

GASTRIC NEOPLASMS.

Done by group : A1

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- Epidemiology : 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 : 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

Sex	M>F
Age	Advanced age
Class	Lower
Enviromental factors	
Diet and smoking	High in salted , smoked or preserved food Low in fruits and vegetables
H.pylori	3-6 fold
Chronic atrophic gastritis and Int.metaplasia	
Adenomatous gastric polyps and FAP	10-20%
Previous gastric surgery	2-6 fold
Pernicious anemia	10%
Ménétrier's disease (Giant hypertrophic gastritis)	10%
Family history of gastric cancer	10%
Blood type A	
Hypogammaglobulinemia	47 fold

- Diet

Appears to be correlated with a high intake of:

(a) Preserved foods (high salt, nitrates, nitrites).

(b) Pickled vegetables

(c) 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** increased 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 → 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

- 5th – 7th decades, and have few symptoms or signs.
- DX is usually made on barium meal or coincidentally during endoscopy.
- Risk for malignant degeneration is 10-20% and increase 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

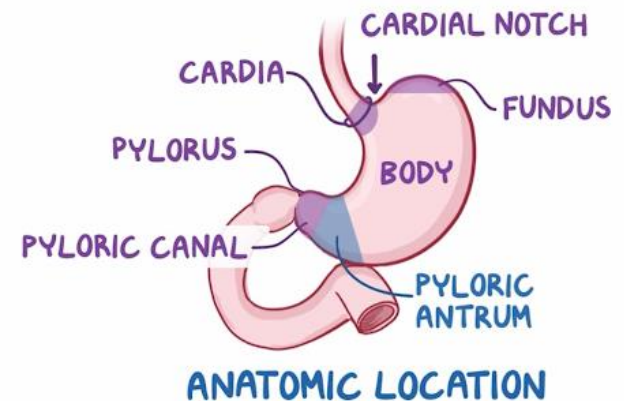
- Gastric surgery for benign conditions increase the risk by **2-6 folds**. Mostly 15-20 years after Billroth II
- Events analogous to H. pylori infection is present. Partial gastrectomy and vagotomy causes hypo- or achlorhydria, allowing bacterial overgrowth with increase conversion of nitrites to nitrosamines
- Ca in the gastric remnant have a poor prognosis (tend to present at a more **advanced stage** and in **older patients**)
- **Surveillance** in postgastrectomy patients may improve 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 and/or chromosomal anomalies during the development of the immune system.
 - **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 environmental conditions.

Pathology

- Gastric cancer, one of the leading causes of cancer-related deaths globally, primarily arises from the stomach lining. It includes several histological types, with adenocarcinoma being the most common form.
- Site
- While gastric cancer used to commonly arise in the antral and pyloric regions, the incidence of tumors in the cardia and gastroesophageal junction (GEJ) has increased. Tumors more frequently affect the lesser curvature than the greater curvature, with a significant rise in **cardia** cancer among **smokers**.
- Macroscopic Classification of Gastric Cancer
- Adenocarcinomas can be divided into the following subtypes:
 - 1. Fungating or polypoid.
 - 2. Ulcerating.
 - 3. Superficial spreading.
 - 4. Diffusely spreading (linitis plastica).



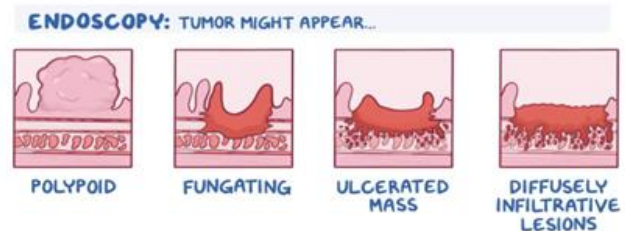
PATHOLOGY (CLASSIFICATION)

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

1) Bormann 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)

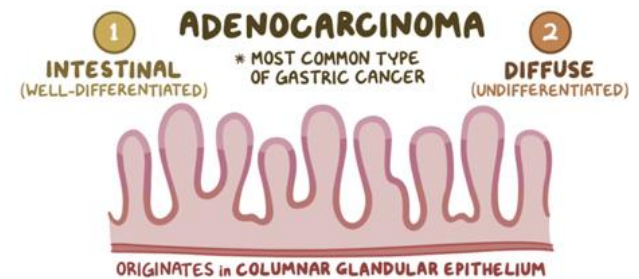


4. Diffusely infiltrating carcinoma (type IV). (linitis plastica)

2) Broeders histologic grading system : (depends on type and degree of differentiation)

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 (Anaplastic).



