Staging of Gastric Cancer

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Disclosures

- None
Disclosures

• Lead, Cancer Care Ontario/Program in Evidence-Based Care Gastric Cancer Guidelines

• Sherif and MaryLou Hanna Chair in Surgical Oncology Research
NCCN Guidelines Version 3.2015
Gastric Cancer

WORKUP
- H&P
- Upper GI endoscopy and biopsy
- Chest/abdomen/pelvic CT with oral and IV contrast
- PET-CT evaluation if no evidence of M1 disease and if clinically indicated
- CBC and comprehensive chemistry profile
- Endoscopic ultrasound (EUS) if no evidence of M1 disease (preferred)
- Endoscopic resection (ER) may contribute to accurate staging of early-stage cancers
- Nutritional assessment and counseling
- Biopsy of metastatic disease as clinically indicated
- HER2-neu testing if metastatic adenocarcinoma is documented/suspected
- Assess Siewert category
- Smoking cessation advice, counseling, and pharmacotherapy
- Screen for family history

CLINICAL STAGE
- Tis or T1a
- Locoregional (M0)
- Stage IV (M1)

ADDITIONAL EVALUATION
- Medically fit
- Non-surgical candidate
- Medically fit, potentially resectable
- Consider laparoscopy (category 2B)
- Non-surgical candidate

Multidisciplinary review preferred

Palliative Management (see GAST-7)

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.

See Principles of Endoscopic Staging and Therapy (GAST-A).
May not be appropriate for T1 patients.
EMR may also be therapeutic for early-stage disease/lesions.
See Principles of Pathologic Review and HER2-neu Testing (GAST-B).
See Principles of Surgery (GAST-C).
Smoking cessation guidelines are available from the U.S. Public Health Service at: http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/update/treating_tobacco_use08.pdf
See Principles of Genetic Risk Assessment for Gastric Cancer (GAST-D). Also see NCCN Guidelines for Colorectal Cancer Screening and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.

See Staging (ST-1) for tumor classification.
Medically able to tolerate major abdominal surgery.
Medically unfit patients or medically fit patients who decline surgery.
Laparoscopy is performed to evaluate for peritoneal spread when considering chemoradiation or surgery. Laparoscopy is not indicated if a palliative resection is planned. Laparoscopy is indicated for clinical stage T1b or higher.
See Principles of Multidisciplinary Team Approach (GAST-E).
NCCN Guidelines Version 3.2015
Gastric Cancer

FINAL STAGE

Non-surgical candidate

Medically fit

Tis or T1a

Tis or T1a

T1b

T2 or higher, Any N

Medically fit, potentially resectable

Laparoscopic findings of Locoregional disease (M0)

Medically fit, unresectable

Laparoscopic findings of metastatic disease (M1)

PRIMARY TREATMENT

ERa

ERa

or Surgeryb

Surgeryc,m

or

Preoperative chemotherapy (category 1)

or Preoperative chemoradiation (category 2B)

Concurrent fluoropyrimidine- or taxane-based chemoradiation (category 1)

or Chemotherapy

Concurrent fluoropyrimidine- or taxane-based chemoradiation (category 1) (Definitive)

or Palliative Management (see GAST-7)

Palliative Management (see GAST-7)

Endoscopic surveillancea

Surgical Outcomes for Patients Who Have Not Received Preoperative Therapy (see GAST-3)

Surgical Outcomes for Patients Who Have Received Preoperative Therapy (see GAST-4)

Post Treatment Assessment/Additional Management (see GAST-5)

Post Treatment Assessment/Additional Management (see GAST-5)

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.

See Principles of Endoscopic Staging and Therapy (GAST-A)

See Principles of Surgery (GAST-C)

See Staging (ST-1) for tumor classification

Medically able to tolerate major abdominal surgery

Medically unfit patients or medically fit patients who decline surgery

Surgery as primary therapy is appropriate for ≥T1b cancer or actively bleeding cancer, or when postoperative therapy is preferred.

