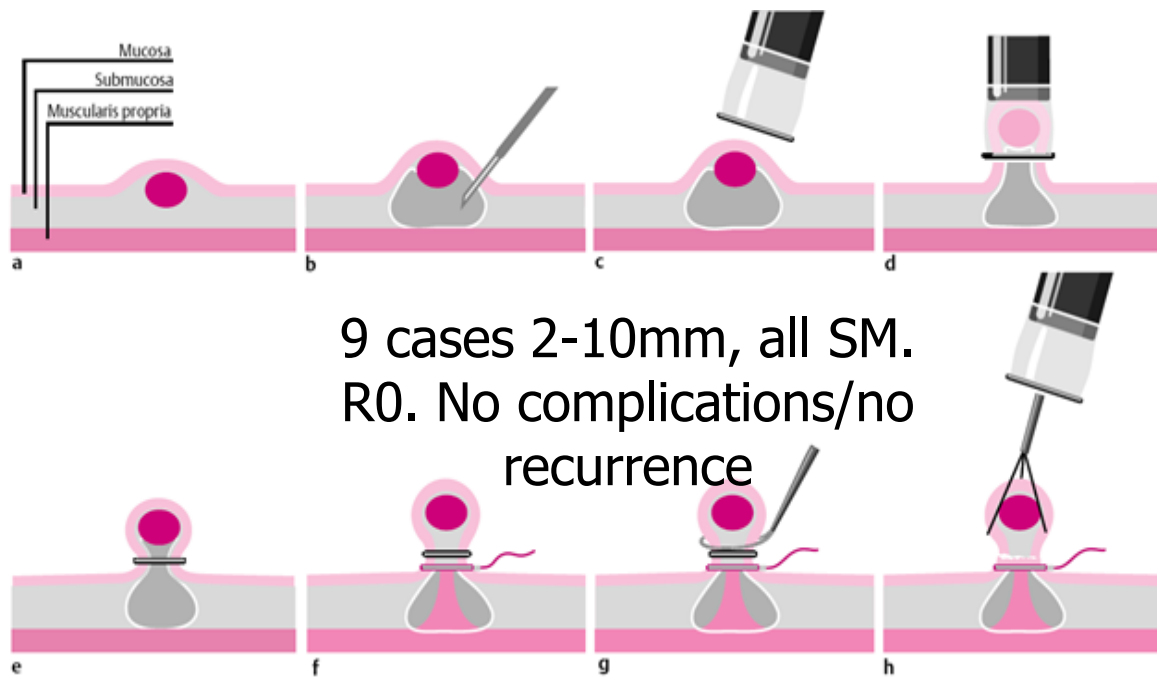
Image courtesy of A. V. Tsolakis

ESMR-L (single ligation)

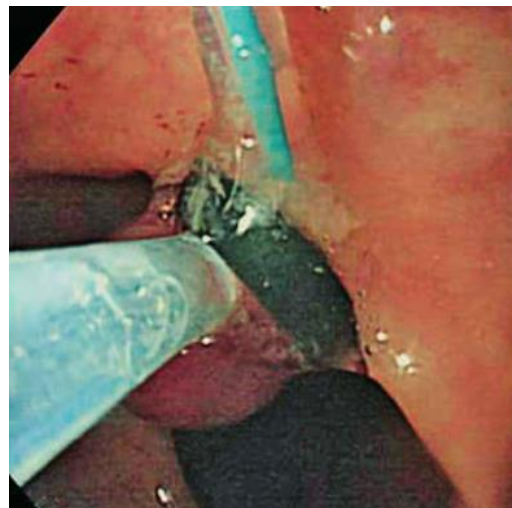
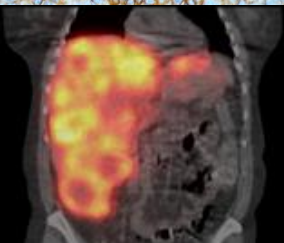
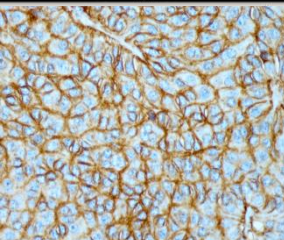
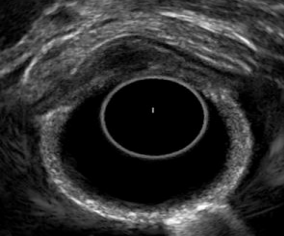
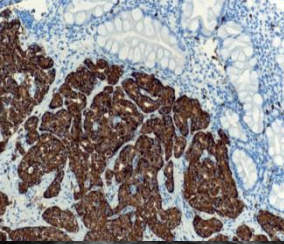
- 61 patients, 63 lesions 2-12 mm
- 60/63 completely resected
- Minor bleeding in 5 cases, no perforations
- All SM lesions at pathology
- No recurrence at f/u (1 year)



