Origin and Classification of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NTEs)

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NEUROENDOCRINE CELLS *of the* PANCREAS *and* GI TRACT

- More that 15 different types of cells in the digestive system
- Belong to the diffuse endocrine cell system
- Originate from both ectodermal and endodermal progenitors
- Express morphological and functional markers originally described in neurons and neural crest-derived cells
- Produce peptides, biogenic amines or neuroregulatory substances
- Some cells retain their differentiation when proliferate and form tumors, while others do not

NEUROENDOCRINE CELLS *of the* PANCREAS *and* GI TRACT

Cell type	Main product	Stomach Body-Andrum-Duodenum			Small intestine Jejunum-Ileum		Large intestine Appendix-Colon-Rectum		
EC	5HT, sub P			+	+	+	+	+	+
D	SMS	+	+	+	+	+	+	+	+
L	Glu-like P			f	+	+	+	+	+
A	Glucagon	f							
PP	Pancr Polyp		f	+	f	f		f	f
B	Insulin								
X	End-like P	+							
ECL	Histamine	+							
G	Gastrin		+	+					
CCK	Cholecystokin			+	+	f			
S	Secretin			+	+				
GIP	Gas Inhib P			+	+	f			
Mo	Molitin			+	+	f			
N	Neurotensin			+	+	f			
P	Unknown	+	+	+	f	f		f	f
D?	Ghrelin	+							

TUMOR MARKERS *for* NEUROENDOCRINE CELLS

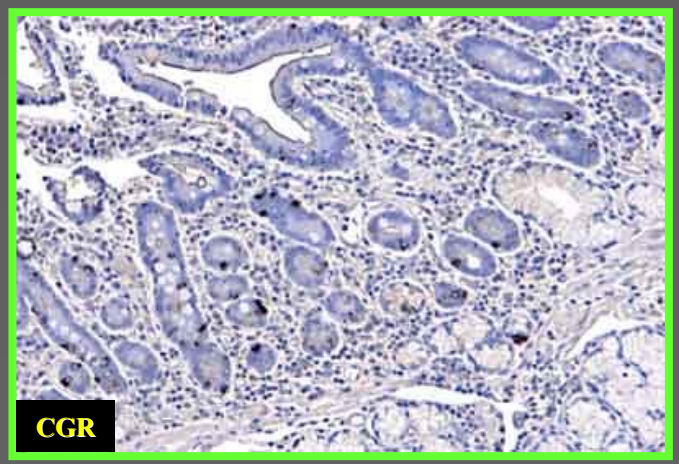
General Markers

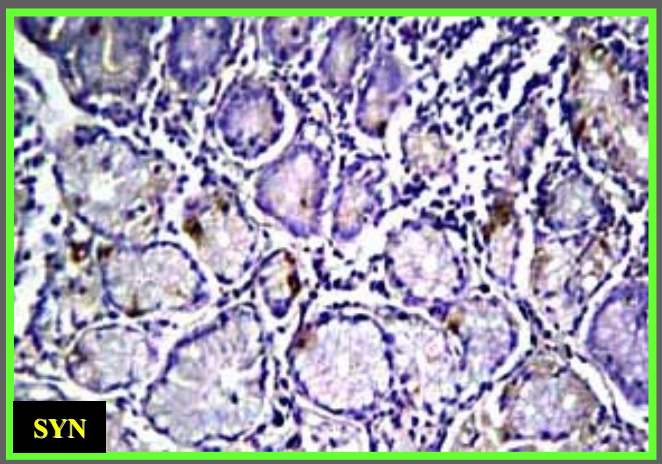
- A wide spectrum of broad-specific markers
- No true “gold standard” has been agreed so far
  - Neuron Specific Enolase (γγ-NSE more specific)
  - Chromogranin A (matrix of secretory granules)
  - Synaptophysin (not related to secretory granules)
  - PGP 9.5, Leu7 (CD57), 7B2 protein, Synaptic proteins (SNAP-23, SNAP-25, Rab3A)

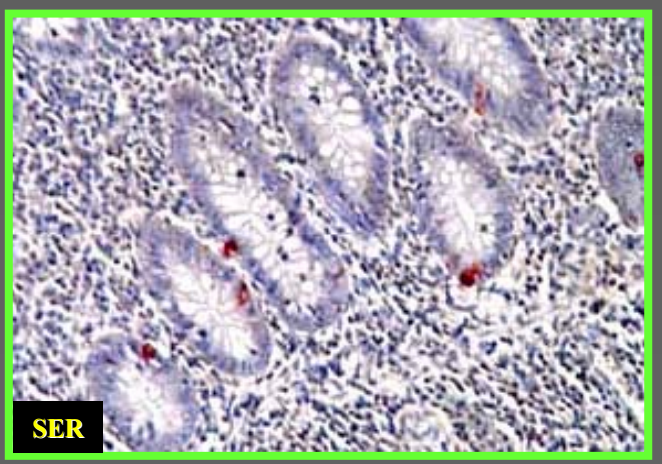
Specific Markers

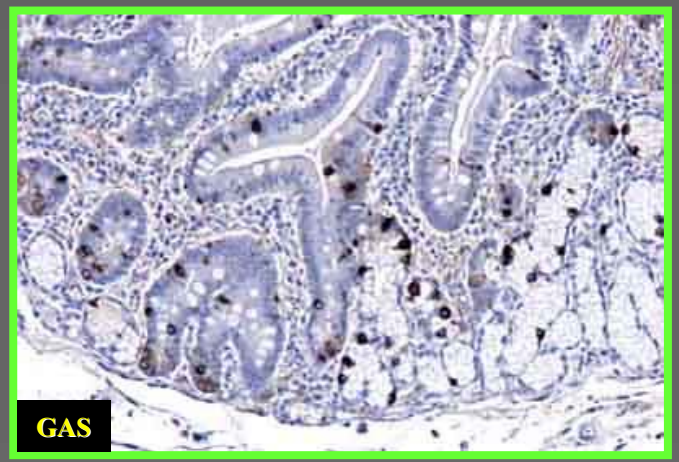
- Specific antibodies against biogenic amines and peptide hormones

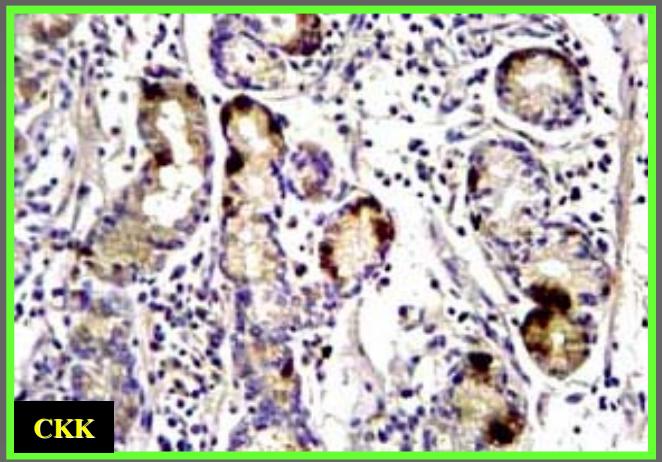
NEUROENDOCRINE CELLS *of the* GI TRACT

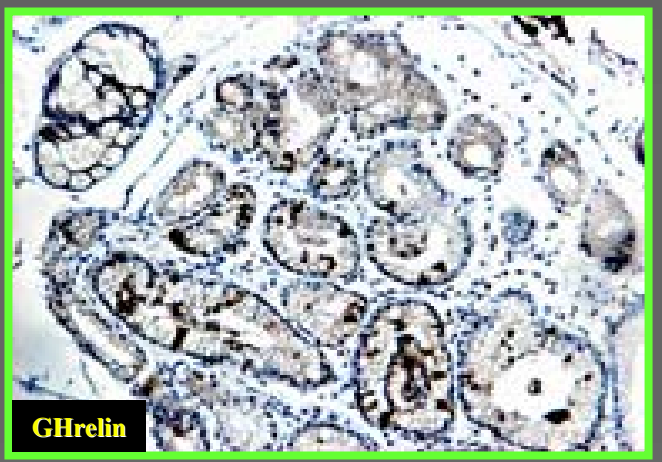


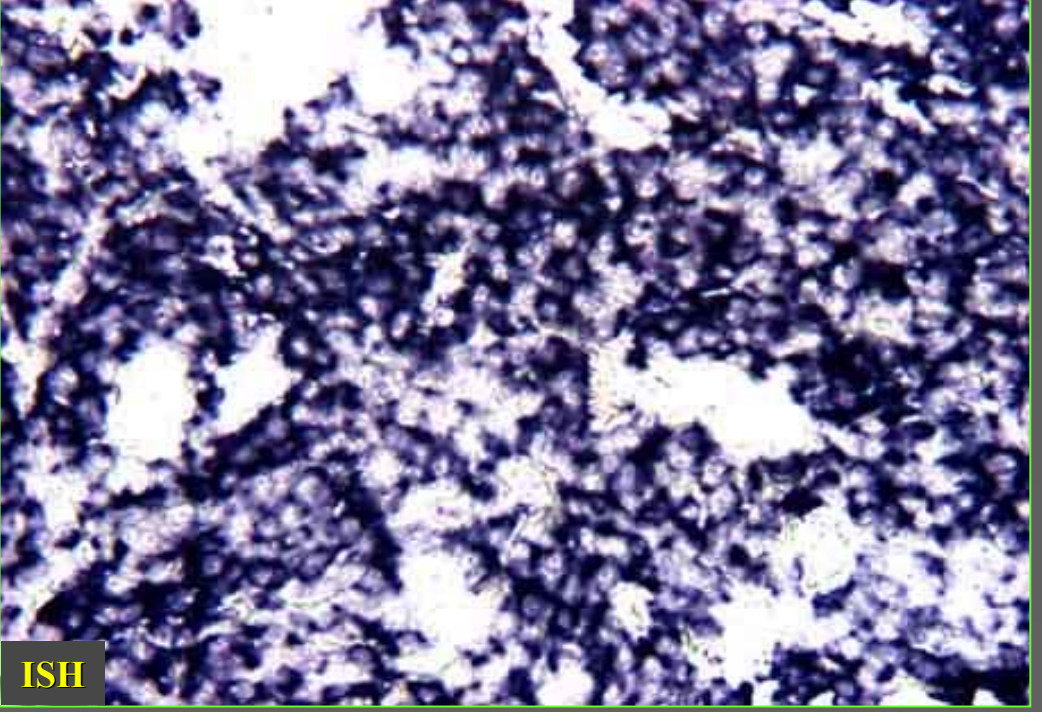








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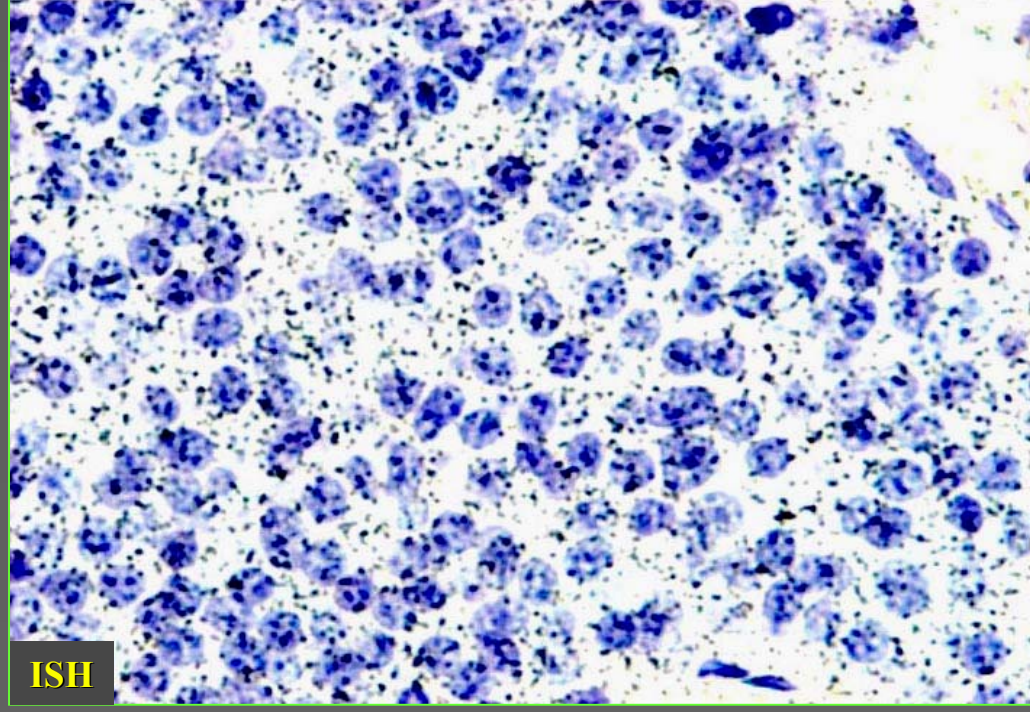
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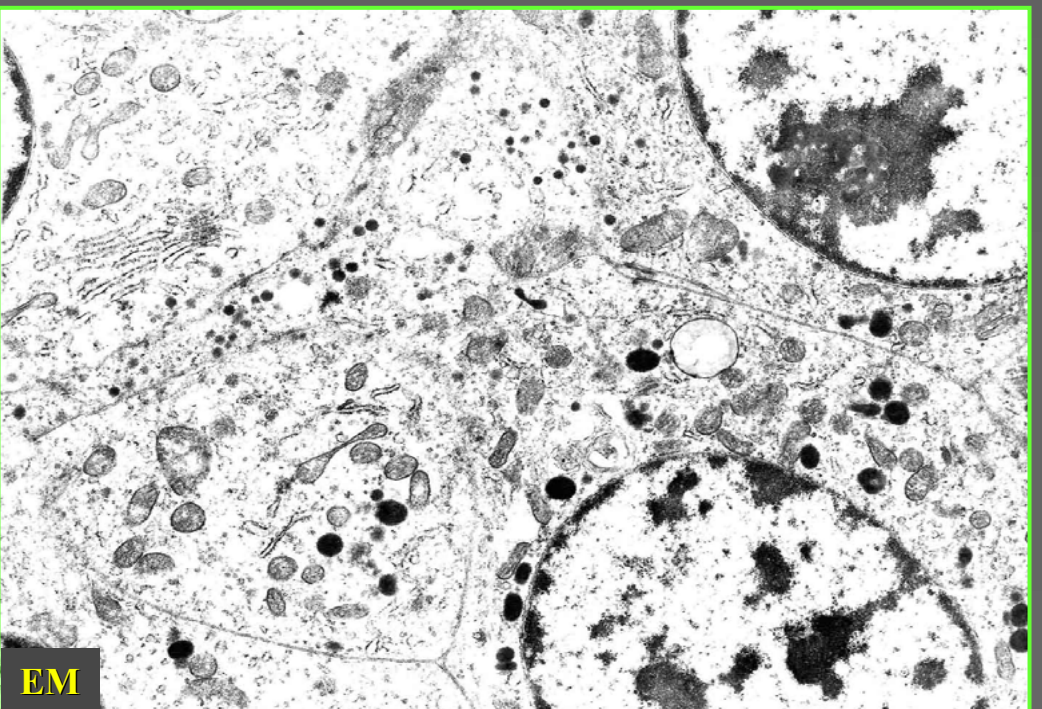
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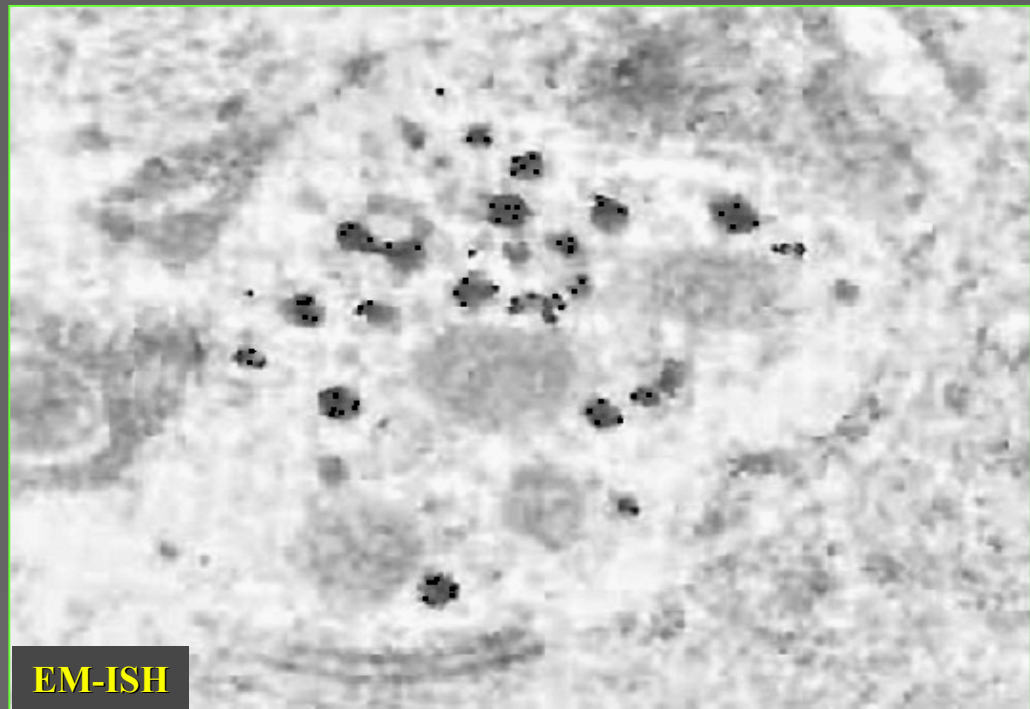
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Nomenclature of GEP-NETs

