Gastric Cancer: Surgery and Regional Therapy
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Epidemiology
- Gastric cancer is second leading cause of cancer specific mortality worldwide (989,600 cases; 738,000 deaths) accounting for 8% new cancer cases
- Fourth leading cause of cancer death in the United States (21,320 cases; 10,540 deaths)
- Incidence in Japan 8x higher than US
- More common in men
- More common in Asians, blacks, native americans and US Hispanics
- Peak age is 7th decade
- Incidence of proximal gastric cancer increasing

Risk factors
- Etiology
  - H. pylori infection (90% intestinal type and 30% diffuse type)
  - Exposure to carcinogens (tobacco, salt, nitrates)
  - Pernicious anemia
  - Obesity
  - Adenomatous Polyp
  - Previous gastric surgery
  - Familial history of gastric cancer

Global incidence of gastric cancer in men*
**Histologic Types (Lauren Classification)**
- Intestinal Type (well differentiated)
  - Arises from gastric mucosa
  - Most common in high risk patient populations
  - Related to environmental factors
  - Associated with older patients and distal tumors
  - Incidence is decreasing
  - Better prognosis
- Diffuse Type (linitis plastica)
  - Poorly differentiated signet ring cells
  - Loss of expression of E-cadherin, a key intercellular adhesion molecule which maintains organization of epithelial tissue
  - Arises within lamina propria of stomach wall and grows in infiltrative/submucosal pattern
  - Associated with females, younger patients and proximal tumors
  - Associated with early metastases
  - Incidence is increasing

**Gastric carcinogenic sequence**
- normal gastric mucosa
  \[\downarrow\] H. pylori infection
- atrophic gastritis
  \[\downarrow\]
- intestinal metaplasia
  \[\downarrow\]
- dysplasia
  \[\downarrow\]
- invasive adenocarcinoma

**Hereditary Diffuse Gastric Cancer**
- Inherited form of diffuse type gastric cancer
- CDH1 mutations identified in 30-50% of affected kindreds
- Autosomal dominant trait with high penetrance
- Lifetime cumulative risk for gastric cancer is between 40 and 67% in men and 60-83% in women
- Affected patients develop gastric cancer at early age (average 38)
- Asymptomatic carriers of germline truncating mutations in E-cadherin should have prophylactic gastrectomy, although age is unclear
Clinical Features

Clinical Presentation
- Vague abdominal pain, weight loss, anemia and early satiety are most common presenting symptoms
- Massive bleeding and perforation rare
- 25% of patients have a gastric ulcer
  - All gastric ulcers should be followed to complete healing and those that do not heal should undergo resection

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- 25% of patients have a gastric ulcer
  - All gastric ulcers should be followed to complete healing and those that do not heal should undergo resection

Diagnosis

- Upper gastrointestinal endoscopy is best test for anatomic localization of tumor and tissue diagnosis
- During endoscopy any gastric ulcer should be biopsied
  - Single biopsy has 70% sensitivity for diagnosing an existing gastric cancer
  - Seven biopsies from ulcer base and margin increases sensitivity to >98%
- Diagnosis of diffuse type gastric cancer endoscopically can be difficult because it is submucosal lesion
- Screening not cost effective in low risk groups

Staging

Two major classification systems
- Most elaborate is the Japanese classification, based upon anatomic location, particularly of lymph node stations
- Most commonly used pathologic staging system is AJCC/UICC system
  - T Stage – depth of gastric wall invasion
  - N Stage – number of nodal metastases identified
  - M Stage – presence of distant metastases

Clinical Staging

- Directs the initial approach to therapy
- Patients with locoregional disease (Stage I-III) are potentially curable
- If tumor invades through submucosa (T2 or higher) or there is high suspicion of nodal involvement patient should be referred for multidisciplinary evaluation
- Patients with stage IV disease are usually referred for palliative therapy depending on symptoms and functional status
**Abdominopelvic CT**
- Dynamic CT imaging should be performed to evaluate for:
  - Regional and distant nodal disease
  - Local extension to adjacent organs
  - Liver metastases
  - Peritoneal metastases
- CT accurately assess T stage in only 50-70% of patients;
- Sensitivity for nodal metastases is limited for nodes <0.8cm; in addition false positives can be attributed to inflammatory lymphadenopathy
- Sensitivity for nodal metastases ranges from 65 to 97% and specificity from 49 to 90%

