PATHOLOGY OF GI TUMORS

DR. SARITA
Prof. & Head
Dept. of Pathology,
GGSMC, Faridkot
TUMOURS OF OESOPHAGUS

BENIGN TUMOURS

1. EPITHELIAL
   SSE- Papilloma
   Columnar– Adenoma

2. STROMAL
   Fibroma
   Neurofibroma
   Haemangiom.
Benign neoplasms & tumor-like lesions

• Esophageal benign neoplasms are mostly of mesenchymal origin (non-epithelial): leiomyomas, lipomas, hemangiomas, neurofibromas.

• Two distinctive lesions:
  • Fibrovascular polyp
  • Squamous papilloma
Squamous papilloma

Low magnification: fronds of thickened squamous epithelium supported by connective tissue cores

Some have HPV-related cytologic changes or evidence of HPV DNA by in-situ hybridization methods

If squamous papilloma identified, respiratory tract should be examined for HPV-related papillomatosis (especially children)
Malignant neoplasms of esophagus - An overview

• Malignant tumors of esophagus comprise 6% of all gastrointestinal cancers.
• Problem: often asymptomatic until late, when they are deeply invasive or already metastatic.

• Worldwide: 90% squamous / 10% adenocarcinoma.

• Incidence of adenocarcinoma rising steadily since 1970, almost always arising in Barrett esophagus.
<table>
<thead>
<tr>
<th>Squamous Carcinoma</th>
<th>Descriptor</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F = 4:1; high incidence Iran, China, Puerto Rico (environmental initiators)</td>
<td>Epidemiology</td>
<td>M:F = 7:1; &gt;95% from Barrett metaplasia; &lt;5% from submucosal glands</td>
</tr>
<tr>
<td>Initiators: environmental carcinogens; promoters: nutritional deficiencies (vitamins A, B1, B2, B6, trace metals)</td>
<td>Pathogenesis</td>
<td>Barrett dysplasia: early mutation or overexpression of p53; amplification cERB-B2, cyclin D, cyclin E</td>
</tr>
<tr>
<td>Ethanol, tobacco, achalasia, chronic esophagitis, Plummer-Vinson syndrome</td>
<td>Clinical Risk Factors</td>
<td>chronic reflux esophagitis tobacco, obesity</td>
</tr>
<tr>
<td>20% upper third 50% middle third 30% lower third</td>
<td>Anatomic Distribution</td>
<td>&gt;95% lower third</td>
</tr>
<tr>
<td>5 yr. survival: 5-10% --75% 5 yr. survival if T1 lesion --25% 5 yr. survival for all cases subjected to surgery</td>
<td>Prognosis</td>
<td>5 yr. survival: 25% &gt;80% 5 yr. survival with esophagectomy for T1 lesion</td>
</tr>
</tbody>
</table>
Squamous CA: gross pathology

Exophytic polypoid (obstructing lesion)

Ulcerated stricture (dysphagia)

Early, superficial T1 lesion, good prognosis
SQUAMOUS CELL CA- HISTOLOGY

Grade 1  well differentiated
Grade 11  moderately differentiated
Grade 111 poorly differentiated
M/E—Adenocarcinoma.

Site – lower 1/3rd (from Barrett's)
Majority of carcinomas are mucin producing adeno carcinoma of gastric type or intestinal type
Spread of esophageal carcinoma

1. LOCAL SPREAD

Most imp - both transverse and longitudinal........

longitudinal   Stomach below,
               Hypo pharynx above.
               Trachea – tracheo esophageal fistula

transverse    Larynx --- hoarseness
               Mediastinum, lungs, Trachea,
               bronchi, 
               pleura, aorta, etc.
2. LYMPHATIC SPREAD

Submucosal lymphatics ---- multiple satellite nodules
Cervical Lymphadenopathy

. Paraoesophageal Lymphadenopathy.
Tracheobronchial Lymphadenopathy.
. Sub diaphragmatic Lymphadenopathy.

