Surgery for Gastric Carcinoma and Premalignant Lesions

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BC Surgical Oncology Network
Upper GI and Hepatobiliary Cancer Update
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Gastric Cancer – Incidence Worldwide

Data adapted from GLOBOCAN, International Agency for research on Cancer

World cancer report
By Bernard W. Stewart, Paul Kleihues, International Agency for Research on Cancer

globally: 4th cancer, 2nd cancer-related death
Gastric Cancer in Canada
New Cases and Deaths, 2008

New Cases
- Total: 3000
- Women: 1000
- Men: 1000

Deaths
- Total: 1500
- Women: 500
- Men: 1000

NCIC, 2008
Surgery of Gastric Cancer and Premalignant Lesions

Overview

Evidence

- Investigation & Clinical staging
- Extent of resection/LN dissection
- Surgical issues re: Adjuvant/Neoadjuvant Rx

Issues

- Premalignant lesions
- Early Gastric Cancer
- Familial DGC
- Quality of resection
  - Laparoscopic gastrectomy
- Advanced GC management
Case of Mr. A. H.

65 year old healthy man
1 year of dyspepsia, anemia
Endoscopy: antral tumour
path: invasive adenocarcinoma,
diffuse type
After UGI scope and Bx, my routine pretreatment workup of gastric cancer would be:

a. CT-AP, CXR

b. CT-AP, CXR, laparoscopy

c. CT-AP, CXR, laparoscopy, EUS

d. CT-AP, CXR, laparoscopy, EUS, PET
Improvements in Staging of Gastric Cancer

Laparoscopy

- Staging accuracy $\geq 90\%$
- Resectability accuracy $\approx 90\%$
- Altered treatment plan in 20-30%

Semin Oncol 1996; 3: 347
Ann Surg 1997; 3: 262
Current Surgery 2005; 62: 35
Improvements in Staging of Gastric Cancer

Endoscopic Ultrasound

T stage: accuracy $\approx 80\%$

N stage: accuracy $\approx 75\%$

Resectability:

sensitivity $\approx 90\%$

specificity $\approx 85\%$

Surg Endosc 2000; 14: 951
Tumori 2000; 86: 139
Surg Endosc 2006; 20: 559
World J Gastroenterol 2006; 12: 43
Improvements in Staging of Gastric Cancer

T stage: accuracy ≈ 80%

N stage: accuracy ≈ 70%

Resectability:
- Sensitivity: ≈ 90%
- Specificity: ≈ 85%

Figure 1 Early and advanced gastric cancer cases. A: Endoscopic view of superficial depressed type of early gastric cancer; B: EUS image shows cancer invasion of 1st and 2nd (mucosal) layers of gastric wall, while 3rd (submucosal) layer is clear (T1 category). Histopathological findings of the surgically resected specimen corresponded with the EUS findings; C: Endoscopic view of advanced Borrmann II type of gastric cancer; D: EUS images show disruption of 1-4 layers of the gastric wall with hypoechoic cancer tissue, but 5th (serosal) layer is not involved (T2 category).

5 layers of the wall
### Staging of Gastric Cancer

**FDG-PET and LN Status:**
Systematic Review

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Study and year</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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</tbody>
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Kwee & Kwee, Gastric Cancer 2009; 12:6-22
Staging of Gastric Cancer

FDG-PET

Approx 30% of GC are NOT PET avid
In those which are, prognosis depends on PET response to preop chemotherapy
Prognosis of PET non avid GC is same as non-responders

Ott et al., Gastric Cancer 2008; 11:1-9
Treatment Planning

Case of Mr. A. H.

EUS: T3 N+ (5 enlarged perigastric nodes)

Laparoscopy clear

Good performance status
For clinical stage T3N+M0 antral cancer in a fit patient, my next step would be:

a. resect
b. 3 cycles chemo
c. PET scan
d. chemo + RT
Gastric Cancer

POSTLAPAROSCOPY STAGING

Medically fit,\textsuperscript{b} potentially resectable

- M0
- M1

Medically fit,\textsuperscript{b} unresectable

- M0
- M1

Medically unfit

- M0
- M1

T1 or less (by clinical staging) → Surgery\textsuperscript{d,e}

T2 or higher (by clinical staging or N+) → Preoperative chemotherapy → Surgery\textsuperscript{e}

Surgical Outcomes (see GAST-3)

RT, 45-50.4 Gy + concurrent 5-FU-based radiosensitization (category 1) or Chemotherapy\textsuperscript{f} → Surgical Outcomes (see GAST-3)

RT, 45-50.4 Gy + concurrent 5-FU-based radiosensitization (category 1) or Salvage Therapy (see GAST-4) → Salvage Therapy (see GAST-4)

Salvage Therapy (see GAST-4)

\textsuperscript{b}Medically able to tolerate major abdominal surgery.

\textsuperscript{d}Surgery as primary therapy is appropriate for T1 cancer or actively bleeding cancer, or when postoperative adjuvant therapy is preferred.

