COMBINED-MODALITY APPROACHES FOR ESOPHAGEAL CANCER: Update on Recent Prospective Clinical Trials
NO DISCLOSURES
ESOPHAGEAL CANCER
PRINCIPLES AND PRACTICE

Written by recognized leaders from all specialties involved in esophageal cancer, Esophageal Cancer: Principles and Practice presents a multidisciplinary approach to the complexities of esophageal cancer. Structured into seven major sections, this book includes the expertise of every medical specialty from the team—surgery, medical oncology, radiation oncology, gastroenterology, pathology, radiology, palliative medicine, nutrition, nurse specialists as well as basic, translational, and molecular science related research pertaining to neoplasia of the esophagus.

Comprehensive coverage including:

- the biology of esophageal cancer with a particular emphasis on the pathogenesis, molecular biology, and epidemiology of Barrett's esophagus and esophageal intraepithelial neoplasia (EIN)
- esophageal imaging and staging
- the principles and rationale of therapeutic approaches for esophageal cancer
- the clinical background, gross findings, histology and presentation of all benign and malignant neoplasms of the esophagus
- surgical techniques including pre- and post operative management as well as prevention and management of complications
- the techniques used to provide effective palliation for the patient with advanced locoregional or distant disease
- rationale and current understanding of molecular progression

With its multidisciplinary approach and comprehensive coverage, Esophageal Cancer: Principles and Practice is an indispensable resource for all practitioners who participate in the management of esophageal cancer.

Editors
Blair A. Jobe
Charles R. Thomas, Jr.
John C. Hunter

Associate Editors
A. William Blackstock, Jr.
Gregorio Chejfec
Claude Deschamps
Raj K. Goyal
Heinz-Josef Lenz
Valerie W. Rusch

Jobe Thomas Hunter

ESOPHAGEAL CANCER
PRINCIPLES AND PRACTICE
Esophageal Cancer: 2009

- 16,500 New Cases In United States
- Past 20 yrs: AdenoCa > SCC
- Half of patients unresectable/metastatic at presentation

<table>
<thead>
<tr>
<th>Stage</th>
<th>5 Year S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized (25%)</td>
<td>27%</td>
</tr>
<tr>
<td>Regional (40%)</td>
<td>13%</td>
</tr>
<tr>
<td>Distant (35%)</td>
<td>2%</td>
</tr>
</tbody>
</table>
Algorithm for Staging

- History and Physical
  - Cannot ignore weight loss, performance status and lymph nodes

- Endoscopic Ultrasonography
  - Best for T and N evaluation

- CT Scan
  - Misses up to 50% of nodes close and distant

- PET Scan
  - More sensitive than CT for distant disease, possibly nodal disease
History of Present Illness

- 60 yo Male Smoker with 3 mo h/o
  - dysphagia
  - no hiccups
  - no reflux
  - no satiety
EUS

Figure 15: A, Normal anatomy of the esophageal wall; B, endoscopic ultrasonography (EUS) image.

Figure 19: Esophageal carcinoma staging progression from T1 to T4 with corresponding endoscopic ultrasonography images.

Tumor (T) disrupting the normal 5 layers of the esophageal wall (arrows). Malignant lymph nodes (LN) are present around the tumor. A = aorta

Courtesy of Johns Hopkins Medicine and eusimaging.com
$SUV_{\text{max}} = 17$

$SUV_{\text{max}} = 1.9$

**Figure 3.** On the top are axial slices of a CT and FDG-PET demonstrating an abnormality. PET/CT fusion on the bottom left correlate the area of increase uptake on FDG-PET with the anatomic information provided by CT.

Yang GY et al, GI Cancer Research 2007
<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th>AJCC TNM</th>
<th>5-year OS</th>
</tr>
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<tbody>
<tr>
<td>Stage 0</td>
<td>TisN0M0</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>T1N0M0</td>
<td>80-90%</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2-T3N0M0</td>
<td>50%</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T1-2N1M0</td>
<td>20%</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3N1M0</td>
<td>10-15%</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>M1a</td>
<td>10%</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>M1b</td>
<td>Anecdotal</td>
</tr>
</tbody>
</table>
FIG. 1. The relationship between the sigmoid curves representing tumor control probability (TCP) and normal tissue complication probability is termed the therapeutic ratio.
Discussion Points: Stage II & III Disease

- RT Alone = Poor OS
- Surgery Alone = Poor OS
- CRT > RT
- 50.4 Gy CRT remains standard but high LF rate
- ? CRT = CRT/Surgery (Squamous Cell Ca)
- CRT/Surgery >/= Surgery (Adenocarinoma)
- How to Treat GE Junction
- Role of Conformal RT
Deciphering Protein Molecular Signatures in Cancer Tissues to Aid in Diagnosis, Prognosis, and Therapy

Richard M. Caprioli

Department of Biochemistry and the Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, Tennessee

Figure 1. Process for discovery on molecular signatures consists of the integration of three basic components: (top, left) physician/patient interaction encompassing patient history and other clinical information, acquisition of the appropriate tissue sample and pathology; (right) analytic component involving tissue preparation, MS data acquisition, raw data normalization, and validation; (bottom, left) biocomputational processing to identify protein signatures at high confidence levels and with appropriate validation relevant to the clinical question at hand.
Chemoradiation Alone
RTOG 85-01

5-FU  1000 mg/m2 x 4 d
CDDP  75 mg/m2 d 1
RT    50 Gy

RT    64 Gy

Week
1 5 8 11

NEJM 326: 1593-98, 1992
# RTOG 85-01

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>ChemoRT</th>
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</thead>
<tbody>
<tr>
<td><strong># Pts</strong></td>
<td>62</td>
<td>61</td>
</tr>
<tr>
<td><strong>% 5-year Survival</strong></td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td><strong>% Local Failure</strong></td>
<td>66</td>
<td>47</td>
</tr>
</tbody>
</table>

*JAMA 281:1623-7, 1999*
INT 0123 – RTOG 9405

Stratify

Weight loss
≥ or < 10%

Tumor size
≤ or > 5 cm

Histology
Adeno
Squamous

Randomize

5-FU/CDDP X 4
+ 64.8 Gy

5-FU/CDDP X 4
+ 50.4 Gy

JCO 20(5):1167-74, 2002
## INT 0123 – RTOG 9405

<table>
<thead>
<tr>
<th></th>
<th>64.8Gy</th>
<th>50.4Gy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td># Entered</td>
<td>118</td>
<td>118</td>
<td>236</td>
</tr>
<tr>
<td># Eligible</td>
<td>109</td>
<td>109</td>
<td>218</td>
</tr>
<tr>
<td>Rx-Death</td>
<td>11(11%)</td>
<td>2(2%)</td>
<td>13(6%)</td>
</tr>
<tr>
<td>Cancer-Death</td>
<td>44(41%)</td>
<td>56(61%)</td>
<td>100(46%)</td>
</tr>
<tr>
<td>Median Surv</td>
<td>13 mo</td>
<td>18 mo</td>
<td>NS</td>
</tr>
<tr>
<td>3-Yr Surv</td>
<td>22%(11 at risk)</td>
<td>33%(19 at risk)</td>
<td>NS</td>
</tr>
<tr>
<td>3-Yr DFS</td>
<td>16%(8 at risk)</td>
<td>24%(12 at risk)</td>
<td>NS</td>
</tr>
<tr>
<td>Local/reg F</td>
<td>56%</td>
<td>52%</td>
<td></td>
</tr>
</tbody>
</table>
INT 0123

50.4 Gy  17.6 M  38%
64.8 Gy  12.9 M  29%

p=0.14 (log-rank)