ESMR-DL (double ligation)



9 cases 2-10mm, all SM.
R0. No complications/no
recurrence



ESD vs. EMR vs. modified EMR (mEMR)

- Complete resection rates higher in ESD vs EMR but comparable to mEMR (band ligation or cap)
- No local recurrences in ESD group (209 cases) + mEMR group (90 cases) and 5/328 in the EMR group
- Bleeding in 3/209 ESD cases, 2/328 EMR cases and 1/90 mEMR cases
- Perforation in 2/328 EMRs, 3/209 ESDs and 1/90 mEMRs

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; mEMR, modified endoscopic mucosal resection.

Zhou X, et al. *J Gastroenterol Hepatol.* 2014;29:259-268



EMR vs. strip (double channel) and hybrid (precutting)

- 190 subcentimeter rectal NETs.
- EMR (n=47), strip (n=75), hybrid (n=68)
- Complete resection rates higher in strip (62/75) and hybrid (47/68) vs EMR (24/47)
- No local recurrences
- Similar procedure time and complication rate



Long term outcomes of ESD in patients with rectal NETs

- 239 patients, rectal NETs <20mm, 177 cases <10mm and 62 cases 10-19mm, f/u 52 months (range 25-94m)
- R0 in 216 cases (90,4%), lateral margin involvement 1 case (0.4%), deep margin involvement 23 cases (9.6%)
- Bleeding in 6 cases (2.5%), perforation in 2 cases (0.85%)
- No local recurrence BUT distant metastases in 6 patients

Table 4. Characteristics of Colorectal Carcinoids Treated by ESD With Distant Metastasis in Follow-up Period

Patient	Sex	Age (y)	Date of treatment	Size (mm)	Location	Sub mucosal invasion	Lympho vascular infiltration	Tumor grade	Positive tumor margin	Metastasis organ	Metastasis date ^a
1	M	45	Dec 3, 2007	10	Rectum	Yes	No	1	Yes	Liver	Mar 26, 2014
2	M	64	Jan 22, 2008	10	Transverse	No	Yes	1	Yes	Liver	Oct 15, 2009
3	F	60	Feb 24, 2009	5	Rectum	No	No	2	No	Liver	Jul 21, 2014
4	M	60	Oct 27, 2009	15	Rectum	Yes	No	2	No	Liver	Aug 23, 2010
5	M	40	Aug 12, 2010	5	Rectum	Yes	Yes	1	No	Liver	Oct 12, 2013
6	M	52	May 24, 2011	15	Rectum	No	No	1	No	Liver	May 27, 2013

