Welcome to
Master Class for Oncologists
Miami, FL
December 19, 2009

Session 1:
7:30 AM - 8:15 AM
Update on Esophagogastric Cancers:
Weighing the Therapeutic Options
Peter C. Enzinger, MD
Dana-Farber Cancer Institute
& Harvard Medical School

Presenter Disclosure Information

The following relationships exist related to
this presentation:

- Dr Enzinger serves as a speaker/consultant for sanofi-
  aventis U.S., Pfizer Inc., Roche, Genentech, and
  ImClone/Bristol-Myers Squibb.

Off Label/Investigational Discussion:
Use of irinotecan, oxaliplatin, and capecitabine for
metastatic esophagogastric cancer

Incidence of Esophageal Cancer: 16,470 new cases and 14,530
deaths in 2009

Risk Factors: Esophageal CA

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>SCC</th>
<th>ADC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Barrett's Esophagus</td>
<td>---</td>
<td>+++</td>
</tr>
<tr>
<td>Weekly Reflux Symptoms</td>
<td>---</td>
<td>+</td>
</tr>
<tr>
<td>Obesity</td>
<td>++</td>
<td>---</td>
</tr>
<tr>
<td>Tobacco/Alcohol</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Caustic Injury to esophagus</td>
<td>+++</td>
<td>---</td>
</tr>
<tr>
<td>Acid Reflux Symptoms</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Barrett's Esophagus</td>
<td>---</td>
<td>+++</td>
</tr>
<tr>
<td>History of head &amp; neck cancer</td>
<td>+++</td>
<td>---</td>
</tr>
<tr>
<td>History of breast cancer</td>
<td>+++</td>
<td>---</td>
</tr>
<tr>
<td>Frequent consumption of hot beverages</td>
<td>++</td>
<td>---</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>---</td>
<td>+++</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>---</td>
<td>+++</td>
</tr>
</tbody>
</table>

++++ = > 8-fold risk
+++ = 4-8-fold risk
++ = 2-4-fold risk
+ = < 2-fold risk
- = Conflicting studies
--- = No proven risk

Tobacco/Alcohol and Esophageal Cancer

Odds Ratio

<table>
<thead>
<tr>
<th>Cigarettes per Day</th>
<th>Drinks per Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1-19</td>
<td>1</td>
</tr>
<tr>
<td>20-29</td>
<td>2</td>
</tr>
<tr>
<td>30-39</td>
<td>3</td>
</tr>
<tr>
<td>40+</td>
<td>4</td>
</tr>
<tr>
<td>3.5</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>14.5</td>
<td>7</td>
</tr>
<tr>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>28.5</td>
<td>9</td>
</tr>
<tr>
<td>36+</td>
<td>10</td>
</tr>
</tbody>
</table>

Data from Takezaki 2000, Wu 2001 and Brown 2001

Adenocarcinoma
Squamous Cell Carcinoma
Adenocarcinoma
Squamous Cell Carcinoma

Neoplastic Progression of Barrett’s Esophagus

2003 AJCC Classification of Esophageal Carcinoma

Neoplastic Progression of Barrett’s Esophagus

GERD
1/7 Americans

Squamous epithelium 10%/yr
Metaplasia 6%/yr
Low-Grade Dysplasia 1%/yr
High-Grade Dysplasia 5%/yr
ADC 5%/yr
METS

Oxidative stress
Inflammation
↑G1&G2
↑COX-2
↑BCL-2

Early Genetic Events:
P53 mutation; p16 mutation/methylation
EGF(R), telomerase RNA
Late Genetic Events:
4 N (G2) anaplasity of G13q and LOH of G13q/18q

c-erbB2
E-cadherin-cat

2003 AJCC Classification of Esophageal Carcinoma

Stage Tumor Node Metastasis
0 Tis N0 M0
I T1 N0 M0
IIA T2a N0 M0
IIB T2b N1 M0
III T3 N1 M0
T4 Any N M0
IVA Any T Any N M1a
IVB Any T Any N M1b

Incidence of Gastric Adenocarcinoma

Females in USA
Males in USA

Risk Factors for Gastric Adenocarcinoma

• Nutritional
  – Low fat or protein consumption
  – Salted meat or fish
  – High Nitrate consumption
• Environmental
  – Poor food preparation (smoked)
  – Lack of refrigeration
  – Poor drinking water (well water)
  – Occupation (rubber, coal workers)
  – Smoking (1.6x)
  – Low social class
• Medical
  – Prior gastric surgery
  – Helicobacter pylori infection (2x)
  – Gastric atrophy and gastritis

