ESOPHAGEAL CANCER

Contemporary Treatment Approaches

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Disclosures

• None
Learning Objectives

• Review current epidemiologic changes in esophageal and gastric cancers
• Discuss current treatment strategies of esophageal cancer: adjuvant and neoadjuvant treatment and surgery, definitive chemoradiation
• Summarize the future of treatment: newer randomized trials, alternative treatment strategies and integration of novel agents
Esophageal and Gastric Cancer Outline

• Epidemiology and Workup
• Treatment of Early Stage (T1)
• Treatment of Locally Advanced (T2-4,N+)
• Dysphagia Palliation
• Dose and Technique
• Current Trials and Future Directions
Epidemiology
2008 Worldwide Statistics

• Eighth most common cancer worldwide
  • 482,300 new cases
  • 406,800 deaths
• Squamous cell carcinoma in Asia and East Africa
• Adenocarcinoma in the West

## Estimated Deaths

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>951,000</td>
</tr>
<tr>
<td>Liver</td>
<td>478,300</td>
</tr>
<tr>
<td>Stomach</td>
<td>464,400</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>320,600</td>
</tr>
<tr>
<td><strong>Esophagus</strong></td>
<td><strong>276,100</strong></td>
</tr>
<tr>
<td>Prostate</td>
<td>258,400</td>
</tr>
<tr>
<td>Leukemia</td>
<td>143,700</td>
</tr>
<tr>
<td>Pancreas</td>
<td>138,100</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>112,300</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>109,500</td>
</tr>
<tr>
<td><strong>All sites but skin</strong></td>
<td><strong>4,225,700</strong></td>
</tr>
</tbody>
</table>


MAYO CLINIC
Epidemiology
Esophageal Carcinoma U.S Incidence

- 17,990 new cases in U.S in 2013
- 15,210 deaths in U.S. in 2013
- Incidence of ACA increased > 350%
  - 17% of esophageal cancers in 1970s
  - 60% of esophageal cancers in 1995
- Death rate in males ↑ 7% 1990 to 2007
- 5-yr survival 5% in 1970s, 19% since 1999

Siegel, CA Cancer J Clin 63:11-30, 2013
Devesa, Cancer 83:2049-53, 1998
Epidemiology
Esophageal Adenocarcinoma

• Seattle SEER data
  • 5.3 ACA/ 100,000/ year
  • 800% increase since 1974

• Utah SEER data
  • 2.4 ACA/ 100,000/ year
  • 300% increase since 1974

Kubo, Cancer 2002, 95:2096-102
Esophageal Cancer

Workup

• Endoscopic biopsy
• CT abdomen and pelvis
• If CT negative: EUS for T and N staging
• PET: 15% have occult metastatic disease
Esophageal Cancer
Treatment T1a

- T1a (lamina propria or muscularis mucosae invasion)
  - Very low risk of distant mets (<3%)
  - Very low risk of nodal mets
  - Endoscopic mucosal resection without surgery adequate
Esophageal Cancer
Treatment T1b

- T1b (invades submucosa)
- Standard of care is esophagectomy
- Non-surgical candidate
  - 45-50 Gy + 2 drug chemo
  - 60 Gy + 5-FU
Stage I Esophageal Cancer
Primary Radiation Therapy

- 68 stage I esophageal cancer pts
  - 18 mucosal
  - 50 submucosal

- EBRT alone: 66 Gy
- EBRT 56-60 Gy + brachy
  - LDR 5 Gy x 2
  - HDR 3 Gy x 3

Ishikawa, J Gastro Hepatology 21:1290-1296, 2006
Stage I Esophageal Cancer
Primary Radiation Therapy

- 68 stage I esophageal cancer pts
- 5-yr S 59%
- 5-yr LC 82%
- 5-yr CSS 80%
  - Mucosal 100%
  - Submucosal 75%
- 2 RT related fistula deaths

Ishikawa, J Gastro Hepatology 21:1290-1296, 2006
Chemoradiation versus Surgery
Stage I SQC Esophagus

