Current Management of
Gastric Cancer

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Incidence & mortality (global)

- 4th most common cancer (934,000 cases for 2012)
- 2nd leading cause of death (700,000 cases for 2012)
- Decreasing incidence (2nd most common cancer in 1990’s)

Gastric cancer epidemiology

**Incidence & mortality (US)**

- **Uncommon cancer (outside top 10 in incidence and mortality)**

### Estimated New Cancer Cases and Deaths by Sex for All Sites

<table>
<thead>
<tr>
<th></th>
<th>Estimated New Cases</th>
<th></th>
<th>Estimated Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both Sexes</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>All sites</td>
<td>1,399,790</td>
<td>720,280</td>
<td>679,510</td>
</tr>
<tr>
<td>Breast</td>
<td>214,640</td>
<td>1,720</td>
<td>212,920</td>
</tr>
<tr>
<td>Prostate</td>
<td>234,460</td>
<td>234,460</td>
<td>81,770</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>174,470</td>
<td>92,700</td>
<td>81,770</td>
</tr>
<tr>
<td>Stomach</td>
<td>22,280</td>
<td>13,400</td>
<td>8,880</td>
</tr>
<tr>
<td>Small intestine</td>
<td>6,170</td>
<td>3,160</td>
<td>3,010</td>
</tr>
<tr>
<td>Colon†</td>
<td>106,680</td>
<td>49,220</td>
<td>57,460</td>
</tr>
<tr>
<td>Rectum</td>
<td>41,930</td>
<td>23,580</td>
<td>18,350</td>
</tr>
</tbody>
</table>

Gastric cancer epidemiology

Incidence & mortality (US)

Gastric cancer epidemiology

Pathologic classification

- Adenocarcinoma (90 - 95%), lymphoma, GIST
- Lauren’s classification of adenocarcinoma

- Well diff, polypoid, fungating
  Distal stomach
  H. Pylori, gastric atrophy
  Older age, lower socioeconomic
  Decreasing incidence

- Signet ring cell, diffuse thickening
  Proximal stomach
  Genetic predisposition
  Young age, higher socioeconomic
  Increasing incidence

Lauren P. Acta Pathol Microbiol Scand 1965;64:31-49
Gastric cancer epidemiology

Intestinal versus diffuse types

Gastric intestinal vs diffuse types
## Gastric cancer epidemiology

### Risk factors

<table>
<thead>
<tr>
<th>Category</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental</td>
<td><em>H pylori</em></td>
</tr>
<tr>
<td></td>
<td>High salt and nitrite content in preserved food</td>
</tr>
<tr>
<td></td>
<td>Smoking, obesity, lower socioeconomic class</td>
</tr>
<tr>
<td>Genetics</td>
<td>E cadherin mutation, CDH1</td>
</tr>
<tr>
<td></td>
<td>HNPCC/Lynch. MMR</td>
</tr>
<tr>
<td></td>
<td>FAP, APC</td>
</tr>
<tr>
<td></td>
<td>Blood group type A</td>
</tr>
<tr>
<td>Associated</td>
<td>Pernicious anaemia, prior gastric surgery, irradiation</td>
</tr>
<tr>
<td>conditions</td>
<td></td>
</tr>
</tbody>
</table>
Gastric cancer
Symptoms and Signs

- Symptoms may reflect site of tumor origin
  - Proximal: dysphagia, indigestion
  - Distal: early satiety or GOO

- Physical signs occur late
  - Abdominal mass
  - Cachexia
  - Malignant ascites
  - Lymphadenopathy
    - Left supraclavicular (Virchow’s)
    - Periumbilical (Sister Mary Joseph)

- Routine screening is not performed in the U.S.
- Screening is performed in Japan where the incidence of gastric cancer is higher - 62 per 100,000 males
Gastric cancer
Making a diagnosis

- Upper endoscopy for initial evaluation
- Gastric distensibility
- Features of suspicious ulcer
  - Location
  - Surrounding mass
  - Irregular folds and base
- Multiple biopsies increase sensitivity for diagnosis of malignant ulcers (>98% with seven or more biopsies)
Gastric cancer staging - goals

- Determine extent of locoregional disease
  - Preoperative chemotherapy?
  - Details of surgical resection