Initially

- «Carcinoids», to describe low malignant tumors with organoid histological structure causing carcinoid syndrome
- Carcinoid syndrome is due to secretion of serotonin, histamine, tachikinines
  - *Only 1.6% of GEP-NETs*

Recently

- «Neuroendocrine» tumors

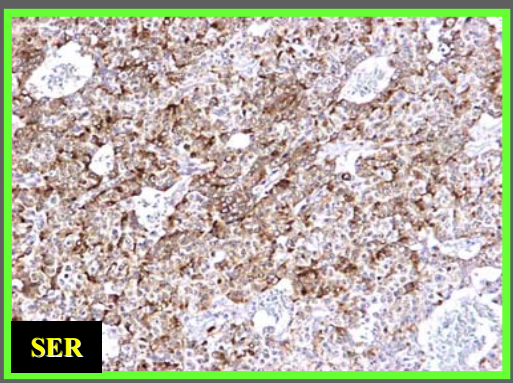
To date

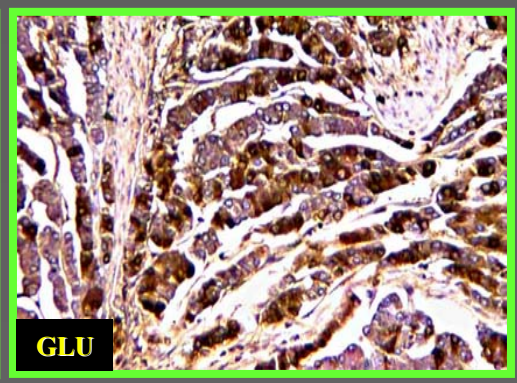
- «Endocrine» tumors
  - *Functioning associated with clinical syndrome*
  - *Nonsyndromic when not associated*

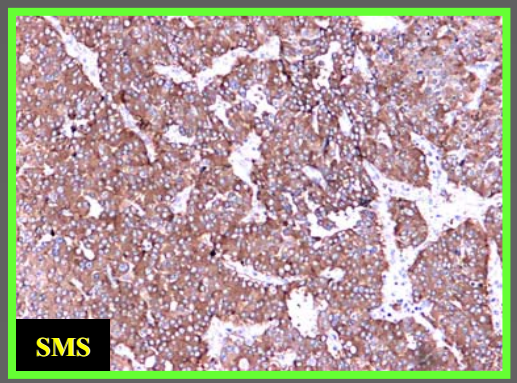
Characteristics of GEP-NETs

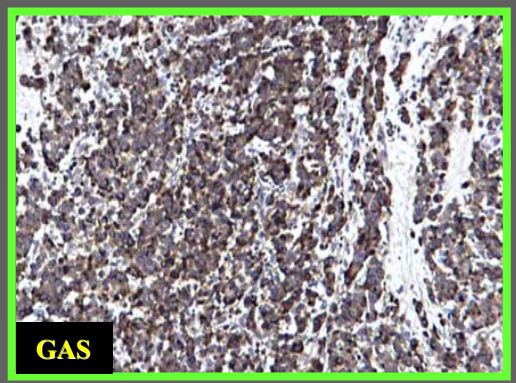
- They originate from cells of the diffuse endocrine system
- Incidence ~2/100,000 for the GI in the USA, UK and Central Europe
- They are reported with increasing frequency
- They cover a wide spectrum of biologic activities (heterogeneous differentiation, hormone production)
- Difficult to classify and predict their behavior with accuracy
- Differentiated endocrine tumors are often suspected by histology alone
- Immunohistochemistry is necessary to confirm their nature

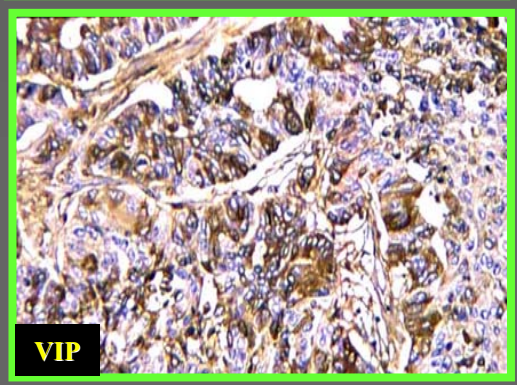
Immunophenotype of GEP-NETs

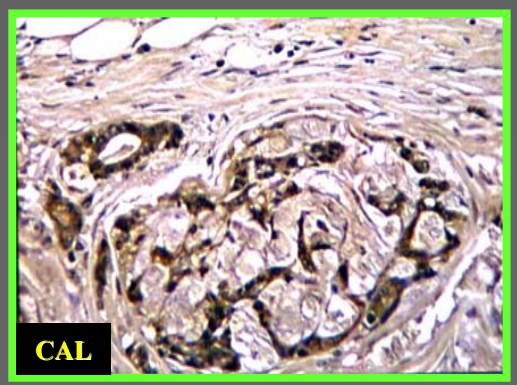


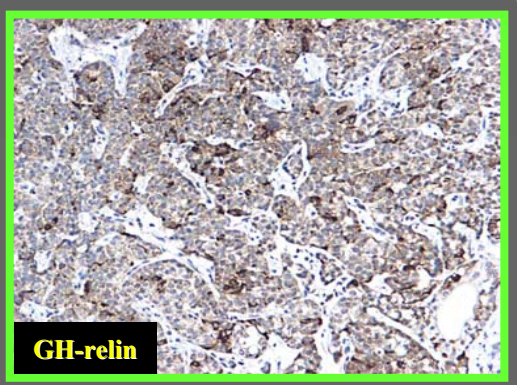


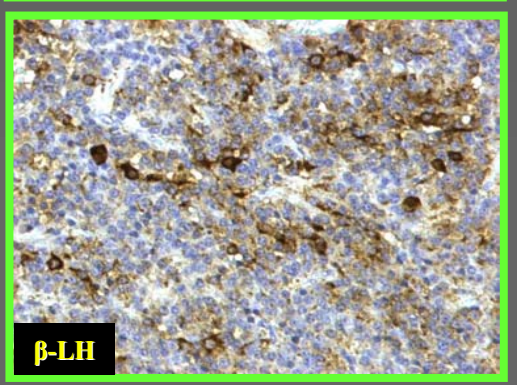












WHO 2000 Classification of GEP-NETs

- **Well-Differentiated Neuroendocrine Tumor *(«Carcinoid»)***
- **Well-Differentiated Neuroendocrine Carcinoma *(Malignant «Carcinoid»)***
- **Poorly Differentiated Neuroendocrine Carcinoma *or Small Cell Carcinoma***
- **Mixed Neuroendocrine - Exocrine Carcinoma**

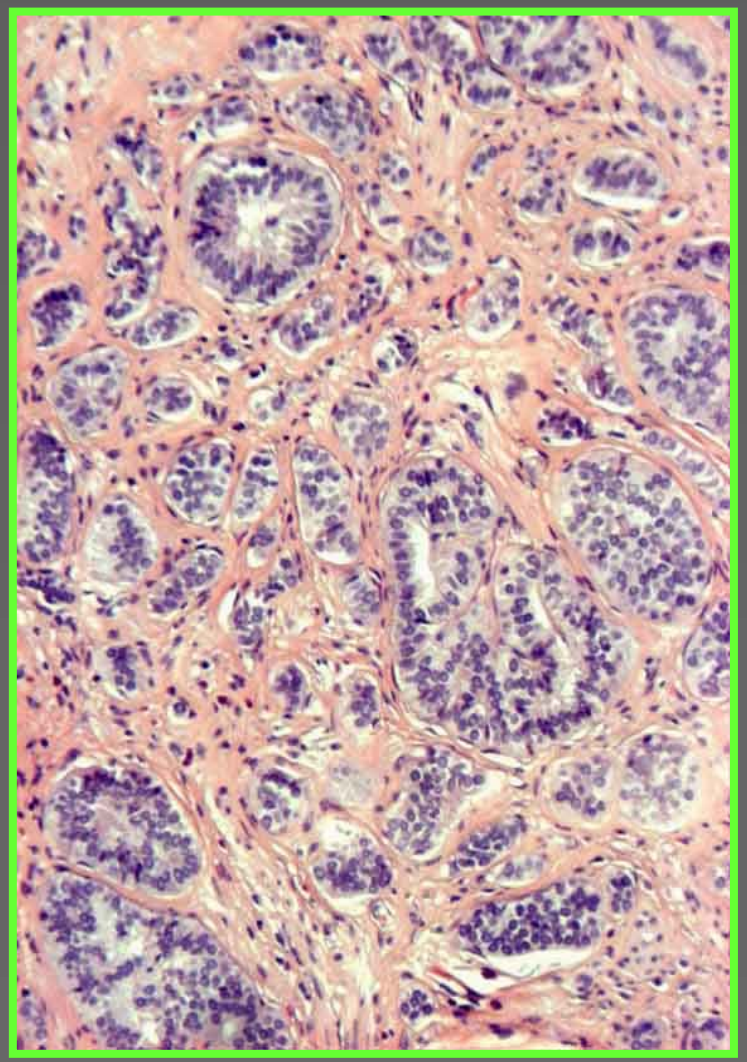
WHO 2000 Classification of GEP-NETs

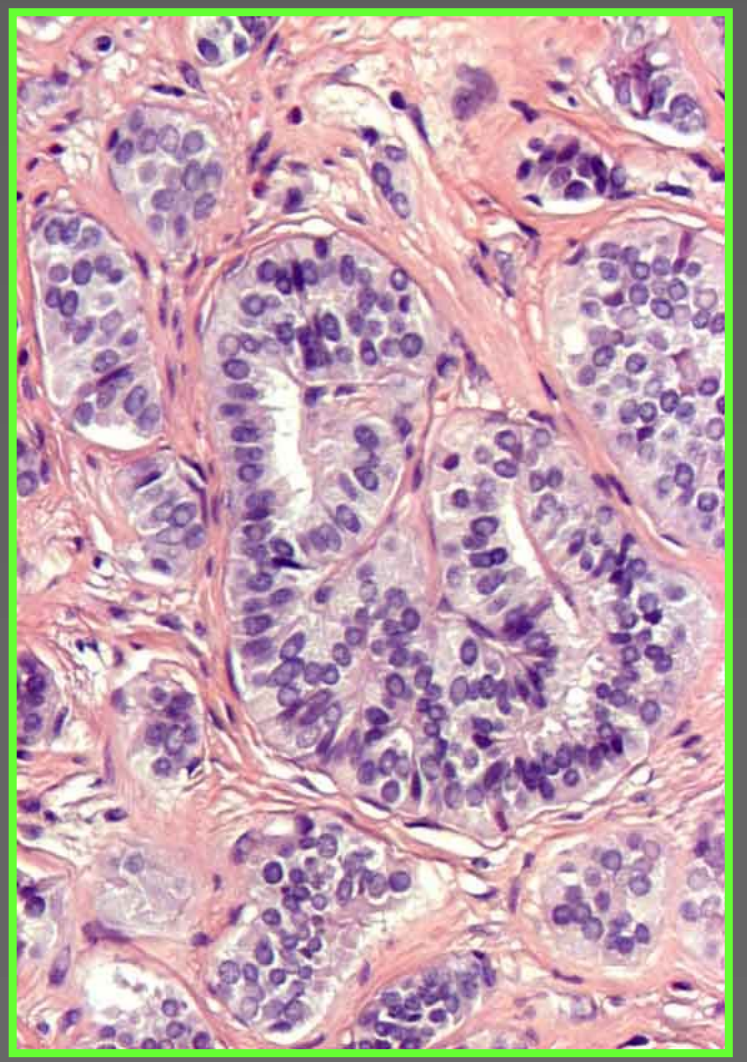
- Cell differentiation
- Cell proliferation
- Tumor size
- Level of infiltration
- Presence of necrosis
- Presence of angioinvasion
- Presence of metastases
- Endocrine functional activity
- Other pathological clinical associations

Histologic Features of Well-Differentiated NETs

- Monomorphous cell population
- Mild or no atypia
- Solid, trabecular or pseudoglandular cell nests
- Restricted to the mucosa or submucosa
- Absence of angioinvasion
- Tumor size <1 cm
- Mitoses: <2/10 HPF - Ki-67: <2%

