UPPER GASTROINTESTINAL TRACT MALIGNANCIES

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Mayo Clinic
ASTRO Spring Refresher
April 13, 2012
Disclosure

- Speaker at Imedex CME event
Learning Objectives

• Describe the indications for the use of radiotherapy and the appropriate radiotherapy regimens for treatment of upper gastrointestinal tract malignancies.

• Describe modern radiation techniques and expected outcomes for patients with upper gastrointestinal tract malignancies.
When treating liver metastases with 60 Gy in 3 fraction SBRT, what is the best dose limit parameter for the liver?

a. $V_{30\text{Gy}} < 50\%$

b. $V_{15\text{Gy}} < 50\%$

c. 700 cc nml liver < 15 Gy

d. 700 cc nml liver < 30 Gy

e. Mean liver dose < 25 Gy
Upper GI Malignancies

Outline

• Esophageal Cancer Primary Therapy
• Gastric Cancer Adjuvant
• Pancreatic Cancer
  • Locally Advanced
  • Surgical Adjuvant
• Hepatobiliary Malignancies
  • Cholangioca
  • Liver mets
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-Worldwide

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
</table>
| Lung & bronchus               | 951,000                 | 458,400
| Liver                         | 478,300                 | 427,400
| Stomach                       | 464,400                 | 288,100
| Colon & rectum                | 320,600                 | 275,100
| **Esophagus**                 | **276,100**             | **273,600**
| Prostate                      | 258,400                 | 217,600
| Leukemia                      | 143,700                 | 140,200
| Pancreas                      | 138,100                 | 130,700
| Urinary bladder               | 112,300                 | 127,900
| Non-Hodgkin lymphoma          | 109,500                 | 113,800
| All sites but skin            | 4,225,700               | 3,345,800

- **Breast**
- **Lung & bronchus**
- **Colon & rectum**
- **Cervix uteri**
- **Stomach**
- **Liver**
- **Ovary**
- **Esophagus**
- **Pancreas**
- **Urinary bladder**
- **Leukemia**

Epidemiology
Esophageal Carcinoma U.S Incidence

- 16,980 new cases in U.S in 2011
- 14,710 deaths in U.S. in 2011
- 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

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
## 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>10</td>
<td></td>
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<tr>
<td>Millikan (Rush)</td>
<td>157</td>
<td>50</td>
<td>44</td>
<td>34</td>
<td>16</td>
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<td>O’Rourke (Austral.)</td>
<td>116</td>
<td>53</td>
<td>57</td>
<td>15</td>
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<td>Fok (Hong Kong)</td>
<td>218</td>
<td>66</td>
<td>28</td>
<td>50</td>
<td>14</td>
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<td>Zhang (Beijing)</td>
<td>3603</td>
<td>58</td>
<td>45</td>
<td>27</td>
<td>13</td>
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<tr>
<td>Nakadi (Belgium)</td>
<td>101</td>
<td>91</td>
<td>52</td>
<td></td>
<td>18</td>
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<tr>
<td>Visbal (Mayo)</td>
<td>220</td>
<td>94</td>
<td>36</td>
<td>14</td>
<td>10</td>
</tr>
</tbody>
</table>
Esophageal Cancer
General treatment recommendations

- Squamous cell carcinoma
  - cT2N0: surgery vs chemoradiation
  - T3-4 or N+: chemoradiation

- Adenocarcinoma
  - cT2N0: surgery vs preop chemoradiation
  - T3-4 or N+: preop chemoradiation

- Stage IV: chemo + 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: RT + Chemo
RTOG 8501 Schema

64 Gy / 32 fractions
123 pts
108 SQC
15 ACA

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

RTOG 8501
Survival by Treatment Arm

Alive (%)

RT + chemotherapy

RT only

Years from randomization

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

<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>

T2-4 or N+ SQC of esophagus: 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

CTCT Day 1Day 1 Day 22Day 22

A: Surgery days 50-60
B: Chemoradiation

46 Gy

Work-up days 38-41

CTCT Day 1Day 1 Day 22Day 22

20 Gy

Day 43
Day 64
Day 92

XRTXRT

B: Chemoradiation

15 Gy

Work-up days 38-41

CTCT Day 1Day 1 Day 22Day 22

15 Gy

A: Surgery days 50-60
B: Chemoradiation

Day 43
Day 64
Day 92

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

Graph showing survival rates over time (months) for two arms: Arm A (surgery) and Arm B (chemoradiation). The graph indicates a comparison of survival outcomes between the two treatment groups. The data is sourced from Bedenne JCO 25:1160-1168, 2007.
T2-4 or N+ ACA of esophagus: 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 → surgery
CDDP, 75 mg/m² weeks 1,6

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

Survival (%)

P=0.01

Multimodal therapy (n=58)

Surgery alone (n=55)

## 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

surgery alone

5-FU + CDDP + 50.4 Gy followed by surgery

Closed Early (56 pts) due to poor accrual
Overall survival (%) vs. Years from study entry for different treatment modalities. The graph shows a significant difference between Trimodality and Surgery with a p-value of <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

- Surgery
  - 363 pts
  - T2-3N0-1
  - 86 SQC
  - 273 ACA
  - 41.4 Gy
  - CBDCA → S
  - paclitaxel

- Med S
  - 26 mos
  - 48%

- 3-yr S
  - 49 mos
  - 59%

A.V. Gaast, ASCO 2010
cT2-4 or N+ ACA Esophagus: CT versus CT/RT followed by surgery?
Esophageal Cancer: Neoadjuvant Chemo  
MRC-OE02

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

5-FU  
CDDP  

5-FU → Surgery  
Surgery → CDDP

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

Surgery  
Surgery

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

Preoperative radiotherapy allowed (9%), same on both arms

MRC Lancet 359:1727-33, 2002
MRC-OE02

Pt at risk (events)  Years

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tbody>
<tr>
<td>CS</td>
<td>400 (164)</td>
<td>231 (73)</td>
<td>143 (26)</td>
<td>81 (13)</td>
<td>36 (2)</td>
<td>14</td>
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<tr>
<td>S</td>
<td>402 (185)</td>
<td>212 (76)</td>
<td>124 (32)</td>
<td>70 (18)</td>
<td>28 (5)</td>
<td>10</td>
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</table>

P=0.004

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

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

<table>
<thead>
<tr>
<th></th>
<th>Med S</th>
<th>1 yr S</th>
<th>2 yr S</th>
</tr>
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<tbody>
<tr>
<td>Preop* CDDP 5-FU x3</td>
<td>16.1 mo</td>
<td>62%</td>
<td>38%</td>
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<tr>
<td>Surgery</td>
<td>16.8 mo</td>
<td>62%</td>
<td>40%</td>
</tr>
</tbody>
</table>

*467 pts

*1.5% neutropenic sepsis deaths

Additional 2 cycles of chemotherapy postop

## Esophageal Cancer

### Neoadjuvant Chemo: INT 0113, RTOG 8911

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

*1.5% neutropenic sepsis deaths
*29% LF in R0, 41% in R1

Esophageal Cancer
Neoadjuvant Chemo: INT 0113, RTOG 8911

Overall survival (%)

No. of patients at risk
Chemotherapy surgery 136 73 42 28 15
Surgery 138 81 45 27 16
Phase III Study of Preoperative ChemoRT or Chemo in GE Junction Adenocarcinoma (POET)
T3-4 GE junction ACA

