Esophageal Cancer:
Is There a Standard Treatment?

Michael Y. Chang, MD, MPH
Kaiser Los Angeles Medical Center
National Surgical Symposium
4/3/2008
Esophageal Cancer Epidemiology

- Annually in the US:
  - 13,900 new cases
  - 13,000 deaths (7th leading cause of cancer death in men)
- Lifetime risk: 0.8% men, 0.3% women
- Mean age at diagnosis: 67 years
- Overall incidence increased 20% over past 30 years
  - Incidence of squamous cell has decreased
  - Incidence of adenocarcinoma increased 450% in white males
Esophageal Cancer Pathology

- Squamous cell carcinoma + adenocarcinoma = 90%
  - Adenocarcinoma – 75% in distal esophagus
  - Squamous cell – middle or distal esophagus

- Pathogenesis
  - Oxidative damage from smoking or GERD initiates the carcinogenesis process

- At diagnosis over 50% have metastatic disease or unresectable tumors

- Symptoms: Dysphagia 74%, Weight loss 57%, Odynophagia 17%
Diagnostic Studies

- Esophagogram - Stricture or ulceration
- Endoscopy - Friable mass, ulcer
- CT chest, abdomen, pelvis

- EUS – tumor stage, regional lymph nodes
  - Meta-analysis, World J Gastro 3-2008
  - 49 studies (n=2558)
  - T stage sensitivity & specificity > 90%
  - N stage sensitivity & specificity > 90%
  - FNA suspicious regional lymph nodes
Diagnostic Studies

- PET – ACSOG Z0060 (Meyers, 2007)
  - Multi-institutional, 189 patients
  - No metastatic disease by CT
  - PET detected distant disease –
    - at least 5%
    - as high as 14%
  - False positive 3%
  - False negative n=7 (3.7%)
- Thoracoscopic, laparoscopic staging

Enzinger, 2003
Staging & Survival

- Overall 5 year survival 14%
- Survival after surgery for stage 0 to III.

Table 2. Five-Year Survival Rates for Esophageal Carcinoma, According to the Tumor–Node–Metastasis Classification.*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor</th>
<th>Node</th>
<th>Metastasis</th>
<th>5-Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>Tis</td>
<td>N0</td>
<td>MO</td>
<td>&gt;95</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>MO</td>
<td>50–80</td>
</tr>
<tr>
<td>II A</td>
<td>T2-3</td>
<td>N0</td>
<td>MO</td>
<td>30–40</td>
</tr>
<tr>
<td>II B</td>
<td>T1-2</td>
<td>N1</td>
<td>MO</td>
<td>10–30</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N1</td>
<td>MO</td>
<td>10–15</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>Any N</td>
<td>MO</td>
<td></td>
</tr>
<tr>
<td>IVA</td>
<td>Any T</td>
<td>Any N</td>
<td>M1a</td>
<td>&lt;5</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1b</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Enzinger, 2003
Staging & Survival

- Rice, 2003 JTCVS
- Cleveland Clinic prospective database
- 480 Esophagectomy
- No induction therapy
- Only 2 patients lost to follow-up
- All cause mortality
Surgery

- Esophagectomy operations
  - Ivor Lewis – R thoracotomy, laparotomy
    - Chest anastomosis
    - Transhiatal – Laparotomy, L neck
    - Neck anastomosis
  - Three field – R thoracotomy, laparotomy, L neck
    - Neck anastomosis
  - Minimally invasive versions of the above

Luketich, 2000
Transthoracic resection (3 field) vs. transhiatal

- Hulscher, NEJM, 2002 (Netherlands)
- Randomized trial 220 patients
- No difference in stage
- Transthoracic higher morbidity
- Survival: no difference
Surgery

• Complications
  – Operative mortality: 5 – 10%
  • Some studies report mortality 17 – 23% using Medicare data (Birkmeyer, NEJM 2002)
  – Perioperative complications: 25 – 40%
Radiation Therapy

• Preop radiation therapy + surgery
  – 5 randomized trials
  – None showed survival advantage with preop RT

• Postop radiation therapy
  – No survival advantage
Chemotherapy

- Preop chemo + surgery
  - 2 large randomized trials – cisplatin, 5-FU
    - Kelson, NEJM 1998
      - 440 patients
      - 3 cycles preop, 1 cycle post-op
      - No survival benefit
    - Medical Research Council, Lancet 2002
      - 802 patients, 9% also received radiation
      - 2 cycles preop
      - 2 year survival: 43% vs 34%
Chemotherapy

- Adjuvant chemotherapy
  - 3 phase III trials comparing surgery + adjuvant chemotherapy vs surgery alone
    - No difference in survival
  - Meta-analysis of randomized and non-randomized data also showed no difference in survival
Chemotherapy and Radiation Only

- **Stahl, JCO 2005**
  - Randomized trial chemo-RT + surgery vs. chemo-RT alone
  - Squamous cell carcinoma only
  - 172 patients. T3-T4. Median follow up 6 years
  - Surgery improved local control, but not survival

- **Bedene, JCO 2007**
  - No survival difference
Chemotherapy, Radiation, Surgery