Well-Differentiated NET

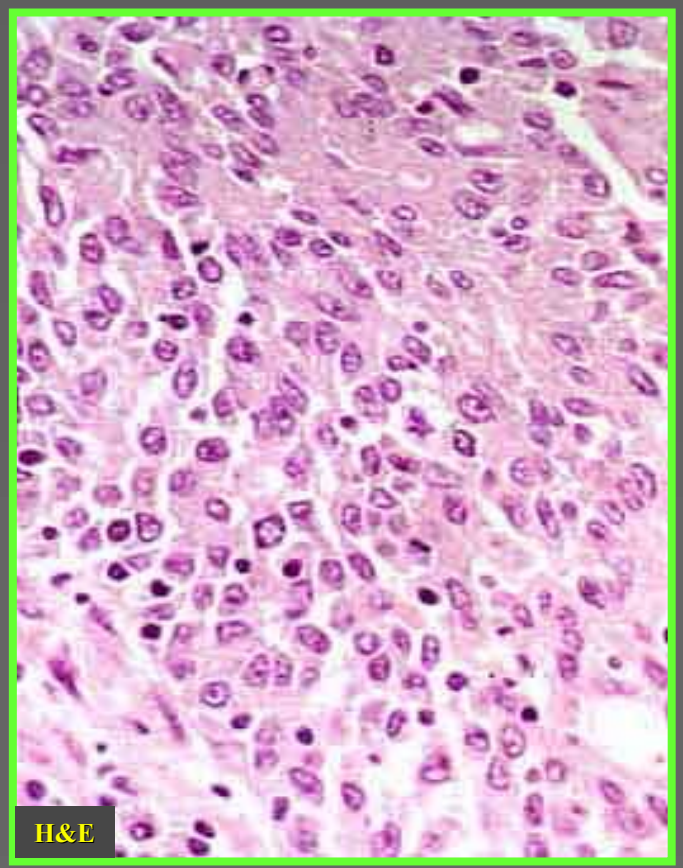


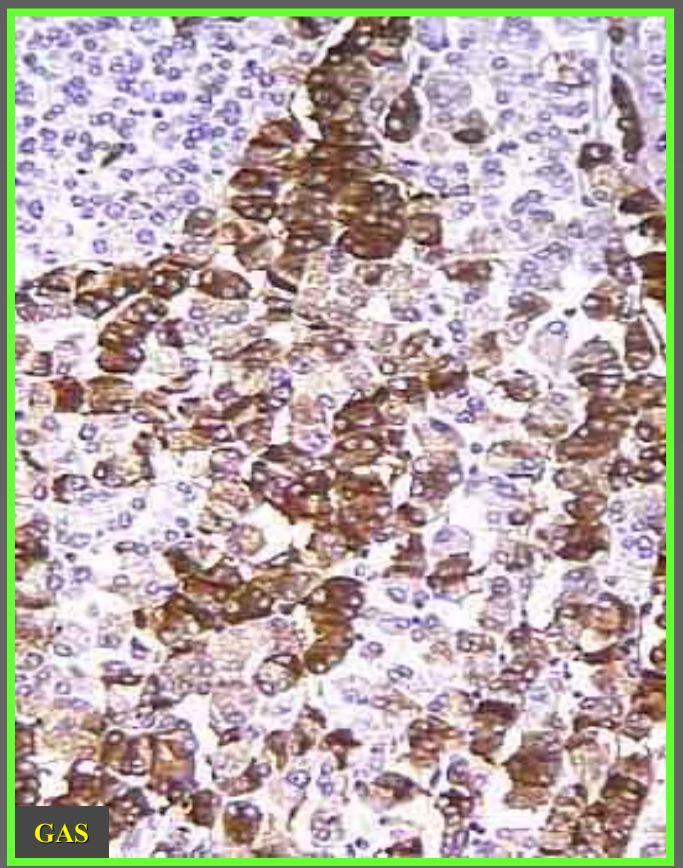


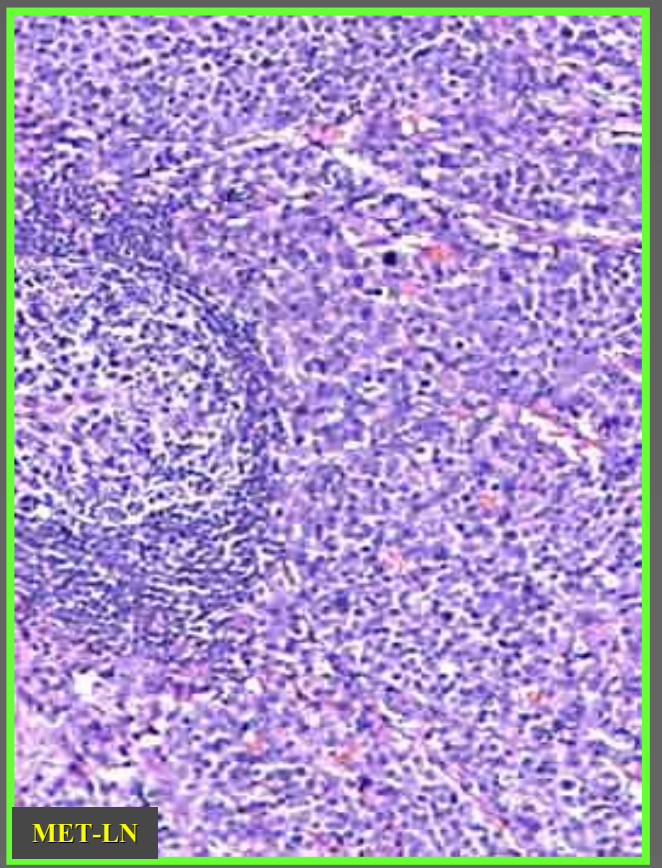
Histologic Features of Well-Differentiated NE Carcinomas

- Malignant endocrine tumor cells
- Moderate atypia
- Solid-trabecular nests, or less well-defined cellular aggregates
- Deep invasion of the gut wall (muscularis propria or beyond)
- Often metastases to regional lymph nodes or liver
- Size: >1 cm
- Mitoses: >2/10 HPF - Ki-67: >2%

Well-Differentiated NE Carcinoma



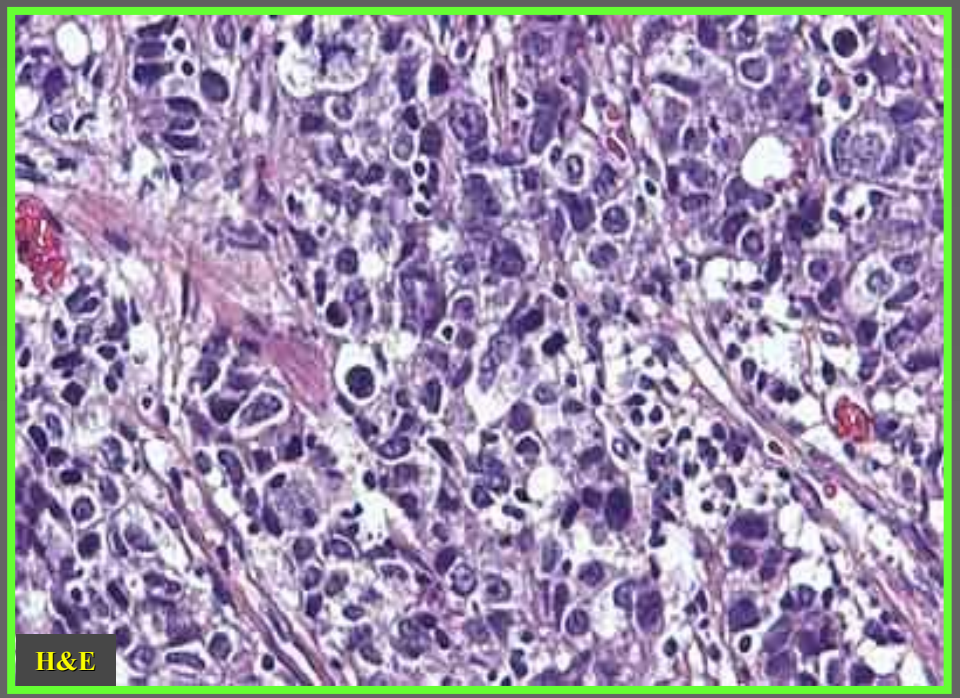


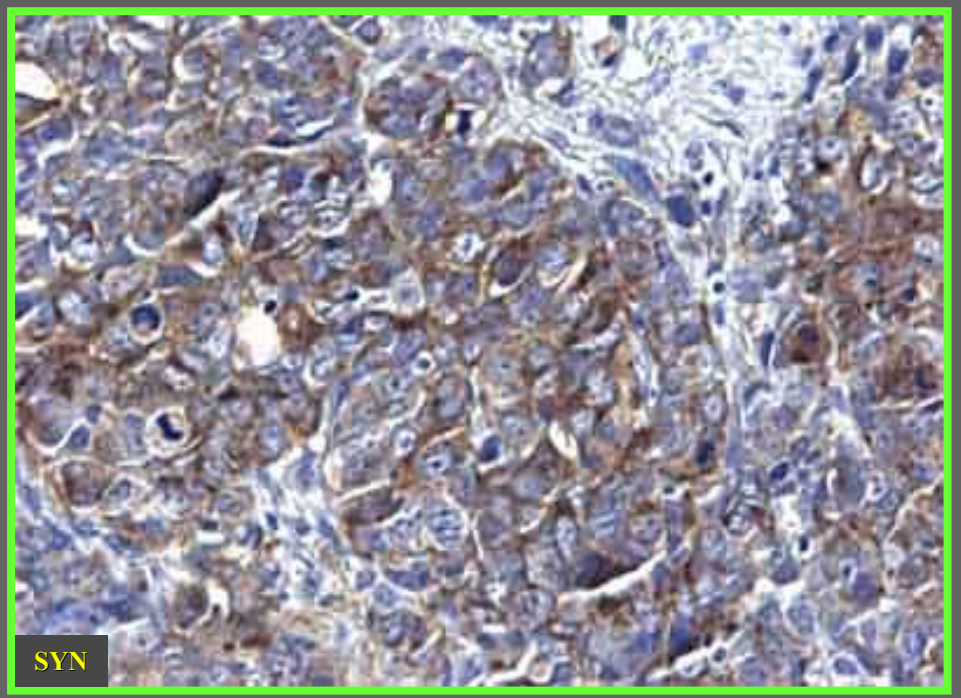


Histologic Features of Poorly Differentiated NE Carcinomas

- Highly atypical, small to intermediate-sized tumor cells
- Large, often ill-defined aggregates
- Deep invasion or destruction of the gut wall
- Often necrosis and angionvasion and/or perineural invasion
- Local and distant metastases
- Size: >1 cm
- Mitoses: >10/10 HPF - Ki-67: >15%
- p53 often positive to both local and distant metastases

Poorly Differentiated NE Carcinoma

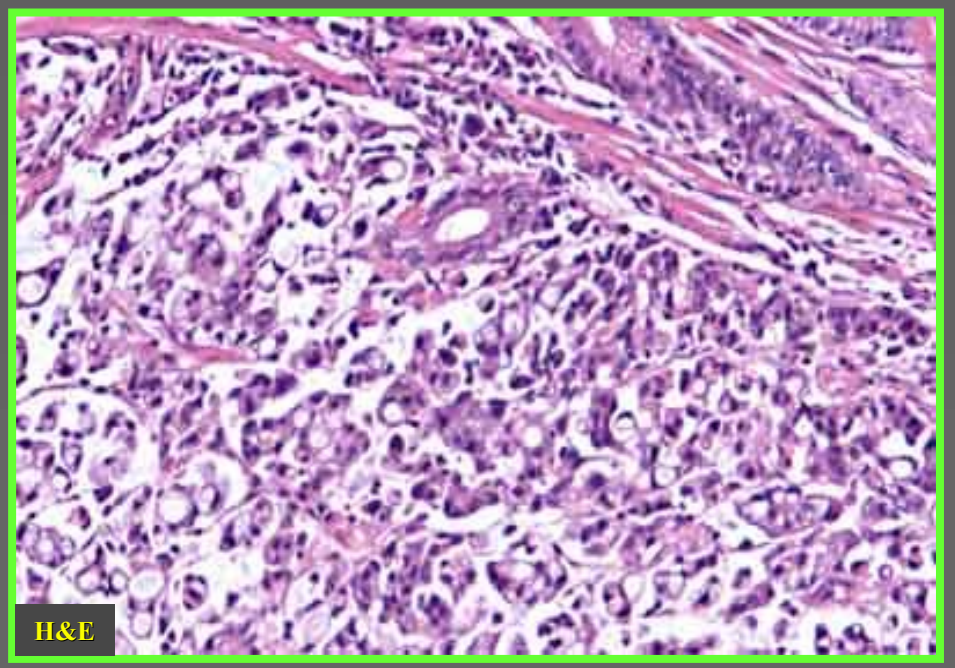


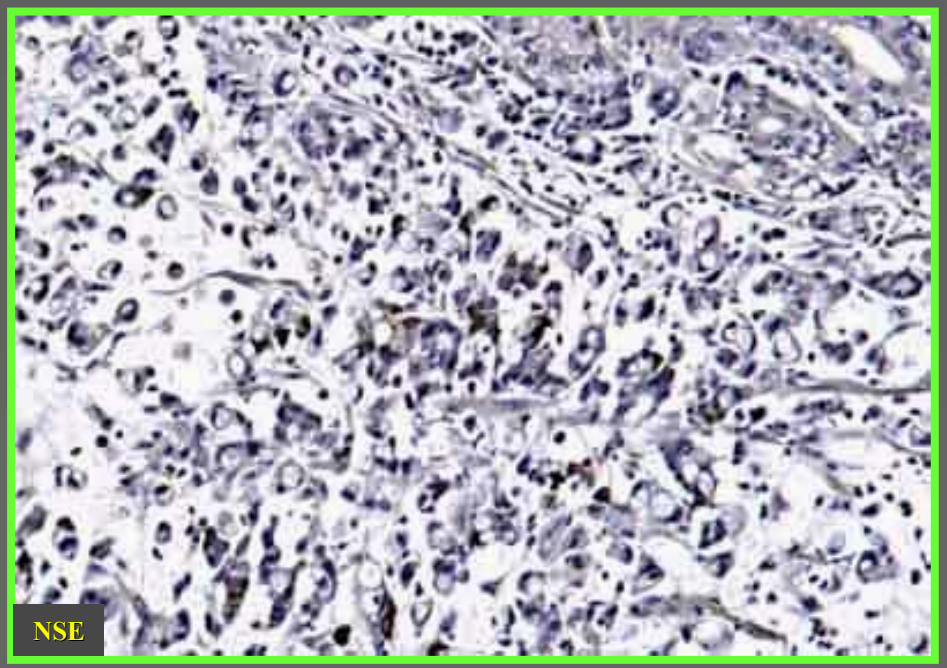


Histologic Features of Mixed NE-Exocrine Carcinomas

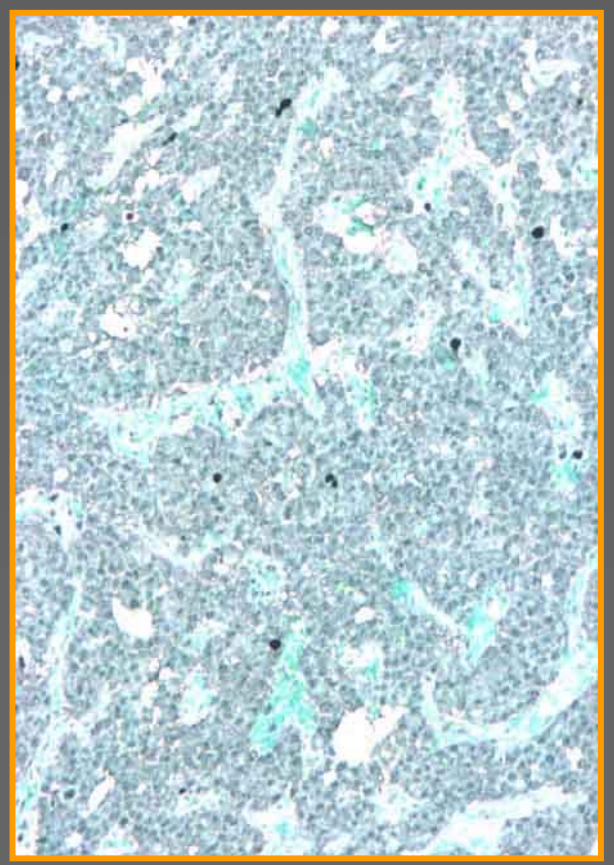
- Unusual bimorphous tumors
- Prominent exocrine cells (acinar or ductal) admixed with at least 30% endocrine component
  - *Scattered or small aggregates of endocrine cells, often occur in nonendocrine tumors: no clinical significance*
- Biological behavior of the exocrine component

