Endoscopic Management of the Common Neuroendocrine Tumors of the Gut

Douglas O. Faigel MD FASGE

Professor of Medicine

Oregon Health & Science University

Portland, OR

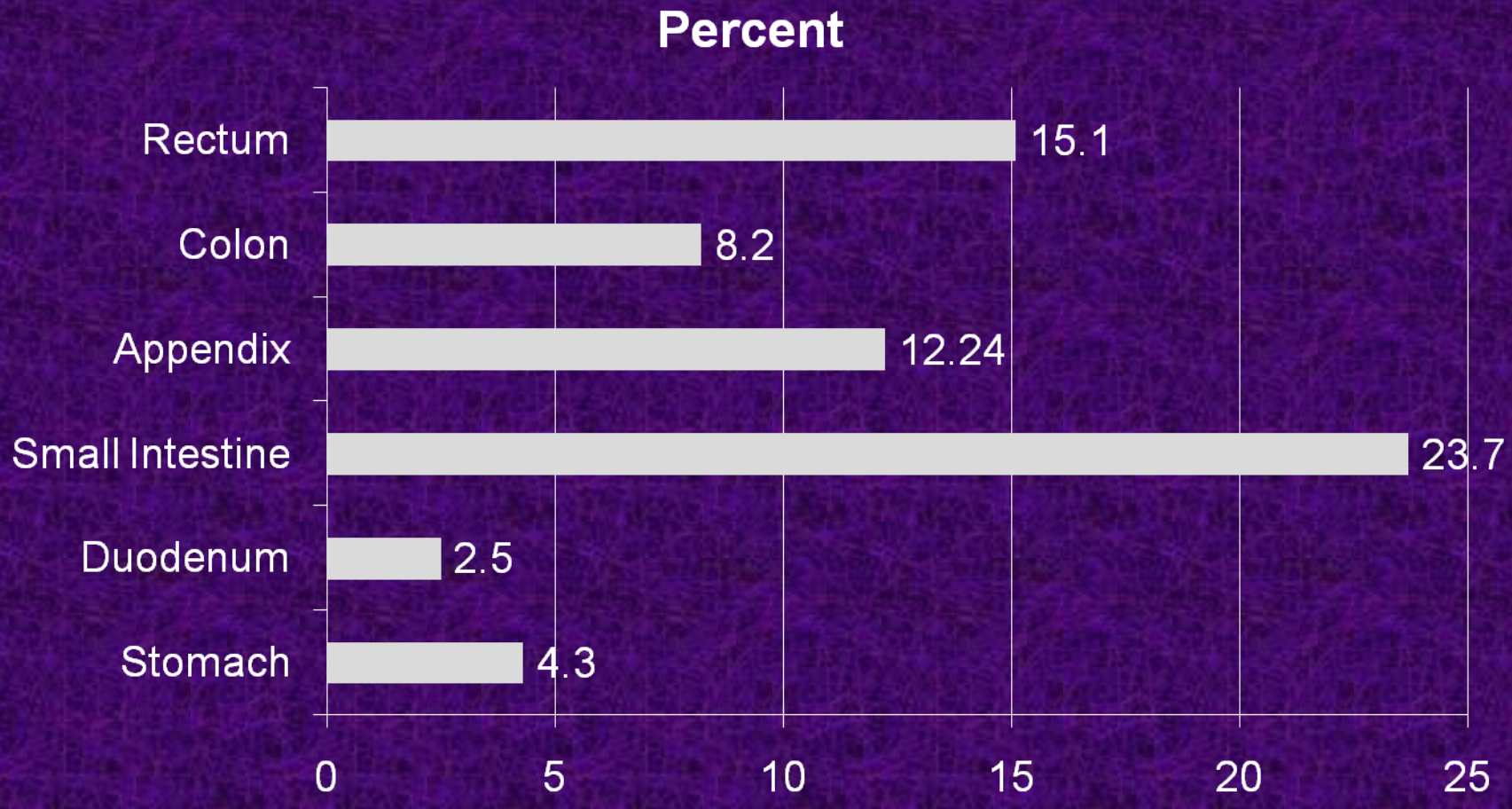
OHSU

Oregon Health & Science University

Outline

- Common sites where neuroendocrine tumors are encountered in the gut
- Pathologic types and their frequency
- Malignant potential of NE tumors of the gut
- Role of EUS in evaluation
- Role of EMR
- Follow-up for recurrence and metastasis
- Mangement of recurrent gastric carcinoids in atrophic gastritis

Distribution of Gut NET



Modlin Cancer 2003

Endoscopic NET

- Tumors amenable to endoscopic evaluation and treatment
  - Rectum (70%)
  - Stomach (20%)
