Gastric cancer

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Anatomy

- Five layers: Mucosa, submucosa, muscular layer, subserosal layer, serosal layer.
- Peritoneum of greater sac covers anterior surface
- A portion of lesser sac drapes posteriorly over stomach.
- The GE junction has limited serosal covering.
The site of the lesion is classified on basis of relationship to long axis of stomach.
- 40% lower part
- 40% middle part
- 15% upper part
- 10% more than one part
- Recently the # of lesions proximally has increased.
Introduction

- second most common cancer worldwide after lung cancer.
- 90% of all tumors of the stomach are malignant.
- 80% to 90% of patients are initially seen with locally advanced or metastatic disease.
- Epidemic in Japan, China, eastern Europe, Middle East, Russia, and South America
Introduction

- The three most common primary malignant gastric neoplasms are:
  - adenocarcinoma (95%),
  - lymphoma (4%),
  - malignant GIST (1%)
- Rare primary malignancies include carcinoid, angiosarcoma, carcinosarcoma, and squamous cell carcinoma.
Adenocarcinoma

Epidemiology

- there has been a dramatic decrease in the gastric cancer incidence and death rate
- gastric cancer is a disease of the elderly
- twice as common in blacks as in whites
- younger patients, tumors are more often of the diffuse variety and tend to be large, aggressive, and more poorly differentiated, sometimes infiltrating the entire stomach (linitis plastic).
- lower socioeconomic status
Etiology

- pernicious anemia,
- blood group A,
- or a family history of gastric cancer.
- patients migrate from a high-incidence region to a low-incidence region (intestinal form of gastric cancer)
Etiology

Genetic Factors
High-salt diet

Type A blood

- Pernicious anemia

- Family history

- HNCC
**Acquired Factors**

- High-nitrate diet
- Smokee
- Low vitamin A and C
- Cigarette smoking
- *Helicobacter pylori*
- Epstein-Barr virus
- Radiation exposure
- Previous gastric surgery
- Coal workers
- Rubber workers
Protective Factors

- Raw vegetables
- Citrus fruits
- Antioxidants—vitamins A and C
- Selenium, zinc, iron
- Green tea
Diet low in vitamin C, E, High-salt diet

H pylori

Chronic superficial gastritis

Atrophic gastritis

Intestinal metaplasia

Dysplasia

Cancer
Pathology

Dysplasia

- precursor to gastric adenocarcinoma
- EMR
- gastric resection
- endoscopic biopsy surveillance, and *Helicobacter* eradication.
Early Gastric Cancer

- adenocarcinoma limited to the mucosa and submucosa of the stomach, regardless of lymph node status
- 10% of patients with early gastric cancer will have lymph node metastases.
- 70% of early gastric cancers are well differentiated
- Small intramucosal lesions can be treated with EMR
most important prognostic indicators in gastric cancer are both histological:
- lymph node involvement
- depth of tumor invasion
Adenocarcinoma is classified according to the most unfavorable microscopic element present: tubular, papillary, mucinous, signet-ring cells.

Also identified by gross appearance: ulcerative, polypoid, scirrous, superficial spreading, multicentric, or Barrett ectopic.

Variety of other schemes: Borrmann, Lauren.
Borrmann Classification

- 5 categories
- Type I: polypoid or fungating
- Type II: ulcerating lesions with elevated borders
- Type III: ulceration with invasion of wall
- Type IV: diffuse infiltration
- Type V: cannot be classified
Non-infected mucosa

H. pylori

Host cytokine gene polymorphisms

Chronic active gastritis

Presence of CAG island

Microsatellite instability

Atrophic gastritis

Intestinal metaplasia

Low grade dysplasia

High grade dysplasia

Gastric cancer (intestinal type)

p53

APC/β catenin
Lauren classification separates gastric cancers into:

- intestinal type (53%),
- diffuse type (33%),
- and unclassified (14%).
The intestinal variant

- gastric mucosa; glandular in origin, well differentiated.
- men, in older patients, distal part of the stomach.
- endemic
- arise from precancerous lesions.
- associated with *Helicobacter pylori* infection, chronic atrophic gastritis, intestinal metaplasia, and dietary factors.
diffuse-type

