Esophageal and GE Junction Adenocarcinoma: the Role of Chemotherapy

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Disclosure

- Research Support
  - Genentech
  - Bristol Myers Squibb / Imclone
  - Sanofi-Aventis
  - Bayer

Esophageal and Gastric Carcinoma US Incidence in 2011

- 38,500 new cases
  - Gastric: 21,520 (56%)
  - Esophagus: 16,980 (44%)

- Male > Female

- Decline in Gastric Cancer Incidence

- Increase in Esophageal, GE JX, cardia adeno

  - Gastric: 16% → 18% → 27%
  - Esophageal: 5% → 10% → 19%

Jemal et al, CA 61: 212-236; 2011
Esophageal Cancer is a Systemic Disease

- 40-50% of patients present with Stage IV disease
- 60-80% of patients even with locoregional disease die, usually of metastatic disease with or without local failure
- Autopsy series:
  - 231 patients
  - Performed in short interval after surgery in 57%
  - Residual cancer found in 81% of cases
  - 41% had persistent intra thoracic lymph nodes

Chan Pathology 18: 400; 1986

PET SCAN:
- Staging (15% occult mets), and Determine Response to Preop Chemo

SUV = 10.6
### RTOG 85-01 Patterns of Recurrence

- **Chemo Radiotherapy Reduced Local Recurrence**
  - RT alone: 68%
  - ChemoRT: 46%

- **Chemo Radiotherapy Reduced Distant Recurrence**
  - RT alone: 30%
  - ChemoRT: 16%

- **Addition of chemotherapy to RT has local and systemic effects**
Esophageal Cancer
MULTIMODALITY STUDIES

- Chemo followed by Surgery
- Concurrent RT + Chemo + / - Surgery

Esophageal and GE Junction Adeno:
Consensus on Adjuvant Therapy

- T2-3 or N+: Something more than surgery alone should be done
- Preop chemo ECF, CF improves overall survival in some but not all trials
  - Predominant approach in Europe
  - MAGIC (ECF): 13% ↑ OS at 5 yr (120 pts esophageal)
  - FFCD / FNLC (CF): 14% ↑ OS at 5 yr (180 pts esophageal) same as MAGIC, no epirubicin

Cunningham. NEJM 355: 11; 2006; Boige J Clin Oncol 18: 4510; 2007

Esophageal and GE Junction Adeno:
Consensus on Adjuvant Therapy

- Preop chemo CF marginal or failed:
  - MRC 0E0-2 (CF): 800 pts
    - 5 year update: 6% (17% 23%)
  - U.S. INT 113 (CF): 450 pts
    - No impact on OS
  - EORTC 40954 (CF): Half of 144 pts GE junction
    - No impact on OS

Preop Chemo Meta Analysis: 2100 pts, Overall Survival (Thirion ASCO 2007)

![Graph showing survival over time with absolute benefit at 5 years: 4.3%](image)

| Squamous: 4% | Adeno: 7% |

Esophageal and GE Junction Adeno: Consensus on Adjuvant Therapy

- Preop chemo + RT has mixed results
- Three of 6 modern trials failed
- Path CR in 10-40%
- 5 yr OS 25-35%
- Phase III: small, inconclusive (<100-250 patients)
  - Local Recurrence reduced
  - Trends toward ↑ Survival
  - Path CR: ↑ Survival


Esophageal Cancer and the Role of Surgery?