Mixed NE-Exocrine Carcinoma



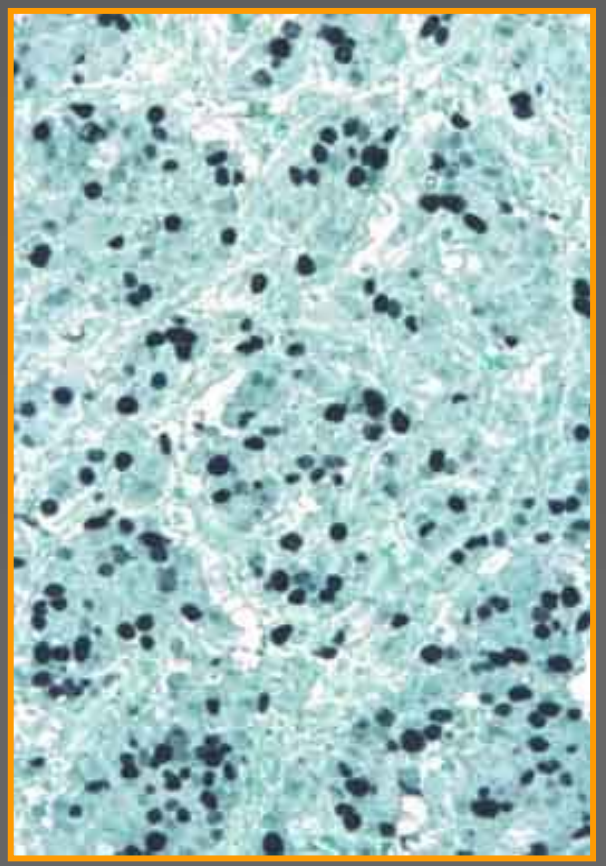


Estimation of Cell Proliferation in NETs with Ki-67 (MIB-1)



Well-Differentiated Endocrine Tumor

Well-Differentiated Endocrine Carcinoma



Poorly Differentiated Endocrine Carcinoma

Biologic Behavior of GEP-NET of the GI Tract

- Benign behavior
  - Non functioning, non angioinvasive restricted to the mucosa or submucosa
  - Size <1 cm (stomach, small intestine), or *size* <2 cm (appendix, large bowel)
  - *Size <1 cm: nearly always 100% benign, size <2 cm 80% benign (stomach)*
- Uncertain behavior
  - Non functioning, non angioinvasive restricted to the mucosa or submucosa
  - Size >1 cm (stomach, small intestine), or >2 cm (appendix, large bowel), or angioinvasive
- Malignant behavior
  - Angioinvasive, deeply invasive (muscularis propria or beyond), or with metastases
  - Size >1 cm (stomach, small intestine) or >2 cm (appendix, large bowel)

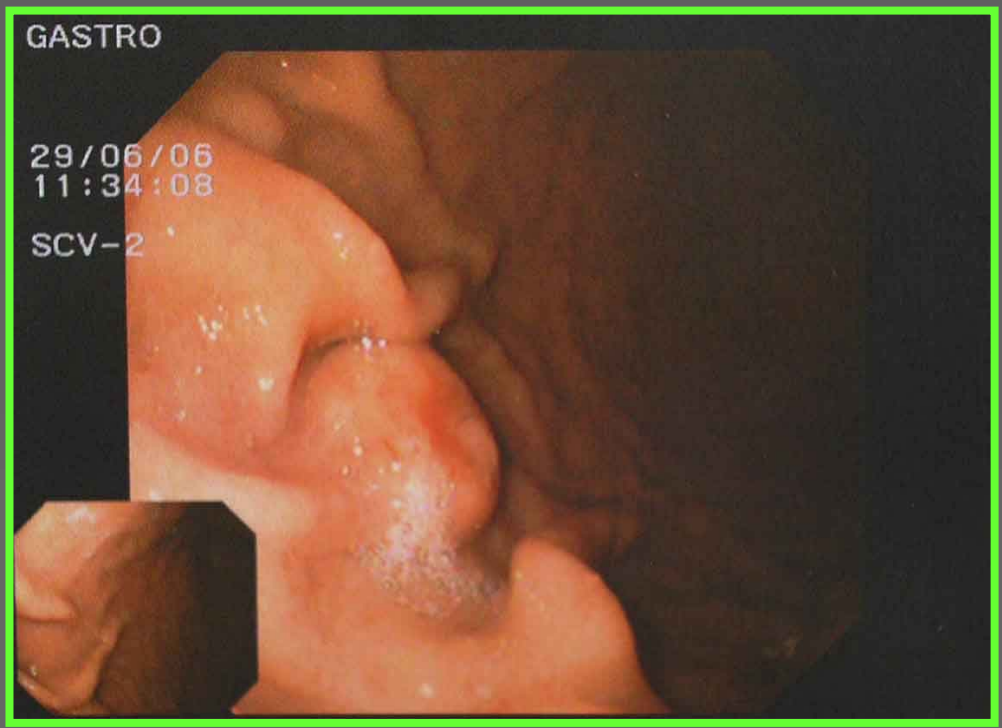
Clinicopathological Correlations of Gastric NETs

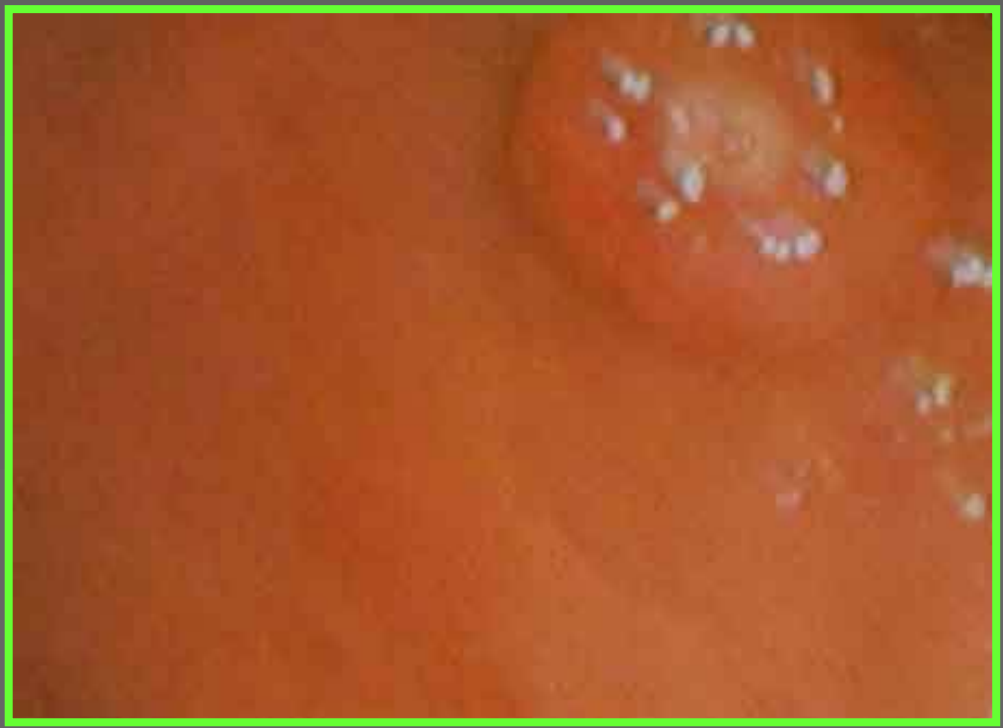
- Most are well-differentiated, nonfunctioning tumors arising in the mucosa in the corpus or fundus
- Often multiple and usually benign
- Gastrinomas arise *in the antropyloric region*
  - *Small multiple submucosal nodules often associated with metastases*
- Type I associated with autoimmune chronic atrophic gastritis (A-CAG)
- Type II represent gastrinomas associated with MEN-1 and ZES
- Type III all the remaining NETs

Clinicopathological Correlations of Gastric NETs

- Gastric NETs
  - *Most are of type I*
  - *Type II represent 5% and type III tumors 15%*
- *Hypergastrinemia is due to uncontrolled hormone secretion*
  - *Primary due to a gastrinoma*
  - *Secondary as a response of antral gastrin-producing cells to achlorhydria associated with endocrine cell hyperplasia*
- A-CAG is caused by antibodies to parietal cells of the oxyntic mucosa (with or without pernicious anemia) leading to increased gastrin secretion
- A few histamine or serotonin-producing tumors when metastasize produce “atypical” carcinoid syndrome

