Multi-Modality Therapy of Esophageal Cancer

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Worldwide Cancer Rates

• Esophageal cancer
  – 8\textsuperscript{th} in incidence, 6\textsuperscript{th} in mortality
  – 412,327 new cases; 337,501 deaths

• Gastric cancer
  – 2\textsuperscript{nd} in incidence & mortality
  – 876,341 new cases; 646,567 deaths

Globoscan 2000: Cancer Incidence, Mortality and Prevalence
Worldwide, Version 1.0
Relative Change in Cancer Incidence in the United States (1975-2001)

Rate ratio (relative to 1975)

- Esophageal Adenocarcinoma
- Melanoma
- Prostate Cancer
- Breast Cancer
- Lung Cancer
- Colorectal Cancer

Pohl H and Welch HG. *J Natl Cancer Inst* 2005;95:142-146
# Results of Surgery for Cancer of the Esophagus

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>#Pts(^+)</th>
<th>Resection</th>
<th>Mortality</th>
<th>5-Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orringer (1999)</td>
<td>800</td>
<td>THE</td>
<td>4.5%</td>
<td>23%</td>
</tr>
<tr>
<td>Ellis (1999)</td>
<td>455</td>
<td>TTE</td>
<td>3%</td>
<td>25%</td>
</tr>
<tr>
<td>Adam (1996)</td>
<td>597</td>
<td>TTE</td>
<td>7%</td>
<td>16%</td>
</tr>
<tr>
<td>Swisher (1995)</td>
<td>316</td>
<td>TTE</td>
<td>5%</td>
<td>16%</td>
</tr>
<tr>
<td>Lieberman (1995)</td>
<td>258</td>
<td>TTE</td>
<td>5%</td>
<td>27%</td>
</tr>
<tr>
<td>Putnam (1994)</td>
<td>134</td>
<td>TTE</td>
<td>8%</td>
<td>18%</td>
</tr>
<tr>
<td>Vigneswaran (1993)</td>
<td>131</td>
<td>THE</td>
<td>2%</td>
<td>21%</td>
</tr>
<tr>
<td>Gelfind (1992)</td>
<td>160(^*)</td>
<td>THE</td>
<td>1%</td>
<td>21%</td>
</tr>
</tbody>
</table>

THE = transhiatal esophagectomy; TTE = transthoracic esophagectomy

\(^*\) adenocarcinoma only
\(^+\) adenocarcinoma and squamous cell histologies
Staging Esophageal Adenocarcinoma

The relationship between depth of invasion and node metastases

Mucosa

Submucosa

Muscularis Propria

Lamina Propria

Muscularis Mucosa
Barium Esophagram of Distal Esophageal Carcinoma
Staging Esophageal Adenocarcinoma

The relationship between the number of node metastases and the likelihood of systemic disease

- 100% likelihood of systemic metastases if >10 involved nodes
- <5% likelihood if 0, 1-3, or 4-10 involved nodes
Staging Early Esophageal Adenocarcinoma

- Endoscopic examination
  - Size, location
- Endoscopic ultrasound
  - Depth (beyond SM), nodes
- Endoscopic mucosal resection
  - Mucosal vs submucosal
CT Image of Distal Esophageal Carcinoma
Survival After Esophagectomy by Stage

Treatment Options for Localized Esophageal Cancer

• Surgical
  – Surgery alone
  – Preop chemoradiation
  – Preop chemotherapy (UK)

• Non-surgical
  – Definitive chemoradiation
Non-Surgical Management

- **Squamous cell ca** – head & neck (larynx, oropharynx, NPC) and anal ca are models for cure and organ preservation without surgery.

- **Adenoca** – surgery is mainstay of curative rx for G-I tract ca, clinical trials focus on neoadjuvant and adjuvant rx.
Chemo-Radiation

- Standard of care
  
  RT 50.4 Gy and
  cisplatin + infusional 5-fluorouracil x 4 courses
INT R85-01: Radiotherapy vs Radiotherapy + Chemorx for Esophageal Cancer Confined to the Thorax

- RT 64 Gy
- RT 50.4 Gy + Cisplatin/5-FU weeks 1, 5, 8, 11

Results

3-yr & 5-yr survival 0 vs 30%, 0 vs 26%
Med. Survival 9 vs 14 mos
Site of first failure (at 12 mos)
  - Local recurrence 68 vs 46%
  - Distant 29 vs 16%