See Principles of Systemic Therapy (GAST-F)

See Principles of Radiation Therapy (GAST-G)
All patients should be staged prior to treatment
All patients should be staged prior to treatment

• Why?
All patients should be staged prior to treatment
All patients should be staged prior to treatment
All patients should be staged prior to treatment

– T1N0, <3 cm
  • Consideration of endoscopic removal

– Locally advanced
  • Consideration of downstaging

– M1 disease
  • Consideration of multimodal options
All patients should be staged prior to treatment

- CT scan Chest, Abdo, Pelvis
  - T-stage-72% accuracy
  - N-stage-66% accuracy
  - M-stage-81% accuracy
    - Review of 40 articles (3758 patients)
    - Seevaratnam et al, 2012
All patients should be staged prior to treatment

- **CT scan Chest, Abdo, Pelvis**
  - T-stage-72% accuracy
  - N-stage-66% accuracy
  - M-stage-81% accuracy
    - Review of 40 articles (3758 patients)
    - Seevaratnam et al, 2012

- **Ontario data, 2005-08**
  - 2414 patients with GC at 116 hospitals
  - NPV for local invasion 87%
  - NPV for nodes 43%
  - NPV for M1 53%
    - Kagedan et al, under review
All patients should be staged prior to treatment

- **CT scan Chest, Abdo, Pelvis**
  - T-stage-72% accuracy
  - N-stage-66% accuracy
  - M-stage-81% accuracy
  - Low NPV for M1 disease
- **Diagnostic Laparoscopy for T3/T4, N+, Diffuse**
  - Changes management up to 43% of cases
    - Leake et al, 2012
- **EUS, PET, MRI**
  - In situations where management will change
Laparoscopic Staging

Laparoscopy Rates

- **Ontario**
  - 4.6% of curative resections
  - 52.3% (205 of 392) of the non-therapeutic OR group
    » Coburn, JSO, 2010

- **US**
  - 8% of curative resections
  - 19% of the non-therapeutic OR group
    » Karanicolas, JACS, 2011
Laparoscopic Staging

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  – 4.6% of curative resections
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• US
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  – 19% of the non-therapeutic OR group
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Questions?
The Best Chance for Cure

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Survival and Quality of Life
Survival and Quality of Life

Patients who benefit from intervention
Survival and Quality of Life

Patients who do not survive, regardless of intervention

Patients who benefit from intervention
Survival and Quality of Life

Patients who do not survive, regardless of intervention

Patients who benefit from intervention

Patients who would have survived anyhow
Survival and Quality of Life

Patients who do not survive, regardless of intervention

Patients who benefit from intervention

Patients who would have survived anyhow
All gastric cancer patients should be discussed at an MCC
All gastric cancer patients should be discussed at an MCC
MAGIC vs MacDonald?
Adjuvant Chemo-radiation (MacDonald/0116 Protocol)

- Surgery alone vs. Surgery then 5FU + 45Gy
  - “Curative” surgery
  - Very selective trial enrollment
  - 32% needed change in XRT plan
  - 30% couldn’t complete Rx
  - 1% mortality in C-XRT arm
  - D2 LN dissection was specified in protocol
    - 10% D2
    - 36% D1
    - 54% D0

MacDonald, NEJM, 2001
Neoadjuvant Chemotherapy (MAGIC Protocol)

Surgery Alone (n=250) vs. ECF/Surgery/ECF (n=253)

- Only 41.6% completed all 6 cycles of chemo
- Only 50% had post-op chemo
- Despite lack of completion of therapy- OS and DFS benefits

Progression-Free Survival

Overall Survival

Cunningham, NEJM, 2006
Adjuvant Chemotherapy (Japanese Protocol)

Surgery Alone vs. Surgery + chemotherapy
- 5-FU analog
- May have different responsiveness in Asian populations

Sakuramoto, NEJM, 2007
ARTIST trial-JCO 2012

- XP vs XP and Rads following D2 gastrectomy
  - 458 patients
    - Excluded Stage Ia and Ib (T2aN0), positive margins, M1 on final path, D1 dissection
  - 75% completed XP
  - 82% completed XP/XRT/XP

- “Negative Trial”
ARTIST trial—Was it “Negative”?
ARTIST trial—Was it “Negative”?