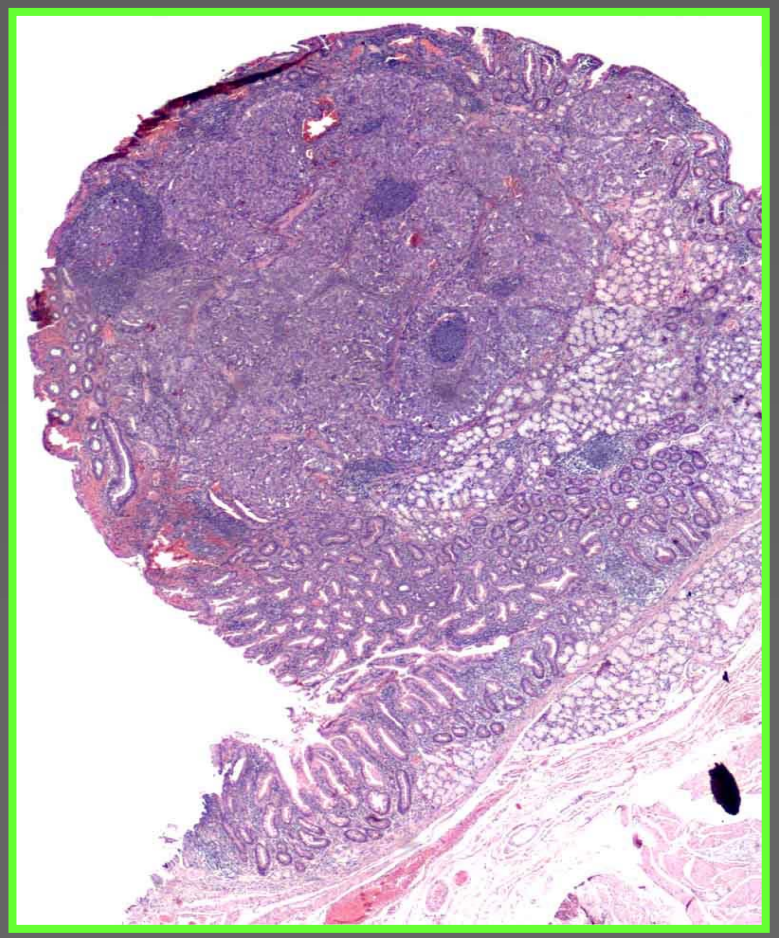
Gastric NETs presented as Polyp

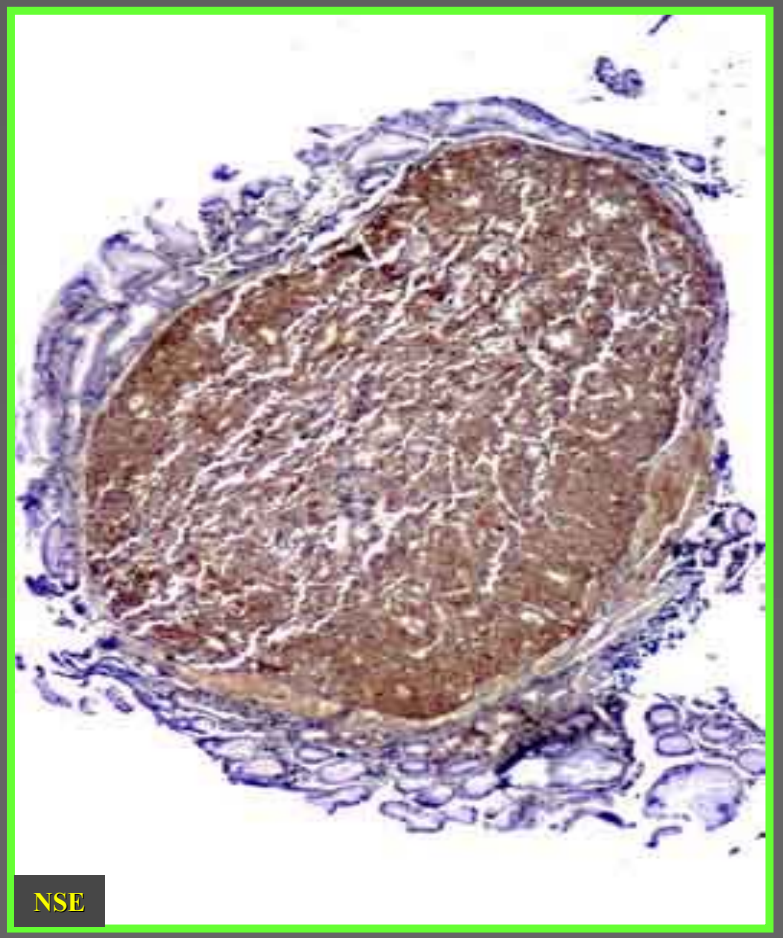




Typical endoscopic features of polyp

Gastric NETs presented as Polyp



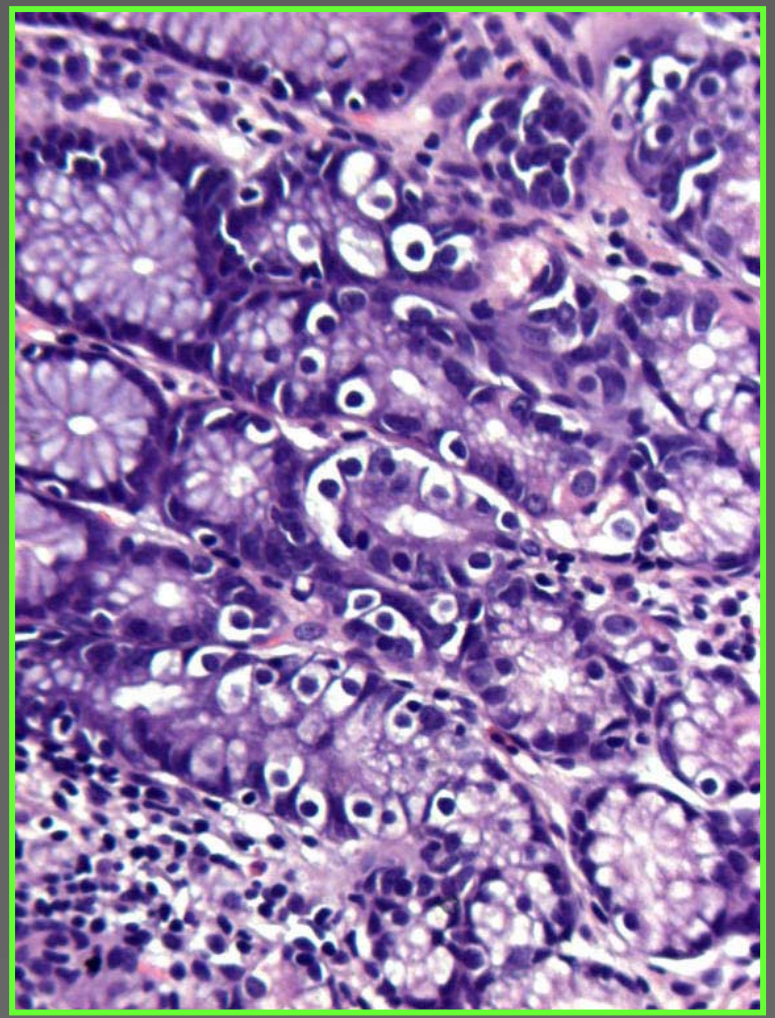


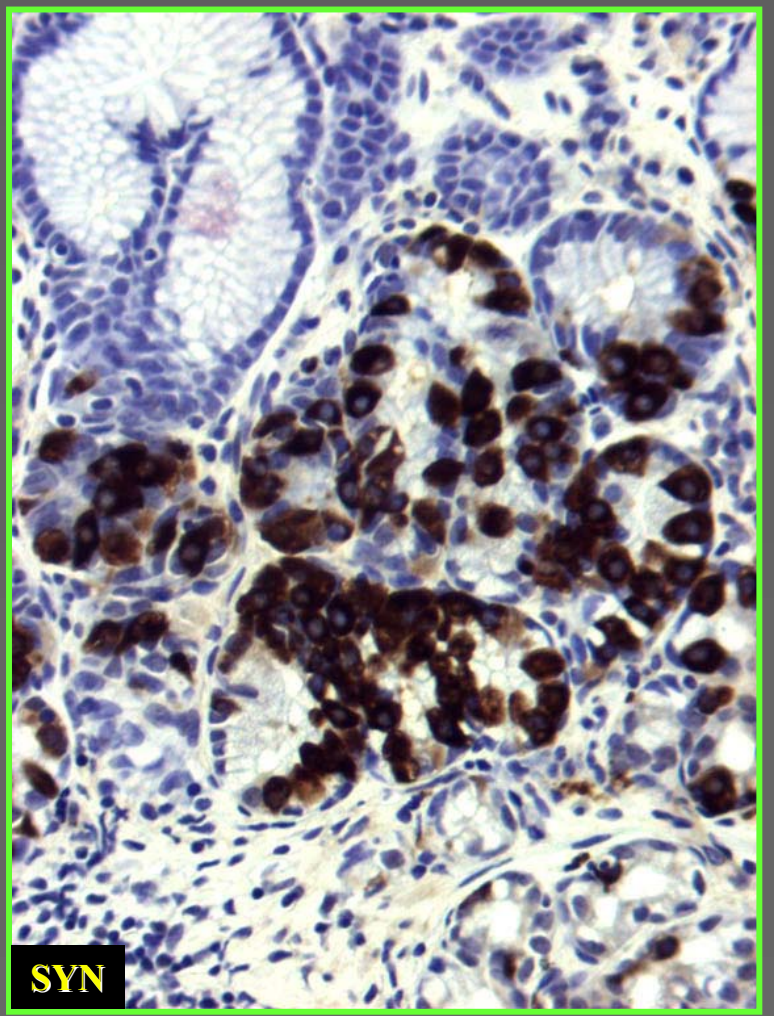
Typical neuroendocrine tumor

Hyperplastic - Dysplastic Gastric Neuroendocrine Lesions

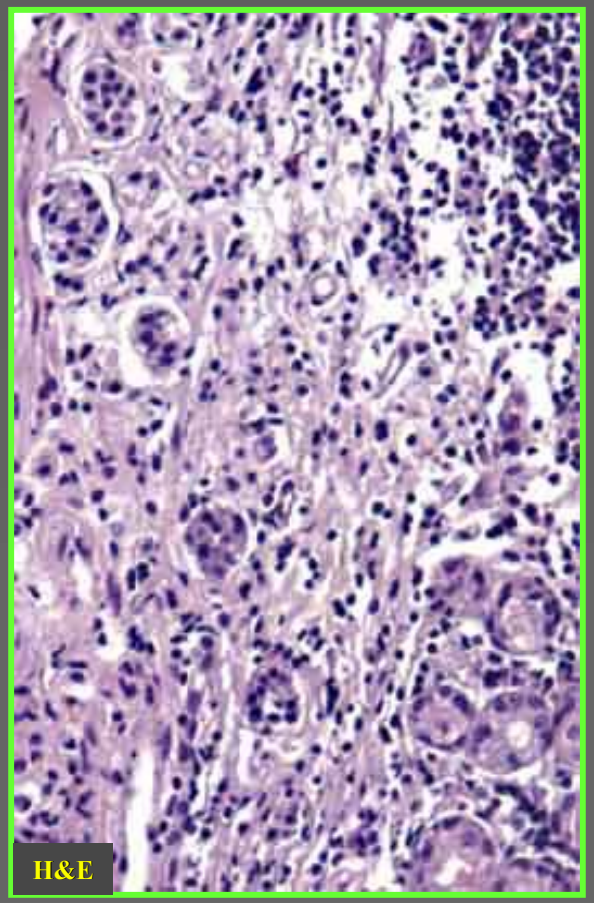
- Various types of endocrine cell hyperplasia in the gastric mucosa of hypergastrinemic subjects
- NETs also associated with dysplastic (precarcinoid) lesions
- The sequence hyperplasia - dysplasia of endocrine cells considered as precursor lesions
  - *Minute (0.15 mm-0.5 mm) nodular growths of mildly atypical cells with a tendency to fuse and invade the submucosa*
    - *Diffuse type*
    - *Linear type*
    - *Micronodular type*
    - *Adenomatoid type*

Hyperplastic - Dysplastic Gastric Neuroendocrine Lesions

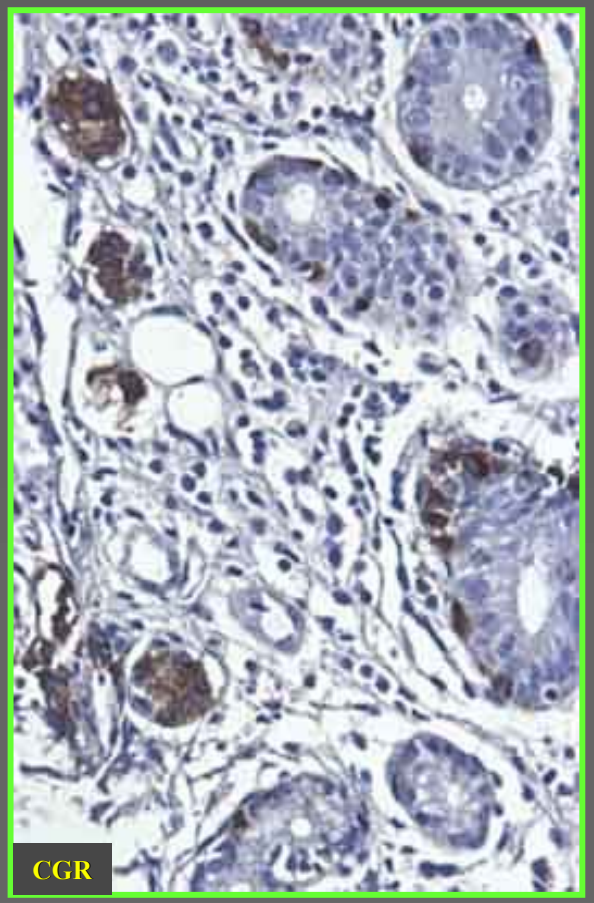




Dysplastic (Precarcinoid) Lesions of the Stomach



Micronodular



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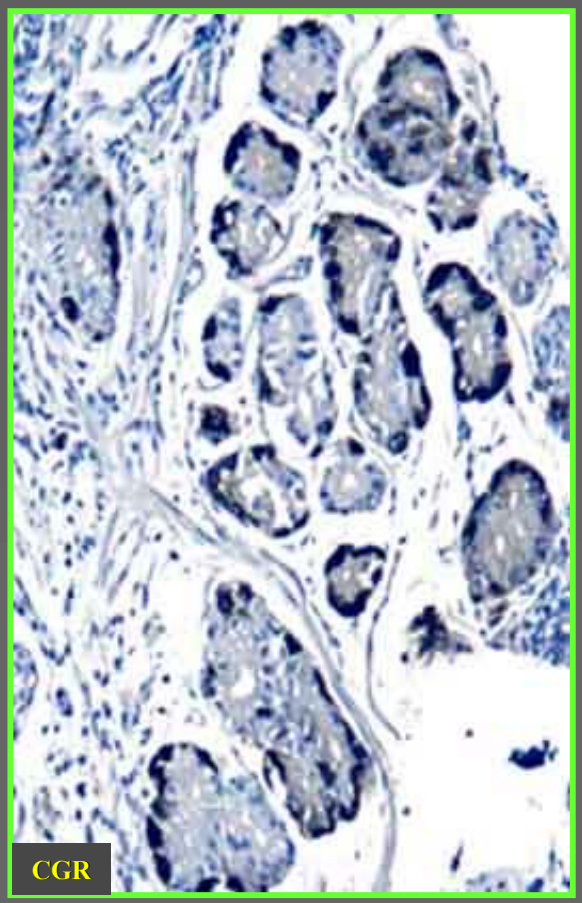
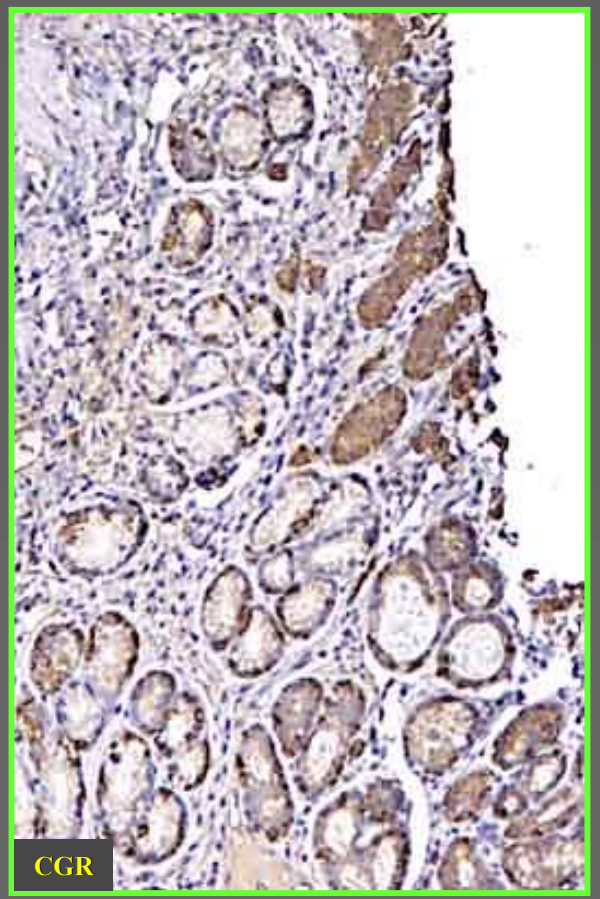
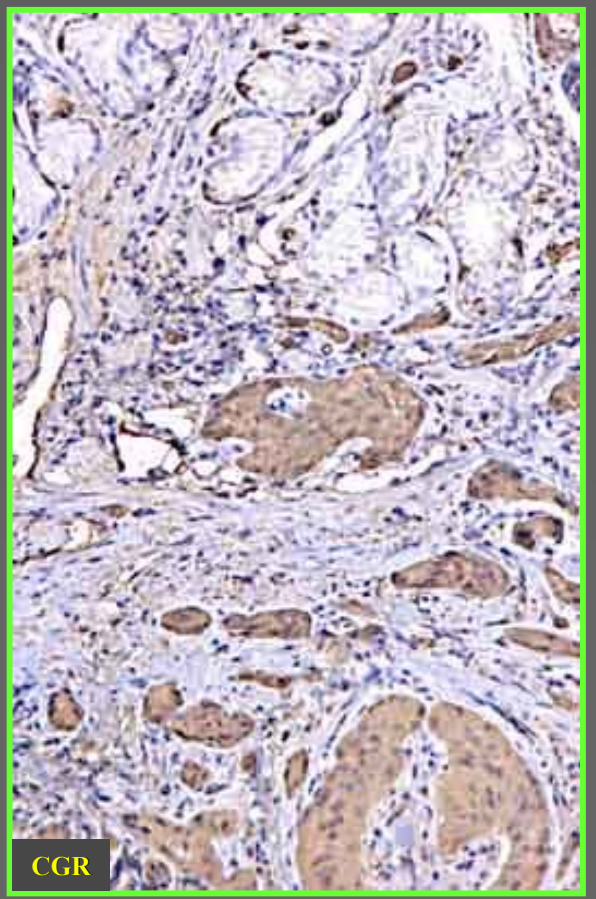


Linear

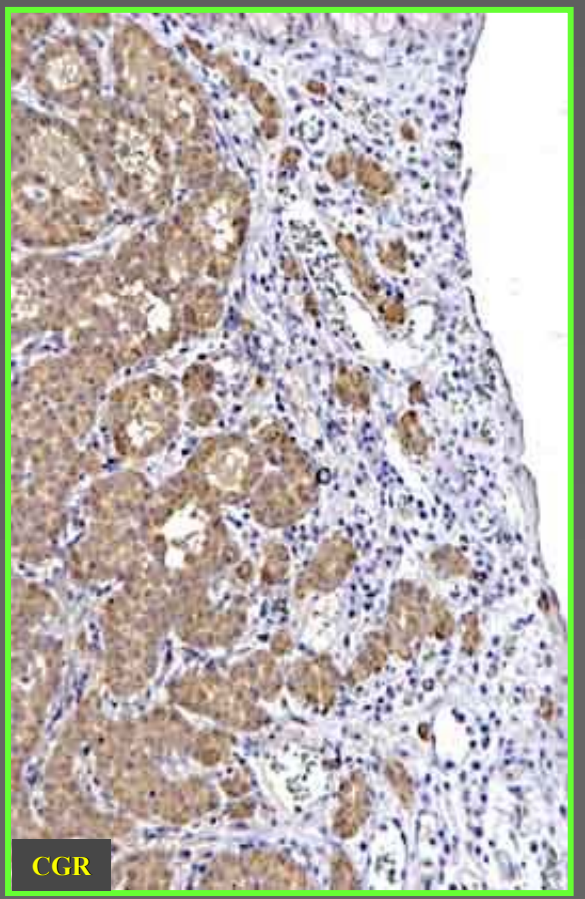
Dysplastic (Precarcinoid) Lesions of the Stomach