Arm A

1. PLF I
2. PLF II
3. PLF III (3 weeks)
4. Surgery

1. PLF I
2. PLF II
3. 15 x 2 Gy in 3 weeks
4. 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: 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 Adenocarcinoma (POET)

Overall Survival

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

Survival

P=0.07

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

Strata

Randomized Arm A
Censored randomized Arm A
Randomized Arm B
Censored randomized Arm B

Survival distribution function

P=0.06

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

Study
- Roth
- Nygaard
- Maipang
- Schlag
- Law
- Kelsen
- Ancona
- MRC
- All

Favors chemotherapy
0.2 0.5 1

Favors surgery alone
2 2.5 3 3.5 4 4.5 5

Australian Meta-Analysis
Chemotherapy and RT vs Surgery Alone

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

- Walsh
- Tepper
- All

0.2 0.5 1 2 5

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 ($P = 0.05$)

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 Technique
Esophageal Cancer
EBRT Dose Escalation, RTOG 94-05

5FU+CDDP + 50.4 Gy / 28

5FU+CDDP + 64.8 Gy / 36

RT fields = tumor + 5 cm longitudinal margins

298 pts/4 yrs
T1-4 NxM0
SQC or ACA
No tumor within 2 cm of stomach
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>SQC</th>
<th>ACA</th>
<th>Med S</th>
<th>2 yr S</th>
<th>LRF</th>
<th>TR death</th>
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<tbody>
<tr>
<td>187</td>
<td>31</td>
<td>50.4 Gy</td>
<td>18 mo</td>
<td>40%</td>
<td>52%</td>
</tr>
<tr>
<td>64.8 Gy</td>
<td>13 mo</td>
<td>31%</td>
<td>56%</td>
<td>11 pts*</td>
<td></td>
</tr>
</tbody>
</table>

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

Minsky, JCO 20:1167, 2002
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
Esophageal Cancer Planning

OAR limits

- Spinal cord max 45 Gy
- Lung: $V_{20} < 30\%, V_{10} < 40\%, V_5 < 60\%$, mean < 20 Gy
- Heart: $V_{30} < 100\%, V_{40} < 50\%$
- Liver: mean < 25 Gy, $V_{30} < 50\%$
- Kidney: combined $V_{20} < 30\%$
Esophageal Cancer Planning

3D vs. IMRT

• Lung toxicity with IMRT in trimodality patients?

• MDACC series (2012 GI symposium)
  • 208 3D patients
  • 165 IMRT patients
  • Less pulmonary complications (ARDS, effusion, pneumonia, resp. insufficiency) with IMRT
Esophageal Cancer
Future Directions

- Individualized therapy
  - RTOG 1010: evaluating trastuzumab in HER-2+ patients
  - CALGB 80803: prediction of response with PET
- Organ preservation
GASTRIC CANCER

Adjuvant Therapy
### Incidence in United States, 2011

**Carcinoma of the Stomach**

<table>
<thead>
<tr>
<th></th>
<th>New Cases</th>
<th>Deaths</th>
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</thead>
<tbody>
<tr>
<td>Any GI</td>
<td>277,570</td>
<td>139,250</td>
</tr>
<tr>
<td>Esophagus</td>
<td>16,980</td>
<td>14,710</td>
</tr>
<tr>
<td>Stomach</td>
<td>21,520</td>
<td>10,340</td>
</tr>
</tbody>
</table>

**Stomach Ca:** >30% death rate decline since 1990

Siegel, CA Cancer J Clin 61:212-236, 2011
Worldwide Epidemiology
Carcinoma of the Stomach

• 989,600 new cases in 2008
• 738,000 deaths
• 8% of total cancers, 10% of deaths
• Substantial decrease in most of the world

Gastric Cancer
Indications for Radiation Therapy

- Penetration through muscularis propria (T3-4 or posterior wall T2)
- Regional lymph node involvement
Patterns of Failure
University of Minnesota Reoperative Series

- 107 patients with gastric cancer
- 68 patients 2nd look laparotomy
- 39 patients symptomatic 2nd look

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Only</th>
<th>Component</th>
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<tbody>
<tr>
<td>LRF</td>
<td>29%</td>
<td>88%</td>
</tr>
<tr>
<td>PS</td>
<td>4%</td>
<td>54%</td>
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<tr>
<td>DM</td>
<td>6%</td>
<td>29%</td>
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</table>

Gunderson, IJROBP 8:1-11, 1982
Mayo Adjuvant CT-RT Trial

Gastric Cancer

62 resected pts, 1965-1974 (pre rand)
81% node +

Observation

<table>
<thead>
<tr>
<th></th>
<th>5 year survival</th>
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<tr>
<td></td>
<td>All</td>
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<tr>
<td>Observation</td>
<td>4%</td>
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<tr>
<td></td>
<td>23%</td>
</tr>
</tbody>
</table>

P < 0.05

3750 cGy/24
5-FU 15 mg/kg x 3d

*10 refused RT, 3/10 survived 5 years

Moertel, JCO, 1984
Gastric Cancer Adjuvant Therapy
Intergroup 0116

T3-4 and/or N+
Complete resection
85% node +
603 pts

Observation

R

5-FU
CF
x1

45 Gy
5-FU
CF

5-FU
CF
x 2

Macdonald, NEJM 345:725, 2001
Intergroup Gastric Adjuvant Study

Survival

Survival (%)

P=0.005

Chemo-RT 3 yr S 50%

Surgery only 3 yr S 41%

NEJM 345:725, 2001

Months after registration
Gastric Surgical Intergroup Trial
Relapse Patterns

- **Local**
  - Observation: 19%
  - Radiochemotherapy: 7%

- **Regional**
  - Observation: 46%
  - Radiochemotherapy: 27%

- **Distant**
  - Observation: 12%
  - Radiochemotherapy: 13%

Courtesy of S. Smalley
Gastric Cancer Adjuvant Therapy
Intergroup 0116 Criticisms

• Radiation made up for bad surgery
  • No D2 dissection mandated
  • No D1 dissection in many pts
• No need for radiation – perioperative chemotherapy is adequate
**Surgical Quality Control**

**Gastric Adjuvant Intergroup 0116**

- D2 dissection recommended but not mandated
- Surgical checklist, operative note and pathology report utilized

<table>
<thead>
<tr>
<th>D</th>
<th>No. Pts</th>
<th>Med S</th>
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<tbody>
<tr>
<td>D0</td>
<td>299 (54%)</td>
<td>27 mo</td>
</tr>
<tr>
<td>D1</td>
<td>198 (36%)</td>
<td>29 mo</td>
</tr>
<tr>
<td>D2</td>
<td>54 (10%)</td>
<td>48 mo</td>
</tr>
</tbody>
</table>

Gastric Cancer
Lymph Node Stations

- Lesser curvature 1,3,5 N1
- Greater curvature 2,4,6 N1
- Left gastric 7 N2
- Common hepatic 8 N2
- Celiac 9 N2
- Splenic 10,11 N2
- Extraregional 12-16 N3,N4

Maruyama, European J Cancer 34:1480-1489, 1998
Gastric Cancer
British D2 resection study

737 patients, 337 advanced disease
400 eligible
96% followed > 3 yrs

5 yr survival

D1 35%
D2 33%

Cuschieri, Br J Cancer 79:1522-30, 1999
MRC D1 vs D2 Resection Trial

Survival

Survival (%)

D1 resection

D2 resection

Years

Br J Cancer 79:1522, 1999
### MRC D1 vs D2 Resection Trial
#### Morbidity and Mortality