3. HAEMATOGENOUS SPREAD--- rare, can involve lung, liver etc.
Esophagus

• The specimen received are:
• Mucosal biopsies
• Resection specimen (partial or total esophagectomy)
INTERPRETATION OF THE ESOPHAGEAL BIOPSY

1. Is the esophageal biopsy normal or abnormal?
APPROACH TO INTERPRETATION OF NEOPLASTIC LESIONS

- What is the tumour type and differentiation?
- Does the biopsy include normal esophageal mucosa?
- Is there any overlying squamous dysplasia, glandular dysplasia or Barrett's metaplasia?
- Is it possible to comment on the submucosal invasion in the biopsy specimen?
- Extent of invasion in resection specimen (Layers involved)
- Presence or absence of LVE (Lympho-vascular emboli)
- Lymph node status
- Distant spread
PATHOLOGY OF STOMACH

Four anatomical regions

- Cardia
- Fundus
- Body
- Antrum

Highly vascular mucosa

Majority of gastric lesions are in antrum and cardia.

Fundus and body spared- rich blood supply.
Tumours of Stomach

Non neoplastic (Polyps)
- Hyperplastic polyp
- Inflammatory polyp
- Hamartomatous polyp

Neoplastic tumours
- Benign
- Malignant
ADENOMA....Stomach

- Rare in Stomach.
- Pyloric Antrum.
- **M/E-DYSPLASTIC CELLS** within gastric glands.

- By definition all gastric adenomas have epithelial dysplasia.

- Gastric adenoma being removed endoscopically.
- **Solitary.**
- < 2cm. in dia.
- Commonly located in the antrum.
Adenoma....Stomach

Villous gastric adenoma (non-pedunculated)
CARCINOMA STOMACH

- > 90% of malignancies of stomach- **Adenoca. stomach**.
- Leading cause of death in parts where its incidence is high.
- **SITES-PYLORIC CANAL BODY, CARDIA OR FUNDUS.**
CLASSIFICATION CA. STOMACH

MOST USEFUL CLASSIFICATION-
LAUREN’S CLASSIFICATION-
2 TYPES

1. INTESTINAL GASTRIC CA.
Tumour with intestinal morphology .....Form polypoidal growths.
Usually arises from intestinal metaplasia.
Composed of glandular structure.
Adenocarcinoma stomach

2. DIFFUSE GASTRIC CARCINOMA

Infiltrates deeply into stomach without forming obvious polypoidal mass but spreading within the wall.

Composed of mucin secreting signet ring cells.

POOR PROGNOSIS.
Ca. Stomach

Ulcerative type

Polypoidal type
LINITIS PLASTICA...Leather bottle
Stomach....Scirrhous-type adenocarcinoma

• Stomach wall is thickened due to desmoplasia.
• Lumen of the stomach is reduced.

**M/E**

**SIGNET RING CELLS.**

• But due to excessive desmoplasia....cancer may be difficult to find.
Morphology.....Ca.Stomach.....M/E

Signet ring type Gastric adenocarcinoma
SPREAD....Ca. Stomach

1. DIRECT-
Local extension into mucosa, submucosa, - muscularis & serosa.
TRANSCOELOMIC DISSEMINATION ...e.g. OVARIES ............
KRUKENBERG TUMOUR.

OTHER ORGANS-OMENTUM, PANCREAS, LIVER, CBD, SPLEEN,
DIAPHRAGM, T. COLON etc.

2. LYMPHATIC-TO REGIONAL LYMPH NODES.
   - SUPRACLAVICULAR L. NODES.
   - VIRCHOW’S SIGN.

• COMMON IN SCHIRROUS TYPE GASTRIC CARCINOMA.
• **3. HAEMATOLOGICAL SPREAD**
  
  • Common in poorly differentiated carcinoma.
  Liver, lungs, brain, kidney, bones
  Adrenal, subcutaneous tissue.

