Esophageal and GE Junction Cancer: Combined Modality Therapy

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Disclosure

- Research Funding
  - Roche-Genentech
  - Bayer
Objectives

- Review results of combined modality therapy trials in esophageal cancer using
  - Preop chemo
  - Preop combined chemoradiation
- Review the use of chemoradiation alone in squamous cancer
- Review results for PET scan imaging and esophageal cancer
- Review ongoing targeted therapy trials in esophageal cancer
Esophageal and Gastric Carcinoma US Incidence in 2012

- 38,780 new cases
- Decline in Gastric Cancer Incidence
- Increase in Esophageal, GE JX, cardia adeno
  - Gastric: 16% → 18% → 27%
  - Esophageal: 5% → 10% → 19%
- Highly virulent diseases with poor outcome

Siegell et al, CA 62: 10-29; 2012
### Gastric and Esophageal Cancer: New AJCC Staging

#### Gastric
- **T1a**: lamina propria/ musc mucosa
- **T1b**: submucosal
- **T2**: muscle
- **T3**: transmural to adventitia
- **T4a**: into serosa / peritoneum (old T3)
- **T4b**: into adjacent organ
- **N1**: 1-2 nodes
- **N2**: 3-6 nodes
- **N3a**: 7-15 nodes
- **N3b**: 16+ nodes
- **M1**: distant metastases
- **Stage I**: T1N0-1, T2N0
- **Stage II**: T3N0, T2N1, T1N2
- **Stage III**: T3N1-2, T4N0, T2N2
- **Stage IV**: T4N1, M1

#### Esophageal Adeno
- **T1a**: intramucosal
- **T1b**: submucosal
- **T2**: muscle
- **T3**: transmural / adventitia
- **T4a**: pleura
- **T4b**: aorta
- **N1**: 1-2 nodes
- **N2**: 3-6 nodes
- **N3**: 7+ nodes
- **M1**: distant metastases
- **Stage IAB**: T1-2N0 (grade)
- **Stage IIAB**: T3N0, T1-2N1, T2N0 (gr)
- **Stage IIIAB**: T3N1-2, T4aN0, T1-2N2
- **Stage IIIC**: N3, T4aN1-2, T4b
- **Stage IV**: M1
New AJCC Staging: Survival in over 4600 pts with esophageal and GEJ cancer

Rice Cancer 2010
Esophagus, GEJ Preop therapy:
T2-3 or N+
T1A: EMR
T1B: Primary resection
PET SCAN:
Staging (15% occult mets), and Determine Response to Preop Chemo

SUV = 10.6

SUV = 2.2
Chemoradiotherapy: Esophageal Cancer

RTOG Trial 85-01: Non operative Trial

Esophageal Ca Squamous Adeno

6400 cGy Alone

5000 cGy + 5FU + Cisplatin + 2 cycles 5FU + Cisplatin

Local Recurrence: 45%

Surgeon’s argument for resection after ChemoRT
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: Surgery 1980’s, 1990’s

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Stage</th>
<th>Technique</th>
<th>5 yr O.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akiyama</td>
<td>913 pts</td>
<td>SCC</td>
<td>TTE (2, 3 field)</td>
<td>43%</td>
</tr>
<tr>
<td>Ando</td>
<td>419 pts</td>
<td>93% SCC</td>
<td>TTE (2, 3 field) / THE</td>
<td>40%</td>
</tr>
<tr>
<td>Hulscher</td>
<td>220 pts</td>
<td>AC</td>
<td>THE vs TTE</td>
<td>29-39%</td>
</tr>
</tbody>
</table>

- 3 vs 2 field, en bloc resection ➔ greater morbidity with unclear survival impact

Gastroesophageal Junction Tumors: Classification and Treatment

- **Siewart Classification**
  - **Type I**: lesions with center 1-5 cm proximal to the GE junction
  - **Type II**: lesions with center 1 cm proximal to and 2 cm distal to the GE junction
  - **Type III**: lesions with center 2-5 cm distal to the GE junction

- **Surgery is most common treatment**
  - 30% of GE junction tumors are unresectable
  - > 50% relapse following complete resection

Esophageal and GEJ Adenocarcinoma: Adjuvant Therapy Improves OS

- 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
  - MAGIC (ECF): 13% ↑ OS at 5 yr (75% gastric, 25% esophageal)
    - No improvement in RO resection
  - FFCD / FNLC (CF): 14% ↑ OS at 5 yr (gastric and esophageal cancer) ➔ same as MAGIC, no epirubicin
    - Improved R0 resection by 10%
Esophageal Adenocarcinoma: Adjuvant Therapy Improves OS