• Surgery or CT/RT: patient choice
• 60 Gy in 30, split course
• 5-FU 400 d 1-5, 8-12
• CDDP 40 d 1, 8
• 5FU/CDDP x 2 after CT/RT

Ariga, IJROBP 75(2): 348-356, 2009
Chemoradiation versus Surgery
Stage I SQC Esophagus

Ariga, IJROBP 75(2): 348-356, 2009
Esophageal Cancer
General treatment recommendations

- T2N0
  - Surgery
  - Chemoradiation
  - Trimodality

- T3-4 and/or N+
  - Chemoradiation
  - Trimodality

- Stage IV: RT or CT/RT for dysphagia
Esophageal Cancer
Mayo surgical results

- 220 patients: Ivor Lewis resection
  - 188 ACA, 31 SQC, 1 leiomyosarcoma
- Surgical mortality: 1.4%
- 5 year overall survival 25%
  - pTisN0 10 pts 80% 5 yr S
  - pT1N0 19 pts 94% 5 yr S
  - pT2-3N0 38 pts 36% 5 yr S
  - pT1-2/N+ 28 pts 14% 5 yr S
  - pT3-4N+ 111 pts 10% 5 yr S
  - M+ 14 pts 0% 5 yr S

## Esophageal Cancer: Surgery

### Surgical results by stage

<table>
<thead>
<tr>
<th>Author</th>
<th>#pts</th>
<th>I</th>
<th>IIA</th>
<th>IIB</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watson (UK)</td>
<td>164</td>
<td>71</td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Millikan (Rush)</td>
<td>157</td>
<td>50</td>
<td>44</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>O’Rourke (Austral.)</td>
<td>116</td>
<td>53</td>
<td></td>
<td>57</td>
<td>15</td>
</tr>
<tr>
<td>Fok (Hong Kong)</td>
<td>218</td>
<td>66</td>
<td>28</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Zhang (Beijing)</td>
<td>3603</td>
<td>58</td>
<td>45</td>
<td>27</td>
<td>13</td>
</tr>
<tr>
<td>Nakadi (Belgium)</td>
<td>101</td>
<td>91</td>
<td></td>
<td>52</td>
<td>18</td>
</tr>
<tr>
<td>Visbal (Mayo)</td>
<td>220</td>
<td>94</td>
<td>36</td>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>
Esophageal Cancer
Edinburgh series

- 720 patients 1949-1967
- All squamous cell carcinomas
- Radical surgery: 11% 5 yr survival
- Radical irradiation: 17% 5 yr survival
- Conclusion: radiation is preferred for SQC, surgery for ACA

Esophageal Cancer: RT + Chemo

RTOG 8501 Schema


64 Gy / 32 fractions

50 Gy in 25 fractions
5FU, 1 gm/m²/day x 4 d weeks 1,5,8,11
CDDP, 75 mg/m² IV bolus weeks 1,5,8,11

123 pts
108 SQC
15 ACA
RTOG 8501
Survival by Treatment Arm

Alive (%) vs. Years from randomization

RT only vs. RT + chemotherapy

P < 0.0001

RTOG 8501
Time to Local Failure by Treatment Arm

% with local disease

RT only
RT + chemotherapy

P=0.05

Years from randomization

RTOG 8501
Time to Distant Metastases by Treatment Arm

### Esophageal Cancer: RT + Chemo

**RTOG 8501: Toxicity**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>RT + chemo</th>
<th>RT alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>severe</td>
<td>44%</td>
<td>25%</td>
</tr>
<tr>
<td>life threatening</td>
<td>20%</td>
<td>3%</td>
</tr>
<tr>
<td>fatal</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Is routine surgery following chemoradiation indicated?
Esophageal Cancer
RT/CT +/- Surgery: German Study

172 pts
T3-4
N0-1
SQC

FLEP* ▶ 40 Gy+CDDP+ETOP ▶ Surgery

FLEP ▶ 65 Gy+CDDP+ETOP

*FLEP = bolus 5-FU, leucovorin, etoposide, cisplatin

Stahl, JCO 23:2310-17, 2005
No overall difference, surgery patients less likely to die of cancer and more likely to die of treatment related complications