**Endoscopic Ultrasound (EUS)**
- Most reliable nonsurgical method for evaluating depth of invasion of primary gastric cancers.
- Accuracy of EUS for differentiation of individual tumor stages (T1 to T4 tumors) ranges from 77% to 93%.
- Experience of operator markedly influences these rates.
- EUS provides a more accurate prediction of T stage than CT.
- In contrast accuracy for nodal staging (65 to 90%) is only slightly greater than CT
- EUS guided FNA of suspicious nodes adds to this accuracy

**FDG-PET Imaging**
- Role of PET is controversial and evolving
- Can be used to confirm malignant involvement of CT detected lymphadenopathy
- Most diffuse type gastric cancers are not FDG avid
- More sensitive than CT for detection of distant metastases but poor for peritoneal carcinomatosis
- May be useful in assessment of response of tumors to neoadjuvant treatment

**Diagnostic laparoscopy**
- Utilized to assess for small volume peritoneal carcinomatosis
- Peritoneal cytology utilized to look for microscopic free peritoneal tumor cells
- 25% of patients with T3 – T4 or N(+) have radiographic occult disease identified by laparoscopy
- Only 4% of T1 – T2 or N0 disease have any findings on laparoscopy
- Utilized prior to administration of neoadjuvant chemotherapy
Peritoneal Cytology

Bentrem, Ann Surg Oncol 2005

371 R0 resections with staging laparoscopy and washings
Incidence, Risk factors, Prognostic value of positive cytology

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Peritoneal Cytology

Positive peritoneal washings as only site of M1 disease and patients with gross metastatic disease fare equally poorly

Surgical resection with therapeutic intent in the presence of known M1 disease portends a poor outcome

The absence of detectable M1 disease after systemic chemotherapy is associated with a survival benefit

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T Stage Correlates with (+) LN

- T1a - <5%
- T1b – 20%
- T2 – 50%
- T3 – 70%
- T4 – 90%
TNM Classification

- Tis: Cancer cells only in mucosa
- T1a: into lamina propria or muscularis mucosa
- T1b: into the submucosa
- T2: into muscularis propria
- T3: into the subserosa
- T4a: into serosa
- T4b: into nearby organs or structures

- N0: No spread to LN
- N1: 1-2 regional LN
- N2: 3-6 regional LN
- N3: >7 regional LN

- M0: No distant mets
- M1: Distant mets

Stage Grouping

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Survival by AJCC stage – curative resection

Surgical Management

Dysplasia
Progression of LGD/HGD to Cancer

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<th>Author (year)</th>
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<th>HGD progression</th>
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<td>48 months</td>
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<td>3%</td>
<td>212 months</td>
<td>10%</td>
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Progression of Dysplasia

- Progression in low grade dysplasia is from 0% - 23% in various studies
- Progression in high grade dysplasia is 60 - 85% in multiple studies
- Most experts recommend endoscopic surveillance in patients with LGD
- Most experts recommend endoscopic or surgical resection for management of patients with evidence of HGD

Progression of Dysplasia

- > 1 year endoscopic followup of 90 low-grade and 16 high-grade gastric dysplasia cases
  - Low-grade: 53.3% regression
  - 31.1% no change
  - 15.4% progression
  - 8.8% progression to cancer (mean 48 months [21-85])
- High-grade: 0/16 regression
  - 5/16 no change
  - 11/16 progression to cancer (mean 34 months [13-72])

Surgical Management

Early Gastric Cancer

Rugge, et al., Gut 2003
Early Gastric Cancer (EGC)

- EGC defined as adenocarcinoma limited to mucosa and submucosa regardless of LN involvement (T1Nx)
- Reflects that EGC represents a more favorable/curable subset of gastric cancers compared to more invasive gastric cancers (T2-T4Nx)
- EGC identified more often now with the upward trend reflecting mass screening and improved technology
- Still uncommon in US given lack of screening endoscopy in low risk patient population

Endoscopic Resection of EGC

- Developed 20 years ago, defined over the last two decades as an alternative to gastrectomy for early gastric cancers
- Endoscopically developing a plane submucosally and resecting affected tissue in one piece
- Advantages include decreased morbidity and mortality, potential increased quality of life post procedure
- Disadvantages include increased risk of nodal disease, metachronous disease, incomplete resection

Early Gastric Cancer (EGC)

- In Western countries early gastric cancers comprise <15% of gastric cancers diagnosed
- Frequency of early gastric cancer:
  - Japan - 78 cases/100,000
  - United States - 10 cases/100,000

Surgical Management

Locoregional Disease
Gastrectomy

- Resection offers best chance for survival for patients with localized gastric cancer
- As previously discussed adjuvant or perioperative chemotherapy or chemoradiotherapy can improve outcomes over surgery alone
- Optimal therapy depends on accurate staging of extent of disease