- lamina propria,
- invasive growth pattern
- less related to environmental factors
- younger patients; proximal part of the stomach.
- characterized by noncohesive malignant cells diffusely infiltrating the stomach
- spread rapidly in the submucosa, as well as by transmural extension and lymphatic invasion \textit{linitis plastica}.
- Peritoneal metastases are also more common
- worse prognosis.
TNM staging of gastric cancer by the International Union Against Cancer and American Joint Committee on Cancer

**T: Primary tumor**
- Tis Carcinoma in situ; intraepithelial tumor without invasion of lamina propria
- T1 Tumor invades lamina propria or submucosa
- T2 Tumor invades muscularis propria or subserosa
- T3 Tumor penetrates serosa (visceral peritoneum) without invasion of adjacent structures
- T4 Tumor invades adjacent structures

**N: Regional lymph node**
- N0 No regional lymph node metastasis
- N1 Metastasis in 1 to 6 regional lymph nodes
- N2 Metastasis in 7 to 15 lymph nodes
- N3 Metastasis in more than 15 regional lymph nodes

**M: Distant metastasis**
- Mo No distant metastasis
- M1 Distant metastasis
Staging
The most common symptoms are
- weight loss
- decreased food intake due to anorexia and early satiety.
- Abdominal pain (usually not severe and often ignored)
- nausea, vomiting, and bloating
- chronic occult blood loss is common and manifests as iron deficiency anemia and heme-positive stool
Physical examination usually is normal

- weight loss
- Supraclavicular L.N (on the left referred to as Virchow's node),
- abdominal mass
- carcinomatosis (including Krukenberg's tumor of the ovary).
- A palpable umbilical nodule (Sister Joseph's nodule)
- Rectal exam may reveal heme-positive stool and hard nodularity extraluminally and anteriorly, indicating so-called drop metastases, or rectal shelf of Blumer in the pouch of Douglas.
Diagnostic Evaluation

- endoscopy and biopsy
- *double-contrast barium upper GI examination*
- abdominal/pelvic CT scanning with IV and oral contrast
- MRI
- EUS
- Positron Emission Tomography Scanning
- Staging Laparoscopy and Peritoneal Cytology
- Serum tumor markers, CEA, CA 19-9, CA-125, CA 72-4, and β-HCG, *sensitivities are generally low—in the 40% to 50% range*
Surgical resection is the only curative treatment for gastric cancer.

The goal of curative surgical treatment is resection of all tumor.

All margins (proximal, distal, and radial) should be negative and an adequate lymphadenectomy performed.

Gross margins beyond 5 cm may be desirable.

Frozen section confirmation of negative margins is important when performing operation for cure.
con’t

- More than 15 resected lymph nodes are required for adequate staging
- The primary tumor may be resected en bloc with adjacent involved organs
Early Gastric cancer

- confined to mucosa.
- Endoscopic mucosal resection may be an emerging treatment for superficial **gastric cancer**

- greater than 90% of patients treated by gastrectomy with lymphadenectomy will survive beyond 5 years
Stage I and II Gastric Cancer

- Surgical resection including regional lymphadenectomy
- **subtotal gastrectomy is the procedure of choice**
- When the lesion involves the cardia, proximal subtotal gastrectomy or total gastrectomy (including a sufficient length of esophagus).
- If the lesion diffusely involves the stomach, total gastrectomy is required
- Postoperative adjuvant chemoradiation using 5-fluorouracil and leucovorin is now the standard of care for suitable patients following surgical resection
Stage III Gastric Cancer

Up to 15% of selected stage III patients can be cured by surgery alone, particularly if lymph node involvement is minimal (<7 lymph nodes).

