New standards in endoscopy in gastric, duodenal, pancreatic and rectal NETs

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NETs are not uniformly distributed within the **GI tract**.

In the SEER 17 registry gastroentero--pancreatic NETs made approximately 61% of NETs.

The following sites were identified as common locations for NETs:

- rectum (17.7%)
- small intestine (17.3%)
- colon (10.1%)
- pancreas (7.0%)
- stomach (6.0%)
- appendix (3.1%)

GI NETs may be encountered during endoscopy under several circumstances.

The **first scenario** is during endoscopic examination for a functioning NET diagnosed by serological or biochemical tests (for instance, a suspected gastrinoma based on markedly elevated gastrin level and diarrhea).

Second scenario

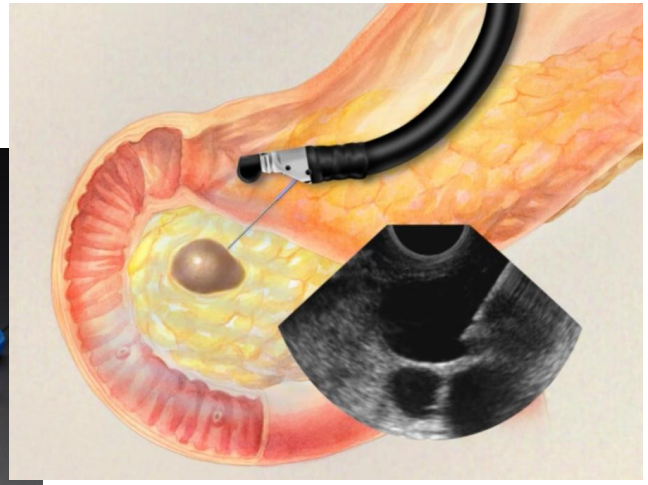
Hormonally inactive NETs may be discovered during evaluation of other symptoms such as GI bleeding or abdominal pain caused by the tumors themselves.

Third scenario

NETs may be incidentally discovered during endoscopy for upper GI symptoms, during screening colonoscopy, or because of CT-scan/MRI.

NETs

Final diagnosis is histologic/cytologic



Basuroy et al. APT 2015

Gastric NETs

	Type1	Type 2	Type 3
%	70-80	5-6	14-25
Localization	Body, fundus	Body, fundus, antrum	antrum
Endoscopic features	Multiple (60%), small, polypoid	Multiple, small, polypoid	Single, large, ulcerated
Association	Atrophic gastritis	Gastrinoma/MEN-1	sporadic
Gastrin	high	high	normal
Metastases	2-5%	10-30%	50-100%

Gastric NETs

A careful inspection of the mucosa for multiple small lesions is advised, as type 1 and type 2 GCs are commonly multifocal.

Biopsies should be taken from:

- suspected gastric lesion
- gastric mucosa: 2 from antrum and 4 from the body/fundus
  (to assess the presence of atrophic gastritis and intestinal metaplasia)

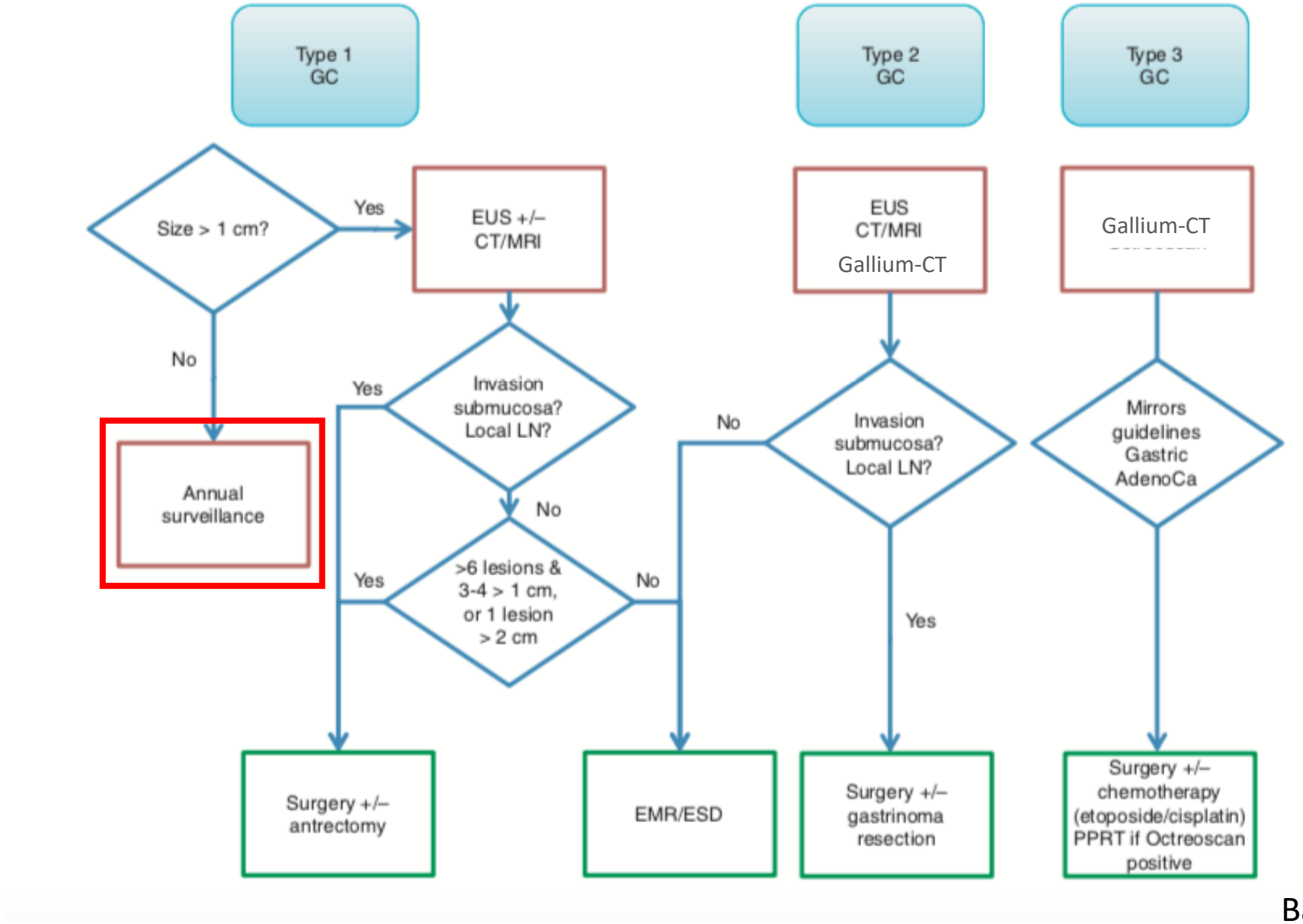
Basuroy et al. APT 2015

Endoscopic treatments

- Endoscopic resection could be considered for tumors <20 mm and without invasion of muscolaris propria
- Lesions >20 mm and/or with invasion of muscolar layer carry high risk for metastasis
- NETs of the ampulla, duodenum, small bowel and rectum, also with size <11 mm, are considered to be at high risk of deep invasion and metastasis

Boskoski et al. Exp Rev Gastroenterol Hepatol 2013

Gastric NETs: a management algorythm

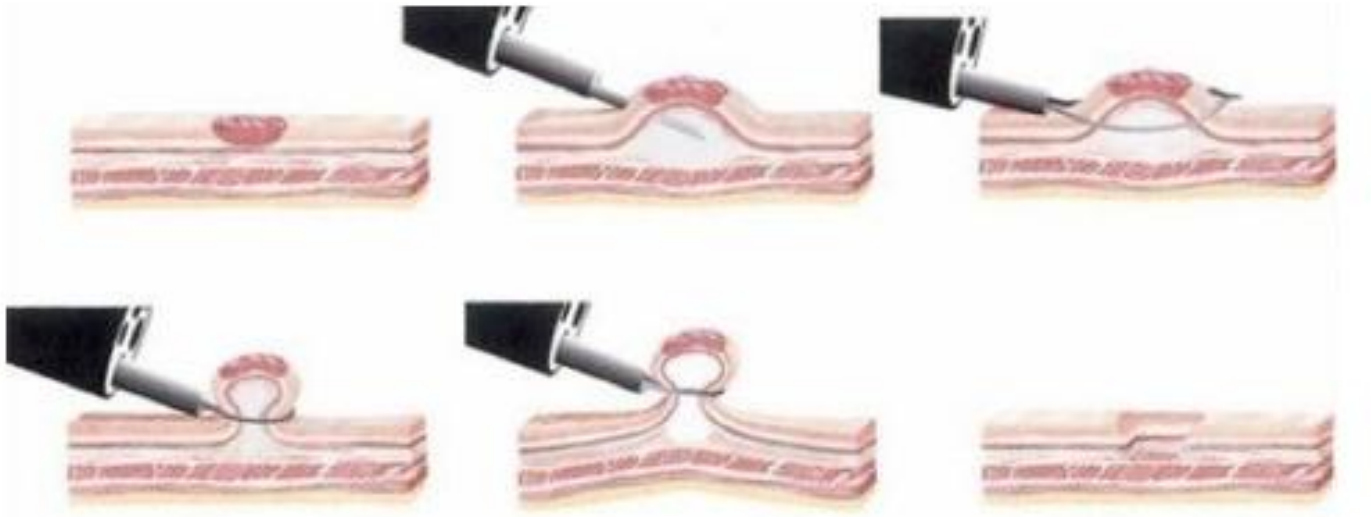


Basuroy et al. APT 2015

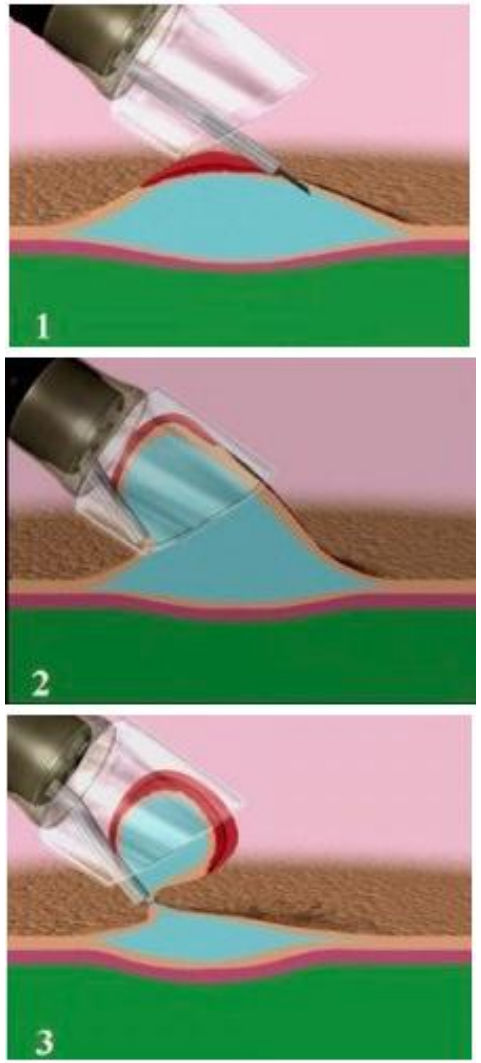
Endoscopic treatments: how to remove?

