Gastric Neoplasms

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Objectives:

Gastric neoplasms: Benign & Malignant

1. Understanding pathology of gastric adenocarcinoma.

- Intestinal type
- Diffuse (Signet ring).

2. Pathology of gastric lymphoma.
3. Other gastric neoplasms: Neuroendocrine, GIST.

Dysplasia

Chronic gastritis exposes the epithelium to inflammation-related free radical damage and results in sustained attempts at repair, leading to increased epithelial proliferation. Over time, this can lead to the accumulation of genetic alterations that result in carcinoma. Preinvasive in situ lesions can be recognized histologically as dysplasia, which is marked by variations in epithelial cell size, shape, and orientation along with coarse chromatin texture, hyperchromasia, and nuclear enlargement. These overlap with and are sometimes difficult to distinguish from injury-associated regenerative changes.

Gastric tumors

Polyps

Uncommon 0.4% of adults at autopsy as compared to colon polyps in 25-50% of adults at autopsy.

Many types

Hyperplastic- response to damage

Fundic gland polyp: small hamartoma.

Note:

(hyperplastic and fundic gland polyps have no malignant potential)

Adenomatous polyp have malignant potential!

GASTRIC POLYPS AND TUMORS

Gastric Polyps

Polyps are identified in up to 5% of upper gastrointestinal tract endoscopies.

Many different types of polyps occur in the stomach.

Inflammatory and Hyperplastic Polyps

Up to 75% of gastric polyps are considered to be inflammatory or hyperplastic in origin. This distinction is artificial, however, as inflammatory and hyperplastic polyps lie at opposite ends of the morphologic spectrum of a single entity with varying degrees of inflammation. These polyps most commonly affect individuals between 50 and 60 years of age and usually arise in a background of chronic gastritis, which initiates the injury that leads to reactive hyperplasia and polyp formation.

polyps associated with H. pylori gastritis, may regress after bacterial eradication.

The frequency with which dysplasia, a precancerous in situ lesion, develops in these polyps correlates with size: there is a significant increase in risk with polyps larger than 1.5 cm.

Fundic Gland Polyps

- **FAP associated type-familial type**
- **Proton pump treatment associated type-sporadic type**

Fundic gland polyps occur **sporadically** and in individuals with familial adenomatous polyposis (FAP).

Polyps associated with FAP may show dysplasia, but almost **never** progress to become malignant.

The incidence of sporadic lesions has increased markedly as a result of the widespread use of proton pump inhibitors.

This likely results from increased gastrin secretion in response to reduced acidity, leading to gastrin-driven glandular hyperplasia. Fundic gland polyps are nearly always asymptomatic and are usually an incidental finding.

Morphology: These well circumscribed polyps occur in the gastric body and fundus, are often multiple, and are composed of cystically dilated, irregular glands lined by flattened parietal and chief cells.

Precancerous lesions

- Dysplasia
  - Irregular glands, enlarged, hyperchromatic, irregularly outlined, crowded nuclei with mitoses.

  High grade dysplasia = in situ carcinoma = intraepithelial neoplasia.