**SISTER MARY JOSEPH NODULE**-PERIUMBILICAL

**SUBCUTANEOUS NODULE**
GIST

- MC mesenchymal neoplasm of GIT
- Origin
  - Interstitial cells of Cajal (ICC)
    - Pacemaker cells
    - Present in myenteric plexus
    - Coordinate gut peristalsis
  - CD34+ stem cells which differentiate towards ICC phenotype
- 95% are +ve for c-KIT (CD 117)
- 35% of c-KIT negative GISTs are +ve for PDGFR-α mutation
- c-KIT & PDGFR-α mutation – alternative oncogenic mechanisms
- 70% +ve for CD 34
Cut surface is solid and shows foci of hemorrhage.
Spindle Cell GIST

- Oval uniform blunt-ended nuclei with abundant eosinophilic slightly fibrillary cytoplasm

- Pattern:
  - Cellular sheets
  - Fascicles with whorled or Palisaded patterns

- Cells are separated by hyalinized or calcified stroma

- Large areas of liquefactive necrosis are seen
Epithelioid GISTs

- Most occur in the fundus of the stomach

- Rounded cells with abundant prominent cleared cytoplasm & well defined cell borders

- The tumour cells are arranged in sheets, rather than fascicles
Mixed type

- Admixture of spindled and epithelioid tumours cells or an intermediate cell type is observed.

- The epithelioid and mixed cell types are significantly more often found in gastric GIST.
Immunohistochemistry

Markers used include:

- CD34
- KIT
- DOG1
- PDGFR-alpha
- SDHB
- SMA and h-caldesmon
- S100, CD56 and NSE
- Desmin

Strong membranous CD117 staining
MALTOMAS

• Nearly 5% of all gastric malignancies are primary lymphomas.....m/c is extranodal marginal zone B-cell Lymphoma

Extranodal marginal zone B-cell lymphoma usually arises at sites of chronic inflammation

• In stomach, MALT is induced as a result of chronic gastritis (H. pylori infection is the m/c inducer in stomach.)
The tumour cells surround reactive follicles and infiltrate the mucosa. The follicles have a typical starry-sky appearance.

Gastric lymph node involved by MALT lymphoma. The tumour cells infiltrate the marginal zones and spread into the interfollicular areas.
Neoplastic marginal zone B-cells with nuclei resembling those of centrocytes, but with more abundant cytoplasm.

The cells of this MALT lymphoma have abundant pale staining cytoplasm leading to a monocytoid appearance.
Plasma-cell differentiation (arrows) and Dutcher bodies (arrowhead)
MALTOMAS

- Immunophenotypically neoplastic cells express pan B cell markers, CD19, CD20, CD22, CD79a, PAX5
- Immunoglobulins show clonal rearrangement, high loads of somatic hypermutation
- MALT lymphomas have recurrent translocations
- m/c is t(11;18), (q21;q21)
APPROACH TO INTERPRETATION OF MALIGNANCIES OF STOMACH

Procedures
• Endoscopic Resection
• Gastrectomy (Partial or Complete)
• Tumor site:
• Fundus: Anterior wall, posterior wall
• Body and antrum:
• Anterior wall
• Posterior wall
• Lesser curvature
• Greater curvature
APPROACH TO INTERPRETATION OF MALIGNANCIES OF STOMACH

Histologic Type

• Adenocarcinoma, intestinal type
• Adenocarcinoma, diffuse type
• Papillary adenocarcinoma
• Tubular adenocarcinoma
• Mucinous adenocarcinoma (greater than 50% mucinous)
• Signet-ring cell carcinoma (greater than 50% signet-ring cells)
• Other (specify): Carcinoma, not otherwise specified
APPROACH TO INTERPRETATION OF MALIGNANCIES OF STOMACH

• Microscopic Extent of Tumor
  - High-grade dysplasia/carcinoma in situ
  - Tumor invades lamina propria
  - Tumor invades muscularis mucosae
  - Tumor invades submucosa
  - Tumor invades muscularis propria
  - Tumor invades subserosal connective tissue
  - Tumor penetrates serosa (visceral peritoneum)
  - Tumor directly invades adjacent structures (specify):
    - Tumor penetrates to the surface of the visceral peritoneum (serosa)
      AND directly invades adjacent structures (specify: ____________________________)
  - Margins (select all that apply)
APPROACH TO INTERPRETATION OF MALIGNANCIES OF STOMACH