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Resection</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D1</td>
<td>D2</td>
<td></td>
</tr>
<tr>
<td>Hospital mortality (%)</td>
<td>6.5</td>
<td>13</td>
<td>0.04</td>
</tr>
<tr>
<td>Postop morbidity (%)</td>
<td>28</td>
<td>46</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Lancet 347:995, 1996*
Gastric Cancer
Dutch D2 resection study

1989 - 1993
996 pts entered
711 curative resection

<table>
<thead>
<tr>
<th>Comp.</th>
<th>PO Death</th>
<th>5 yr S</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>25%</td>
<td>4%</td>
<td>45%</td>
</tr>
<tr>
<td>D2</td>
<td>43%</td>
<td>10%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Dutch D1 vs D2 Resection Trial in Patients with Gastric Cancer

Survival

Survival (%)

Years after surgery

NEJM 340:908, 1999
Hartgrink JCO 22:2069-77, 2005

Curative resections

All eligible pt
Dutch D1 vs D2 Resection Trial
Survival in Patients with R0 Resection, Excluding Hospital Deaths*

NEJM 340:908, 1999

* Increased operative mortality, complications, reoperation in D2 arm
Dutch D1 vs D2 Resection Trial

Overall survival (%)

Years after randomization

<table>
<thead>
<tr>
<th>Years after randomization</th>
<th>D1</th>
<th>D2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>380</td>
<td>331</td>
</tr>
<tr>
<td>2.5</td>
<td>231</td>
<td>191</td>
</tr>
<tr>
<td>5</td>
<td>174</td>
<td>158</td>
</tr>
<tr>
<td>7.5</td>
<td>149</td>
<td>138</td>
</tr>
<tr>
<td>10</td>
<td>132</td>
<td>125</td>
</tr>
<tr>
<td>12.5</td>
<td>108</td>
<td>110</td>
</tr>
<tr>
<td>15</td>
<td>47</td>
<td>70</td>
</tr>
</tbody>
</table>

P = 0.34

No. at risk

Dutch D1 vs D2 Resection Trial

Disease-free survival (%)

P=0.31

Recurrence (%)

P=0.10

Years after randomization

No. at risk

D1

380 218 168 144 130 100 47

380 215 168 144 141 110 96

D2

331 185 152 136 123 109 71

331 185 152 133 124 109 92

Surgical Quality Control
Maruyama Index

• Based on 3843 Japanese patient database, all had D2 resections

• risk of nodal involvement at each of 16 stations based on: age, sex, Borrmann type, tumor size, location, depth, histology

• Index predicts likelihood of involved nodes in undissected nodal groups

Hundahl, Annals of Surgical Oncology 9:278-286, 2002
Intergroup 0116 Survival by MI

<table>
<thead>
<tr>
<th>MI&lt;5</th>
<th>Mi&gt;5</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>65</td>
</tr>
<tr>
<td>Events</td>
<td>27</td>
</tr>
<tr>
<td>Median in months</td>
<td>NR</td>
</tr>
</tbody>
</table>

P=0.005

Gastric Cancer
Adjuvant Therapy - Intergroup 0116

- Multivariate analysis
  - pathologic variables: T and N stage
  - surgical variables: type of gastrectomy, D level, Maruyama index
- No evidence of differing effect of adjuvant therapy in any subgroup

Hundahl, Annals of Surgical Oncology 9:278-286, 2002
# Gastric Cancer

## Dutch D2 resection study

<table>
<thead>
<tr>
<th>Group</th>
<th>5-yr S T3</th>
<th>5-yr S N+</th>
<th>5-yr S All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch D1</td>
<td>16%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Dutch D2</td>
<td>22%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>0116 S</td>
<td></td>
<td></td>
<td>~26%</td>
</tr>
<tr>
<td>0116 S + RT/CT</td>
<td></td>
<td></td>
<td>~44%</td>
</tr>
</tbody>
</table>

Macdonald, NEJM 345:725, 2001
### Gastric Cancer - Adjuvant Chemo

**MAGIC Trial (MRC ST02)**

- **503 pts**
- **ACA stomach**
- **EG junction**
- **lower esophagus**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5 yr OS</th>
<th>Curative resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECF x3 → S → ECF x3</td>
<td>36%</td>
<td>69%</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>23%</td>
<td>66%</td>
</tr>
</tbody>
</table>

**OS HR 0.75, P = 0.009**

*Cunningham, N Engl J Med 355:11-20, 2006*
MAGIC Trial Survival

Overall survival

Months

No. at risk
Perioperative chemotherapy 250 168 111 79 52 38 27
Surgery 253 155 80 50 31 18 9

P=0.009

MRC Lancet 359:1727-33, 2002
Overall survival of eligible patients (n=56)

P=0.17

Surgery

FAMTX

## Gastric Cancer - Adjuvant Chemo-RT

**CALGB 80801**

<table>
<thead>
<tr>
<th>Arm</th>
<th>Treatment</th>
<th>Median Survival</th>
<th>3-yr OS</th>
<th>3-yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5FU/LV→5FU/RT→5FU/LV</td>
<td>37 mos</td>
<td>50%</td>
<td>46%</td>
</tr>
<tr>
<td>2</td>
<td>ECF→5-FU/RT→ECF</td>
<td>38 mos</td>
<td>52%</td>
<td>47%</td>
</tr>
</tbody>
</table>

*P = 0.80*

Fuchs, JCO 29:15s, 4003, 2011
Gastric Cancer - Adjuvant Chemo
Meta-meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Yr</th>
<th># trials</th>
<th>OR</th>
<th>95% conf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janunger*</td>
<td>2002</td>
<td>21</td>
<td>0.84</td>
<td>0.74 - 0.96</td>
</tr>
<tr>
<td>Hu</td>
<td>2002</td>
<td>14</td>
<td>0.56</td>
<td>0.40 - 0.79</td>
</tr>
<tr>
<td>Panzini</td>
<td>2002</td>
<td>17</td>
<td>0.72</td>
<td>0.62 - 0.84</td>
</tr>
<tr>
<td>Mari</td>
<td>2000</td>
<td>20</td>
<td>0.82</td>
<td>0.75 - 0.89</td>
</tr>
<tr>
<td>Earle**</td>
<td>1999</td>
<td>13</td>
<td>0.80</td>
<td>0.66 - 0.97</td>
</tr>
<tr>
<td>Hermans</td>
<td>1993</td>
<td>11</td>
<td>0.88</td>
<td>0.78 - 1.08</td>
</tr>
</tbody>
</table>

*When Asian trials excluded, OR = 0.90 (0.83 - 1.12)
**Asian trials excluded
## Gastric Cancer Adjuvant Therapy
### MAGIC and 0116

<table>
<thead>
<tr>
<th></th>
<th>S alone</th>
<th>CMT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5 yr survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0116</td>
<td>26%</td>
<td>44%</td>
</tr>
<tr>
<td>MAGIC</td>
<td>23%</td>
<td>36%</td>
</tr>
<tr>
<td><strong>Local relapse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0116</td>
<td>19%</td>
<td>7%</td>
</tr>
<tr>
<td>MAGIC*</td>
<td>21%</td>
<td>14%</td>
</tr>
</tbody>
</table>

*24% of patients who died had LR prior to death*
Gastric Adjuvant Therapy
CRITICS trial – DCCG, GOF

