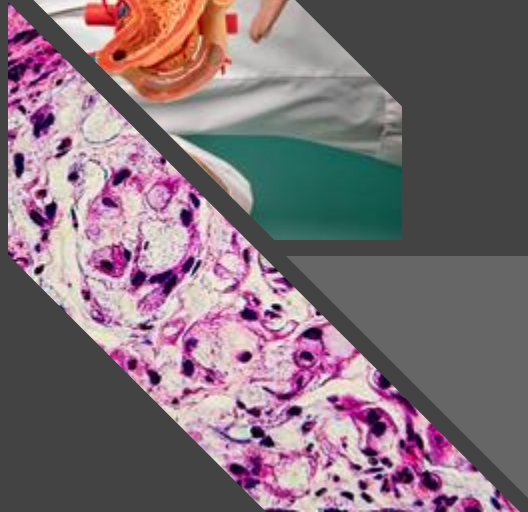
# Gastric Neoplasms

Done By: Group A2



# Epidemiology 1 : Incidence

- Although it is steadily declining in incidence, GC remains one of the **most common and deadly** neoplasms in the world.
  - GC is the third leading cause of cancer deaths worldwide, following only lung and colorectal cancer in overall mortality.

- GC is also one of the most **behaviourally** influenced, and thus preventable, of major cancers.

- GC is more prevalent in **males**.

- The incidence of GC is highly variable by region and culture.

# EPIDEMIOLOGY 2: SURVIVAL

- The 5-year survival rate for GC is 31% in the US. Average survival rates reflect the fact that most cases diagnosed are already metastatic.

- The 5-year survival rate for pre-metastatic diagnosis is 67%.

# ETIOLOGY AND RISK FACTORS

| | | |
|---|---|---|
| 1 | Sex | M > F |
| 2 | Age | Advanced age |
| 3 | Class | Lower |
| 4 | Environmental factors | |
| 5 | Diet & smoking | High in salted, smoked, or preserved foods<br><br>Low in fruits and vegetables |
| 6 | H. Pylori | 3-6 fold |
| 7 | Chronic atrophic gastritis and Int. metaplasia | |

| | | |
|---|---|---|
| 8 | Adenomatous gastric polyps and FAP | 10-20% |
| 9 | Previous gastric surgery | 2-6 fold |
| 10 | Pernicious anemia | 10% |
| 11 | Ménétrier's disease (Giant hypertrophic gastritis) | 10% |
| 12 | Family history of gastric cancer | 10% |
| 13 | Blood type A | |
| 14 | Hypogammaglobulinemia | 47-fold |

# DIET

- Appears to be correlated with a high intake of:
  - Preserved foods ( ↑salt, nitrates, nitrites).
  - Pickled vegetables
  - Salt
- Nitrates and nitrites → N-nitrosamines (carcinogens)
- Free radical–induced injury by nitrosamines are potentially damaging.
- Ascorbic acid can prevent the conversion of nitrites to nitrosamines).
- Ascorbic acid and beta-carotene act as antioxidants.

# HELICOBACTER PYLORI

- Parallels between rates of GC and H. pylori infection.
- 3-6-fold ↑ risk of GC in individuals with H. pylori.
- Infection causes >80% of chronic gastritis cases. → chronic atrophic gastritis → metaplasia → GC.
- Toxins such as ammonia and acetaldehyde are produced, which cause inflammation and epithelial damage.
- It causes epithelial cell proliferation and production of growth regulatory peptides. recruitment of inflammatory cells (neutrophils) are augmented. These neutrophils generate free radicals and chloramine, both of which cause direct DNA damage.
- 35-89% of GC could be prevented by eradication.
- Associated more with intestinal than the diffuse type. More with CA of the antrum, fundus, and body than CA of the cardia.

# ADENOMATOUS GASTRIC POLYPS

- DX is usually made on barium meal or coincidentally during endoscopy
- Risk for malignant degeneration is 10-20% and ↑ for polyps ≥ 2 cm.
- Pedunculated polyps should be removed
- Endoscopically for pathologic exam.
- Sessile polyps > 2 cm. treated with wedge resection + a margin of normal mucosa.
- Patients with multiple polyposis should be considered for gastrectomy.