50.4 Gy
64.8 Gy

50.4 Gy  109  59  24  6
64.8 Gy  107  42  17  6
**FIG. 1.** The relationship between the sigmoid curves representing tumor control probability (TCP) and normal tissue complication probability is termed the therapeutic ratio.
Potential Targets

**EGF Receptor Signal Transduction Pathway**

- Cetuximab
- Panitumumab
- Erlotinib
- Gefitinib

**Signaling Pathways Activated by VEGF**

- Bevacizumab
- Sunitinib
- Sorafenib
Cetuximab plus cisplatin, irinotecan, & thoracic radiotherapy as definitive treatment for locally advanced, unresectable esophageal cancer: a phase II trial, SWOG-0414

CR Thomas,1 BH Goldman,2 JK Benedetti,2 HJ Lenz,3 T Beeker,4 JL Abbruzzese,5 CD Blanke6

1Knight Cancer Institute & OHSU, Portland, OR; 2Southwest Oncology Group, Seattle WA; 3University of Southern California, Los Angeles, CA; 4Gulf Coast MB-CCOP/Southern Cancer Center; 5MD Anderson Cancer Center, Houston, TX; 6University of British Columbia Vancouver, BC, Canada;
SWOG-0414: Definitive Rx for EC

- RTOG-8501 established definitive concomitant chemoradiotherapy as a standard of care for pts with locally advanced EC
  - median overall survival (OS) for pts has changed little over the past 2 decades.
- Based on phase I-II data of CDDP, CPT11, & TRT and separate phase I-III data of cetuximab, SWOG GI Committee designed a phase II trial (S0414) to test this novel combined-modality approach.
- Specific aims were to assess:
  - 1) 2-yr OS,
  - 2) toxicity profile,
  - 3) objective response rate (RR),
  - 4) progression-free survival (PFS), and
  - 5) association between gene expression levels & germline polymorphisms involved in DNA repair, drug metabolism, & the EGFR pathway, and clinical outcome.
SWOG-0414: Definitive Rx for EC

Methods

• Eligibility: cT4M0 disease or medically unresectable, biopsy-proven, primary EC (squamous cell or adenocarcinoma), thoracic-GE junction location, with adequate major organ function.
• Cetuximab 400 mg/m² day 1 (cycle 1)
• Cetuximab 250 mg/m² day 8, 15 (cycle 1), then day 1, 8, & 15 for subsequent cycles
• CDDP 30 mg/m² day 1 & 8 (all cycles)
• Irinotecan 65 mg/m²/days 1 & 8 (all cycles)
• TRT 50.5 Gy @ 1.8 Gy/fx (28 fxs), beginning day 1 of cycle 3
• Planned accrual was 75 adeno pts & 25 squamous cell pts, with the regimen considered of further interest if 2-yr OS ≥ 43%.
SWOG-0414: Definitive Rx for EC

**Results**

- **22 pts enrolled & 21 evaluable**
  - 1 ineligible (tumor < 20 cm from incisors)

- **21 pts are considered in this analysis**
  - 15 men (93%)
  - ECOG PStatus 0-1/2=20/1
  - Adeno/SCCA=10/11
  - Caucasian/Non-Caucasian=15/6
  - Median age: 61 yrs

- **17 pts evaluable by RECIST criteria**
  - 1 cCR (6%) & 2 cPR (12%), 3 Stable Dx (18%)
Progression-Free Survival
Eligible Patients with Follow-up
Data as of August 18, 2009

Overall Survival
Eligible Patients with Follow-up
Data as of August 18, 2009

PFS 6.4 mos

Overall Survival
11.2 mos
Grade III/IV Toxicities

• 2 deaths were due to protocol treatment (sudden death & GI necrosis)
• 6 pts had Gr 4 toxicities.
• 48% & 29% of pts had Gr 3 & 4 toxicity, respectively
  – 52% hematologic
  – 24% fatigue
  – 24% diarrhea
  – 19% nausea/emesis
  – 19% dehydration
  – 19% anorexia.
**SWOG-0414: Definitive Rx for EC**

**Conclusions**

- Concomitant cetuximab, CDDP, CPT11, & TRT was poorly tolerated in the first cooperative group trial with this regimen.
- Mortality approached 10%.
- However, single-institution phase II cetuximab-based CRT has yielded encouraging results in preliminary analyses.
- Hence, the SWOG GI Comm. endorses enrollment on RTOG-0436 to further define the therapeutic ratio of cetuximab-based combined-modality Rx.
Neoadjuvant Esophagus
ECOG 2205: Test of Cetuximab

Phase II

• E2205 Study to Measure Response Rate and Toxicity of Neoadjuvant Chemoradiotherapy with FOLFOX plus Cetuximab followed by Post-Operative Docetaxel and Cetuximab in Patients with Operable Adenocarcinoma of the Esophagus

– Closed prematurely.

• 4 deaths, pulmonary complications
RTOG 1010 Eligibility

• Overexpression of HER2 3+ by IHC or or amplification of the HER2 gene by FISH (ratio > 2.0) centrally assessed.
  – Siewart I/II Adenocarcinoma esophagus/GEJ
  – Confirmed operable for cure and all disease in radiation field
  – Treatment naïve

• Stratify: + celiac nodes vs - celiac nodes

• RANDOMIZE

• Arm 1 Radiation (45 Gy), oxaliplatin, 5-FU, and trastuzumab followed by surgery 5-8 weeks after completion of radiation Then maintenance trastuzumab, every 3 weeks for 13 treatments or

• Arm 2 Radiation (45 Gy), oxaliplatin, and 5-FU followed by surgery 5-8 weeks after completion of radiation

• Statistics: 480 patients to DFS increases from 15 mos to 27 mos
Chemoradiation & Surgery
Neo-adj ChemoRT Followed by Surgery vs. ChemoRT alone

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>No.</th>
<th>% Histologic Type</th>
<th>3 year survival (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedenne¹</td>
<td>Cis, 5FU and 46Gy * then Surgery</td>
<td>129</td>
<td>90% SCC</td>
<td>30%</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Cis, 5FU and 65Gy</td>
<td>130</td>
<td>90% SCC</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>Stahl²</td>
<td>Cis, 5FU, LV, Etoposide then 40Gy/Cis, Etop and Surgery</td>
<td>86</td>
<td>100% SCC</td>
<td>31%</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>Induction then Cis, Etop and 65Gy</td>
<td>86</td>
<td>100% SCC</td>
<td>24%</td>
<td></td>
</tr>
</tbody>
</table>

* Only responders randomized

¹JCO 25: 1160-68, 2007
²JCO, 23: 2310-17, 2005
FFCD 9102

A

Survival (%)

Time (months)

Patients at risk
Arm A (surgery) 129 108 79 51 31 25 23 17 13
Arm B (chemoradiation) 130 122 84 61 40 29 25 21 14

German Esophageal Cancer Study Group: Overall Survival

Stahl et al.: JCO, 23: 2310-17, 2005
German Esophageal Cancer Study Group: Freedom from Local Progression

