Upper Gastrointestinal

Friday, March 2, 2018
2:00 p.m. – 2:45 p.m.
Social Q&A

Use your phone, tablet, or laptop to

➢ Submit questions to speakers and moderators
➢ Answer interactive questions / audience response polls

astro.org/RefresherSocialQA
# Faculty Disclosures

Faculty and Committee disclosures are also on the 2018 ASTRO Annual Refresher Course website.

<table>
<thead>
<tr>
<th>Name</th>
<th>Employment</th>
<th>Funding Sources</th>
<th>Ownership or Investments</th>
<th>Leadership</th>
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<tbody>
<tr>
<td>Albert Koong, MD, PhD, FASTRO</td>
<td>MD Anderson Cancer Center</td>
<td>None</td>
<td>None</td>
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</tr>
</tbody>
</table>
ASTRO Refresher: Upper GI

Albert C. Koong MD, PhD, FACR, FASTRO
Dallas/Fort Worth Living Legend Professorship
Chair, Department of Radiation Oncology
The University of Texas MD Anderson Cancer Center
@ACKoongMDPhD
Disclosures

• None
Harvey 33 trillion gallons
Katrina 6.5 trillion gallons
Learning Objectives

• Update on management of esophagus and GE junction cancer

• Update on management of gastric cancer

• Update on management of locally advanced pancreatic cancer
U.S. Esophageal Cancer Statistics 2017

- 16,940 new cases
- 15,690 deaths
- ~10% overexpress her2
- Adenocarcinomas increasing, ~75%
Staging

- **Tumor Stage:**
  - T1: lamina propria
  - T2: muscularis propria
  - T3: adventitia
  - T4a: adjacent structures but resectable (pleura, pericardium, diaphragm)
  - T4b: adjacent structures but unresectable (aorta, vertebral bodies, trachea)

- **N Stage:**
  - N1 – 1-2 nodes
  - N2 – 3-6 nodes
  - N3 – 7+ nodes

- **M Stage:**
  - M1 - mets
## RTOG 85-01

<table>
<thead>
<tr>
<th></th>
<th>Median OS</th>
<th>5-Yr OS</th>
<th>LF@ 2 yrs</th>
<th>G3 Toxicity</th>
<th>G4 Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT Alone</td>
<td>9 months</td>
<td>0</td>
<td>66%</td>
<td>25%</td>
<td>3%</td>
</tr>
<tr>
<td>CRT</td>
<td>14 months</td>
<td>26%</td>
<td>45%</td>
<td>44%</td>
<td>20%</td>
</tr>
<tr>
<td><em>p</em></td>
<td>p&lt;0.001</td>
<td>p=0.0123</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Radiation alone is palliative treatment
- High local failure rate even with CRT
- Toxicity significantly increased with CRT
Dose Escalation?
Int 0123/RTOG 94-05

- 5-FU + CDDP + 5040 cGy
  - Med S*: 18.1 mo
  - LRF/Dz*: 52%
  - 218 pts

- 5-FU + CDDP + 6480 cGy
  - Med S*: 13.0 mo
  - LRF/Dz*: 56%

*not statistically significant

Minsky et al, JCO 2002
Dose Escalation?
Int 0123/RTOG 94-05

218 pts

5-FU + CDDP + 5040 cGy

5-FU + CDDP + 6480 cGy

G4 G5

41 2

33 11

Minsky et al, JCO 2002
Meta-analysis: CMT for Esophageal Cancer

22 studies identified from previous meta-analysis
318 studies identified from database searches
76 additional records identified from other sources

302 studies after duplicates removed
Title and abstracts screened for eligibility

35 abstracts reviewed
3 excluded
1 (An, 2001): abstract not available in English and no further details provided by author
2 (Peng, 2008, and Wang, 2001): full text not in English insufficient detail in abstract and no further details provided by author