  - Duodenum (10%)
- Others
  - Colon: mostly large symptomatic cecal masses
  - Distal jejunum and ileum: Dx by capsule and enteroscopy (Surgically treated)

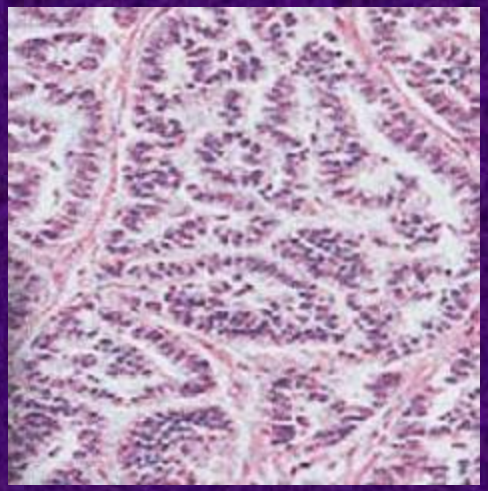
Pathology

- Neuroendocrine tumors
  - No longer “carcinoid”
  - Well differentiated
  - Mucosa/submucosa and no mets
- Neuroendocrine carcinoma
  - Well differentiated
  - MP invasion or metastases
- Small Cell Carcinoma
  - Poorly differentiated

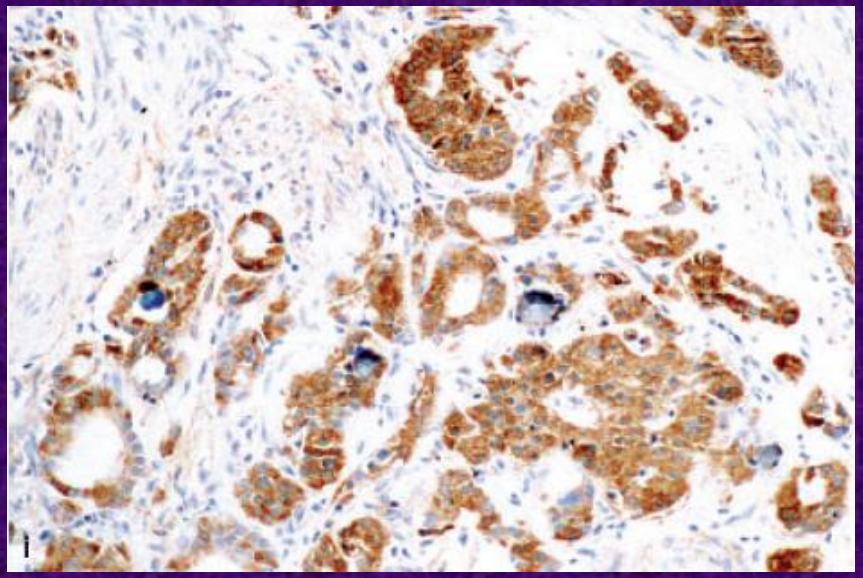
Pathology

- Solid nests of cells
- Open nuclei with speckled chromatin
- Small nucleoli
- Variable quantities of eosinophilic cytoplasm
- NE Markers:
  - Chromogranin
  - Neuron-specific enolase (NSE)
  - Gastrin, somatostatin, serotonin