R

ECC x 3 → D1+ surgery → ECC x 3

ECC x 3 → D1+ surgery → CT/RT

Ib-IVa
Gastric
GEJ
788 pts

ECC: Epirubicin 50mg/m2, CDDP 60 mg/m2, capecitabine 1000 mg/m2 bid
CT/RT: 45 Gy in 25 fractions + capecitabine 575 mg/m2 bid
Gastric Adjuvant Therapy
ARTIST trial – 한국

Lb-IVa
D2
Gastric
458 pts
2004-8

R

CP x 6

CP x 2 → CT/RT → CP x 2

CP: Capecitabine 1000 mg/m2 bid, CDDP 60 mg/m2
CT/RT: 45 Gy in 25 fractions + capecitabine 825 mg/m2 bid
Gastric Adjuvant – Artist Trial

Disease-free survival

All pts

P=0.0862

Treatment | No. | Event (no.) | 12 | 24 | 36 | 48 | 60 | 72
---|---|---|---|---|---|---|---|---
XP/XRT/XP | 230 | 55 | 21 | 44 | 49 | 53 | 55 | 55
XP | 228 | 72 | 15 | 39 | 46 | 67 | 70 | 70

Gastric Adjuvant – Artist Trial

Node + pts

\[ P = 0.0365 \]

Gastric Cancer: Radiation Technique
### Impact of Site of Primary Lesion and TN Stage

#### Irradiation Treatment Volumes - EG Junction

<table>
<thead>
<tr>
<th>TN Stage</th>
<th>Remaining Stomach</th>
<th>Tumor Bed Volumes*</th>
<th>Nodal Volumes</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3N0; post wall T2N0</td>
<td>Dependent on surg-path findings**</td>
<td>Medial L hemi-diaphragm, adj body of pancreas</td>
<td>None or perigastric ± periesophageal†</td>
</tr>
<tr>
<td>T4N0</td>
<td>Dependent on surg-path findings**</td>
<td>As for T3N0 plus site(s) of adherence with 3-5 cm margin</td>
<td>Nodes related to site of adherence; perigastric, periesoph</td>
</tr>
<tr>
<td>T1-2N+</td>
<td>Preferable</td>
<td>Not indicated for T1</td>
<td>Periesoph, mediast, perigastric, celiac</td>
</tr>
<tr>
<td>T3-4N+</td>
<td>Preferable</td>
<td>As for T3, T4N0</td>
<td>As for T1-2N+ and T4N0</td>
</tr>
</tbody>
</table>

* Use preop imaging (CT, barium swallow), surgical clips and postop imaging (CT)

**Optional if >5 cm surg/path margins and substantial increased morbidity risk

† Optional if D1+D2 resection and ≥15 nodes examined by pathologist
<table>
<thead>
<tr>
<th>TN Stage</th>
<th>Remaining Stomach</th>
<th>Tumor Bed Volumes*</th>
<th>Nodal Volumes</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3N0; post wall T2N0</td>
<td>Dependent on surg-path findings**</td>
<td>Medial L hemi-diaphragm, body of pancreas (± tail)</td>
<td>None or perigastric</td>
</tr>
<tr>
<td>T4N0</td>
<td>Prefer but depends on surg-path**</td>
<td>As for T3N0 plus site(s) of adherence with 3-5 cm margin</td>
<td>Nodes related to site of adherence ± perigastric, celiac, periesoph, mediast</td>
</tr>
<tr>
<td>T1-2N+</td>
<td>Preferable</td>
<td>Not indicated for T1</td>
<td>Perigastric, celiac, splenic, suprapanc, ± periesoph, panc- duod†, porta-hepatis†</td>
</tr>
<tr>
<td>T3-4N+</td>
<td>Preferable</td>
<td>As for T3, T4N0</td>
<td>As for T1-2N+ and T4N0</td>
</tr>
</tbody>
</table>

*Use preop imaging (CT, barium swallow), surgical clips and postop imaging (CT)

**Optional if >5 cm surg/path margins and substantial increased morbidity risk

†Optional if D1 + D2 resection and 15 nodes examined by pathologist
### Impact of Site of Primary Lesion and TN Stage

#### Irradiation Treatment Volumes - Body/Middle 1/3 Stomach

<table>
<thead>
<tr>
<th>TN Stage</th>
<th>Remaining Stomach</th>
<th>Tumor Bed Volumes*</th>
<th>Nodal Volumes</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3N0; post wall T2N0</td>
<td>Yes</td>
<td>Body of pancreas (± tail)</td>
<td>None or perigastric</td>
</tr>
<tr>
<td>T4N0</td>
<td>Yes</td>
<td>As for T3N0 plus sites(s) of adherence</td>
<td>Nodes related to site of adherence</td>
</tr>
<tr>
<td>T1-2N+</td>
<td>Yes</td>
<td>Not indicated for T1</td>
<td>Perigastric, celiac, suprapanc, splenic, panc-duod, porta-hepatitis</td>
</tr>
<tr>
<td>T3-4N+</td>
<td>Yes</td>
<td>As for T3, T4N0</td>
<td>As for T1-2N+ and T4N0</td>
</tr>
</tbody>
</table>

*Use preop imaging (CT, barium swallow), surgical clips and postop imaging (CT, barium swallow)*
<table>
<thead>
<tr>
<th>TN Stage</th>
<th>Remaining Stomach</th>
<th>Tumor Bed Volumes*</th>
<th>Nodal Volumes</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3N0; post wall T2N0</td>
<td>Dependent on surg-path**</td>
<td>Head of pancreas (± body)</td>
<td>None or perigastric</td>
</tr>
<tr>
<td>T4N0</td>
<td>Prefer but depends on surg-path**</td>
<td>As for T3N0 plus site(s) of adherence with 3-5 cm margin</td>
<td>Nodes related to site(s) of adherence ± perigastric, panc-duod</td>
</tr>
<tr>
<td>T1-2N+</td>
<td>Preferable</td>
<td>Not indicated for T1</td>
<td>Perigastric, panc-duod, porta-hepatitis, celiac, suprapanc; opt-spl hilum†</td>
</tr>
<tr>
<td>T3-4N+</td>
<td>Preferable</td>
<td>As for T3, T4N0</td>
<td>As for T1-2N+ and T4N0</td>
</tr>
</tbody>
</table>

*Use preop imaging (CT, barium swallow), surgical clips and postop imaging (CT)

**Optional if >5 cm surg/path margins and substantial increased morbidity risk

†Exclude if D1 + D2 dissection with ≥15 nodes examined and only 1-2 N+
Optimized Irradiation Fields – Gastric Antral Primary – T3N1

- **Tumor bed:** Head of pancreas, 1st and 2nd part of duodenum
- **Nodal volumes:** Perigastric, panc-duod, porta-hepatis, celiac, supra-panc; optional - splenic hilum
- **Gastric remnant:** To be included
- **Tolerance organs/structures:** Kidneys, liver, spinal cord
Gastric Cancer Planning
OAR limits

- Spinal cord max 45 Gy
- Lung: V20 < 20%
- Heart: V40<30%
- Liver: mean < 25 Gy, V30< 50%
- Kidney: combined V20 < 30%
- Small bowel: V45 < 150 cc, V30 < 300 cc
GE Junction Cancer: Post-op RT
PANCREATIC CANCER
Locally Advanced
Surgical Adjuvant Therapy
## Incidence in United States, 2011

**Carcinoma of the Pancreas**

<table>
<thead>
<tr>
<th></th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any GI</td>
<td>277,570</td>
<td>139,250</td>
</tr>
<tr>
<td>Pancreas</td>
<td>44,030</td>
<td>37,660</td>
</tr>
</tbody>
</table>

