Epithelial and lymphoid neoplasms of the stomach

Gastric cancer – treatment and prognosis

- Complete resection of the whole tumor remains the only approach to treat this disease. Since gastric cancer is usually asymptomatic in its early stages, many people are diagnosed at an advanced stage when the tumor is inoperable. In addition, because other conventional treatments (radiotherapy and chemotherapy) have only modest efficacy for those with advanced/metastatic gastric cancer, the prognosis in such cases is poor.

Gastric cancer: Siegel RL, Miller KD, Jemal A.

- Gastric cancer (GC) is among the most common malignancies worldwide and the second leading cause of cancer-related deaths.
- Classifications, that have prognostic and predictive value:
  - Anatomical classification (Borrmann classification and Siewert and Stein classification),
  - histological classification (WHO classification and Lauren’s classification),
  - and extent of disease (early gastric cancer vs advanced cancer).

Epidemiology

- In the United States, gastric cancer ranks 14th in incidence among the major types of cancer.
- Estimated new cases and deaths from gastric cancer in the United States in 2018:
  - New cases: 26,240.
  - Deaths: 10,800.
- The incidence of gastric cancer depends on the geographic area, showing that there are different factors that influence the incidence, survival rate and mortality.
- Nearly 60% of the incidence of gastric cancer is located in East Asia (China, Korea and Japan), East Europe and the Andean Region of South America.

Gastric cancer incidence: Scand J Gastroenterol Volume 53, 2018

- Scand J of Gastroenterol Volume 53, 2018
- PDQ Cancer Information Summaries 2018, USA
Epidemiology
- The worldwide incidence of gastric cancer has declined rapidly over the recent few decades, however, this trend reflects the decreasing incidence of cancers arising in the distal stomach and intestinal type.
- Proximal cancers arising in the gastro-esophageal junction have in fact been increasing in incidence (related to Barrett esophagus and GERD?); (different etiology)

GERD
- Gastroesophageal reflux disease: transient relaxation of lower esophageal sphincter causes reflux of acid and bile into the distal esophagus
- Complications of GERD:
  - Barrett’s esophagus: (squamous cell epithelium transforms into gastric-type glandular epithelium with intestinal metaplasia) in distal e. due to injury
  - ulceration with stricture formation
  - glandular dysplasia with risk for adenocarcinoma

Prevention modalities in cancer
- Treatment of gastroesophageal reflux disease decreases the risk for developing adenocarcinoma arising from Barrett’s esophagus

GASTRIC CANCER - epidemiology
- Incidence varies with geography: lower rates in North America, Northern Europe and Africa, and highest rates in Japan, East Asia and East Europe
- Males > females
- Average age at diagnosis in seventh decade of life

Risk factors for gastric cardia and noncardia cancers
- Cardia
  - Age
  - Male sex
  - Tobacco smoking
  - Race
  - Family history
  - Low physical activity
  - Fiber intake
  - Radiation
  - —
  - —
  - —
- Non cardia
  - age
  - Male sex
  - Tobacco smoking
  - Race
  - Family history
  - Low physical activity
  - Fiber intake
  - Radiation
  - H. pylori
  - Low socioeconomic status
  - High intake of salty and smoked food
  - Low consumption of fruits and vegetables
  - Obesity
  - GERD
Risk factors

Environmental factors
- Diet: rich in nitrates, salt, smoked foods, and complex carbohydrates

Protective factors
- Diet rich in fresh fruits and vegetables are associated with reduced cancer risk through their antioxidant properties

Risk factors – a history of prior gastrectomy

Hypochlorhydria, bile reflux and gastritis in the residual gastric stump
Gastric stump cancer (GSC) is a separate subtype of GC, defined as a carcinoma that occurs in the gastric remnant at least 5 years after the surgery for peptic ulcer.
GSC represents from 1.1% to 7% of all.
After 15 years from the gastrectomy, the risk of GSC is increased four- to sevenfold compared with the healthy population

Risk factors
- Low socioeconomic status
- Autoimmune gastritis (Pernicious anemia)

Autoimmune gastritis
- An immune-mediated chronic gastritis where the antibodies are directed against parietal cells and intrinsic factor, resulting in loss of oxyntic cells, hypochlorhydria and vitamin B deficiency
- 5% of all cases of chronic gastritis
- Affects individuals of northern European or Scandinavian descent
- Mainly white women in their fifties or sixties

Autoimmune gastritis
Clinical symptoms
- Abdominal pain
- Weight loss
- Pernicious anemia
- Rarely: subacute degeneration of the spinal cord related to vitamin B12 deficiency
- Other immune-related disorders such as Hashimoto thyroiditis, type 1 diabetes mellitus, adrenal insufficiency
Autoimmune gastritis