Proposed Cascade of Pathologic Events in Gastric Adenocarcinoma

Salt N-nitroso carcinogens Chronic inflammation and reactive oxygen species

Helicobacter pylori Salt B-carotene
Normal Superficial gastritis Atrophic gastritis Metaplasia Dysplasia Carcinoma

Higher pH Bacterial growth + nitrate
Gastric ascorbic acid N=0
mutagens

inhibition promotion

Adapted from Correa

1997 AJCC Classification of Gastric Carcinoma


1997 AJCC Classification of Gastric Carcinoma


2003 AJCC Staging Classification of Gastric Carcinoma

Primary Tumor Stage

T1a: a tumor that invades the muscularis propria
T1b: a tumor that invades the subserosa
Which one of the following strategies has NOT been shown in the setting of a randomized trial to extend survival in a 68 yo man (PS 0, no significant comorbidities) with locally advanced GE junction adenocarcinoma?

1. Chemotherapy surgery chemoradiation therapy
2. Chemotherapy surgery chemotherapy
3. Chemoradiation therapy surgery
4. Surgery chemotherapy chemoradiation chemotherapy

What Can Surgery Accomplish?

Esophageal Cancer Treated With Surgery

Does Adjuvant Chemotherapy Improve Surgery Outcomes?

Neoadjuvant Chemotherapy Compared with Surgery Alone for Localized Esophageal Cancer

FNLCC ACCORD 07-FFCD 9703 Trial: Schema

Randomization

CT + S

S

Within 4 weeks

Resection

Follow-up

Stage II-IVA
75% distal esophagus or GEJ ADC

FP x 3/4 or no treatment

FP x 1/2 every 28 days

4 - 6 weeks Resection

4 - 6 weeks Resection

FP + S

(+) FP = 5FU: 800 mg/m² CI x 5 days - CDDP: 100 mg/m² at d1 or d2, 1-hr infusion

Boige, ASCO 2007

FP x 3/4 or no treatment

Follow-up

(*) FP = 5FU: 800 mg/m² CI x 5 days - CDDP: 100 mg/m² at d1 or d2, 1-hr infusion

Beige, ASCO 2007
**ACCORD 07: Pathological Results**

<table>
<thead>
<tr>
<th>Tumor stage</th>
<th>S</th>
<th>CT + S</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>0%</td>
<td>3%</td>
<td>0.16</td>
</tr>
<tr>
<td>T1, T2</td>
<td>32%</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>T3, T4</td>
<td>68%</td>
<td>58%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nodal status (%)</th>
<th>S</th>
<th>CT + S</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-</td>
<td>20%</td>
<td>33%</td>
<td>0.054</td>
</tr>
<tr>
<td>N+</td>
<td>80%</td>
<td>67%</td>
<td></td>
</tr>
</tbody>
</table>

N: number of nodes removed

Median: 19
Range: (2 - 82)

**ACCORD 07: Overall Survival**

![Graph showing overall survival rates](image)

At risk: 111 79 53 38 27 16 13 7

5-year OS: 24% (95% CI, 16%-33%) vs 38% (95% CI, 28%-47%)

Log rank P-value = 0.021
Hazard Ratio, 0.69 (95% CI, 0.50-0.95)

**Localized Esophageal Cancer**

Does Neoadjuvant Chemoradiation Therapy Improve Surgery Outcomes?

**POET: Schema**

<table>
<thead>
<tr>
<th>Arm A</th>
<th>PLF I</th>
<th>PLF II</th>
<th>PLF III (3 weeks)</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Week</td>
<td>6</td>
<td>7</td>
<td>1314</td>
<td>17</td>
</tr>
<tr>
<td>PLF</td>
<td>15 x 2 Gy in 3 weeks</td>
<td>PE (1 week)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm B</th>
<th>PLF I</th>
<th>PLF II</th>
<th>PE (1 week)</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 x 2 Gy in 3 weeks</td>
<td>PE (1 week)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**POET: Downstaging**

<table>
<thead>
<tr>
<th></th>
<th>Arm A (n = 49)</th>
<th>Arm B (n = 45)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Path CR</td>
<td>2%</td>
<td>16%</td>
<td>0.03</td>
</tr>
<tr>
<td>T1-4N0M0</td>
<td>35%</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>Node neg.</td>
<td>37%</td>
<td>64%</td>
<td>0.01</td>
</tr>
<tr>
<td>T0-4N+M0</td>
<td>55%</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>T1-4N+M1</td>
<td>8%</td>
<td>4%</td>
<td></td>
</tr>
</tbody>
</table>
Can Surgery Improve the Outcomes of Chemoradiation?