- Evaluate for metastatic disease

- Provide prognostic information

- Characterize or predict tumor behavior (response to neoadjuvant therapy)
Gastric cancer staging

- Exam
- Upper endoscopy
  - Appearance/size, location, linitus
- CT chest/abdomen/pelvis (contrast enhanced)
- Selective use – EUS, PET, diagnostic laparoscopy
Gastric Cancer:  
CT in Staging of Gastric Cancer

• Accurate preoperative staging essential to tailoring therapy for individual patients

• Although widely available and non-invasive, CT historically inaccurate for assessing$^{1,2}$:
  • Depth of primary tumor
  • Presence of lymph node metastasis
  • Accuracy 40-50%, understaging 10-35%, overstaging 6-14%

Gastric cancer staging
EUS

- Evaluate gastric wall invasion and locoregional lymph nodes (adds T/N stage to information gained from EGD)
- Allows for image-guided FNA of suspicious extraluminal masses (nodes)
- Requires operator skill and experience
Gastric Cancer: CT in Staging of Gastric Cancer

- 51 consecutive patients preoperatively evaluated with both CT (3 mm cuts) and EUS
- Studies reviewed prospectively in blinded fashion
- Results compared with histopathology of resected specimens

<table>
<thead>
<tr>
<th></th>
<th>T stage*</th>
<th>N stage*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helical CT</td>
<td>76%</td>
<td>70%</td>
</tr>
<tr>
<td>EUS</td>
<td>86%</td>
<td>90%</td>
</tr>
</tbody>
</table>

* Accuracy of preoperative assessment in comparison to final pathology

## Detection of Synchronous Metastases

- Radiographic (CT scan, liver US) 50-60%
- Laparoscopy (radiographically occult) 25-30%
- Peritoneal cytology 6-7%

### Sites for Synchronous Metastases (for patients explored)*

- Peritoneum 50%
  - lesser sac
  - sub-diaphragmatic
  - pelvis
- Non-regional lymph nodes 25%
- Liver 15-20%
- Ovary (Krukenberg’s tumor) 2%
- Multiple (≥ 2 sites) 40-50%

Peritoneal cytology (micro mets) present in 6.5% of patients without macro mets*

Micro M1 = Macro M1

- **Median survival:** 12 mos
- **3-yr survival:** 0%

Predictors of poor outcome for resected patients with M1 disease

- Persistent mets after pre-op chemo
- N3 disease
- Need for total gastrectomy or extra organ resection

Capturing chemoresponsive patients
Gastric Cancer: PET for Assessing Response to Therapy

- 44 consecutive patients with locally advanced gastric carcinoma
- Preoperative chemotherapy with 5-FU, Leukovorin, and Cisplatin x 2 cycles followed by surgical resection
- Baseline PET followed by repeat PET 14 days after initiation of chemotherapy

Gastric Cancer – Treatment
Surgical Treatment of Gastric Cancer

- No Surgery: 22%
- No Resection: 19%
- Palliative Resection: 12%
- Curative Resection: 47%

MSKCC 7/1/1995 – 6/30/2014  n = 3384
Gastric Cancer Prognosis Based on Stage

Preoperative clinical stage

Pathologic stage
EGD: biopsy-proven gastric adenocarcinoma

CT scan (abdomen, pelvis)

EUS

Low risk
uT1-2 N0

High risk
uT3-4 N1-2

Staging laparoscopy (at time of resection)

pM1 disease

R0 resection with D2 LND

Low risk
pT1-2 N0

High risk
pT3-4 N1-2

Adjuvant chemoradiation or clinical trial

Staging laparoscopy with cytologic washings

Neoadjuvant chemotherapy

R0 resection with D2 LND

Adjuvant chemotherapy or clinical trial

pM1 disease

Low risk
pT1-2 N0

High risk
pT3-4 N1-2

pM1 disease
Surgery and Perioperative Chemotherapy Compared with Surgery alone for Adenocarcinoma of the Stomach

MAGIC Trial

- 503 patients
- Treatment groups
  - surgery + perioperative chemo vs. surgery alone
- Improved 5-yr overall survival
  - 36% vs. 23%

Cunningham et al, NEJM, 2006
Perioperative Chemotherapy for Adenocarcinoma of the Stomach

FLOT superior to ECF/ECX

- 716 patients
- Multicenter RCT, 2010-2015, 38 German centers
- Treatment groups
  - FLOT4 + surgery + FLOT4 vs.
  - ECF3 + surgery + ECF3
- Improved OS
  - Median 50 mos vs. 35 mos

27% major toxicity in each group

Al-Batran, FLOT4-AIO, Lancet, 2019
Surgical Treatment of Gastric Cancer

- Surgery for Localized Disease
  - Extent of Local Resection
  - Extent of Lymphadenectomy

- Surgery for Metastatic or Recurrent Disease
Is total gastrectomy necessary?