Stahl, JCO 23:2310-17, 2005
Locoregional Control-German Study

Stahl, JCO 23:2310-17, 2005
FFCD 9102: Phase III Study of ChemoRT vs ChemoRT followed by Surgery

FFCD 9102: Phase III Study of ChemoRT vs ChemoRT followed by Surgery

Survival vs Time (months)

Arm A (surgery)
Arm B (chemoradiation)

# CT/RT vs Surgery Alone

## Esophageal Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>4-yr Survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Chiu 2005 (CURE, China)</td>
<td>55*</td>
</tr>
<tr>
<td>Gray 2005 (Minnie Pearl)</td>
<td>49</td>
</tr>
<tr>
<td>Stahl 2005/2008 (Germany)</td>
<td>30</td>
</tr>
<tr>
<td>Sun 2006 (Jinan, China)</td>
<td>31</td>
</tr>
<tr>
<td>Bedenne 2007 (FFCD 9102)</td>
<td>23</td>
</tr>
<tr>
<td>Carstens 2007 (Scandinavia)</td>
<td>23</td>
</tr>
</tbody>
</table>

*2-year

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Pottgen, Cancer Treatment Rev 38(2012): 599-604
Surgery vs. Chemoradiation followed by Surgery?
Esophageal Cancer: Preop RT + CT
Dublin Trial

113 pts, all ACA

- Surgical resection alone
- 40 Gy / 15 fractions
  - 5FU, 15 mg/kg/day x 5 d, weeks 1,6
  - CDDP, 75 mg/m² weeks 1,6
  → surgery

Walsh, NEJM 335:462-467, 1996.
Esophageal Cancer: Preop RT + CT
Dublin Trial Results

Survival (%)

Months

Surgery alone (n=55)
Multimodal therapy (n=58)

P=0.01

## Esophageal Cancer: Preop RT + CT
### Dublin Trial Results

<table>
<thead>
<tr>
<th>treatment</th>
<th>hospital mortality</th>
<th>median survival</th>
<th>3 yr S</th>
<th>5 yr S*</th>
</tr>
</thead>
<tbody>
<tr>
<td>surgery alone (55)</td>
<td>4%</td>
<td>12 mo.</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>preop RT/CT (58)</td>
<td>9%</td>
<td>17 mo.</td>
<td>32%</td>
<td>29%</td>
</tr>
</tbody>
</table>

*p = 0.01

*crude survival, all patients followed > 5 yrs

**Esophageal Cancer: Preop RT + CT**  
**Dublin Trial, Pathologic Stage**

<table>
<thead>
<tr>
<th>Tumor stage</th>
<th>Surgery* (N = 55)</th>
<th>RT /CT + S (N = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2a</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>2b</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

*Expected 5-yr survival at Mayo based on stage distribution: 8%*
Esophageal Cancer: Preop RT + CT
CALGB C-9781

500 pts/ 5 yrs
SQC or ACA
T1-3 NxM0
Resectable
Not more than
2 cm into cardia

5-FU + CDDP + 50.4 Gy
followed by surgery

surgery alone

Closed Early (56 pts) due to poor accrual
CALGB 9781

Overall survival (%)

Years from study entry

P<0.008

Adapted from Krasna et al: ASCO GI Symposium, 2006 Original: www.asco.org
**CROSS Phase III trial**

**Preop CT/RT vs S alone**

- 366 pts
- T2-3N0-1
- 84 SQC
- 275 ACA

**Surgery**
- 41.4 Gy
- CBDCA → S paclitaxel

<table>
<thead>
<tr>
<th></th>
<th>Med S</th>
<th>5-yr S</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgery</strong></td>
<td>24 mos</td>
<td>34%</td>
</tr>
<tr>
<td><strong>49 mos</strong></td>
<td>47%</td>
<td></td>
</tr>
</tbody>
</table>

\[ P = 0.003 \]