Micronodular



Diffuse

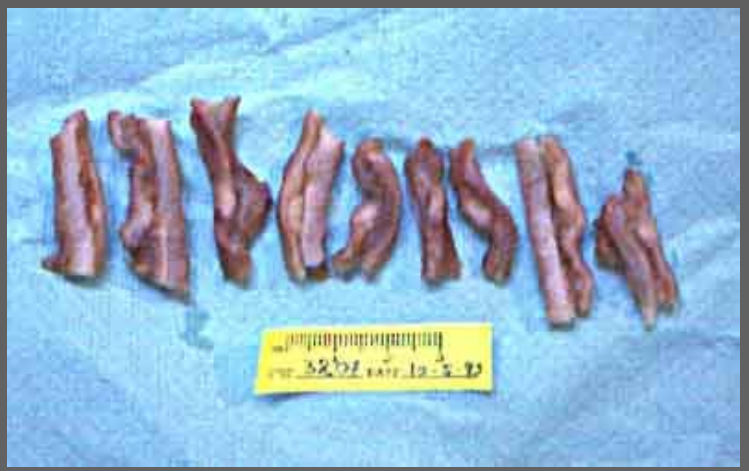


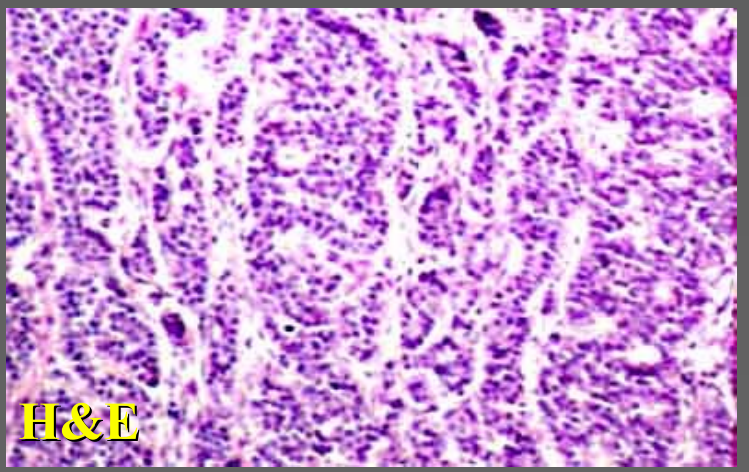
Tumor formation

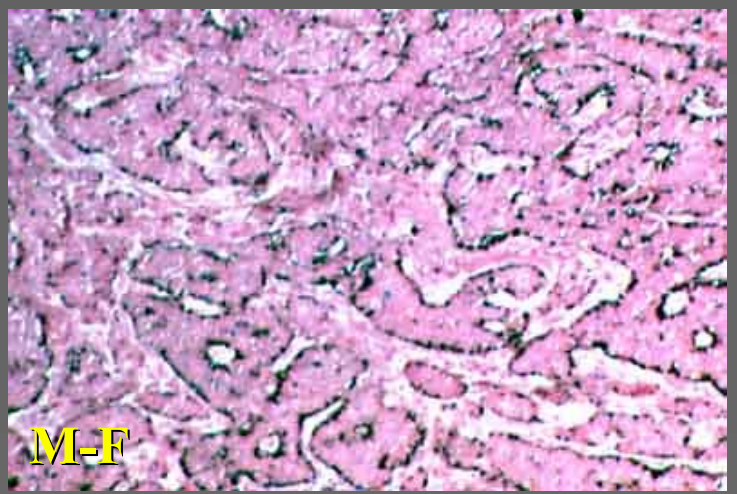
Surgical Management of Gastric NETs

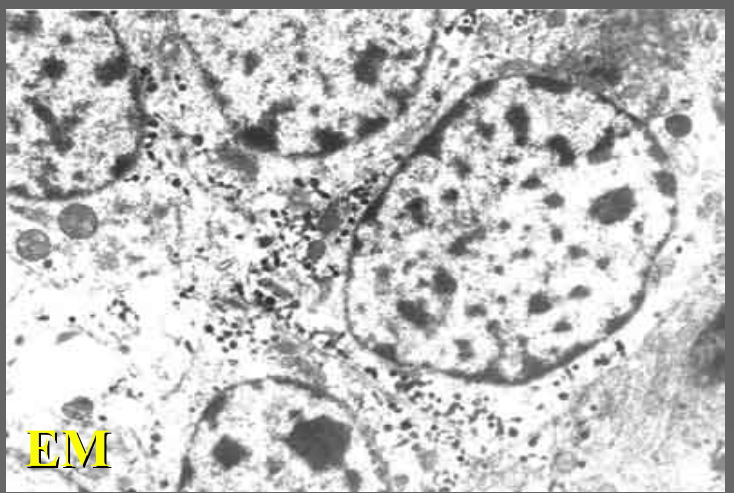
- Polypoid type I NETs < 1cm associated with A-CAG can be endoscopically excised
- Tumors measuring more > 1 cm or multiple, more than 3-5 lesions, require local excision of all accessible fundic lesions
- Antrectomy in extreme uncontrolled cases

Well-differentiated Neuroendocrine Tumors of the Duodenum and Upper Jejunum





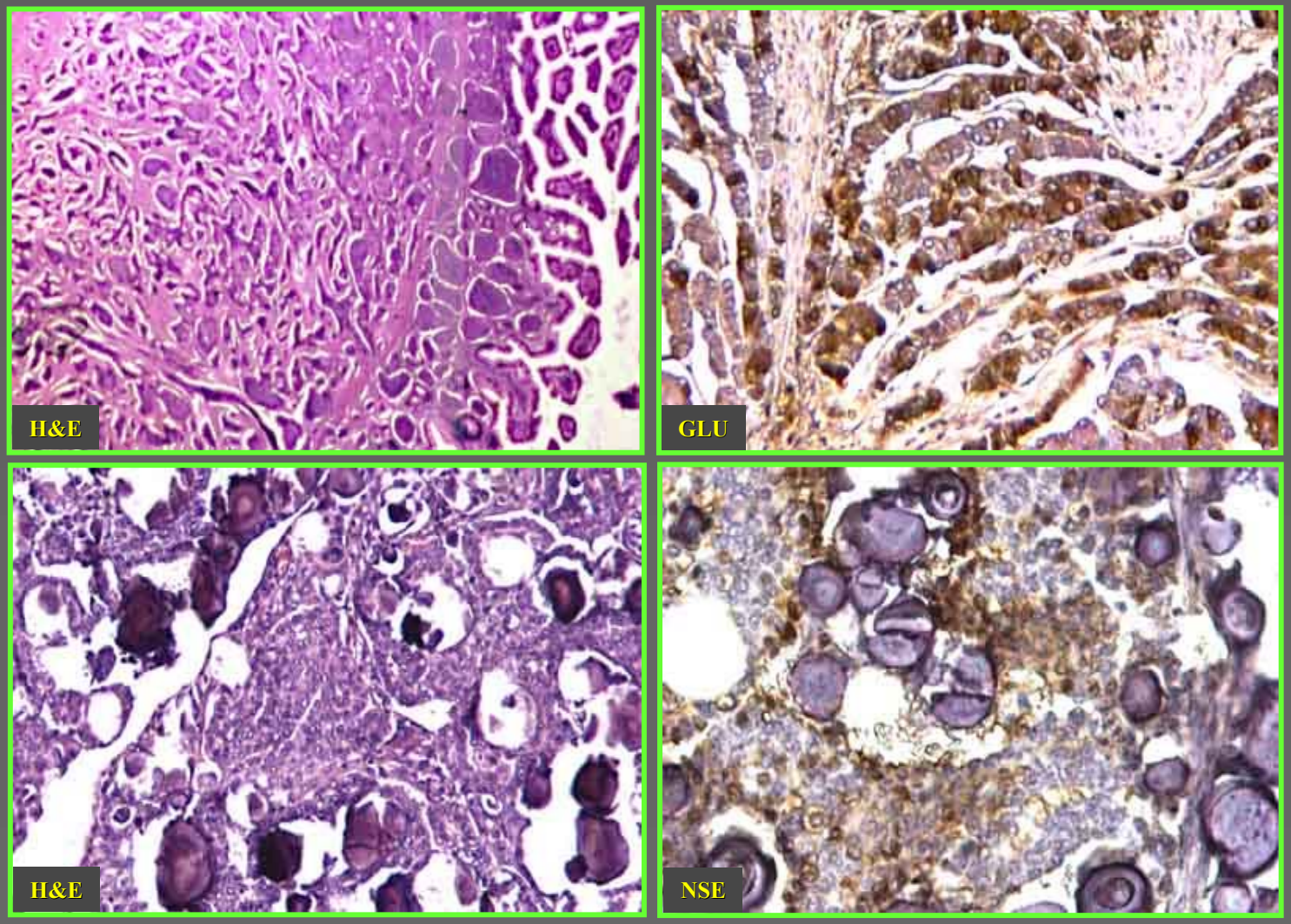




Clinicopathological Correlations of Neuroendocrine Tumors of the Duodenum and Upper Jejunum

- Gastrinomas may be multiple, especially when found in association with the MEN 1 syndrome
- Gastrinomas may be very small (a few millimeters), even when metastatic to regional lymph nodes
- SMS-producing tumors are often large, deeply invasive and metastatic to regional lymph nodes
- SMS-producing tumors often cause obstruction of bile flow and may be associated with Recklinghausen disease

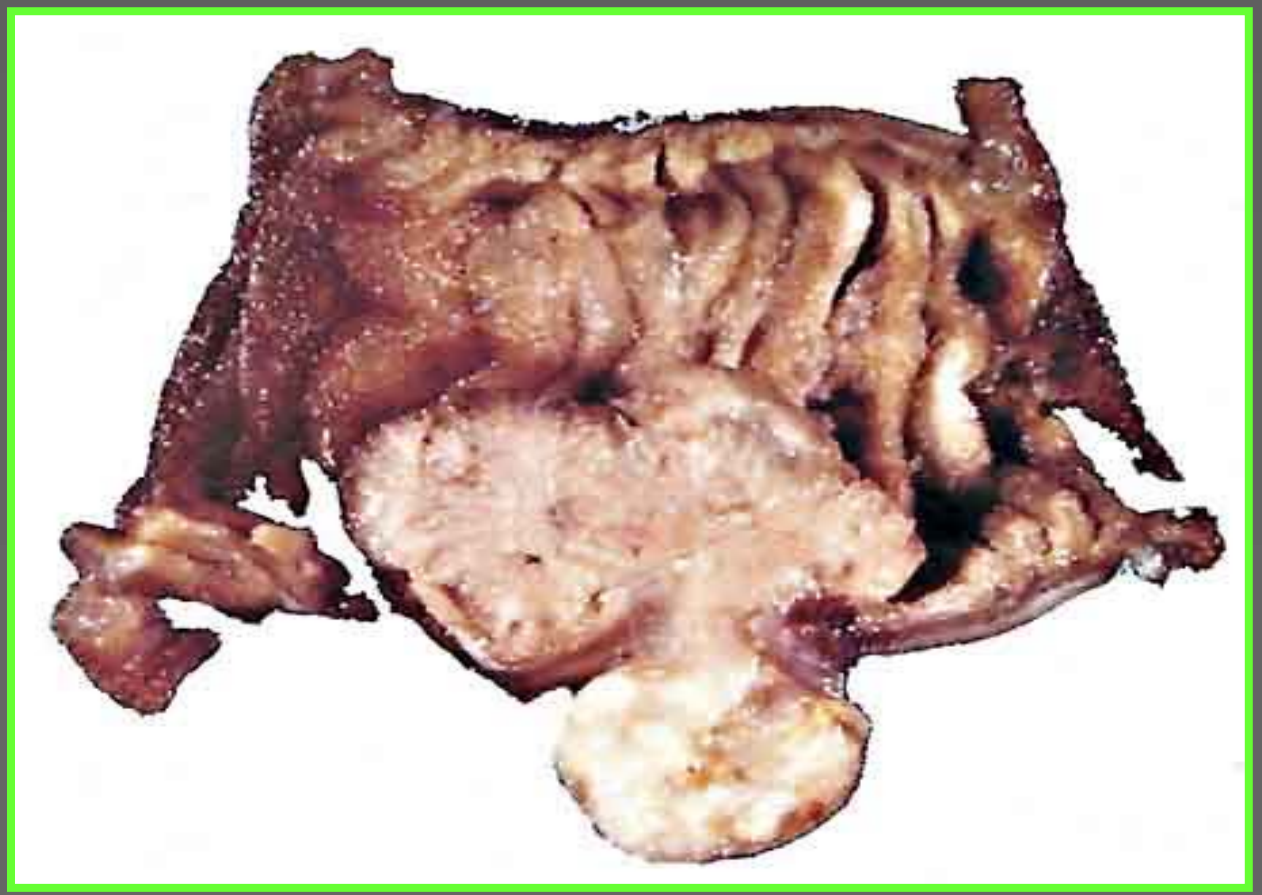
Well-Differentiated Neuroendocrine Carcinoma of the Jejunum and Colon



Clinicopathological Correlations of Neuroendocrine Tumors of the Ileum and Large Intestine

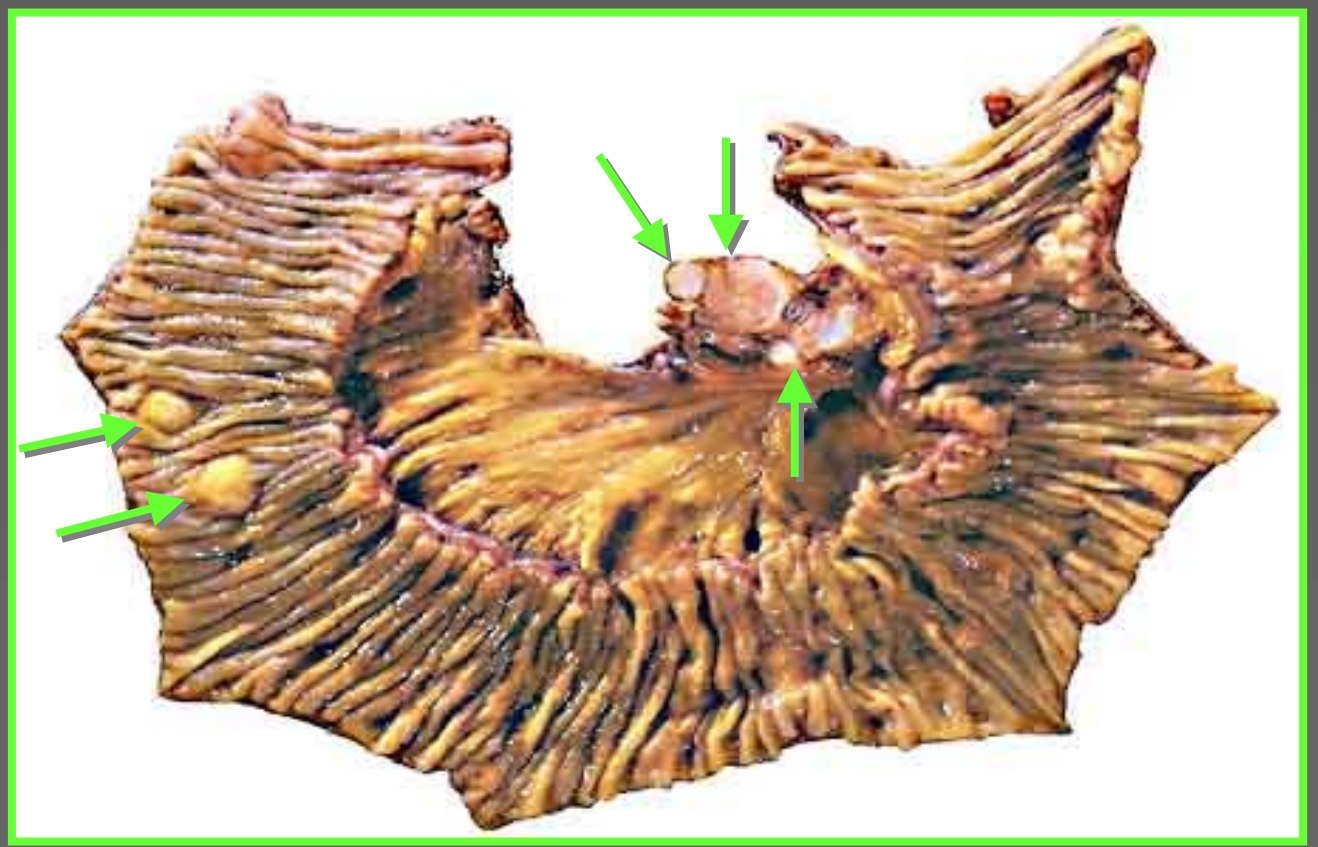
- Most are well-differentiated
- Frequently multiple
- Only a minority of cases metastatic to the liver cause the typical "carcinoid syndrome" with flushing, blood pressure changes, endocardial fibroelastosis, etc.
- Most tumors of the rectum and distal colon: Ser, PP
- Only tumors of the small intestine: enteroglucagon

Intestinal Neuroendocrine Tumor ???