- Disparate results with these two trials
- Increase in R0 resection rate in French and not MAGIC trials
- French trial small and underpowered, 200 pts
  - ? Imbalance with earlier stage patients on chemo arm leading to
    - 1) increased R0 resection and
    - 2) better survival

Esophageal Adenocarcinoma: Adjuvant Therapy Improves OS

- Negative or Equivocal Trials of Preop Chemo
  - MRC 0E0-2 (CF): Esophageal Cancer
    - 5 year update: 6%, no impact on distant recurrence, only local recurrence
    - Improved R0 resection rate by 9%
  - U.S. INT 113 (CF): no impact on OS, R0 resection
  - EORTC 40954 (CF): no impact on OS, improved RO resection 15%
  - Inconsistent results across trials

Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

- 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)

Van Hagen et al NEJM 366: 2074; 2012
CROSS: Major Results

- EUS staged patients
- T3N0-1 75%, median age 60
- 74% Adenocarcinoma
- 93% received all courses chemotherapy
  - 23% had ≥ grade 3 toxicity from pre-op therapy
- Post-operative morbidity and mortality almost identical (mortality 3.7-3.8%)
Resection rate and resection margins

Resection rate of all randomized patients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>CRT + surgery</th>
<th>Surgery alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>186/188 (99%)</td>
<td>168/178 (95%)</td>
<td>111/161 (69%)</td>
</tr>
</tbody>
</table>

Resection margins

<table>
<thead>
<tr>
<th>Procedure</th>
<th>CRT + surgery</th>
<th>Surgery alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0 111/161 (69%)</td>
<td>148/161 (92%)</td>
<td>p&lt;0.002</td>
</tr>
</tbody>
</table>

R0 = no tumor within 1 mm of the resection margins
CROSS: Overall Survival

- 5-year survival 47% versus 34%
- Median survival 49.4 versus 24 months, HR 0.66, p = 0.003
  - Squamous HR 0.453, Adeno HR 0.732
  - Squamous path CR 49%, Adeno 23% (p = 0.008)
Overall Survival Improved with Chemo RT + Surgery
### Subgroups: Impact on OS with Chemo RT

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Univariate Hazard Ratio (95% CI)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P Value for Adjusted Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>0.657 (0.495–0.871)</td>
<td>0.665 (0.500–0.884)</td>
<td>0.005</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.913 (0.482–1.729)</td>
<td>0.928 (0.487–1.766)</td>
<td>0.82</td>
</tr>
<tr>
<td>Male</td>
<td>0.612 (0.446–0.841)</td>
<td>0.614 (0.447–0.845)</td>
<td>0.003</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.627 (0.056–6.970)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0.732 (0.524–0.998)</td>
<td>0.741 (0.536–1.024)</td>
<td>0.07</td>
</tr>
<tr>
<td>Squamous-cell carcinoma</td>
<td>0.453 (0.243–0.844)</td>
<td>0.422 (0.226–0.783)</td>
<td>0.007</td>
</tr>
<tr>
<td>Clinical N stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.414 (0.234–0.732)</td>
<td>0.422 (0.239–0.747)</td>
<td>0.003</td>
</tr>
<tr>
<td>1</td>
<td>0.793 (0.567–1.108)</td>
<td>0.807 (0.576–1.130)</td>
<td>0.21</td>
</tr>
<tr>
<td>Could not be determined</td>
<td>0.552 (0.066–4.602)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO performance score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.617 (0.452–0.844)</td>
<td>0.625 (0.456–0.857)</td>
<td>0.004</td>
</tr>
<tr>
<td>1</td>
<td>0.864 (0.433–1.726)</td>
<td>0.898 (0.753–1.631)</td>
<td>0.77</td>
</tr>
</tbody>
</table>
Preop Chemo vs ChemoRT

**Treatment**

**Arm A**
- PLF 2 x 6 weeks
- PLF, 3 weeks
- Surgery

Weeks:
- 1
- 13
- 17
- 21

**Arm B**
- PLF 2 x 6 weeks
- 15 x 2 Gy, 3 weeks
- Surgery
- PE, 1 week

**Notes**:
- **P**: Cisplatin
- **E**: Etoposide
- **LF**: Leukovorin / 5-FU
- Erythropoetin alpha recommended in both arms to keep the Hb-level between 11.5 and 12.5 g/dL