- pCR 23% ACA
- 49% SQC

Van Hagen, N Eng J Med 2012;366:2074-84
CROSS Phase III trial
Preop CT/RT vs S alone

Van Hagen, N Eng J Med 2012;366:2074-84
CROSS Phase III trial
Preop CT/RT vs S alone

Van Hagen, N Eng J Med 2012;366:2074-84
CROSS Phase III trial
Preop CT/RT vs S alone

Surgery

374 pts
T2-3N0-1
90 SQC
282 ACA

41.4 Gy

34% 14% 35%
LRR  peritoneal heme mets

P < .001  P < .001  P = .025

14%* 4% 29%

*Relapse in RT fields: 5%

V. Oppedijk, JCO 2014;32:385-391
FFCD 9901
Preop CT/RT vs S alone

195 pts
30 centers
9 years
SQC 137
ACA 57

195 pts
30 centers
9 years
SQC 137
ACA 57

Surgery

45 Gy
CDDP → S
5-FU

3-yr S 5-yr S Hosp. mort.
53% 34% 3.4%
P = 0.94

48% 41% 11.1%
P = .05

Mariette, JCO 32:2416-2427, 2014
AGONY
Not All Pain Is Gain.
**FFCD 9901**  
Preop CT/RT vs S alone

- 195 pts  
- 30 centers  
- 9 years  
- SQC 137  
- ACA 57

**Surgery**

<table>
<thead>
<tr>
<th>LRR</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td>P = .02</td>
<td>P = .31</td>
</tr>
</tbody>
</table>

- 45 Gy  
- CDDP $\rightarrow$ S  
- 5-FU

Mariette, JCO 32:2416-2427, 2014
Kaplan-Meier estimates of overall survival by treatment arm measured from study entry to death resulting from any cause.

HR (CRT v S) = 0.99 (95% CI, 0.69 to 1.30), P = .94
CT versus CT/RT followed by surgery?
Esophageal Cancer: Neoadjuvant Chemo
MRC-OE02

802 pts, resectable
SQC (247)
ACA (533)

5-FU → Surgery
CDDP

Surgery

Med S 2 yr S
17 mo 43%
13.5 mo 34%

P = 0.004

Preoperative radiotherapy allowed (9%), same on both arms
MRC Lancet 359:1727-33, 2002
MRC-OE02

Survival (%)

Years

Pt at risk (events)

CS

400 (164) 231 (73) 143 (26) 81 (13) 36 (2) 14

S

402 (185) 212 (76) 124 (32) 70 (18) 28 (5) 10

P=0.004

MRC Lancet 359:1727-33, 2002
## Esophageal Cancer

**Neoadjuvant Chemo: INT 0113, RTOG 8911**

<table>
<thead>
<tr>
<th>Preop*</th>
<th>Med S</th>
<th>1 yr S</th>
<th>2 yr S</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDDP</td>
<td>16.1 mo</td>
<td>62%</td>
<td>38%</td>
</tr>
<tr>
<td>5-FU</td>
<td>16.8 mo</td>
<td>62%</td>
<td>40%</td>
</tr>
</tbody>
</table>

*1.5% neutropenic sepsis deaths
Additional 2 cycles of chemotherapy postop

## Esophageal Cancer

**Neoadjuvant Chemo:** INT 0113, RTOG 8911


<table>
<thead>
<tr>
<th>Treatment</th>
<th>Med S</th>
<th>2 yr S</th>
<th>LF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop*</td>
<td>16.1 mo</td>
<td>38%</td>
<td>27%</td>
</tr>
<tr>
<td>CDDP 5-FU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU x3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>16.8 mo</td>
<td>40%</td>
<td>29%*</td>
</tr>
</tbody>
</table>

*443 pts 207 SQC 236 ACA

*1.5% neutropenic sepsis deaths

*29% LF in R0, 41% in R1

Esophageal Cancer

Neoadjuvant Chemo: INT 0113, RTOG 8911

Overall survival (%)

Years

Chemotherapy plus surgery (n=233)