- Potential benefit of total gastrectomy\(^1\)
  - More effective prevention of esophageal obstruction
  - Wider margins
  - Removal of broader nodal basin

- MSKCC experience\(^2\)
  - Prospective (1985-1995)
  - 98 pts with proximal cancer undergoing resection
  - Proximal (n=65) vs total gastrectomy (n=33)

\(^1\)Papachristou DN, Fortner JG. *Ann Surg* 1996
Gastric cancer - resection

Is total gastrectomy necessary?

- Recurrence
  - No difference in time to recurrence, local recurrence rate
  - Increase in distant recurrence rate may reflect surgical selection

<table>
<thead>
<tr>
<th></th>
<th>Local (n)</th>
<th>Distant (n)</th>
<th>RFS (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal</td>
<td>18</td>
<td>6</td>
<td>15.7</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>5</td>
<td>18</td>
</tr>
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</table>

Gastric cancer - resection
Resect locally advanced disease?

- Up to 25% of patients may require removal of additional organs for R0 resection (e.g., spleen, pancreas, colon, liver)
- No overall survival difference


Stage 3A
Gastric cancer - resection

Re-resect positive margins?

- Up to 20% of patients with positive margins\(^1\)
- Overall survival improved with negative margins

\(^1\)Papachristou DN, Fortner JG. *Ann Surg* 1996
\(^2\)Kim SH, *et al.* *JOGS,* 1998
Gastric cancer - resection

Re-resect positive margins?... when

- Patients with adequately sampled nodes and > 5 positive nodes

\(^1\)Kim SH, et al. JOGS, 1998
Extent of gastrectomy

- Wide margins necessary to ensure R0 resection for diffuse type cancers
- Total gastrectomy not necessary if adequate margins can be obtained
- Involvement of adjacent organs does not preclude resection
- Re-resection of positive margins only necessary among patients with negative nodes
Gastric cancer

Treatment of regional disease

No benefit to D2 over D1 LND in Western RCTs

Evidence that trends toward improved survival in advanced stage disease are the result of stage migration →

EXTENDED LYMPH-NODE DISSECTION FOR GASTRIC CANCER

J.J. Bonenkamp, J. Hermans, M. Sasako, and C.J.H. van de Velde, for the Dutch Gastric Cancer Group*

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>D1</th>
<th>D2</th>
<th>P Value*</th>
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</thead>
<tbody>
<tr>
<td>Age ≤65 yr</td>
<td>178</td>
<td>168</td>
<td>0.90</td>
</tr>
<tr>
<td>Age &gt;65 yr</td>
<td>202</td>
<td>163</td>
<td>0.87</td>
</tr>
<tr>
<td>Pathological stage†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>98</td>
<td>85</td>
<td>0.69</td>
</tr>
<tr>
<td>T2</td>
<td>181</td>
<td>152</td>
<td>0.87</td>
</tr>
<tr>
<td>T3</td>
<td>94</td>
<td>82</td>
<td>0.93</td>
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<tr>
<td>Tumor—node—metastasis (TNM) stage‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>76</td>
<td>69</td>
<td>0.88</td>
</tr>
<tr>
<td>IB</td>
<td>97</td>
<td>64</td>
<td>0.65</td>
</tr>
<tr>
<td>II</td>
<td>105</td>
<td>66</td>
<td>0.29</td>
</tr>
<tr>
<td>IIIA</td>
<td>70</td>
<td>72</td>
<td>0.07</td>
</tr>
<tr>
<td>IIIB</td>
<td>16</td>
<td>39</td>
<td>0.61</td>
</tr>
<tr>
<td>IV</td>
<td>12</td>
<td>18</td>
<td>0.09</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>175</td>
<td>146</td>
<td>0.84</td>
</tr>
<tr>
<td>Positive</td>
<td>205</td>
<td>185</td>
<td>0.72</td>
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<tr>
<td>Gastrocrony</td>
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<tr>
<td>Partial</td>
<td>265</td>
<td>205</td>
<td>0.63</td>
</tr>
<tr>
<td>Total</td>
<td>115</td>
<td>126</td>
<td>0.84</td>
</tr>
<tr>
<td>All patients</td>
<td>380</td>
<td>331</td>
<td>0.99</td>
</tr>
</tbody>
</table>