INT 0123: Intensification of RT with Concurrent Chemotherapy

- Cisplatin + 5-FU x 4 courses
  - RT 50.4 Gy, 1.8 Gy/fx

- Cisplatin + 5-FU x 4 courses
  - RT 64.8 Gy, 1.8 Gy/fx

- Closed after first interim analysis due to increased toxicity in the high dose RT group with low potential for survival improvement
Time to L/R failure

L/R failure at 24 mos, 50 vs 55%

Survival

MST 18 vs 13 mos, 2-yr 40% vs 31%

Minsky BD. J Clin Oncol 2002;20:1167-1174
Chemoradiation as Definitive Treatment

- Significant survival benefit with 50.4 Gy RT + CF compared to radiotherapy alone
- Data almost exclusively in squamous cell cancers
- Local recurrence rate is reduced but still high
Should Squamous Cell Carcinoma and Adenocarcinoma Be Treated Differently?
Squamous Cell Carcinoma of the Esophagus CRT Followed By Surgery vs CRT Alone

German Esophageal Cancer Study Group (J Clin Oncology 2005; 23:2310-7)

- Comparable overall 2-yr survival (39.9% vs 35.4%)
- Surgical group had better 2-yr local PFS (64.3% vs 40.7%)
- Surgical group had increased toxicity (12.8% vs 3.5%)
Squamous Cell Carcinoma of the Esophagus
CRT Followed by Surgery vs CRT Alone

FFCD 9102 Trial (J Clin Oncol 2007; 25:1160-8)
• 259 pts with T3 tumors (90% squamous cell)
• Responders to initial CRT randomized to surgery vs definitive CRT
• No difference in 2-yr survival (40% vs 34%)
• Higher local recurrence in nonsurgical group
• Toxicity higher in surgical group (9.3% vs 0.8%)
Squamous Cell Carcinoma of the Esophagus

- Definitive CRT is an acceptable treatment option
- Lower mortality but high risk of local recurrence
- If periop mortality is minimized, oncologic outcome may be enhanced with addition of resection
Carcinoma of the Distal Esophagus and Gastroesophageal Junction
Adenocarcinoma of the Esophagus and GEJ Siewert Classification
HISTORY

Neoadjuvant Radiation Therapy vs Surgery

- Six prospective randomized trials
- No survival benefit
- Meta-analysis: No clear benefit
HISTORY
Neoadjuvant Chemotherapy vs Surgery

• Intergroup 113: No benefit
• MRC (OE02) trial: Positive benefit for neoadjuvant group (5 yr: 23% vs 17%)
• MAGIC trial (gastric and GEJ): Significant benefit for periop chemo group
  (5 yr: 36% vs 23%)
<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Pts</th>
<th>Chemotherapy</th>
<th>XRT (Gy)</th>
<th>3-yr Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urba (2001)</td>
<td>50</td>
<td>CCDP/5FU/Vin</td>
<td>45</td>
<td>Surg: 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Multi: 30</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td></td>
<td></td>
<td>Multi: 32*</td>
</tr>
<tr>
<td>EORTC (1997)</td>
<td>139</td>
<td>CDDP</td>
<td>37</td>
<td>Surg: 37</td>
</tr>
<tr>
<td></td>
<td>143</td>
<td></td>
<td></td>
<td>Multi: 39</td>
</tr>
<tr>
<td>Australasian (2005)</td>
<td>128</td>
<td>CDDP/5FU</td>
<td>35</td>
<td>Surg: N/A</td>
</tr>
<tr>
<td></td>
<td>128</td>
<td></td>
<td></td>
<td>21.7 mo. median</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Multi: N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18.5 mo. median</td>
</tr>
<tr>
<td>CALBG 9781 (2008)</td>
<td>30</td>
<td>CDDP/5FU</td>
<td>50.4</td>
<td>Surg: 16</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td></td>
<td></td>
<td>Multi: 39* (5 yr)</td>
</tr>
</tbody>
</table>

* = Statistically significant
Survival of Patients with Esophageal Adenocarcinoma – Intent to Treat