Stahl et al.: JCO, 23: 2310-17, 2005
<table>
<thead>
<tr>
<th>Author</th>
<th>Chemo</th>
<th>RT Dose (Gy)</th>
<th>No. of Patients</th>
<th>% Histologic Type</th>
<th>3 year survival (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walsh</td>
<td>Cis, 5FU</td>
<td>40</td>
<td>58</td>
<td>100% ACA</td>
<td>32</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Surgery alone</td>
<td></td>
<td>55</td>
<td>100% ACA</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Bosset</td>
<td>Cis</td>
<td>37</td>
<td>143</td>
<td>100% SCC</td>
<td>38</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>Surgery alone</td>
<td></td>
<td>139</td>
<td>100% SCC</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Urba</td>
<td>Cis, 5FU, Vincristine</td>
<td>45</td>
<td>50</td>
<td>26% SCC, 74% ACA</td>
<td>30</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>Surgery alone</td>
<td></td>
<td>50</td>
<td>24% SCC, 76% ACA</td>
<td>16</td>
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<tr>
<td>Burmeister</td>
<td>Cis, 5FU</td>
<td>35</td>
<td>128</td>
<td>35% SCC, 63% ACA</td>
<td>36</td>
<td>0.57</td>
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<td></td>
<td>Surgery alone</td>
<td></td>
<td>128</td>
<td>39% SCC, 61% ACA</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Krasna</td>
<td>Cis, 5FU</td>
<td>50.4</td>
<td>30</td>
<td>23% SCC, 77% ACA</td>
<td>65</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Surgery alone</td>
<td></td>
<td>26</td>
<td>27% SCC, 73% ACA</td>
<td>20</td>
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</table>
Figure 1: Phase III intergroup trial CALGB C9781 comparing preoperative combined-modality therapy vs surgery alone in patients with clinically resectable squamous cell carcinoma or adenocarcinoma of the esophagus. CALGB = Cancer and Leukemia Group B; CDDP = cisplatin; 5-FU = fluorouracil; RT = radiation therapy.

closed early due to poor accrual
CALGB 9781

- 56 pts randomized to pre-operative chemoradiation
- Improved overall survival (39% vs 16% at 5 years)
- Overall response rate 80% (40% pCR)

FIG. 1. The relationship between the sigmoid curves representing tumor control probability (TCP) and normal tissue complication probability is termed the therapeutic ratio.
Oxaliplatin (OXP) plus protracted infusion 5-fluorouracil (PIFU) and external beam radiation (EBRT) for potentially curable esophageal adenocarcinoma (EA) a Southwest Oncology Group phase II trial with molecular correlates (S0356)

L. Leichman,¹ B.H. Goldman,² J.K. Benedetti,² C.L. Corless³ K.G. Billingsley,³ C.R. Thomas,³ S. Iqbal,⁴ H. Lenz,⁴ P.J. Gold,⁶ C. Blanke⁵

¹Desert Regional Medical Center, Palm Springs, CA; ²Southwest Oncology Group, Seattle WA; ³Oregon Health and Science University, Portland, OR; ⁴University of Southern California, Los Angeles, CA; ⁵University of British Columbia Vancouver, BC, Canada; ⁶Swedish Cancer Institute, Seattle, WA
S0356: Neoadjuvant Tx for EA

Background

• Neoadjuvant chemotherapy (CTX) + radiation (EBRT) prior to surgery is a curative approach for patients with esophageal adenocarcinoma (EA)
  – Other accepted treatments: surgery alone or CTX and EBRT

• The extent of tumor down-staging after CTX and XRT is the most important prognostic indicator for PFS and OS
  – Complete pathologic response (pCR)=best outcome
S0356: Neoadjuvant Tx for EA

**Background**

- A phase IB trial at RPCI tested OXP + PI 5FU with EBRT prior to surgery
  - pCR rate 38%
  - Efficacy predicted by an *inverse* relationship to intratumoral repair genes, XPA
S0356: Neoadjuvant Tx for EA

Methods: Treatment Plan

- OXP 85 mg/m² IVPB days 1, 15 and 29
- PI 5FU 180 mg/m²/days 8-43.
- EBRT 180/d 8-43 (25 fx, total 45 Gy)
- Esophagectomy 2-4 weeks after CTX/XRT
- Second cycle of OXP and PI 5FU 4-6 weeks postop
- Follow-up observation at 3 month intervals
- Mandated central pathology review pre-op and post-op
S0356: Neoadjuvant Tx for EA

Methods: Trial Design

• Objectives:
  – Assess pCR rate, PFS and OS.
  – Assess frequency and severity of toxicities
  – Explore intratumoral parameters thought to be relevant to pCR (ERCC-1, XPA, TS, γGT and γGCS)
S0356: Neoadjuvant Tx for EA

Methods: Trial Design

- 2-stage design:
  - 45 patients enrolled in 1st stage.
  - Sufficient activity was observed to accrue 45 more.
  - 30 or more patients with pCR out of 90 total would be sufficient to reject null hypothesis that the true pCR rate is ≤25%.
S0356: Neoadjuvant Tx for EA

Methods: Inclusion Criteria

- EA only
  - Patients > 18 years
  - Clinical stage II or III; Zubrod PS ≤ 2
  - Endoscopic ultrasound only for tumors that do not form a clear mass on CT scan
  - Pre-tx PET scans mandatory
  - Tumors < 2 cm into the gastric cardia
  - Standard hematologic/non-hematologic parameters
S0356: Neoadjuvant Tx for EA

Results

• 98 patients enrolled;
  – 6 ineligible
  – 2 did not receive any protocol therapy
• 90 patients are considered in this analysis
  – 84 men (93%)
  – 6 women
  – Median age: 61.7 years
### Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range)</strong></td>
<td>62.0 (41.6-83.1)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>86 (93%)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (7%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>85 (96%)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
</tr>
<tr>
<td><strong>Performance status</strong></td>
<td>54/37 (59%/41%)</td>
</tr>
<tr>
<td>0/1</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
</tr>
<tr>
<td><strong>Primary Site</strong></td>
<td>54 (60%)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>36 (40%)</td>
</tr>
<tr>
<td>GE Junction</td>
<td>2</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
</tr>
</tbody>
</table>
S0356: Neoadjuvant Tx for EA

Results: Surgery

- 77 (86%) patients underwent esophagectomy
  - Four patients (4.4%) died while receiving protocol therapy
    - 2 patients (2.2%) died prior to surgery
    - 2 patients (2.6%) coded as postoperative mortalities
  - 2 patients refused surgery
  - 9 patients (10%) either progressed on therapy or were denied surgery by the treating physician
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3 (N (%)</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood/Bone Marrow</td>
<td>9 (10)</td>
<td>7 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Constitutional (Fatigue/Anorexia)</td>
<td>29 (31)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gastrointestinal (Diarrhea/ Nausea/Mucositis</td>
<td>37 (40)</td>
<td>1 (1)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Infection</td>
<td>9 (10)</td>
<td>3 (3)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Metabolic (hypokalemia/ hyponatremia/renal</td>
<td>10 (11)</td>
<td>3 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>2 (2)</td>
<td>1 (1)*</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>11 (12)</td>
<td>8 (9)</td>
<td>2 (2)**</td>
</tr>
</tbody>
</table>

*One patient with cerebrovascular accident
**Two patients with Acute Respiratory Distress Syndrome (ARDS)
S0356: Neoadjuvant Tx for EA

Results: pCR rate

• Central review confirmed 27 patients (34%; 95% CI: 25%-45%) had pCR, 10 patients (10%) had either $T_{\text{insitu}}N0M0$ or $T1N0M0$.
  –Central review discordant < 5% of local pathology results
Complete Response pCR

27 (28.5%) patients = pCR (centrally confirmed)

10 patients had either $T_{\text{in-situ}}\ N0M0$ or $T1N0M0$
37 patients (40%) underwent postoperative chemotherapy with OXP 85 mg/m$^2$ days 1, 15 and 29 plus PI 5FU 180 mg/m$^2$ days 1-29.