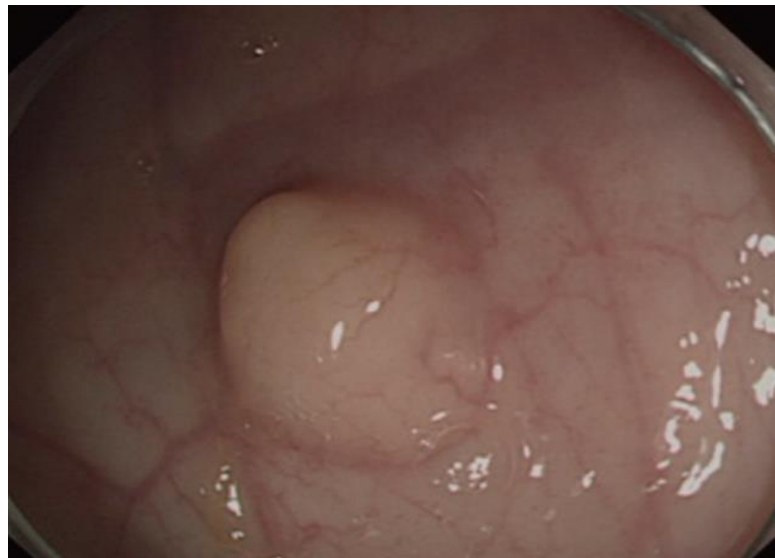
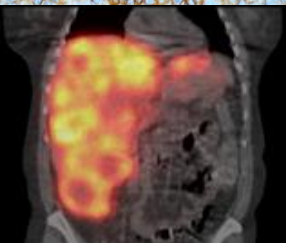
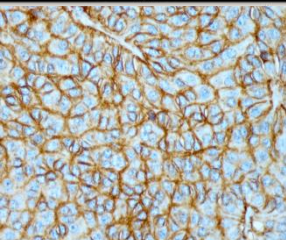
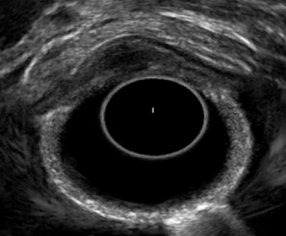
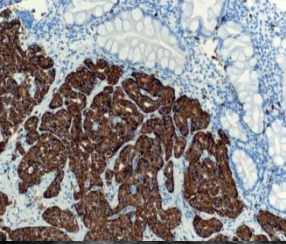
- 10 years follow up even after radical excision according to ENETS guidelines

ENETS, European Neuroendocrine Tumor Society

Chen T et al. *Clin Gastro Hep* 2015; Caplin M et al. *Neuroendocrinology* 2012; 95:88–97