# University of Michigan Results

(median f/u = 8.2 yrs)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Surgery</th>
<th>C/RT + Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med. Survival</td>
<td>17.6 mos.</td>
<td>16.9 mos.</td>
</tr>
<tr>
<td>3-year Survival</td>
<td>16%</td>
<td>30%</td>
</tr>
<tr>
<td>Path CR (med, 3-yr)</td>
<td></td>
<td>50 mos, 64%</td>
</tr>
<tr>
<td>Residual ca (med, 3yr)</td>
<td></td>
<td>12 mos, 19%</td>
</tr>
<tr>
<td>L/R Failure</td>
<td>42%</td>
<td>19%</td>
</tr>
<tr>
<td>Distant Failure</td>
<td>60%</td>
<td>65%</td>
</tr>
</tbody>
</table>

Urba SG. J Clin Oncol 2001;19:305-513
Preoperative Chemotherapy

• Preoperative cisplatin-based chemotherapy results in a 50% response rate by clinical assessment. pCR rate ~5%

• Conflicting results from randomized trials for benefit from preop chemotherapy
## Trials Comparing Pre-operative Chemotherapy to Immediate Surgery

<table>
<thead>
<tr>
<th>Series</th>
<th># Pts</th>
<th>Hist.</th>
<th>Treatment</th>
<th>Median</th>
<th>2-yr</th>
<th>3-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelsen</td>
<td>440</td>
<td>S&amp;A</td>
<td>Surgery</td>
<td>16 mos</td>
<td>37%</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CF(3)→S</td>
<td>15 mos</td>
<td>35%</td>
<td>26%</td>
</tr>
<tr>
<td>Kok*</td>
<td>161</td>
<td>S</td>
<td>Surgery</td>
<td>11 mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CE→S</td>
<td>18.5 mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRC*</td>
<td>802</td>
<td>S&amp;A</td>
<td>Surgery</td>
<td>13 mos</td>
<td>34%</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CF(2)→S</td>
<td>17 mos</td>
<td>43%</td>
<td>32%</td>
</tr>
</tbody>
</table>

*Significant difference
### Intergroup O113 Trial Results

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Chemo + Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible patients (54% AC)</td>
<td>227</td>
<td>213</td>
</tr>
<tr>
<td>Surgery performed</td>
<td>92%</td>
<td>80%</td>
</tr>
<tr>
<td>Curative resection (R0)</td>
<td>59%</td>
<td>62%</td>
</tr>
<tr>
<td>Median survival R0</td>
<td>25 mos</td>
<td>27.4 mos</td>
</tr>
<tr>
<td>Median survival, all pts</td>
<td>16.1 mos</td>
<td>14.9 mos</td>
</tr>
<tr>
<td>Survival: 2 year</td>
<td>37%</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td>26%</td>
<td>23%</td>
</tr>
<tr>
<td>Treatment mortality</td>
<td>6%</td>
<td>7%</td>
</tr>
</tbody>
</table>

## MRC Phase III Trial

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Chemo + Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible patients (66% AC)</td>
<td>402</td>
<td>400</td>
</tr>
<tr>
<td>Surgery performed</td>
<td>97%</td>
<td>92%</td>
</tr>
<tr>
<td>Curative resection (R0)</td>
<td>54%</td>
<td>60%</td>
</tr>
<tr>
<td>Median survival, all pts</td>
<td>13.3 mos</td>
<td>16.8 mos</td>
</tr>
<tr>
<td>*Survival: 2 year</td>
<td>34%</td>
<td>43%</td>
</tr>
<tr>
<td>3 year</td>
<td>25%</td>
<td>32%</td>
</tr>
<tr>
<td>Treatment mortality</td>
<td>10%</td>
<td>10%</td>
</tr>
</tbody>
</table>

*p=0.004; hazard ratio 0.79; reduction in risk of death - 21%

*Medical Research Council. Lancet 359:1727, 2002*
Intergroup O113 Trial
Late term Results -

• Only survival benefit seen with RO resection – both arms
• Those patients in chemotherapy arm with objective response to therapy appeared to have late term analysis survival advantage.

Kelsen - 2007
Cross Trial

van Hagen P., et al.

“Preoperative Chemoradiotherapy for esophageal or junction cancer”

N Engl J Med 2012;366:2074-84
Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectable esophageal or esophagogastric junction cancer: Results from a multicenter randomized phase III study.