• Lymph node status
• Perineural invasion
• Local versus distant spread
• Ancillary findings
• IHC
Figure 2. Definitions of T1, T2, and T3. Tumor invading the lamina propria is classified as T1a (left side or T1 illustration), whereas tumor invading the submucosa is classified as T1b (right side). T2 tumor invades the muscularis propria. T3 tumor invades the subserosal adipose tissue. Modified from: Greene FL, Compton CC, Fritz AG, et al. eds. AJCC Cancer Staging Atlas. New York, NY: Springer-Verlag; 2002.
Tumors and polyps of Colon

• A mass protruding from m/m into the lumen—polyp.
• More common in colon but can also occur in esophagus, stomach & S.I.

  – 1. Sessile

• 2. Pedunculated Polyps
  • 1. Non neoplastic
  • 2. Neoplastic
NEOPLASTIC POLYP

1. Benign Polyps
   - Adenoma
     - Tubular
     - Villous
     - Tubulovillous

2. Malignant Polyps
   - Adenocarcinoma
   - Leiomyosarcoma
   - Lymphoma
Neoplastic polyps

Adenomas

• Benign neoplastic polyps.
• As a result of neoplastic epithelial proliferation overlying the muscularis mucosae.
• Colorectal adenomas are characterized by the presence of epithelial dysplasia.
• Are precursors of majority of the colorectal adenocarcinomas.
Colonic Adenoma.....M/E and gross

- Colorectal adenomas are characterized by the presence of epithelial dysplasia.
Neoplastic polyps

3 subtypes......

1. **Tubular Adenoma** (tubular glands)
2. **Villous Adenoma** (villous projections)
3. **Tubulovillous Adenoma** (mixture of the two.)
1. Tubular Adenoma

- **Most common** neoplastic polyp.
- Singly / multiple (familial polyposis syndrome).

**Gross**

- Single or multiple.
- Sessile or pedunculated.
- <1cm or large.
- Malignant transformation.......upto 5%.

**M/E**-Lining epithelium with decreased mucus secreting capacity.

- **Disordered** epithelium with large hyperchromatic nuclei.
- Increased mitotic activity
- Variable degree of **cytological atypia** can be present
2. Villous Adenoma

- Less common.
- Size can go up to 10 cm.
- Sessile.
- Malignant transformation..... 30%.

M/E

Many slender finger like villi arising from muscularis mucosae. Villi having fibrovascular core....covered by epithelial cells(benign to atypical cells).

3. Tubulovillous Adenoma.....Mixed pattern.
Neoplastic polyps

VILLOUS ADENOMA

Pedunculated Tubular Adenoma
FAMILIAL POLYPOSION SYNDROMES

• Group of disorders with multiple polyposis of the colon.

• Have familial basis.

• Autosomal dominant inheritance pattern.

• Imp. conditions included in familial polyposis are.....
FAMILIAL POLYPOYSIS SYNDROMES

1. FAMILIAL POLYPOESIS COLI (FAP) (Familial Adenomatous Polyposis.)

2. GARDNERS SYNDROME.

3. TURCOT SYNDROME.

4. JUVENILE POLYPOESIS SYNDROME.
FAMILIAL ADENOMATOUS POLYPOsis (FAP)

- Hereditary (Familial disease).
- Multiple polyps. (average -1000)
- Also called Adenomatosis or FAP.

Precancerous. Malignant potential in FAP is very high – CA. develops in 100% of untreated cases over a period of several yrs.

- D/D------MULTIPLE ADENOMAS COLON. (HERE THE NO. OF POLYPS < 100). FAP is asso. with a variety of extra-intestinal manifestations....

Congenital hypertrophy of the retinal pigment epithelium. ......which is generally detected at birth.