- Adenoma

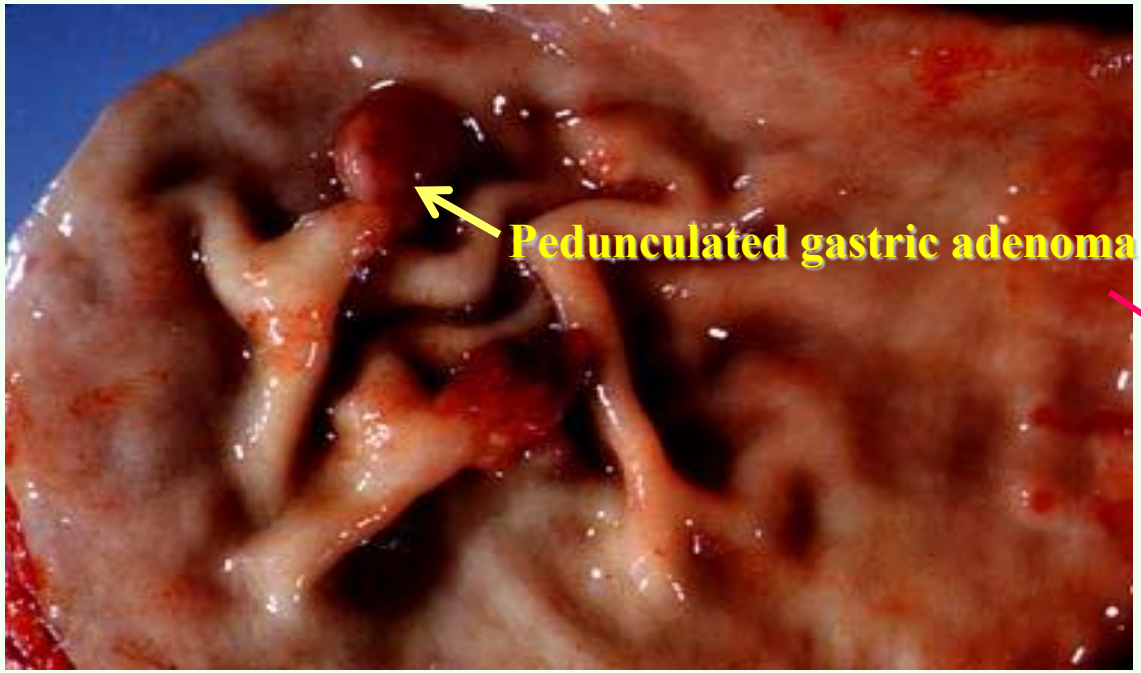
Gastric adenoma represents up to 10% of gastric polyps and is an important precursor to gastric adenocarcinoma.

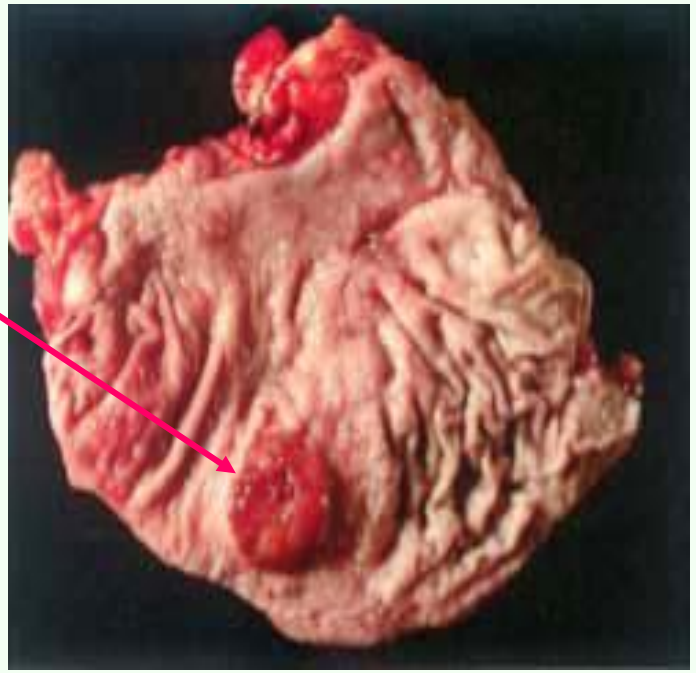
Its incidence increases with age and varies among different populations in parallel with that of gastric adenocarcinoma.
Patients Age: 50 and 60 years.
Males/Female incidence **3:1**
Gastric adenomas almost always occur on a background of chronic gastritis with atrophy and intestinal metaplasia and exhibit epithelial dysplasia, which can be classified as low or high grade.

The risk for development of adenocarcinoma

Related to the size of the adenoma and is particularly elevated with lesions greater than 2 cm in diameter.

Overall, the risk of malignant transformation is far greater than with colonic polyps, and areas of carcinoma may be present in up to 30% of gastric adenomas at the time of excision.





Gastric adenoma

Gross photograph showing a large polyp in the stomach.