Localized Esophageal Cancer

Prospective Randomized Intergroup Study:
Radiation Therapy vs Chemotherapy + Radiation Therapy for Localized SCC or ADC of the Esophagus

Chemoradiation Therapy With or Without Surgery:
French Phase III Trial

- A total of 455 patients with localized esophageal cancer were given 2 courses of 5-FU/cisplatin plus radiation therapy.
- 259/455 patients experienced a "partial response", were considered operative candidates, and entered the randomized component of the trial.


Patients: (N = 177) uT3-4,N0-1, M0 with SCC

Chemoradiation Therapy With or Without Surgery: German Phase III Trial (Schema)

**Randomize**

- Chemoradiation: Cisplatin+Etoposide + 40 Gy RT → Surgery
- Chemoradiation: Cisplatin+Etoposide + > 60 Gy RT

**Chemoradiation Therapy With or Without Surgery: German Phase III Trial (Results)**

<table>
<thead>
<tr>
<th>Arm</th>
<th>Completed Treatment</th>
<th>Treatment Mortality</th>
<th>3-yr Local Recurrence</th>
<th>Median Survival</th>
<th>3-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A</td>
<td>C/RT -95</td>
<td>62%</td>
<td>12.8%</td>
<td>41%</td>
<td>16 mos.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B</td>
<td>C/RT</td>
<td>85%</td>
<td>3.5%</td>
<td>64%</td>
<td>15 mos.</td>
</tr>
</tbody>
</table>


**C/RT +/- Surgery for Esophageal SCC**

Median survival (N=172):
- Arm A (C/RT -95) -16.4 months
- Arm B (C/RT only)-14.9 months

- 31.3% (P=0.02)
- 24.4%

**Conclusions from these Results**

**Localized Esophageal**

Pre-operative cisplatin/5-FU chemotherapy offers a small survival advantage in distal esophageal and GE junction cancer.

Neoadjuvant cisplatin-based chemoradiation offers a greater survival advantage with better local control but increased surgical morbidity.

Surgery may not be needed in patients who have a clinical response to chemoradiation.

**Localized Gastric Cancer**

**What Can Surgery Accomplish?**

**Gastric Cancer**

Survival in 633 patients, according to 1997 TNM stage
Prospective Studies of Total Gastrectomy (TG) vs Subtotal Gastrectomy (DST) for Distal Gastric Cancer

Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>DST</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gouzi 1989</td>
<td>169</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>Bozzetti 1999</td>
<td>648</td>
<td>64</td>
<td>62</td>
</tr>
</tbody>
</table>

What is the Ideal Extent of Lymphadenectomy?

- **D0**: Removes less than all relevant N1 nodes
- **D1**: Requires the dissection of the N1 nodes (1–6)*
- **D2**: Includes the N1 and N2 nodes (7–11)
- **D3**: Includes the N1, N2, and N3 nodes (12–15)
- **D4**: Includes the N1, N2, N3, and N4 nodes (16)

*nodes 2, 4 remain if distal subtotal gastrectomy

Randomized Study of D1 and D2 Dissection for Gastric Cancer

711 patients undergoing curative resection of gastric cancer

<table>
<thead>
<tr>
<th></th>
<th>Peri-Op Morbidity</th>
<th>Peri-Op Mortality</th>
<th>Median Hospital Stay (days)</th>
<th>5-Year Survival</th>
<th>11-Year Survival</th>
<th>(*P = 0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>D1</strong> Dissection</td>
<td>25%</td>
<td>4%</td>
<td>14</td>
<td>45%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td><strong>D2</strong> Dissection</td>
<td>43%</td>
<td>10%</td>
<td>16</td>
<td>47%</td>
<td>35%</td>
<td></td>
</tr>
</tbody>
</table>


What are Proven Strategies to Enhance Outcomes for Surgical Resection?