Molecular parameters thought to be predictive for pCR are being analyzed.
S0356 RESULTS

Kaplan-Meier plot of progression-free survival

Median PFS ~ 20 months

Progression-Free Survival

N 92
Events 55
Median in Months 20.8
S0356 RESULTS

Overall Survival

3-year survival ~ 48%

N 92
Events 47
Median in Months 33.7
Overall Survival by Pathologic Complete Response
Conclusions

• OXP + PI 5FU with EBRT for EA is a regimen that should be considered when patients EA will be treated with neoadjuvant chemotherapy and radiation prior to surgery.

• *Postoperative systemic therapy* is difficult to complete, regardless of the regimen.
  – Future trials should consider front-loading all systemic therapy
S0356: Neoadjuvant Tx for EA

Conclusions

• The next generation of neoadjuvant esophageal trials from SWOG will test the role of repair genes in selecting therapy for EA.

– Come to GI ASCO!
Oxaliplatin (OXP) plus protracted infusion 5-fluorouracil (PIFU) and external beam radiation (EBRT) for potentially curable esophageal adenocarcinoma (EA) a Southwest Oncology Group phase II trial with molecular correlates (S0356)

L. Leichman,¹ B.H. Goldman,² J.K. Benedetti,² C.L. Corless³ K.G. Billingsley,³ C.R. Thomas,³ S. Iqbal,⁴ H. Lenz,⁴ P.J. Gold,⁶ C. Blanke⁵

¹Desert Regional Medical Center, Palm Springs, CA; ²Southwest Oncology Group, Seattle WA; ³Oregon Health and Science University, Portland, OR; ⁴University of Southern California, Los Angeles, CA; ⁵University of British Columbia Vancouver, BC, Canada; ⁶Swedish Cancer Institute, Seattle, WA
S0356: Neoadjuvant Tx for EA

Background

• Neoadjuvant chemotherapy (CTX) + radiation (EBRT) prior to surgery is a curative approach for patients with esophageal adenocarcinoma (EA)
  – Other accepted treatments: surgery alone or CTX and EBRT

• The extent of tumor down-staging after CTX and XRT is the most important prognostic indicator for PFS and OS
  – Complete pathologic response (pCR)=best outcome
Background

• Over 25 years no specific neoadjuvant regimen has become “the standard”
  – pCR rates < 30%
  – Median OS < 2 yrs

• In contrast to the growing number of predictive biomarkers for anti-cancer agents, there is no established biomarkers to select patients who will benefit most from chemo-radiation.
  – Hence, current Rx is not tailored to the patient’s tumor

• Identification of these biomarkers may help to select the adequate treatment strategy in esophageal adenocarcinoma to potentially increase the cure rate.
• ERCC1 has been shown to be a critical gene in DNA repair
  – NER pathway - recognizes and removes platinum-induced DNA adducts
  – DSBR pathway- repairs radiation-induced damage

• A prospective clinical trial showed increased benefit of chemotherapy when patients with advanced NSCLC have their treatment selected based on ERCC1 mRNA levels (Cobo et al. J Clin Oncol 2007)
ERCC1 down-regulation sensitizes cells to platinum compounds

Youn et al. Cancer Res 2004
## Tumor ERCC1 mRNA Levels

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>NSCLC</th>
<th>Colorectal</th>
<th>Esophageal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Value</strong></td>
<td>1.65</td>
<td>1.15</td>
<td>1.92</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>0.14-13.4</td>
<td>0.34-4.66</td>
<td>0.33-5.29</td>
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<tr>
<td><strong>% with low expression</strong></td>
<td>57%</td>
<td>78%</td>
<td>42%</td>
</tr>
<tr>
<td><strong>References</strong></td>
<td>Cobo et al. JCO.2007</td>
<td>Lenz et al. ASCO. 2008</td>
<td>Current study</td>
</tr>
<tr>
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<td>Tumor</td>
<td>Setting</td>
<td>Patients Nb (low ERCC1)</td>
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Methods: Trial Design

• Objectives:
  – Assess pCR rate, PFS and OS.
  – Assess frequency and severity of toxicities
  – Prospectively measure intratumoral parameters thought to be relevant to pCR (mRNA ERCC-1, XPA, TS, γGT and γGCS)

• To validate ERCC1 gene expression (predefined cutoff of 1.7) for the first time as a biomarker predicting outcome in patients treated with oxaliplatin-based chemotherapy in combination with radiation.
SWOG 0356 Treatment Design

- **Tumor biopsy**
  - CTX + EBRT
    - D1
    - D8
    - D15
    - D22
    - D29
    - D36
    - D43
  - OHP 85 mg/m²
  - PI 5FU 180 mg/m²/day
  - EBRT 180 cGy/day

- **Surgery**
- **CTX**
Eligibility Criteria

• EA only
  – Patients > 18 years
  – Clinical stage II or III; Zubrod PS ≤ 2
  – Endoscopic ultrasound only for tumors that do not form a clear mass on CT scan
  – Pre-tx PET scans mandatory
  – Tumors < 2 cm into the gastric cardia (Siewert I-II)
  – Standard hematologic/non-hematologic parameters
Patients Characteristics

February 2005 to August 2008

98 patients registered

5 ineligible patients*

92 eligible for clinical outcome evaluation and this study

<table>
<thead>
<tr>
<th></th>
<th>N=92</th>
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<tr>
<td>Other</td>
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</tr>
<tr>
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</tr>
<tr>
<td><strong>Performance Status</strong></td>
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</tr>
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<td>0/1</td>
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</tbody>
</table>

*2 squamous tumors and 3 with biopsy/scans performed >28 days from protocol entry
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<th>Gene Expression Dataset (N=55)</th>
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</table>
S0356: Neoadjuvant Tx for EA

Results: Surgery

• 77 (86%) patients underwent esophagectomy
  – Four patients (4.4%) died while receiving protocol therapy
    • 2 patients (2.2%) died prior to surgery
    • 2 patients (2.6%) coded as postoperative mortalities
  – 2 patients refused surgery
  – 9 patients (10%) either progressed on therapy or were denied surgery by the treating physician
# S0356 Toxicities (Adverse Events)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3 (N (%)</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood/Bone Marrow</td>
<td>9 (10)</td>
<td>7 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Constitutional (Fatigue/Anorexia)</td>
<td>29 (31)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gastrointestinal (Diarrhea/ Nausea/Mucositis)</td>
<td>37 (40)</td>
<td>1 (1)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Infection</td>
<td>9 (10)</td>
<td>3 (3)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Metabolic (hypokalemia/ hyponatremia/renal)</td>
<td>10 (11)</td>
<td>3 (3)</td>
<td>0 (0)</td>
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<tr>
<td>Neurologic</td>
<td>2 (2)</td>
<td>1 (1)*</td>
<td>0 (0)</td>
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<tr>
<td>Pulmonary</td>
<td>11 (12)</td>
<td>8 (9)</td>
<td>2 (2)**</td>
</tr>
</tbody>
</table>

* One patient with cerebrovascular accident
** Two patients with Acute Respiratory Distress Syndrome (ARDS)
Complete Response pCR

27 (28.5%) patients = pCR (centrally confirmed)

10 patients had either $T_{in-situ}$ N0M0 or T1N0M0
S0356: Neoadjuvant Tx for EA

Results

• 37 patients (40%) underwent postoperative chemotherapy with OXP 85 mg/m$^2$ days 1, 15 and 29 plus PI 5FU 180 mg/m$^2$ days 1-29.