This can serve as an adjunct to early screening
FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

**GROSS**

500-2500 adenomas carpeting the colonic mucosal surface. (*At least 100 polyps are necessary for diagnosis of classic FAP.*)

**M/E**

Majority are *tubular adenomas.*
PREVENTIVE MEASURES... in FAP

• EARLY DETECTION OF DISEASE IN SIBLINGS & FIRST DEGREE RELATIVES.

• PROPHYLACTIC COLECTOMY
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Colorectal Polyps</th>
<th>Extracolonic Lesions</th>
<th>Genetics</th>
<th>Risk of Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial adenomatous polyposis</td>
<td>Adenomatous polyps (100s to 1000s)</td>
<td>Duodenal/periampullary adenomas, gastric fundic gland polyps, congenital</td>
<td>Autosomal dominant APC mutation</td>
<td>100% risk of colorectal carcinoma (mean age 35-40 years) 3% to 5% risk of</td>
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<td></td>
<td>hypertrophy of the retinal pigment epithelium</td>
<td></td>
<td>duodenal/periampullary carcinoma</td>
</tr>
<tr>
<td>Gardner's syndrome</td>
<td>Adenomatous polyps (100s to 1000s)</td>
<td>Osteomas, epidermoid cysts, dental abnormalities, fibromas, desmoid</td>
<td>Autosomal dominant APC mutation</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tumors (especially mesenteric)</td>
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</tr>
<tr>
<td>Turcot's syndrome</td>
<td>Adenomatous polyps (100s to 1000s)</td>
<td>Central nervous system tumors (especially medulloblastoma)</td>
<td>Autosomal dominant APC mutation</td>
<td>Same as above</td>
</tr>
<tr>
<td>Attenuated familial adenomatous</td>
<td>&lt;100 Adenomatous polyps</td>
<td>Similar to conventional familial adenomatous polyposis</td>
<td>Autosomal dominant APC mutation</td>
<td>80% risk of colorectal carcinoma (mean age, 50 years)</td>
</tr>
<tr>
<td>polyposis</td>
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<tr>
<td>MYH-associated polyposis</td>
<td>Usually 15-100 adenomatous polyps</td>
<td>Uncertain</td>
<td>Autosomal recessive MYH mutations</td>
<td>High risk of colorectal carcinoma</td>
</tr>
</tbody>
</table>
Colorectal tumors - Carcinogenesis

- Two distinct pathways
  - APC/β-Catenin Pathway
  - Microsatellite instability pathway
- Both involve stepwise accumulation of multiple mutations
- Genes involved & mechanisms are different
APC/β-Catenin Pathway
Adenoma → Carcinoma Sequence
APC/β-Catenin Pathway

Loss of Adenomatous Polyposis Coli Gene

- 5q21
- Dual Function
  - Tumor Suppressor Gene- Inhibition of signal transduction
  - Gatekeeper Gene – regulates levels of β-catenin (a member of cadherin based cell adhesive complex)
- 80% colorectal cancer have APC mutation
- Half of tumors without APC mutations have β-catenin mutations.
- Mutations in APC gene
  - Missense
  - Frameshift
  - Deletions
  - Location- 60% in upstream region of exon 15, the mutation cluster region
Microsatellite Instability Pathway

- Genetic lesions in DNA mismatch repair genes
- Present in 15% of sporadic cases and in HNPCC Syndrome
- No clearly identifiable morphological correlates
- MSI-H Tumors

- **Germline mutations in any of 5 genes** involved in DNA repair responsible
  - hMSH 2 (2p22) responsible for 90% of cases
  - hMLH 1 (3p21)
  - hMSH 6 (2p21)
  - hPMS 1 (2q31-33)
  - hPMS 2 (7p22)
Microsatellite Instability Pathway

• Distinct Features of Tumors
  – Proximal colonic location
  – Mucinous histology
  – Infiltration by lymphocytes
  – More likely to be diploid
  – More likely to have a larger primary at diagnosis and node negative
  – Better long term prognosis
Microsatellite Instability Pathway