Power Calculations

- 448 patients
- 80% power to detect HR 1.450 with 2 sided alpha=0.05
- Final analysis scheduled at 227 events, but performed at 127 events
  - Fewer deaths than expected due to accrual of more patients with stage 1b/2 than expected
ARTIST trial

“Negative”?

- 60% of patients were Stage 1b and 2
- Estimated 8 years of follow-up before planned analysis could occur
- ARTIST-2 trial
  - Node positive patients
So, which is the better treatment?

MacDonald

MAGIC

ARTIST

Figure 1. Overall Survival among All Eligible Patients, According to Treatment-Group Assignment.

The median duration of survival was 27 months in the surgery-only group and 36 months in the chemoradiotherapy group. The difference in overall survival was significant (P=0.005 by a two-sided log-rank test). A total of 160 of the 281 patients in the chemoradiotherapy group and 197 of the 274 patients in the surgery-only group died during the follow-up period.

2011 Guidelines-CCO/PEBC considers them equivalent

Underscores the importance of discussing each case at a multidisciplinary tumor board
D1 vs D2?

To be, or not to be, that is the question:
Whether 'tis Nobler in the mind to suffer
The Slings and Arrows of outrageous Fortune,
Or to take Arms against a Sea of troubles,
And by opposing end them…

William Shakespeare
D2 LND for curative intent resection
D1 for palliative, T1, or comorbidities
Extent of LN dissection

D1 Resection

D2 Resection

D3 Resection

D4 Resection
MRC RCT: D1 vs D2 Dissection  
Lancet 1996

Dutch RCT: D1 vs D2 Dissection  
NEJM 1999

*p<0.04
1990’s D1 vs D2 trials

• Old-school resection
  – Protocol included a distal panc and splenectomy
  – Most of the complications/deaths came from the distal panc/splenectomy

• Low surgeon volumes of resection in both
1990’s D1 vs D2 trials

• Old-school resection
  – Protocol included a distal panc and splenectomy
  – Most of the complications/deaths came from the distal panc/splenectomy

• Low surgeon volumes of resection in both
Morbidity and Mortality for D1 and D2 LN dissection, Deguili et al, BJS 2010

• Italian Gastric Study Group
  – 1994, phase II trial to establish safety of D2 dissection, with pancreas-preservation
    • 20.9% morbidity; 3.1% mortality

• Starting June 1998, 267 patients randomized intraoperatively
  – Spleen only removed if tumour was in the left part of the upper stomach
  – Pancreas only removed if direct invasion suspected
  – No adjuvant or neo-adjuvant therapy
Italian Phase III Trial-D1 vs D2

- 20% of registered patients refused trial due to perception that D2 was associated with better survival
- Several surgeons participating in the Phase II trial would not join the RCT (10 of the original 18 surgeons participated)
Table 3 Short-term outcome