Pancreas Ca: #4 cause of death in both sexes

Siegel, CA Cancer J Clin 61:212-236, 2011
Worldwide Epidemiology
Carcinoma of the Pancreas

- 266,000 deaths worldwide in 2008
- Developed countries
  - 165,100 new cases in 2008
  - 161,800 deaths in 2008

Major Breakthroughs
Pancreatic Adenocarcinoma

1. 1935: Whipple describes pancreaticoduodenectomy

2. 1965: Childs and Moertel report improved survival with RT/5-FU

3. 1997: Burris reports 1-yr survival of 18% with gemcitabine vs. 2% 5-FU

4. 2011: FOLFIRINOX
Pancreatic Cancer

- Unresectable Disease
- Surgical Adjuvant Therapy
Locally Advanced Pancreatic Cancer: Chemotherapy alone?
Pancreas Adenocarcinoma
Locally Advanced & Metastatic Disease

Adapted from: Burris: JCO 15:2403, 1997
CALGB 80303 Trial Design

Advanced pancreatic cancer n=590

Randomize

Gemcitabine

Gemcitabine Bevacizumab

Gemcitabine Placebo

Stratification

• Performance status: 0/1 vs 2
• Extent of disease: metastatic vs locally advanced
• Prior radiation: yes/no

Kinder et al: ASCO, 2007
CALGB 80303
Progression-Free Survival by Treatment Arm

Proportion surviving

Bevacizumab 4.9 mo
Placebo 4.7 mo

P=0.99

Months from study entry

Kindler et al: ASCO, 2007
Metastatic Pancreas ACA
ACCORD4/PRODIGE11

- 342 PS 0-1 metastatic pancreas ca pts
- 59% body and tail primary
- 14% biliary stent
- Randomized to:
  - Gemcitabine x 6 mos
  - FOLFIRINOX x 6 mos

Conroy, NEJM 2011; 364:1817-25
Overall Survival - ACCORD4/PRODIGE11

Hazard ratio 0.57 (95% CI 0.45-0.73)
P<0.001 by stratified log-rank test

Conroy: NEJM 2011; 364:1817-25
Locally Advanced Pancreatic Cancer: Chemoradiation
Pancreas Adenocarcinoma
Locally Advanced Disease

64 patients
Unresectable pancreas ACA

Mean S

35-40 Gy + saline
6.3 mo
P<0.05

35-40 Gy + 5-FU, 15 mg/kg x 3
10.4 mo

RT fields not specified
Moertel, Lancet 2:865, 1969
Pancreas Adenocarcinoma
Locally Advanced Disease

Adapted from: Moertel and Colleagues: Lancet 2:865, 1969

- 5-FU + EBRT (32 patients)
- EBRT + saline (32 patients)

P<0.05

Probability of survival (%)

Months

0.0 0.2 0.4 0.6 0.8 1.0

0 5 10 15 20
# Pancreas Adenocarcinoma

## Unresectable: GITSG #1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Survival (wk)</th>
<th>1-year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 Gy</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>40 Gy + 5-FU</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>60 Gy + 5-FU</td>
<td>39</td>
<td>40</td>
</tr>
</tbody>
</table>

RT: Split course in 20 Gy increments; initial 40 Gy was to “entire pancreas”, final 20 Gy to tumor. 3 days bolus 5-FU with each course, then weekly.  

**References:**  
Int J Rad Oncol Biol Phys 5:1643, 1979  
Cancer 48:1705, 1981
Pancreas Adenocarcinoma

Unresectable: GITSG #1

Adapted from: Cancer 48:1705, 1981
Chemoradiation versus Chemotherapy alone?
Chemoradiation for Ca Pancreas
Common Sense Rationale

- Chemotherapy is relatively ineffective for pancreatic cancer
- Chemotherapy alone not curative for any GI malignancy
- If local disease is not controlled, metastatic disease cannot be controlled
- Local disease is symptomatic
Pancreas Adenocarcinoma

Unresectable: ECOG
(Stomach Cancer Included)

- 40 Gy +
- 5-FU, 600 x 3,
- then 600 weekly

Med S (mo)

- 8.2

- 5-FU, 600 weekly
- 8.3

RT field: “...smallest size that could reasonably encompass the tumor.”

22% of patients cancelled or not eligible, problem with RT in 10%

Klaassen: JCO 3:373, 1985
Pancreas Adenocarcinoma

Unresectable: ECOG

Adapted from: Klaassen: JCO 3:373, 1985
### Pancreas Adenocarcinoma

**Unresectable: GITSG #3**

<table>
<thead>
<tr>
<th></th>
<th>Med S (wk)</th>
<th>1-yr S (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMF x 2 yr</td>
<td>32</td>
<td>19</td>
</tr>
<tr>
<td>54 Gy + 5-FU (350 x 3) x 2 + SMF</td>
<td>42</td>
<td>41</td>
</tr>
</tbody>
</table>

*RT fields not specified*

*P<0.02*

- **43 patients**
- **Unresectable pancreas ACA**

GITSG: JNCI 80:751, 1988
Pancreas Adenocarcinoma

Unresectable: GITSG #3

Survival (%)

Weeks

Adapted from: GITSG: JNCI 80:751, 1988
Pancreas Adenocarcinoma
French Study

119 patients

ChemoRT (60 Gy in 30 fractions, CIFU, CDDP) → Gemcitabine

12% on RT arm no RT, only 42% at least 75% of RT/CT dose

Chauffert, Annals of Oncology, May 2008
## Pancreas Adenocarcinoma
### French Study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>1-year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChemoRT</td>
<td>32</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>53</td>
</tr>
</tbody>
</table>

Chauffert, Annals of Oncology, May 2008
Pancreas Cancer
Unresectable: French Study

Survival (%)

| Months | ChemoRT | Gemcitabine |
P|--------|---------|-------------|
| 0      | 100     | 100         |
| 6      | 80      | 80          |
| 12     | 60      | 60          |
| 18     | 40      | 40          |
| 24     | 20      | 20          |
| 30     | 0       | 0           |
| 36     | 0       | 0           |

P = 0.057

Adapted from Chauffert et al: ASCO, 2006
**Locally Advanced Pancreatic ACA**

**ECOG E4201**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Survival (mo)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT + Gem</td>
<td>11.1</td>
<td>0.17</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>9.2</td>
<td></td>
</tr>
</tbody>
</table>

Loehrer, J Clin Oncol 29:4105-4112, 2011
Locally Advanced Pancreatic ACA
ECOG E4201

<table>
<thead>
<tr>
<th>Survival</th>
<th>GEM alone</th>
<th>GEM plus RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>29</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total no. of Patients</th>
<th>Dead</th>
<th>Alive</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEM</td>
<td>37</td>
<td>0</td>
<td>9.2</td>
</tr>
<tr>
<td>GEM + RT</td>
<td>34</td>
<td>0</td>
<td>11.1</td>
</tr>
</tbody>
</table>

Survival:
- GEM alone
- GEM plus RT

Overall survival (probability)