32 full-text articles assessed for eligibility
8 excluded
2 (Cunningham, 2006, and Schulze-Mahrer, 2007): results for gastro-esophageal junction and oesophageal tumours not available separately; most patients received gastrectomy
2 (Bokharyen, 2009, and Soo, 2006): both abstracts describe the same study; insufficient information available from abstract and no response from authors
1 (Boige, 2009): abstract not used; insufficient data on subgroups; final publication (10/2013) used because additional information available to meet inclusion criteria
1 (Kok, 1997): abstract not used because updated results available (Boonetra2007) after contacting authors

24 included in meta-analysis
## Meta-analysis: CMT for Esophageal Cancer

### Table A

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy (total)</th>
<th>Surgery alone (total)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth et al.</td>
<td>39</td>
<td>29</td>
<td>0.71 (0.56–0.89)</td>
</tr>
<tr>
<td>Mangaard et al.</td>
<td>15</td>
<td>15</td>
<td>0.72 (0.50–1.05)</td>
</tr>
<tr>
<td>Schlag et al.</td>
<td>22</td>
<td>24</td>
<td>0.97 (0.94–1.01)</td>
</tr>
<tr>
<td>Meining et al.</td>
<td>24</td>
<td>24</td>
<td>0.84 (0.79–0.90)</td>
</tr>
<tr>
<td>Low et al.</td>
<td>74</td>
<td>73</td>
<td>0.80 (0.73–0.89)</td>
</tr>
<tr>
<td>Roesler et al.</td>
<td>86</td>
<td>64</td>
<td>0.90 (0.79–1.03)</td>
</tr>
<tr>
<td>Kelsen et al.</td>
<td>234</td>
<td>234</td>
<td>0.95 (0.91–1.00)</td>
</tr>
<tr>
<td>Annane et al.</td>
<td>41</td>
<td>41</td>
<td>0.94 (0.87–1.01)</td>
</tr>
<tr>
<td>Total</td>
<td>1015</td>
<td></td>
<td>0.92 (0.81–1.05)</td>
</tr>
</tbody>
</table>

**Heterogeneity:** $I^2 = 15.72\%$ (95% CI 0–41%), $P = 0.43$%

Test for overall effect: Z = 2.05 (p = 0.04)

### Table B

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy (total)</th>
<th>Surgery alone (total)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous-cellcarcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roth et al.</td>
<td>19</td>
<td>20</td>
<td>0.74 (0.56–1.00)</td>
</tr>
<tr>
<td>Mangaard et al.</td>
<td>15</td>
<td>15</td>
<td>0.72 (0.50–1.03)</td>
</tr>
<tr>
<td>Schlag et al.</td>
<td>22</td>
<td>24</td>
<td>0.93 (0.87–1.00)</td>
</tr>
<tr>
<td>Meining et al.</td>
<td>24</td>
<td>22</td>
<td>0.81 (0.76–0.87)</td>
</tr>
<tr>
<td>Low et al.</td>
<td>74</td>
<td>73</td>
<td>0.80 (0.72–0.88)</td>
</tr>
<tr>
<td>Roesler et al.</td>
<td>86</td>
<td>64</td>
<td>0.95 (0.87–1.04)</td>
</tr>
<tr>
<td>Kelsen et al.</td>
<td>110</td>
<td>110</td>
<td>0.94 (0.87–1.01)</td>
</tr>
<tr>
<td>Annane et al.</td>
<td>48</td>
<td>48</td>
<td>0.93 (0.85–1.02)</td>
</tr>
<tr>
<td>Total</td>
<td>554</td>
<td></td>
<td>0.82 (0.73–0.94)</td>
</tr>
</tbody>
</table>

**Heterogeneity:** $I^2 = 13.70\%$ (95% CI 0–38%), $P = 0.46$%

Test for overall effect: Z = 2.14 (p = 0.04)

| Adenocarcinoma |                |                       |                       |
| Kelsen et al.  | 110                | 110                   | 0.96 (0.79–1.16)      |
| Annane et al.  | 265                | 265                   | 0.93 (0.76–1.13)      |
| Ychou et al.   | 85                 | 84                    | 0.93 (0.84–1.03)      |
| Subtotal       | 470                |                       | 0.92 (0.84–1.00)      |