- Removal by sampling forceps
- EMR (Endoscopic Mucosal Resection)
- ESD (Endoscopic Submucosal Dissection)
- Full-thickness resection

EMR

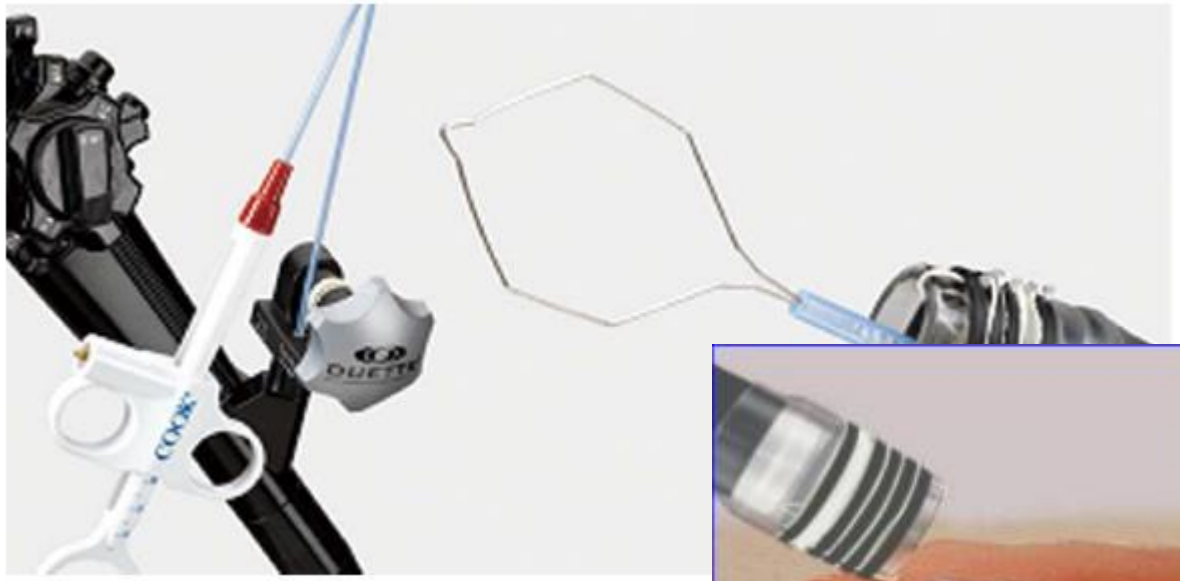


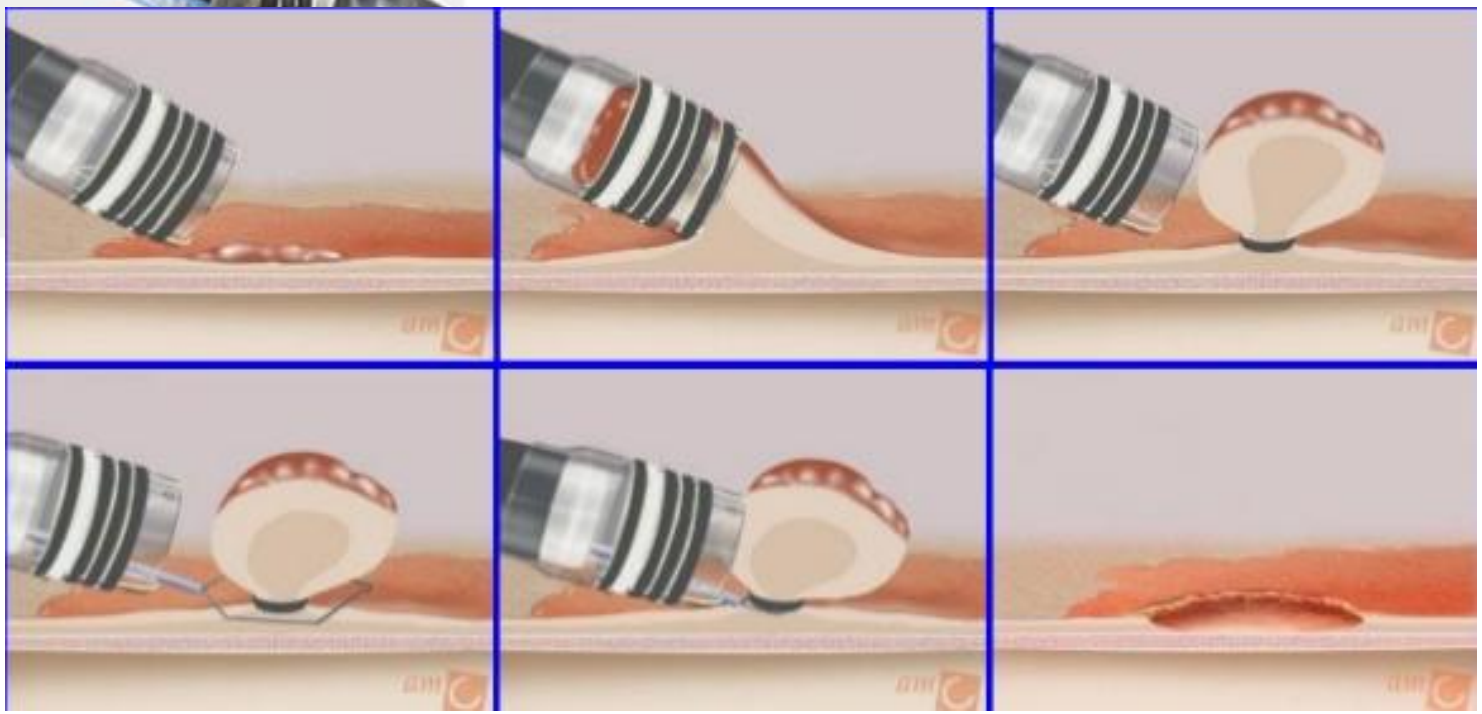
Lift and cut



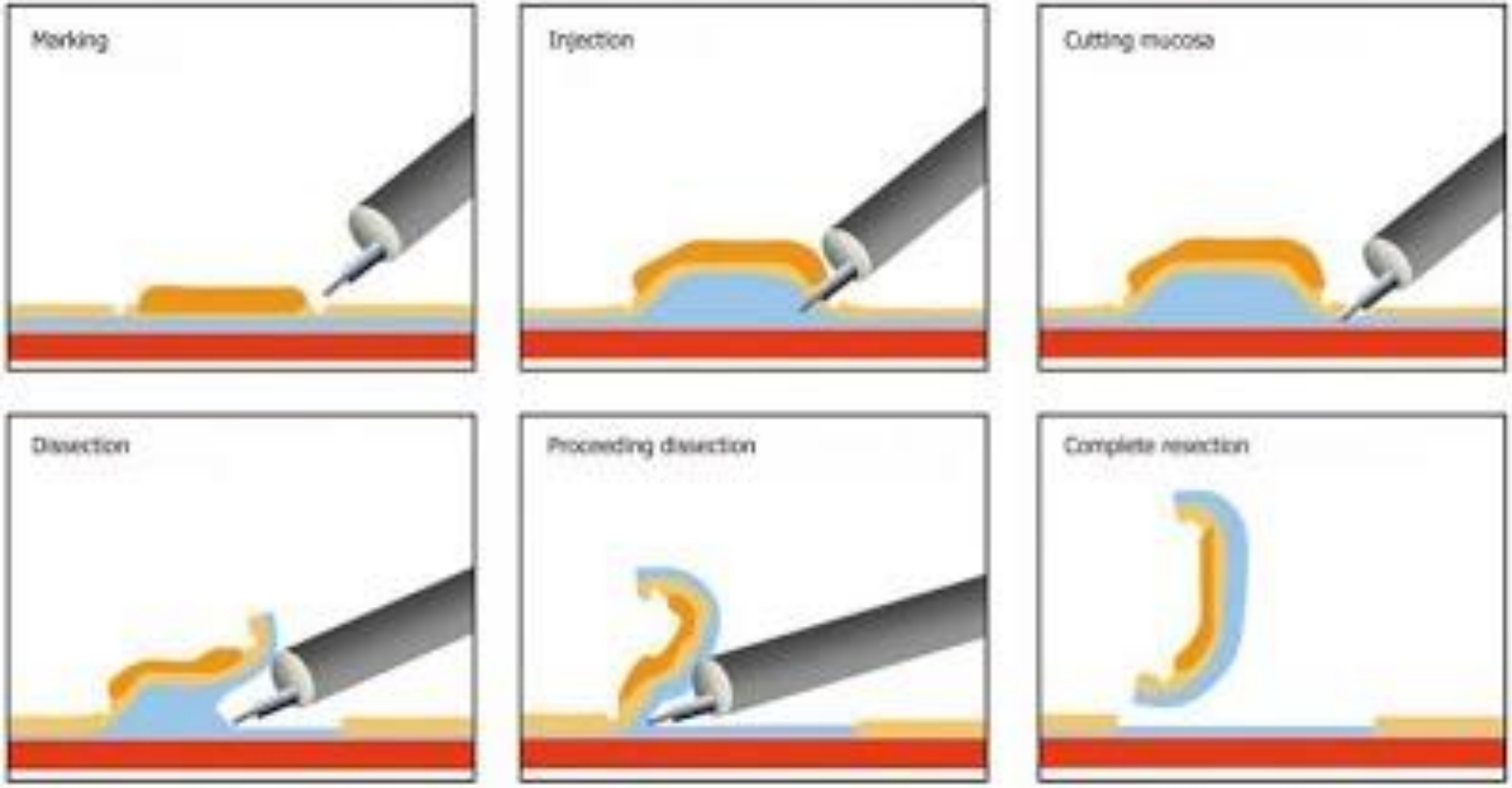
Suck and cut

EMR: Multi Band Mucosectomy

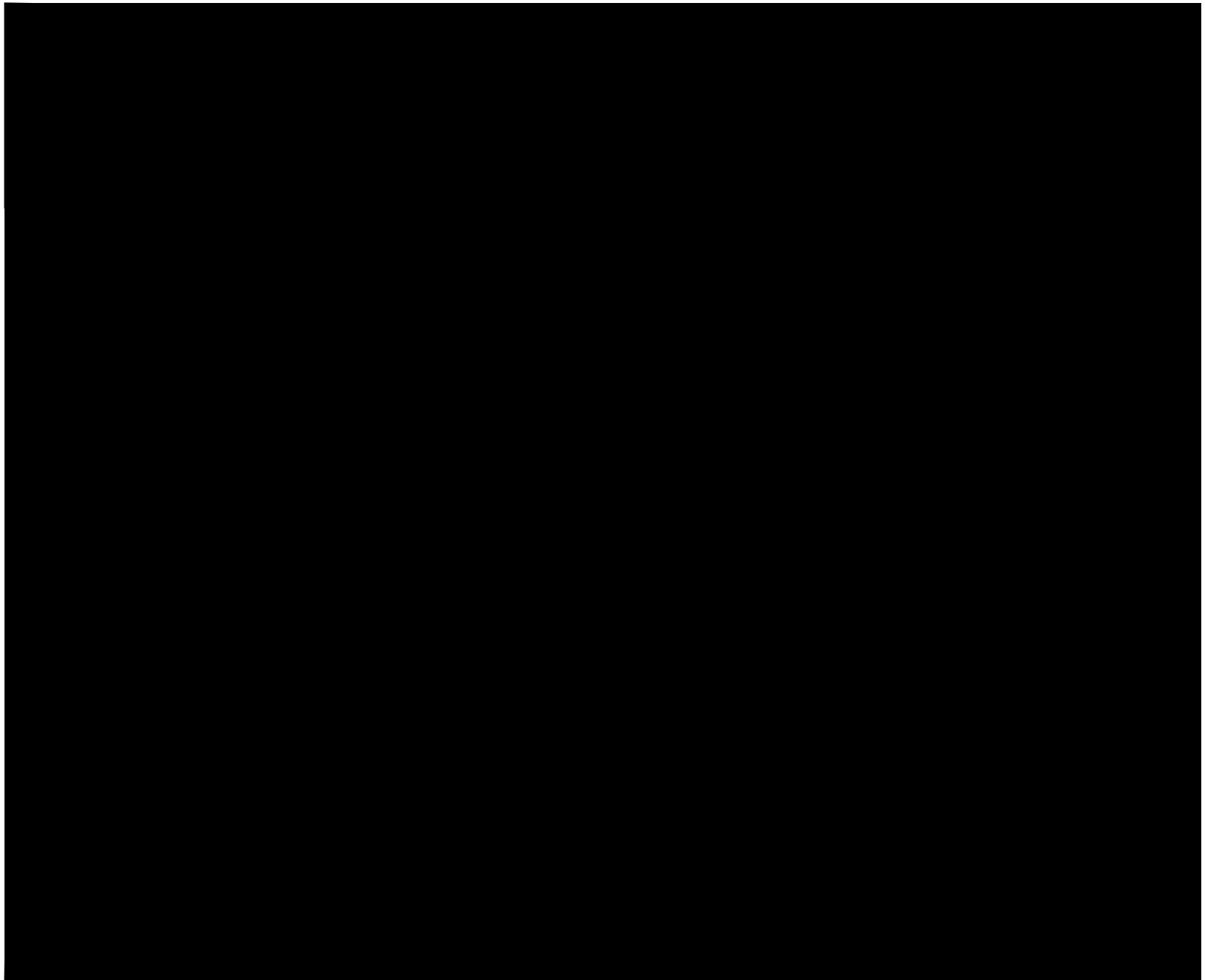




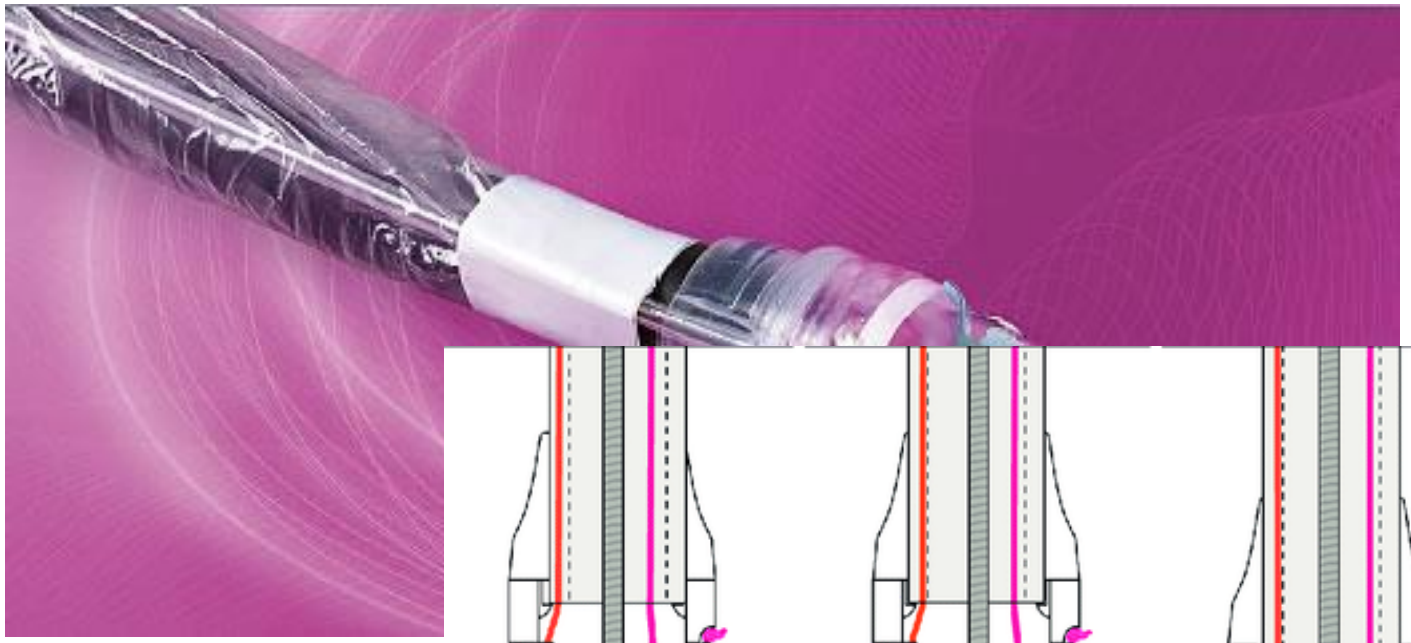
ESD (Endoscopic Submucosal Dissection)



Gastric NETs: ESD

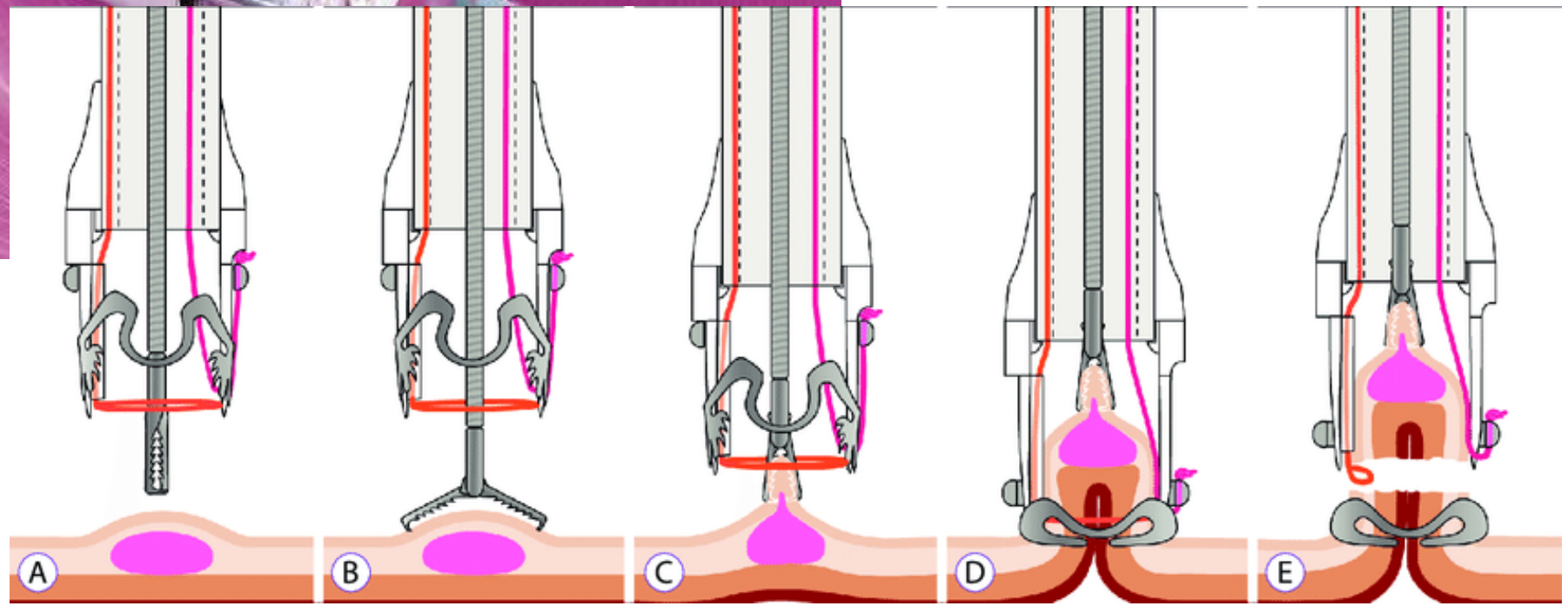


Full Thickness Resection Device (FTRD)



Used for:

- Recurrent adenoma
- Rectal carcinoma T1
- Non-lifting lesions



all wall layers

Type I Gastric Carcinoids: A Prospective Study on Endoscopic Management and Recurrence Rate

33 patients with type I gastric NETs treated endoscopically → 55% removed by forceps, 45% by snare

In all cases, histological margins were lesion-free and the pts did not need a short-term control to complete eradication

During a 46-month median follow-up, survival was 100% and no metastases occurred

Merola et al. Dig Dis Sci 2014

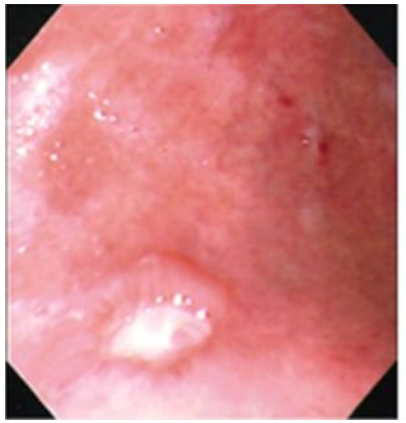
Gastric NETs

Long-Term Results of Endoscopic Resection for Type I Gastric Neuroendocrine Tumors

AHMET UYGUN, MD,[1] ABDURRAHMAN KADAYIFCI, MD,[2]* ZULFIKAR POLAT, MD,[1]
KEMALETTIN YILMAZ, MD,[1] ARMAGAN GUNAL, MD,[3] HAKAN DEMIR, MD,[1] AND SAIT BAGCI, MD[1]
[1]*Division of Gastroenterology, Gulhane Military Medical Academy, Ankara, Turkey*
[2]*Division of Gastroenterology, Faculty of Medicine, University of Gaziantep, Gaziantep, Turkey*
[3]*Department of Pathology, Gulhane Military Medical Academy, Ankara, Turkey*

Prospective study
22 polyps removed by EMR in pts with type I gastric NETs (without metastases):