Surgery (n=234)

No. of patients at risk
Chemotherapy surgery 136 73 42 28 15
Surgery 138 81 45 27 16

MAYO CLINIC
Phase III Study of Preoperative ChemoRT or Chemo in GE Junction Adenocarcinoma (POET)

T3-4 GE junction ACA

**Arm A**

- PLF I
- PLF II
- PLF III (3 weeks)
- Surgery

**Arm B**

- PLF: Cisplatin 50mg/m2, 1h, d 1, 15, 29. Leukovorin/5-FU 500 mg/m2 d 1, 8, 15, 22, 29, 36
- PE (1 week)

- PE: Cisplatin 50 mg/m2, 1h, d 2+8. Etoposide 80 mg/m2, 1h, d 3-5

Stahl, JCO 27:851, 2009
### Phase III Study of Preoperative ChemoRT or Chemo in GE Junction ACA (POET)

**T3-4 GE junction ACA**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CT alone</th>
<th>CT + RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>2%</td>
<td>16%</td>
</tr>
<tr>
<td>ypN0</td>
<td>38%</td>
<td>64%</td>
</tr>
<tr>
<td>3-yr Survival</td>
<td>28%</td>
<td>47%</td>
</tr>
</tbody>
</table>

*Stahl, JCO 27:851, 2009*
Phase III Study of Preoperative ChemoRT or Chemo in GE Junction Adenocarcinoma (POET)

Overall Survival

Strata
- 5FU/CDDP → S (2% pCR)
- CT→CDDP/etop/ 30 Gy/15→S (16% pCR)

Survival

Years

Arm B (60)

Arm A (59)

Stahl, JCO 27:851, 2009
Phase III Study of Preoperative ChemoRT or Chemo in GE Junction Adenocarcinoma (POET)

Freedom from Local Tumor Progression

Survival distribution function

Strata
- Randomized Arm A
- Censored randomized Arm A
- Randomized Arm B
- Censored randomized Arm B

P=0.06

Years

Arm B

Arm A

Stahl, JCO 27:851, 2009
Australian Meta-Analysis
Chemotherapy vs Surgery Alone

Australian Meta-Analysis
Chemotherapy and RT vs Surgery Alone

Study
Nygaard  Apinop  LePrise  Bosset  Urba  Walsh  Burmeister  Lee  All (published)

Walsh  Burmeister  Lee  All (published)

Favors chemoradiotherapy
Favors surgery alone

Australian Meta-Analysis

- Hazard ratio for all cause mortality for preoperative chemoRT was 0.81 ($P = 0.002$)
- Hazard ratio for all cause mortality for preoperative chemotherapy was 0.90 ($P = 0.05$)

Australian Meta-Analysis Update

• Compared 12 CT/RT trials and 7 CT trials
• All cause mortality HR for CT/RT vs. CT alone: 0.88 (p= 0.07)

Australian Meta-Analysis Update

• Added 7 trials, 1255 pts

• Neoadjuvant CT/RT vs S alone
  • Mortality HR: 0.78
    • ACA only: 0.75
    • SQC only: 0.80

• Neoadjuvant CT only
  • Mortality HR: 0.87
    • ACA only: 0.83
    • SQC only: 0.92

Neoadjuvant chemoradiation: does choice of regimen make a difference?
### Effect of Regimen on pCR rate

**Neoadjuvant CT/RT Esophageal Cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>CT</th>
<th>RT</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>POET</td>
<td>5-FU/CDDP</td>
<td>30/15</td>
<td>16% ACA*</td>
</tr>
<tr>
<td>Australasian IG 9401</td>
<td>5-FU/CDDP</td>
<td>35/15</td>
<td>8% ACA</td>
</tr>
<tr>
<td>Australia ph II</td>
<td>5-FU/CDDP</td>
<td>35/15</td>
<td>13% ACA**</td>
</tr>
<tr>
<td>CROSS</td>
<td>Carbo/Paclitaxel</td>
<td>41.4/23</td>
<td>23% ACA</td>
</tr>
<tr>
<td>FFCD 9901</td>
<td>5-FU/CDDP</td>
<td>45/25</td>
<td>33% both</td>
</tr>
<tr>
<td>CALGB</td>
<td>5-FU/CDDP</td>
<td>50.4/28</td>
<td>40% both</td>
</tr>
</tbody>
</table>