Grades : G1-G4 for **well**, **moderately**, **poorly**, and undifferentiated tumors.
Nearly all stomach cancers are adenocarcinomas

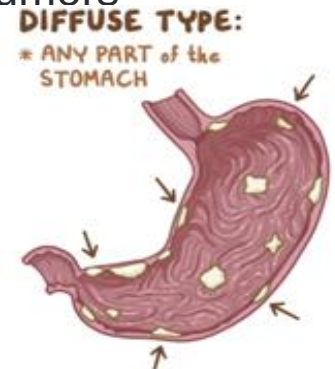
3) The Lauren classification system categorizes gastric cancer into two main types based on histological and morphological characteristics:

1. Intestinal Type: STOMACH CELLS → RESEMBLE INTESTINAL EPITHELIUM = METAPLASIA

- Glandular structure.
- Diffuse inflammatory cell infiltration and frequent intestinal metaplasia.
- Preceded by a pre-cancerous process, predominant in regions with a high incidence of gastric cancer.
- As regional gastric cancer risk decreases, it experiences most of the reduction.

2. Diffuse Type:

- Tiny clusters of small cells.
- Widespread through the mucosa, with less inflammatory infiltration.
- More common in **women**, **younger** patients, and regions where gastric cancer is less prevalent.
- As the incidence of gastric cancer in the cardia increases, diffuse-type tumors are seen with higher frequency.
- Frequent lymphatic invasion, intraperitoneal metastases, with a **poorer prognosis**.



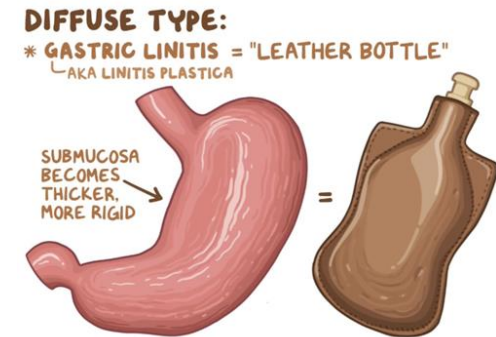
LINITIS PLASTICA

- Linitis plastica is a type of adenocarcinoma and accounts for 3–19% Of gastric adenocarcinomas. Causes of cancerous linitis plastica are commonly primary gastric cancer, but in rarer cases could be metastatic infiltration of the stomach, particularly breast and lung carcinoma. It is not associated with *H. pylori* infection or chronic gastritis.

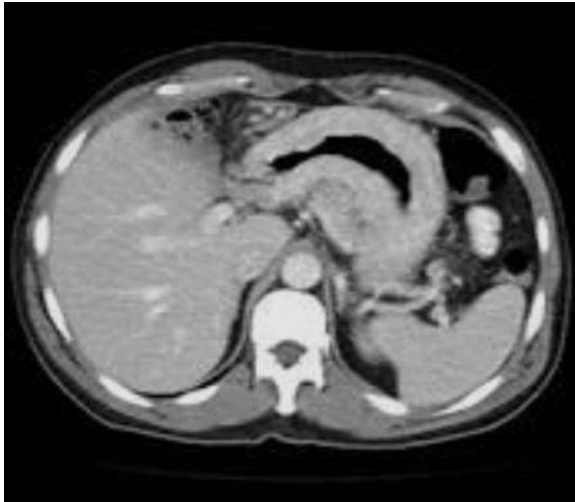
- The risk factors are undefined, except for rare inherited mutations in E-cadherin. The hereditary form of this cancer, Hereditary Diffuse Gastric Cancer, accounts for only 1–3% of gastric adenocarcinomas. Somatic mutations in this gene are found in about 50% of diffuse-type gastric carcinomas.

- Diffuse stomach cancer is characterized by the presence of poorly differentiated tumor cells. Under a microscope, these appear as signet ring cells, meaning that mucin droplets are visible that displace the nucleus to one side.