• Molecular parameters thought to be predictive for pCR were analyzed.
Progression-Free Survival (PFS)

- \(N\) = 92
- Events = 55
- Median in Months = 20.8
- 3 year PFS = 37.0%

Overall Survival (OS)

- \(N\) = 92
- Events = 47
- Median in Months = 33.7
- 3-year OS = 46.5%

Median follow-up of 36.8 months
Post-Eosophagectomy Overall Survival by Pathologic CR

Overall Survival by Pathologic Complete Response
Gene Expression

Laser Capture Micro-dissection

RNA Extracted

RNA

Reverse Transcription

cDNA

PCR with TaqMan®

Data Analysis
# Genes Analyzed for mRNA Levels

92 pts -> 92 pre-treatment samples -> 55 with sufficient tumor tissue

<table>
<thead>
<tr>
<th>Genes</th>
<th>Number of patients</th>
<th>Median expression level (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSTP1</td>
<td>55</td>
<td>1.61 (0.52-8.73)</td>
</tr>
<tr>
<td>ERCC1</td>
<td>53</td>
<td>1.92 (0.33-5.29)</td>
</tr>
<tr>
<td>TP</td>
<td>52</td>
<td>8.93 (1.36-38.45)</td>
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<tr>
<td>TS</td>
<td>50</td>
<td>3.32 (0.92-8.62)</td>
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<tr>
<td>DPD</td>
<td>39</td>
<td>0.57 (0-2.22)</td>
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<tr>
<td>RRM1</td>
<td>26</td>
<td>1.75 (0.35-5.81)</td>
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<tr>
<td>XPD</td>
<td>19</td>
<td>1.88 (0.76-3.60)</td>
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<tr>
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Progression-Free Survival (PFS)

N  | Events  | Median in Months
---|---------|-----------------
92 | 55      | 20.8

3 year PFS 37.0%

Overall Survival (OS)

N  | Events  | Median in Months
---|---------|-----------------
92 | 47      | 33.7

3-year OS 46.5%

Median follow-up of 36.8 months
PFS by ERCC1 mRNA Levels

\[ \text{Median follow-up of 36.8 months} \]

For ERCC1 mRNA levels ≤1.7:
- \( N = 22 \)
- Median = NR
- 2-year PFS = 67%
- HR (95% CI) = 1.0 (ref)
- \( p^* = 0.0058 \)

For ERCC1 mRNA levels >1.7:
- \( N = 31 \)
- Median = 14.8 mos
- 2-year PFS = 17%
- HR (95% CI) = 2.97 (1.37-6.45)

*p value unadjusted for multiple comparisons
**Progression-Free Survival (PFS)**

- **N**: 92
- **Events**: 55
- **Median in Months**: 20.8

3 year PFS 37.0%

**Overall Survival (OS)**

- **N**: 92
- **Events**: 47
- **Median in Months**: 33.7

3-year OS 46.5%

Median follow-up of 36.8 months
OS by ERCC1 mRNA Levels

- **≤ 1.7**
  - N: 22
  - Median: NR
  - 2-year OS: 72%
  - HR (95% CI): 1.0 (ref)
  - p*: 0.047

- **> 1.7**
  - N: 31
  - Median: 22.4 mos
  - 2-year OS: 37%
  - HR (95% CI): 2.32 (1.01-5.31)

*Median follow-up of 36.8 months*

*p value unadjusted for multiple comparisons*
Molecular Correlate Study Limitations

• Small sample size.

• Lack of sufficient tissue collection.

• Lack of complete clinical staging (no endoscopic ultrasound).
S0356: Neoadjuvant Tx for EA
Conclusions (1)

• OXP + PI 5FU with EBRT for EA is a regimen that should be considered when patients EA will be treated with neoadjuvant chemotherapy and radiation prior to surgery.

• *Postoperative systemic therapy* is difficult to complete, regardless of the regimen.
  – Future trials should consider front-loading all systemic therapy
Conclusions (2)

- Our pre-established ERCC1 mRNA cutoff of 1.7 predicted PFS and OS in patients with esophageal adenocarcinoma treated with oxaliplatin-based chemoradiation within a prospective cooperative group study.

- This pre-specified cutoff was further validated by using recursive partitioning (optimal cutoff of 1.66).

- Genomic polymorphisms analyzed were not associated with outcome in this study. (data not shown)

- Next generation of neoadjuvant esophageal trials from SWOG will test the role of repair genes in selecting therapy for EA.
Conclusions (3)

- ERCC1 mRNA level is a very promising pre-treatment biomarker in patients with localized esophageal adenocarcinoma treated with trimodality treatment.

- Biomarker studies are feasible within cooperative groups.

- ERCC1 gene expression is associated with outcome in stage II-III esophageal adenocarcinoma patients treated with preoperative platinum-based chemoradiation.
Acknowledgments

The patients and their families and Investigators who participated in SWOG 0356

Heinz-Josef Lenz

Response Genetics: Kathleen D. Danenberg.

SWOG Statistics: Bryan Goldman.

Funded by SWOG award 5-U10-CA058882-18

Pierre Bohanes was partially funded by Cancer & Solidarité Fondation
Other Results

• The optimal split for ERCC1 gene expression is 1.66 (recursive partitioning for PFS; $p=0.04$)

• None of the other accessed mRNA levels were associated with outcome
  – DNA-repair: XPD, RRM1
  – Platinum detoxification: GSTP1
  – 5-FU metabolism: TS, TP, DPD
Genotyping

- DNA was extracted from FFPE tumor samples (Qiagen, CA, USA).
- Genotyping was performed by using PCR-RFLP technique.
- Performed in 91 patients (out of 92 eligible)
  - ERCC1 118C>T
  - ERCC1 8092C>A
  - GSTP1 Ile105Val
  - RAD51 135G>C
  - XPD 156A>C
  - XPD Lys751Gln
  - XRCC1 Arg391Gln
  - XRCC3 Thr241Met
  - MTHFR 677C>T
  - MTHFR 1298A>C
  - TS 3’UTR 6bp+/6bp-
  - TS 5’UTR VNTR
  - TS 5’UTR G/C SNP

None are significant after adjusting for multiple comparisons
Assigning Treatment for Patients Based on ERCC1 for Advanced/Metastatic Gastric Cancer or GEJ Tumors

Pre-therapy gastric cancer specimen for ERCC-1 quantitation and HER2 status

ERCC 1
- low
  - FOLFOX +/- Trastuzumab

ERCC1
- high
  - CPT-11/Docetaxel +/- Trastuzumab
Objectives

1.1 To assess progression-free survival in patients with chemotherapy-naive, advanced, metastatic adenocarcinoma of the stomach and gastroesophageal (GE) junction assigned to treatment with chemotherapy based on mRNA levels of ERCC1.

1.2 To assess the feasibility of performing a marker-directed trial in the setting of an NCI-sponsored cooperative group.

1.3 To assess overall survival and response (in the subset of patients with measurable disease) in this group of patients.

1.4 To assess frequency and severity of toxicities in each treatment arm.

1.5 To perform further correlative studies, evaluating additional genes in the fluoropyrimidine and DNA repair pathway.
**SWOG Proposal Built on S0356**

**Esophageal Adenocarcinoma Siewart I & II Clinical Stages II/III**

**Pre-treatment PET/CT then induction chemotherapy:**

- mFOLFOX6 days 1, 15, 29
- PI FU 180 mg/m² x day 43 x 4 weeks
- Oxaliplatin 85 mg/m² days 43, 57, and 61
- Trastuzumab for HER2 3+ or amplified

*With*

**Concurrent EBRT 4500 cGy in 180 cGy fx**

**Referral for surgical resection 4-6 weeks post-RT.**
CROSS Trial (ASCO 2010)

- Phase III randomized trial evaluating pre-operative chemoradiation using carboplatin, paclitaxel and concurrent radiotherapy versus surgery alone reported at ASCO

90% underwent rsxn

pCR rate: 27%

3-year OS: 59 v. 48%

MS: 49 v. 26 mos
CURRENTLY RECOMMENDED CLINICAL TRIAL FOR CLINICALLY **RESECTABLE** ESOPHAGEAL ADENOCARCINOMA

### 1.3 Study Design

#### 1.3.1 Accrual Goal

Assuming a type I and II error of 0.1, 63 analyzable patients will be required to differentiate between a complete pathologic response (pCR) of 0.20 and 0.35. Adjusting this figure by 10% to account for ineligibility or loss, a total sample size of 69 patients will be required for the study.