CROSS study group
Chemoradiotherapy treatment regimen:

- 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)
Toxicity of treatment (chemoradiotherapy)

Major toxicities (grade 3-5 CTC 3.0)

Hematologic: n=12 (6.8%)
  Grade 3: n=12
  Grade 4: n=0
  Grade 5: n=0

Non-hematologic: n=28 (16%)
  Grade 3: n=26
  Grade 4: n=1
  Grade 5: n=1
## Resection rate and resection margins

Resection rate of all randomised patients

<table>
<thead>
<tr>
<th></th>
<th>Surgery alone</th>
<th>CRT + surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>162/188 (86%)</td>
<td>157/175 (90%)</td>
</tr>
</tbody>
</table>

Resection margins

<table>
<thead>
<tr>
<th></th>
<th>Surgery alone</th>
<th>CRT + surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>110 (67%)</td>
<td>145 (92.3%)</td>
</tr>
<tr>
<td>R1</td>
<td>52 (33%)</td>
<td>12 (7.6%)</td>
</tr>
</tbody>
</table>

R0 = no tumor within 1 mm of the resection margins
## Morbidity and Mortality (postoperative)

<table>
<thead>
<tr>
<th></th>
<th>Surgery alone</th>
<th>CRT + Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary complications</td>
<td>66%</td>
<td>69%</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>24%</td>
<td>23%</td>
</tr>
<tr>
<td>Chylothorax</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td>Mediastinitis</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Anastomotic leakage</td>
<td>25%</td>
<td>22%</td>
</tr>
</tbody>
</table>

In-hospital mortality      | 7 (3.8%)      | 6 (3.4%)      |
Follow-up and survival

Median follow-up 32 months

<table>
<thead>
<tr>
<th></th>
<th>Surgery alone</th>
<th>CRT + Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year survival rate</td>
<td>70%</td>
<td>82%</td>
</tr>
<tr>
<td>2 year survival rate</td>
<td>52%</td>
<td>67%</td>
</tr>
<tr>
<td>3 year survival rate</td>
<td>48%</td>
<td>59%</td>
</tr>
<tr>
<td>Median survival</td>
<td>26 months</td>
<td>49 months</td>
</tr>
</tbody>
</table>
Overall survival

HR 0.67  95% CI (0.49 - 0.91)

No’s at risk
Surgery alone
CRT + surgery

<table>
<thead>
<tr>
<th></th>
<th>188</th>
<th>131</th>
<th>71</th>
<th>44</th>
<th>22</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery alone</td>
<td>175</td>
<td>144</td>
<td>85</td>
<td>55</td>
<td>30</td>
<td>2</td>
</tr>
</tbody>
</table>

CROSS study
HR’s (95% CI) for death according to baseline variables

Overall: 0.67 (0.49 – 0.91)
N0: 0.49 (0.27 – 0.90)
N1: 0.72 (0.50 – 1.04)
Male: 0.62 (0.44 – 0.87)
Female: 0.92 (0.45 – 1.89)
AC: 0.82 (0.58 – 1.16)
SCC: 0.34 (0.17 – 0.68)
WHO 0: 0.67 (0.49 – 0.94)
WHO 1: 0.67 (0.32 – 1.41)

Favors preoperative CRT | Favors surgery alone

19 CROSS study
Results of Chemoradiation Followed by Surgery

• Two-thirds downstaged, 25-30% no residual disease (pCR)
• Survival mirrors final pathologic stage, not initial stage eg. Stage 0 or I, 60% 5-year survival
• Surgery important to remove residual microscopic disease in partial responders
• Local-regional failure significantly decreased
• Randomized trials show improved survival – ~35% at 3 years versus 6-15% with surgery alone.
Implications for Clinical Practice

• Surgery should be part of the treatment of all patients with resectable disease who are medically fit

• Based on the data in the aggregate (randomized trials, meta-analyses, experience of major centers), chemoradiation followed by surgery provides the best chance for long-term survival for patient with resectable, stages II and III disease.
Unanswered Questions

• Should all operable patients undergo surgery?

• What chemotherapy regimen to use?

• How can we improve upon current results?
What About the T2N0 Patient?
Targeted Agents
Hallmarks of Cancer

- Self-sufficiency in growth signals
- Evading apoptosis
- Sustained angiogenesis
- Limitless replicative potential
- Insensitivity to anti-growth signals
- Tissue invasion and metastasis

Chemosensitivity Testing

• Assess genes involved in the metabolism and function of chemotherapeutic agents to predict response in a patient

• ERCC1 and XPA
  – DNA repair genes (XPA binds to cisplatin-damaged DNA)
  – High levels predict poor response to cisplatin compounds