<table>
<thead>
<tr>
<th></th>
<th>D1 gastrectomy</th>
<th>D2 gastrectomy</th>
<th>$P_\chi$</th>
<th>Total</th>
<th>$P_\chi$</th>
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<tbody>
<tr>
<td>Non-surgical complications</td>
<td>10 of 133 (7.5)</td>
<td>16 of 134 (11.9)</td>
<td>0.223</td>
<td>26 of 267 (9.7)</td>
<td></td>
</tr>
<tr>
<td>Surgical complications</td>
<td>9 of 133 (6.8)</td>
<td>10 of 134 (7.5)</td>
<td>0.625</td>
<td>19 of 267 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Total morbidity</td>
<td>16 of 133 (12.0)</td>
<td>24 of 133 (17.9)</td>
<td>0.176</td>
<td>40 of 267 (15.0)</td>
<td></td>
</tr>
<tr>
<td>Total gastrectomy</td>
<td>0 of 35 (17)</td>
<td>6 of 31 (19)</td>
<td>0.186</td>
<td>12 of 66 (18)</td>
<td>0.401</td>
</tr>
<tr>
<td>Distal gastrectomy</td>
<td>10 of 98 (10)</td>
<td>18 of 103 (17.5)</td>
<td>0.137</td>
<td>28 of 201 (13.9)</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>8 of 63 (13)</td>
<td>12 of 57 (21)</td>
<td>0.220</td>
<td>20 of 120 (16.7)</td>
<td>0.569</td>
</tr>
<tr>
<td>N+</td>
<td>8 of 68 (12)</td>
<td>12 of 74 (18)</td>
<td>0.446</td>
<td>20 of 142 (14.1)</td>
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</tr>
<tr>
<td>&lt; 70 years</td>
<td>10 of 68 (11)</td>
<td>15 of 99 (15)</td>
<td>0.447</td>
<td>25 of 167 (13.4)</td>
<td>0.259</td>
</tr>
<tr>
<td>≥ 70 years</td>
<td>0 of 45 (13)</td>
<td>9 of 35 (20)</td>
<td>0.159</td>
<td>15 of 80 (19)</td>
<td></td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>4 of 133 (3.0)</td>
<td>3 of 134 (2.2)</td>
<td>0.722</td>
<td>7 of 267 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Total gastrectomy</td>
<td>3 of 35 (9)</td>
<td>2 of 31 (6)</td>
<td>1.000</td>
<td>5 of 66 (8)</td>
<td>0.011</td>
</tr>
<tr>
<td>Distal gastrectomy</td>
<td>1 of 98 (1)</td>
<td>1 of 103 (1.0)</td>
<td>1.000</td>
<td>2 of 201 (1.6)</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>1 of 83 (2)</td>
<td>1 of 57 (2)</td>
<td>1.000</td>
<td>2 of 120 (1.7)</td>
<td>0.459</td>
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<tr>
<td>N+</td>
<td>3 of 68 (4)</td>
<td>2 of 74 (3)</td>
<td>0.670</td>
<td>5 of 142 (3.5)</td>
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</tr>
<tr>
<td>&lt; 70 years</td>
<td>2 of 68 (2)</td>
<td>2 of 99 (2)</td>
<td>1.000</td>
<td>4 of 187 (2.1)</td>
<td>0.431</td>
</tr>
<tr>
<td>≥ 70 years</td>
<td>2 of 45 (4)</td>
<td>1 of 35 (3)</td>
<td>1.000</td>
<td>3 of 80 (4)</td>
<td></td>
</tr>
</tbody>
</table>

Values in parentheses are percentages. *Three and +two patients had both surgical and non-surgical complications. †D1 versus D2 ($\chi^2$ test except where indicated). $\|$D1 versus other variable in total group ($\chi^2$ test except where indicated). §Fisher's exact test.
Degiuli et al, BJS, 2014

• 267 patients randomized intra-operatively

• Overall survival
  – 66.5 % vs 64.2% (p=0.70)
Degiuli et al, BJS, 2014

• 267 patients randomized intra-operatively

• Overall survival
  – 66.5 % vs 64.2% (p=0.70)

• Is this a ‘negative’ trial, or simply underpowered?