- 18 pts with polyps <1 cm
- 4 pts with polyps 1-2 cm



Uygun et al. J Surg Oncol 2014

Gastric NETs

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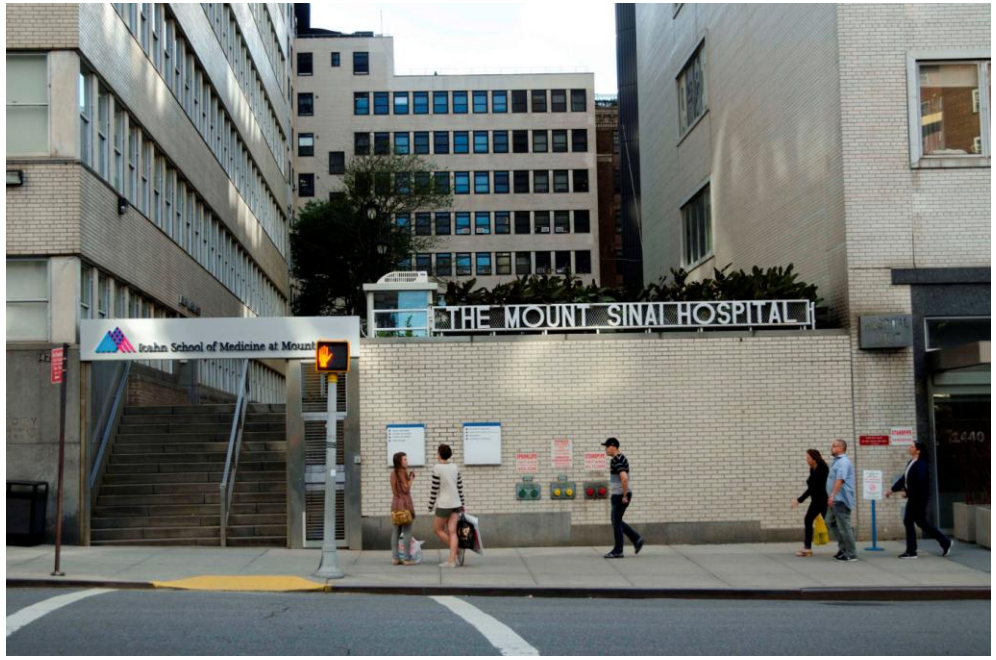
- All lesions were successfully removed
- After a median follow-up of 7 years, only four patients (18%) had recurrence and endoscopic resection was performed again with success

- Only in one case was necessary surgery due to a perforation after mucosal resection

Uygun et al. J Surg Oncol 2014

Management and Disease Outcome of Type I Gastric Neuroendocrine Tumors: The Mount Sinai Experience

William C. Chen · Richard R. P. Warner · Stephen C. Ward · Noam Harpaz · Celia M. Divino · Steven H. Itzkowitz · Michelle K. Kim



Fifty-six patients were identified with gastric NETs type I between 1993 and 2012 at Mount Sinai Hospital

- history of pernicious anemia in 33 pts (86%)
- 83% of tumors were low grade (G1), 17% were intermediate grade (G2)

Mount Sinai

Chen et al. Dig Dis Sci 2014

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Therapy	N (%)
Somatostatin therapy	17 (32%)
Endoscopic resection	16 (28%)
Surgical resection	26 (46%)

Indipendently by the therapy

Overall 5-year and 10-year survival following diagnosis of type I gastric NET was 98%, whereas disease-specific survival was 100%

Mount Sinai

Chen et al. Dig Dis Sci 2014

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No endoscopic or pathologic features, resulted related to higher risk of more advanced disease:

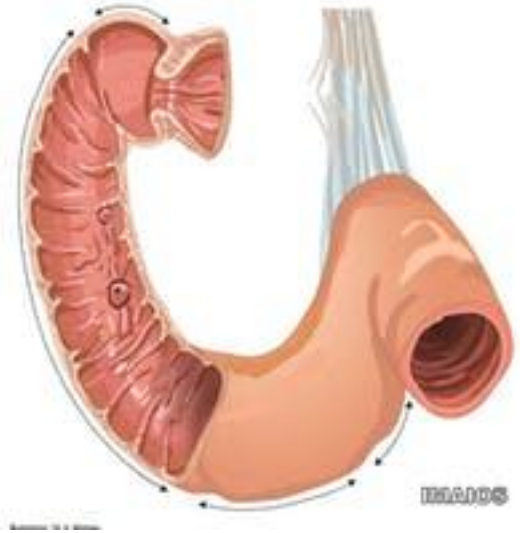
- mean tumor size (2.0 vs. 11.5mm)
- location (fundus/body vs. unknown)
- depth (submucosa vs. mucosa)
- concurrent dysplasia or adenocarcinoma (both vs. neither)