**Heterogeneity:** $I^2 = 11.73\%$ (95% CI 0–23%), $P = 0.19$%

Test for overall effect: Z = 2.08 (p = 0.04)

### Footnotes

- Favors Surgery Alone
- Favors Chemotherapy

Sjoquist et al., Lancet Onc 2011

**Figure**: Favoring surgery alone or chemotherapy in esophageal cancer patients.
Meta-analysis: CMT for Esophageal Cancer

Favors ChemoXRT

Favors Surgery Alone

Sjoquist et al, Lancet Onc 2011
56 patients randomized
  • 75% adeno, 25% SCCA

Trial stopped due to poor accrual
  • 30 pts – chemo/RT → surgery
  • 26 pts – surgery alone
  • RT – 50.4 Gy in 28 fx’s
  • Chemo – cisplatin/5FU x 2

Med OS – 4.5 yrs (CRT-S) vs 1.8 yrs (S) (p=0.002)
CROSS Regimen

Radiotherapy (3D CRT)
- 41.4 Gy in 1.8 Gy fractions
- GTV (primary and enlarged regional LNs)
- PTV (4 cm proximal and distal, 1.5 cm radial)

Chemotherapy (weekly)
- Paclitaxel 50 mg/m²
- Caboplatin (AUC=2)

Surgery: 4-6 wks after chemoXRT

van Hagen et al, NEJM 2012
CROSS Results

van Hagen et al, NEJM 2012
CROSS Results

• 92% chemoXRT-surgery group had R0 resection vs. 69% surgery only (p<0.001)
• LN+ 31% chemoXRT-surgery vs. LN+ 75% in surgery only (p<0.001)

• pCR 23% in ACA
• pCR 49% SCCA

van Hagen et al, NEJM 2012
CROSS Toxicities

ChemoXRT-Surgery

• <13% any non-hematologic toxicity (G3 or higher)
  
• Pulm tox (46%)
• Cardiac tox (21%)
• Anastamotic leak (22%)

Surgery Alone

• Pulm tox (44%)
• Cardiac tox (17%)
• Anastamotic leak (30%)

van Hagen et al, NEJM 2012
CROSS Long-Term Results

Shapiro et al, Lancet Onc 2015
CROSS Long Term Results: Median OS 49 mo for CRT-S vs. 24 mo for S alone

<table>
<thead>
<tr>
<th></th>
<th>Chemo-XRT Surgery</th>
<th>Surgery Alone</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local-regional Progression</td>
<td>39 (22%)</td>
<td>72 (38%)</td>
<td>0.45 (0.30-0.66)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Distant Progression</td>
<td>70 (39%)</td>
<td>90 (48%)</td>
<td>0.63 (0.46-0.87)</td>
<td>0.0040</td>
</tr>
<tr>
<td>Overall Progression</td>
<td>87 (49%)</td>
<td>124 (66%)</td>
<td>0.58 (0.44-0.76)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Shapiro et al, Lancet Onc 2015
Summary

• Whenever possible, combined modality therapy is treatment of choice for patients with esophageal cancer.

• SCCA have higher pCR than ACA.
KEYNOTE-028

Patients screened (n = 90)

Patients without tumor samples evaluable for PD-L1 expression (n = 7; 8%)

Patients with tumor samples evaluable for PD-L1 expression (n = 83; 92%)

Patients with PD-L1-negative tumors (n = 46; 55%)

Patients with PD-L1-positive tumors (n = 37; 45%)

Patients who did not meet study inclusion criteria (n = 14; 38%)

Patients enrolled (n = 23; 62%)