- Radical surgery: Curative resectional procedures are confined to patients who at the time of surgical exploration do not have extensive nodal involvement.
Stage IV Gastric Cancer

- Endoscopic destruction of obstruction of the gastric cardia.
- Stenting
- Palliative resection should be reserved for patients with continued bleeding or obstruction.
- Palliative radiation therapy may also alleviate bleeding, pain, and obstruction.
- Treatment options
  - Palliative chemotherapy with
    - fluorouracil
Extent of Lymphadenectomy

- The Japanese Research Society for Gastric Cancer has numbered the lymph node stations that potentially drain the stomach. Generally these are grouped into level
- D1 (i.e., stations 3 to 6),
- D2 (i.e., stations 1, 2, 7, 8, and 11)
- D3 (i.e., stations 9, 10, and 12) nodes
• D₁ nodes are perigastric,
• D₂ nodes are along the hepatic and splenic arteries,
• and D₃ nodes are the most distant.
1. Right cardial
2. Left cardial
3. Lesser curvature
4. Greater curvature
5. Suprapyloric
6. Infrapyloric
7. Left gastric
8. Common hepatic
9. Celiac
10. Splenic hilus
11. Splenic artery
13. Retropancreatic
14. Mesenteric root
15. Transverse mesocolon
16. Paraaortic
Chemotherapy and Radiation for Gastric Cancer

- Neoadjuvant or postoperative chemotherapy and/or radiation therapy.
- Adjuvant postoperative 5-fluorouracil-based chemotherapy following curative resection for localized gastric cancer demonstrated no survival benefit.
- Adjuvant external-beam radiation therapy with combined chemotherapy is currently being evaluated.
Endoscopic Resection

- tumors <2 cm in size
- node negative
- confined to the mucosa on EUS, in the absence of other gastric lesions
Survival is dependent on pathologic stage (TNM stage) and degree of tumor differentiation.

Other important prognostic factors are sex, age, primary gastric site, tumor size, and tumor depth.

The actuarial 5-year survival for resected gastric adenocarcinoma stages 1, 2, and 3 is about 75%, 50%, and 25%,
Prognosis

<table>
<thead>
<tr>
<th>Depth of Invasion</th>
<th>% with Lymph Node Involvement</th>
<th>Five Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Gastric Cancer</td>
<td>Mucosa</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Submucosa</td>
<td>14%</td>
</tr>
<tr>
<td>Advanced Gastric Cancer</td>
<td>Muscularis</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td>Serosa</td>
<td>66%</td>
</tr>
</tbody>
</table>
patients with familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, gastric adenomas, Menetrier's disease, intestinal metaplasia or dysplasia, and remote gastrectomy or gastrojejunostomy.

should have periodic endoscopy and biopsy.
• account for about 4% of gastric malignancies
• half of patients with B-cell non-Hodgkin's lymphoma have involvement of the GI tract
• The stomach is the most common site of primary GI lymphoma
• In populations with a high incidence of gastric lymphoma, there is a high incidence of *H. pylori* infection
• Deep biopsy is recommended given submucosal location
• Better prognosis than for gastric adenocarcinoma.
• **Antibiotic therapy** directed against *H. pylori* results in regression of many early MALT lesions
• Total gastrectomy
Low-grade (indolent) MALT

- Confined to gastric wall
  - No t(11:18) translocation
    - **H. pylori** eradication therapy
      - Re-evaluate at 12 months
      - Lymphoma regression
        - Close follow-up
      - Lymphoma persists
      - Stage I
        - XRT**
      - Stage II
        - Chemo** + XRT*
  - Lymph node involvement
    - t(11:18) translocation
    - **H. pylori** eradication therapy
      - Re-evaluate at 3–6 months
      - Lymphoma regression
    - Lymphoma persists
    - Stage III or IV
    - **H. pylori** eradication therapy
      - and chemo** +/- XRT*

*XRT: external beam radiation therapy, approximately 30 Gy with 10 Gy boost
**Chemo: chemotherapy regimens include chlorambucil, fludarabinel, and cyclophosphamide, vincristine, prednisone (COP) +/- rituximab

High-grade (aggressive)

- Stage I, II, III
  - Chemo* + XRT**
  - No residual disease
    - Follow-up
  - Residual disease
    - Further chemotherapy
    - Surgery
- Stage IV
  - Chemo* +/- XRT**

*Chemo: chemotherapy regimen usually cyclophosphamide, doxorobicin, vincristine, prednisone (CHOP) +/- rituximab
**XRT: external beam radiation, approximately 30 Gy with 10 Gy boost
Gastrointestinal Stromal Tumor

- GISTs arise from interstitial cells of Cajal (ICC)
- Prognosis in patients with GIST tumors depends mostly on tumor size and mitotic count, and metastasis (hematogenous route)
- Almost all GISTs (and almost no smooth muscle tumors) express c-KIT (CD117)
- Almost all smooth muscle tumors (and almost no GISTs) express actin and desmin
80% of GIST have KIT mutation, that lead to constitutive activation of c-KIT receptor.