Mount Sinai

Chen et al. Dig Dis Sci 2014

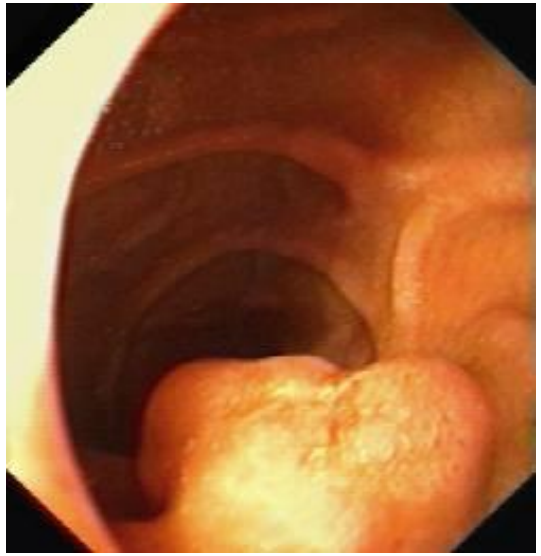
Duodenal NETs

Duodenal NETs are classified in five types based on their pathohistological features:



- duodenal gastrinomas
- duodenal somatostatinomas
- poorly differentiated neuroendocrine carcinomas (predominantly ampullary)
- non-functioning duodenal NETs
- duodenal gangliocytic paragangliomas

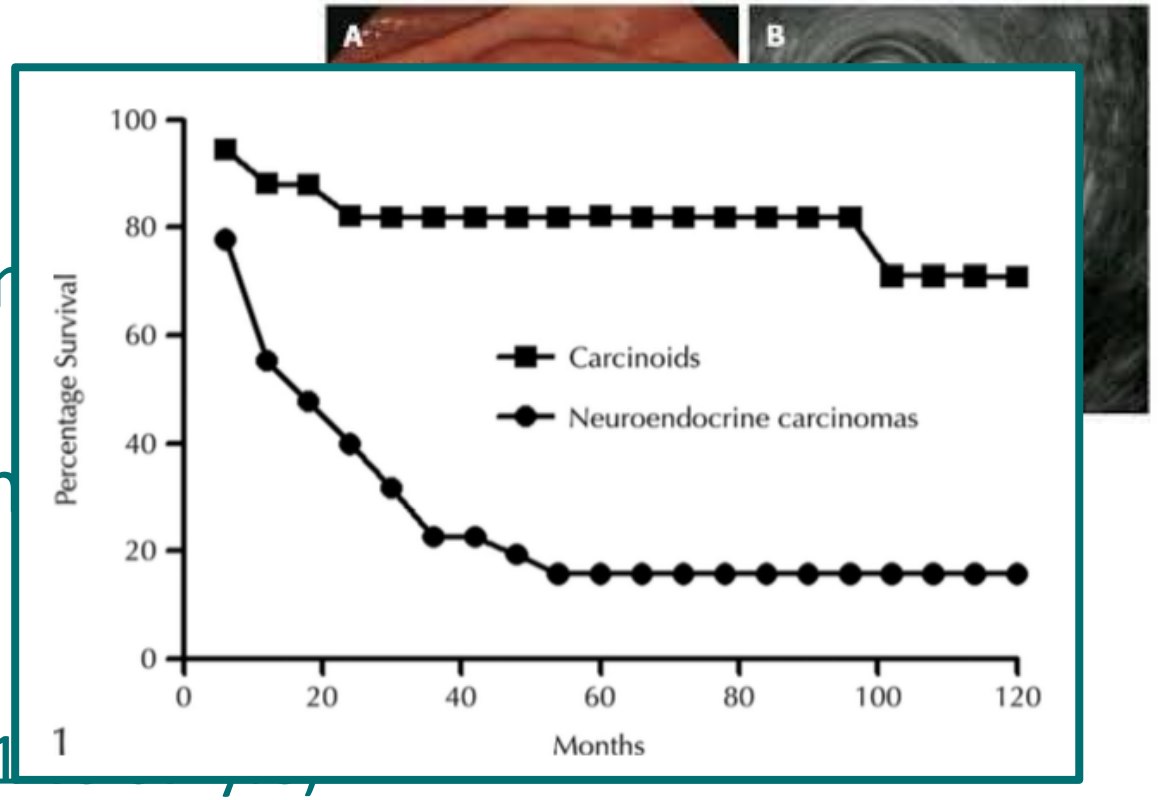
Duodenal NETs



Doudenal gastrinomas are the most common type

- 50–60% of all duodenal NETs
- sporadic or associated with MEN1 syndrome
- First or second portion of duodenum
- Lymph node metastasis are not uncommon at the time of the diagnosis even if they are usually <10 mm and limited to the mucosa or submucosa

Ampullary NETs



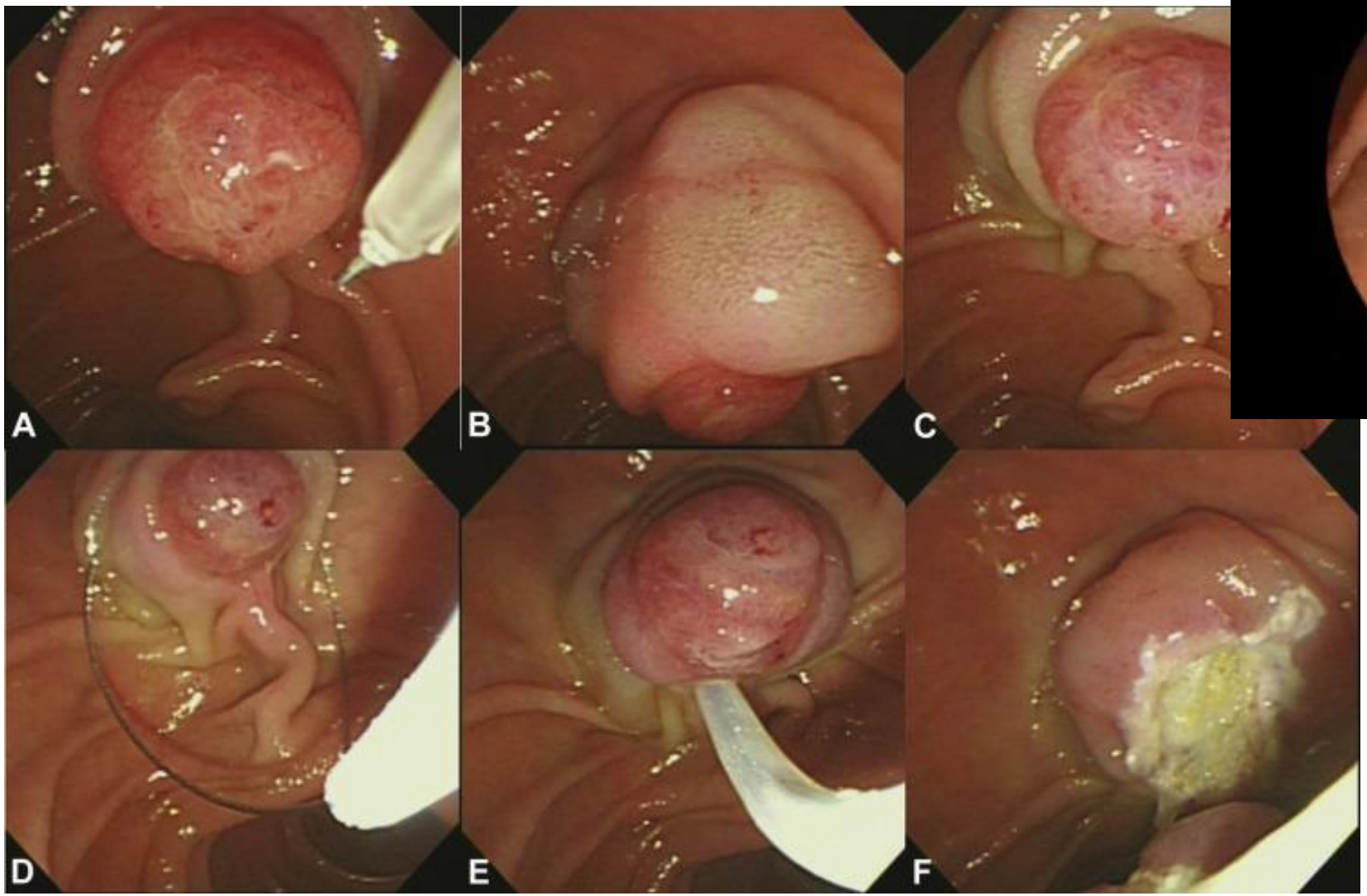
SEER 17 recorded 139 NETs of the am

- 82 were carcinoid tumors
- 57 were high-grade (HG) NE carcin

- Man>woman
- Carcinoids in younger pts (mean age 61
- Lymph nodes metastasis in carcinoids were less frequent respect to NE carcinomas (28% vs 62%)
- 10-year survival rates of patients with carcinoid tumors were 71%, while for HG NE carcinomas was 15.7%.

Albores-Savedra et al. Arch Patol Lab Med 2010

Duodenal and ampullary NETs: endoscopic treatment



Endoscopic full-thickness resection of gastric and duodenal subepithelial lesions using a new, flat-based over-the-scope clip

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- No
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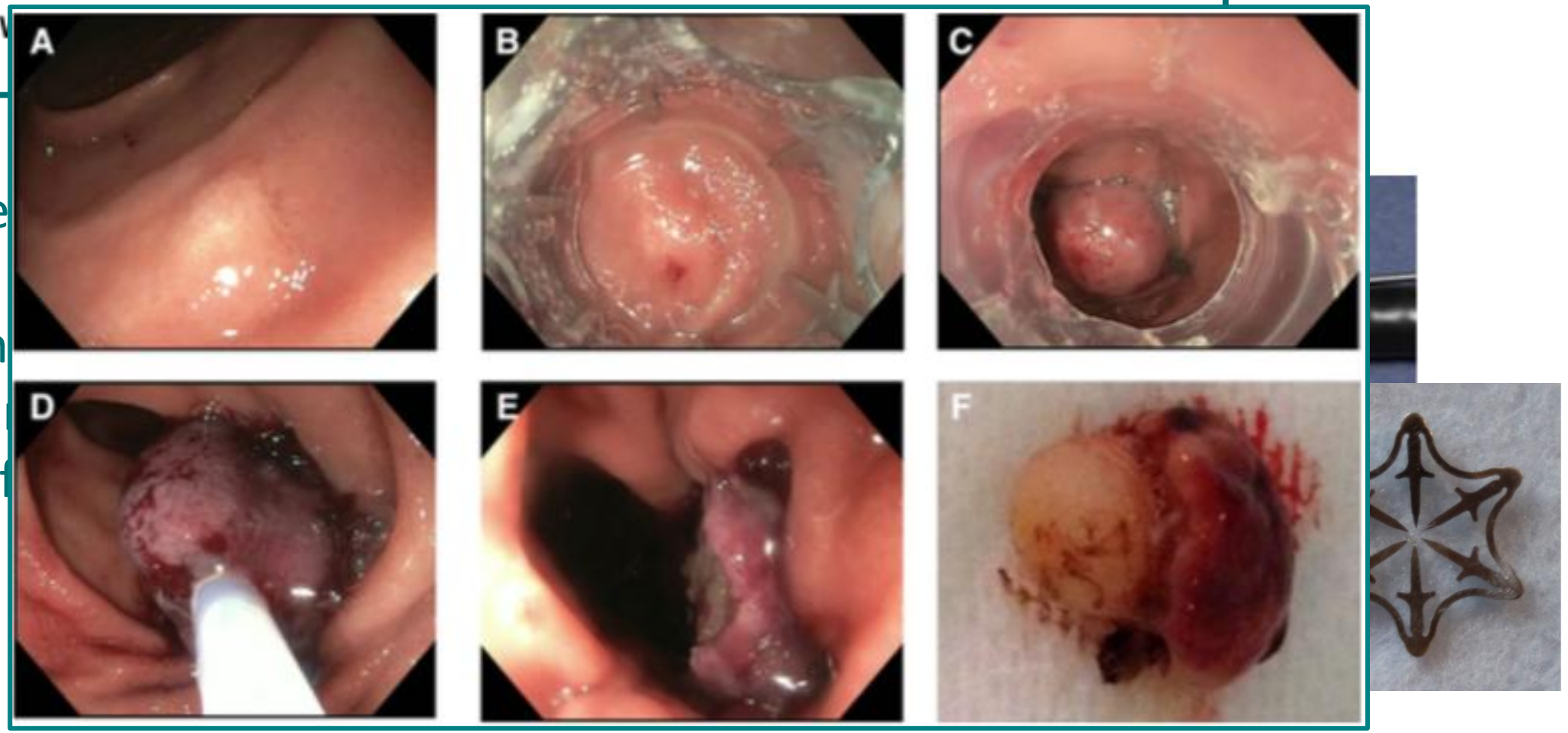
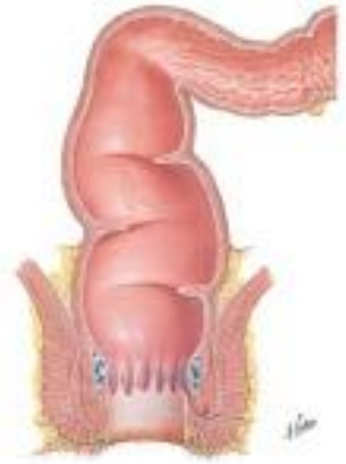