Pembrolizumab (anti-PD-L1) for recurrence after standard therapy

Doi et al, JCO 2018
Overall Response Rate 30%

3 out of 7 (43%) with PR had prior radiation

Doi et al, JCO 2018
Data to be Discussed

• Esophagus and GE junction cancer

• Gastric cancer

• Locally advanced pancreatic cancer
Gastric Cancer Epidemiology

• 28,000 new cases and 10,960 deaths in the US in 2017
• 2\textsuperscript{nd} leading cause of cancer death worldwide after lung cancer
• In Japan, 70 cases per 100,000 compared with 10 per 100,000 in the US
• Incidence inversely correlated with socioeconomic status
Staging 7\textsuperscript{th} Edition

- **T-stage**
  - T\textsuperscript{1a} – lamina propria/muscularis mucosae
  - T\textsuperscript{1b} – submucosa
  - T\textsuperscript{2} – muscularis propria
  - T\textsuperscript{3} – subserosa
  - T\textsuperscript{4a} – serosa (peritoneum)
  - T\textsuperscript{4b} – adjacent structures

- **N-stage**
  - N\textsuperscript{1} – 1-2 nodes
  - N\textsuperscript{2} – 3-6 nodes
  - N\textsuperscript{3a} – 7-15 nodes
  - N\textsuperscript{3b} – >15 nodes

- **M-stage**
  - M\textsuperscript{0} or M\textsuperscript{1}
Surgical Considerations

D1

D1+

D2

Total gastrectomy
# Survival and Recurrence Free Benefits With Different Lymphadenectomy for Resectable Gastric Cancer: A Meta-Analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Exp[(O-E) / V], Fixed, 95% CI</th>
<th>Hazard Ratio</th>
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<tr>
<td>Dutch trial</td>
<td>23.8%</td>
<td>0.92 [0.64, 1.33]</td>
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<tr>
<td>Taiwan trial</td>
<td>16.9%</td>
<td>0.49 [0.32, 0.76]</td>
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<tr>
<td>UK trial</td>
<td>59.3%</td>
<td>1.10 [0.87, 1.39]</td>
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<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>0.92 [0.77, 1.10]</td>
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</tr>
</tbody>
</table>

Heterogeneity: Chi² = 10.21, df = 2 (P = 0.006); I² = 80%

Test for overall effect: Z = 0.92 (P = 0.36)

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**Fig. 2.** Meta-analysis of OS comparing D1 with D2 gastrectomy.

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D2 lymphadenectomy with spleen and pancreas preservation offers the greatest survival benefit

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*Jiang et al, J Surg Onc, 2013*
INT-0016: MacDonald regimen

558 pts with resected GEJ or gastric adenocarcinoma (all stages) → Randomize

No further treatment N=275

Post-operative chemoradiotherapy N=281

D1: 5FU+leucovorin
D28-63: 4500 cGy +5FU
D64 + 92: 5FU+leucovorin
TOTAL TIME: 3.5 mo

<10% underwent D2 surgery

\[ p = 0.005 \]

\[ P < 0.001 \]

Figure 1. Overall Survival among All Eligible Patients, According to Treatment Group Assignment.

Figure 2. Relapse-free Survival among All Eligible Patients, According to Treatment Group Assignments.

Key Points

• Patients were randomized after surgery – stage Ib-IV – R0 resection

• 54% of patients had D0 resection indicating poor surgery and high risk of LRR

• CRT arm had more distant relapses and less LRR indicating OS benefit due to lower LRR

• 35% of treatment plans required revision due to minor or major deviations in field design (final: 6.5% major deviations)
Gastric Cancer-U Minn 2nd Look Series
Patterns of Relapse
Updated Analysis of SWOG-Directed Intergroup Study 0116: A Phase III Trial of Adjuvant Radiochemotherapy Versus Observation After Curative Gastric Cancer Resection


• Update with 10 years of follow-up
• 2\textsuperscript{nd} Cancers – 21 (CRT) vs 8 (surgery) – p=0.21
MAGIC: Medical Research Council on Adjuvant Gastric Infusional Chemotherapy