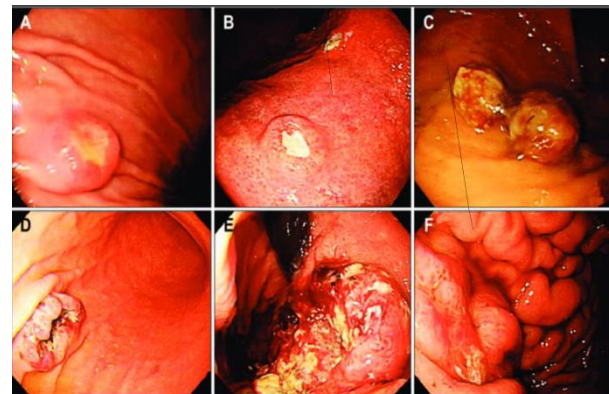
- Symptoms of linitis plastica do not usually present until the disease is in an advanced stage, making early diagnosis difficult. Symptoms are similar to those of stomach cancer including difficulty swallowing, weight loss, indigestion, and vomiting.



LINITIS PLASTICA



Narrow and indistensible stomach lumen



Endoscopic appearance of metastatic tumors in the stomach.

METASTASIS

1. Regional lymphatics. (Lymphatic spread)

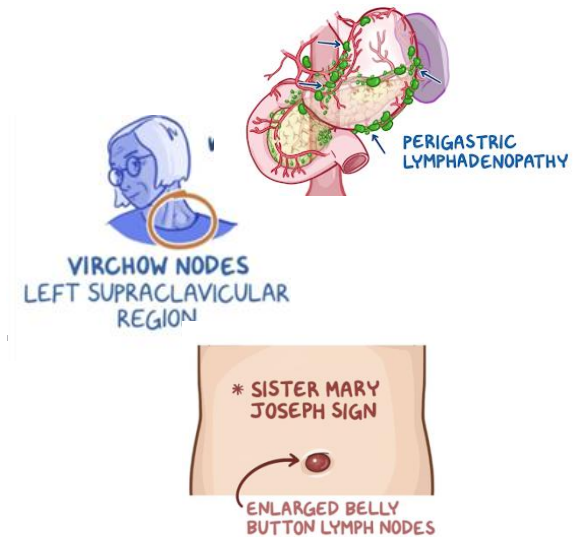
- Left supraclavicular adenopathy (Virchow's node).
- Umbilical adenopathy (Sister Mary Joseph's node)

2. Hematogenous (portal and systemic circulation).

3. Within the gastric wall.

4. Direct invasion of adjacent organs.

5. Involved gastric serosa can seed metastases throughout the peritoneum. (transcoelomic spread of gastric cancer)

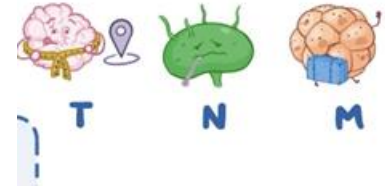


metastases may involve the rectovesical pouch / Douglas pouch (Bloomer's shelf) or ovary (Krukenberg tumor)