Williams Histopath 2007



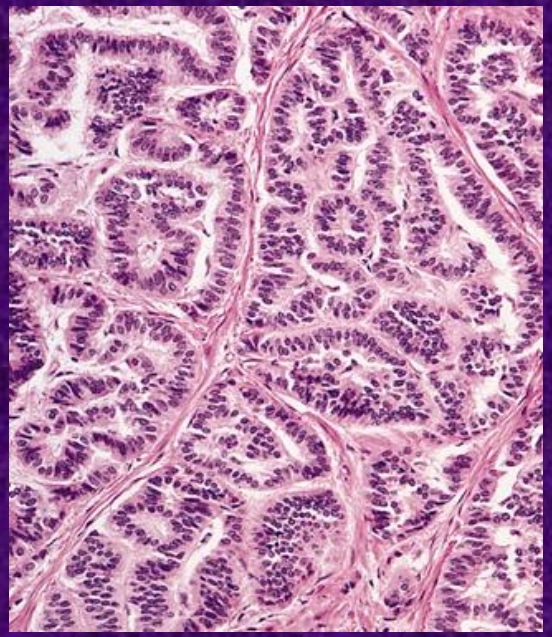
Benign NET



Periampulary Somatostatinoma

Gastric NET

- Three types:
  - Type I (chronic atrophic gastritis)
    - “good”
  - Type II (ZE syndrome)
    - “less good”
  - Type III (sporadic)
    - “bad”
- 10-30% of all GI NET
  - Increasingly recognized
    - Pre-endoscopic era: 1.9% of all carcinoids



Gastric NET

- Type I
  - Most common type (65%)
  - Chronic atrophic gastritis and hypergastrinemia
    - Pernicious anemia (check B12 level)
    - Autoimmune gastritis
    - Thyroid disease
  - Generally small (<1 cm) and multiple
  - Body and Fundus
    - Incidentally found
  - ECL lesion
  - Slow growth
    - Regional and distant mets extremely rare (<5-9%)
    - 5-year survival >95%

Gastric NET

- Type II (15%)
  - Zollinger-Ellison Syndrome
    - MEN-1
  - Gastrinoma-derived hypergastrinemia
  - ECL lesion
  - Slow growth
  - May metastasize more often than Type I
  - Prognosis determined by gastrinoma prognosis

Gastric NET

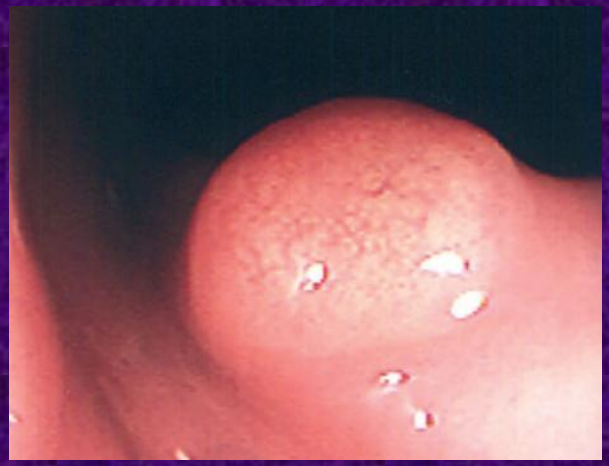
- Type III (20%)
  - Sporadic
  - More likely to be symptomatic
  - High incidence of metastasis
    - Nodes 55%
    - Liver 24%
  - Poor prognosis
    - 5-year survival <35%
  - Treatment: surgery

Duodenal NET

- 5 types
  - Gastrinomas (65%)
    - Sporadic or MEN-1
    - Cause ZE syndrome
  - Somatostatinomas (15%)
  - Nonfunctioning NET
  - NE carcinomas
    - Typically ampullary
  - Gangliocytic paraganliomas