- Adenocarcinoma
  - Lower rate of pathologic complete response
  - Surgery considered for most patients
    - Chemo RT alone: Elderly, co morbidities
    - Delay surgery in responders, use as a salvage procedure
- Squamous Cancer
  - Higher rate of pathologic complete response
  - In 2 phase III trials of Chemo RT
    - No survival benefit for surgery, in particular in responding pts
    - Reduced local recurrence with surgery did not improve survival
  - Surgery for non responders, biopsy + residual disease, younger good PS patients
New Agents In Combined ChemoRT

- **RTOG 0113**: PF vs PC
  - Median survival 28.7 mos PF vs 14.9 mos PC
  - Neither arm met 1 year survival primary endpoint
- **ECOG 1302**: Pac FU / RT vs Pac Cis / RT
  - Path CR’s 14-16%, OS 21-35 months, adenocarcinoma
- **SWOG S0-356**: Oxaliplatin + 5-FU + XRT: preop
  - 27% path CR in adenocarcinoma, OS 33 months
  - No pre therapy EUS or PET scan required
- **Single institutions**: EGFR TKI’s, Bevacizumab + chemo RT

CROSS Active Treatment Arm

- Paclitaxel 50mg/m² + Carboplatin AUC=2 on days 1, 8, 15, 22 and 29
- Concurrent radiotherapy of 41.4 Gy in 23 fractions of 1.8 Gy
- Surgery within 6 weeks after completion of chemoradiotherapy (THE/TTE)
- Major eligibility: Adeno- or squamous histology; N1 or >T2, PS < 2
- Primary objective: Median overall survival 22 months (versus 16)

CROSS: Major Results

- EUS staged patients
- T3N0-1 75%, median age 60
- 74% Adenocarcinoma
- 23% had grade 3 toxicity from pre-op therapy
- R0 resection rate: 92% versus 67%  
  - 27% had pathologic complete remissions
- Post-operative morbidity and mortality almost identical (mortality 3.7-3.8%)
HR 0.67  95% CI (.49 - .91)   P=0.012

CROSS: Overall Survival

- 1-year survival 67 versus 52%
- 2-year survival 59 versus 48%
- Median survival 49 versus 26 months, HR 0.67, p = 0.011
- Squamous HR 0.24, Adeno HR 0.82

Baseline characteristics (2)

<table>
<thead>
<tr>
<th></th>
<th>Surgery alone</th>
<th>CRT + Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>Median 60 (36-73)</td>
<td>60 (37-79)</td>
</tr>
<tr>
<td>Dysphagia score</td>
<td>Median 1 (0-4)</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td>Tumor length (cm)</td>
<td>Median 4 (1-10)</td>
<td>4 (1-13)</td>
</tr>
<tr>
<td>Tumor location</td>
<td>proximal 4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>mid 18</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>distal 145</td>
<td>122</td>
</tr>
<tr>
<td></td>
<td>GEJ 21</td>
<td>23</td>
</tr>
</tbody>
</table>

HR's (95% CI) for death according to baseline variables

- 0.67 (0.49 – 0.91)
- 0.49 (0.27 – 0.90)
- 0.72 (0.50 – 1.04)
- 0.62 (0.44 – 0.87)
- 0.92 (0.45 – 1.89)
- 0.82 (0.58 – 1.16)
- 0.34 (0.17 – 0.68)
- 0.67 (0.49 – 0.94)
- 0.67 (0.32 – 1.41)
How does preop therapy improve outcome?
- Achieve pathologic CR  OS 60-70%
  - Rare with preop chemo
  - ChemoRT: 9% to 30%
- Histopathologic response
  - < 10% residual disease
- Achieve N0 status
- Increase rate of R0 resection
  - Mixed results with chemo and chemoRT
  - Not consistently achieved with preop therapy

Preop Chemo vs Chemo RT: Stahl

<table>
<thead>
<tr>
<th>Arm</th>
<th>Pts</th>
<th>R0</th>
<th>μCR</th>
<th>N0</th>
<th>Median Survival</th>
<th>3 yr OS</th>
<th>Local Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>59</td>
<td>70%</td>
<td>2%</td>
<td>37%</td>
<td>21 mos</td>
<td>28%</td>
<td>59%</td>
</tr>
<tr>
<td>Chemo RT</td>
<td>60</td>
<td>72%</td>
<td>16%</td>
<td>64%</td>
<td>33 mos</td>
<td>47%</td>
<td>77%</td>
</tr>
</tbody>
</table>