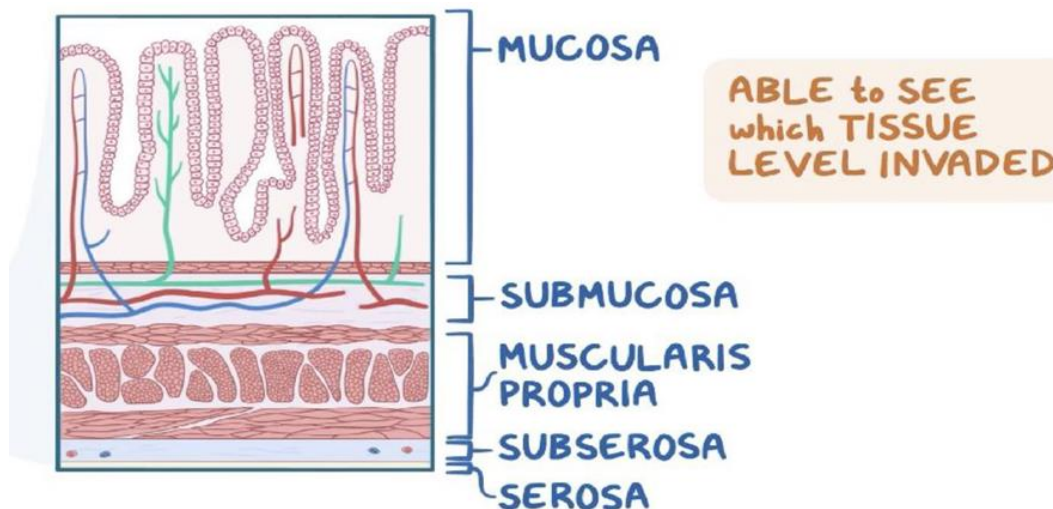
MOLECULAR GENETICS

- Molecular and chromosomal alterations can lead to the development of gastric cancer, as these changes disrupt normal cellular functions and promote uncontrolled growth of cancerous cells.
- 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)

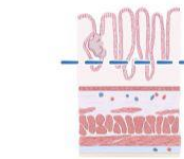


- Gastric cancer is staged according to the characteristics of the primary tumor (T), nodal metastases (N), and presence of metastatic disease (M)
- The most important prognostic indicators remain the depth of penetration, local regional lymph nodes metastasis, and involvement of adjacent organs.

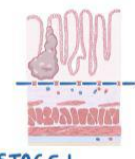


Primary tumour (T)

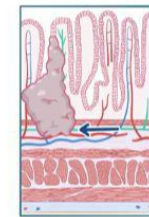
TX:	Primary tumor cannot be assessed
T0:	No evidence of primary tumor
Tis:	● Carcinoma <i>in situ</i> : intraepithelial tumor without invasion of the lamina propria
T1:	● Tumor invades lamina propria or submucosa
T2:	
T2a:	Tumor invades muscularis propria
T2b:	Tumor invades subserosa
T3:	Tumor penetrates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



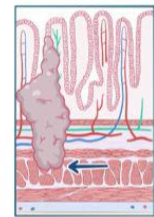
STAGE I
↳ hasn't invaded lamina propria



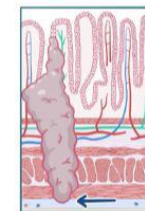
STAGE I
↳ if invaded lamina propria, but hasn't invaded submucosa



Stage I
SUBMUCOSA



Stage II a
MUSCULARIS PROPRIA



Stage II b
SUBSEROAL TISSUE

NODAL INVOLVEMENT (N)

- The regional lymph nodes are the perigastric 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, retropancreatic, mesenteric, and para-aortic, is classified as distant metastasis

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

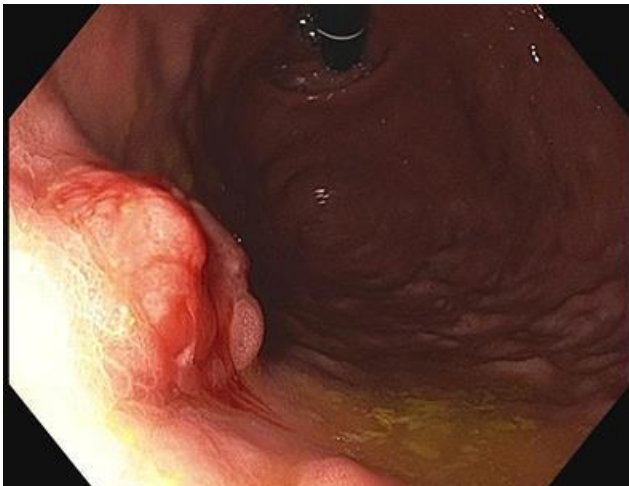
- 5.2 million screened → 6414 have Ca, and 98.7% had operations. (54% of detected cases, 62% of which were early Ca).
- Defined as disease involving the mucosa or submucosa (may be fairly large).
- 5-6% of mucosal and 15 -20% of submucosal early Ca are accompanied by positive lymph nodes.

Three types of macroscopic lesions are described:

- Protruded (type I).
- Superficial (type II).
- Excavated (type III).