• Or, have we asked the wrong question?
Degiuli et al, BJS, 2014

- 267 patients randomized intraoperatively
- Overall survival
  - 66.5 % vs 64.2% (p=0.70)
- Disease-specific survivals
  - T1 cancers
    - 98.0% vs 82.9% (p=0.01)
  - T2+ cancers
    - 38.4% vs 59.5% (p=0.055)
Meta-analysis of D1 vs D2 by stage, El-Sedfy et al, ASO 2014

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>D2 Events</th>
<th>D1 Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch Trial: Bonekamp'99</td>
<td>156</td>
<td>151</td>
<td>307</td>
<td>68.5</td>
<td>1.09 (0.81, 1.46)</td>
<td>1999</td>
</tr>
<tr>
<td>MRC Trial: Caughey'99</td>
<td>66</td>
<td>40</td>
<td>106</td>
<td>37.4</td>
<td>0.91 (0.60, 1.38)</td>
<td>1999</td>
</tr>
<tr>
<td>Taiwan Trial: Wu'06</td>
<td>64</td>
<td>111</td>
<td>175</td>
<td>42.8</td>
<td>1.59 (1.11, 2.23)</td>
<td>2004</td>
</tr>
<tr>
<td>ICGC R01: Deguill14</td>
<td>29</td>
<td>134</td>
<td>163</td>
<td>46.2</td>
<td>0.49 (0.15, 1.46)</td>
<td>2014</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>776</strong></td>
<td><strong>823</strong></td>
<td><strong>1,600.00%</strong></td>
<td><strong>463.60</strong></td>
<td><strong>1.11 (0.84, 1.47)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>365</strong></td>
<td><strong>369</strong></td>
<td>****</td>
<td>****</td>
<td><strong>Heterogeneity: Tau^2 = 0.04; Chi^2 = 5.44, df = 1 (P = 0.14); I^2 = 45%</strong></td>
<td><strong>Test for overall effect: Z = 0.71 (P = 0.47)</strong></td>
</tr>
</tbody>
</table>

(a)

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<td>Dutch Trial: Bonekamp'99</td>
<td>65</td>
<td>85</td>
<td>150</td>
<td>47.5</td>
<td>1.65 (0.53, 2.08)</td>
<td>1999</td>
</tr>
<tr>
<td>MRC Trial: Caughey'99</td>
<td>27</td>
<td>40</td>
<td>67</td>
<td>36.5</td>
<td>0.62 (0.24, 1.59)</td>
<td>1999</td>
</tr>
<tr>
<td>ICGC R01: Deguill14</td>
<td>32</td>
<td>59</td>
<td>91</td>
<td>46.5</td>
<td>0.10 (0.01, 0.83)</td>
<td>2014</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>164</strong></td>
<td><strong>195</strong></td>
<td><strong>360.00%</strong></td>
<td><strong>112.0</strong></td>
<td><strong>0.60 (0.23, 1.57)</strong></td>
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</tbody>
</table>

(b)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>D2 Events</th>
<th>D1 Events</th>
<th>Total</th>
<th>Weight</th>
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<th>Year</th>
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</thead>
<tbody>
<tr>
<td>Dutch Trial: Bonekamp'99</td>
<td>67</td>
<td>152</td>
<td>219</td>
<td>52.7</td>
<td>0.97 (0.61, 1.50)</td>
<td>1999</td>
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<tr>
<td>MRC Trial: Caughey'99</td>
<td>22</td>
<td>69</td>
<td>91</td>
<td>34.5</td>
<td>0.76 (0.32, 1.83)</td>
<td>1999</td>
</tr>
<tr>
<td>ICGC R01: Deguill14</td>
<td>43</td>
<td>15</td>
<td>58</td>
<td>24.2</td>
<td>1.99 (0.82, 4.70)</td>
<td>2014</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>276</strong></td>
<td><strong>286</strong></td>
<td><strong>562.00%</strong></td>
<td><strong>124.2</strong></td>
<td><strong>1.65 (0.67, 4.64)</strong></td>
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</tbody>
</table>