• Thymidylate Synthase (TS)
  – TS is an enzyme essential for DNA synthesis
  – Major mechanism of action of the fluoropyrimidines (5-FU) is TS inhibition
  – High TS tumor levels predict poor response to 5-FU
Chemosensitivity Testing

- Topoisomerase I
  - Decreased levels associated with resistance to CPT-11
- Apoptosis genes bcl-2, bax
  - Upregulation may sensitize cells to CPT-11
- p53
  - Modulates sensitivity to drugs including 5-FU, etoposide, adriamycin, and cisplatin
- COX-2
  - Frequently overexpressed in esophageal cancer
  - Overexpression leads to decreased E-cadherin expression
  - Increased expression may indicate response to Celebrex
Panitumumab
Cetuximab

EGFR/HER Family receptor

PLC

PKC

Ras

Raf

MEK

ERK/MAPK

Sunitinib
Vatalanib
ZD 6474

Lonafarnib

Sorafenib

Chemotherapy

Investigational Agent

Currently Approved

Inhibition of programmed cell death (apoptosis)

Tumor cell proliferation

Tumor cell invasion metastasis

Development of tumor vasculature (angiogenesis)

Conclusion

- Multimodality therapy is part of the standard of care management of patients with localized esophageal cancer
- Distant metastasis remains the major cause of death
- Identifying prognostic markers and testing molecularly targeted therapeutics are next steps for improving pCR rates and long term survival
THANK YOU
Survival by EGF-R Expression
Gibson M. Clin Ca Res, 2003

Kaplan-Meier survival estimates, by EGFR IRScat analysis time

IRS Score \(\leq 1\)
IRS Score 2-5
IRS Score 6-9
IRS Score >9

\(p = 0.01\) by log rank test
ECOG: Randomized Phase II Trial of Preop Oxaliplatin/FU +/- Cetuximab

**Preoperative**

Arm A: oxaliplatin/5-FU + RT (50.4 Gy)
Arm B: oxaliplatin/5-FU + RT + cetuximab + adjuvant cetuximab following surgery

**Primary endpoint:** To determine pCR rates of oxali/FU/RT with/ without cetuximab
LET'S GO BUCS!
THANK YOU
# Squamous Cell Ca and Adenoca Are Distinct Clinical Entities

<table>
<thead>
<tr>
<th></th>
<th>Squamous cell</th>
<th>Adenoca</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiologic factors</strong></td>
<td>tobacco</td>
<td>GERD, diet obesity</td>
</tr>
<tr>
<td></td>
<td>alcohol</td>
<td></td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>upper/mid</td>
<td>distal, G-EJ cardia</td>
</tr>
<tr>
<td><strong>Pattern of first failure</strong></td>
<td>local-regional</td>
<td>distant</td>
</tr>
<tr>
<td>Site</td>
<td>Esophagus</td>
<td>Cardia</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Nodal Spread</td>
<td>peri-esophageal</td>
<td>peri-esophageal</td>
</tr>
<tr>
<td></td>
<td>pericardial</td>
<td>pericardial</td>
</tr>
<tr>
<td></td>
<td>celiac</td>
<td>celiac</td>
</tr>
<tr>
<td></td>
<td>left gastric</td>
<td>left gastric</td>
</tr>
<tr>
<td>Recurrence</td>
<td>80% distant</td>
<td>80% distant</td>
</tr>
</tbody>
</table>
Chemoradiation as Definitive Treatment

• None of the randomized trials included adequate pretreatment staging (e.g. EUS) to reliably correlate outcome with pretreatment local-regional extent

• There is no reliable indicator of microscopic persistent disease after chemoradiation
  – High false negative rate from biopsy
  – EUS unreliable after chemoradiation
  – PET??

• Indicated for unresectable or medically unfit patients
Multimodality Therapy for Resectable Esophageal Cancer

- Chemoradiation followed by surgery
  - Common practice in US based on the results of phase II and III trials

- Chemotherapy followed by surgery
  - Standard of care in UK
  - Considered ineffective treatment in US
## Pre-operative Chemoradiation