# PREVIOUS GASTRIC SURGERY

- Gastric surgery for benign conditions ? the risk by 2-6 folds
- Events analogous to h. pylori infection is present. Partial gastrectomy and vagotomy causes hypo- or achlorhydria, allowing bacterial overgrowth with ↑ conversion of nitrites to nitrosamines.
- CA in the gastric remnant have a poor prognosis (tend to present at a more advanced stage and in older patients).
- Surveillance in post-gastrectomy patients mayimprove survival.

# HYPOGAMMAGLOBULINEMIA

- It is a disorder caused by low serum immunoglobulin or antibody levels.
- Hypogammaglobulinemia is the most common primary immunodeficiency and encompasses a majority of immune-compromised patients.
- This condition predisposes children and adults to recurrent infections, allergies, neoplasms, and autoimmunity.
- Hypogammaglobulinemia can be of primary or secondary origin.
    - Primary immunodeficiencies result from genetic disorders
    - Secondary causes are usually induced by an external or acquired factor such as a corticosteroid or immunosuppressant drug, nutritional disorders, infections, chemotherapy, malignancy, nephrotic syndrome, other metabolic diseases, and hazardous.

# PATHOLOGY

- Nearly all stomach cancers are adenocarcinomas
- Adenocarcinoma of the stomach begins in the mucus-producing cells in the innermost lining of the stomach, and is divided into two main classes, depending on where it forms in the stomach:

1. Gastric cardia cancer begins in the top inch of the stomach, just below where it meets the oesophagus. Most adenocarcinomas are found in the gastric cardia.
    - There is a much higher incidence of tumors of the cardia in smokers than of tumors elsewhere in the stoma
2. Non-cardia gastric cancer is cancer that begins in all other sections of the stomach.

# PATHOLOGY

- Adenocarcinoma of the stomach also may be described as intestinal or diffuse, depending on how the cells look under a microscope:
    - Intestinal adenocarcinomas are well differentiated, meaning the cancer cells look similar to normal cells under a microscope.
    - Diffuse adenocarcinomas are undifferentiated or poorly differentiated, as 10-15% of tumors are diffuse in character .the cancer cells look different from normal cells under a microscope. Diffuse adenocarcinomas tend to grow and spread more quickly than the intestinal type and be harder to treat.

# PATHOLOGY (CLASSIFICATION)

- Bormann classification
- Broeder's histologic grading system
- Ming's classification
- Lauren classification

Bormann classification remains the most widely used, and divides gastric carcinomas into four distinct types :

1. Polypoid carcinoma (type I)
2. Fungating carcinoma (type II)
3. Ulcerating carcinoma (type III)
4. Diffusely infiltrating carcinoma (type IV).

The latter is also referred to as **linitis plastica** when it involves the majority of the stomach

# LAUREN CLASSIFICATION

| Intestinal-type Tumors | Diffuse-type Tumors |
| --- | --- |
| Glandular structure | Tiny clusters of small cells |
| Diffuse inflammatory cell infiltration and frequent intestinal metaplasia | Widespread through the mucosa, less inflammatory infiltration |
| Preceded by a pre-cancerous process and predominate in region with ↑ incidence of gastric Ca | More often in women, in younger patients, and in regions where gastric cancer is less common |
| As regional gastric cancer risk is ↓, it experiences most of the reduction. | As the incidence of gastric Ca in the cardia ↑, it is seen with ↑ frequency. |
| | Frequent lymphatic invasion, intraperitoneal metastases, have a poorer prognosis. |

# HISTOPATHOLOGIC TYPES:

- adenocarcinoma (intestinal, diffuse, and mixed).
- Papillary, tubular, or mucinous adenocarcinoma. signet ring cell carcinoma.
- Adenosquamous carcinoma.
- Squamous cell carcinoma.
- Small cell carcinoma.
- Mixed adenocarcinoma and choriocarcinoma
- Undifferentiated carcinoma.