*Stahl J Clin Oncol: 27: 836; 2009*
**Preop Chemo vs Chemo RT: Stahl**

- EUS, laparoscopy staged pts
- Siewert I-III, T3-4 adenocarcinoma

<table>
<thead>
<tr>
<th>Arm</th>
<th>Pts</th>
<th>R0</th>
<th>pCR</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% P = 0.07</td>
<td>77% P = 0.06</td>
</tr>
</tbody>
</table>

Stahl J Clin Oncol: 27: 836; 2009
Overall Survival

MDACC Seq. Phase II Experience: Preop C vs Preop CRT

Swisher et al., Ann Thor Surg, 2010
Preop Chemo vs Surgery Alone: 2062 patients, 10 Trials

- HR favoring Chemo 0.87 (p = 0.005)
- Squamous: HR 0.92, p = 0.18)
- Adeno: HR 0.83, p = 0.01)

Sjoquist Lancet Oncol 12: 681; 2011
Preop Chemo RT vs Surgery Alone: 1932 patients, 13 trials

- **HR favoring Chemo RT** 0.78 (p < 0.0001)
- **Squamous HR** 0.8 (p = 0.004)
- **Adeno HR** 0.75 (p = 0.02)

Sjoquist Lancet Oncol 12: 681; 2011
Prognostic Factors after Chemo RT

- Patients achieving a pathologic CR have 50-70% long term survival
  - 90% treatment effect has similar survival to path CR pts
- Superior survival for N0 versus N+ disease
- Early response during induction chemotherapy on PET scan: Prognostic for improved survival
- Molecular prognostic factors
**Prognostic Factors for Chemort**

- **IHC:** EGFR, COX-2, p53, Bcl-2/Bax/BclX-I, Survivin expression: no correlation with pathologic response
- **Ajani (ASCO 2011 4927):** NF-KB, Gli-1, Sonic Hedgehog correlate with path CR
- **RT PCR:** genes may influence response and survival
  - 5-FU targets: TS, TP, DPD
  - Cisplatin targets: ERCC-1
    - Correlated with OS but not response in SWOG FU/oxali trial (Leichman GI ASCO 2011)
    - Not validated
- **SNP analysis, gene hyper methylation:** not validated
- **No marker validated prospectively, or used to assign therapy**
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 + / - Surgery
    - 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
  - Surgery for younger, good PS patients
**ChemoRT + / - Surgery: FFCD 9102, Squamous**

455 pts treated, 259 responders randomized: Non responders excluded.

<table>
<thead>
<tr>
<th>Author</th>
<th>Pt No.</th>
<th>Histol.</th>
<th>Therapy</th>
<th>Med. Surv.</th>
<th>O.S.</th>
<th>Local Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedenne</td>
<td>259</td>
<td>Squam</td>
<td>Chemo RT + S</td>
<td>17.7 mos</td>
<td>34%</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemo RT</td>
<td>19.3 mos</td>
<td>40%</td>
<td>57%</td>
</tr>
</tbody>
</table>

Bedenne et al JCO 25: 1160; 2007
Bedenne L et al. JCO 2007;25:1160-1168
Esophageal Cancer: Predictive Accuracy of post ChemoRT Endoscopy

- 137 patients: Cisplatin based chemo RT → surgery
  - → EGD and biopsy → Surgery
- 104 patients (76%) negative biopsy post therapy
  - Poor Predictor: Only 35% had pathologic local complete remission at surgery
- A negative biopsy better predictor for squamous cell carcinoma (p <0.001)
- More accurate assessment to predict Path CR

Sarkari JCO 24: Abs 4024, 182, 2006
PET Scan and Path CR: Esophageal Cancer

- 493 pts preop chemoRT, 87% cisplatin based chemoradiation
- PET scan prior, after chemoradiation
- 80% Adeno
- PET response not associated with pCR or nodal disease
- In squamous cancer patients: SUV response correlated with pCR
  - SUV reduction < 50%, 50-75%: pCR 29-44%
  - SUV reduction > 75%: pCR 85%

Rizk J Clin Oncol 27: Abstr 4552; 2009
Esophageal Cancer Multidisciplinary therapy

- Esophageal Cancer
- Something more than surgery alone for T2-3 or N+ Disease
  - Preop chemo, chemo + RT improve OS
- Results trend better for chemo + RT
  - More path CR’s, enhanced rates of R0 resection
  - Carbo + Paclitaxel + RT + Surgery a new standard
- TOPGEAR: Chemo vs Chemo + RT preop (Australia, Europe, Canada)
- Induction chemo followed by chemo RT
  - Use of PET scan to direct therapy (CALGB 80803)
Treatment Plan: MUNICON-1 trial

Response definition: Decrease of the SUV\textsubscript{mean} \( \frac{\text{PET}_{d14}}{\text{PET}_{\text{baseline}}} \geq 35\% \)