\textsuperscript{e}See Principles of Surgery (GAST-A).

\textsuperscript{f}See Principles of Systemic Therapy (GAST-B).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Extent of Resection/Dissection

I. Extent of Gastrectomy
II. Extent of Lymphadenectomy
III. Margins
French and Italian RCT Antral Ca
TG vs STG: Longterm Survival

French n=169  Italian n=618

The Great Debate: D1 vs. D2
D1 Dissection

- Level 1 nodes (perigastric, stations 1 - 6)
  - right & left cardiac (1 & 2)
  - lesser & greater curve (3 & 4)
  - supra- and infra- pyloric (5 & 6)
- Omentum
D2 Dissection

- Level 1 nodes (perigastric, stations 1 - 6)
- Level 2 nodes (intermediate, stations 7 - 9)
  - left gastric (7), common hepatic (8), celiac (9)
- stations 10 (splenic hilum) and 11 (splenic artery) nodes
- omental bursa, anterior leaf of mesocolon
D2 Dissection for Gastric Cancer
MRC RCT: D1 vs D2 Dissection
Longterm Survival

% alive at 5 years

Disease free survival
Overall survival

Br J Cancer 1999 79: 1522
Dutch RCT: D1 vs D2 Dissection
Longterm Survival

% alive at 5 years

NEJM 1999; 340:908
Dutch RCT: D1 vs D2 Dissection
Very Longterm Survival

% alive at 11 years

D1, n=380
D2, n=331

median f/u time = 11 years

Dutch RCT: D1 vs D2 Dissection

Very Very Longterm Survival

Median f/u time = 15 years

Lancet Oncol 2010; 11: 439
Dutch RCT: D1 vs D2 Dissection
Postoperative M & M Rates

* p<0.004

Morbidity

Mortality

D1, n=380
D2, n=331

NEJM 1999; 340:908
MRC RCT: D1 vs D2 Dissection
Postoperative M & M Rates

* p<0.04

The Lancet 1996 347:995
"Standard" D2 Dissection: Japanese RCT & Italian multicentre phase II trial

Morbidity Mortality

IGCSG, n=191
67 total gastrexs
49 splenectomies

GCSSG of JCOG, n=263
102 total gastrexs
98 splenectomies

Br J Cancer 2004; 90: 1727
Survival after “Standard” D2 Dissection

Overall 5 yr. survival [\%]

100
80
60
40
20
0

(191)
(466)
(375)
(446)

IGCSG, phase II
MSKCC, prosp DB
Chile, prosp cohrt
Seoul, method NS

Br J Cancer 2004; 90: 1727
Gastrointest Surg 1999; 3: 24
Dig Surg 1999; 16: 385
Extent of Lymphadenectomy: Cochrane Review – D2

- more dangerous when
  - spleen/panc resected
  - surgeon inexperienced
- studies limited by
  - learning curves, poor compliance
  - contamination
- no PROVEN survival benefit
- MAY benefit
  - T3+
  - Stage II & IIIa

McCulloch et al, The Cochrane Collaboration, 2005
Taiwanese: D1 vs D3 Dissection

• 1993-1999
• 335 patients registered
• 221 eligible & randomized
• 64 did “not fit” histologically
• 156 treated “per protocol”
• Median f/u for 110 survivors = 94.5 mos.
• Per protocol 5 yr. OS = 51% in D3 (n=76) and 45% in D1 (n=80)
• “D3 or not D3…that is not the question”

Lancet Oncology 2006; 7:309
Japanese: D2 vs D2+PANDissection

- Japan Clinical Oncology Group
- 1995-2001
- 24 hospitals
- D2  n=263
- D2 + PAND n=260
- no difference in recurrence-free or overall survival

Sasako et al., NEJM 2008, 359:453-62
Extent of Lymphadenectomy:  

**Current Recommendations**

- obtain adequate # of nodes for accurate staging

- **D2:** not harmful in expert hands
  - more nodes = better staging
  - direct survival benefit unclear

- **D1+/D1.5** should be the minimum standard
Margin status – should you check?

R Status Determines Prognosis

% alive at 5 years

R0: n=1038
R1: n=193
R2: n=293

M. Karpeh, MSKCC, SSO 2002
Incidence of Positive Margins

\[ \propto \text{Tumor Depth} \]

**PROXIMAL MARGIN**

- \( \leq \) muscularis propria
  - \( N = 125 \)
- \( > \) serosa
  - \( N = 157 \)

**DISTAL MARGIN**

- \( \leq \) muscularis propria
  - \( N = 127 \)
- \( > \) serosa
  - \( N = 154 \)

“Safe” Gross Margin $\propto$ Tumor Depth

Fresh specimen examined by pathologist and gross margin measured.

Margin status – should you check?