Localized Gastric Cancer

Intergroup Protocol 0116 Adjuvant Therapy for Gastric Cancer

Stratify
- depth of tumor penetration
- number involved nodes
- location of tumor
- extent of surgery

5-FU/leucovorin + 4500 cGy radiation

**Localized Gastric:**

Post-operative 5-FU-based chemoradiation therapy remains the standard of care for muscle-invasive or LN positive disease.

The MAGIC trial demonstrates that pre- and post-operative ECF improves survival. It may be particularly beneficial for downstaging extensive local disease.

**What are the Active Agents and Combinations for this Disease?**

**Localized Gastroesophageal Junction Cancer?**

Which one of the following strategies has NOT been shown in the setting of a randomized trial to extend survival in a 68 yo man (PS 0, no significant comorbidities) with locally advanced GE junction adenocarcinoma?

1. Chemotherapy → surgery → chemoradiation therapy
2. Chemotherapy → surgery → chemotherapy
3. Chemoradiation therapy → surgery
4. Surgery → chemotherapy → chemoradiation → chemotherapy
Prior to selecting systemic treatment, which of the following molecular studies should be performed on tumor tissue from a 73 yo man with gastric cancer metastatic to liver and lungs?

1. EGFR
2. K-ras
3. HER-2/neu
4. MSI
5. c-KIT
Advanced Esophagogastric Cancer:
Newer Agents

Class
Antimetabolite
Heavy Metal
Taxane
Topoisomerase Inhibitor

Agent
Capecitabine
Oxaliplatin
Paclitaxel
Irinotecan

MOA
Reduces thymidine production and competes with uridine triphosphate for incorporation into RNA
Produces intrastrand and interstrand platinum-DNA cross-links
Binds to and stabilizes tubulin inhibiting microtubule disassembly
Inhibits topoisomerase I

Response
26%
21%
13%
21%

S-1
Inhibits thymidylate synthase and CDHP, and competes with uridine triphosphate for incorporation into RNA

26%


CDHP = 5-chloro-2,4-dihydroxypyridine; na = not available.

REAL-2: Schema
Previously untreated patients with locally advanced or metastatic esophagogastric cancer

REAL-2: Survival (ITT)

Capecitabine / Cisplatin vs. 5-FU / Cisplatin

Progression-Free Survival

Estimated probability

Median PFS

HR = 0.81 (95% Cl, 0.63—1.04)
Compared to HR upper limit 1.25, P = 0.0008

- ORR: FP (29%) XP (41%)
- MS: FP (9.3 mo) XP (10.5 mo)
- Toxicity: Similar
- Conclusions: XP is non-inferior to FP (HR, 0.8; 95% CI, 0.6–0.9)

Kang. ASCO 2006

Capecitabine / Cisplatin vs. 5-FU / Cisplatin

Primary endpoint: Superiority for TTP
Secondary endpoints: Response rate (RR), time to treatment failure (TTF), overall survival (OS), safety

N = 112

FLP - 5-FU 2000 mg/m2 24-hr
Leucovorin 85 mg/m2 d1
Oxaliplatin 85 mg/m2 d1
q2 w

N = 106

FKL - 5-FU 2000 mg/m2 24-hr
Leucovorin 85 mg/m2 d1
Cisplatin 50 mg/m2 d1
q2 w


5-FU/LV + Oxaliplatin vs 5-FU/LV + Cisplatin

Schema

Primary endpoint: Non-inferiority in PFS, HR <1.4
Secondary endpoints: Response rate (RR), time to response (TTR), overall survival (OS), safety

N=160
XP - Capecitabine 1000/m2 twice daily d1-14
Cisplatin 80/m2 d1 q3 weeks

N=156
FP - 5-FU 800 mg/m2 d1-5
Cisplatin 80 mg/m2 d1 q3 weeks

Kang. ASCO 2006
Prior to selecting systemic treatment, which of the following molecular studies should be performed on tumor tissue from a 73 yo man with gastric cancer metastatic to liver and lungs?

1. EGFR
2. K-ras
3. HER-2/neu
4. MSI
5. c-KIT

Conclusions from these Results

Metastatic Esophagogastric:

The most active single agents are the 5-fluoro-pyrimidines, platinum analogues, taxanes, and irinotecan.

Combinations of fluoropyrimidine and platinum remain the standard of care. Trastuzumab should be added for HER2/neu 2-3+ or FISH+ tumors.

Weekly irinotecan/cisplatin is most convenient. FOLFOX is best for patients with hepatic or renal insufficiency.