### 1.4 Schema

[Diagram showing clinical trial schema with stages: Registration, Cisplatin treatment (Week 1, 3, 5, 7, 9), Docetaxel treatment (Week 1, 3, 5, 7, 9), Panitumumab (6mg/kg) treatment (Week 1, 3, 5, 7, 9), RT 5040 cGy (180 cGy/day x 28 days) begin Week 5, Esophagectomy, Follow-up.]
Z4051: A Phase II Study of Neoadjuvant Therapy with Cisplatin, Docetaxel, Panitumumab Plus Radiation Therapy Followed By Surgery in Patients with Locally Advanced Adenocarcinoma of the Distal Esophagus

**Primary Objective:** Path CR

**Secondary Objectives:** Near complete path response, OS, DFS, safety, value of DNA hypermethylation as a predictor of response and survival
Esophageal Cancer: PET scan response to Induction Chemo

- Weber: Preop chemo
- PET scan performed at day 14
- PET responders: SUV decline \( \geq 35\% \)
- PET responders had improved 2 yr survival: 60\% vs 37\% for non responders
- PET prognostic for survival

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

- Use of PET to change induction therapy

Treatment Plan: MUNICON-1 trial

AEG type I-II

PET d0

CTx

PET d14

CTx: 3 months

Responder

Non-Responder

Resection

Resection

Response definition: Decrease of the SUV\textsubscript{mean} \(\frac{\text{PET}_d14}{\text{PET}_{\text{baseline}}} > 35\%\)

Overall survival (intention-to-treat-analysis)

Median survival [95% CI] in months:

**Metabolic Responder:** Not reached

**Metabolic Non-Responder:** 25.8 [19.4; 32.3]

Hazard ratio 2.13 [1.14-3.99]
Log-rank p-value: p<0.015

Median follow-up: 28.0 months
Comparison with historic cohort

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

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

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

Survival (median)
Responders: not reached
Non-Responders: 26 months
RTOG 0436 (In Development): Phase III Trial Evaluating the Addition of Cetuximab to Paclitaxel, Platinum and RT for patients with Esophageal Cancer Treated Without Surgery

**CURRENTLY RECOMMENDED CLINICAL TRIAL FOR CLINICALLY UNRESECTABLE ESOPHAGEAL ADENOCARCINOMA**

**Histology**
- Adenocarcinoma
- Squamous Cell

**Tumor size**
- < 5 cm
- > 5 cm

**Celiac Nodes**
- Absent
- Present

**Randomize**

**ARM 1**
RT + Paclitaxel + Cisplatin + Cetuximab

**ARM 2**
RT + Paclitaxel + Cisplatin

**RT** 50.4 Gy/1.8 Gy

**Cetuximab** 400 mg/m² day 1 then 250 mg/m² weekly

**Paclitaxel** 50 mg/m² weekly

**Cisplatin** 25 mg/m² weekly
RTOG 0436: Phase III Trial Evaluating the Addition of Cetuximab to Paclitaxel, Platinum and RT for Patients with Esophageal Cancer Treated Without Surgery

- Histology
  - Adenocarcinoma
  - Squamous Cell
- Tumor Size
  - < 5 cm
  - ≥ 5 cm
- Celiac Nodes
  - Absent
  - Present

**ARM 1**
RT + Paclitaxel + Cisplatin + Cetuximab

**ARM 2**
RT+ Paclitaxel + Cisplatin

RT 50.4 Gy/1.8 Gy
Cetuximab 400 mg/m² day 1 then 250 mg/m²2 weekly
Paclitaxel 50 mg/m²2 weekly
Cisplatin 25 mg/m²2 weekly
Esophageal Cancer: Future Studies

**US**

- **Inoperable**
  - Intergroup: EBRT + Paclitaxel / CDDP C225

- **Operable**
  - Novel CMT regimens + “Salvage” Surgery
Phase III Study of Neoadjuvant Trastuzumab and Chemoradiation for Esophageal Adenocarcinoma

- **HER-2 (+) (FISH)**
  - **CHEMORADIATION** → **SURGERY**
  - **TRASTUZUMAB + CHEMORADIATION** → **SURGERY + TRASTUZUMAB (1 YR)**
- **HER-2 (-) (FISH)** → **ALTERNATIVE STUDIES**

Chemoradiation: Investigators choice

Sample Size = 138 Her-2 (+) Pts, 90% Power to Increase 3-Yr Survival from 20% to 45%, 1-Sided α = 0.05
GE Junction
Siewert Classification

Type I
+ 5 cm

Type II
+ 1 cm
- 2 cm

Type III
- 5 cm
Esophageal Treatment Approaches

Neoadjuvant Chemoradiation +/- Surgery
Adjuvant and Peri-operative Approaches in Resectable GE Junction/Gastric

Adjuvant chemoradiation

Int 0116/SWOG 2001
20% GE junction

Perioperative chemotherapy

MAGIC 2007
25% GE junction/distal esophagus
INT 0116: Post-operative Chemoradiation for Gastric Cancer

- 556 patients randomized after gastrectomy to surgery or post-operative 5-FU chemoradiation
- Improved survival directly related to improvement in locoregional control
- 54% of patients underwent D0 dissection

Gastric Adjuvant Trial INT 0116
Overall Survival

![Graph showing survival rates with different treatments.

- Chemoradiotherapy
- Surgery only

P = 0.005
2-Sided Log-Rank

## INT 0116: ≥ G3 Toxicities CRT

<table>
<thead>
<tr>
<th>Type of Toxicity</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>54</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>33</td>
</tr>
<tr>
<td>Flu like</td>
<td>9</td>
</tr>
<tr>
<td>Infection</td>
<td>6</td>
</tr>
<tr>
<td>Neurological</td>
<td>4</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>4</td>
</tr>
<tr>
<td>Pain</td>
<td>3</td>
</tr>
<tr>
<td>Metabolic</td>
<td>2</td>
</tr>
<tr>
<td>Hepatic</td>
<td>1</td>
</tr>
<tr>
<td>Lung</td>
<td>1</td>
</tr>
<tr>
<td>Death*</td>
<td>1</td>
</tr>
</tbody>
</table>

Toxicities of 281 pts assigned to adjuvant therapy

* 1 cardiac event
  1 case of sepsis
  1 case of pulmonary fibrosis
CALGB 80101

Randomize

5FU/LV → 5FU/RT → 5FU/LV → 5FU/LV

ECF → 5FU/RT → ECF → ECF

N = 825
META-ANALYSIS OF PREOP CHEMOTHERAPY (Thirion et al, ASCO 2007)

4% BENEFIT WITH PREOP CHEMOTHERAPY @ 5 YRS

7% SURVIVAL BENEFIT FOR ADENOCARCINOMA WITH PREOP CHEMOTHERAPY

4% SURVIVAL BENEFIT FOR SCARM CARCINOMA WITH PREOP CHEMOTHERAPY
MAGIC Trial

Randomize

C-S-C

ECF x 3 cycles

Resection

Resection

ECF x 3 cycles

Follow-up

250 pts

253 pts

Cunningham et al. NEJM 355:11-20, 2006
MAGIC Results

Peri-op chemo arm

• Tumors smaller (no pCR)
• Less nodal disease (gastric cases)