- Most KIT mutation in GIST affect **exon 11**

- However in some cases, the mutation is present in **exon 9, 13 or 17**.

Mutation in KIT are observed in both sporadic & hereditary cases.
# Immunohistochemical schema for the differential diagnosis of spindle cell tumors of the gastrointestinal tract

<table>
<thead>
<tr>
<th>Type</th>
<th>CD117</th>
<th>CD34</th>
<th>SMA*</th>
<th>S100 Protein</th>
<th>Desmin</th>
</tr>
</thead>
<tbody>
<tr>
<td>GISTs</td>
<td>+ (&gt;95 percent)</td>
<td>+ (60-70 percent)</td>
<td>+/- (30-40 percent)</td>
<td>- (5 percent +)</td>
<td>Very rare</td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>-</td>
<td>+ (10-15 percent)</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

* Alpha smooth muscle actin.

GISTs cellular morphology ranges from:

- Spindle cell type 70%
- Epithelial type 20%
- Mixed 10%
Determinants of malignant behaviour in GIST

- ALL GISTs are now regarded potential malignancy
- Clinical behaviour of GIST is variable
- 1- Tumor size
- 2- Mitotic rate
- 3- Site of origin
Two thirds of all GISTs occur in the stomach
GISTs are submucosal tumors that are slow growing
Diagnosis is by endoscopy and biopsy
EUS may be helpful
Most gastric GISTs occur in the body of the stomach
They are almost always solitary
• Wedge resection with clear margins is adequate surgical treatment.
• En bloc resection of involved surrounding organs is appropriate to remove all tumor when the primary is large and invasive
• Imatinib (Gleevec), a chemotherapeutic agent that blocks the activity of the tyrosine kinase product of c-kit
- En Block resection is necessary because of dense adhesions

  - Segmental resection of the stomach or intestine should be performed with goal of achieving –ve resection margin

  - Wider resection of uninvolved tissue is of no additional benefit

  - Routine lymphadenectomy is unnecessary because nodal mets are rare
Primary localized disease

- Unresectable or resection requiring extensive surgery or risk of organ dysfunction

  - Resectable
    - Surgery
    - ? postop imatinib
  - Imatinib

Recurrent or metastatic disease

- Consider resection of primary with minimal metastatic disease especially when symptomatic

  - Imatinib
    - Still unresectable
      - Response/stable disease
      - Focal progression
      - Diffuse progression
        - Surgery*
        - Embolization*
        - RFA*
        - Sunitinib
        - Other new agents
      - Continue imatinib
    * If all gross disease or all imatinib-resistant disease is treatable

RFA = radiofrequency ablation
Management of refractory or intolerant patient

- Switching to an alternative TK inhibitor

(Sunitinib)

It’s powerful selection TK inhibitor
Muli-targeted inhibitor
Prognosis:

- depends on

1- Adequacy of resection
2- Tumor size
3- Mitotic activity

Approximately =20% of malignant lesion have already metastasis at diagnosis
### Proposed approach for defining risk of aggressive behavior in gastrointestinal stromal tumors

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Size*</th>
<th>Mitotic count*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low risk</td>
<td>&lt;2 cm</td>
<td>&lt;5 per 50 HPF</td>
</tr>
<tr>
<td>Low risk</td>
<td>2-5 cm</td>
<td>&lt;5 per 50 HPF</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>&lt;5 cm</td>
<td>6-10 per 50 HPF</td>
</tr>
<tr>
<td></td>
<td>5-10 cm</td>
<td>&lt;5 per 50 HPF</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt;5 cm</td>
<td>&gt;5 per 50 HPF</td>
</tr>
<tr>
<td></td>
<td>&gt;10 cm</td>
<td>Any mitotic rate</td>
</tr>
<tr>
<td></td>
<td>Any size</td>
<td>&gt;10 per 50 HPF</td>
</tr>
</tbody>
</table>
Thank You