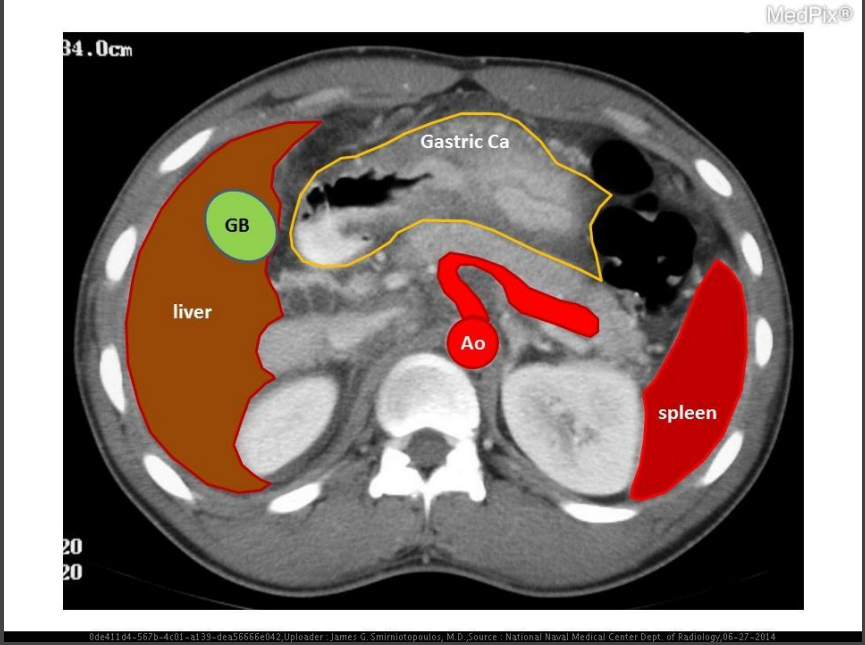
# HISTOPATHOLOGIC TYPES:

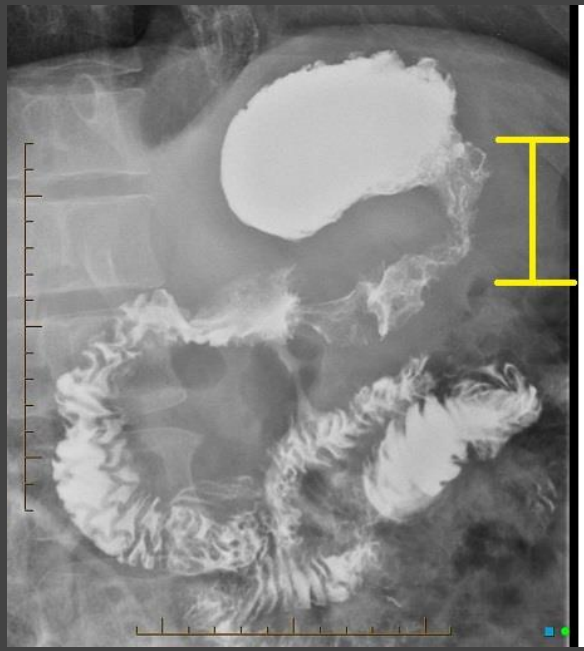
- Grading stages, G1-G4:
  - G1 WELL DIFFERENTIATED
  - G2 MODERETLY DIFFERENTIANTED
  - G3 POORLY DIFFERENTIATED
  - G4 UNDIFFERENTIATED TUMOR

# LINITIS PLASTICA

- **Definition**:
  - **Linitis plastica** is a type of adenocarcinoma that spreads to the muscles of the stomach wall and makes it thicker and more rigid.
  - This means that the stomach can't hold as much and doesn't stretch or move as it should when you're digesting food.
  - The term is also used to describe The condition of a rigid, non-distensible stomach, Which may be caused, by a non-malignant condition such as a caustic injury to the stomach.
  - Most common Cause of linitis plastica is PRIMARY GASTRIC CANCER , but in rarer cases it could be an effect of metastatic infiltration of the stomach especially lung and breast carcinoma.

# LINITIS PLASTICA



Narrow and indistensible stomach lumen

# LINITIS PLASTICA

- **Symptoms:**

  Linitis plastica doesn't usually cause symptoms until it has grown quite large or spread. Because of this it can be difficult to diagnose early, which then makes it harder to treat.

  When it does cause symptoms, they are similar to stomach cancer symptoms, which include Difficulty swallowing, weight loss, indigestion and vomiting

- **Etiology:**

  The Etiology of Linitis Plastica is not fully understood, and a lot of research is done to uncover the exact cause of the disease.
  Gastric cancer in general and LP as a subcategory are more prevalent in the American and Asian populations, especially in Japan, Korea, and China. This could be related to the type of food, mainly low fiber diet, or the ethnicity of the population. On the other hand, LP is not associated with H.pylori infection or chronic active gastritis. Genetic factors play an important role, such as the CDH1 gene and the HER2 gene.