Indicators of Unresectability

- Distant metastatic disease
- Invasion of major vascular structure such as aorta, celiac axis, hepatic artery or proximal splenic artery
- Bulky lymphadenopathy fixed to pancreatic head that may require pancreaticoduodenectomy
- Lymph nodes considered outside surgical resection field such as porta hepatis, aortocaval, inferior or posterior to pancreas or mediastinal (3rd or 4th echelon nodes in the Japanese nomenclature)

Surgical resection

- Two main surgical issues in surgical management of curable gastric cancer
  - Extent of gastric resection – depends on location of lesion within stomach
  - Extent of lymphadenectomy – depends on extent of lymph node involvement

Extent of Surgical Resection

Distal Tumors
Distal Gastric Adenocarcinoma

- Two studies have prospectively randomized patients to total versus subtotal gastrectomy for surgical treatment of distal gastric cancer
- Studies show no benefit for total gastrectomy compared to subtotal gastrectomy

Total versus Subtotal Gastrectomy

- French Study
  - Randomized 169 patients with tumors of distal stomach
  - Five year survival was no different between groups
  - Complication and perioperative mortality rates similar (32 and 1.3% for total and 34 and 3.2% for subtotal)
- Italian Gastrointestinal Study Group
  - Randomized trial of 618 patients with tumors of distal stomach
  - No difference in 5 year survival between patients having a subtotal or total gastrectomy (65% vs. 62%)
  - Morbidity and mortality data were not reported

Extent of Surgical Resection

Proximal Tumors

Proximal gastric adenocarcinoma

- Total gastrectomy with Roux-en-Y esophagojejunostomy is preferred treatment over a proximal gastrectomy
  - Roux-en-Y is associated with much lower risk of reflux esophagitis compared to 1/3 of patients who develop reflux esophagitis after proximal gastrectomy
  - Proximal subtotal gastrectomy may fail to remove lymph nodes along lesser curvature which are most common site of nodal metastases
Extent of Lymph Node Dissection

- One of most controversial areas in surgical management of gastric cancer
- D1 LN dissection involves a perigastric LN dissection (stations 1-6)
Extent of Lymph Node Dissection

- One of most controversial areas in surgical management of gastric cancer
- D1 LN dissection involves a perigastric LN dissection (stations 1-6)
- D2 lymphadenectomy is an extended LN dissection that entails removing all nodes along the hepatic, left gastric, celiac and splenic arteries (stations 1-11)
Japanese surgeon routinely perform extended lymphadenectomy due to survival benefit demonstrated in Eastern literature.

Randomized studies in Western series demonstrated increased morbidity with D2 LN dissection but no benefit in terms of improved survival over D1 LN dissection.

Need at least 16 nodes to properly stage patient.

Two arguments against routine use of extended lymphadenectomy:
- Higher associated morbidity and mortality
- Lack of a survival benefit for extended lymphadenectomy in most large randomized studies

MRC Trial (Medical Research Council)
- Random assignment trial of 400 patients to D1 or D2 lymphadenectomy
- Post-op morbidity and mortality higher in D2 group (46% vs. 28% and 13% vs. 6%)
- Five year survival rates were similar (33% versus 35%)

Dutch Trial
- Largest randomized trial from Dutch Gastric Cancer Group
- Randomized 711 patients treated with curative intent to D1 vs. D2 LN dissection
- Japanese surgeon trained and monitored operative procedures of 11 Dutch surgeons
- Postoperative morbidity (43% vs. 25%) and mortality (10% vs. 4%) higher in D2 group
- Most recent 15 year follow up revealed:
  - Overall survival – 21% in D1 versus 29% in D2 (p=0.34)
  - Lower local regional recurrence rates with D2 (22% in D1 versus 12% in D2)
  - Gastric cancer related death higher in D1 group (48% vs. 37%)
D1 versus D2 LN dissection
- Many clinicians considered above trials flawed
- Dutch trial assumed increase in survival from 20-32% - likely an overestimate of potential benefit
- 40% of patients with early gastric cancer (unexpected high proportion unanticipated) who would be unlikely to derive benefit
- Both studies significantly underpowered for the group of patients with N2 disease who would be expected to derive a long term benefit.
- Operative mortality of 10-13% would not be expected in high volume centers