503 pts with resectable GEJ or gastric adenocarcinoma (≥Stage II)

42% underwent D2 surgery

Randomize

Surgery alone
N=253

Surgery + Peri-operative chemo
N=250

ECF: 3 cycles preop and 3 cycles postop
TOTAL TIME: 3.6 mo

p<0.001

<table>
<thead>
<tr>
<th>Variable</th>
<th>Perioperative Chemotherapy</th>
<th>Surgery Alone</th>
<th>Hazard Ratio</th>
<th>P for trend</th>
<th>P for interaction</th>
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<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;60 yr</td>
<td>61/108</td>
<td>75/104</td>
<td></td>
<td></td>
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<tr>
<td>60–69 yr</td>
<td>56/91</td>
<td>59/95</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≥70 yr</td>
<td>32/51</td>
<td>36/54</td>
<td></td>
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</tr>
<tr>
<td>Total</td>
<td>149/250</td>
<td>170/253</td>
<td></td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Male</td>
<td>126/205</td>
<td>127/191</td>
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<td>0.50</td>
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<td>Female</td>
<td>23/45</td>
<td>43/62</td>
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<tr>
<td>Total</td>
<td>149/250</td>
<td>170/253</td>
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<td>WHO performance status</td>
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</tr>
<tr>
<td>0</td>
<td>93/169</td>
<td>112/173</td>
<td></td>
<td></td>
<td>0.63</td>
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<td>1</td>
<td>56/81</td>
<td>58/80</td>
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<tr>
<td>Total</td>
<td>149/250</td>
<td>170/253</td>
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<tr>
<td>Site of primary tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower esophagus</td>
<td>23/37</td>
<td>25/36</td>
<td></td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>Esophagogastric junction</td>
<td>13/28</td>
<td>23/30</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Stomach</td>
<td>113/185</td>
<td>122/187</td>
<td></td>
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<tr>
<td>Total</td>
<td>149/250</td>
<td>170/253</td>
<td></td>
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</tr>
</tbody>
</table>
Efficacy: Magic Trial

- 85% had ≥D1 resection
- Tumor size
  - 3 cm (CS) vs 5 cm (S) – p<0.001
- T1/T2
  - 52% (CS) vs 37% (S) – p=0.002
- N0/N1 disease
  - 84% (CS) vs 70% (S) – p=0.01
- 5-yr OS
  - 36% (CS) vs 23% (S) – p=0.009

Cunningham et al, NEJM, 2006
MAGIC Tolerability

• 237 patients started preoperative chemo
  • 215 completed 3 cycles
• 209 patients went to surgery
• 137 patients started postop chemotherapy
  • 104 completed all assigned chemotherapy
• Only 42% of original randomized patients

Courtesy of H. Mamon
## Comparison of 0116 and MAGIC

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<thead>
<tr>
<th></th>
<th>0116</th>
<th>MAGIC</th>
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<tbody>
<tr>
<td></td>
<td>S</td>
<td>S+C</td>
</tr>
<tr>
<td>Survival</td>
<td>41% (3-yr)</td>
<td>50% (3-yr)</td>
</tr>
<tr>
<td></td>
<td>23% (5-yr)</td>
<td>36% (5-yr)</td>
</tr>
<tr>
<td>Median OS</td>
<td>27m</td>
<td>36m</td>
</tr>
<tr>
<td></td>
<td>20m*</td>
<td>24m*</td>
</tr>
<tr>
<td>Hazard Ratio for Death</td>
<td>1.35</td>
<td>1.33</td>
</tr>
<tr>
<td>Hazard Ratio for Relapse</td>
<td>1.52</td>
<td>1.52</td>
</tr>
</tbody>
</table>

*Courtesy of H. Mamon*
Comparison of 0116 and MAGIC

• Due to different trial design, the studies are not directly comparable

• Both the control and treatment arms, as would be expected, do better when randomization occurs after surgery