Solitary, exophytic, ulcerative tumor

Intestinal Neuroendocrine Tumor ???



- Multifocal small tumors
- Multiple metastases to regional lymph nodes

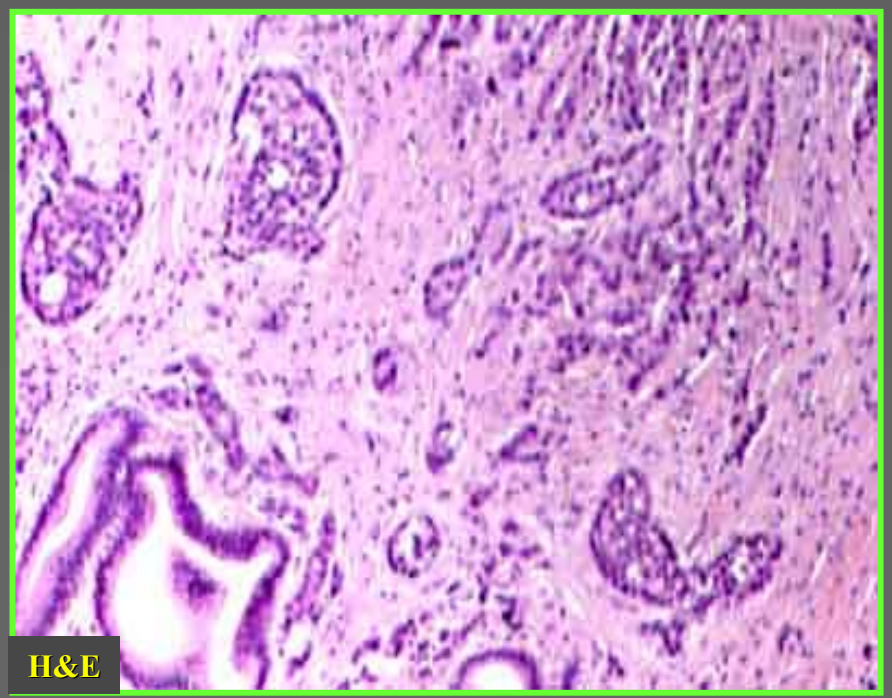
Well-differentiated Neuroendocrine Tumors of the Appendix

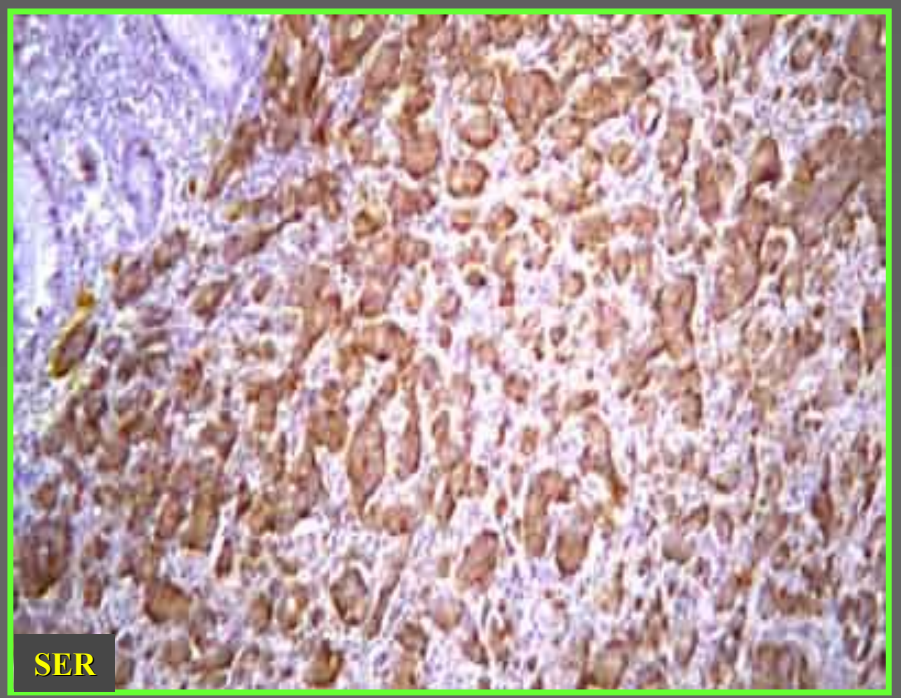
Usual localization at the apex

- *Macroscopic configuration of the tumor*

Well-differentiated Endocrine Tumor «Carcinoid» of the Appendix

- Low grade malignant
  - *Serotonin-producing tumors*

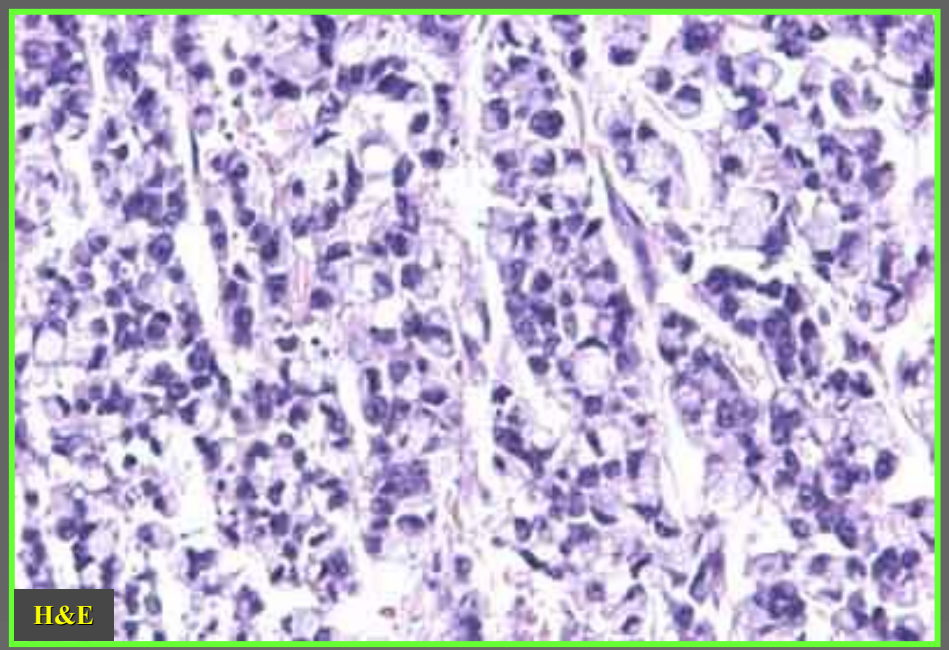


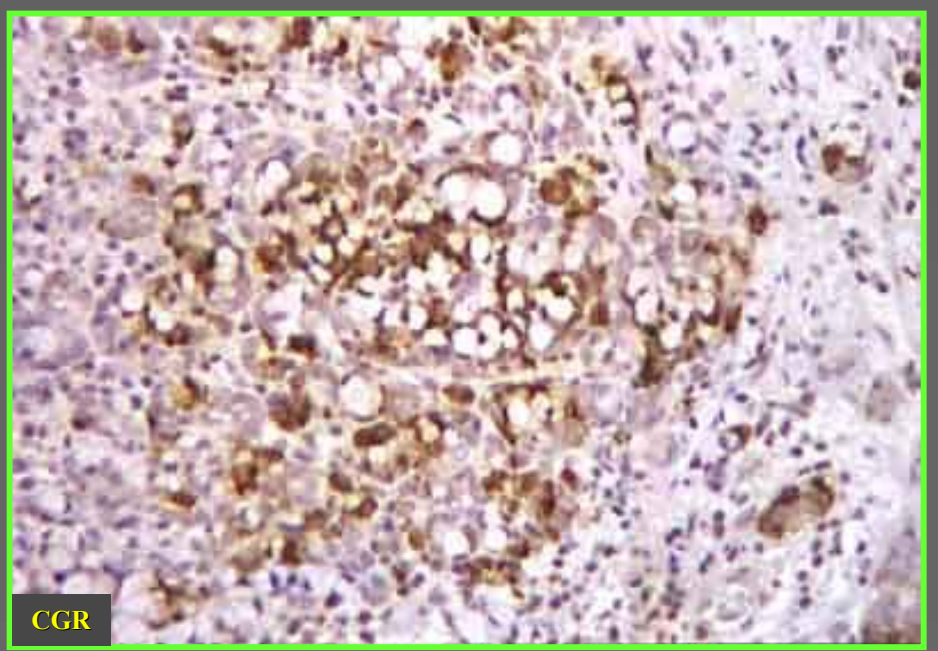


Mixed Neuroendocrine-Exocrine Carcinoma of the Appendix

Low grade malignant

- *Goblet-cell carcinoid*





Clinicopathological Correlations of Neuroendocrine Tumors of the Appendix

- There are usually 0.5 cm or less in size
- They arise in the mucosa and submucosa and infiltrate the wall
- Most tumors confined to the appendix show benign behavior
- Localization at the base of the appendix, increases the risk of tumor spread
- Few well-differentiated endocrine carcinomas invade the mesoappendix with or without lymph nodes or distant metastases
- Carcinoid syndrome is very rare; it is associated with massive metastases to the liver or retroperitoneum

WHO 2004 CLASSIFICATION *of* PANCREATIC TUMORS

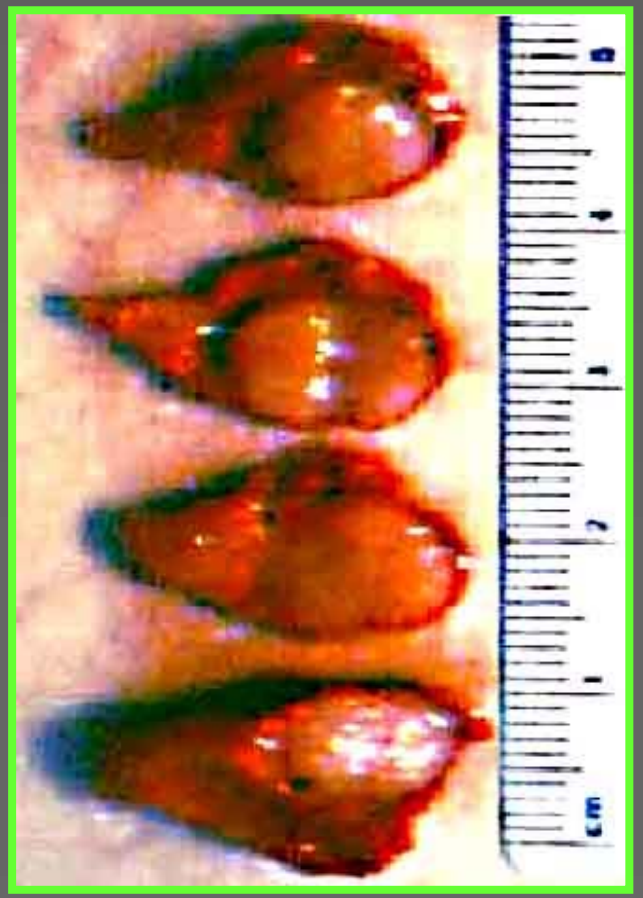
- Well-Differentiated Endocrine Tumor
- Well-Differentiated Endocrine Carcinoma
- Poorly Differentiated Endocrine Carcinoma
- Mixed Endocrine-Exocrine Carcinoma

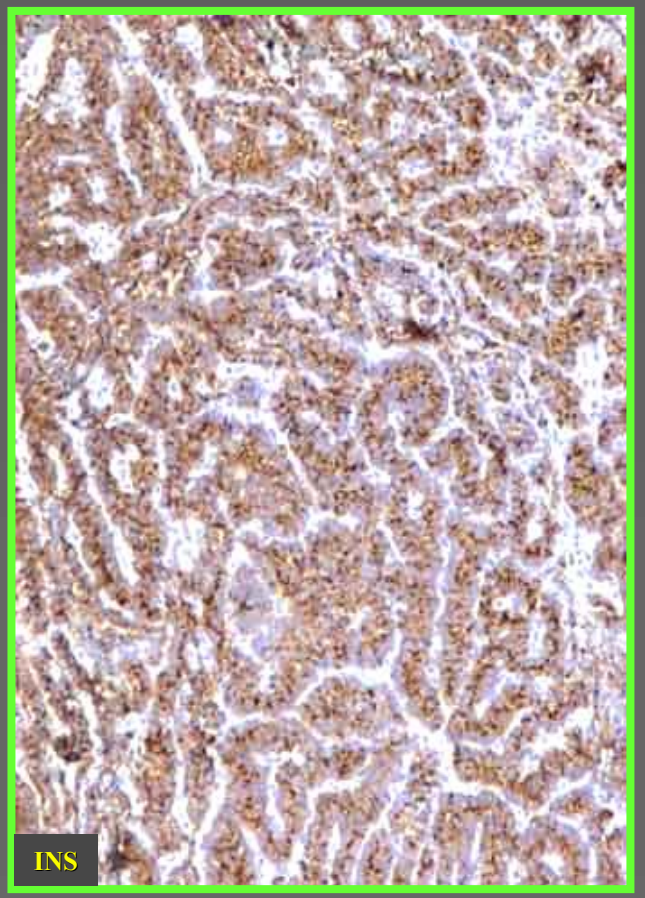
Well-differentiated Endocrine Tumors of the Pancreas

- Functioning tumors
  - *Gastrinoma*
  - *Insulinoma*
  - *VIPoma*
  - *Glucagonoma*
  - *Somatostatinoma*
  - *Inappropriate syndrome tumor*
- Nonfunctioning tumors
  - *Variable immunoreactivity*
  - *Microadenoma: 0.05 cm-<0.5 cm*