P=0.34

# Unresectable Pancreatic Cancer

## Summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>RT/CT</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo</td>
<td>40 Gy + 5-FU</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>GTSG 1</td>
<td>40 Gy + 5-FU</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>GTSG 1</td>
<td>60 Gy + 5-FU</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>GTSG 2</td>
<td>60 Gy + 5-FU</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>GTSG 3</td>
<td>54 Gy + 5-FU</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>GTSG 3</td>
<td>SMF</td>
<td></td>
<td>19%</td>
</tr>
<tr>
<td>ECOG</td>
<td>40 Gy + 5-FU</td>
<td>28%</td>
<td>28%</td>
</tr>
<tr>
<td>NCCTG</td>
<td>50.4 Gy + CDDP/Gem</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>French</td>
<td>60 Gy + 5-FU/CDDP</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>French</td>
<td>Gem</td>
<td></td>
<td>53%</td>
</tr>
<tr>
<td>E 4201</td>
<td>Gem +/-50.4 Gy</td>
<td>50%</td>
<td>32%</td>
</tr>
</tbody>
</table>
Chemoradiation: Are there benefits beyond extended survival time?
Pancreas Cancer
Locally Advanced Disease: Taipei Study

34 patients
Unresectable pancreas ACA

RT + gem 14.5 mo
P<0.027

RT + bolus 5FU 7.1 mo

RT: 50.4 to 61.2 Gy at 1.8 per day; 45 Gy to tumor and nodes, then boost
Pancreas Cancer
Locally Advanced Disease: Taipei Study

Survival (%)

RT + GEM

RT + 5-FU

P=0.027

Time (months)

0 3 6 9 12 15 18 21 24 27 30 33

Pancreas Cancer
Locally Advanced Disease: Taipei Study

- Better pain control with Gemcitabine
- Higher average monthly KPS with Gemcitabine
- Significantly more quality adjusted months with Gemcitabine
Pancreas Cancer
Locally Advanced Disease: Kagoshima University Study (Japan)

34 patients
Unresectable pancreas ACA

Observation
Mean S 6.4 mo
1 Yr S 0.0%
P=0.0009

RT + PVI 5FU
RT: 50.4 Gy in 28 fractions in most patients, including tumor and regional nodes
Pancreas Cancer
Locally Advanced Disease:
Kagoshima University Study (Japan)

Adapted from Shinchi et al: Int J Rad Oncol Biol Phys 53:146-150, 2002
Pancreas Cancer
Locally Advanced Disease: Kagoshima University Study (Japan)

- Better average KPS with RT and continuous infusion 5FU
- Number of hospital days per month of survival was better (fewer) with RT and more continuous infusion 5FU
- 80% of patients in the active treatment group experienced pain relief, with a median duration of pain relief of 5.2 months
Pancreas Adenocarcinoma
Locally Advanced Disease

Overall Survival (n=47)

Median survival 10.2 mo

Adapted from: Haddock, JCO 25:2567-2572, 2007
Pancreas Cancer
NCCTG Phase II Study

Overall improvement in symptom distress score

$4.7 \pm 14.1 \quad P=0.06$

Haddock et al: JCO, June 2007
<table>
<thead>
<tr>
<th>QoL subscale</th>
<th>Mean ± std (last QOL – baseline; n=33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite</td>
<td>8.3±26.3</td>
<td>0.07</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12.9±3.01</td>
<td>0.03</td>
</tr>
<tr>
<td>Frequency of pain</td>
<td>21.2±26.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outlook</td>
<td>16.7±30.4</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Haddock et al: JCO, June 2007
## Pancreas Cancer
### Locally Advanced Disease

<table>
<thead>
<tr>
<th>QoL subscale</th>
<th>Mean ± std</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(last QOL – baseline; n=33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of pain</td>
<td>12.7±30.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Severity of pain</td>
<td>10.6±31.8</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Haddock: Linear Analogue Self-Assessment. JCO, 2007
Pancreatic Cancer

• Unresectable Disease
• Surgical Adjuvant Therapy
Important Clinical Trials

- **GITSG** Cancer 1987;59:2006-2010
- **EORTC** JH Klinkenbijl, Ann Surg 1999;230:776-84
- **RTOG 9704** WF Regine, JAMA 2008;299:1019-1026
- **ESPAC-1** Neoptolemos: Lancet 2001;358:1576-85,
  Neoptolemos: NEJM 2004;350:1200-10
- **CONKO-001** H Oettle, JAMA 2007;297:267-277
Pancreas Cancer Adjuvant Therapy

GITSG Phase III Trial

Survival (%)

Months

Chemotherapy + radiotherapy

Control

P=0.03

Adapted from: Arch Surg 120:899, 1985
Pancreas Cancer Adjuvant Therapy

EORTC Phase III Trial

P = 0.099 (2 sided)
< 0.05 if one sided test used

Survival (%)

Years

Adapted from: Ann Surg 244:332, 2006
Pancreas Adenocarcinoma
Surgical Adjuvant Therapy

<table>
<thead>
<tr>
<th></th>
<th>Med S</th>
<th>2 yr S</th>
<th>5 yr S</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 Gy split bolus 5 FU</td>
<td>21 mo</td>
<td>43%</td>
<td>14%</td>
</tr>
<tr>
<td>observation</td>
<td>11 mo</td>
<td>18%</td>
<td>5%</td>
</tr>
<tr>
<td>EORTC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 Gy split bolus 5 FU</td>
<td>17 mo</td>
<td>37%</td>
<td>20%</td>
</tr>
<tr>
<td>observation</td>
<td>13 mo</td>
<td>23%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Pancreas Cancer Adjuvant Therapy

ESPAC-1 Trial

- 61 centers in 11 countries
- 40 Gy split course + bolus 5-FU
- RT fields, technique: Not specified, no central audit
- Chemo = 6 cycles 5-FU/CF
Pancreas Adenocarcinoma
Surgical Adjuvant Therapy

ESPAC-1 Study

2/94-5/97
541/289 patients
61/53 centers
11 countries

40 Gy split + 5-FU

5-FU + CF x 6

40 Gy split + 5-FU → 5-FU/CF x 6

Observation

Neoptolemos: Lancet 358:1576, 2001
Neoptolemos: NEJM 350:1200, 2004
Pancreas Cancer: ESPAC-1 Trial
Survival – Chemoradiotherapy vs None

Adapted from: Neoptolemos et al: NEJM 350:1204, 2004
Pancreas Cancer: ESPAC-1 Trial
Survival – Chemotherapy vs None

Adjuvant chemo vs No adjuvant chemo

Survival (%)

P = 0.009

Adapted from: Neoptolemos et al: NEJM 350:1204, 2004
## Pancreas Ductal Cancer

### Survival: Surgery vs. Surgery + CT-RT

<table>
<thead>
<tr>
<th>Series</th>
<th>Observation</th>
<th></th>
<th>Chemo-RT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pt (no.)</td>
<td>Median (mo)</td>
<td>5 yr (%)</td>
</tr>
<tr>
<td></td>
<td>Pt (no.)</td>
<td>Med. (mo)</td>
<td>5 yr (%)</td>
</tr>
<tr>
<td>GTSG</td>
<td>22</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>EORTC</td>
<td>54</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>ESPAC-1</td>
<td>69</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>145</td>
<td>14-20</td>
<td>7-13</td>
</tr>
</tbody>
</table>
Pancreas Adenocarcinoma
CONKO-001 Postoperative Adjuvant Study

368 patients resected pancreas cancer patients

5-yr S
Observation 5%
Gemcitabine 21%
P = 0.005

Oettle and Colleagues: JAMA 297:267, 2007
Pancreas Adenocarcinoma
CONKO-001 Postoperative Adjuvant Study

Overall Survival

Cumulative %

Observation

Gemcitabine

P=0.005

Adapted from: Oettle and Colleagues:  JAMA 297:267, 2007
## Pancreas Cancer
### Locoregional relapse