Kappelle et al. Surg Endosc 2018

Rectal NETs



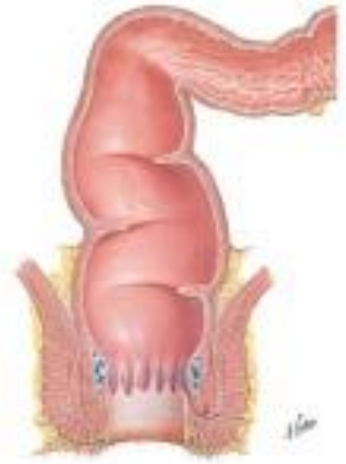
Rectum is one of the most frequent location for NETs (12-17%)

The metastatic potential of a rectal carcinoid tumor, as well as its clinical behavior, is generally proportional to tumor size

Usually small rectal NETs of 10 mm or less in size, and no infiltration in the muscularis propria, can be removed endoscopically

Heo et al. Surg Endosc 2014

Rectal NETs



Nevertheless metastatic involvement could occur in 3% of RNETs with a diameter of 10 mm or less

Several parameters have been suggested as predictive criteria in assessment of the malignant potential:

- tumor size
- tumor endoscopic features
- lymphovascular invasion
- muscularis propria invasion
- histological growth patterns

Heo et al. Surg Endosc 2014

Rectal NETs

ORIGINAL ARTICLE

Retrospective Study

Clinical impact of atypical endoscopic features in rectal neuroendocrine tumors

Jong Hee Hyun, Seong Dae Lee, Eui Gon Youk, Jae Bum Lee, Enu-Jung Lee, Hee Jin Chang, Dae Kyung Sohn

217 patients included in the study were evaluated for endoscopic features of RNETs:

Typical features:

- smooth surface, sessile shape, pink or yellow colour

Atypical features:

- ulcerated/depressed surface, semipedunculated/ulcerofungating shape, hyperemic colour

Hyun et al. WJG 2015

Rectal NETs

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	Univariate analysis			Multivariate analysis	
	Metastasis (-)	Metastasis (+)	*P* value	OR (95%CI)	*P* value
Gender			0.183	-	-
Male	144 (92.3)	12 (7.7)			
Female	88 (96.7)	3 (3.3)			
Age (yr)			1.000	-	-
⩽ 50	113 (94.2)	7 (5.8)			
> 50	119 (93.7)	8 (6.3)			
Size (mm)			< 0.001	11.53 (2.51-52.93)	0.002
< 10	219 (98.6)	3 (1.4)			
⩾ 10, < 20	13 (59.1)	9 (40.9)			
⩾ 20	0 (0)	3 (100)			
Tumor shape			< 0.001	-	-
Sessile	205 (97.6)	5 (2.4)			
Semipedunculated	27 (77.1)				
Ulcerofungating	0 (0)				
Surface change					
Smooth	222 (97.8)				
Depressed/eroded	10 (55.6)				
Ulcerated	0 (0)				
Color					
Normal or yellow	210 (96.8)	7 (3.2)			
Hyperemia	22 (73.3)	8 (26.7)			
Atypical features, any			< 0.001	4.38 (0.92-20.80)	0.064
Typical features	189 (98.4)	3 (1.6)			
Atypical features	43 (78.2)	12 (21.8)			

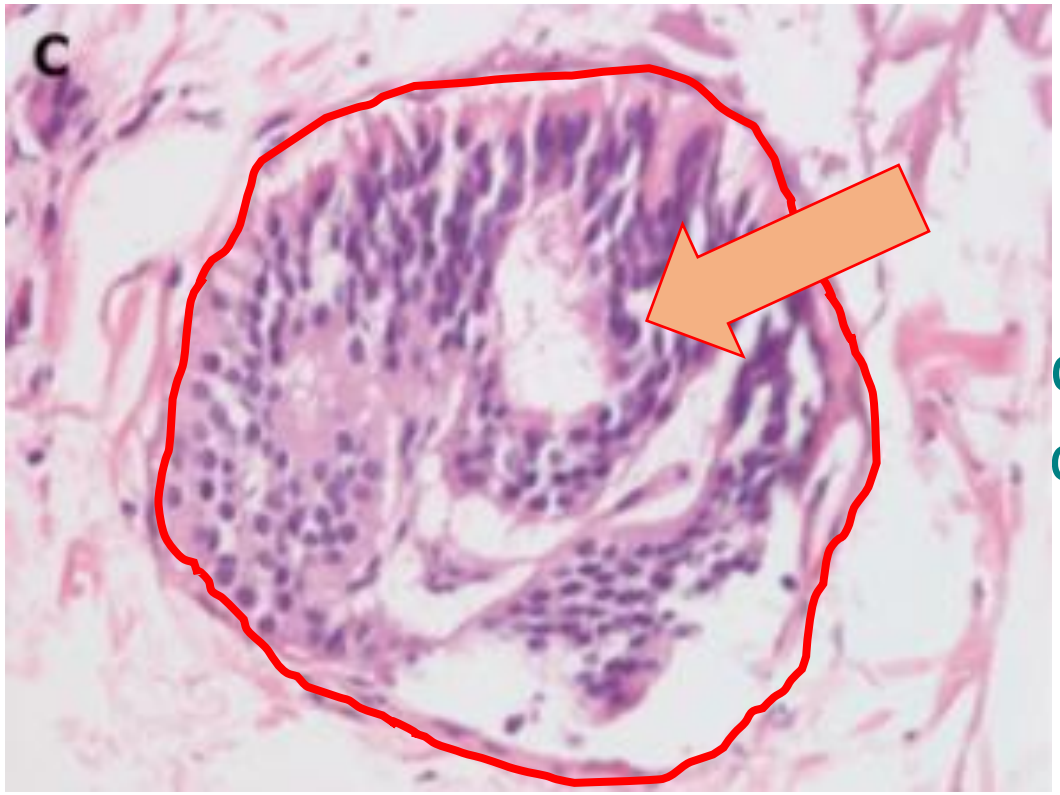
Atypical endoscopic features as well as tumor size, resulted predictive factors of LNM in patients with rectal NETs

Hyun et al. WJG 2015

Retrospective Study

Lymphovascular invasion in more than one-quarter of small rectal neuroendocrine tumors

Mi Jung Kwon, Ho Suk Kang, Jae Seung Soh, Hyun Lim, Jong Hyeok Kim, Choong Kee Park, Hye-Rim Park, Eun Sook Nam



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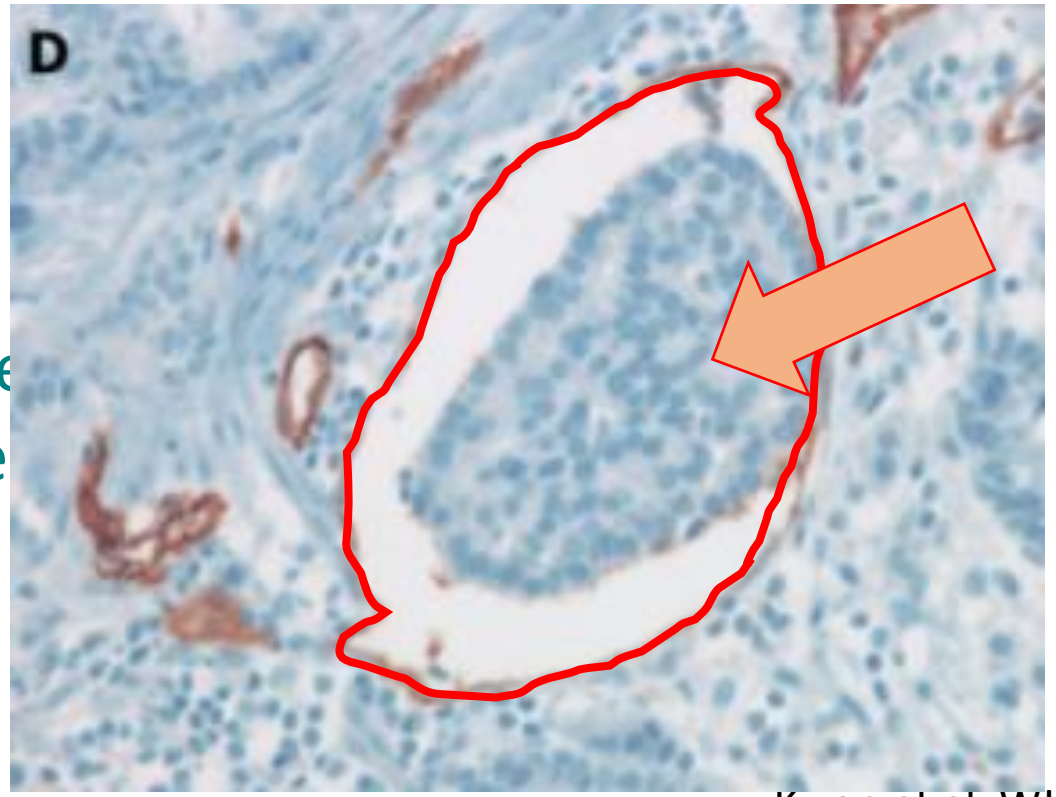

Kwon et al. WJG 2016

Retrospective Study

Lymphovascular invasion in more than one-quarter of small rectal neuroendocrine tumors

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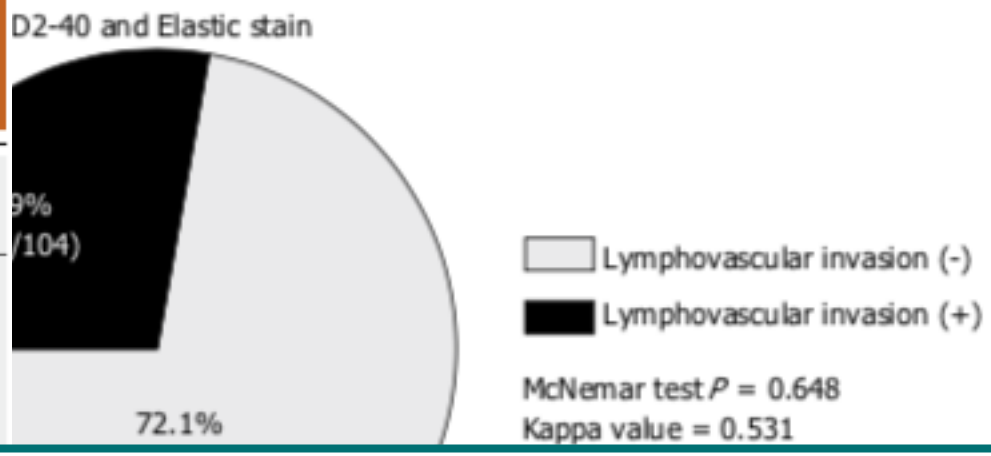
Table 4 Outcomes of endoscopic resection procedures in relation to tumor size, margin status, and lymphovascular invasion *n* (%)

	ESMR-L *n* = 57	ESD *n* = 41	*P* vaule
LVI			0.955
Absent	42 (58.3)	30 (41.7)	
Present	15 (58.2)	11 (42.3)	
Tumor size			0.192
⩽ 5 mm	38 (66.7)		
> 5 mm	19 (33.3)		
Resection outcome			
Complete (R0)	50 (87.7)		
Incomplete (R1)	7 (12.3)		
Safety resection margin (μm)	725 ± 872		



An excellent prognosis was found in the small rectal NETs. There was no recurrence or metastasis in patients with LVI during follow-up period of 28.8 mo in the study.