D2 versus D3 LN dissection
- JCOG trial 9501
  - Multicenter Japan Clinical Oncology Group (JCOG) randomly assigned 523 patients to a D2 versus a D3 LN dissection.
  - Complication rate in D3 group significantly higher (28% vs. 21%) although no differences in major complications or mortality (0.8% in both arms)
  - Five year recurrence free survival (63% in both groups) and overall survival (70% vs. 69%) were no better after extended lymphadenectomy

Laparoscopic Gastrectomy
- Predominantly utilized for early gastric cancer
- Role in advanced gastric cancer is unclear
- Types of gastric operations:
  - Staging – diagnostic laparoscopy with peritoneal washings
  - Resection
    - Laparoscopic Subtotal gastrectomy
    - Laparoscopic Total gastrectomy
    - Laparoscopic Proximal Gastrectomy
  - Palliative Bypass

Theoretical Advantages
- Decreased pain
- Shorter hospital stay
- Less intraoperative blood loss
- Fewer complications
- Quicker recovery of intestinal function
- Improved cosmesis
Concerns

- Oncologic equivalence?
  - Adequacy of lymph node dissection and surgical margins
- Longer operative time
- Need for advanced instrumentation
- Long learning curve

Results

- A multitude of retrospective reports and case control reports comparing laparoscopic and open gastrectomy for the treatment of early gastric cancer from both Western and Eastern countries
- All studies demonstrated laparoscopic gastrectomy to be safe with equivalent results to open surgery
- At least 5 prospective randomized studies comparing laparoscopic and open gastrectomy for early gastric cancer

Results

- A meta-Analysis of these studies revealed:
  - LADG associated with less blood loss, less analgesic requirements and lower rate of complications
  - LADG associated with longer operative time and decreased number of lymph nodes harvested
  - No difference demonstrated for resumption of oral intake, duration of hospital stay, tumor recurrence or mortality

<table>
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Ohtani et al. J Gastrointest Surg 2010
**Surgeon and Institution Experience**

- United states Intergroup Trial 0116 provided sobering overview of current surgical practice in patients with resectable gastric cancer
  - Of 556 patients, 54% <D1 LN dissection, 36% with D1 LN dissection and 10% with D2 dissection
- Fewer than 1/3 of Americans undergoing gastric cancer surgery have 15 or more LNs examined, even in academic and high volume hospitals
- Mortality rates under 2% can be expected at high volume centers in the US

**Institutional Volume**

- Recent study in state of Texas looked at 1800 gastrectomies performed in 214 hospitals over a 3 year period.
- High volume centers characterized by > 15 resections per year, low volume as <3.
- Hospital mortality was 1.1% at high volume versus 6.2% for low volume and 5.2% for intermediate volume.
- Impact on long term disease free or overall survival is less clear.

**Regional Therapy**

Peritoneal Carcinomatosis

**Intraperitoneal Chemotherapy for Gastric Cancer**

- Peritoneal metastases are a common site of spread for gastric cancer
- Patients with gastric cancer and peritoneal carcinomatosis have a very poor prognosis with median survival of 3 months without treatment
- Systemic chemotherapy is largely ineffective against peritoneal carcinomatosis
Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

- Utilized in combination with cytoreductive surgery for treatment of advanced cancers limited to peritoneal cavity
- All visible tumor from the peritoneal cavity is removed (cytoreductive surgery or debulking)
- Sterile solution containing heated chemotherapeutic agent is continuously circulated through the abdominal cavity for set period of time

HIPEC and Gastric Cancer

- Best quality study is randomized controlled trial by Kuramoto et al
- Randomized patients with positive peritoneal cytology and no macroscopic peritoneal disease to surgery alone versus surgery and HIPEC.
- Revealed improved survival with addition of HIPEC.

CRS and HIPEC

- Role of CRS and HIPEC in patients with macroscopic peritoneal disease is unclear
- Studies looking at this are mostly retrospective, poorly designed and conclusions on efficacy of this treatment are unproven

Montefiore-Einstein Center for Cancer Care Phase II Trial

- Cytoreduction + Hyperthermic Intraperitoneal Mitomycin C + Standard Systemic Chemotherapy in Patients with Peritoneal Carcinomatosis
- Eligible patients are patients with ECOG performance status ≤1 and cytologically or biopsy proven carcinomatosis from gastric cancer (other histologies included in trial are appendiceal, colorectal, pseudomyxoma and peritoneal mesothelioma).
Phase II Trial

- Primary Objective is to evaluate technical parameters including completeness of cytoreduction, achievement of hyperthermia, morbidity and mortality.

- Secondary objectives are to evaluate progression free survival, overall survival, and quality of life.

Thank you.