### Local Relapse Following Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th># pts</th>
<th>% + margins</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG</td>
<td>22</td>
<td>0</td>
<td>33%</td>
</tr>
<tr>
<td>EORTC</td>
<td>103</td>
<td>19%</td>
<td>36%</td>
</tr>
<tr>
<td>CONKO-001</td>
<td>182</td>
<td>19%</td>
<td>41%</td>
</tr>
</tbody>
</table>

### Local Relapse Following Surgery + chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th># pts</th>
<th>% + margins</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESPAC-1</td>
<td>289</td>
<td>18%</td>
<td>34%</td>
</tr>
<tr>
<td>CONKO-001</td>
<td>182</td>
<td>19%</td>
<td>34%</td>
</tr>
</tbody>
</table>

*63% of relapse pts had local component*
Pancreas Adenocarcinoma
Surgical Adjuvant Therapy

RTOG 97-04: Closed July 2002
330 patients
5 years

Potentially curative resection

R

PVI 5-FU

Weekly Gem

RT PVI 5-FU

RT PVI 5-FU

Weekly Gem

Chemo duration is 3 wk pre-RT and 12 wk post-RT
Pancreas Adenocarcinoma
Surgical Adjuvant Therapy: RTOG 97-04
Results in Patients with Pancreatic Head Tumors

![Graph showing survival rates for CRT + GEM and CRT + 5-FU compared to randomization years.]

- CRT + GEM: 138/187
- CRT + 5-FU: 161/201

Alive (%) vs Years from randomization

P=0.09

Survival After Pancreaticoduodenectomy
Observation vs Adjuvant Chemoradiation (n=1,092)

Adjuvant therapy, P<0.001

mOS CRT Obs
21.1 mo 22.3%
15.5 mo

2-yr OS 44.7% 16.1%
5-yr OS 34.6%

Chemoradiation
Observation only

Survival

Follow-up (years)

Hu: 2008 GI Symposium, Mayo-Johns Hopkins series
John’s Hopkins – Mayo Clinic Series

Matched-Pair Analysis

- N=248 Surgery Only
- N=248 Surgery + Adjuvant CRT
  - N=496
  - Matched on age, gender, institution, T-stage, margin positivity, node positivity, histologic grade

Hu, 2008 GI Symposium
Matched-Pair Analysis: Survival After Pancreaticoduodenectomy
Observation vs Adjuvant Chemoradiation (n=496)

- **Adjuvant therapy, P<0.001**
  - mOS: CRT 21.9 mo, Obs 14.3 mo
  - 2-yr OS: CRT 45.5%, Obs 31.4%
  - 5-yr OS: CRT 25.4%, Obs 12.2%

**Adj CRT RR: 0.59 (0.48-0.72)**

**Follow-up (years)**

Hu: 2008 GI Symposium
**Pancreas Adenocarcinoma**

**Surgical Adjuvant Therapy**

<table>
<thead>
<tr>
<th>+ margins</th>
<th>Obs</th>
<th>CT</th>
<th>RT-CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG</td>
<td>0</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>EORTC</td>
<td>19%</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>ESPAC-1</td>
<td>28%</td>
<td>11</td>
<td>29</td>
</tr>
<tr>
<td>CONKO-001</td>
<td>19%</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>RTOG 9704</td>
<td>35%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mayo – JH</td>
<td>35%</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>NPCT</td>
<td>0%</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>
Pancreas Cancer
RTOG 0848

- Gem x 5 → restage if NED:
  - Gem x 5 → restage
  - Erlotinib

- RT + Cape
  - Gem
  - RT + Cape
  - Gem
  - Erlotinib
Pancreatic Cancer
Future Directions

• Effective systemic therapy?
  • Advances likely to be in small steps
  • Multiple targets may be required
  • Maintenance therapy will be required
• The importance of local control will ↑
• Individualization of treatment
• Move towards preoperative therapy
Pancreatic Cancer Relapse Patterns
Johns Hopkins Autopsy series

- 76 pancreatic cancer autopsies
- 22 resected pts: 73% local relapse
- 5/6 positive margin patients local relapse
- 88% metastatic disease: some <10 mets, some > 1000 mets
- 30% locally destructive, 70% widely metastatic
- Loss of DPC4 predictive of widely metastatic pattern

Iacobuzio, JCO 27:1806-1813, 2009
Pancreatic Cancer – Individualized Rx
RTOG 1201

- Assessment of SMAD4/DPC4 status

- Intact SMAD4/DPC4:
  - Gem x 3 → IMRT 63 Gy + cape

- Loss of SMAD4/DPC4:
  - Gem x 3 → 50.4 Gy + cape
  - FOLFIRINOX x 3 → 50.4 Gy + cape
Pancreatic Cancer: Radiation Technique
Pancreas Cancer
Quality Assurance

• RTOG 9704: decreased survival when RTQA score not per protocol

<table>
<thead>
<tr>
<th>Study</th>
<th>Median Survival</th>
<th>3-yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONKO-001</td>
<td>22 mo</td>
<td>34%</td>
</tr>
<tr>
<td>RTOG 9704</td>
<td>25 mo</td>
<td>46%</td>
</tr>
</tbody>
</table>

(\text{CA 19-9} \leq 90 \text{ RTQA per protocol})

Pancreas Cancer
Dose Fractionation

• 5040 cGy in 28 fractions is standard for both unresectable and adjuvant

• Duodenum is dose limiting for head tumors
Pancreas Cancer
Treatment Volumes

• RTOG 0848 atlas

• CTV includes:
  • Proximal CA
  • Proximal SMA
  • PV anterior to SVC
  • Preop GTV
  • PJ
  • Aorta
Radiotherapy – Traditional fields

- 45 Gy in 25 fractions
  - Tumor bed
  - Lymphatics (Celiac, SMA, first echelon nodes)
  - Porta hepatis
- Boost tumor bed to 50.4 Gy
Pancreatic Cancer
Modern technique

• IV contrast for GTV delineation
• Motion management
• Daily IGRT
• Limited volumes
  • GTV + 10 mm = CTV
  • CTV + 20 mm sup/inf, 10 mm radial = PTV
Pancreas Cancer Planning
OAR Limits

- Spinal cord max 45 Gy
- Kidneys combined V18 < 30%
- If one kidney V18 < 15%
- Liver mean < 25 Gy, V30 < 50%
- Stomach max 54 Gy, V45 < 15%
- Small intestine max 54 Gy, V45 < 150 cc, V30 < 300 cc
Pancreas
Four Field Isodoses
Six Field Isodoses
Pancreas
DVH Comparison

4 Field

6 Field

Volume (%)

Dose (cGy)

Right kidney

Left kidney

Right kidney

Left kidney
IMRT dose distribution
HEPATOBILIARY MALIGNANCIES
Epidemiology
2011 USA

- Liver + IHBD
  - 26,190 new cases
  - 19,590 deaths

- Gall bladder + EHBD
  - 9250 new cases
  - 3300 deaths
AMPULLARY CARCINOMA
Ampullary Carcinoma

Risk Factors

- T3-T4
- Positive margins
- Positive nodes
- High histologic grade
Ampullary Cancer
EORTC Phase III Trial