**Laboratory findings**
- Serum gastrin – elevated
- Gastric pH – alkaline or neutral
- Vitamin B12 level – reduced
- H pylori serology – usually negative
- Antiparietal and intrinsic factor antibodies – positive

**Endoscopic findings**
- Thinning of body mucosa with prominent submucosal vascular pattern, which becomes visible as a result of mucosal atrophy

Autoimmune gastritis

- Body fundic mucosal biopsy in a patient with longstanding autoimmune gastritis. Chief cells and parietal cells are not seen, while chronic inflammation is readily identified

Autoimmunity and gastric cancer

- Recent research has shown that neoplastic transformation of autoimmune gastritis is as high as 10% and that autoimmune gastritis should be considered a pre-neoplastic disorder with an annual incidence of gastric cancer of 0.3%
- Intestinal metaplasia with dysplasia of the gastric corpus-fundus mucosa and hyperplasia of chromaffin cells, which are typical features of late-stage autoimmune gastritis, are considered precursor lesions.
- Autoimmune gastritis has been associated with the development of two types of gastric neoplasms: intestinal type and type I gastric carcinoid.

Gastric cancer - risk factors

- *Helicobacter pylori* infection (increases the risk for both intestinal and diffuse type)
- The risk is significantly increased if the *H. pylori* infection is acquired in childhood or is present for greater than 10 years prior to diagnosis of cancer
- *H. pylori* infection may also be associated with the risk seen in people with blood group A, because it adheres to the Lewis blood group and facilitates chronic infection in these individuals

*Helicobacter pylori* gastritis

- In developing countries up to 75% of population over 25 years of age are infected
- In developed countries the overall prevalence is over 50%, exceeding 60% in adults over 60
- *H. pylori* is a flagellated, gram-negative rod
- The WHO has classified *H. pylori* as a class I human carcinogen of gastric cancer
**H pylori gastritis**

- Clinical symptoms: abdominal pain, nausea, vomiting, dyspepsia, weight loss, iron-deficiency anemia
- Microscopic findings: marked lymphoplasmacytic inflammation, erosions, lymphoid aggregates (follicles, hyperplasia)

**H pylori gastritis**

- Antral mucosa with chronic active gastritis (HE)
- Helicobacter pylori
- (Giemsa)

**Prevention modalities in cancer**

- Treatment of H.pylori infection decreases risk for developing lymphoma and adenocarcinoma of the stomach

**H pylori gastritis**

- Over time, H pylori gastritis progresses to
  - Pangastitis -
  - Multifocal atrophic gastritis -
  - Intestinal metaplasia -
  - Reduced acid secretion -
  ---- increased risk of gastric adenocarcinoma

**Intestinal metaplasia**

- Intestinal metaplasia of gastric mucosa with sulfomucin-secreting goblet cells

**Intestinal metaplasia in gastric antral mucosa**

- The open arrows point to residual antral type epithelium, whereas the solid arrows point to the intestinal metaplasia associated areas that have replaced the normal antral type glandular epithelium.
Gastric cancer - risk factors

Epstein-Barr virus (EBV)-the exact pathogenesis remains unknown
- Approximately 10% of gastric adenocarcinomas are associated with EBV infection
- EBV-positive tumors tend to occur in the proximal stomach and most commonly have a diffuse morphology

Genetic alterations

The vast majority of gastric cancers occur sporadically, but patients with
- Li-Fraumeni syndrome
- germline mutation in adenomatous polyposis coli APC genes
all have increased risk for developing gastric cancer
- Loss of E-cadherin function is involved in the development of familial, diffuse gastric cancer

Gastric cancer - gross findings

Location
- in the pylorus and antrum (50-60%)
- cardia 25%
- the body or fundus 15-25%
Type of growth
- Exophytic
- Flat
- Ulcerated

Endoscopic image of elevated and ulcerate gastric adenocarcinoma

Exophytic gastric cancer

Microscopic findings

- The large majority (90 - 95 %) of gastric cancers are adenocarcinomas, which arise from the glands of the most superficial layer, or the mucosa, of the stomach.

The Lauren classification system
- intestinal subtype
- diffuse
**Microscopic findings**

Lauren classification

- Intestinal subtype histologically resembles colorectal adenocarcinoma (well-formed glands lined by columnar epithelial cells). Intraluminal mucin is often present.

![Intestinal-type gastric adenocarcinoma](image)

**Microscopic findings**

Lauren classification

Diffuse-type gastric adenocarcinoma is composed of individual or poorly formed nests of cells growing in an infiltrative pattern.

- Cells take on a signet-ring cell appearance with the intracytoplasmic mucin pushing the nucleus of the cell to the periphery.
- The amount of mucin may be highly variable.