### Selected Non-Randomized Trials

<table>
<thead>
<tr>
<th>Author</th>
<th>#</th>
<th>Histology</th>
<th>Surgery</th>
<th>(%)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naunheim</td>
<td>47</td>
<td>S &amp; A</td>
<td>39</td>
<td>21</td>
<td>3-Yr – 40%</td>
</tr>
<tr>
<td>Forastiere</td>
<td>43</td>
<td>S &amp; A</td>
<td>39</td>
<td>27</td>
<td>3-Yr – 46%</td>
</tr>
<tr>
<td>Forastiere</td>
<td>50</td>
<td>S &amp; A</td>
<td>47</td>
<td>40</td>
<td>2-Yr – 58%</td>
</tr>
<tr>
<td>Bates</td>
<td>35</td>
<td>S &amp; A</td>
<td>33</td>
<td>51</td>
<td>3-Yr – 40%</td>
</tr>
<tr>
<td>Malhaire</td>
<td>56</td>
<td>S</td>
<td>54</td>
<td>38</td>
<td>3-Yr – 55%</td>
</tr>
<tr>
<td>Stahl</td>
<td>72</td>
<td>S &amp; A</td>
<td>49</td>
<td>33</td>
<td>3-Yr – 33%</td>
</tr>
<tr>
<td>Jones</td>
<td>66</td>
<td>S &amp; A</td>
<td>54</td>
<td>41</td>
<td>3-Yr – 45%</td>
</tr>
<tr>
<td>Adelstein</td>
<td>72</td>
<td>S &amp; A</td>
<td>67</td>
<td>27</td>
<td>3-Yr – 44%</td>
</tr>
<tr>
<td>Posner</td>
<td>44</td>
<td>S &amp; A</td>
<td>37</td>
<td>24</td>
<td>2-Yr – 52%</td>
</tr>
<tr>
<td>Raoul</td>
<td>32</td>
<td>S</td>
<td>29</td>
<td>56</td>
<td>3-Yr – 52%</td>
</tr>
<tr>
<td>Heath</td>
<td>42</td>
<td>S &amp; A</td>
<td>39</td>
<td>26</td>
<td>2-Yr – 62%</td>
</tr>
<tr>
<td>Kleinberg</td>
<td>92</td>
<td>S &amp; A</td>
<td>92</td>
<td>33</td>
<td>5-yr – 40%</td>
</tr>
</tbody>
</table>
Conclusion

- No data currently exists to suggest that intensifying current therapeutic regimens improves pCR or survival.
- Phase III trials are essential due to the occurrence of stage migration (PET).
- Adenocarcinoma and squamous cell carcinoma should be studied separately.
Two Meta-Analyses Of Controlled Trials Of Chemoradiation Followed By Surgery Vs Surgery

• Urschel JD. Amer J Surg, 2003 (9 trials, 1,116 pts)
• Fiorica F. Gut, 2004 (6 trials, 764 pts)

• Odds ratios show significant 3-yr survival advantage with chemoradiotherapy-surgery (OR > 1 favors surgery)
  - 0.66 ( p=0.016)
  - 0.53 ( p=0.03)

• Other findings:
  - Rx mortality less with surgery OR 1.63, p=0.053
  - R0 resection sign for chemorad-S OR 0.53, p=0.007
  - LR failure sign for chemorad-S OR 0.38, p=0.0002
## Randomized Trials of Pre-Operative Chemoradiation

<table>
<thead>
<tr>
<th>Series</th>
<th>Histology</th>
<th>Treatment</th>
<th>Path #</th>
<th>% CR</th>
<th>Survival 3 years</th>
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</thead>
<tbody>
<tr>
<td>Urba</td>
<td>adeno+squam</td>
<td>Surgery</td>
<td>50</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pre-op chemo+ 45 Gy</td>
<td>50</td>
<td>28%</td>
<td>30%</td>
</tr>
<tr>
<td>Walsh</td>
<td>adeno</td>
<td>Surgery</td>
<td>55</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pre-op chemo+ 40 Gy</td>
<td>58</td>
<td>25%</td>
<td>32%*</td>
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<tr>
<td>Bossett</td>
<td>squam stg I&amp;II</td>
<td>Surgery</td>
<td>139</td>
<td>36%</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pre-op chemo+ 37 G</td>
<td>142</td>
<td>26%</td>
<td>36%</td>
</tr>
</tbody>
</table>

*difference statistically significant, cisplatin/5-FU-based chemotherapy
Prognostic Markers

• EGFR
• Bcl-XL
• P53
• VEGF
• Thymidylate synthase
• Dihydropyrimidine dehydrogenase
• Glutathione s-transferase
Anti-Angiogenesis

• Chronic oral chemotherapy with UFT
  – UFT = uracil and tegafur

  – Blocks the angiogenic responses elicited by high levels of VEGF production by tumors