• The hazard ratios for death and recurrence are similar with either approach

• Conclusion: Perioperative chemotherapy and postoperative chemoradiation are both valid approaches in the management of locally advanced gastric adenocarcinoma

Courtesy of H. Mamon
Meta-Analysis: Adjuvant RT in Resected Gastric Cancer

Ohri et al, IJROBP 2013
ARTIST Trial (Randomized after D2 Resection): Postop Capecitabine-Cisplatin vs. Postop Chemoradiotherapy

- 458 patients randomly assigned to postoperative chemo vs chemo/RT
- Excluded Stage IA/B, mets, and R1/2 patients
- All patients had ≥D2 dissection
- Chemo – cisplatin/cap x 6
- CRT – cis/cap x 2 → cap/RT → cis/cap x 2
- RT – 45 Gy at 1.8 Gy/fx

Park et al, JCO 2014
Park et al, JCO 2014

Registered (N = 458)

Randomly assigned to XP (n = 228)  
Randomly assigned to XPRT (n = 230)

Submitted tissue for biomarker
XP (n = 415)
XPRT (n = 211)

Treated with XP (n = 226)
Treated with XPRT (n = 227)

Completed XP (n = 172) 75%
Completed XPRT (n = 188) 82%

Relapse (n = 79)
No relapse (n = 149)

Release (n = 62)
No relapse (n = 168)

Alive (n = 10)
Alive (n = 149)

Alive (n = 5)
Alive (n = 164)
Overall Survival

130 death events occurred
Hazard ratio 1.130 (95% CI, 0.776 to 1.647)
P = .5272

Disease-Free Survival

141 recurrence events occurred
Hazard ratio 0.745 (95% CI, 0.520 to 1.060)
P = .0922

Park et al, JCO 2014
<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.740</td>
<td>0.520 to 1.050</td>
</tr>
<tr>
<td>ECGPS 0</td>
<td>0.665</td>
<td>0.392 to 1.129</td>
</tr>
<tr>
<td>ECGPS 1</td>
<td>0.835</td>
<td>0.544 to 1.290</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td></td>
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</tr>
<tr>
<td>Subtotal</td>
<td>0.793</td>
<td>0.485 to 1.271</td>
</tr>
<tr>
<td>Total</td>
<td>0.701</td>
<td>0.438 to 1.121</td>
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<tr>
<td>LN</td>
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<td>Negative</td>
<td>1.359</td>
<td>0.477 to 3.876</td>
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<td>0.700</td>
<td>0.462 to 0.994</td>
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<td>&lt; 0.083</td>
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<td>0.407 to 1.252</td>
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<td>≥ 0.083</td>
<td>0.708</td>
<td>0.466 to 1.019</td>
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<td>I/II</td>
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<td>0.367 to 1.181</td>
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<td>III/IV (M0)</td>
<td>0.703</td>
<td>0.530 to 1.017</td>
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<td>Intestinal</td>
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<td>0.543 to 1.255</td>
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<td>0-2+</td>
<td>0.749</td>
<td>0.533 to 1.053</td>
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<td>≥ 3</td>
<td>0.976</td>
<td>0.197 to 4.842</td>
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<td>0-2+</td>
<td>0.749</td>
<td>0.534 to 1.060</td>
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<td>≥ 3</td>
<td>1.414</td>
<td>0.196 to 10.197</td>
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<td>1.167</td>
<td>0.313</td>
<td>4.347</td>
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<td>MLH1 Loss</td>
<td>0.798</td>
<td>0.544 to 1.143</td>
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<td>E-cadherin</td>
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<td>0.160 to 2.007</td>
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<td>E-cadherin Loss</td>
<td>0.859</td>
<td>0.581 to 1.247</td>
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CRITICS Trial (ASCO 2016)