![Gastric adenocarcinoma, diffuse type signet ring cell carcinoma](image)

**Gastric adenocarcinoma, mucinous type**

- A strong desmoplastic response to the tumor cells may be present, contributing to the firm, rigid wall – a "leather bottle" stomach, termed *linitis plastica*.

![Linitis plastica](image)
Microscopic findings
Lauren classification
• Some tumors show features of both intestinal and diffuse types and thus are classified as mixed

Immunohistochemical features
• Gastric adenocarcinomas are cytokeratin (CK), epithelial membrane antigen (EMA), and carcinoembryonic antigen (CEA) positive
• CK7/CK20 profiles vary considerably, with the majority being CK7 positive and CK20 negative

WHO Classification of Carcinoma of the Stomach 2018
• Adenocarcinoma
  • Papillary adenocarcinoma - Exophytic with elongated frond-like tumor extensions with fibrovascular cores; usually low grade
  • Tubular adenocarcinoma - Dilated or slit-like branching tubules; usually low grade, although poorly differentiated variants are described.
  • Mucinous adenocarcinoma - Contains more than 50% extracellular mucin pools. May contain scattered signet-ring cells.
  • Poorly cohesive carcinomas, including signet-ring cell carcinoma and other variants - Tumor cells infiltrate as isolated single cells or small aggregates. Signet-ring cell carcinoma is predominantly composed of signet-ring cells containing a clear droplet of cytoplasmic mucin displacing the nucleus. Other variants of poorly cohesive carcinoma may resemble mononuclear inflammatory cells.
  • Mixed carcinoma - Mixture of morphologically identifiable components such as tubular, papillary, and poorly cohesive patterns.

WHO Classification of Carcinoma of the Stomach 2018
• Adenosquamous carcinoma - Mixture of glandular and squamous neoplastic components; the squamous component should comprise at least 25% of tumor volume
• Carcinoma with lymphoid stroma (medullary carcinoma) - Poorly developed glandular structures associated with a prominent lymphoid infiltrate in the stroma. Associated with Epstein-Barr virus infection and may have a more favorable prognosis

WHO Classification of Carcinoma of the Stomach 2018
• Neuroendocrine carcinoma (large cell, small cell, mixed) - Poorly differentiated high-grade carcinoma with diffuse synaptophysin expression and faint or focal positivity for chromogranin A
Hepatoid adenocarcinoma (HAC)
- a rare type of extrahepatic tumor that has a morphological similarity to hepatocellular carcinoma (HCC)
- an extremely poor prognosis
- occurs in older people - the average patient age is 63.5 years, and the male-to-female ratio is 2.32:1.
- the most common location is the antrum (60.2%)

Gastric hepatoid adenocarcinoma (alfa-fetoprotein secreting)
- Tumor cells are arranged in a trabecular and solid pattern B,C. Positively-stained alpha-fetoprotein (D,E)

WHO classification
- Gastric adenocarcinoma:
  - Papillary
  - Tubular
  - Mucinous
  - Signet-ring cell
  - Adenosquamous
  - Undifferentiated
- These may be further classified into moderately or poorly differentiated

Histologic Grade
For adenocarcinomas, a histologic grading system that is based on the extent of glandular differentiation is suggested, as shown below.
- Grade X Cannot be assessed
- Grade 1 Well differentiated (greater than 95% of tumor composed of glands)
- Grade 2 Moderately differentiated (50% to 95% of tumor composed of glands)
- Grade 3 Poorly differentiated (49% or less of tumor composed of glands)
- Signet-ring cell carcinomas are high grade and are classified as grade 3.

Gastric cancer - treatment and prognosis
- The depth of invasion and the extent of nodal and distant metastasis at the time of diagnosis is the most powerful prognostic indicators for gastric cancer
- When possible, surgical resection remains the preferred treatment
- 5-year survival rate for advanced gastric cancer is below 20%

Early gastric cancers
- are defined as those confined to the mucosa and submucosa of the stomach regardless of lymph node status (with or without regional lymph node metastases)
- 5-year survival rate can exceed 90% (even if lymph node metastases are present)
Early gastric cancer (EGC) is defined as invasive gastric cancer that invades no more deeply than the submucosa, irrespective of lymph node metastasis (T1, any N).

- Five-year survival rate is relatively good only in Japan, where it reaches 90%. In European countries, survival rates vary from ~10% to 30%.
- High survival rate in Japan is probably achieved by early diagnosis by endoscopic examinations and consecutive early tumor resection.

Early gastric cancer has been identified in Japan, where there is active screening of patients at high-risk for gastric cancer.