Etiologic factors of stomach carcinoma

1. Related to socioeconomic level and diet.
2. High incidence in Japan, actually is decreasing in the Western world, continue to be high in Asia and Russia.
3. Smoked, salted foods.
4. Low fresh vegetable diet.
5. Nitrosamines.
6. Chronic gastritis with atrophy and metaplasia.
7. H. pylori infection.
8. Intestinal reflux.
9. Blood group A.
10. Relatives with stomach cancer.

Malignant neoplasms of the stomach:

- Gastric Adenocarcinoma (~ 95%).
- Lymphoma.
- Carcinoid.
- Gastrointestinal stromal tumors.

Gastric carcinoma

Adenocarcinoma is the most common malignancy of the stomach, accounting for more than 90% of all gastric cancers. 8% of all deaths from cancer.

Early symptoms resemble those of chronic gastritis, including dyspepsia, dysphagia, and nausea. As a result, the cancer is often diagnosed at advanced stages when clinical manifestations such as weight loss, anorexia, altered bowel habits, anemia, and hemorrhage trigger diagnostic evaluation.

Epidemiology

- Geographic distribution
- Socioeconomic groups is more common in lower socioeconomic groups
- Gastric lesions: Incresed in individuals with multifocal mucosal atrophy and intestinal metaplasia.

Peptic ulcer disease does not impart an increased risk for development of gastric cancer, but patients who have had partial gastrectomies for peptic ulcer disease have a slightly higher risk for developing cancer in the residual gastric stump as a result of hypochlorhydria, bile reflux, and chronic gastritis.

Pathogenesis.

- **Mutations**

Familial gastric cancer have provided important insights into the pathogenesis of sporadic cases.

Germline mutations in CDH1, which encodes E-cadherin, a protein that contributes to epithelial intercellular adhesion, are associated with familial gastric cancers, usually of the diffuse type.

Somatic mutations in CDH1 are present in about 50% of sporadic diffuse gastric tumors, and E-cadherin expression is drastically decreased in the rest, often by methylation of the CDH1 promoter.

Loss of E-cadherin function is a key step in the development of diffuse gastric cancer.

patients with FAP caused by germline loss of function mutations in the adenomatous polyposis coli gene (APC), a negative regulator of the WNT pathway, are at increased risk for development of intestinal-type gastric cancer.

Sporadic intestinal-type gastric cancer is associated with several genetic abnormalities, including

Acquired gain-of-function mutations of b-catenin, a protein that is negatively regulated by the APC protein, further implicating hyperactive WNT signaling in this subtype of gastric carcinoma.

TP53 mutations are present in a majority of sporadic gastric cancers of both histologic types, which also exhibit amplification of the gene encoding the HER2 tyrosine kinase in approximately 10% to 20% of cases.

H. pylori. Chronic gastritis:

Most commonly due to H. pylori infection, promotes the development and progression of cancers, another example of the prooncogenic effect of certain types of chronic inflammation These oncogenic effects may be related to increased epithelial proliferation in response to chronic damage, epigenetic changes associated with intestinal metaplasia, and suppression of local adaptive immunity, an alteration that may be seen in chronically inflamed tissues.

Epstein-Barr virus (EBV).

Up to 10% of gastric adenocarcinomas are associated with Epstein-Barr virus (EBV) infection.

The precise role of EBV in the development of gastric adenocarcinomas remains to be defined, it is notable that **EBV episomes** in these tumors are clonal, supporting the hypothesis that infection precedes neoplastic transformation. Further, TP53 mutations are uncommon in EBV-positive gastric tumors, suggesting that the molecular pathogenesis of these cancers is distinct from that of other gastric adenocarcinomas. Morphologically, EBV-positive tumors tend to occur in the proximal stomach, usually have diffuse growth pattern, and are often associated with a marked lymphocytic infiltrate

- Sites: classically prepyloric, antral and lesser curvature.
- Macroscopic types (Borrmann I-IV):