- Preop chemotherapy and radiation therapy + surgery
  - 8 randomized studies
  - All but 2 studies suffered from small sample size
  - One single institution trial showed a survival benefit

<table>
<thead>
<tr>
<th>Study, Year, and Group</th>
<th>No. of Patients</th>
<th>Histologic Diagnosis</th>
<th>Chemotherapy</th>
<th>Total Dose of Radiotherapy</th>
<th>Median Survival</th>
<th>3-yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nygaard et al., 1992</td>
<td>41/47</td>
<td>Squamous-cell carcinoma</td>
<td>Cisplatin, bleomycin</td>
<td>3500†</td>
<td>NA/NA</td>
<td>9/17</td>
</tr>
<tr>
<td>Le Prise et al., 1994</td>
<td>41/45</td>
<td>Squamous-cell carcinoma</td>
<td>Cisplatin, fluorouracil</td>
<td>2000†</td>
<td>10/10</td>
<td>10/19</td>
</tr>
<tr>
<td>Apinop et al., 1994</td>
<td>34/35</td>
<td>Squamous-cell carcinoma</td>
<td>Cisplatin, fluorouracil</td>
<td>4000</td>
<td>7/10</td>
<td>20/26</td>
</tr>
<tr>
<td>Walsh et al., 1996</td>
<td>55/58</td>
<td>Adenocarcinoma</td>
<td>Cisplatin, fluorouracil</td>
<td>4000</td>
<td>11/16</td>
<td>6/32</td>
</tr>
<tr>
<td>Bosset et al., 1997</td>
<td>139/143</td>
<td>Squamous-cell carcinoma</td>
<td>Cisplatin</td>
<td>3700</td>
<td>19/19</td>
<td>37/39</td>
</tr>
<tr>
<td>Law et al., 1998</td>
<td>30/30</td>
<td>Squamous-cell carcinoma</td>
<td>Cisplatin, fluorouracil</td>
<td>4000</td>
<td>27/26</td>
<td>NA/NA</td>
</tr>
<tr>
<td>Urba et al., 2001</td>
<td>50/50</td>
<td>Squamous-cell carcinoma (25%) and adenocarcinoma (75%)</td>
<td>Cisplatin, vinblastine, fluorouracil</td>
<td>4500</td>
<td>18/17</td>
<td>16/30</td>
</tr>
<tr>
<td>Burmeister et al., 2002</td>
<td>128/128</td>
<td>Squamous-cell carcinoma (9%) and adenocarcinoma (61%)</td>
<td>Cisplatin, fluorouracil</td>
<td>3500</td>
<td>22/19</td>
<td>NA/NA</td>
</tr>
</tbody>
</table>
• NEJM, 1996. Single institution randomized trial.
• 113 patients – 58 multimodality, 55 surgery only
• Preop staging: PE, CXR, abd US, EGD
• 2 cycles cisplatin & 5 FU + radiation 40 Gy
• 5 surgical approaches at discretion of surgeon
• Median followup 18 months
• 3 year survival
  – 32% vs. 6% (P=0.01)
Meta-analysis of Multi-modality Therapy

• Greer, Surgery 2005
  – 6 Randomized controlled trials
  – Multimodality therapy has a small, non-statistically significant improvement in survival

• Gebski, Lancet Oncology 2007
  – 10 Randomized controlled trials
  – Multimodality therapy improved survival by 13% at 2 years (p=0.04)
CALGB 9781, JCO, March 2008

- Multi-institutional US trial intended to answer the question of preop chemo, RT followed by surgery
- Groups
  - 2 cycles cisplatin & 5 FU with radiation 50 Gy, followed by surgery
  - Surgery alone
- Planned 475 patients for enrollment
- Only 56 patients enrolled in 3 years (1997 – 2000). Closed for poor accrual
  - Physician bias, patient preference
  - Multi-modality 30 patients, surgery only 26 patients
• Preop staging: EGD, CT, bone scan
  – EUS (50%) and thoracoscopy / laparoscopy (25%) were recommended
• No difference in patient characteristics
  – Trimodality: 67% N0, 33% N1
  – Surgery: 85% N0, 15% N1
  – 75% Adenocarcinoma
• Surgery:
  – Ivor Lewis 30
  – Three field 8
  – Transhiatal 6
CALGB 9781, JCO, March 2008

- Median follow-up 6 years
- Intention to treat analysis
- Median survival: 4.5 yrs vs. 1.8 yrs
- 5 yr survival: 39% vs. 16%
- Improved survival
- Toxicity manageable
- No increase in operative mortality

![Graph showing survival rates](image)

**Fig 2.** Kaplan-Meier estimates of overall survival (OS) by treatment arm measured from study entry until death from any cause. (*) NE, not estimable. †Asymptotic results for OS were comparable to those obtained using the exact method.
Conclusion

- Surgery only – No
- Preop radiation + surgery – No
- Preop chemo + surgery – Maybe
- Preop chemo-RT + surgery – Probably Yes
- Chemo-RT only – Probably Yes for squamous cell
- Post-op chemo – Probably No
- Post-op RT - No