(c)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>D2 Events</th>
<th>D1 Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
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<tbody>
<tr>
<td>Dutch Trial: Bonekamp'99</td>
<td>15</td>
<td>12</td>
<td>27</td>
<td>43.1</td>
<td>1.48 (0.69, 1.77)</td>
<td>1999</td>
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<tr>
<td>MRC Trial: Caughey'99</td>
<td>15</td>
<td>36</td>
<td>51</td>
<td>30.1</td>
<td>1.76 (0.72, 4.28)</td>
<td>1999</td>
</tr>
<tr>
<td>ICGC R01: Deguill14</td>
<td>15</td>
<td>77</td>
<td>92</td>
<td>39.0</td>
<td>1.76 (0.72, 4.28)</td>
<td>2014</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>265</strong></td>
<td><strong>216</strong></td>
<td><strong>480.00%</strong></td>
<td><strong>121.5</strong></td>
<td><strong>1.64 (0.69, 2.67)</strong></td>
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</tr>
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</table>

(d)

<table>
<thead>
<tr>
<th>D1</th>
<th>D2</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td></td>
</tr>
</tbody>
</table>

Sunnybrook
HEALTH SCIENCES CENTRE
when it matters
MOST
Meta-analysis of D1 vs D2 by stage, El-Sedfy et al, ASO 2014

Node negative

Node positive

(a)

(b)
TME?
TME?
Total Mesogastric Excision
TME?
Total Mesogastriac Excision
D2 LND for curative intent resection
D1 for palliative, T1, or comorbidities

Deaths due to Gastric Cancer, 15-yr Survival of Dutch Trial, Songun, Lancet Oncology 2010

All Stages T2-4, N+ only

Italian RCT, Degiuli, BJS 2014

Figure: Cumulative risk of death due to gastric cancer and due to other causes in patients treated with curative intent (n=711)
D1: standardised limited lymphadenectomy; D2: standardised extended lymphadenectomy.
Surgery should aim at achieving an R0 margin
Surgery should aim at achieving an R0 margin.
Surgery should aim at achieving an R0 margin

- 2005-08 Ontario
  - 2414 GC cases
  - 1476 operations
  - 904 resections
  - 691 ‘curative’ resections
  - 610 full path data
  - 171 positive margins (28%)
  - Unpublished
Surgery should aim at achieving an R0 margin

• Caveat
  Biology is King, Patient selection is Queen

• Extended resections are unlikely to benefit patients with >5 LN positive
Laparoscopic Gastrectomy

- Meta-analysis of 6 RCT
- 629 patients with EGC
  - Patients with ADVANCED CA were EXCLUDED from these trials
- Less post-operative early morbidity
  \[ RR = 0.61, \ p = 0.01 \]
- Longer OR time
  +86 minutes
- Less blood loss
  -108 cc
- Decreased LN harvest
  -4.88 LN
- Earlier Oral intake
  -0.48 day
- Shorter hospital stay
  -2.03 days
- Similar mortality \( (p=0.32) \)
  - Chen, SLEPT 2009
Another look at the Laparoscopic RCT’s…

- Oncologic outcomes have not been determined

<table>
<thead>
<tr>
<th>Author</th>
<th>N=</th>
<th>Stage</th>
<th>Cancer Location</th>
<th>Number of Institutions</th>
<th>Surgeon volume</th>
<th>Survival Measured?</th>
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<tbody>
<tr>
<td>Kitano</td>
<td>14/14</td>
<td>EGC</td>
<td>Distal</td>
<td>1</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Hayashi</td>
<td>14/14</td>
<td>EGC</td>
<td>Distal</td>
<td>1</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Lee</td>
<td>24/23</td>
<td>EGC</td>
<td>Distal</td>
<td>1</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Kim, YW</td>
<td>82/82</td>
<td>EGC</td>
<td>Distal</td>
<td>1</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Kim, HH</td>
<td>179/163</td>
<td>EGC</td>
<td>Distal</td>
<td>10</td>
<td>NR</td>
<td>No</td>
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<tr>
<td>Huscher</td>
<td>30/29</td>
<td>EGC/AGC</td>
<td>Distal</td>
<td>1</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Lee</td>
<td>24/23</td>
<td>EGC</td>
<td>Distal</td>
<td>1</td>
<td>NR</td>
<td>No</td>
</tr>
</tbody>
</table>
KLASS Trials