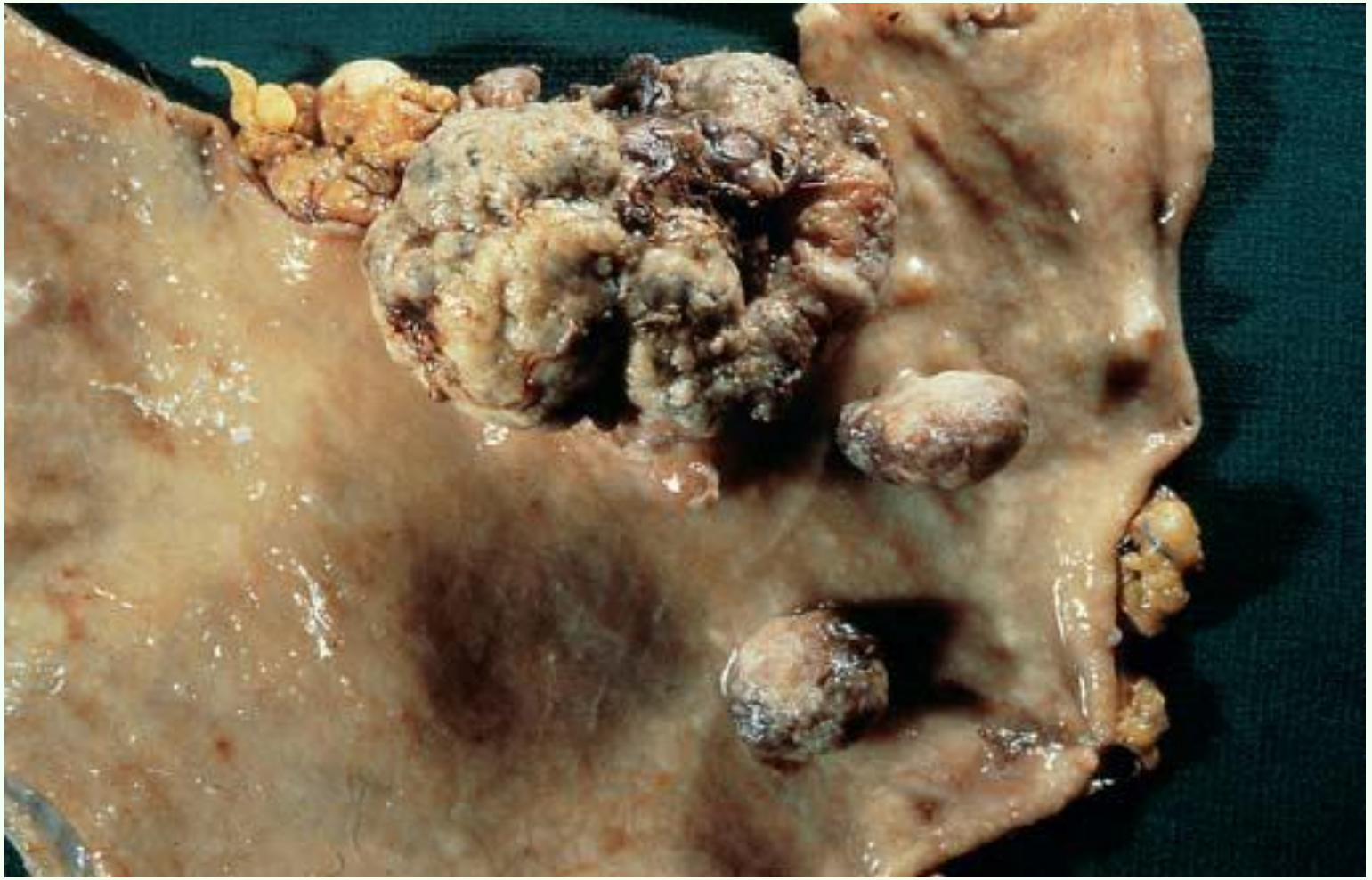
  polypoid, ulcerative, ulcerating and infiltrating, infiltrating.
- Microscopic types (Laurens):

  Intestinal:

  Gland forming, distal, better differentiated, usually old.

  Diffuse:

  Proximal, intracellular mucus, signet ring cells, less differentiated, usually young patient.