Trial design

- Chemotherapy → Surgery → Chemotherapy
- Tissue and Blood Banking
- Health-Related Quality of Life
- Chemotherapy → Surgery → Chemoradiotherapy

Stratified for: Center, Histological type, Tumor localization
### Treatment Details

**Chemotherapy:**
Pre-operative and post-operative: 3x ECC or EOC q3 wks
- Epirubicin 50 mg/m² day 1; Cisplatin 60 mg/m² day 1; Capecitabine 1000 mg/m² b.i.d. 1-14
- Epirubicin 50 mg/m² day 1; Oxaliplatin 130 mg/m² day 1; Capecitabine 625 mg/m² b.i.d. 1-21

**Surgery:**
Total / partial gastrectomy + en bloc N1 and N2 lymph nodes
- D1+ resection: lymph node stations 1-9 and 11; no splenectomy or pancreatectomy
- Removal of ≥15 lymph nodes
- Quality assurance: Maruyama Index

**Chemoradiotherapy:**
Post-operative: 45 Gy in 25 fractions combined with CC
- 3D-CRT or IMRT; CTV includes tumor bed, anastomoses, draining lymph node stations
- Concurrent during RT: Cisplatin 20 mg/m² weekly; Capecitabine 575 mg/m² b.i.d./d.d.w.d.
- Quality assurance: central review of RT plans
CRITICS Trial (ASCO 2016)

Results: Study Profile

- Total randomized: n=788
- Randomization:
  - n=393
  - n=395

- 3x CT:
  - For randomized: n=334
  - For randomization: n=318

- Surgery:
  - Started surgery: n=371
  - Underwent curative surgery: n=316

- Treatment:
  - Started post-operative treatment: n=238
  - Completed treatment: n=184

- CRT:
  - n=248
  - n=205
• Adjuvant chemoradiotherapy or perioperative chemotherapy are acceptable treatment options for gastric cancer.
Data to be Discussed

• Esophagus and GE junction cancer

• Gastric cancer

• Locally advanced pancreatic cancer
U.S. Pancreas Cancer Statistics 2017

• 53,670 new cases
• 43,090 deaths
• ~95% adenocarcinomas
• 4th leading cause of cancer deaths
ECOG 4201: Locally Advanced Pancreatic Cancer

Stratify:
• PS (0 vs 1)
• Weight loss >10% vs ≤10%

ARM A: INDUCTION
GEMCITABINE 1000mg/M2
Once weekly x 6 weeks

1 week rest

ARM B: INDUCTION
GEMCITABINE 600mg/M2
Once weekly x 6 weeks
CONCURRENT RT 180 cGy/day
5 days a week x 6 weeks
Total dose 50.4 Gy

4 weeks rest

ARM A: CONSOLIDATION
GEMCITABINE 1000mg/M2
Once weekly x 3 weeks
Followed by 1 week rest x 5 cycles
1 cycle = 4 weeks

ARM B: CONSOLIDATION
GEMCITABINE 1000mg/M2
Once weekly x 3 weeks
Followed by 1 week rest x 5 cycles
1 cycle = 4 weeks

Loehrer et al JCO 2011
Radiation Therapy

- 50.4 Gy at 1.8 Gy/fraction
- 3D conformal RT used – no IMRT
- 39.6 Gy initially to tumor plus regional elective nodes
- 10.8 Gy boost to GTV + 2 cm margin
- Concurrent Gemcitabine 600 mg/m²

Loehrer et al JCO 2011
Accrual

• Target accrual of 316 patients

• Only 74 patients enrolled

• 71 patients eligible for analysis

Loehrer et al. JCO 2011
## Compliance

<table>
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<tr>
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<th>Gem + CRT</th>
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<tr>
<td>No. cycles of gemcitabine</td>
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<td>3</td>
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<tr>
<td>Completed all chemo</td>
<td>30%</td>
<td>29%</td>
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<tr>
<td>Chemo dose reductions</td>
<td>43%</td>
<td>38%</td>
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</table>