*pCR 2% CT alone*  
**pCR 0% CT alone**
Dysphagia Palliation
Stage IV Esophageal Cancer
Dysphagia Palliation

• RT or CT/RT is preferred over stent
• Use small fields
• 70-90% dysphagia relief
• 50-70% dysphagia-free until death
• Transient worsening in 30%
Esophageal Cancer: Radiation Dose and Technique
Esophageal Cancer
Radiation Dose Escalation

• Rationale: 50% local failure with 50 Gy + 5-FU/CDDP

• Studies:
  • RTOG 92-07: brachy boost
  • RTOG 94-05: EBRT dose escalation to 64.8 Gy
Esophageal Cancer
French Brachytherapy Study

FRE-CURIE-HDD
EU-96013

326 patients
T1-3
SQC esophagus < 7 cm length
Inoperable or refuses surgery

5-FU
CDDP
EBRT x 5 weeks

HDR brachy +
CT x 2

CT x 2
Esophageal Cancer
RTOG Brachytherapy Study 92-07

- 50 Gy + 5-FU + CDDP + HDR brachy
- HDR: 5 Gy x 3 initially, then 5 Gy x 2

Problems:
- grade 4 toxicity: 26%
- grade 5 toxicity: 8%
- fistula: 12%

Esophageal Cancer
EBRT Dose Escalation, RTOG 94-05

5FU+CDDP + 50.4 Gy / 28

5FU+CDDP + 64.8 Gy / 36

298 pts/4 yrs
T1-4 NxM0
SQC or ACA
No tumor within 2 cm of stomach

RT fields = tumor + 5 cm longitudinal margins
Esophageal Cancer
EBRT Dose Escalation, RTOG 94-05

Minsky et al: JCO 20:1167, 2002
Esophageal Cancer
EBRT Dose Escalation, RTOG 94-05

<table>
<thead>
<tr>
<th>Dose</th>
<th>Median Survival</th>
<th>2 yr Survival</th>
<th>Local Failure Rate</th>
<th>2 yr TR death</th>
</tr>
</thead>
<tbody>
<tr>
<td>50.4 Gy</td>
<td>18 mo</td>
<td>40%</td>
<td>52%</td>
<td>2 pts</td>
</tr>
<tr>
<td>64.8 Gy</td>
<td>13 mo</td>
<td>31%</td>
<td>56%</td>
<td>11 pts*</td>
</tr>
</tbody>
</table>

*7/11 deaths at doses not greater than 50.4 Gy

Minsky, JCO 20:1167, 2002
> 50 Gy + 4 cycles 5-FU/CDDP

RTOG results

<table>
<thead>
<tr>
<th>Study</th>
<th># pts</th>
<th>dose</th>
<th>gr 5 tox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Int 0123</td>
<td>109</td>
<td>64.8 Gy</td>
<td>10%</td>
</tr>
<tr>
<td>RTOG 9012</td>
<td>45</td>
<td>64.8 Gy</td>
<td>9%</td>
</tr>
<tr>
<td>RTOG 9207</td>
<td>49</td>
<td>50 Gy + 15-20 Gy (brachy)</td>
<td>10%</td>
</tr>
</tbody>
</table>
Esophageal Cancer
Treatment Volumes

- **RTOG 8501**: 30 Gy to entire esophagus, 20 Gy boost
- **RTOG 9405**: 5 cm longitudinal, 2 cm radial to field edge
- Contour GTV (CT, endoscopy report, image fusion)
- **CTV**: GTV + 3-4 cm longitudinal, 1 cm radial expansion
RTOG 1010
Radiation Guidelines