Rectal NET

- Typically asymptomatic
- Found incidentally or with painless BRBPR
- Small mobile submucosal nodule
- Increasingly recognized
  - "Incidence" increased 8-10x in last 35 yrs
- Metastasize 4-18%
  - Rare in tumors< 1cm
- 5-year survival 88%



Malignant Potential

- Size
  - <1 cm good
  - >2 cm bad
  - In between?
- Histology
  - Well differentiated good
  - Poorly differentiated bad
  - Gastrin/Somatostatin bad
- Depth of invasion
  - Mucosa/SM good
  - Muscularis propria bad
- Mets
  - None good
  - Any (nodes, liver) bad
- Etiology (bad)
  - Type III Gastric
  - Duodenum MEN-1
    - Hormone syndrome

Role of EUS

- Diagnosis
  - If prior biopsy non-Dx
  - Dark round lesion
  - 2nd-3rd layers
- Measuring Size
  - Remember <1 cm good
- Depth of invasion
  - 90% accurate
  - Remember MP bad
- Detecting lymph nodes
  - EUS-FNA
- Selection for EMR

Yoshikane H GIE 1993

Endoscopic Mucosal Resection

- Patient Selection:
- Gastric NET
  - Type 1 (Atrophic Gastritis)
    - Type 2? (ZE Syndrome – rare)
    - Well differentiated
  - Size <1-2 cm
  - Number of macroscopic tumors ≤5
    - Tumors >5 mm
  - EUS:
    - No MP invasion, nodes metastases

Type I: Size, Depth, Metastases

- 65 pts Sweden
  - 51 Type 1
- Predictor of depth:
  - Size
  - Independent of #
- Predictor of mets
  - Penetration of MP
  - Independent of #
- Number did not predict depth, mets or survival

Borch Ann Surg 2005

TABLE 4. Relation Between the Depth of Tumor Infiltration in the Gastric Wall and Tumor Diameter Among Patients With Type 1 Gastric Carcinoid and Relation Between the Depth of Tumor Infiltration in the Gastric Wall and Occurrence of Metastases Among Patients With Type 1 Gastric Carcinoid

	Maximum Tumor Diameter (mm)*			
	Solitary Tumor		Multicentric Tumor	
Depth of Tumor Infiltration	No.	Median (range)	No.	Median (range)
Mucosa	6	7 (4–10)	10	5 (5–7)
Submucosa	8	10 (5–35)	18	10 (6–23)
Muscularis propria	1	14	3	12 (7–35)
Subserosa	1	40	2	18 (10–25)
Serosa	1	80	1	50

	Metastases (the Most Distant)†			
	None	Perigastric Lymph Node	Regional Lymph Node	Extra-Regional/ Liver
Mucosa	16	0	0	0
Submucosa	25	0	0	1
Muscularis propria	4	0	0	0
Subserosa	2	1	0	0
Serosa	0	0	2	0
Total	47	1	2	1

*$P = 0.078$ for solitary tumors and $P = 0.0002$ for multicentric tumors (Kruskall-Wallis test).

†$P = 0.0001$ (χ^2 analysis).

Rectal Carcinoid

- Pt selection for EMR
- Size ≤ 1 cm*
  - Mets ≤ 1 cm: 0-4%
  - Mets >1 cm: 4-18%
    - Nodes: 0-4% for 1 cm, 4-16% 1-2 cm, up to 40% for >2 cm
    - Liver mets: None if <2cm
- Well differentiated
- EUS: No MP invasion, no nodes
  - Depth: 90-100% accurate

*Modlin Cancer 2003, *,**Kobayashi DisColRect 2005, *Soga Cancer 2005
*Kwaan Arch Surg 2008, Konishi Gut 2007