    Remain silent, often found in autopsies

Well-Differentiated Endocrine Tumors of the Pancreas





Well-Differentiated Endocrine Tumors of the Pancreas

- Benign behavior
  - Confined to the pancreas, non-angioinvasive
  - Size <2 cm, Mitoses <2/10 HPF, Ki-67 <2%
- Uncertain behavior
  - Confined to the pancreas
  - Size >2 cm, Mitoses >2/10 HPF, Ki-67 >2% or angioinvasive
  - *Size <3 cm: Probability of benign behavior 90%*

Well-Differentiated Endocrine Carcinoma of the Pancreas

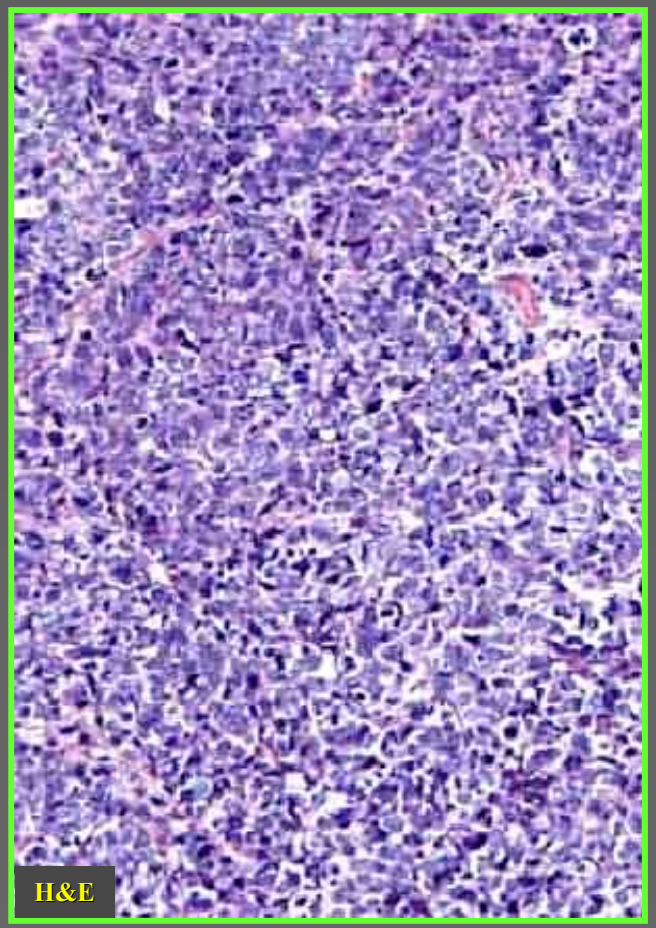
- Low grade malignant tumors
  - Gross local invasion and/or metastases (LN, liver)
  - Size >3 cm, Mitoses >2-10/10 HPF, Ki-67 >5%
- Functioning tumors
  - *Gastrinoma, Insulinoma, VIPoma, Glucagonoma, Somatostatinoma, Inappropriate syndrome tumor*
- Nonfunctioning tumors
  - Variable immunoreactivity

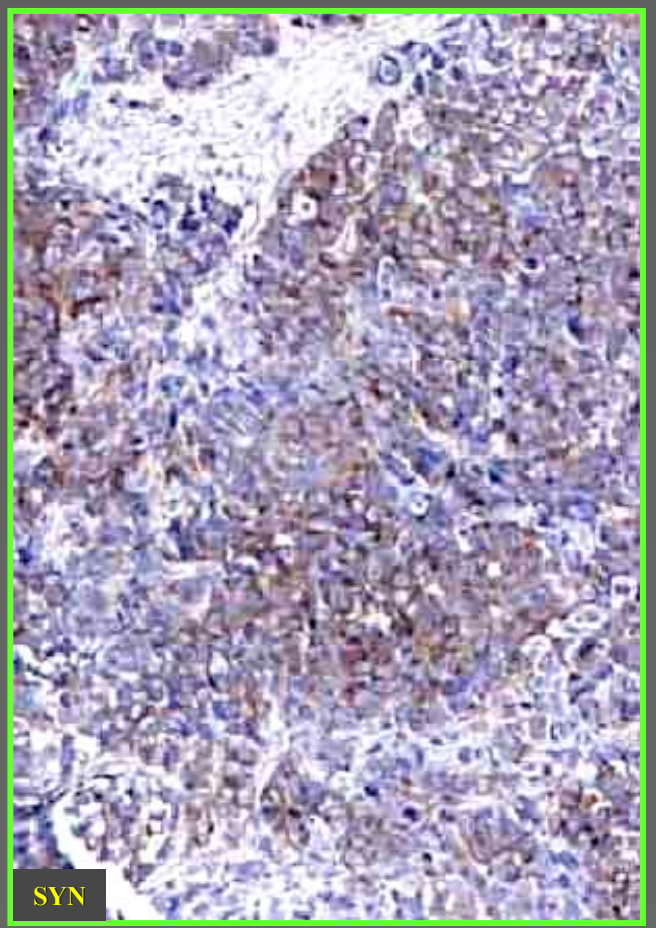
Poorly Differentiated Endocrine Carcinoma of the Pancreas

- High grade malignant tumors
  - Prominent angioinvasion or perineural invasion
  - Distant metastases (liver and often extra-abdominal sites)
  - Mitoses >10/10 HPF - Ki-67: >15%

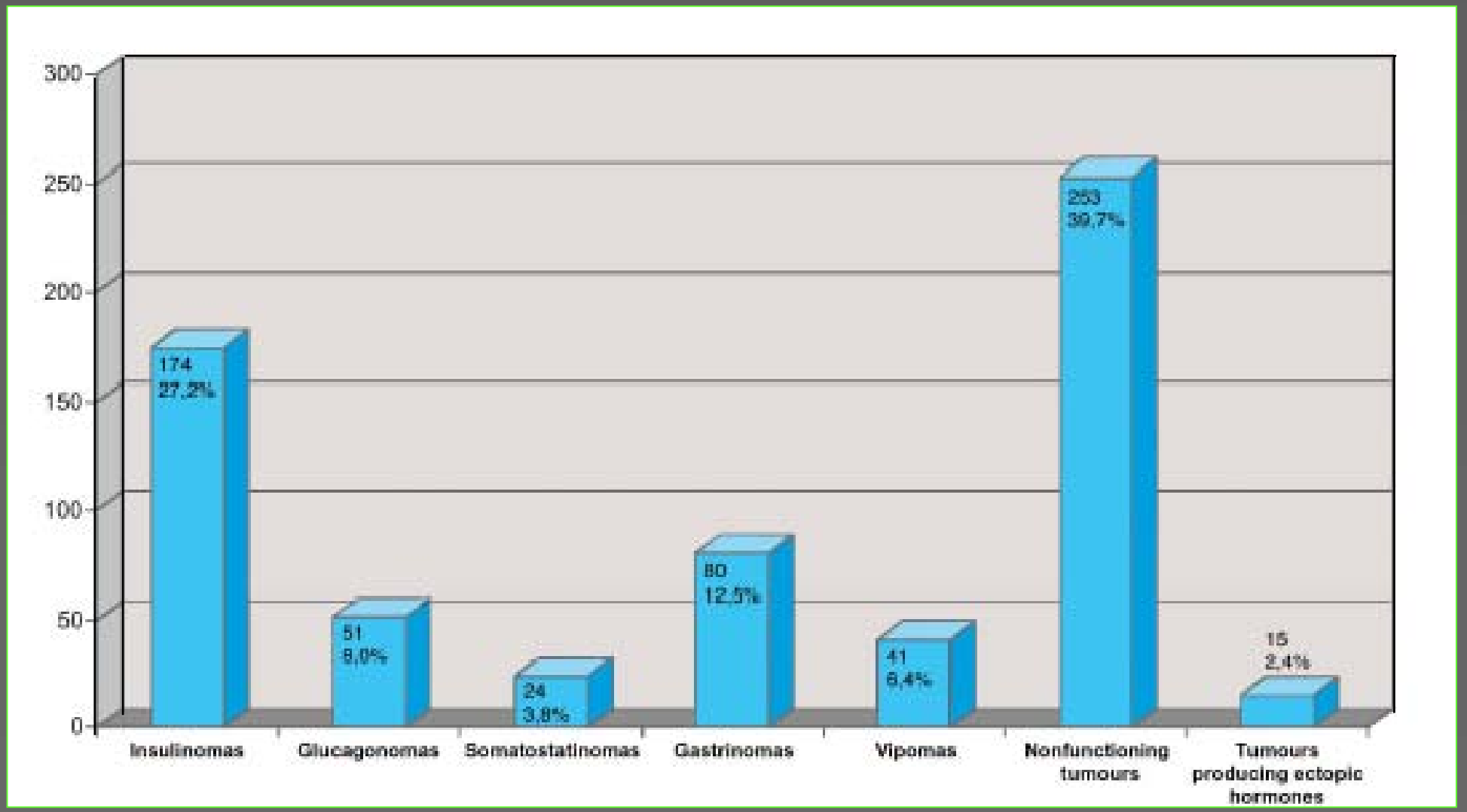
    Often p53 protein immunoreactivity

Poorly Differentiated Endocrine Carcinoma of the Pancreas





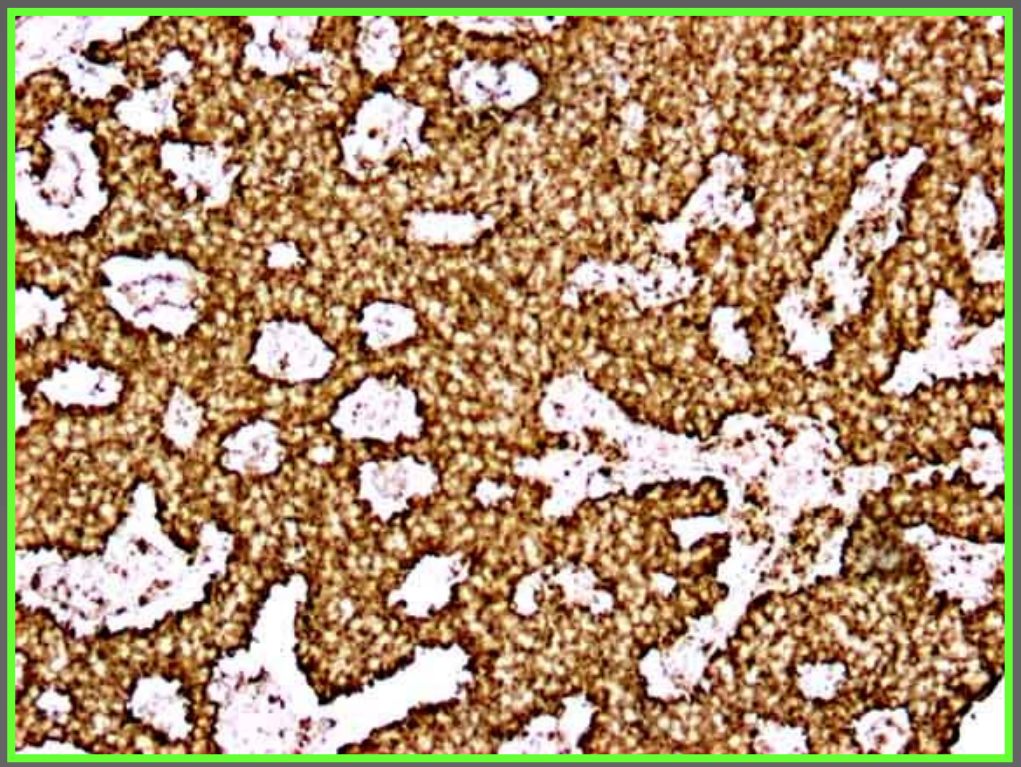
Frequency of Endocrine Tumor of the Pancreas



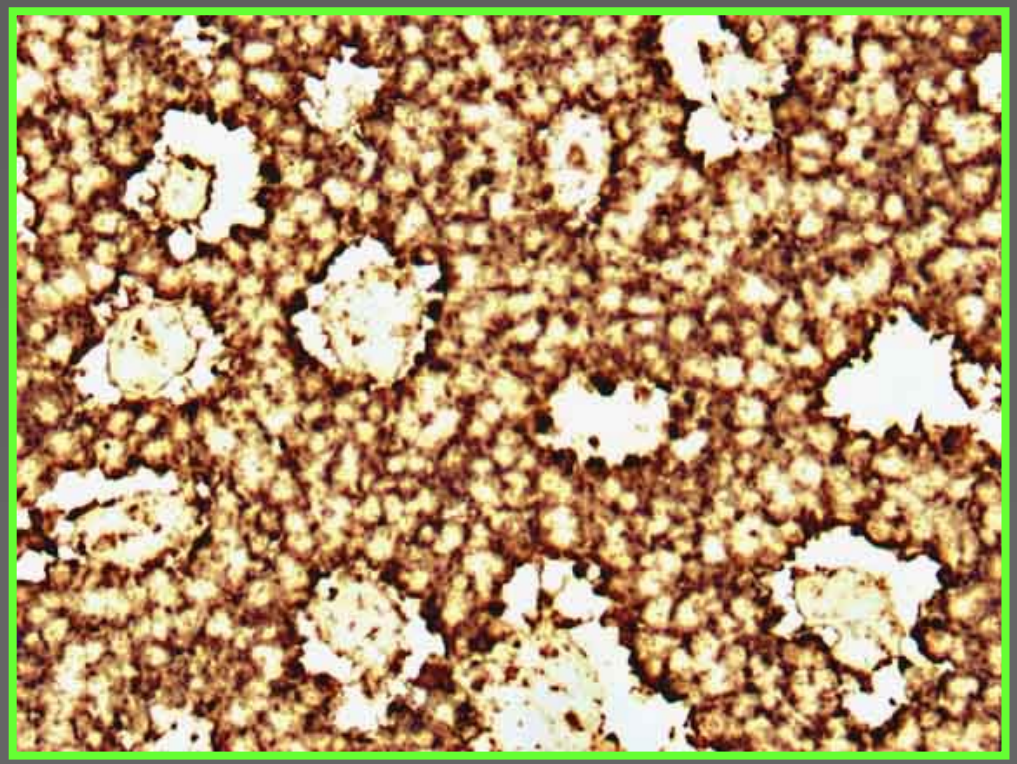
Targeted Therapy

- Presence of somatostatin receptors in NETs enables immunohistochemical detection
- Knowledge of the receptor status is very important for clinicians regarding the effectiveness of somatostatin targeted therapy (sst2 and sst5) and evaluation of the octreoscan (sst2)

Targeted Therapy



sst2A



sst3

Comment

- Recent advances have greatly contributed in expanding the knowledge on endocrine cells and their tumor counterparts
- Novel peptides are being tested or remain to be discovered
- Characterization of candidate tumors, which are negative for known markers and thus, require precise classification

Comment

The WHO Classification

Based on morphologic, immunohistochemical characteristics and clinical features

Represents a morphofunctional diagnostic approach

Provides useful information to clinicians regarding prognosis and further therapeutic strategies

WHO Classification of Tumours of Endocrine Organs
Consensus Conference, International Agency for Research on Cancer, Lyon, France - 23-26 April 2003

Thank you