Comparison with historic cohort

Ott et al. J Clin Oncol 2006;24:4692-8
CTx for 12 weeks in all patients

MUNICON-1 study; 2007
CTx stopped after 2wks in Non-Responders

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

Survival (median)
Responders: not reached
Non-Responders: 26 months
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**
PET Scan Directed Therapy Trial Design: CALGB 80803

T3/4 or N1 Esophageal Adenocarcinoma

PET/CT: Induction Chemo: modified FOLFOX6 days 1,15, 22 or Carbo/Taxol days 1,8,22,29

PET Scan day 29-35

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

Surgical resection 6 weeks post-RT

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

Hypothesis: changing chemo in PET nonresponding patients will improve pCR during chemo + RT
U.S. Intergroup 116 (SWOG 9008)
Gastric Cancer: Post Op Adjuvant RT + 5-FU

Resected Gastric Cancer

No Further Therapy

5 Cycles 5-FU/LV + XRT Cycle 2-3

Macdonald NEJM 345: 725-730; 2001
Post Op ChemoRT: Gastric INT 116

- 20% were GE JXN tumors
- Similar survival benefit in this subset
- Post Op Chemo RT in GE JXN cancer

Overall Survival

Macdonald NEJM 345: 725-730; 2001
Post-op Chemoradiation: GE junction: Larger post op RT field poorly tolerated
After Preop therapy and surgery, what about post op Chemo RT?

- Should non responding pts, or any pts, get chemo and RT post op?
- Question addressed by an ongoing trial:
  - CRITICS Trial (Netherlands)
    - Preop Chemo ➔ Surgery ➔ Post op Chemo + / - RT
- Post op chemo RT after preop therapy and surgery should not be done outside of a trial
Molecular Targets: Esophagogastric Cancer

- KRAS mutation: < 5-10%
- BRAF mutation: < 5%
- EGFr IHC over expression: 50-80%
  - EGFr mutation: < 5%
- CMET amplification: < 10%
  - IHC over expression 40%
- HER2 over expression: 10-25%
  - Trastuzumab + chemo improves OS in HER2+ disease

Mammano Anticancer Res 26: 3547; 2006
Lee Oncogene 22: 6942; 2003
Yano Oncol Rep 15: 65; 2006
Gold GI CA Symp 2008 Abs 96
**ToGA trial design**

Phase III, randomized, open-label, international, multicenter study

3807 patients screened
810 HER2-positive (22.1%) → HER2-positive advanced GC (n=584) →

- 5-FU or capecitabine\(^a\) + cisplatin (n=290)
- 5-FU or capecitabine\(^a\) + cisplatin + trastuzumab (n=294)

**Stratification factors**
- advanced vs metastatic
- GC vs GEJ
- measurable vs non-measurable
- ECOG PS 0-1 vs 2
- capecitabine vs 5-FU

Bang Lancet Oncol 2010
Primary end point: OS

<table>
<thead>
<tr>
<th>Event</th>
<th>Median OS</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC + T</td>
<td>167</td>
<td>13.8</td>
<td>0.74</td>
<td>0.60, 0.91</td>
</tr>
<tr>
<td>FC</td>
<td>182</td>
<td>11.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. at risk:
- FC + T: 294, 277, 246, 209, 173, 147, 113, 90, 71, 56, 43, 30, 21, 13, 12, 6, 4, 1, 0
- FC: 290, 266, 223, 185, 143, 117, 90, 64, 47, 32, 24, 16, 14, 7, 6, 5, 0, 0, 0

T, trastuzumab
RTOG 1010: Trastuzumab and Chemoradiation for Esophageal + GEJ Adenocarcinoma

- 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
Nonoperative ChemoRT Trials: Phase III

U.S. RTOG 0436

Esophageal Carcinoma: Chemorxrt

- RT + Pac/Cis + Cetuximab
- RT + Pac/Cis - Cetuximab
MAGIC 2 Trial

- 3 cycles of pre, 3 cycles of post op chemo
- ECX: epirubicin, cisplatin, capecitabine
- Randomization: + / - Anti VEGF Antibody Bevacizumab (Avastin)
Esophageal Cancer: Summary

- Poor survival with Surgery Alone
- Chemoradiotherapy Standard
  - nonoperative management
- Preoperative Therapy
  - Chemo (U.K., Magic)
  - Chemoradiotherapy (U.S.)
    - Carboplatin + Paclitaxel + RT a new standard option
  - Observation without surgery for CR
    - Surgery to salvage PR patients
    - Acceptable approach for squamous cancers