P = 0.07
P = 0.06

Stahl J Clin Oncol: 27: 836; 2009

Induction Chemotherapy Prior to Chemo RT
- Allows response assessment to chemo prior to adding RT
- Relieves dysphagia
- Feeding tube placement in MSKCC Trials
  - Phase II Induction Paclitaxel/Cisplatin  Paclitaxel/Cisplatin/RT  Surgery
    - Dysphagia improved in 92%
    - 5% feeding tubes
  - Phase II Induction Irinotecan/Cisplatin  Irinotecan/Cisplatin/RT  Surgery
    - Dysphagia improved in 75%
    - 6% required feeding tubes
Benefit from Preop Chemo assessed by PET scan

- Ott: 65 pts, preop chemo 12 wks 5-FU Cisplatin
- PET responders: SUV decline > 35% day 14
- Major histopathologic response in only 18% of all pts
- Benefit, response were limited to PET responders
  - Histopathologic response: 44% vs 5%
  - 3 yr OS: 70% vs 35%

- Lordick: MUNICON Trial: PET non responders referred for immediate surgery, PET responders completed 12 wks of preop therapy

Comparison with historic cohort

Ott et al. J Clin Oncol 2006;24:4692-8
Lordick Lancet Oncol 8: 797, 2007

CTx for 12 weeks in all patients

Survival (median)
Responders: not reached
Non-Responders: 18 months

Survival (median)
PET-Responder
PET-Non-Responder

Survival (median)
PET-Responder
PET-Non-Responder

Survival (median)
PET-Responder
PET-Non-Responder

Esophageal Cancer: PET scan trials

- It is unlikely that nonresponding pts will gain from continuing the same chemo
- What is non response?
  - MUNICON: A threshold of response has to be reached for preop chemo to have an actual impact
  - Discontinuing inactive chemo did not adversely affect outcome
Phase II: Preop Induction Chemo, then Irinotecan/Cisplatin/RT: IRB 02-045

<table>
<thead>
<tr>
<th>Induction</th>
<th>ChemoRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET</td>
<td>PET</td>
</tr>
</tbody>
</table>

Cisplatin
Ind: 30 mg/m²
RT: 30 mg/m²

Irinotecan
Ind: 65 mg/m²
RT: 65 mg/m²

Radiotherapy,
5040 cGy
180 cGy/wk

Week 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

Time to Progression as a Function of SUV Decline: > 35% vs < 35%

Post induction PET scan: Progressive disease in Patient #1

SUV 11.7 ➔ 12.8, new celiac and PE nodes post induction irinotecan/cisplatin

SUV 4.5 post 5-FU/paclitaxel + RT ➔ path CR at surgery
PET Scan Directed Therapy Trial Design: CALGB 80803

PET responders: ≥ 35% SUV decrease: continue same chemo + concurrent RT (5040cGy in 180cGy fx)

PET non-responders: < 35% SUV decrease: Cross over to alternate chemo + RT (5040cGy in 180cGy fx)

Surgical resection 6 weeks post-RT

Hypothesis: changing chemo in PET non-responding patients will improve pCR during chemo + RT

Gastric Cancer Chemotherapy: What regimen to use?

- DCF > CF, at price of high toxicity
- Oxaliplatin + Capecitabine: Non inferior
- Doublets: Preferred chemo backbone
- CALGB 80403: FOLFOX = ECF > Irino/Cis, + Cetuximab