ORIGINAL ARTICLE—ALIMENTARY TRACT

Excellent prognosis following endoscopic resection of patients with rectal neuroendocrine tumors despite the frequent presence of lymphovascular invasion

Masau Sekiguchi[1,2] · Shigeki Sekine[3] · Taku Sakamoto[1] · Yosuke Otake[1] · Takeshi Nakajima[1] · Takahisa Matsuda[1] · Hirokazu Taniguchi[3] · Ryoji Kushima[3] · Yuichiro Ohe[2] · Yutaka Saito[1]

Retrospectively analyzed the clinicopathological features and outcomes of 86 patients with 90 rectal NETs who had been treated by Endoscopic Resection (ER)

- EMR
- ESMR-L
- ESD

Sekiguchi et al. J Gastroenterol 2015

Endoscopic resection procedure, *n* (%)	
Polypectomy/EMR	3 (3.3 %)
ESMR-L	83 (92.2 %)
ESD	4 (4.4 %)
Tumor size (mm), median (range)	5.0 mm (2–13)
Tumor depth, *n* (%)	
Submucosa	90 (100 %)
Ulceration/depression, *n* (%)	
Present	3 (3.3 %)
Absent	87 (96.7 %)
Ki-67 labeling index (%), median (range)	0.9 (0.1–2.9)
Tumor grade, *n* (%)	
Grade 1	90 (100 %)
Lymphatic invasion, D2-40/synaptophysin, *n* (%)	
Positive	23 (25.6 %)
Negative	67 (74.4 %)
Venous invasion, CD31/synaptophysin, *n* (%)	
Positive	9 (10.0 %)
Negative	81 (90.0 %)
Venous invasion, elastic staining, *n* (%)	
Positive	33 (36.7 %)
Negative	57 (63.3 %)
Cut margin of the resected specimen, *n* (%)	
R0	87 (96.7 %)
R1	2 (2.2 %)
RX	1 (1.1 %)

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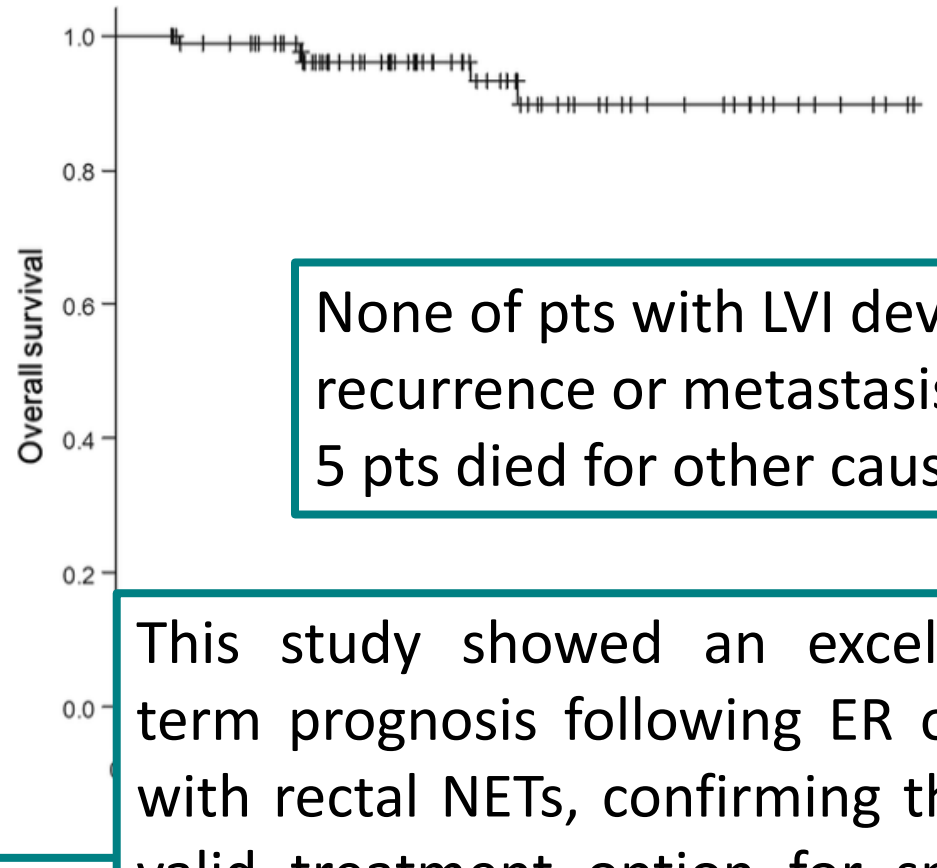
presenc



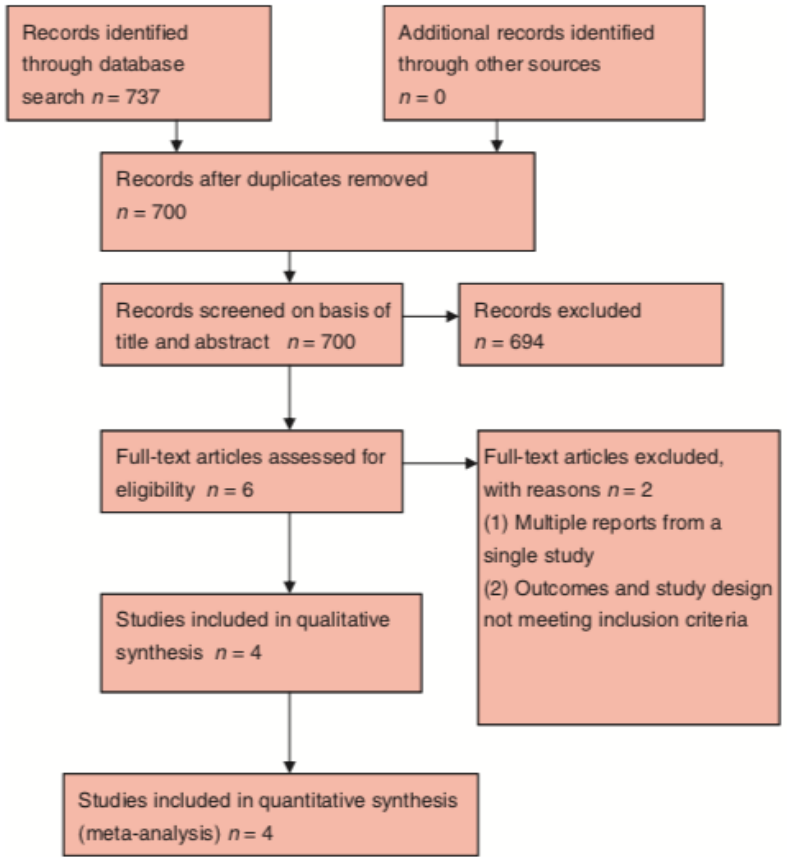
None of pts with LVI developed recurrence or metastasis,
5 pts died for other causes

This study showed an excellent long-term prognosis following ER of patients with rectal NETs, confirming that ER is a valid treatment option for small rectal NETs.

Sekiguchi et al. J Gastroenterol 2015

Endoscopic mucosal resection *vs* endoscopic submucosal dissection for rectal carcinoid tumours: a systematic review and meta-analysis

D.-D. Zhong, L.-M. Shao and J.-T. Cai



4 retrospective and monocentric studies

274 patients with rectal NET removed by EMR or ESD

Zhong et al. Colorectal Dis 2013

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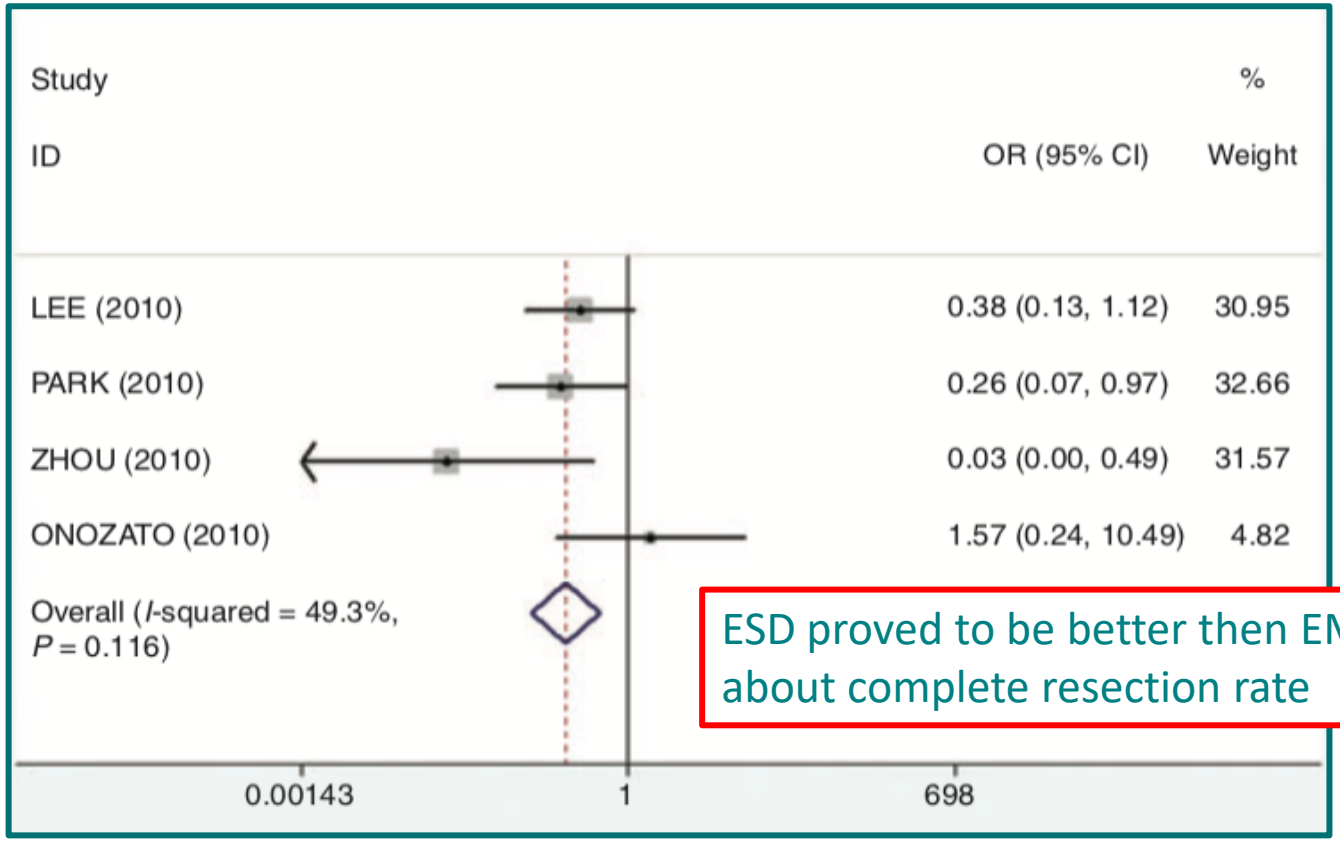
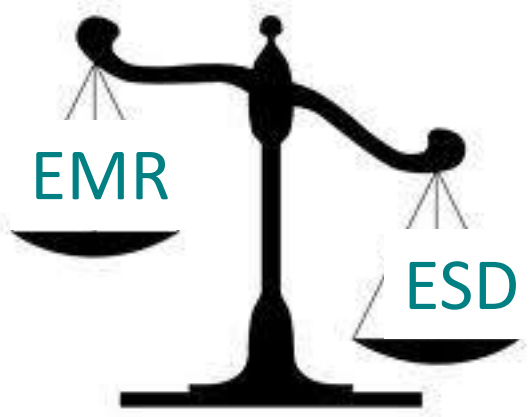


