Radiation Therapy for Gastro-esophageal Cancer

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DISCLOSURES
NONE

Terminology
- Substantial confusion as to biology related to site of origin of tumors in the stomach and esophagus
- Epidemiology of classical esophageal, gastric and GE junction cancers are distinct
- Clinical trials have been designed for gastric or esophageal cancers with variable numbers of patients with GE junction tumors included
Terminology

- Unclear relevance of many published studies to true GE junction tumors
  - Recent gastric trials have generally included primarily classical gastric cancers, with about 20-25% of GE junction cancers
  - Recent esophageal trials from the US have included a majority of patients with GE junction adenocarcinomas
- These trials may be more reflective of appropriate management strategies

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GASTRIC CARCINOMA - MGH

<table>
<thead>
<tr>
<th>Stage</th>
<th>Total Local-Regional Failure</th>
<th>Local-Regional Failure Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B1</td>
<td>9/16 (59%)</td>
<td>1/16 (8%)</td>
</tr>
<tr>
<td>B2</td>
<td>6/12 (66%)</td>
<td>1/12 (8%)</td>
</tr>
<tr>
<td>B3</td>
<td>2/5 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>C1</td>
<td>4/17 (24%)</td>
<td>2/17 (12%)</td>
</tr>
<tr>
<td>C2</td>
<td>10/44 (23%)</td>
<td>10/44 (23%)</td>
</tr>
<tr>
<td>C3</td>
<td>10/32 (31%)</td>
<td>7/32 (22%)</td>
</tr>
</tbody>
</table>

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University of Minnesota
Re-operation Series

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number failed</th>
<th>Local-regional failure</th>
<th>Local-regional failure alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>10/12 (83%)</td>
<td>9/12 (75%)</td>
<td>4/12 (33%)</td>
</tr>
<tr>
<td>C</td>
<td>68/89 (76%)</td>
<td>59/89 (66%)</td>
<td>17/89 (19%)</td>
</tr>
</tbody>
</table>

Gunderson
55% of pts with tumor recurrence had a local recurrence

Gastric Cancer - Sites of Recurrence - MSKCC

Local Regional - 199 patients
- Lymph nodes: 48%
- Anastomosis: 32%
- Gastric bed: 20%

Distant - 188 patients
- Liver: 37%
- Lung: 16%
- Bone: 16%
- Lymph nodes: 14%
- Brain: 6%

Gastric Cardia

- Surgery vs preoperative radiation therapy
- Limited radiation fields
- 5-year survival: 20% vs 30%
- Local failure: 52% vs 39%
- Distant metastases: no difference

Zhang - IJROBP - 1998
SWOG 9008/INT 0116

RESECTED GASTRIC CANCER SCHEMA

RESECTED
STAGE III-IV (MO)
GASTRIC
ADENOCARCINOMA

OBSERVATION

5-FU/LV FULV
5-FU/LV

R A N D O M M

4,500 cGy

Macdonald, Smalley et al

SWOG 9008/INT 0116

BASELINE DISEASE CHARACTERISTICS

OBS(275) RX(281)

T-STAGE

% T1-T2 31% 31%
% T3 61% 62%
% T4 8% 6%

NO. + NODES

% None 16% 14%
% 1-3 41% 42%
% 4+ 43% 43%

LOCATION OF PRIMARY

Antrum 56% 53%
Corpus 25% 24%
Cardia 18% 21%
Multicentric 0.4% 2%
SWOG 9008/INT 0116

Relapse Free Survival by Treatment Arm

Overall Survival by Treatment Arm

Sites of recurrence

SWOG 9008/INT 0116

obs (n=176)  rx (n=112)

<table>
<thead>
<tr>
<th>Sites</th>
<th>obs</th>
<th>rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>local</td>
<td>51</td>
<td>21</td>
</tr>
<tr>
<td>regional</td>
<td>126</td>
<td>76</td>
</tr>
<tr>
<td>distant</td>
<td>32</td>
<td>36</td>
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</tbody>
</table>
MAGIC Trial

- 3 cycles ECF preoperatively
- Surgical resection
- 3 cycles ECF postoperatively

- ECF
  - Epirubicin: 50 mg/m²/d, d1
  - Cisplatin: 60 mg/m²/d, d1
  - 5-FU: 200 mg/m²/d x 21 d

- Approximately 25% of patients with GE junction or esophageal cancer
- No obvious difference in outcome on site of primary

Progression-free and Overall Survival

Patterns of Failure

<table>
<thead>
<tr>
<th></th>
<th>Local Recurrence</th>
<th>Distant metastases</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>20.6%</td>
<td>36.8%</td>
</tr>
<tr>
<td>Peri-operative chemotherapy</td>
<td>14.4%</td>
<td>24.4%</td>
</tr>
</tbody>
</table>