Polypoid gastric adenocarcinoma Note the absence of rugal folds due to the presence of atrophic gastritis

Clinical Presentation

Asymptomatic

Early:

Vague epigastric discomfort / indigestion

Pain is constant, nonradiating, unrelieved by food digestion

More advanced disease:

Weight loss

Anorexia

Fatigue

Emesis

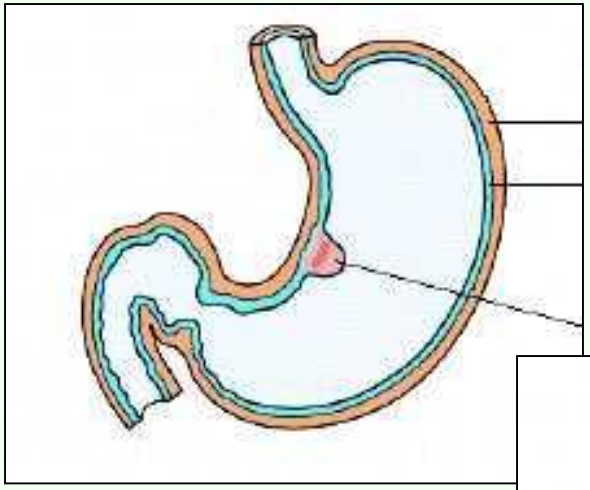
Symptoms dependent on location

Proximal

Distal

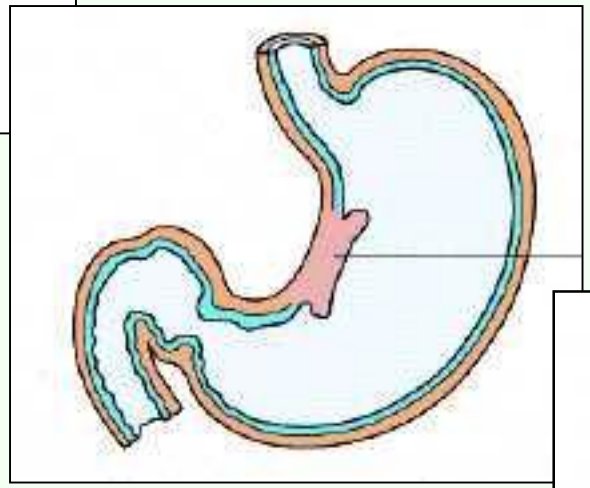
Diffuse gastric ca. presented with GI bleeding, obstruction

