Chemoradiotherapy in Resectable Gastric Cancer

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Allan Blair Cancer Centre
Saskatchewan Cancer Agency

Overview

- Natural history of resected gastric cancer
- Trials of (chemo)radiotherapy in perioperative management
  - INT0116; ARTIST
- Current active trials
  - TOPGEAR; ARTIST II; CRITICS
- Toxicity, volumes, and technique
Outcome with Surgery Alone

- Surgery required for cure but outcomes with surgery alone can be poor
- Dependent on many prognostic factors
  - T-stage, N+, type of surgery, margins, histology
  - Nomograms
- From clinical trial data (Stage IB to IV M0)
  - 3 yr OS 41%
  - 5 yr OS 23%
- To improve on poor outcomes:
  - What drives poor outcome? What are patterns of relapse?

Sites of Relapse

- Local/Regional
  - Anastomosis
  - Gastric remnant
  - Nodal
- Regional/Distant
  - Peritoneal
  - Hepatic
- Distant
  - Hematogenous metastasis outside of peritoneal cavity
Gunderson and Sosin, IJ RO BP 1982

- Re-operation series
- 24% patients had LRF as only site, 72% as component of failure

Landry et al, IJ RO BP 1990

- MGH
- 88/130 patients recurred
- LRF as component of failure 38%
- LRF as sole failure 16%
- T3/4 >35% LRR, >50% DM
Yoo et al, BJ S 2000

Table 1 Patterns of recurrence in gastric cancer

<table>
<thead>
<tr>
<th>Patterns of Recurrence</th>
<th>Alone</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loco-regional</td>
<td>96 (19.3)</td>
<td>165 (20.5)</td>
</tr>
<tr>
<td>Anastomosis or stump</td>
<td>84 (10.6)</td>
<td>80 (15.7)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>34 (6.7)</td>
<td>69 (13.4)</td>
</tr>
<tr>
<td>Adjacent organ</td>
<td>10 (2.2)</td>
<td>13 (2.8)</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>172 (33.9)</td>
<td>223 (43.9)</td>
</tr>
<tr>
<td>Hematogenous</td>
<td>133 (26.2)</td>
<td>174 (34.3)</td>
</tr>
<tr>
<td>Liver</td>
<td>75 (14.8)</td>
<td>96 (18.9)</td>
</tr>
<tr>
<td>Lung</td>
<td>26 (5.1)</td>
<td>35 (6.9)</td>
</tr>
<tr>
<td>Bone</td>
<td>26 (5.1)</td>
<td>34 (6.7)</td>
</tr>
<tr>
<td>Brain</td>
<td>5 (1.0)</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Testis</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Extra-abdominal nodes*</td>
<td>22 (4.3)</td>
<td>24 (4.7)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages. *Supraclavicular, inguinal or axillary lymph nodes

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910 PART D | Gastrointestinal Tumors

TABLE 45-4 Gastric Cancer: Patterns of Loco-regional Relapse in Clinical, Reoperation, and Autopsy Series

<table>
<thead>
<tr>
<th>Failure Area</th>
<th>Massachusetts General Hospital (Clinical)</th>
<th>University of Minnesota (Reoperation)</th>
<th>McNeer et al. (Autopsy)</th>
<th>Thomson and Robles (Autopsy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 130)</td>
<td>(n = 105)</td>
<td>(n = 92)</td>
<td>(n = 38)</td>
</tr>
<tr>
<td>Gastric bed</td>
<td>27 (21)</td>
<td>66 (53)</td>
<td>49 (82)</td>
<td>19 (59)</td>
</tr>
<tr>
<td>Anastomosis or stump</td>
<td>33 (25)</td>
<td>26 (27)</td>
<td>55 (83)</td>
<td>18 (54)</td>
</tr>
<tr>
<td>Abdominal or stab wound</td>
<td>—</td>
<td>0 (0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Lymph node(s)</td>
<td>11 (9)</td>
<td>45 (38)</td>
<td>48 (52)</td>
<td>—</td>
</tr>
</tbody>
</table>
**Perioperative Therapy**

- Improve rates of LRC, DM, DFS, OS
- Not a strategy for unresectable disease
- Strategies include chemotherapy pre/peri/postop, or chemoradiotherapy
- Little data regarding RT alone (high rates of DM)