# LINITIS PLASTICA

- **Histopathology**

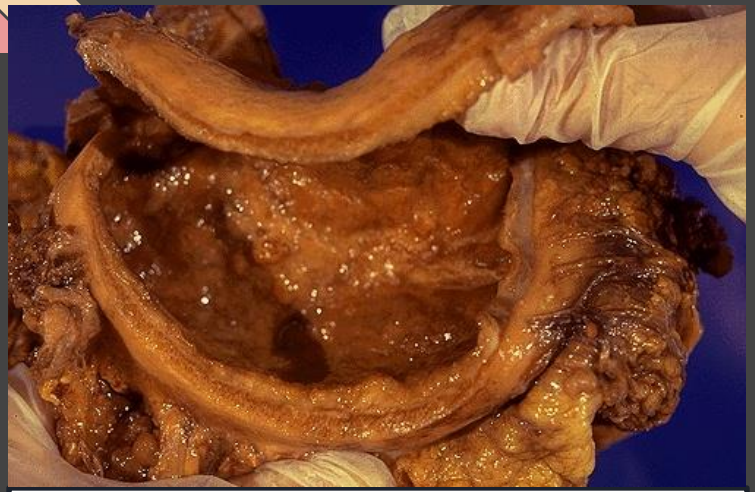
  “Leather bottle” was a term describing the gross appearance of the stomach, where there is limited distensibility of the gastric volume.

  Macroscopic Appearance: Diffuse infiltration of tumorous tissue in the submucosa and muscularis propria layers of the stomach. The gastric wall is markedly rigid and thickened.

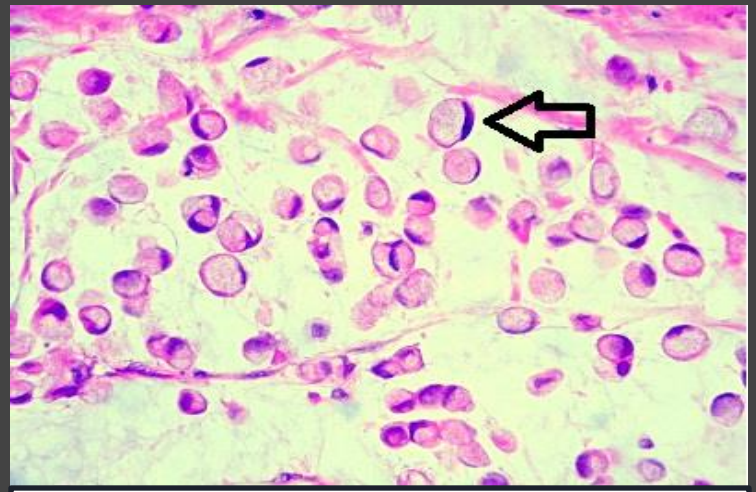
  Microscopic Appearance: Stromal hypertrophy and hyperplasia with poorly differentiated adenocarcinoma and signet ring cells infiltration hence the term “signet cell carcinoma”.

- **Evaluation**

  High-resolution computed tomography CT scan with contrast is the gold standard for initial diagnosis to detect deep gastric wall thickening in the submucosa and muscle layer. Also, it could be helpful in early detection of the disease as false-negative biopsies in LP as it shows diffuse irregular narrowing and rigidity of the stomach.



This is an example of linitis plastica, a diffuse infiltrative gastric adenocarcinoma which gives the stomach a shrunken "leather bottle"



Arrow indicates a signet ring cell characteristic of linitis plastica.

# PATHOLOGY (METASTASIS)

- Regional lymphatics.
- Hematogenous (portal and systemic circulation).
- Within the gastric wall.
- Direct invasion of adjacent organs.
- Involved gastric serosa can seed metastases throughout the peritoneum.

- Examples:
  - Ovary (Krukenberg's tumor) through lymphatic channels .
  - Left supraclavicular adenopathy (Virchow's node) as a distant lymph node , also called trosier sign.

# MOLECULAR GENETICS

- Molecular and chromosomal alterations → development of gastric Ca.

- Deletion of p53 or expression of aberrant p53 protein is associated with transformation. LOH at the p53 locus is found in 68% of gastric tumors.

- Overexpression of EGFR and C-ERBB-2 are early events, whereas p53 mutation is a late event in gastric carcinogenesis.