Gastric cancer - prognosis

Poor prognostic indicators include:
- Older age
- Proximal location
- Venous and/or lymphatic invasion
- CEA levels greater than 10ng/mL

The best predictor of prognosis is the pathologic stage.
Treatment

- Recently, trials have provided some promising results regarding molecular-targeted therapy, raising the possibility that the development of these agents could be a fruitful approach. However, the benefit of molecular-targeted therapy for advanced gastric cancer remains inconclusive.

HER2 (human epidermal growth factor2)

- The proto-oncogene HER2 is a member of the EGF receptor family with tyrosine kinase activity
- HER2 plays a key role in a large number of cellular processes, including cell differentiation, proliferation, motility and signal transduction.
- After the combination of chemotherapy and HER2 targeted therapy (inhibitors) with trastuzumab also known as Herceptin had defined a new standard of care for HER2-positive metastatic GC, other HER2 inhibitors are tested.

Treatment

- In a molecularly selected population, a median overall survival of 13.8 mo has been reached with the use of human epidermal growth factor 2 (HER2) inhibitors in combination with chemotherapy, which has become the standard of care for patients with HER2-overexpressing GC.

HER2 – immunohistochemical reaction

- 3+ intense HER2 immunoreactivity in early gastric cancer.
- Note absence of staining in normal glands

Molecular subtypes of gastric cancer

- Four molecular subtypes of gastric cancer (chromosomal instability CIN, genomical stability GS, microsatellite instability MSI, and Epstein-Barr virus)
- CIN subtype represents approximately 50% of GCs and it mostly occurs in the esophagogastric junction (EGJ)/cardia. CIN GC is related to intestinal type histology.

Molecular subtypes of gastric cancer

- CIN subtype represents approximately 50% of GCs and it mostly occurs in the esophagogastric junction (EGJ)/cardia. CIN GC is related to intestinal type histology.
- CIN results in the loss or gain of function of some “key genes”, including oncogenes and tumor suppressor genes that may be efficaciously targeted by specific inhibitor molecules
**Molecular characterisation of subtypes of gastric carcinomas**

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**Gastric adenoma**
- Adenomas almost always occur on a background of chronic gastritis with atrophy and intestinal metaplasia; by definition adenomas exhibit epithelial dysplasia
- The risk of adca is related to the size of the lesion (>2cm)
- Overall carcinoma may be present in up to 30% of gastric adenomas

**Gastric lymphoma**
- 5% of all gastric malignancies are primary lymphomas
- Extranodal marginal zone B-cell lymphoma
- (In the gut these tumors are referred to as arising in mucosa-associated lymphoid tissue - MALT)
- Associated with *H.pylori* gastritis (prolonged lymphoid proliferations)
- Most common location – gastric body

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**Tubulovillous adenoma with low grade dysplasia**
- On the left dysplastic epithelium.
- On the right normal epithelium for comparison

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**Gastric lymphoma**
- Indolent behavior in low-grade lesions with excellent prognosis (5-year-survival rates 91%)
- Minority of lesions transform to high-grade B-cell lymphomas
- The fifth and sixth decades of life
- Endoscopically: ulcerated (single or multiple), polyloid, edematous or infiltrated folds

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**Gastric lymphoma**
- The gastrointestinal tract is the most frequent site of extranodal lymphoma, and the stomach is involved in up to two-thirds of these cases. 30-45% of all extranodal lymphomas are detected in the stomach
- Primary gastric lymphoma remains a rare disease, representing nearly 2-8% of all tumors of the stomach
- There are some geographic areas, such as north-eastern Italy, where the frequency of primary gastric lymphoma is particularly high

Gastric lymphoma

• B-cell gastric lymphomas include marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT), which account for nearly 50% of gastric lymphomas, and diffuse large B-cell lymphomas (DLBCL), whilst both follicular and mantle cell lymphomas are infrequent.


Antigenic profile of MALT lymphomas

• A specific antigenic profile of MALT lymphomas does not exist, but the B-cells sharing the immunophenotype with marginal zone B-cells present in the spleen, Peyer’s patches and lymph nodes, gastric lymphoma is CD20+, CD5+, CD10-, CD23-, and cyclin D1-.

Gastric MALT lymphoma - clinical symptoms

• Gastric MALT lymphoma in most cases behaves as an indolent disease.
• The clinical presentation of gastric lymphoma is poorly specific, symptoms ranging from vague dyspepsia, including epigastric pain or discomfort centered in the upper abdomen to, less frequently, alarm symptoms, such as gastrointestinal bleeding or persistent vomiting.

Extranodal gastric lymphoma

• diffuse involvement of mucosa and submucosa by small and medium-sized lymphocytes. The native glandular architecture is disrupted.

  • [Image link]

Gastric lymphoma

• Treatment
  ➢ Eradication of H pylori
  ➢ Surgery