**Phase 3 RCT Postoperative CRT**

- INT0116 “Macdonald” trial, updated
- ARTIST (Korean), updated
CHEMORADIOThERAPY AFTER SURGERY COMPARED WITH SURGERY ALONE FOR ADENOCARCINOMA OF THE STOMACH OR GASTROESOPHAGEAL JUNCTION

JOHN S. MACDONALD, M.D., STEPHEN R. SMALLEY, M.D., JACQUELINE BENEDETTI, PH.D., SCOTT A. HUNDAHL, M.D., NORMAN C. ESTES, M.D., GRANT N. STEMMERMANN, M.D., DANIEL G. HALLER, M.D., JAFFER A. AJANI, M.D., LEONARD L. GUNDERSON, M.D., J. MILBURN JESSUP, M.D., AND JAMES A. MARTENSON, M.D.

Study Design

- 556 patients between 1991 and 1998, stage IB to IV M0 (AJCC 1988) gastric or GEJ adenocarcinoma, after curative intent R0 resection
- Randomized to surgery alone or surgery followed by adjuvant CRT
- Randomized postop, so no specific surgical specifications, surgeon described extent of LND
- CRT consisted of 5FU/Leukovorin day 1-5, 5FU/Leukovorin with 45GYy/25# days 1-4 and 23-25 of RT, 2 further cycles
Results

- 80% node positive
- 64% completed treatment as planned
- 273 patients had grade 3+ toxicity, mainly leukopenia and GI (pre-5HT3 receptor antagonists); 3 deaths
- Median survival 36 vs 27 months; relapse-free survival 30 vs 19 months
- 3 year survival 50% vs 41%, HR for death in surgery group 1.35; 3 year relapse-free survival 48% vs 31%, HR for relapse 1.50

Sites of First Relapse

<table>
<thead>
<tr>
<th>Site</th>
<th>Patients with Relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery-only</td>
</tr>
<tr>
<td>(n=177)</td>
<td>(n=120)</td>
</tr>
<tr>
<td>Local</td>
<td>51 (29)</td>
</tr>
<tr>
<td>Regional</td>
<td>132 (72)</td>
</tr>
<tr>
<td>Distant</td>
<td>32 (18)</td>
</tr>
</tbody>
</table>

*Because patients could have relapses at multiple sites, the total numbers of relapses are greater than the numbers of patients in each group who had relapses.
Patterns of Failure

- Reduction in failure in CRT arm is in local and regional disease
- Rates of DM same
- Better local control may drive improved survival

<table>
<thead>
<tr>
<th>Release Status</th>
<th>Redochemo</th>
<th>Control surgery</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No relapse</td>
<td>136</td>
<td>46</td>
<td>182</td>
</tr>
<tr>
<td>Relapse*</td>
<td>147</td>
<td>52</td>
<td>199</td>
</tr>
</tbody>
</table>

*Smaller site of relapse: % of those randomly assigned

- Local
- Regional
- Distant
- Unknown site

- Total

Subgroup Analysis

- Interpret with caution!
- Sex, race, T stage, N stage, D level, location (proximal vs other), Maruyama index, histology (intestinal vs diffuse)
- No difference in benefit among subgroups
- D2 and MI < 5 were only small part of sample
- Only exception is histology, diffuse histology had less/no benefit to CRT
Criticism, aka Surgical Debate

- 54% of patients had a D0 nodal dissection, 36% D1, 10% D2
- Benefit of CRT may be present only because of suboptimal surgery
- Would this benefit stand up in patients who received D2 dissections? (Or at least D1?)
- Can (C)RT compensate for inadequate surgery? OS benefit similar to that seen in Dutch D1/D2 study

In Parallel....Macdonald vs MAGIC

- Perioperative chemotherapy
- Postoperative chemotherapy
- Does RT add to chemotherapy?
Phase III Trial Comparing Capecitabine Plus Cisplatin Versus Capecitabine Plus Cisplatin With Concurrent Capecitabine Radiotherapy in Completely Resected Gastric Cancer With D2 Lymph Node Dissection: The ARTIST Trial

Jeeyun Lee, Do Hoon Lim, Sung Kim, Se Hoon Park, Joon Oh Park, Young Suk Park, Ho Yeong Lim, Min Gew Choi, Tae Sung Sohn, Jae Hyung Noh, Jae Moon Bae, Yong Chan Ahn, Insuk Sohn, Sin Ho Jung, Cheol Keun Park, Kyoung-Mee Kim, and Won Ki Kang