Improvement in 5-year survival: 36% vs. 23%
CRITICS Trial (Ongoing Trial)

Randomize

ECFx3

Cape + Cisplatin + 45 Gy RT

ECF x 3

N = 788
All 3 Approaches Are Acceptable in the Treatment of Resectable GE Junction Cancers

Neoadjuvant chemoradiation

Adjuvant chemoradiation

Perioperative chemotherapy
IMAGING BIOMARKER RESPONSE PROSPECTIVE TRIAL
Phase II Trial of PET Scan-Directed Combined Modality Therapy in Esophageal Cancer

- Phase II data from Germany demonstrate early PET response is prognostic for survival in patients receiving induction chemotherapy
- SUV decrease of ≥ 35% v. <35% used to stratify PET responders v. non-responders
- PET responders had improved 2 yr survival: 60% vs 37% for non responders

Weber J Clin Oncol 19:3058;2001
CALGB Proposed PET-Driven Trial

Esophageal Adenocarcinoma Stewart I/II

Pre-treatment PET/CT then induction chemotherapy: mFOLFOX6 days 1,15

PET Scan day 22-28 to evaluate response to induction chemotherapy

PET-responders (≥ 35% SUV decrease): 5-FU and oxaliplatin days 29, 43, 47 with concurrent RT (5040 cGy in 180 cGy fx)

PET-non-responders (< 35% SUV decrease): irinotecan, docetaxel days 29, 36, 50, 57 with concurrent RT (5040 cGy in 180 cGy fx).

Referral for surgical resection 4-8 weeks post-RT.
Mirror Image of CALGB PET-Driven Trial

Esophageal Adenocarcinoma

Pre-treatment PET/CT then induction chemotherapy: irinotecan/docetaxel

PET Scan day 22-28 to evaluate response to induction chemotherapy

PET-responders (≥ 35% SUV decrease): irinotecan, docetaxel days 29, 36, 50, 57 with concurrent RT (5040 cGy in 180 cGy fx)

PET-non-responders (< 35% SUV decrease): 5-FU and oxaliplatin days 29, 43, 47 with concurrent RT (5040 cGy in 180 cGy fx).

Referral for surgical resection 4-8 weeks post-RT.
MUNICON-1 trial

Response definition: Decrease of the SUV_{mean} \frac{PET_{d14}}{PET_{baseline}} > 35%


Lordick, Lancet Oncol 2007
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
New Randomized Phase II Trial Design

T3/4 or N1 Esophageal Adenoca

PET Scan pre-treatment

Randomize

Induction Chemo:
modified FOLFOX6 days 1,15, 29

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

PET Scan day 36-42

Surgical resection 6 weeks post-RT

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

Induction Chemo:
Carboplatin/ Paclitaxel days 1,8,22,29
Statistical Considerations

• Null hypothesis: pCR rate of 5% versus 20% will be tested among PET non-responders within each induction regimen

• Difference is detectable with 90% power if 45 PET non-responders are studied for each induction regimen (1-sided α=0.25)

• A maximum of 120 patients will be enrolled on each arm (total of 240 patients)
  – Assuming 25% not assessable (inevaluable PET or failure to go to surgery for reasons unrelated to treatment) we will need approximately 60 non-responder

• pCR rate among PET responders and non-responders in each induction therapy will be compared directly as secondary analysis
Statistical Considerations

• With expected number of 45 evaluable non-responders per induction treatment, can detect an increase in 8 mo PFS from 50% to 70% with 83% power (test of binomial proportion, 1-sided \( \alpha=0.036 \), critical value 29).

Interim Analysis

• A two-stage design will be used
• 25 evaluable patients randomized to each arm
  – If 0 or 1 patients have pCR on a treatment regimen, that treatment regimen will be closed to further accrual due to lack of efficacy
  – If 2+ patients experience pCR, an additional 20 evaluable patients will be randomized to each successful treatment arm
Real-time Central PET Review

• Imaging Core Lab at The Ohio State University
  – Blinded Read of diagnostic and therapy assessment studies with electronic tracking
  – Trial progress assessment and reporting
  – Site qualification
  – Site training and QA oversight

• All participating sites will be required to undergo a virtual site visit
PET Interpretation

• A 35% decrease in SUVmax constitutes response
• If discrepancies between local and central review:
  – An adjudicator will blindly determine which interpretation they agree with.
  – if the patient is to remain on protocol, interpretation from the centralized review must be used.
  – If treated per local review, then patient will be coded as a protocol violation and will be taken off protocol
Additional Quality Assurance

• Central pathology review
  – SWOG trial used OHSU for central path review and overturned several pCRs
  – Working with Wendy Frankel to write pathology central review section
• Central radiotherapy review
  – IMRT and 3DCRT allowed
  – QARC overseeing submission of radiotherapy treatment planning data
  – Remote RT Quality Assurance Review after ITC has received complete data for the first 20 cases enrolled, and after every 20 enrolled thereafter
• Surgical quality review
Correlative Science Studies

• ERCC1 expression: predictor of response to platinum agents

• Promoter methylation: predictor of response to combined modality treatment
  – Evaluate status of methylation of nine candidate biomarker genes
  – Measure expression levels of selected specific microRNAs
  – Correlate methylation status with response to chemoradiation

• Stephen Meltzer, MD - correlative science chair
FIG. 1. The relationship between the sigmoid curves representing tumor control probability (TCP) and normal tissue complication probability is termed the therapeutic ratio.
Conformal Radiation Delivery
IMRT
IMRT in Esophageal Cancer

• Several dosimetric studies have been published comparing 3D CRT vs. IMRT
  – Nutting 2000, 2001
  – Wu 2004
  – Zhao 2004
  – Chandra 2005

• These studies show the ability of IMRT to reduce dose to normal tissue while coverage of target remains the same
Conclusions

• No dosimetric parameter predicted for pulmonary complication
• Only clinical factor that was significant on multivariate analysis for development of pulmonary complications was the pre-operative FEV1.
IGRT

• Image Guided Radiation Therapy
• Set-up Verification
  – 3D – MV Portal Verification Films Weekly
  – IMRT – MV Portal Verification Films Daily
• IGRT
  – KV Portal Verification Films
  – Cone-beam CT
Cone-beam CT
Cone-beam CT
PILOT STUDY PROPOSAL:
Atlas Implementation to Optimize Target Delineation for Conformal Radiotherapy in the Cooperative Group Setting:
A Prospective, Randomized In Silico “Sister Study” to Z4051.

Clifton (Dave) Fuller, M.D.
Department of Radiation Oncology
The University of Texas Health Science Center at San Antonio

Charles R. Thomas, Jr., M.D.
Department of Radiation Medicine
Oregon Health and Science University

Tracey Schefter, M.D.
Department of Radiation Oncology
University of Colorado

Dwight Heron, M.D.
Department of Radiation Oncology
University of Pittsburgh

TJ FitzGerald, M.D.
QARC/Department of Radiation Oncology
University of Massachusetts
Introduction

• Modern radiotherapy affords exceptional conformality of dose delivery, such that steep dose gradients may be implemented between target and non-target tissue.

• However, dose delivery is limited, among others, by 2 major factors:
  – Target volume delineation error (input error)
  – Spatial alignment of target volumes with plan geometry (set-up error)

• Lack of data regarding makes evaluation of the impact (dosimetrically and/or clinically) of target volume delineation variability difficult to quantify, and extant studies are limited by small sample size.