Table 3 Paris classification of early gastric cancer (type 0)		
Type 0-I		Protruded type
Type 0-IIa		Superficial elevated type
Type 0-IIb		Flat type
Type 0-IIc		Superficial depressed type
Type 0-III		Excavated type

Type I Protruded type



Type II-a Superficial elevated type



Three types of macroscopic lesions are described

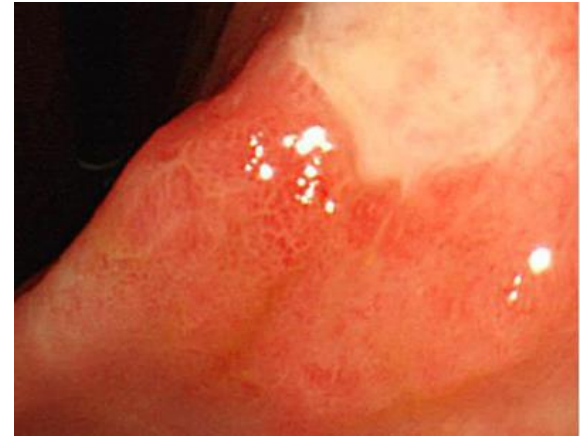
Type II-b Superficial and flat



Type II-c Superficial and deep



Type III Excavated type

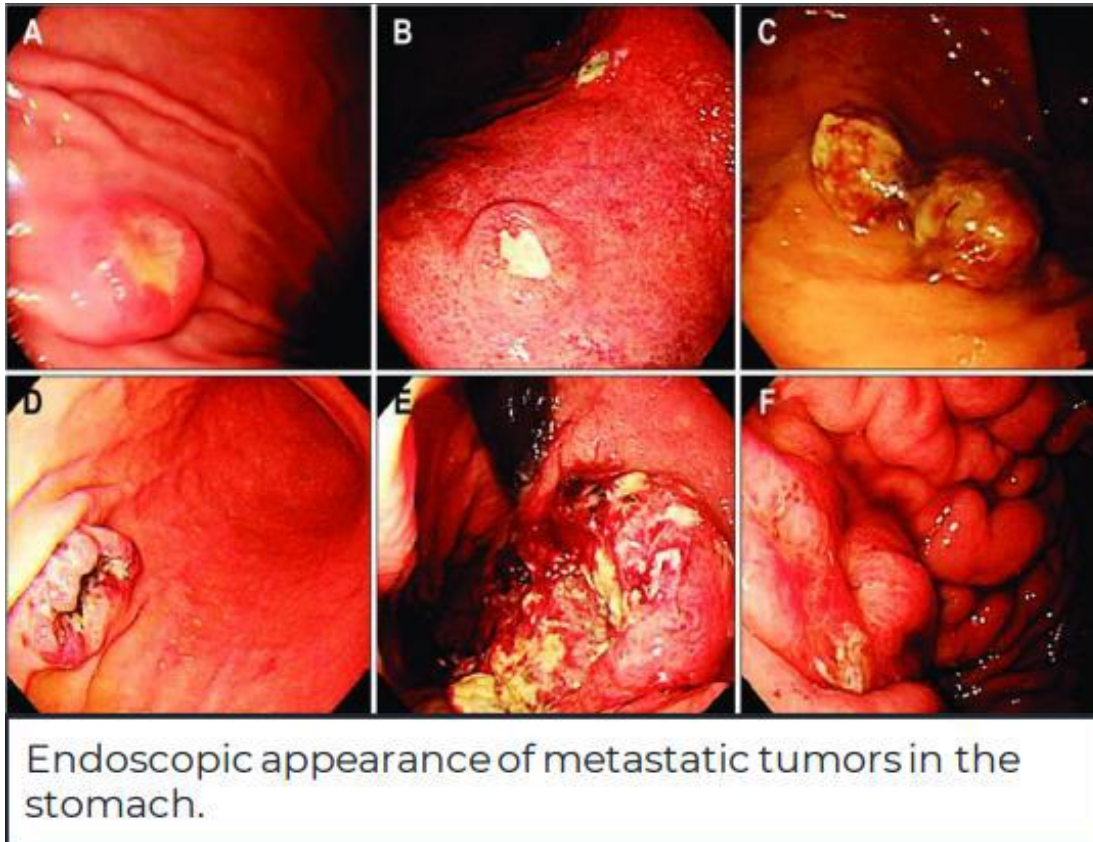


- Five-year survival after resection ranges from 70-95%, depending on the presence of nodal involvement.