# STAGING (TNM CLASSIFICATION)

- Gastric cancer is staged according to the characteristics of the primary tumor (T), nodal metastases (N), and presence of metastatic disease (M).

- The most important prognostic indicators remain the depth of penetration, local regional lymph nodes metastasis, and involvement of adjacent organs.

# PRIMARY TUMOR (T)

| | |
|---|---|
| **TX:** | Primary tumor cannot be assessed |
| **T0:** | No evidence of primary tumor |
| **Tis:** | Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria |
| **T1:** | Tumor invades lamina propria or submucosa |
| **T2:** | |
| **T2a:** | Tumor invades muscularis propria |
| **T2b:** | Tumor invades subserosa |
| **T3:** | Tumor penetrates the serosa (visceral peritoneum) without invading adjacent structures |
| **T4:** | Tumor invade adjacent structures |

# NODAL INVOLVEMENT (N)

- The regional lymph nodes are the peri-gastric nodes, found along the lesser and greater curvatures, and the nodes located along the left gastric, common hepatic, splenic, and celiac arteries.

- Involvement of other intra-abdominal lymph nodes, such as the hepatoduodenal, retro-pancreatic, mesenteric, and para-aortic, is classified as distant metastasis.

# NODAL INVOLVEMENT (N)

| | |
|---|---|
| **NX:** | Regional lymph node (s) cannot be assessed |
| **N0:** | No regional lymph node metastasis |
| **N1:** | Metastasis in **1-6 regional** lymph nodes |
| **N2:** | Metastasis in **7-15 regional** lymph nodes |
| **N3:** | Metastasis in **> 15 regional** lymph nodes |

# DISTANT METASTASIS (M)

| | |
|---|---|
| **MX:** | Distant metastasis cannot be assessed |
| **M0:** | No distant metastasis |
| **M1:** | Distant metastasis |

# EARLY GASTRIC CANCER

- Defined as disease involving the mucosa or submucosa (may be fairly large).

- Mucosal and submucosal early Ca are accompanied by positive lymph nodes.

# EARLY GASTRIC CANCER 1

- Three types of macroscopic lesions are described:
  - Protruded (type I).
  - Superficial (type II).
  - Excavated (type III).

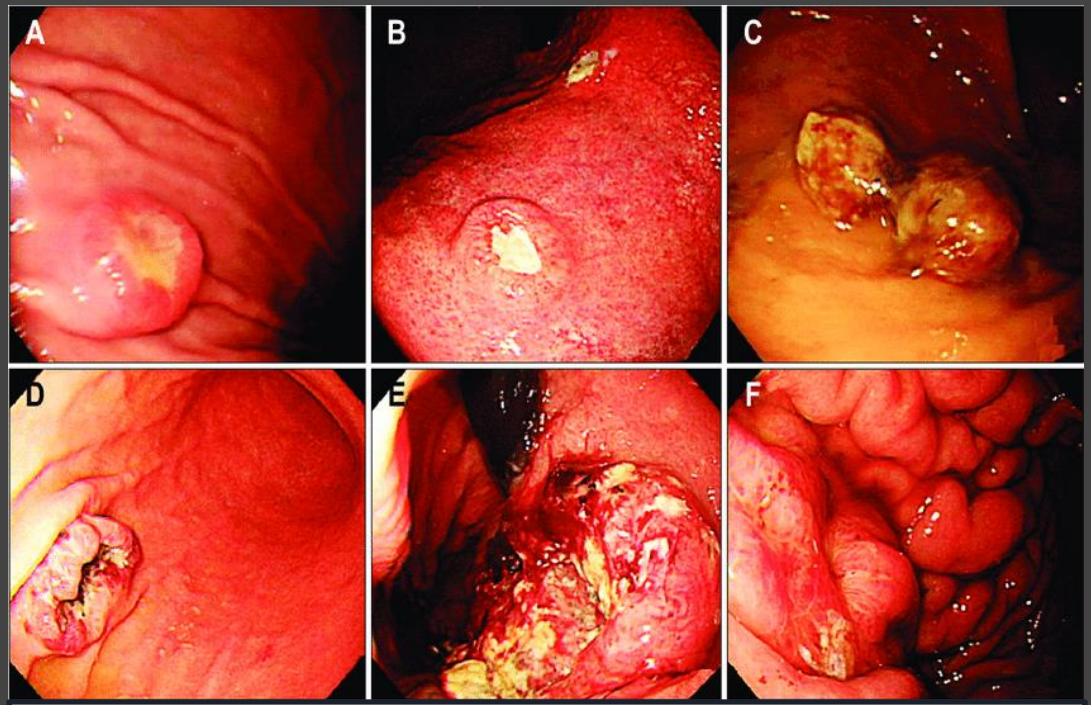
- Five-year survival after resection ranges from 70-95%, depending on the presence of nodal involvement.