Duodenal Carcinoid

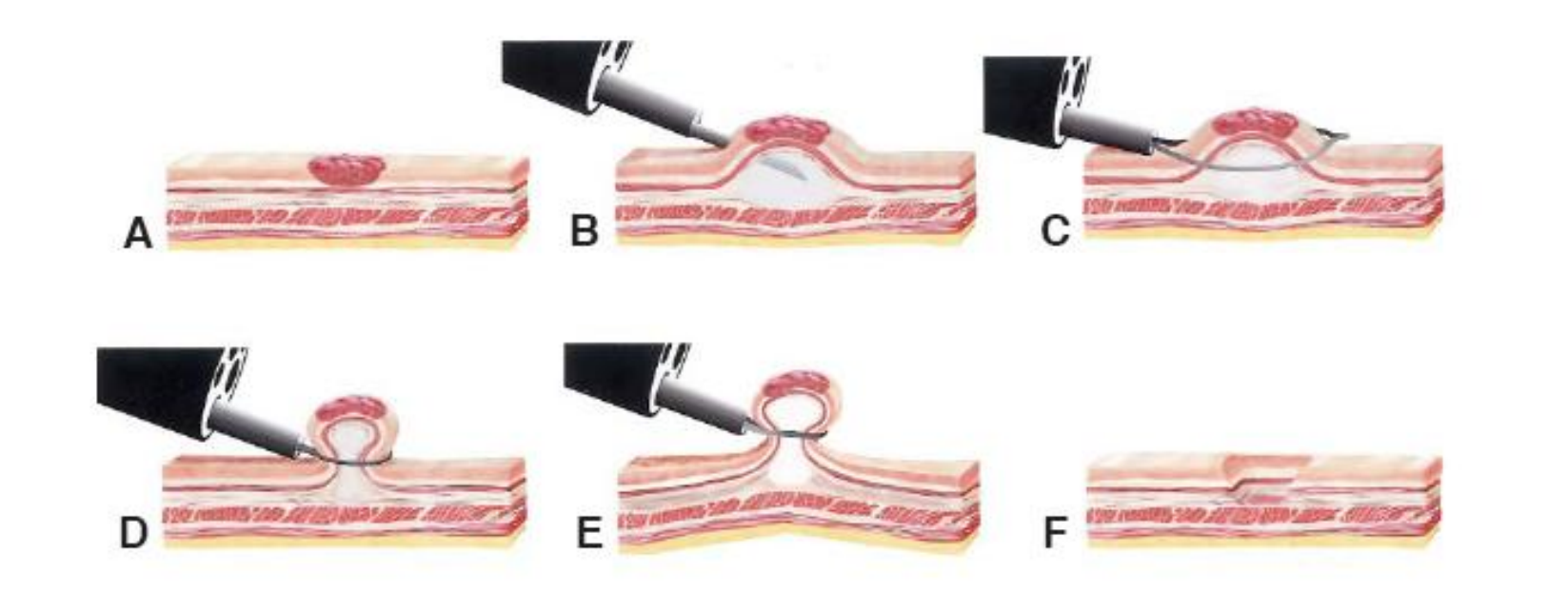
- Pt selection for EMR
- Size ≤ 1cm*
  - Mets or recurrence < 2 cm: rare
  - Mets > 2 cm: up to 100%
    - Mayo clinic series f/u up to 9 years*
- Well differentiated, non-syndromic
  - No MEN-1, ZE syndrome, somatostatinoma
- EUS: no MP invasion, nodes
- Gangliocytic paraganglioma
  - Treat as per endoscopic ampullectomy