Loss of mismatch repair genes

↓

Accumulation of mutations in growth regulating genes

↓

Colorectal carcinoma.
Microsatellite Instability Pathway

**NORMAL COLON**
- Mucosa
- Submucosa
- Muscularis propria

**SESSILE SERRATED ADENOMA**
- Germ-line or somatic (acquired) mutations of mismatch repair genes
- Alteration of second allele by LOH, mutation, or promoter methylation
- Microsatellite instability/"mutator phenotype"

**CARCINOMA**
- Accumulated mutations in genes that regulate growth, differentiation, and/or apoptosis
- e.g., TGFβRII, BAX, TCF-4, IGF2R, others

**MLH1, MSH2** *(MSH6, PMS1, PMS2)*
Microsatellite Instability Pathway

HNPCC (Lynch Syndrome)

• Autosomal Dominant Disorder
• 3% of all colorectal cancers

• One mutant DNA repair gene (first hit) is inherited
  – One allele is normal
  – Cells susceptible to somatic mutation in some organs (second hit)
  – This inactivates the normal allele (LOH)
  – Mutation rates are 1000 times higher than normal
Microsatellite Instability Pathway

HNPCC (Lynch Syndrome)

• Two types
  – **Lynch Type I** – Associated with large bowel tumors only
  – **Lynch type II** - Associated with tumors of endometrium, ovary, stomach, small bowel, renal pelvis etc.

• Few colonic polyps, hence the term non-polyposis

• Life time risk of colorectal carcinoma is 80%
Colorectal Carcinogenesis
Hamartomatous Polyposis Syndromes

• Rare, <1% colorectal cancers
• Adolescent and pediatric population affected

• Peutz Jeghers syndrome
  – Autosomal dominant
  – Multiple hamartomatous polyps throughout GIT
  – Melanotic mucosal and cutaneous pigmentation
  – Patients at increased risk of malignancies of pancreas, breast, lung, ovary and uterus.
  – Mutation of gene STK 11( LKB1) located on ch 19 which encodes a protein with serene/threonine kinase activity.
• Juvenile polyposis syndrome
  – Overlapping clinical features with PJS
  – Polyps confined to colon
  – Increased risk of adenoma and colorectal carcinoma
  – Germline mutations in PTEN & SMAD 4/ DPC 4 gene which encodes TGF-β signaling intermediate.
Colorectal Carcinoma

- 60% in rectum.
- Sigmoid colon, caecum, descending/ascending colon.

**GROSS**

Right sided growth – large, soft, polypoidal mass projecting into the lumen. (liquid nature of the contents of ascending /Right sided colon.)

Left sided growth---napkin ring appearance i.e. they encircle the bowel wall with increased fibrosis forming an annular ring (solid contents of descending Colon permits spread of growth into the bowel wall).
COLORECTAL CARCINOMA

- **M/E** Some tumors may produce abundant mucin which dissects through the wall & helps in early metastasis... *poor prognosis.*
- Some may have **signet ring cells** (like in Gastric Carcinoma)
COLORECTAL CARCINOMA

Dysplastic Glands with desmoplasia

Anaplastic cells with desmoplasia
COLORECTAL CARCINOMA

Complications

• Obstruction.
• Haemorrhage.
• Perforation.
• Secondary infection.

PROGNOSIS

1. Extent of bowel involvement.
2. Presence/absence of metastases.
3. Histological grade of the tumor.
4. Location of the tumor.

But, the most imp. prognostic factor is......

The stage of the disease at the time of diagnosis.
Neuroendocrine tumors (NETs)

- Arise from neuroendocrine cells.
- Many are **benign**, while some are **malignant**.
- They most commonly occur in the intestine, where they are often called **carcinoid** tumors, but they are also found in the pancreas, lung and the rest of the body.
- Although there are many kinds of NETs, they are treated as a group of tissue because the cells of these neoplasms share common features, such as looking similar, having special **secretory granules**, and often producing biogenic **amines** and **polypeptide hormones**.
## Classification of NETs