# ADVANCED GASTRIC CANCER 1

- Suggests invasion of the muscularis or beyond.

- Frequently associated with distant or contiguous spread, have a higher stage.

# ADVANCED GASTRIC CANCER 2




Endoscopic appearance of metastatic tumors in the stomach.

# SYMPTOMS & DIAGNOSIS 1

- Symptoms of early gastric cancer are vague and unspecific. They may mimic symptoms of benign gastric ulcer
- Symptoms may not be evident until a tumor is of sufficient size to interfere with gastric motor activity, cause obstruction, or cause bleeding from an ulcerated tumor
- Family history of gastric cancer in 10% of patients

# SYMPTOMS & DIAGNOSIS 2

1. Indigestion
2. Anorexia
3. Early satiety
4. Weight loss
5. Nausea and vomiting
6. Dysphasia
7. Hematemesis and melena
8. Signs or symptoms of dissemination
9. Abdominal pain or discomfort and ulcer-type pain
10. Bloating of the stomach after meals
11. Weakness and fatigue /asthenia

# ROUTINE LABORATORY TESTS

- Haematocrit, CBC, liver function tests, and stool guaiac (a stool test is positive for blood)
- In advanced disease, laboratory evidence of anemia develops
- Liver function tests are usually abnormal with hepatic metastasis.

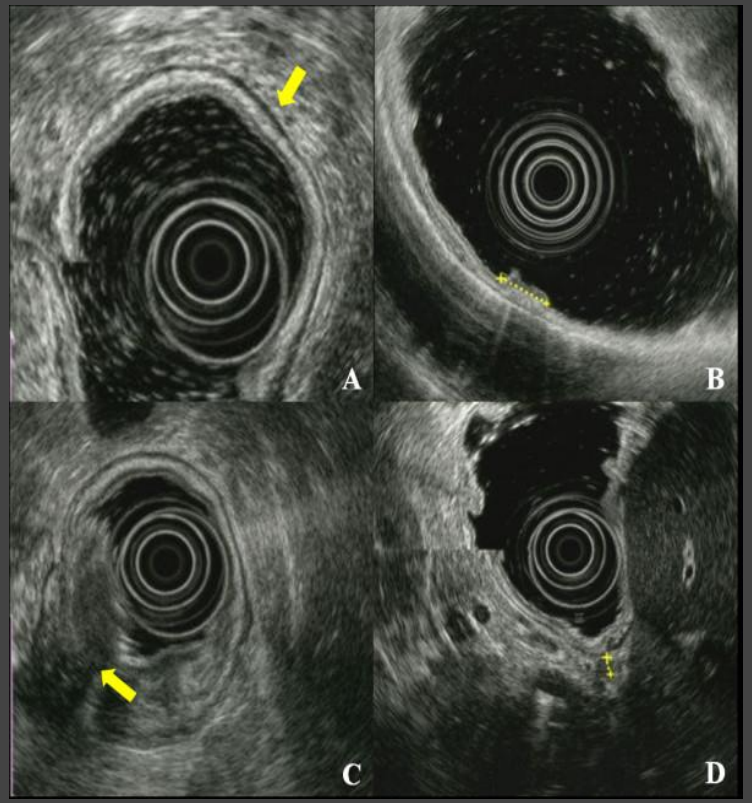
# DOUBLE-CONTRAST BARIUM MEAL

- In Japan screening program, using this technique, 87% of initial subjects are cleared, and 13% are subjected to further examinations.
- Appearance:
  - Polypoid mass.
  - Ulcer crater lies in a mass and does not extend outside the boundary of the gastric wall. Mucosal folds do not radiate toward the centre of the crater, usually > 1 cm and are surrounded by rigid gastric wall on fluoroscopy.
  - Non distensible stomach.

# ENDOSCOPY AND BIOPSY/CYTOLOGY

- Gastritis-like malignant lesions
- Small, plaque like lesions.
- Polyps or small ulcers.
- Ulcerated lesions have elevated margins with shaggy necrotic centres.
- Extensive tumor plaque or large polypoid mass.
- Linitis Plastica is typified by a non distensible stomach.