• KLASS-1 (Ann Surg 2015)
  – 1416 patients with STAGE I GC
  – Randomized Lap vs Open
    • Fewer complications 13% vs 20% open
    • Mostly related to decrease in wound complications
    • Similar leak and operative mortality
      – 0.6% vs 0.3% (open)
KLASS Trials

• KLASS-2
  – Randomized non-inferiority trial
  – cT2-cT4a
  – NO evidence of LN metastasis
  – Subtotal gastrectomy
  – Enrolment-1050 patients
KLASS Trials

• KLASS-3
  – T1N0, T1N1, T2N0
  – Upper lesions/Total gastrectomy
  – Phase II
  – 164 patients enrolled Oct 2012-14
Future ways to improve survival?
Future ways to improve survival?

- **Bursectomy of Lesser Sac**
  - Underpowered; Trial closed prematurely due to introduction of S-1 adj chemo

**JCOG 1001**
- T3/T4 cancers
- 1000 patients
- June 2010-2014

Fujita, Gastric Cancer, 2012
JCOG 0110

Adenoca. in upper 1/3 stomach
T2/T3/T4, N0/N1/N2, Not greater curvature,
Curative op, Lavage cytology (-)

Intra-op. Randomization

Group A (Splenectomy)
Total gastrectomy, D2

Group B (Spleen preserved)
Total gastrectomy, D2

Observation
(Adjuvant with S-1 for pStage II/III)

Slides Courtesy of T Sano
Relapse-free Survival: All 505 cases

HR 0.87 95%CI (0.65-1.17)

Years after randomization

Slides Courtesy of T Sano
Overall Survival

Surgical T

**T2 (MP/SS)**
(N=276)

- **Spleen-preservation**
- **Splenectomy**

**T3-4 (SE/SI)**
(N=229)

- **Spleen-preservation**
- **Splenectomy**

Slides Courtesy of T Sano
Overall Survival
Primary tumor location

“U” (N=427)

“M” or “L” (N=78)

Spleen-preservation

Splenectomy

Slides Courtesy of T Sano
Overall Survival: Post-op Complications

**Infectious complications (N=71)**

<table>
<thead>
<tr>
<th>Classification</th>
<th>N (Number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenectomy</td>
<td>254</td>
</tr>
<tr>
<td>Spleen-preservation</td>
<td>248</td>
</tr>
</tbody>
</table>

**Complication (+)**

**Complication (-)**

Slides Courtesy of T Sano
Recommendations

• All patients should be presented at MCC
• CT Chest, Abdo, Pelvis for staging
• Laparoscopy for more advanced cancers
• D2 LND for >T1N0, curative intent
  – D1 for EGCT1, co-morbidity, palliation
• Negative margins
  – Extended resections useful only if <5 LN
• Don’t perform splenectomy unless direct invasion
Questions?
Management of Stage IV Disease

Natalie Coburn, MD, MPH
Hepato-biliary and Surgical Oncology
Sherif and MaryLou Hanna Chair in Surgical Oncology Research
Associate Professor-
University of Toronto
In M1 cases, non-surgical management is preferred for patients without symptoms.
In M1 cases, non-surgical management is preferred for patients without symptoms

- Systematic Review
- 1939 abstracts
- 59 articles studying outcomes in Stage IV patients
- Only 3 were prospective
- Highly variable definitions
  - “Unresectable” “advanced” “incurable” “palliative”
- Up to 45% morbidity and 21% mortality
- Large patient selection bias
In M1 cases, non-surgical management is preferred for patients without symptoms

- **MSKCC experience**
  - 1993-2002
  - 165 patients M1 + at DL
  - 97 followed at MSKCC
  - Median interval from DL to procedure: 4 m (range 1-35 m)
  - Median survival from first intervention to death: 3 m (range 1-28 m)

Sarela, Ann Surg 2009
In M1 cases, non-surgical management is preferred for patients without symptoms.