Morphologic types of carcinoma of the stomach

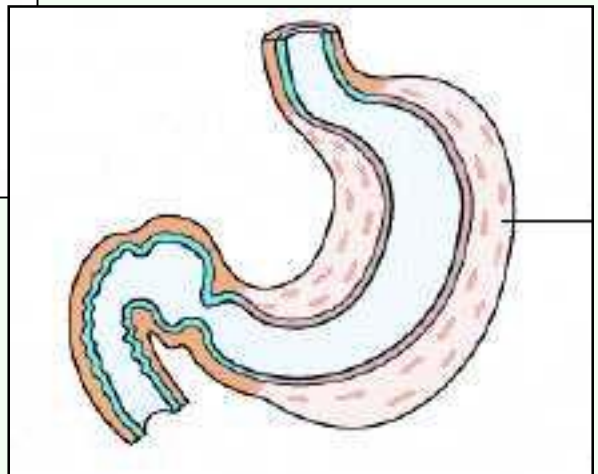


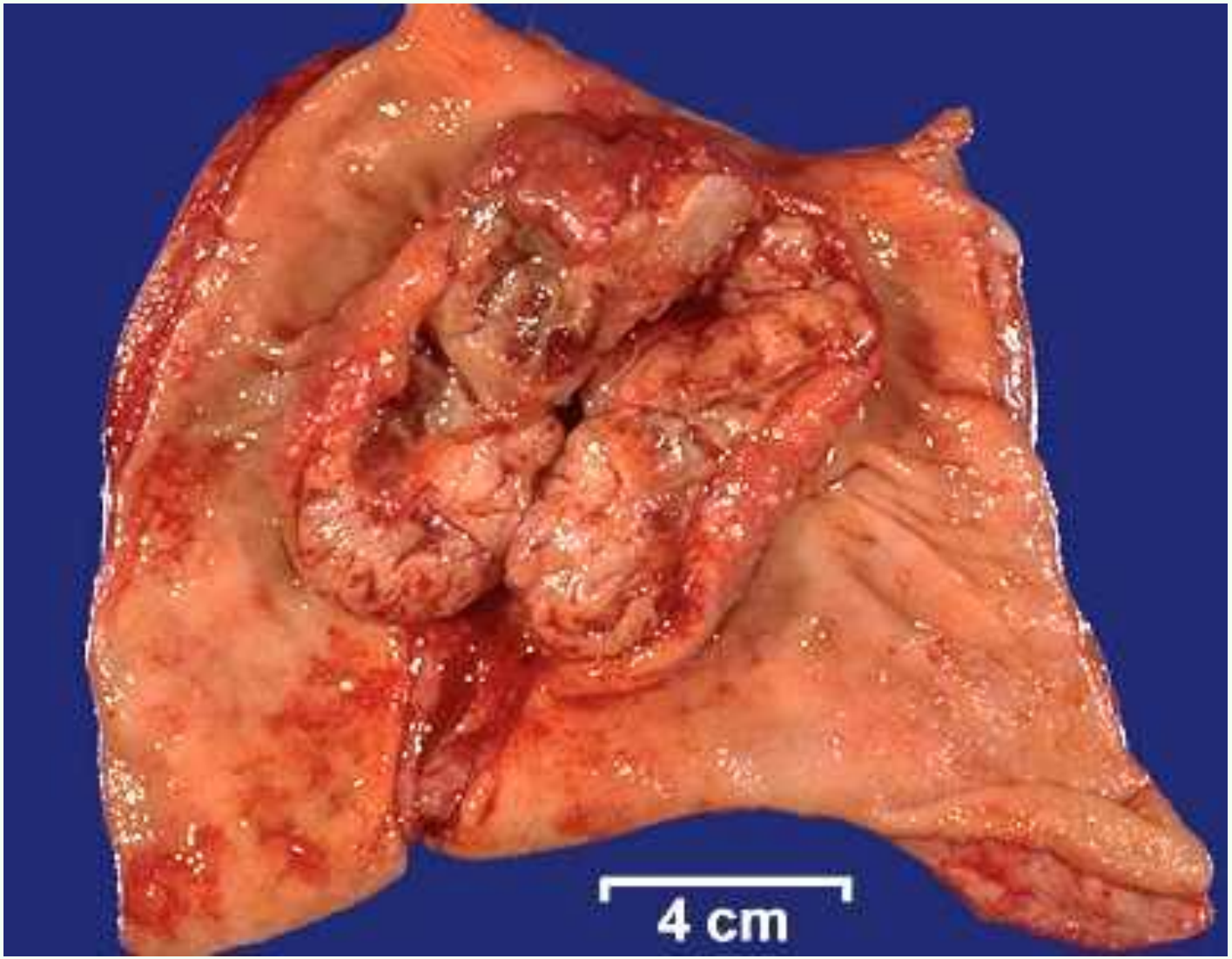
Fungating

Ulcerating

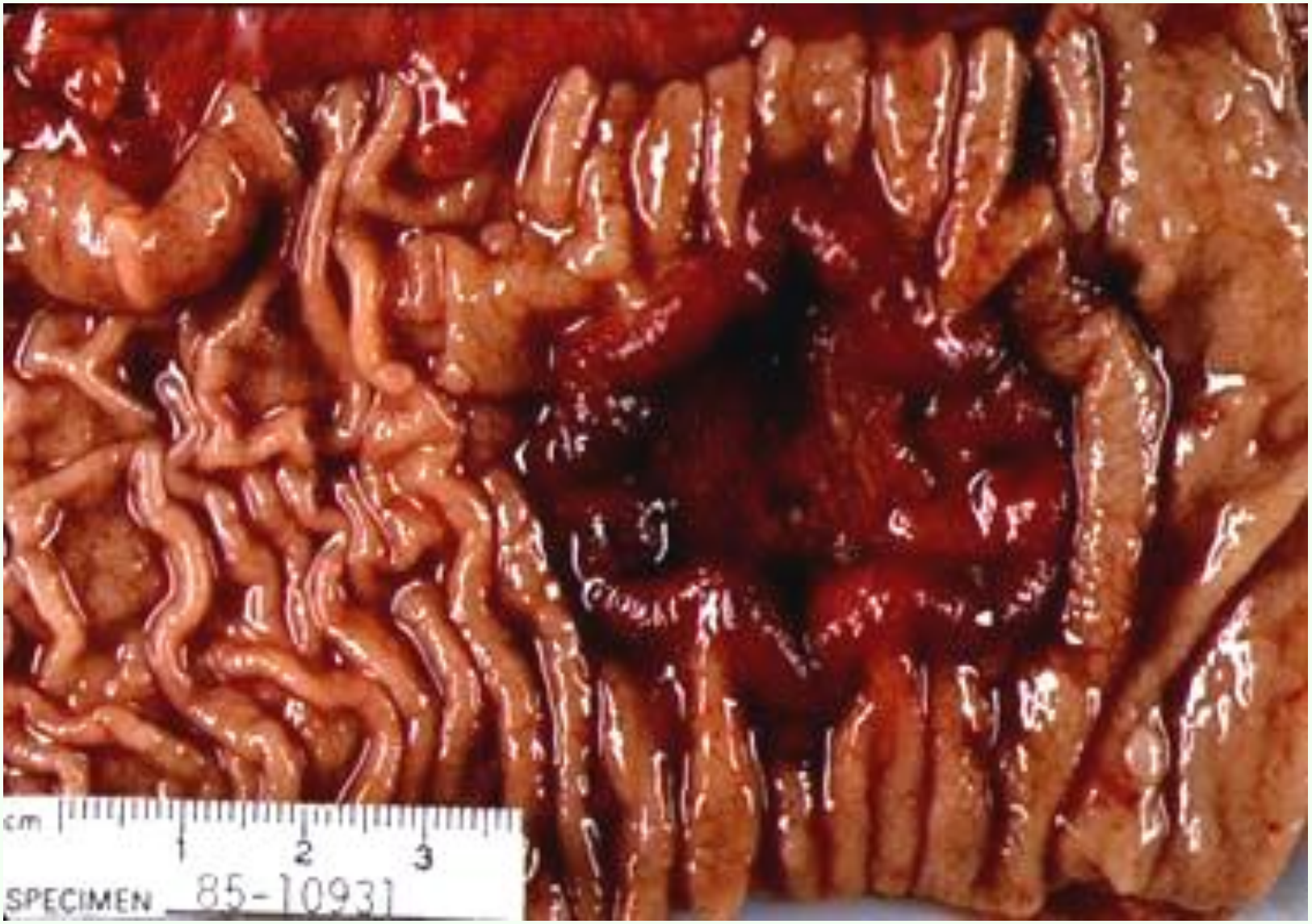


Diffuse



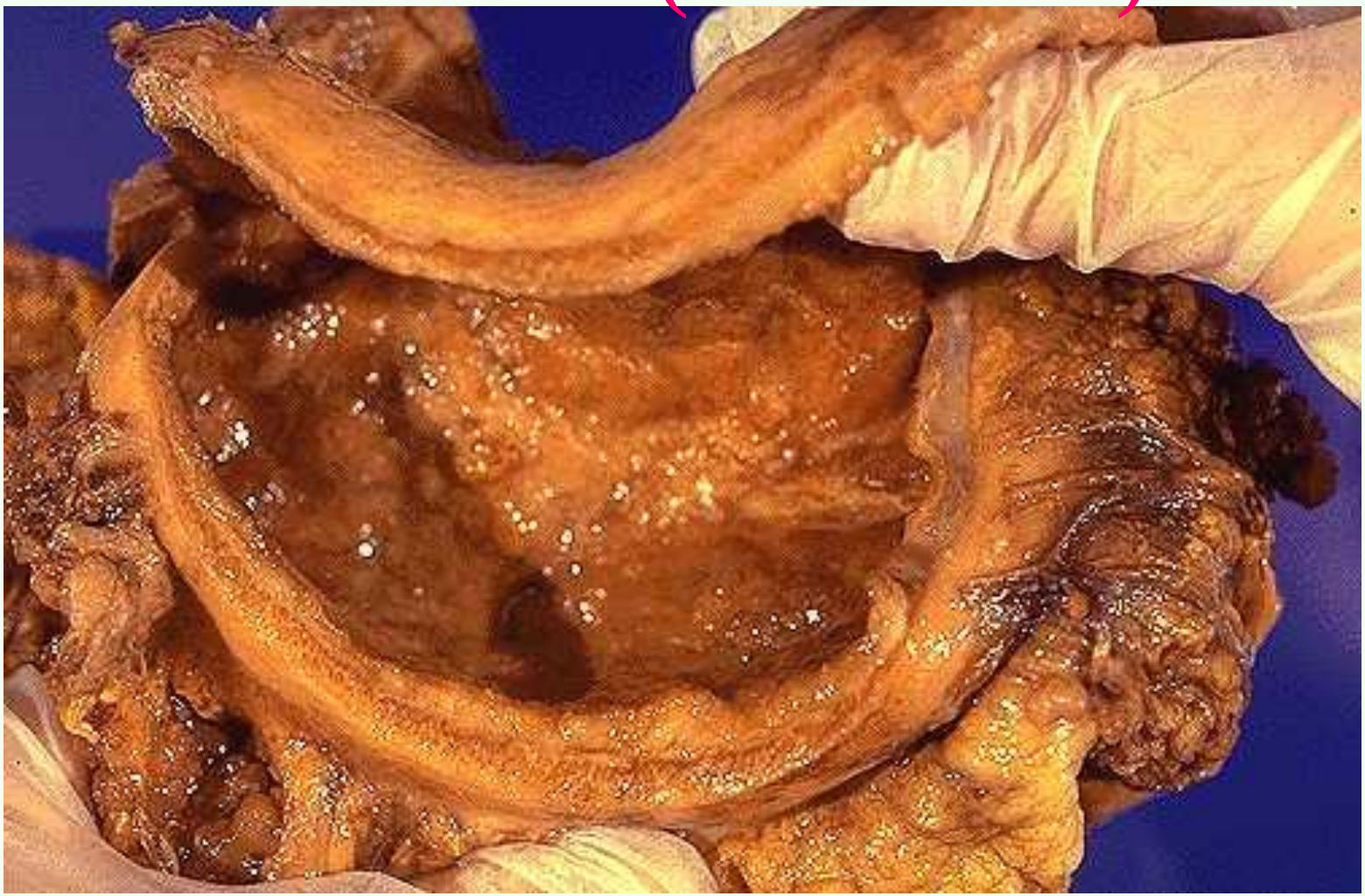


Fungating Carcinoma Stomach



Ulcerating Gastric Carcinoma

Linitis Plastica – Schirrhous Carcinoma (diffuse ca.).



Lymphoma

1.The most common site for extranodal lymphomas is the GI tract, particularly the stomach.

2.The bowel is the most frequent site for Epstein-Barr virus–positive B-cell lymphoproliferations. Nearly 5% of all gastric malignancies are primary lymphomas, the most common of which are indolent extranodal marginal zone B-cell lymphomas. In the gut these tumors are often referred to as lymphomas of MALT, or MALTomas.

Pathogenesis of gastric Imphoma

Extranodal marginal zone B-cell lymphomas usually arise at sites of chronic inflammation.

They can originate in the GI tract at sites of preexisting MALT such as the Peyer patches of the small intestine, but more commonly arisewithin tissues that are normally devoid of organized lymphoid tissue. MALT is not present in the normal stomach but can be induced, typically as a result of chronic gastritis. H. pylori infection is the most common inducer of gastric MALT and therefore is found in association with most gastric MALTomas.

Three translocations are associated with gastric MALToma: t(11;18)(q21;q21), the less common t(1;14)(p22;q32), and t(14;18) (q32;q21). The t(11;18)(q21;q21) translocation brings together the apoptosis inhibitor 2 (API2) gene on chromosome 11 with the “mutated in MALT lymphoma” (MLT1) gene on chromosome 18.