# ENDOSCOPIC ULTRASONOGRAPHY




Endoscopic ultrasonography (EUS)

(A) EUS showing normal layers of gastric wall, with the five-layered echo pattern being clearly visible (arrow).

(B) EUS of early gastric cancer (T1a).

(C) EUS image of advanced gastric cancer (T3).

(D) EUS showing a metastatic lymph node (dotted line).

# COMPUTED TOMOGRAPHY SCAN

- Gastric wall thickening (0.5-4 cm and correlates with tumor penetration)
- Gastric ulceration (polypoid or sessile lesions)
- Invasion of the gastro-hepatic ligament, spleen, or diaphragm
- Distal metastases.

# OTHER DIAGNOSTIC MODALITIES.

- Gastric acid analysis can diagnose patients with hypo- and achlorhydria, which are associated with ↑ risk for gastric ca (should be screened)
- Molecular biologic techniques, (e.g. cytologic evaluation for p53 or p21 protein)

# TREATMENT 1

- Patients with profound weight loss and metabolic complications of their cancer should be treated.
  - Nutrition therapy
  - Physical therapy
  - Medication therapy
  - Surgery
- Patients without obstruction or bleeding but who have distal metastases should not be explored.

# TREATMENT 2

- Patients with obstruction or bleeding should still be considered for exploration, (as palliative resection is better than palliative bypass).
    - Palliative resection involves the removal of the tumor and a margin of surrounding healthy tissue.
    - Palliative bypass surgery involves creating a new pathway for food or fluids to bypass the tumor.
- In patients with metastatic obstructing proximal gastric tumors, prosthetic Endoesophageal tubes or Endoscopic laser therapy can be used.

# TREATMENT 3

- Surgical resection is the only potentially curative therapy.
- The extent of gastric resection should be tailored to the proximal extent of the primary lesion and geared toward obtaining negative proximal and distal margins.
- Different resections for distal, middle, and proximal lesions. In diffuse tumors, total gastrectomy may be the only option available to achieve adequate margins.

# TREATMENT 4

- Surgical resection and lymphadenectomy can be described as follows
  - D0 resection = incomplete removal of peri-gastric LN.
  - D1 resection = complete removal of peri-gastric nodes.
  - D2 resection = D1 +LN along the named arteries of the stomach.
  - D3 resection = D2 + removal of the nodes of the celiac axis.
  - D4 resection = D3 + para-aortic nodes.

# TREATMENT: EARLY GASTRIC CANCER

- D1 resection is usually curative (survival rates of 95%) .
- Endoscopic treatment using cauterization, local injection of drugs, and laser therapy.

# TREATMENT: ADVANCED CANCER

- Gastric resection includes:
  1. Subtotal gastrectomy for antral or pyloric lesions.
  2. Subtotal or total gastrectomy for middle-third lesions).
  3. Total gastrectomy with Esophagojejunostomy for proximal-third gastroesophageal junction (GEJ), or extensive middle-third lesions.
- In addition, the peri-gastric lymph nodes along the lesser and greater curvatures and the lymph nodes along the left gastric artery are typically removed. The lesser and greater omenta are resected.

# TREATMENT (JAPANESE EXPERIENCE)

- Using a systematic approach, the standard operation in Japan for advanced cancer is the D2 dissection with removal of N1 and N2.
- The survival rates over the past 30 years have risen.

# TREATMENT: GEJ CA

- The disease occurs in an older patient population with a high percentage of advanced tumors (50 to 74%).

- Treatment is by a radical operation, usually through a thoracoabdominal approach.

# ADJUVANT THERAPY 1

- Chemotherapy
  - There is a survival benefit for mitomycin C alone or futrafur and mitomycin C.
- Chemoradiotherapy
  - Results are mixed.

# ADJUVANT THERAPY 2

- Chemoimmunotherapy
  - The immune depression encourages the growth of tumor cells in certain patients.
  - Numerous immunomodulators have been found to enhance t-cell function and stimulate natural killer cells.
  - Immunotherapy alone has rarely been shown to be effective against residual tumors.
  - The advantages are greatest in patients with stage iii and iv disease or patients who underwent r0 resection.
    - A R0 resection means that the surgical margin is microscopically-negative for residual tumor