ADVANCED GASTRIC CANCER

- Suggests invasion of the muscularis or beyond
- Frequently associated with distant or contiguous spread, have a higher stage
- It represents < 50% of cases in Japan
- > 80% of cases in US are advanced gastric Ca at the time of diagnosis

ADVANCED GASTRIC CANCER



Diagnosis and symptoms

The early symptoms are vague and unspecified, and they mimic a lot of other pathologies (as Gastric Ulcer)

And it might not show any symptoms till advanced progression (interference with motor activity, **obstruction**, and **bleeding** if the tumor is ulcerated)

Familial history = 10%



Tests for diagnosis

1. Routine Lab tests

A. Hematocrit (Anemic in advanced disease)

B. CBC

C. Liver function tests (Abnormal with hepatic metastasis)

D. Stool guaiac (Stool test (+) = there's blood) picture



2.DOUBLE-CONTRAST BARIUM MEAL (Japanese screening program)

A.87% specificity rate,
and all others gets
further investigation

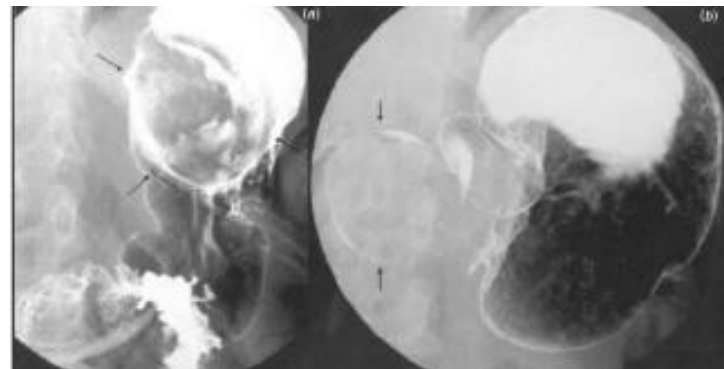


B. Appearance

A. **Polypoid** mass .

B. **Ulcer crater** lies in a mass and does not extend outside the boundary of the gastric wall. Mucosal folds do **not** radiate toward the center of the crater, usually > 1 cm and are surrounded by rigid gastric wall on fluoroscopy.

C. **Non distensible** stomach.



3. Endoscopy and Biopsy/Cytology

A. Gastritis-like malignant lesions

B. Small, plaque like lesions.

C. Polyps or small ulcers.

D. Ulcerated lesions have elevated margins with shaggy necrotic centers.

E. Extensive tumor plaque or large polypoid mass.

F. Linitis Plastica is typified by a non-distensible stomach.

4. Endoscopic Ultrasonography (EUS)

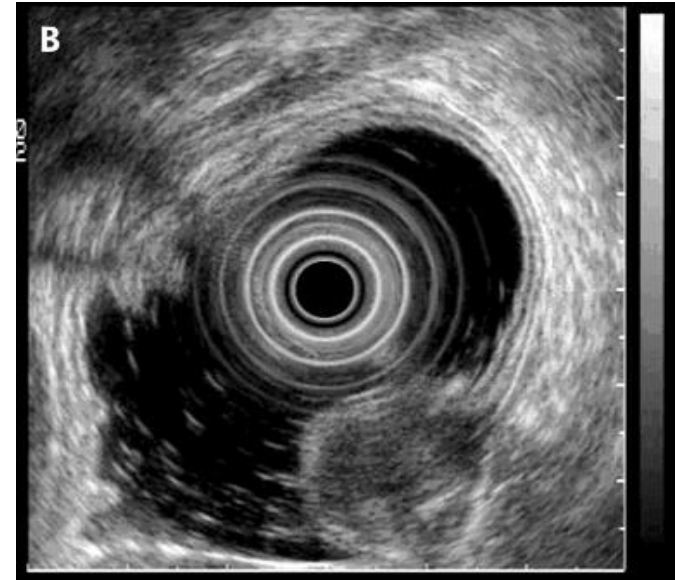
- Picture shows the following:

A. normal layers of gastric wall, with the five layered echo pattern being clearly visible.

B. EUS of early gastric cancer (T1a).

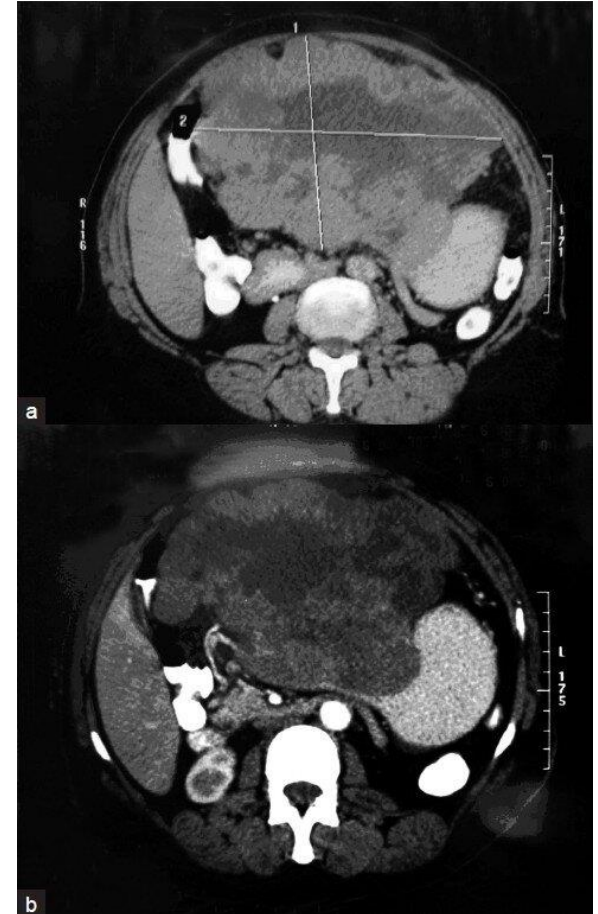
C. EUS image of advanced gastric cancer (T3).

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



5. Computed Tomography scan (CT scan)

- Picture shows the following:
 - A. Gastric wall thickening (0.5-4 cm and correlates with tumor penetration)
 - B. Gastric ulceration (polypoid or sessile lesions)
 - C. Invasion of the gastro-hepatic ligament, spleen, or diaphragm
 - D. Distal metastases



6. Other Diagnostic Modalities

- A. **Gastric acid analysis** can diagnose patients with **hypo** and **achlorhydria**, which are associated with **↑** risk for gastric ca (should be screened)

- B. **Molecular biologic techniques**, (e.g. cytologic evaluation for p53 or p21 protein)

TREATMENT 1

- Patients must be evaluated for **comorbid** conditions
- Patients with profound weight loss and metabolic complications of their cancer should be treated
- Patients **without** obstruction or bleeding but who have **distal metastases** should not be explored
- Patients **with obstruction** or **bleeding** should still be considered for exploration, as **palliative resection** is better than palliative bypass
- In patients with metastatic obstructing proximal gastric tumors, prosthetic **endoesophageal tubes** or **endoscopic laser therapy** can be used

TREATMENT 2

- 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 3

- Surgical resection and lymphadenectomy can be described as follows:
 - **D0 resection** = incomplete removal of perigastric LN
 - **D1 resection** = complete removal of perigastric LN
 - **D2 resection** = D1 + LN 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:

- (a) Subtotal gastrectomy for antral and pyloric lesions

- (b) Subtotal or total gastrectomy for middle-third lesions

- (c) Total gastrectomy with esophagojejunostomy for proximal-third, GEJ, or extensive middle-third lesions

- In addition, the perigastric 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 N 1 and N 2
- Using this standard operation, they reported a postoperative mortality rate of 0.4% for D2 and D3 resections
- The survival rates over the past 30 years have risen from 71% to 76% in Stage II, from 39% to 63% in Stage IIIA, from 28% to 39% in Stage IIIB, and from 2% to 10% in Stage IV disease

TREATMENT: GEJ CA

- Ca of the cardia and GEJ is becoming more prevalent, roughly doubling in incidence over the last 20 years
- 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

- Chemotherapy

- ❖ Randomized trials showed a survival benefit for the treatment group
- ❖ There is a survival benefit for mitomycin C alone or fluorouracil and mitomycin C

- Chemoradiotherapy

- ❖ Results are mixed

- 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