**Conclusion**

- “non-curative resection is unlikely to alter disease progression, and pre-emptive surgical palliation is unnecessary”
PEBC/CCO: In M1 cases, non-surgical management is preferred for patients without symptoms

- **REGATTA TRIAL-ASCO 2015**
  - RCT
  - 330 patients with ‘limited’ metastatic disease
  - Chemo vs Surgery->chemo
    - S-1+Cisplatin
In M1 cases, non-surgical management is preferred for patients without major symptoms

• **REGATTA TRIAL-ASCO 2015**
  – RCT
  – 330 patients with ‘limited’ metastatic disease
  – Chemo vs Surgery->chemo
    • S-1+Cisplatin
  – Trial stopped by DSMB at first interim analysis
Overall Survival (interim analysis)

All randomized patients (n=164)
One-sided $P = 0.66$ by stratified log-rank test
HR for Gastrectomy+chemo, 1.08; 95%CI [0.74, 1.58]

Bayesian predictive probability that the gastrectomy arm will “win” in the final analysis, 13.2%
Early postoperative complications

<table>
<thead>
<tr>
<th>%Grade 2-4</th>
<th>Gastrectomy arm (n=87)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection with normal ANC: wound</td>
<td>5.7%</td>
</tr>
<tr>
<td>Obstruction: GI-small bowel</td>
<td>2.3%</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1.1%</td>
</tr>
<tr>
<td>Ileus</td>
<td>1.1%</td>
</tr>
<tr>
<td>Fever</td>
<td>3.4%</td>
</tr>
<tr>
<td>OVERALL</td>
<td>16.1%</td>
</tr>
</tbody>
</table>

Late adverse reactions/morbidities

<table>
<thead>
<tr>
<th></th>
<th>Chemo (n=73)</th>
<th>Gastrectomy (n=87)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2/3/4</td>
<td>6.8%</td>
<td>16.1%</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>0%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* All operated pts
Subgroup analyses by location of primary tumor

HR for Gastrectomy arm*, 2.23, 95%CI (1.14-4.37)

HR for Gastrectomy arm*, 0.95, (0.57-1.59)

HR for Gastrectomy arm*, 0.63 (0.33-1.21)
### Number of Implemented Cycles of Chemotherapy

<table>
<thead>
<tr>
<th>Tumor Location</th>
<th>Median cycles [IQR] Chemotherapy</th>
<th>Median cycles [IQR] Gastrectomy+Cx</th>
</tr>
</thead>
<tbody>
<tr>
<td>U</td>
<td>6 [4-8] (n=16)</td>
<td>3 [2-5] (n=30)</td>
</tr>
<tr>
<td>M</td>
<td>6 [4.5-8] (n=49)</td>
<td>5 [3.5-8] (n=30)</td>
</tr>
<tr>
<td>L</td>
<td>4 [2-6] (n=21)</td>
<td>6 [3-8] (n=29)</td>
</tr>
<tr>
<td>Total</td>
<td>6 [3-8] (n=74)</td>
<td>5 [3-7] (n=76)</td>
</tr>
</tbody>
</table>
Summary

1. Gastrectomy failed to improve overall survival in AGC with single incurable factor

2. Gastrectomy was safely performed with no mortality but associated with an increase of late AEs and morbidities.

3. Gastrectomy was associated with more frequent and severe chemotherapy related AEs, especially for U lesion or total gastrectomy.

4. In the subgroup analysis, patients with distal gastric cancer had an OS benefit. A second study only in patients with distal gastric cancer may be considered
Questions?