ESD proved to be better then EMR about complete resection rate

Complete resection rate



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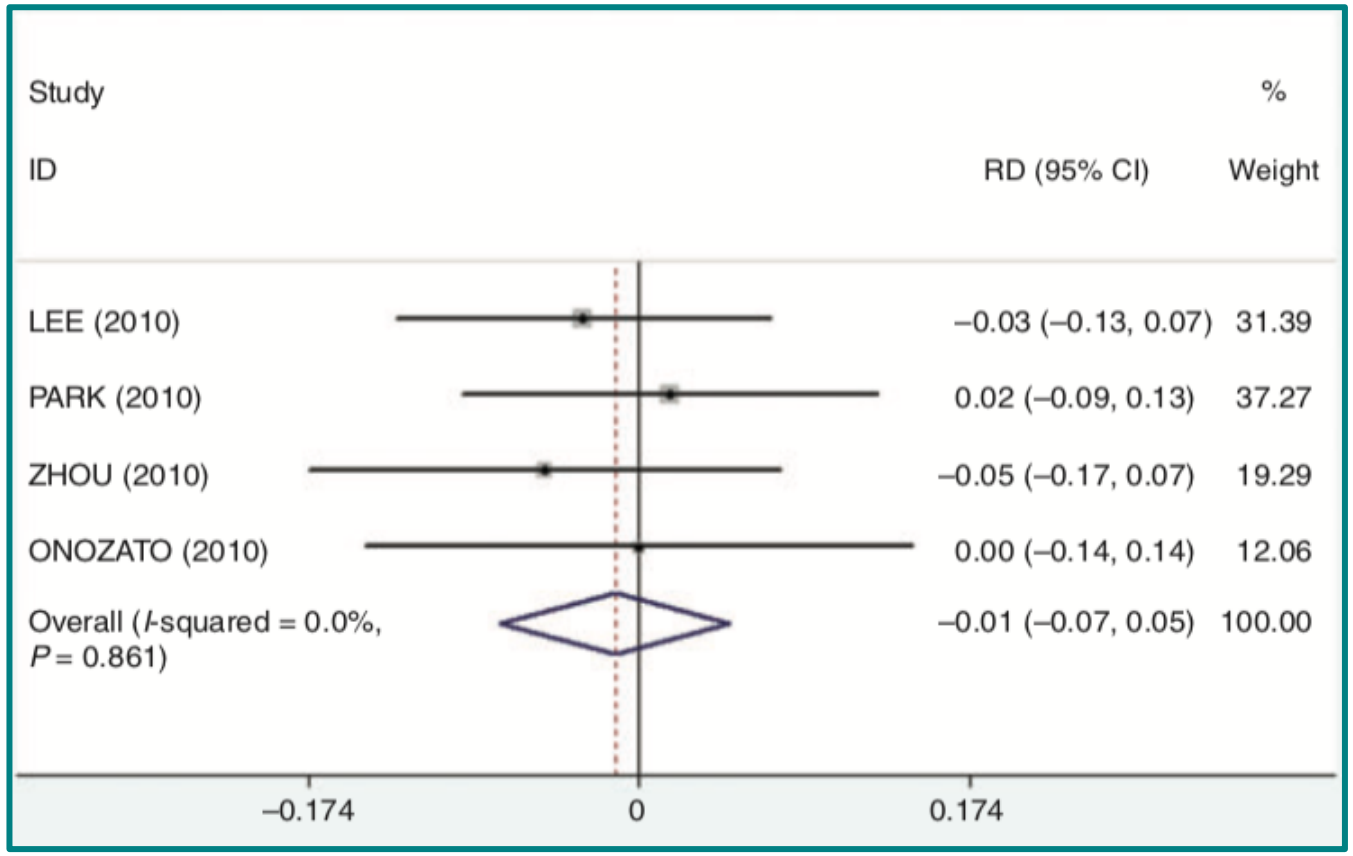
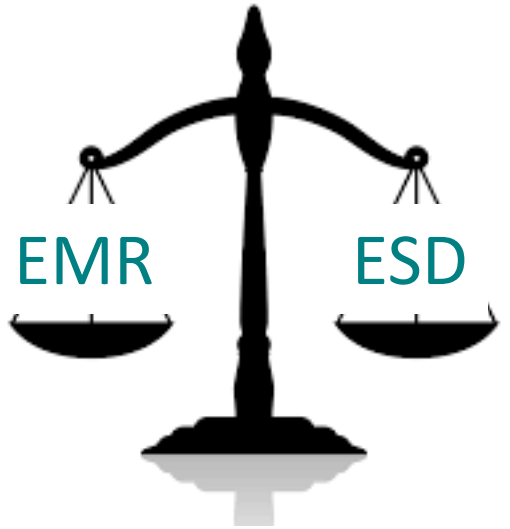


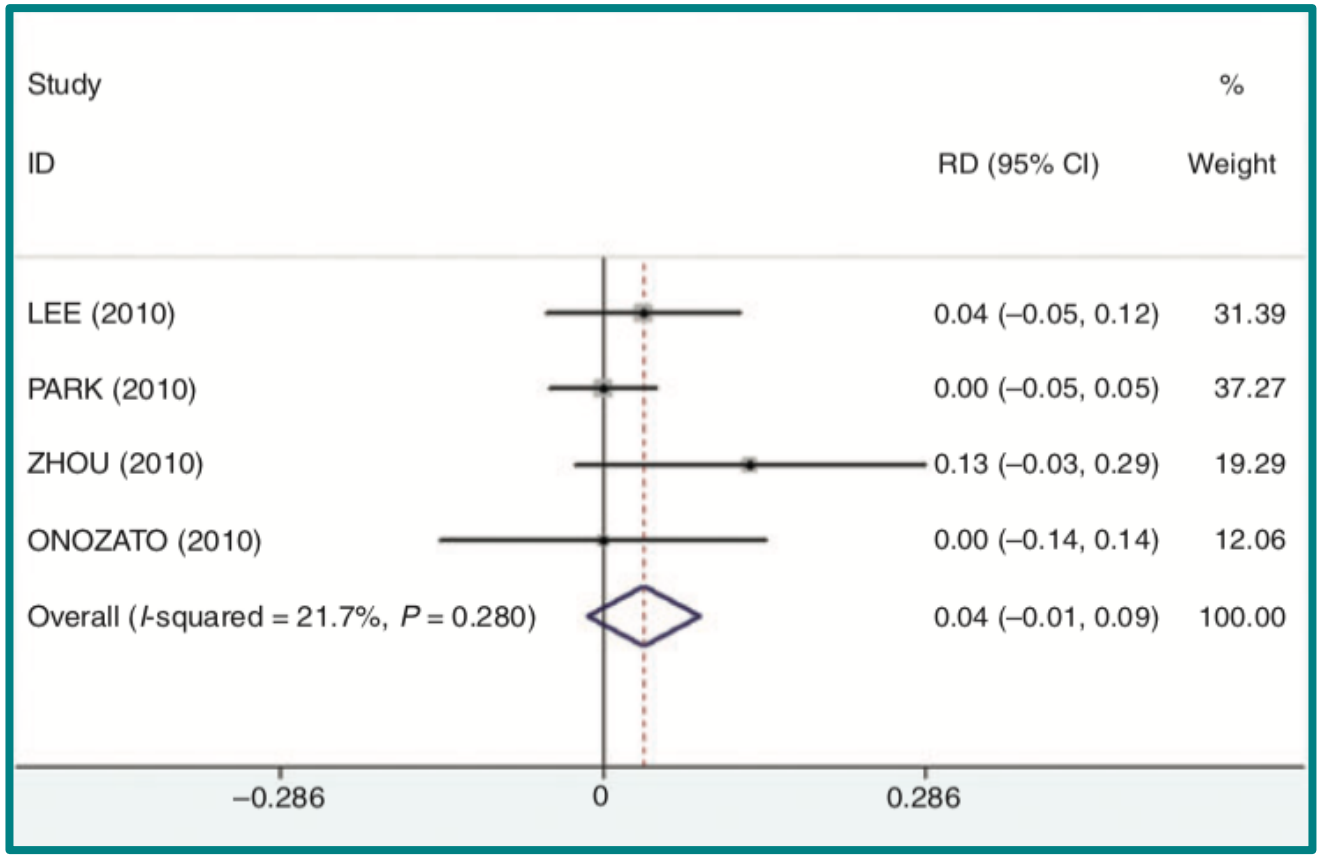
Overall complication rate



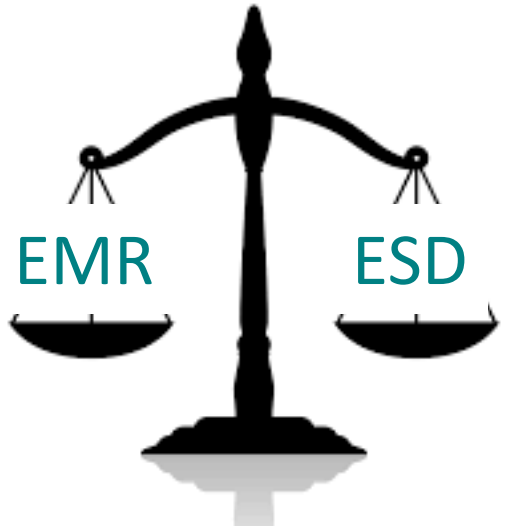
Zhong et al. Colorectal Dis 2013

Endoscopic mucosal resection *vs* endoscopic submucosal dissection for rectal carcinoid tumours: a systematic review and meta-analysis

D.-D. Zhong, L.-M. Shao and J.-T. Cai



Recurrence rate



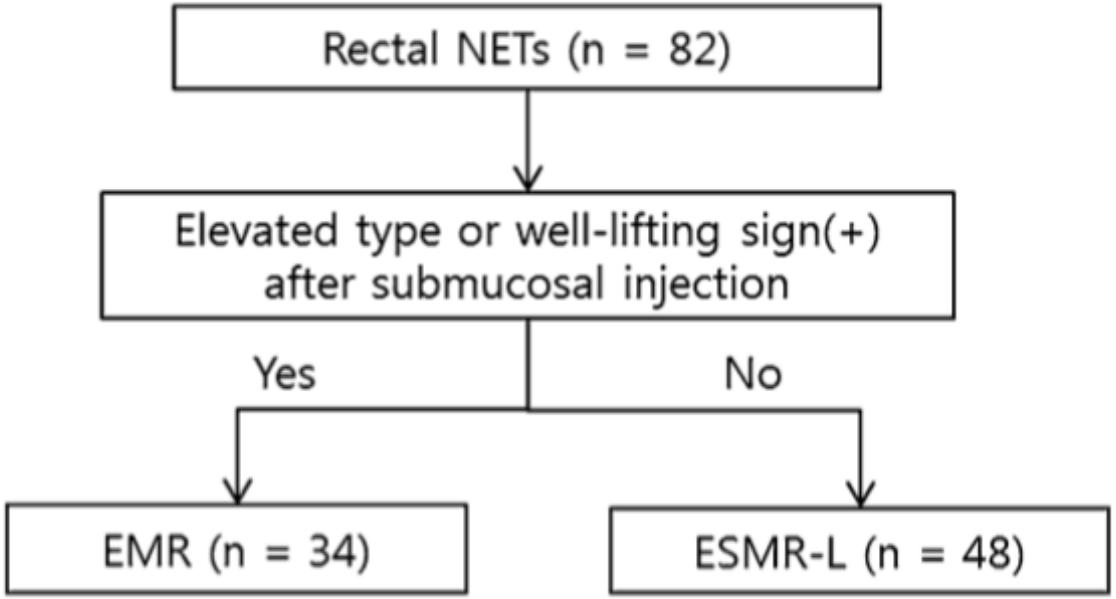
Zhong et al. Colorectal Dis 2013

Rectal NET

A tailored approach for endoscopic treatment of small rectal neuroendocrine tumor

Jun Heo · Seong Woo Jeon · Min Kyu Jung · Sung Kook Kim · Geun Young Shin · Sang Man Park · Sun Young Ahn · Won Kyung Yoon · Min Kim · Yong Hwan Kwon

82 rectal NETs in 77 patients treated by ESMR-L (n = 48) or EMR (n = 34)