NEJM (1999) 340:908-914
Gastric cancer

Treatment of regional disease

Number of LNs examined IS important.

Improved survival in N1 and N2 patients with $\geq 15$ lymph nodes examined, likely due to more accurate staging.

Lymph Node Staging in Gastric Cancer: Is Location More Important Than Number? An Analysis of 1,038 Patients

Martin S. Karpeh, MD,* Larry Leon, PhD,† David Klimstra, MD,‡ and Murray F. Brennan, MD*

Treatment of regional disease

- Extended lymph node dissection (D2) is standard-of-care in Japan and has been associated with improved survival.
- Western randomized controlled trials have shown no survival benefit to D2 over D1 lymph node dissection.
- Examination of $\geq 15$ lymph nodes is recommended for accurate staging.
Gastric Cancer – Management of Metastatic Disease

Surveillance for Metachronous Metastases?

• Single institution, 10-yr period (1985-95)

• Follow-up after curative primary resection: semi-annual abd/pelvis CT scan or U/S, H/P, LFTs, CEA, CA 19-9

• N=197 pts with detectable mets as a result of routine surveillance (45%) or symptom development (55%)
Patterns of Recurrence in Resected Gastric Cancer

Time period: 1985-2000
Total R0 resections: 1,172
Total recurrences: 496 (42%)
Single site recurrences: 68%

Locoregional Recurrence
- Regional LNs: 48%
- Gastric remnant or anastomosis: 32%

Distant Recurrence
- Peritoneum: 35%
- Liver: 37%
- Lung: 16%
- Bone: 16%
- Non-regional LNs: 14%
Resection for Recurrent Gastric Cancer

• Patterns of recurrence:
  - Regional: 56%
  - Carcinomatosis: 53%
  - Liver: 23%
  - Local: 12%

• Asymptomatic pts more likely to be candidates for resection

• Symptomatic pts more likely to have local and/or regional recurrences

No patients were cured after resection for recurrent gastric cancer

Gastric Cancer – Management of Metastatic Disease

Metastatic Gastric Cancer

• 30% of patients will have synchronous metastases at the time of diagnosis of gastric cancer\(^1\)
• 30-50% of patients will develop metastases during/after treatment for gastric cancer\(^2\)

Likelihood of Metastases
• Ascites
• Advanced T stage (T3 and T4)
• Nodal disease
• Symptoms (obstruction, pain, weight loss)
• Whole stomach involvement (linitus plastica)
• Histology (diffuse-type)

\(^1\)Hartgrink, H, Br J Surg 2002, 89:1438-1443
\(^2\)Macdonald, J., NEJM 2001, 345:725-30
Gastric Cancer – Management of Metastatic Disease

Palliation for Incurable Gastric Cancer

• 50% of patients will require palliative intervention prior to death
• 12% or patients require laparotomy for satisfactory palliation
• Mostly gastric complications (obstruction, bleeding, perforation)
• 2/3 of gastric complications managed with an endoscopic procedure (PEG, PEJ, stent)

Accurate diagnosis and tumor location should be confirmed

Staging modalities include CT, PET-CT, EUS

Stage of disease dictates treatment:

- Early stage (T1-2N0) → Surgery

- Advanced stage (T3 or greater, any N+) → Chemo
EGD: biopsy-proven gastric adenocarcinoma

CT scan (abdomen, pelvis)

EUS

Low risk
uT1-2 N0

Staging laparoscopy (at time of resection)

R0 resection with D2 LND

Low risk
pT1-2 N0

Adjuvant chemoradiation or clinical trial

High risk
pT3-4 N1-2

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Neoadjuvant chemotherapy

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pM1 disease