**Study Design**

- Phase 3 RCT, comparison of adjuvant chemotherapy (XP: capecitabine and cisplatin x 6) vs adjuvant CRT (XPx2, CRT, XPx2)
- All patients had curative intent, en bloc resection, R0 margins, D2 lymphadenectomy
- 458 patients accrued between 2004-2008 in Korea
- Primary endpoint DFS
Results

- Treatment completed in 75% of XP vs 82% of XP/CRT/XP
- Median follow up 53 months
- 3 year DFS 78% in CRT vs 74% in CT group (p=0.086)
- Subgroup analysis of 396 N+ patients (86%)
  - 3 year DFS 78% CRT vs 72% CT (p=0.0365)
- Patterns of recurrence
  - LR 4.8% vs 8.3% NS, DM 20.4% vs 24.6% NS

7 Year Update - OS

Fig 3. Overall survival. XP, carboplatin plus cisplatin; XPRT, concurrent chemoradiotherapy with cetuximab plus cisplatin.
7 Year Update - DFS

Fig 2. Disease-free survival. XP: cyclophosphamide plus cisplatin; XRT: concurrent chemoradiotherapy with cyclophosphamide plus cisplatin.

Subgroup Analysis
ARTIST-II

- Active
- N+ after D2 dissection, 3 arms
  - ARTIST-type CRT
  - S1
  - S1 plus oxaliplatin

TO PG EAR

Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma

- Australasian Gastro-intestinal Trials Group
- TROG, EORTC, NCIC-CTG
TOPGÉAR

- RCT of IB to IIIC (AJCC 7th) gastric or Siewert II/III GEJ
- ECF( or X) x 3, gastric resection, ECF( or X) x 3
- ECF( or X) x 2, CRT( C or X, 45/25), gastric resection, ECF( or X) x 3
- Minimum operation D1 dissection

- Primary endpoint OS
- Accrual expected until 2020
- More advanced RT planning techniques allowed

CRITICS

**Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS)**

Johan L Dikken, Johanna W van Sandick, HA Maurits Swellengrebel, Pehr A Lind, Hein Putter, Edwin PM Jansen, Henk Boot, Nicole CT van Grieken, Cornélius J H van de Velde, Marcel Verheij, Annemieke Cats
CRITICS

- International, phase 3 RCT
- Primary endpoint OS

Goal: Risk Stratification for RT

- Extent of lymph node dissection
- Nodal involvement
- Histology (intestinal type vs diffuse)
  - Different proportions between 0116 and ARTIST

Figure 1 Randomization scheme: R: randomization, ECC: esophagus, clipatin: capetobamine.
Toxicity

- One reason why RT historically had little role in gastric cancer
- Upper abdominal fields traditionally large and given through AP-PA technique, TOXIC!
- INT0116, all RT plans centrally reviewed, AP-PA
  - 35% had minor or major deviations, 2/3 of which were underdosing likely due to concerns about tolerance
- ARTIST AP-PA

Old School
**Volume-Based 3D Conformal RT**

- Volumes are contoured on CT slices
- Beam can come from several angles, modified in several ways to improve dose to tumor while limiting dose to normal tissues
- Need to be confident in the areas choosing to treat, concerns about marginal miss

**PRO Gastric Contouring Atlas**

- Atlases developed to give expert guidance on defining relevant anatomy and ensuring reproducibility among radiotherapy plans
- More relevant in era of 3D planning, in particular highly conformal (IMRT/IGRT/VMAT) planning
Treatment Delivery

- Mainly 3D conformal?
  - Beams are shaped but static

- Intensity Modulated Radiation Therapy (IMRT)
  - Several “beamlets” within each beam allow for greater sculpting of radiation dose

- Volumetric Modulated Arc Therapy (VMAT)
  - Similar to IMRT but delivered in arcs, main advantage is shorter treatment time

- Topgear recently modified protocol to allow VMAT

Summary

- Surgery alone results in poor outcomes in advanced adenocarcinoma of the stomach

- Adjuvant therapies offer improvement in OS

- Adjuvant CRT improves OS but may not be relevant in the context of a D2 dissection

- Choosing an “optimal” strategy requires understanding risk stratification factors, and an MDT environment, and clinical trials

- Newer RT planning techniques reduce toxicity