To biopsy or not to biopsy?

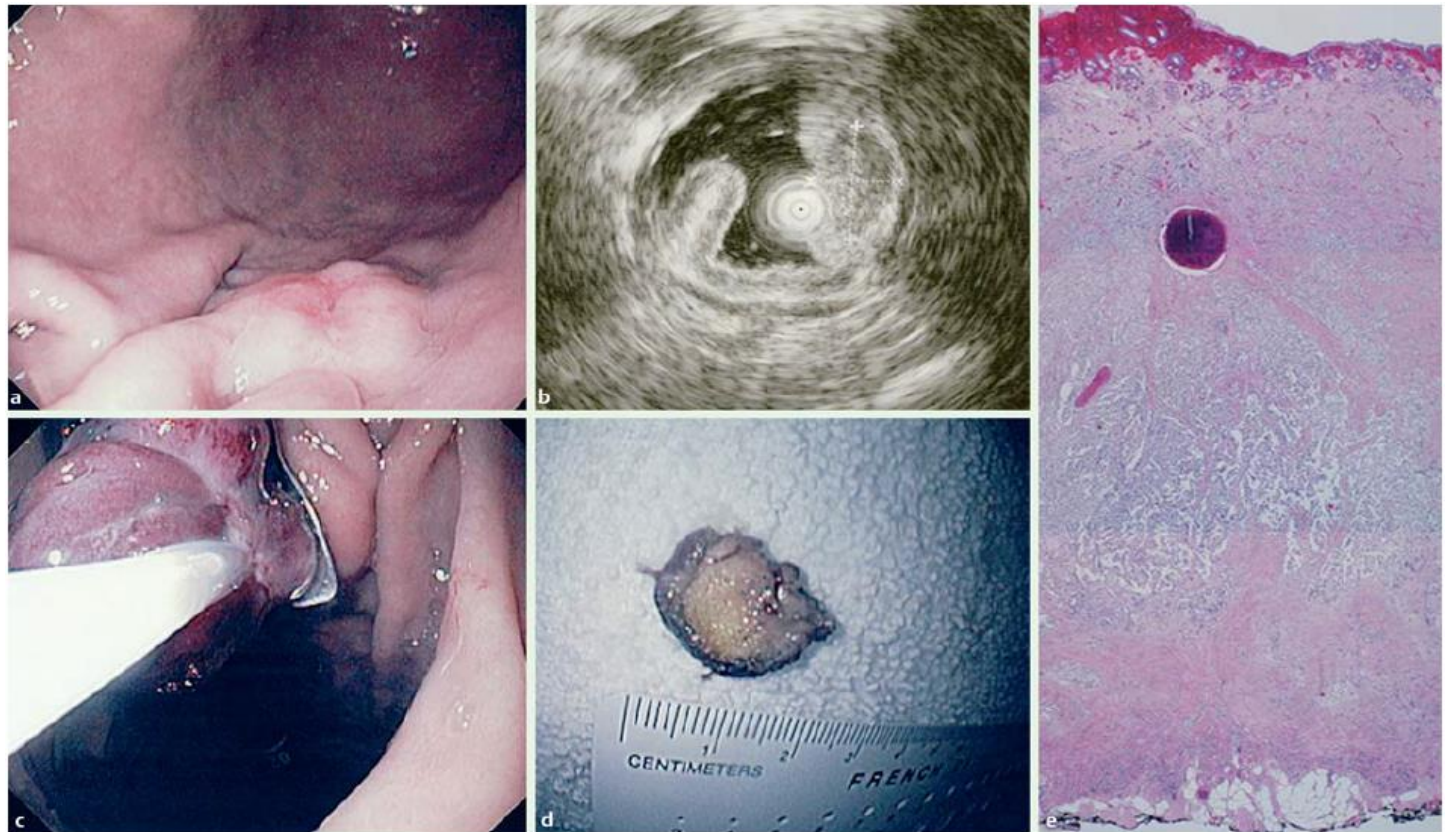
- 98 rectal NETs, size 7.59 ± 2.90 mm (range 3-15) were included. EMR ($n=53$), ESMR-L ($n=11$), ESD ($n=34$).
- 57 cases (58.2%) with preceding biopsies
- Biopsied cases: 3.7 times more likely to fail to completely remove tumors using EMR/ESMR-L/ESD, $P= 0.004$ of incomplete resection



EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection

Lee SP, et al. *J Korean Med Sci.* 2014;29:512-518

OVESCO clip



- 8 patients: GNETs (n=2), dNETs (n=4), rectal NETs (n=1), esophageal granular cell tumor (GCT)
- Mean size 13.4mm, range 9-20mm
- R0 in 7/8 patients (87.5%)
- Full thickness resection in 2/8 (1 GNET and the GCT)

Pancreatic NETs (pNETS)

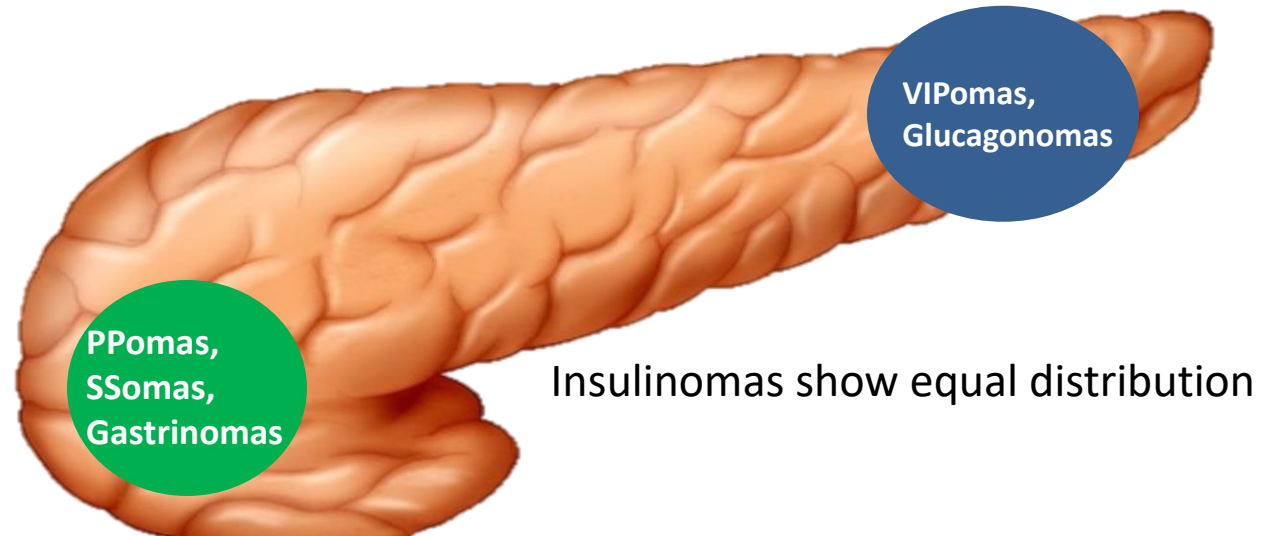


Glucagonoma

Image courtesy of A. V. Tsolakis



Characteristics of pNETs



pNET	Incidence/10 ⁵ /yr	Age	M:F	Malignancy	Biochemistry
NF-pNET	1-3	50	1:1	60-80%	CgA 68% vs CgA+PP 93%
Insulinoma	0.4	47	1.5:1	10%	Insulin, pro-insulin, C-peptide
Gastrinoma	0.05-0.4	48	3:2	>60	Gastrin, PH<2
Glucagonoma	~0.01	52.5	0.8:1	80%	Glucagon
VIPoma	0.005	42	1:1	50-60%	VIP
SSoma	<0.01	55	1:1	>70%	SS

pNET, pancreatic neuroendocrine tumor; VIP, vasoactive intestinal polypeptide; PP, pancreatic polypeptide; SS, somatostatin; NF, nonfunctioning; CgA, Chromogranin A

Tsolakis A, et al. Pancreatic Neuroendocrine Tumors, *Islets of Langerhans*, 2nd Edition, 1375-1406, 2015;

Tsolakis A, et al. Endocrine pancreatic tumors, *Expert Rev Endocrinol Metab* 2008;3(2):187-205

Radiology sensitivity of imaging techniques in pNETs

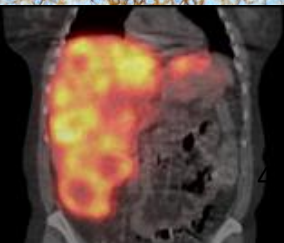
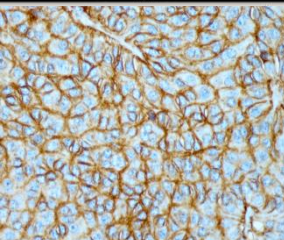
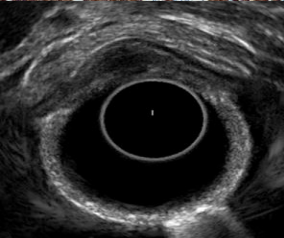
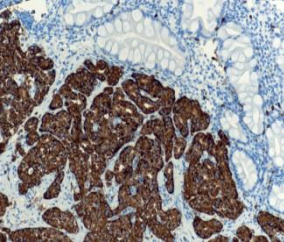
- Abdominal US: ~40%
- CT: ~80%
- MRI: ~80%
- SRS or Ga-PET: Up to 90%, BUT for benign insulinomas <60%
- 5-HTP PET: Up to 90%
- EUS: >90% (and the advantage of FNA), consistently increases the detection of pNET even when other modalities have been performed
- IOUS: 96%-98%

pNETs, pancreatic neuroendocrine tumors; EUS, endoscopic ultrasound; FNA, fine needle aspiration; IOUS, intraoperative ultrasound; SRS, somatostatin receptor scintigraphy, 5-HTP-PET, 5-hydroxytryptophan positron emission tomography; IOUS, intraoperative ultrasound.

James PD, Tsolakis AV, et al., *Gastrointest Endosc.* 2015;81:848-56;

Tsolakis A, et al. Pancreatic Neuroendocrine Tumors, *Islets of Langerhans*, 2nd Edition, 1375-1406, 2015;

Tsolakis A, et al. Endocrine pancreatic tumors, *Expert Rev Endocrinol Metab* 2008;3(2):187-205



Ablation techniques in pNETS

- In selected non metastatic cases not suitable for operation/chemo, ablation techniques can be applied as treatment options in pNETs
- Nonfunctioning and functioning (insulinomas/gastrinomas) pNETs
- EUS guided radiofrequency ablation and ethanol ablation
- Size 3- 27 mm. Multiple sessions may be required
- Complete ablation is feasible
- Side effects: Abdominal pain, mild to severe pancreatitis, minor peritumoral bleeding



Thank you!!!

«Οὐδέν ὄφελος οὔτε χρημάτων οὔτε ἄλλου τινός
ἄτερ ὑγίης»

Ἱπποκράτης

«There is no benefit either from money or from
anything else, without good health»

Hippocrates