Heo et al. Surg Endosc 2014

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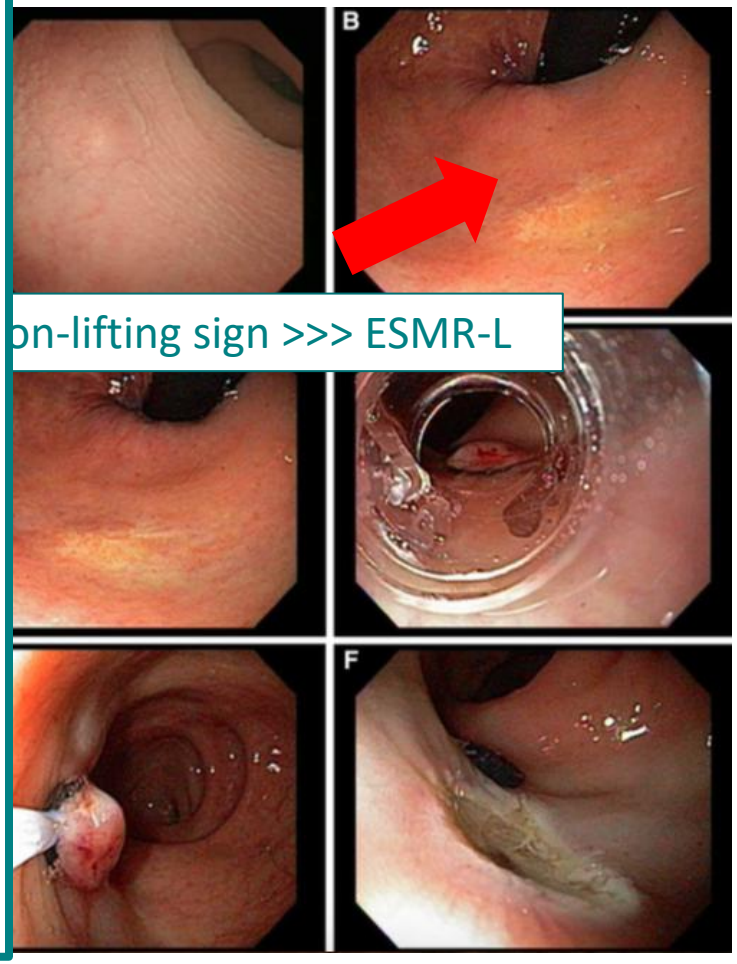
We

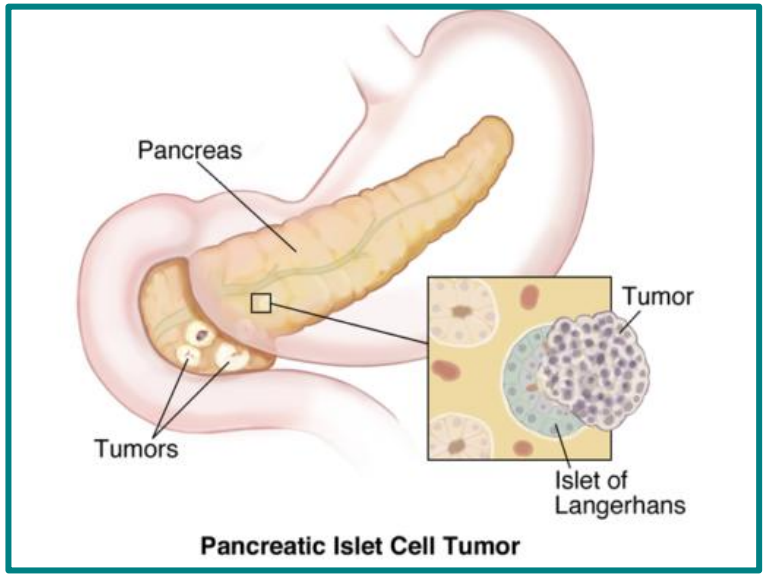
Table 2 Endoscopic and histological complete resection rates for the ESMR-L and EMR groups

	ESMR-L ($n = 48$)	EMR ($n = 34$)	p value
Pathologically measured tumor size, mm			0.007
Mean ± SD	5.3 ± 2.6	7.0 ± 2.8	
Range	2–15	2–16	
Pathologically measured tumor size, *n (%)*			0.136
>10 mm	3 (6.3)	6 (17.6)	
≤10 mm	45 (93.8)	28 (82.4)	
Endoscopic complete resection, *n (%)*[a]	48 (100)	32 (94.1)	0.160
Histological Complete resection, *n (%)*	45 (93.8)	30 (88.2)	0.441
Lateral margin involvement	0 (0)	0 (0)	0.807
Vertical margin involvement	2 (4.2)	4 (11.8)	0.161
Lymphovascular invasion	1 (2.1)	0 (0)	0.403



on-lifting sign >>> ESMR-L

Pancreatic NETs



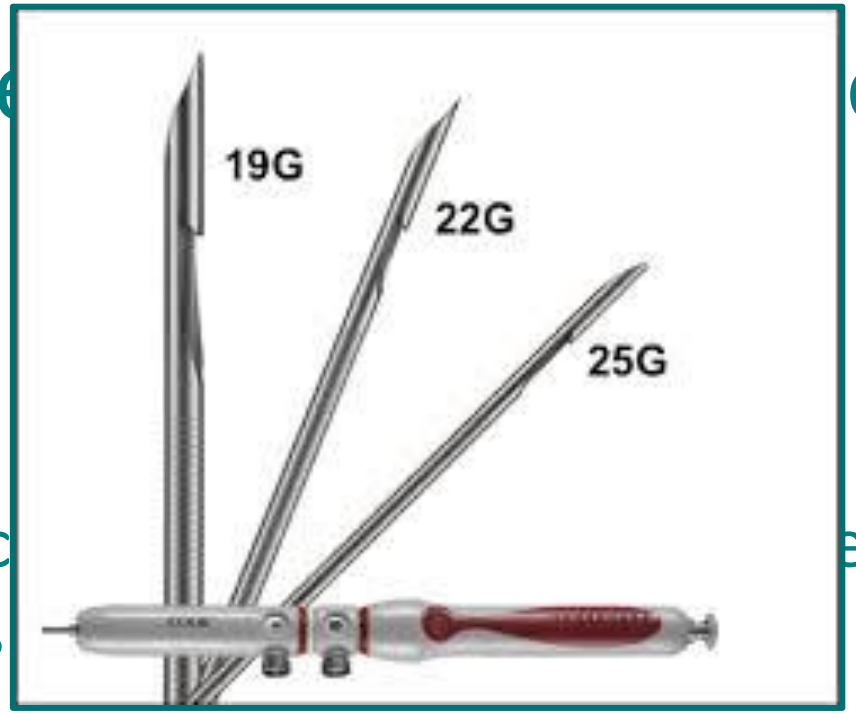
1–2% of all pancreatic tumors

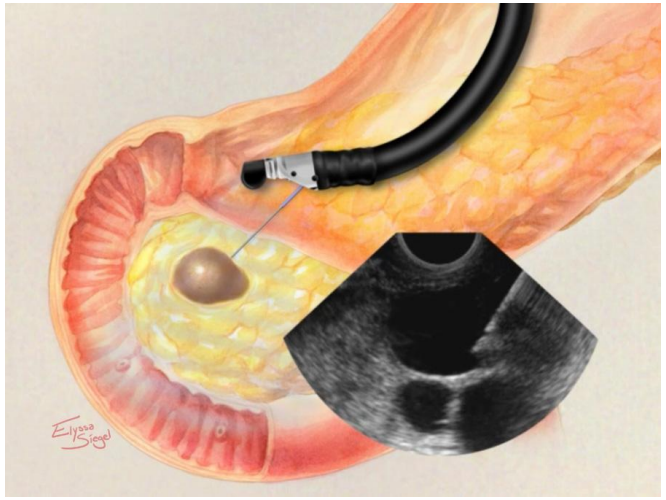
Most PNETs are sporadic, but they can be associated with:

- Multiple Endocrine Neoplasia Type 1 (MEN1) (80-100%)
- Von Hippel Lindau (VHL) syndrome (20%)
- Neurofibromatosis Type 1 (NF1) (10%)
- Tuberous sclerosis (1%)

Rustagi et al. JCGE 2014

Pancre of EUS





- Endosc etect a
  lesions
- EUS can detect the tumor in the pancrea
  (82%) and specificity (95%) (CT negative)
- EUS-guided FNA can often provide a cyto
  (recently FNB)

Rastagi et al. JCGE 2014

Pancreatic NETs: therapeutic role of EUS

Although **surgical resection** is currently considered to be the gold standard for treatment of PNETs.

EUS-guided therapy could be considered for small PNETs in patients who refuse surgery or are poor surgical candidates.

Rustagi et al. JCGE 2014

Pancreatic NETs: therapeutic role of EUS

First use of EUS-guided ablation for NET, was the intraparenchimal injection of ethanol.

Other modalities:

- radiofrequency ablation
- photodynamic therapy
- brachytherapy

In addition, EUS-guided pancreatic cyst ablation using alcohol and paclitaxel that has been described for pancreatic cystic neoplasms.

Rustagi et al. JCGE 2014

US-guided ethanol ablation of insulinomas: a new treatment option

Michael J. Levy, MD,[1] Geoffrey B. Thompson, MD,[3] Mark D. Topazian, MD,[1] Matthew R. Callstrom, MD,[4] Clive S. Grant, MD,[3] Adrian Vella, MD[2]

Rochester, Minnesota, USA

A case series published describing 5 patients with insulinoma who underwent EUS-guided ethanol ablation with complete disappearance of hypoglycemia.

Levy et al. GIE 2012

Pancreatic NETs

TABLE 6. Subsequent course (after final injection)

Pt	Follow-up duration, mo	Average lowest blood sugar level, mg/dL	Average highest blood sugar level, mg/dL	Antihypoglycemic therapy	Associated symptoms*	No. of times sought emergent or urgent medical attention (after therapy)	No. of times sought emergent or urgent medical attention (before therapy)*
1	16	95	120	None	Asymptomatic	0	6
2	13	120	150	Diazoxide 50 mg qd	Asymptomatic	0	6-10
3	35	80	155	None	†	0	>10
4	13	80	125	Diazoxide 20 mg tid	‡	0	Numerous
5	12	110	150	None	Asymptomatic	0	Numerous
6	38	75	110	Diazoxide 50 mg bid	§	0	~20
7	5	65	110	None	Asymptomatic	0	Numerous
8	7	100	125	None	Asymptomatic	0	3

Levy et al. GIE 2012

Pancreatic NETs

Open Access

Therapy of Pancreatic Neuroendocrine Tumors: Fine Needle Intervention including Ethanol and Radiofrequency Ablation

Sundeep Lakhtakia

Department of Gastroenterology, Asian Institute of Gastroenterology, Hyderabad, Telangana, India

Study	*n*	Indication	Size, mm (range)	RF device	Thermo-kinetics	RF session	Outcome: ablation	Recur-rence	Compli-cations
Armellini et al. (2015)[26]	1	PNET	20	18 G, Starmed	-	1	Complete	-	None
Rossi et al. (2014)[28]	1	PNET	9	Habib EUS RFA	10–15 W	1	Complete	None at 34 mo	None
Pai et al. (2015)[10]	2	PNET	27 (15–40)	Habib EUS RFA	20 W, 90–120 secs	1, 2	Change in vascularity, central necrosis	None at 1 mo	None
Lakhtakia et al. (2016)[8]	3	Functional PNET	18 (14–22)	19 G, Starmed	50 W	1	Size reduced, symptom improved	None at 12 mo	None

EUS, endoscopic ultrasound; RFA, radiofrequency ablation; PNET, pancreatic neuroendocrine tumor.

Lakhtakia et al. Clin Endosc 2017

Pancreatic NETs: EUS guided positioning of fiducials

Endoscopic ultrasound (EUS)-guided fiducial placement allows localization of small neuroendocrine tumors during parenchymal-sparing pancreatic surgery

Joanna K. Law · Vikesh K. Singh · Mouen A. Khashab · Ralph H. Hruban · Marcia Irene Canto · Eun Ji Shin · Payal Saxena · Matthew J. Weiss · Timothy M. Pawlik · Christopher L. Wolfgang · Anne Marie Lennon

The placement of fiducials under endoscopic ultrasound (EUS) guidance (EUS-F) has been used to direct stereotactic radiation therapy for pancreatic adenocarcinoma

This report describes two cases in which placement of fiducials was used to guide surgical resection of PNET by using IO-US

Law et al. Surg Endosc 2013

Pancreatic NETs

Other EUS-guided therapies that have been described for pancreatic adenocarcinoma, can also be potentially used in treatment of PNETs, including:

- YAG laser
- injection of several anti-tumor agents
  - TNFerade
  - cytoimplant

Rustagi et al. JCGE 2014

Take-home messages

- Endoscopy and EUS give diagnostic possibilities that are unbeatable in the localization of GI NETs
- Endoscopic therapy is effective and safe for curative resection of small GI NETs
- EMR and ESD are mostly equivalent, ESD should be performed by skilled endoscopist
- EUS-guided approach to pancreatic NETs is a growing field, with new therapeutic options in rapid development
- Treatment of complex cases should be discussed in a multidisciplinary team (Oncologist, Rad-therapist, Surgeon, Endoscopist)

Thank you for your attention

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Ospedale Niguarda Ca' Granda