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Pts</th>
<th>%RR</th>
<th>TTP, mos</th>
<th>OS, mos</th>
</tr>
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<tbody>
<tr>
<td>Oxaliplatin EOX or ECF</td>
<td>489</td>
<td>44%</td>
<td>6.7</td>
<td>10.9</td>
</tr>
<tr>
<td>Cape EOX or ECF</td>
<td>513</td>
<td>45%</td>
<td>6.5</td>
<td>10.4</td>
</tr>
<tr>
<td>XP FLO FUFIRI</td>
<td>160</td>
<td>41%</td>
<td>5.6</td>
<td>10.5</td>
</tr>
<tr>
<td>DCF ECF</td>
<td>109</td>
<td>34%</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>170</td>
<td>32%</td>
<td>5.0</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>221</td>
<td>36%</td>
<td>5.6</td>
<td>9.2</td>
<td></td>
</tr>
<tr>
<td>126</td>
<td>45%</td>
<td>7.4</td>
<td>8.3</td>
<td></td>
</tr>
</tbody>
</table>

CALGB 80403 / ECOG 1206:
Randomized Phase II Study of Standard Chemotherapy + Cetuximab for Metastatic Esophageal Cancer

PC Enzinger, BA Burtness, DR Hollis, D Niedzwiecki, DH Ison, AB Benson 3rd, RJ Mayer, RM Goldberg
**CALGB 80403/ECOG 1206: Response**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RECIST (N=48)</th>
<th>RECIST (N=48)</th>
<th>RECIST (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (%)</td>
<td>61.6%</td>
<td>55.6%</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>3.1-100%</td>
<td>2.7-95%</td>
</tr>
</tbody>
</table>

*RECIST - confirmed; restaging every 6 weeks

**CALGB 80403/ECOG 1206: Survival**

**Molecular Targets: Gastric Cancer**

- KRAS mutation: < 5-10%
- BRAF mutation: < 5%
- EGFr over expression: 50-80%
  - TKI’s inactive in phase II (0-9% RR, rapid POD)
  - Cetuximab monotherapy inactive phase II (3% RR, rapid POD, PFS 1.8 mos)
- EGFr mutation: < 5%
- CMET: < 10%
- HER2 over expression: 10-25%

Nonoperative ChemoRT Trials: Phase III
U.S. RTOG 0436

Esophageal Carcinoma: Chemotherapy

RT + Pac/Cis + Cetuximab
RT + Pac/Cis - Cetuximab

RTOG 1010: Phase III Study of Neoadjuvant Trastuzumab and Chemoradiation for Esophageal Adenocarcinoma (Siewert I, II)

HER-2 (+) (FISH)

TRASTUZUMAB + CHEMORADIATION
SURGERY + TRASTUZUMAB (1 YR)

HER-2 (-) (FISH)
ALTERNATIVE STUDIES

Chemoradiation: Carbo + Paclitaxel, RT 5040 cGy → Surgery Maintenance trastuzumab post op
Sample Size = 130 Her-2 (+) Pts, Increase 3-Yr Survival from 30% to 50%. 520+ pts to be screened

MAGIC 2 Trial

- 3 cycles of pre, 3 cycles of post op chemo
- ECX: epirubicin, cisplatin, capecitabine
- Randomization: + / - Anti VEGF Antibody Bevacizumab (Avastin)
- Safety and feasibility data presented at ASCO 2010
  - Bevacizumab can be administered peri operatively
Esophageal Cancer and Chemotherapy: Summary

- Esophageal Adjuvant
  - Strongest data for preop chemo + RT
    - Weekly carboplatin and paclitaxel new option
    - Nonoperative U.S. trial chemo + RT + / - Cetuximab
    - Operative U.S. trial, HER2+, chemo + RT + / - Trastuzumab

Esophageal and Gastric Cancer: Summary

- Metastatic Disease
  - Two drug regimens preferred (FOLFIRI, FOLFOX, XELOX, Cape-Cis)
  - Marginal benefit for 3 drug regimens (Docetaxel + CF)
    - Good performance status, q 2 week regimen

- Molecular Targeted Therapies
  - VEGF, EGFr pathways
    - Bevacizumab negative despite + trends
    - EGFr antibody, lapatinib trials ongoing + chemo
  - Molecular markers to select therapy: HER2 + ➔
    - Trastuzumab should be used