### Nomenclature and classification for neuroendocrine tumors

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Grade</th>
<th>Mitotic count*</th>
<th>Ki-67 index*</th>
<th>Traditional</th>
<th>ENETS, WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated</td>
<td>Low grade (G1)</td>
<td>&lt;2 per 10 HPF</td>
<td>≤2 percent</td>
<td>Carcinoid, islet cell, pancreatic (neuro)endocrine tumor</td>
<td>Neuroendocrine tumor, Grade 1</td>
</tr>
<tr>
<td></td>
<td>Intermediate grade (G2)</td>
<td>2-20 per 10 HPF</td>
<td>3-20 percent</td>
<td>Carcinoid, atypical carcinoidΔ, islet cell, pancreatic (neuro)endocrine tumor</td>
<td>Neuroendocrine tumor, Grade 2</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>High grade (G3)</td>
<td>&gt;20 per 10 HPF</td>
<td>&gt;20 percent</td>
<td>Small cell carcinoma</td>
<td>Neuroendocrine carcinoma, Grade 3, small cell</td>
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<td></td>
<td>Large cell neuroendocrine carcinoma</td>
<td>Neuroendocrine carcinoma, Grade 3, large cell</td>
</tr>
</tbody>
</table>
Morphological patterns in NENs

• **Insular** (nodular solid nests with peripheral invading cords)

• **Trabecular** (anastomosing trabeculae or ribbons)

• **Glandular** (tubules, rosettes)

• **Poorly differentiated** with no well-organized growth pattern
Type A **(INSULAR OR NESTED GROWTH PATTERN)**

Type B **TRABECULAR GROWTH PATTERN**
TYPE C (ACINAR GROWTH PATTERN)

TYPE D (POORLY DIFFERENTIATED GROWTH PATTERN)
Confirmation of Neuroendocrine Differentiation

- Synaptophysin
- Chromogranin A

WDNETs

- solid pseudopapillary tumor of the pancreas
- adrenal cortical carcinoma

PDNETs
Well-differentiated neuroendocrine tumor (A: Giemsa stain) with (B) chromogranin A, (C) synaptophysin, and (D) AE1/AE3 positivity.
SMALL AND LARGE INTESTINE

• *Specimen received*
  Segmental resection specimens, partial or complete pancreatoduodenectomy, partial, or complete colectomy
• Submucosal biopsies
• *Reporting of neoplastic lesions*
• Tumor site
• Tumor size
• Histologic type
• Histologic grade
REPORTING OF NEOPLASTIC LESIONS

• Microscopic tumor extension
• Margins
• Lympho-vascular invasion
• Regional lymph node status
• Local or Distant spread
• Ancillary studies:
  • MSI
  • IHC
• Comments
CLINICAL IMPLICATIONS

• Early Diagnosis
  – Non invasive detection of neoplasia
    • Examination of stool, urine, gastric juice and plasma for detection of mutant oncogenes & tumor suppressor genes
  – Detection more specific than conventional markers
  – Expensive
    • Not cost effective in routine detection
    • More useful in screening high risk cases of
      – HNPCC
      – Barrett’s esophagus
  – Analysis of nuclear DNA in stools to find gene sequences like APC, K-ras, p53 is helpful in colorectal cancer detection
  – Amount of DNA ↑ in colorectal carcinoma
Early Diagnosis
Genetic Testing in Colorectal Cancers

**FAP**
- APC truncating protein tested (preferred)
- If APC mutation found screen for mutation in family

**HNPCC**
- MSI testing
- If +ve test for hMLH1 & hMSH2 genes
- If mutation found screen family for mutations

**PJS, Juvenile Polyposis**
- Gene mutation analysis
Clinical Implications

Formulation of New Treatments

• Principle inhibition of protooncogenic products or replacement of inactivated tumor suppressor genes
  – Reintroduction of p53, DCC, APC (using viral vectors) or knockout of mutated K-ras → Growth arrest or reversion of colon cancer cell lines

• Imatinib mesylate (STI 571/ Gleevec) (a tyrosine kinase inhibitor) used in GIST treatment → targeted therapeutic approach
THANKS