*Zyromski NJ, J Gastrointest Surg 2001

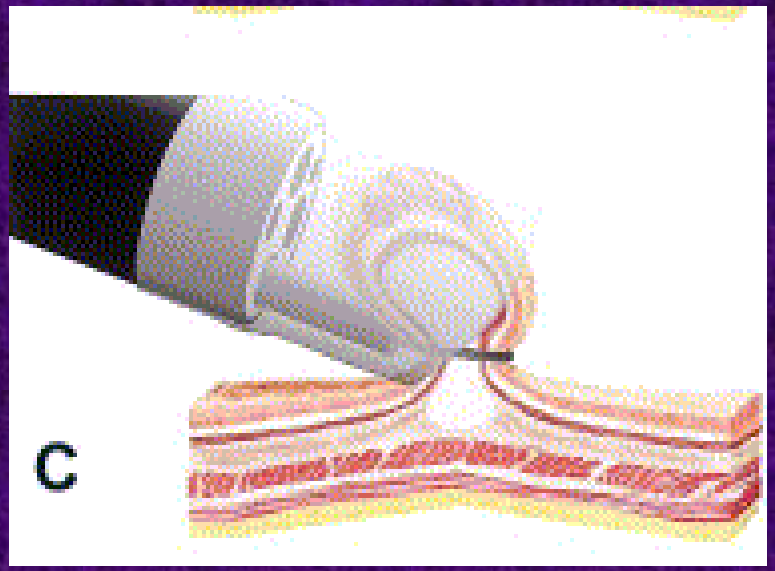
Other pre-EMR Evaluation?

- Tests to consider:
  - CT
  - Octreotide Scan
  - Serum Chromogranin A levels
- For pts who otherwise meet criteria for EMR, these tests are low yield and probably unnecessary
  - A positive test is likely a false-positive
- Use selectively

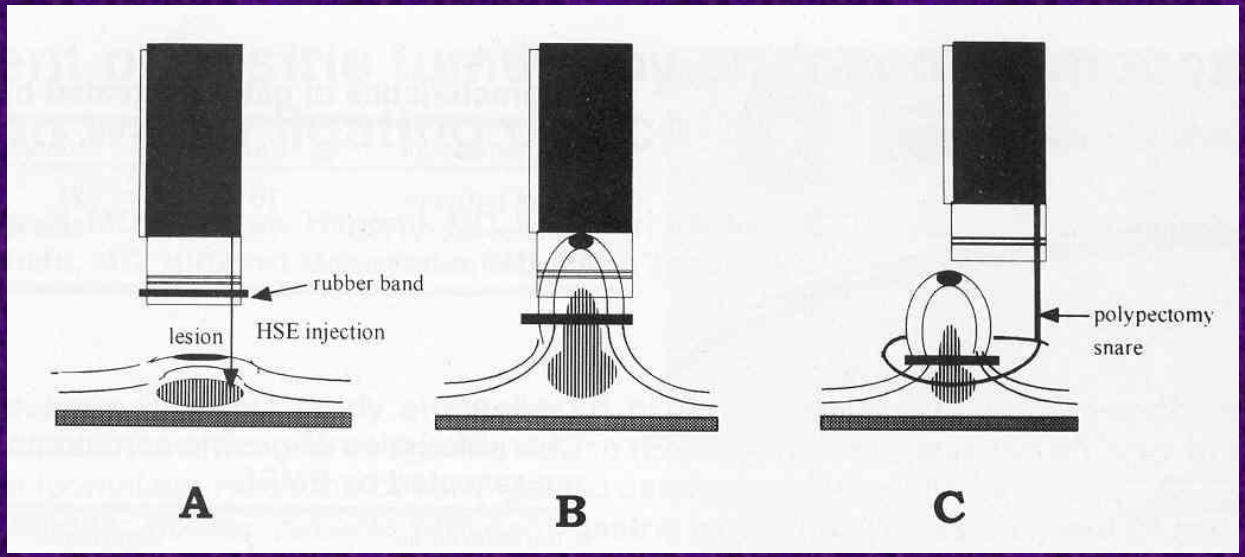
Endoscopic Mucosal Resection: EMR



Cap-assisted EMR



Ligate and Cut



Duodenal Carcinoid

Complications

- Bleeding 10-20%
  - Highest in duodenum and stomach
  - Less in rectum
- Perforation up to 1%