Positive Margins and Survival

Stage II & III, 1985-1997

Kim et al, J Gastrointest Surg 1999; 3:24

Overall Survival (%)

Years

n=47

n=572

p<0.001

NEG MARGIN

POS MARGIN
Frozen Section Analysis and Re-Excision of Positive Margins

> 5 pos nodes

- RE-EXC’D
- NOT RE-EXC’D

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<thead>
<tr>
<th>Years</th>
<th>Overall Survival (%)</th>
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<tbody>
<tr>
<td>0</td>
<td>100</td>
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<tr>
<td>1</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
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n=13

\( p=0.25 \)

\( n=17 \)

\( 80\% \) had T3N+ disease

\( \leq 5 \) pos nodes

\( p=0.03 \)

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<th>Years</th>
<th>Overall Survival (%)</th>
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<tr>
<td>0</td>
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<tr>
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</table>

n=9

\( n=13 \)

Kim et al, J Gastrointest Surg 1999; 3:24
Margin management reported by Ontario general surgeons

Helyer, Coburn, O’Brien, Swallow, ASCO 2006
Helyer et al, Gastric Cancer 2007: 10 (4): 205-14
Case Mr. S.H.
Pathology Report

- diffuse type adenocarcinoma
- tumour penetrates serosa
- proximal and distal margins negative
- 3 of 20 nodes positive

What stage and NOW WHAT?
TNM Staging of Gastric Cancer: T Stage

AJCC 2002, 6th edition

T1 Lamina propria, submucosa
T2 Muscularis propria, subserosa
T3 Penetrates serosa
T4 Adjacent structures

AJCC 2010, 7th edition

T1 Lamina propria, submucosa
  T1a Lamina propria
  T1b Submucosa
T2 Muscularis propria
T3 Subserosa (was T2b)
  T4a Perforates serosa (was T3)
  T4b Adjacent structures
TNM Staging of Gastric Cancer: N Stage

**AJCC 2002, 6th edition**

- **N0** no regional nodes involved
- **N1** 1 to 6 nodes
- **N2** 7 to 15 nodes
- **N3** > 15 nodes

**AJCC 2010, 7th edition**

- **N1** 1 to 2 nodes
- **N2** 3 to 6 nodes (*was N1*)
- **N3a** 7 - 15 nodes (*was N2*)
- **N3b** 16 or more (*was N3*)
## TNM Staging of Gastric Cancer

### AJCC 2002, 6th edition

| Stage 1  | A | T1; N0 |
| Stage 1  | B | T1; N1 |
| Stage 1  |   | T2; N0 |
| Stage 2  |   | T1; N2 |
| Stage 2  |   | T2; N1 |
| Stage 2  |   | T3; N0 |
| Stage 3  | A | T2; N2 |
| Stage 3  | B | T3; N1 |
| Stage 3  |   | T4; N0 |
| Stage 3  |   | T3; N2 |
| Stage 4  |   | T4; N1, N2, N3 |
|          |   | T1, T2, T3; N3 |
|          |   | M1 |

### AJCC 2010, 7th edition

| Stage IA | T1 | N0 |
| Stage IB | T2 | N0 |
| Stage IIA| T3 | N0 |
| Stage IIB| T4a| N0 |
| Stage IIIA| T4a| N1 |
| Stages IIIB, IIIC, IV... | T2 | N3 |

AJCC 2002, 6th edition

AJCC 2010, 7th edition
Intergroup-0116 RCT of Postoperative Adjuvant Chemoradiation

Overall Survival

Disease-free Survival

% alive at 5 years

* p<0.001

NEJM 2001 345:725
Extent of LND in Intergroup 0116

D2 recommended in protocol
LND assessed from surgical checklist

Intergroup-0116 RCT of Postoperative Adjuvant Chemoradiation: M & M

- 32% needed change in XRT plan
- 30% couldn't complete Rx
- 34% Grade IV toxicity
- 1% mortality in C-XRT arm
ONE HOT QUESTION OF TODAY:
What is the role of postoperative adjuvant chemoradiation with D2 dissection?

NB: observational study!

# MRC Trial Neoadjuvant Chemotherapy for Gastric (74%), GE (12%), lower E (14%) Cancer

<table>
<thead>
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<th></th>
<th>Periop Chemo</th>
<th>Surgery only</th>
<th>p</th>
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<tbody>
<tr>
<td>n</td>
<td>250</td>
<td>253</td>
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<tr>
<td>explored [%]</td>
<td>92</td>
<td>96</td>
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<tr>
<td>RO resection [%]</td>
<td>79</td>
<td>70</td>
<td>0.03</td>
</tr>
<tr>
<td>op mortality [%]</td>
<td>6</td>
<td>6</td>
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<tr>
<td>morbidity [%]</td>
<td>46</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>post op stay (d, med)</td>
<td>13</td>
<td>13</td>
<td></td>
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<tr>
<td>OS (%, 5 yr)</td>
<td>36</td>
<td>23</td>
<td>0.009</td>
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It's MAGIC!

Median f/u = 48 mos.