- GTV = Primary tumor + grossly involved nodes
- CTV = GTV + 4 cm superior-inferior and 1 cm radially
- Superior and inferior expansion to follow contour of esophagus and stomach
- Expand to cover para-esophageal and celiac nodes
- PTV = CTV + 0.5 -1 cm
Esophageal Cancer Planning

OAR limits

• Spinal cord max 45 Gy
• Lung: V20 < 30%, V10 < 40%, V5 < 60%, mean < 20 Gy
• Heart: V30 < 100%, V40 < 50%
• Liver: mean < 25 Gy, V30 < 50%
• Kidney: combined V20 < 30%
Esophageal Cancer Planning

3D vs. IMRT

• Lung toxicity with IMRT in trimodality patients?

• MDACC series
  • 413 3D patients
  • 263 IMRT patients
  • IMRT associated with fewer cardiac deaths, no increase in pulmonary deaths

Lin, IJROBP 84(5):1078-1085, 2012
Esophageal Cancer Planning
3D vs. IMRT

Lin, IJROBP 84(5):1078-1085, 2012
RTOG 1010
IMRT Beams

• Five field preferred: distal esophagus
  • LPO 155 degrees
  • LAO 70-80 degrees
  • AP 0 degrees
  • RAO 280-290 degrees
  • RPO 205 degrees
Esophageal Cancer
Future Directions

• Individualized therapy
  • EGFR inhibition
  • RTOG 1010: evaluating trastuzumab in HER-2+ patients
  • CALGB 80803: prediction of response with PET
• Organ preservation
Targeting HER2 Receptor

ToGA Trial

594 pts
Locally advanced, recurrent, or metastatic
Gastric/GE junction ACA
HER2 IHC3+ or FISH+

CT* + trastuzumab 13.8
CT 11.1

P = 0.0046

*CT = cisplatin + 5-FU or capecitabine

Bang, Lancet 2010, 376:687-97
Targeting HER2 Receptor
ToGA Trial

Adapted from Bang, Lancet 2010, 376:687-97
Esophageal Cancer
EGFR Inhibition – SCOPE Trial

Localized Ca Esoph
Non-operative
Ph II-III
258 pts

CT → CT/RT

CT → CT/RT + cetuximab

CT = cisplatin + capecitabine

<table>
<thead>
<tr>
<th></th>
<th>Med S</th>
<th>2-yr S</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mo</td>
<td>56%</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>P = 0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 mo</td>
<td>41%</td>
<td>78%</td>
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</tbody>
</table>

Crosby, 2013 GI Symposium
Esophageal Cancer
EGFR Inhibition – RTOG 0436

Localized Ca Esoph
Non-operative

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ACA 2-yr S</th>
<th>SQC 2-yr S</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT + CT</td>
<td>44%</td>
<td>46%</td>
</tr>
<tr>
<td>RT + CT + cetuximab</td>
<td>42%</td>
<td>43%</td>
</tr>
</tbody>
</table>

CT = cisplatin + paclitaxel

ASCO 2014
Esophageal Cancer
RTOG 1010

160 pts
HER2+
ACA

160 pts
HER2+
ACA

160 pts
HER2+
ACA

50.4 Gy + carbo/paclitaxel + trastuzumab $\rightarrow$ S

50.4 Gy + carbo/paclitaxel $\rightarrow$ S

Primary endpoint DFS, 15 mo $\rightarrow$ 27 mo
454 pts screened, 138 on study
Response Prediction
CALGB 80803 Phase IIR

204 pts
T1N+
T2-4N0/N+

mFOLFOX6 x 3 → PET → CT*/RT → S

Carboplatin x 2 → PET → CT*/RT → S
paclitaxel

*CT = same if SUV max >35% decrease, cross over if <35%

Primary endpoint: 20% pCR in non-responders
>175/204 accrued
Esophageal Cancer
Take home points

• Esophageal Ca common and increasing
• Early stage can be treated with RT
• CT/RT or trimodality better than S alone
• 50 Gy + 2 drug chemo is standard
• CROSS: relapse in RT fields 5%
• Dysphagia relief in 70-90%