Ahmad GIE 2002

EMR Outcome

- Depends primarily on negative margin
  - Gross positive margin – bad
    - Needs additional therapy
  - Microscopic positive at cautery line probably not bad
    - Unlikely to find residual tumor
- Limited data on efficacy and outcome
- Small series and case reports

Outcome: Type I Gastric NET

- Tumors <11 mm
- Complete resection 67-100%
- No recurrence
  - 2-5 year follow-up
- Limitations
  - Small series (20 pts)
  - Variety of techniques
  - Non-standardized follow-up

Higashino Hepatogastr 2004, Spinelli Minerva Chir 1994, Ichikawa Endosc 2003

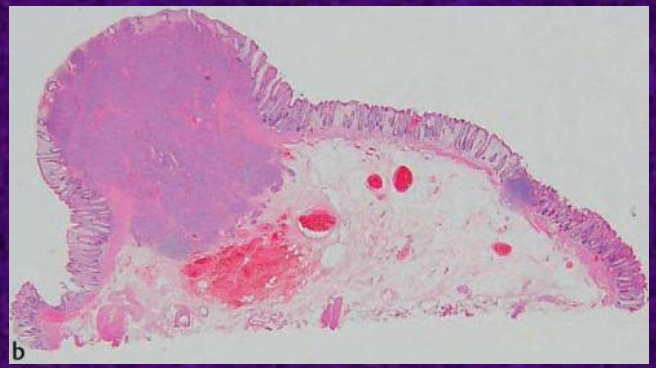
Outcome: Duodenal NET

- Tumors <11 mm
- Complete resection 50-100%
- No recurrences
  - Mean f/u 21 months
- Limitations:
  - Small series (<20 pts)
  - Non-standardized follow-up

Dalenback Endoscopy 2004

Outcome: Rectal Carcinoids

- Tumors <2 cm (most series <11 mm)
- Complete resection
  - 38-100%
  - Higher for cap and ligation: 88-100%
  - Lower for snare: 38-57%
    - One RCT ligation* (n=15), one non randomized cap** (n=16)
    - P<0.05 in each study
  - Recurrence: none
    - 4 series, n=100
    - 1-3 yr follow-up



*Sakata WJ Gastro 2006, **Nagai Endosc 2004
Mashimo J Gastro Hep 2008

Follow-up After EMR

- Endoscopy at 6 months intervals
  - Duodenum and rectum 2-3 years
  - Gastric 2-3 yrs then yearly thereafter
- Role of EUS
  - Lesions >1 cm
  - Microscopically positive margins
    - Re-resect if residual tumor identified vs. surgery
- Octreoscan and Chromogranin A
  - Same indications as EUS

Recurrent Type I Gastric NET

- My definition: tumor(s)>5 mm
  - Smaller: ECL hyperplasia
- Probably common, due to hypergastrinemia
  - Recurrence vs. new tumor
- Probably indolent
  - 8 pts with multiple NET followed for mean 5.8 years without resection, stable disease, no mets*
- Can be retreated with EMR (EUS)
- Symptomatic, young, unwilling to have repeated endoscopies: surgery (e.g. antrectomy)

*Hosokawa Gastric Cancer 2005

Summary

- NET amenable to endoscopic mgt:
  - Type I Gastric (atrophic gastritis)
  - Duodenal (non-syndromic)
    - Gangliocytic paragangliomas
  - Rectal
- EMR for:
  - Tumors <1 cm
  - Well differentiated histology
  - EUS: no MP invasion, no nodes

Summary

- Post-EMR Follow-up
  - Endoscopy Q6 months for 2-3 yrs
    - Indefinite for gastric
  - EUS, Octreoscan, Chromogranin A
    - Higher risk lesions
    - >1 cm, positive margins, poorly differentiated
- Recurrent Type I Gastric NET
  - EMR tumors>5 mm
  - Consider surgery