Adjuvant Therapy in Gastric Cancer: The Evolving U.S. Approach

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New AJCC Staging: Survival in over 13,000 pts with gastric cancer, SEER database

McGhan J Gastro Surg 16: 53; 2012
Adjuvant Therapy in Gastric Cancer Improves OS

- **Post op RT + chemo (U.S.)**
  - 5FU-LV + RT, INT 116:
    - 10% 5 yr OS, HR 0.65
- **Pre and post op chemo (U.K.) without RT**
  - ECF, MAGIC:
    - 13% 5 yr OS, HR 0.75
- **Post op chemo (Asia): 2 trials, 2000 pts, D2 resection, no RT**
  - S-1 (Oral 5-FU), ACTS-GC:
    - 10% 5 yr OS, HR 0.67 (2011 update)
  - Post op Cape-Oxali, CLASSIC Trial:
    - 9% 5 yr OS, HR 0.66

- **Survival improvements with all approaches similar, modest**

U.S. INT 116: Gastric Cancer and post op 5-FU + RT

- Biggest impact in decreasing local recurrence
- Surgical resection: 54% had less than a D1 resection
  - Only 10% had a D2 resection
- Standard of care for gastric cancer in <D1 resection
5-FU/LV: 5-FU 425 mg/m² d1-5, LV 20 mg/m² d1-5

RT: 45 Gy (1.8 Gy X 25 fractions) with 5-FU 200 mg/m²/d CI

ECF (pre-RT): Epirubicin 50 mg/m² d1, Cisplatin 60 mg/m² d1, & 5-FU 200 mg/m²/d CI d1-21

ECF (post-RT): Epirubicin 40 mg/m² d1, Cisplatin 50 mg/m² d1, & 5-FU 200 mg/m²/d CI d1-21
CALGB 80101
Overall Survival by Treatment Arm

P, log rank = 0.80
Locally Advanced Gastric Cancer

Key Eligibility
- T3-4 or N+, non-metastatic
- FDG-PET avid
- Surgical candidate

Pre-op chemo Cycle #1 → FDG-PET

FDG PET Responder
- Cycle #2
- Cycle #3
- Cycle #4
- Cycle #5
- SURGERY
- Cycle #6
- FDG PET Non Responder
- Cycle #1
- Cycle #2
- SURGERY
- Cycle #3
- Cycle #4
- Cycle #5
- SURGERY
- Cycle #6
- Post-op Chemo/RT

Standard Chemo
EOX/ EOF

Salvage Chemo
Docetaxel/ Irinotecan
### Gastric Cancer: Local Failure After Surgery and Adjuvant Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>D2 Resection Rate</th>
<th>Surgery Alone Rate</th>
<th>Surgery + Chemotherapy Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacDonald INT 116, 5-FU + XRT</td>
<td>10%</td>
<td>29%</td>
<td>19%</td>
</tr>
<tr>
<td>Cunningham MAGIC</td>
<td>40-42%</td>
<td>21%</td>
<td>14%</td>
</tr>
<tr>
<td>Sakuramoto S-1</td>
<td>100%</td>
<td>3.2%</td>
<td>2.1%</td>
</tr>
<tr>
<td>CLASSIC XELOX</td>
<td>100%</td>
<td>10%</td>
<td>5%</td>
</tr>
</tbody>
</table>
Gastric Cancer: Recurrence Pattern
Adjuvant Therapy: Distant Failure

- **INT 116:**
  - Peritoneal: S: 72%, FU RT: 65% • 6%
  - Distant: S: 18%, FU + XRT: 33%: • -15%

- **MAGIC:**
  - S: 37%, ECF: 24% • 13%

- **S-1:**
  - Peritoneal: S: 19% S-1: 15% • 4%
  - Distant: S: 13% S-1: 11% • 2%