Cunningham, NEJM, 2006
Esophageal Cancer

- Squamous or adeno, no mets
- RT alone- 6400 cGy
- RT + chemo
  - 5-FU 1000 mg/m² x 4 d, d 1-4 x 4 cycles
  - Cis-platin- 75 mg/m², d 1 x 4 cycles
  - RT- 5000 cGy

Herskovic, NEJM, 1992

Patterns of Failure-
Herskovic, NEJM - 1992

<table>
<thead>
<tr>
<th>First Failure</th>
<th>RT Only (%)</th>
<th>RT + CT- randomized (%)</th>
<th>RT + CT- non-randomized (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>11</td>
<td>36</td>
<td>26</td>
</tr>
<tr>
<td>Local Persistence</td>
<td>37</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>Local-Regional Only</td>
<td>18</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Local/Regional/Distant</td>
<td>13</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Total Local Regional</td>
<td>68%</td>
<td>45%</td>
<td>54%</td>
</tr>
</tbody>
</table>
CALGB 9781-
Chemo/RT + Surg vs Surg alone

STAGE I, II, III esophageal cancer

5FU-1000mg/m² x 4 d
Cisplatin- 100 mg/m²
Chemotherapy weeks 1 and 5

Radiation therapy (50.4 Gy)
Concurrent with chemotherapy

Surgery-3-8 wks later

CALGB 9781 OVERALL SURVIVAL

Esophageal Cancer – Meta-analysis

Tri Modality vs Surgery Alone

Sjoquist, Lancet Oncology, 2011
Esophageal Cancer – Meta-analysis
Tri Modality vs Surgery Alone

Phase III Comparison of Preoperative Chemotherapy Compared With Chemoradiotherapy in Patients With Locally Advanced Adenocarcinoma of the Esophagogastric Junction

Preoperative chemoradiotherapy and dose-escalated chemoradiotherapy without surgery

Sjoquist, Lancet Oncology, 2011

Stahl M et al. JCO 2009;27:851-856

PLF + surgery
PLF + RS (15 Gy) + chemotherapy + surgery

3 year survival- 28% vs 48%


5-FU, leucovorin, platinum, etoposide
Overall survival: preoperative chemoradiation and surgery or chemoradiation without surgery

Freedom from locoregional progression: preoperative chemoradiation and surgery or chemoradiation without surgery

Chemoradiation Followed by Surgery Compared With Chemoradiation Alone in Squamous Cancer of the Esophagus: FFCD 9102
Chemoradiation Followed by Surgery Compared With Chemoradiation Alone in Squamous Cancer of the Esophagus: FFCD 9102

Intent to Treat

Per protocol

More palliative procedures without surgery
No difference in QOL assessment

Hong, Seminars in Rad Onc, 2007

FDG PET - treatment planning

- PET very useful to determine the sites of primary disease and nodal spread - staging
- PET should be used cautiously to determine the exact extent of disease
- Can be difficult to determine length of primary tumor in esophagus from imaging studies
Radiation Therapy Technique

- Treat celiac axis nodes if this does not require a large field extension
- Proximal and distal margins on esophageal lesion are arbitrary
  - Generally recommend 3-5 cm
- Treat para-esophageal nodes in the primary field
- Minimize cardiac and pulmonary irradiation
- Keep spinal cord dose to <45 Gy
- Concurrent chemotherapy based on
  - FU
  - Irinotecan
  - Platinum

Radiation Therapy Technique

- Fields should be primarily AP-PA to minimize pulmonary dose
  - IMRT should be used with caution, especially in preoperative setting
- Off cord for a small percentage of dose
  - Laterals
  - Obliques
- Emphasis should be on the likely surgical margins in para-esophageal soft tissue

Radiation Therapy Technique

- 45 Gy/180 cGy/fx to initial field
- 5.4 Gy cone down
- Liver- Mean dose < 25 Gy
  - 60% of liver < 30 Gy
- Heart- Entire heart < 30 Gy
  - 50% of heart < 40 Gy
- Lung- <20% of lung receiving 30 Gy
Radiation Therapy Technique- Problems

- Cervical esophageal cancers
  - IMRT is often useful
  - Difficult to meet constraints with standard fields

- Postoperative radiation therapy (especially transhiatal esophagectomy)
  - Difficult to treat entire field without excessive morbidity
  - Often need to treat highest risk area, which may be the tumor bed, not the anastomosis

- Strongly prefer preoperative RT

GE Junction cancers

- Local control remains a clinical issue in both gastric and esophageal cancer patients
- Radiation therapy, with concurrent chemotherapy, decreases local failure in both gastric and esophageal cancer
- Treatment regimens with radiation therapy improve survival in both gastric and esophageal cancer
- Radiation therapy remains an important component of the management of GE junction carcinomas

GE Junction Cancers

- The value of chemotherapy in gastric cancer in no way minimizes the value of radiation therapy
- Clinical trials are needed to optimize the combination of the therapeutic modalities
- Need to define which patients are at highest risk for local and systemic failure
- We must improve our understanding of the biology of GE junction tumors