93 periampullary
58% N0
40 Gy Split
5-FU

RT+5FU

P=0.737

Survival in Node + Patients
Mayo – Node + Ampullary

Overall survival

Years

Adjuvant therapy
No adjuvant therapy

P<0.01

Adapted from Bhatia, IJROBP 66:514-19, 2006
# Ampullary Cancer

## Mayo-Johns Hopkins Results

<table>
<thead>
<tr>
<th>treatment</th>
<th>Node +</th>
<th>N+ Med S</th>
<th>N+ S</th>
</tr>
</thead>
<tbody>
<tr>
<td>surgery (120)</td>
<td>36</td>
<td>16 mo.</td>
<td>6%</td>
</tr>
<tr>
<td>S +RT/CT (66)</td>
<td>48</td>
<td>32 mo.</td>
<td>28%</td>
</tr>
</tbody>
</table>

\[ P = 0.004 \]

Narang, Radiation Oncology 6:126, 2011
Survival After Surgical Resection, Node Positive
Observation vs Adjuvant Chemoradiation—Mayo/JH

1. Adjuvant Therapy

2. Chemoradiation

P = 0.004

Survival onl

Years

Narang: Radiation Oncology 6:126, 2011
CHOLANGIOOCARCINOMA
New Cancers in United States

- 1 Cholangiocarcinoma
- 80 prostate cancers
- 115 breast cancers
Extrahepatic Cholangiocarcinoma

Radiotherapy Indications

- Adjuvant therapy following resection
- Preoperative therapy prior to transplant
- Primary therapy
  - EBRT (with chemo)
  - Brachytherapy
  - SBRT
Hilar Cholangiocarcinoma
Surgical Resection

• 15-40% are resectable
• LR after R0 resection: 25-40%
• Positive margins common
• Gross residual in 1/3
• 50% positive nodes
• 5-yr survival 10-40%
Hilar Cholangiocarcinoma

Surgical Resection

- LR after R0 resection: 25-40%
- Locoregional first relapse site
  - 60% of EHCC
  - 15% Gall Bladder Ca
- Does RT reduce the risk of locoregional relapse?
Proximal Bile Duct Cancer – Tsukuba University
R1 Resection ± IOERT, EBRT

Todoroki et al: IJROBP
Proximal Bile Duct Cancer – EORTC

Overall Survival R1 Resection ± XRT

Survival (%)

Surgery alone (n=17)

Postoperative radiation (n=38)

P=0.0005

Hilar Cholangiocarcinoma
SWOG 0809

- Eligibility: T2-4 or N1 or margin +
- Chemo: Gem-Cape x 4 cycles
- Radiation + capecitabine
  - 3D: 5400 – 5940 cGy in 30-33 fx
  - IMRT: 5250-5500 in 25 fx
- Goal: 80 patients
- Endpoints: local relapse and survival
Hilar Cholangiocarcinoma
Adjuvant RT Conclusions

• Most resected patients at high risk of locoregional relapse

• Adjuvant RT may decrease risk

• Indications:
  • R1 or R2 resection
  • Positive nodes?
  • R0 with close margins (T2-4)?

• Caution: liver dose constraints
Unresectable Hilar Cholangiocarcinoma
Unresectable Cholangiocarcinoma

- Radiation + chemo $\rightarrow$ liver transplant
- Radiation + CT as primary therapy
  - Dose
  - Technique
  - Brachytherapy
    - LDR
    - HDR
  - Complications
Liver Transplant
Mayo Protocol

- RT: 4500 cGy in 30 bid fractions
- 3 days bolus 5-FU during RT
- Brachytherapy: 20-30 Gy with 192-Ir
- Continuous infusion 5-FU or capecitabine until transplant
- Exploratory laparotomy
Liver Transplant
Hilar Cholangiocarcinoma

• Rationale:
  • 20-30% resectable
  • > 60% local recurrence rate
  • Distant mets relatively uncommon

• Early results disappointing:
  • 20-30% survival
  • 50 - 60% tumor recurrence
  • 50% of relapses in liver allograft
# Liver Transplant Hilar Cholangiocarcinoma

<table>
<thead>
<tr>
<th>Series</th>
<th>Year</th>
<th># Pts</th>
<th>5 Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pittsburgh</td>
<td>1995</td>
<td>20</td>
<td>20% (3-yr)</td>
</tr>
<tr>
<td>Hannover</td>
<td>1996</td>
<td>25</td>
<td>17%</td>
</tr>
<tr>
<td>Berlin</td>
<td>1999</td>
<td>15</td>
<td>38%</td>
</tr>
<tr>
<td>Spain</td>
<td>2004</td>
<td>36</td>
<td>30%</td>
</tr>
<tr>
<td>Nordic</td>
<td>2004</td>
<td>18</td>
<td>35%</td>
</tr>
<tr>
<td>Canada</td>
<td>2005</td>
<td>10</td>
<td>30% (3-yr)*</td>
</tr>
<tr>
<td>Cincinnati</td>
<td>2000</td>
<td>207</td>
<td>23%**</td>
</tr>
</tbody>
</table>

*incidental, 8/10 relapse
**+ nodes 7 mo. median survival vs. 35 mo.
Patient Survival After Transplantation
1993 – 2009

Years after transplantation

September 1, 2009
Patient Survival After Start of Therapy

1993 – 2009
n=184

Years after start of therapy

September 1, 2009
Survival after Operation

Time (years)

% 100 90 80 70 60 50 40 30 20 10 0

Transplantation (n=38)
Resection (n=26)

Explanted Liver After Neoadjuvant Therapy
Brachytherapy

Hilar Cholangiocarcinoma
Brachytherapy
Cholangiocarcinoma

- Radioactive sources (Iridium-192) placed in bile duct
- Transhepatic catheters (easy)
- ERCP placement (hard)
- Low dose rate: 20-30 Gy over 24-48 hrs
- High dose rate: 4 fractions 4 Gy over 2 days
Brachytherapy

- Applicator (≈10F tube) placed via endoscope at ERCP
Liver Mets

SBRT

- Liver mets: no Rx: med S 3-20 mos
- Resection: 5-yr S 30%+
- Only 20-25% suitable for resection
- RFA local relapse
  - < 3 cm 16%
  - 3-5 cm 26%
  - > 5 cm 60%
Liver Mets
SBRT

- Multi-institutional Phase I-II trial
- Ph II dose: 60 Gy in 3 fractions
- 2-yr LC 92%
- 2-yr LC 100% for < 3cm
- 83% distant progression
- 2-yr OS 30%

Rusthoven, JCO 27:1572-1578, 2009
Liver Mets
SBRT Technique

• Immobilization: custom mold
• Active breathing control or abdominal compression
• Dynamic conformal arcs or multiple non-coplanar static beams ($\geq 7$)
• Dose prescription: 80-90% isodose
• IGRT: orthogonal x-ray or CBCT
Liver Mets
3 fraction SBRT: OAR limits

- 700 cc nml liver < 15 Gy
- Kidney sum: V15 < 35%
- Spinal cord max: 18 Gy
- Chest wall: V30 < 10 cc
- Stomach: max 22 Gy, V 16.5 < 10 cc
- Small bowel: max 22 Gy, V 16.5 < 5 cc
- Skin: V30 < 10 cc
Liver Mets
SBRT Cautions

- RILD
- Bevacizumab: bowel perforations
- Soft tissue necrosis
- Chest wall
  - Rib fracture
  - Neuropathy
- Biliary fibrosis
- Late vascular toxicity
Post-test Question

• When treating liver metastases with 60 Gy in 3 fraction SBRT, what is the best dose limit parameter for the liver?
  a. V30Gy < 50%
  b. V15Gy < 50%
  c. 700 cc nml liver < 15 Gy
  d. 700 cc nml liver < 30 Gy
  e. Mean liver dose < 25 Gy