- **CLASSIC**
  - Peritoneal: S: 12%, XELOX: 10% • 2%
  - Distant: S: 20%, XELOX: 12% • 8%
Does RT Add to D2 Resection?
Adjuvant ChemoRadiotherapy Trial In Stomach Tumors (ARTIST)

- D2 resected gastric adenocarcinoma
- pStage Ib to IV(M0)
- Stratified by (1) stage, (2) type of surgery (STG ν TG)

Primary endpoint: 3-y DFS

XP arm (6 cycles of XP)
- X: capecitabine 2,000 mg/m²/d D1-D14
- P: cisplatin 60 mg/m² D1
- XRT: capecitabine 1,650 mg/m²/d daily concurrently with RT 45 Gy for 5 weeks

XPRT arm (2XP/XRT/2XP)
- X: capecitabine 2,000 mg/m²/d D1-D14
- P: cisplatin 60 mg/m² D1
- XRT: capecitabine 1,650 mg/m²/d daily concurrently with RT 45 Gy for 5 weeks

1 Lee J, J Clin Oncol 2011
Disease-Free Survival

- 141 recurrence events occurred
- Hazard ratio 0.740 (95% CI, 0.520-1.050)
- \( P = 0.9222 \)

Overall Survival

- 130 death events occurred
- Hazard ratio 1.130 (95% CI, 0.775-1.647)
- $P=0.5272$

- Pt at risk: XP 22, RT 0
- XPRT: 23, 220, 20, 184, 178, 171
- XP: 8, 217, 20, 191, 179, 166

Approximately 1.130 death events occurred within the study period.
Disease-Free Survival: by Lymph Node Status

- In 396 patients with LN+ disease, 3-y DFS was 76% vs 72% (P=0.04) \(^1\)

Disease-Free Survival: by Lauren Classification

- In 163 patients with intestinal type, 3-y DFS was 94% vs 83% (P=0.01)¹
What is the role of RT?

● **Gastric Cancer: Extent of Surgery Dictates Need for RT**
  - Higher rates of local recurrence with less than D1-D2
    - Post op RT + 5-FU/LV in less than a D1 resection
  - ARTIST, D2 resection: no clear benefit for post op RT added to adjuvant chemo

● **Esophageal and GEJ Cancer**
  - Preop chemo alone mixed results
  - ECX x 4 no better than 2 cycles of CF (OEO5), R0 60-66%
  - Preop chemo + RT trends superior
    - Enhanced R0 resection, reduced local and distant recurrence
European / Asian Gastric Adjuvant Trials: Is RT required pre or post op?

- **CRITICS Trial (NL):** + / - Postop RT
  - Preop ECX
  - D1 resection
  - Post op chemo + / - RT

- **TROG (Australia):** Preop chemo + / - RT
  - Esophageal and gastric

- **Korea ARTIST 2:** Post op Chemo + / - RT in Node +
Adjuvant Therapy in Gastric Cancer: the U.S. View

- **Less than a D1-D2 resection**
  - Chemo + RT
  - ECF no better post op than 5-FU + LV

- **D1-2 resection**
  - Periop ECF
  - Post op S-1, XELOX

- **RT in D2 resection?**
  - No improvement in DFS or OS: ARTIST
Adjuvant Therapy Improves Survival in GEJ and Gastric Cancer

- Survival impact of current pre and post op therapy is marginal

- In the West: 60-70% die of disease
Future Directions

- Further large trials studying chemotherapy permutations in Esophagogastric Cancer may NOT be warranted

- Developing novel targeted agents
  - VEGF: U.K. MAGIC B Trial +/- Bevacizumab
  - HER2 directed phase II / III preop studies ongoing
  - Immunotherapy

- Validated biomarkers to guide therapy selection
  - PET scan to direct induction chemotherapy
    - Alliance Esophageal 80803 trial completed
    - Alliance gastric trial to open
Comprehensive Molecular Characterization

PD-L1 and PD-L2 Expression Are Elevated in Gastric Cancer