• Consequently, cooperative group efforts to examine target volume variability represent an enticing opportunity for ascertaining the effect of target volume variability, as well as an avenue for potential corrective measures (protocol amendment, QA, automated “scoring”, etc.).
There was a substantial inconsistency in defining the planning target volume, both transversely and longitudinally, among radiation oncologists. The potential benefits of 3D treatment planning with high-precision dose delivery could be offset by this inconsistency in target-volume delineation by radiation oncologists. This may be particularly important for multicenter clinical trials, for which quality assurance of this step will be essential to the interpretation of results.
Z4051 Ancillary Study

• A Phase II Study of Neoadjuvant Therapy with Cisplatin, Docetaxel, Panitumumab Plus Radiation Therapy Therapy Followed by Surgery in Patients with Locally Advanced Adenocarcinoma of the Distal Esophagus
  – ACOSOG approved study
  – Suggests use of PET/CT for target delineation
  – Proposed target volume analysis would be performed as an *in silico* “sister study” for quality assurance of complex imaging integration in this and future trials
  – Anonymized data from a characteristic cases would be used (no HiPPA issues)
  – *Will not affect/modify recommendations for the actual Z4501 protocol*
  – IRB exempt (UTHSCSA IRB #HSC20080166E) as no clinical modifications/alterations will be planned
  – Minimum sample size: 14 users, contouring the same 4 cases twice (paired test/re-test format)
Significance

- Target volume variability represents a clinically relevant error component in clinical trial setting.
- Quantification of the degree of target volume variability in cooperative group settings may serve to minimize “noise” in clinical trials.
- Inclusion of atlas may afford site-specific improvement in target volume delineation.
- Incorporation of rapid central target delineation evaluation may have utility for QA/accreditation.
Specific aims

Primary specific aims include:

• **Summarization of differentials in target volume delineation parameters, as assessed by established target delineation evaluation software, between the expert and non-expert users**

• **Evaluation of the stability or improvement over time target volume delineation parameters in Specific Aim 1 using a time-delayed re-test.**

• **Determination of the impact of a formal atlas-based instructional protocol on target volume delineation concordance with expert-derived target structures.**
Specific aims II

Specified secondary sub-goals include:

- To determine the feasibility of multi-site electronic data collection methods for evaluation of target delineation, plan comparison and user survey.
- To determine specific criteria for target volume “credentialing” in trials where IMRT is to be implemented.
- Evaluation of PET-CT utilization on inter-observer variability.
Study design

Figure 1: Study design

Phase 1

Observers

Contour CT scan

Randomization

Atlas

No Atlas

Phase 2

Re-contour CT scan

Finish

Re-contour CT scan

Finish
Power/Sample size

- Based on inter- and intra-observer correlation estimates from a recently completed pilot series evaluating the effect of atlas utilization for rectal cancer, power and sample size analysis (G*Power 3 statistical software) was performed, assuming:
  - minimum possible asymptotic relative efficiency of $\geq 0.864$ for non-parametric test power,
  - a priori power goal $(1-\beta)$ of 0.8,
  - non-Bonferroni corrected two-tailed $\alpha=0.5$,
  - detection of an effect size of 0.8 (large effect).
  - This resulted in a minimum requisite sample size of 14 observers per randomization arm.
  - A medium effect (effect size 0.5-0.6) would necessitate 21-35 observers.
Thanks

• For greater details please refer to proposal hand-out
  • Questions?
  • Comments?
  • Volunteers?
A 37 y female described lifelong dysphagia with worsening dysphagia over the past 4 months. Endoscopy revealed an esophageal tumor from 26-32 cm. Biopsy revealed poorly differentiated adenocarcinoma. Endoscopic staging demonstrated T2N1M1a disease. PET/CT staging showed uptake only in the distal esophageal tumor (25 SUV).
• The patient was obese at 67 inches and 266 lbs, but was otherwise healthy with no medical problems. Her only medication was aciphex. She stopped smoking in 2000 after a 14 pack year smoking history.
She received neoadjuvant chemo/RT with continuous infusion 5-FU at 225 mg/sqm plus cisplatin at 30 mg/sqm weekly with RT delivered to the distal esophagus including the celiac axis. Total radiation dose was 5040 cGy to the calculated volume given as 28 fractions over 42 days, with TomoTherapy (RT 088) using 6 MV photons with daily CT scan prior to treatment to verify location.
Summary Stage II/III Esophagus/GE Jnx

• Radiation has a well established role in the definitive management of esophageal cancer

• As combined modality strategies seek to optimize therapeutic gains we must carefully consider patient selection

• We must respect the lessons from the past and critically evaluate the ability of new technology to improve the therapeutic ratio.

• *How we deliver the dose is as important as the dose we deliver*
**Esophageal Cancer**

**WORKUP**
- H&P
- Barium swallow (optional)
- Esophagogastroduodenoscopy to visualize entire upper GI tract, if possible
- CBC, SMA-12, Chest/abdominal CT
- Bronchoscopy, if tumor is at or above the carina with no evidence of M1 disease
- Endoscopic ultrasound (EUS), if no evidence of M1 disease with FNA if indicated
- Laparoscopy (optional) if no evidence of M1 disease and tumor is at GE junction
- Biopsy confirmation of suspected metastatic disease
- PET/CT scan if no evidence of M1 disease

**CLINICAL STAGE**
- Stage I–III, IVA\(^a\) (locoregional cancer)
- Stage IVB metastatic cancer

**ADDITIONAL EVALUATION**
(as clinically indicated)
- Multidisciplinary evaluation is encouraged (mandatory for patients with celiac-positive disease)
- Nutritional assessment (for preoperative nutritional support, consider nasogastric or J-tube [PEG is not recommended])
- Barium enema or colonoscopy if colon interposition or bypass planned
- Arteriogram (optional)
  - Consider if performing colon interposition

**MEDICATIONS**
- Medically fit,\(^b\) resectable\(^c,d\) T1–T4,\(^e\) N0–1, NX, or Stage IVA,\(^f\) Metastatic cancer
  - See Primary Treatment (ESOPH-2)
- Medically unfit for surgery, unresectable T4,\(^g\) unresectable stage IVA\(^h\) or Surgery not elected and patient medically able to tolerate chemoradiation
  - See Primary Treatment (ESOPH-4)
- Medically unfit for surgery and patient unable to tolerate chemoradiation
  - See Primary Treatment (ESOPH-4)

**PALLIATIVE THERAPY**
- Metastatic cancer
  - See Palliative Therapy (ESOPH-6)

---

\(^a\) Celiac nodal involvement in cancers of the gastroesophageal junction may still be considered for combined modality therapy.

\(^b\) Medically able to tolerate major abdominal and/or thoracic surgery.

\(^c\) Chemoradiation therapy is the preferred modality for cervical esophageal carcinoma.

\(^d\) See Principles of Surgery (ESOPH-A).

\(^e\) Resectable T4: involvement of pleura, pericardium or diaphragm. T1–T3 tumors are resectable even with regional nodal metastases.

\(^f\) Resectable Stage IVA: Resectable celiac nodes and no involvement of celiac artery, aorta, or other organs.

\(^g\) Unresectable T4: invasion of aorta, trachea, heart, great vessels.

\(^h\) Unresectable Stage IVA: Unresectable celiac nodes with involvement of celiac artery, aorta, or other organs.

---

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Figure 1. Process for discovery on molecular signatures consists of the integration of three basic components: (top, left) physician/patient interaction encompassing patient history and other clinical information, acquisition of the appropriate tissue sample and pathology; (right) analytic component involving tissue preparation, MS data acquisition, raw data normalization, and validation; (bottom, left) biocomputational processing to identify protein signatures at high confidence levels and with appropriate validation relevant to the clinical question at hand.
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G YANG