Loehrer et al JCO 2011
Overall Survival

- Median OS
  - Gem: 9.2 mos
  - CRT: 11.1 mos

P=0.017

Loehrer et al JCO 2011
LAP07 Study for Locally Advanced Pancreas CA: Gem vs Gem/Erlotinib f/b ChemoRT vs Chemo

**EVALUATION**: non progressive

1 month = Gemcitabine 1000 mg/m²/wk x 3

Cape RT

**EVALUATION**: non progressive

Random 1

Random 2

Cape RT

**EVALUATION**: non progressive

Erlotinib with gem: 100 mg/d

150 mg/d as single agent (maintenance)

Secondary surgery allowed at any time

**Primary EP**: OS

Until Progression

**Cape**

*Capecitabine 1600 mg/m²/d plus radiation therapy 54 Gy (5 x 1.8 Gy/d)*
Radiotherapy

• 54 Gy in 30 fractions, 3D CRT
• GTV+3 cm inf-sup direction, GTV+1.5 cm all other directions
  • No prophylactic nodal irradiation
• Concurrent capecitabine 800 mg/m², bid

Hammel et al, JAMA 2016
Figure 2. Kaplan-Meier Curves of Overall Survival and Progression-Free Survival, According to the First Randomization

A  Overall survival probability

HR, 1.19 (95% CI, 0.97-1.45)
Log-rank P = .09

B  Progression-free survival probability

HR, 1.12 (95% CI, 0.92-1.36)
Log-rank P = .26

**Hammel et al, JAMA 2016**
Figure 3. Kaplan-Meier Curves of Overall Survival and Progression-Free Survival, According to the Second Randomization

A  Overall survival probability

B  Progression-free survival probability

Hammel et al, JAMA 2016
LAP07 Radiotherapy Quality (n=133)

- 1 (3%) patient radiotherapy records not available
- 12 (9%) patients did not receive chemoXRT
- 37 (32%) received radiotherapy per protocol
- 59 (50%) had minor deviation
- 21 (18%) had major deviation
- Median OS from 2nd randomization
  - 12.7 mo for per protocol/minor deviation and 10.1 mo for major deviation (p=0.19)
LAP07 Conclusions

- No survival benefit for chemoXRT compared with chemo alone after 4 months of induction chemotherapy in patients with locally advanced pancreatic cancer
- No statistically significant difference in OS 15.2 mo (chemo) vs. 16.5 mo (chemoXRT)
- Interval without additional treatment improved following chemoXRT (6.1 vs. 3.7 mo, p=0.02)
- Local/regional tumor progression decreased with chemoXRT (32% vs. 46%, p=0.04)
Advances in Chemotherapy
Improved OS with Gem-Abraxane vs. Gem Alone

Von Hoff et al, NEJM 2013
Gemcitabine vs. FOLFIRINOX

A Overall Survival

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

No. at Risk

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<th>FOLFIRINOX</th>
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<td>171</td>
<td>134</td>
<td>146</td>
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<tr>
<td>89</td>
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Conroy et al, NEJM 2011

ASTRO Annual Refresher Course • Fort Lauderdale Marriott Harbor Beach Resort & Spa • March 2-4, 2018 REFRESHER18
Can XRT be further optimized?
Potential Advantages of SABR/SBRT

• Improvement in local control

• Shorter course of treatment
  • Allows integration with more intensive systemic chemotherapy
  • Patient convenience

• Cost effective
Successful SBRT/SABR Minimizes Volume Irradiated

• Treat tumor only, typically no prophylactic nodal irradiation
• Account for organ motion
• Achieve sharper dose fall-off gradients to normal tissue
• Requires image guidance to achieve necessary precision
Stanford Pancreatic Cancer SABR Experience

- Median OS: 13.6 months
- N=167

Pollom et al, IJROBP 2014
No Difference in Local Recurrence Between Single and Multi-Fraction SBRT
Less GI Toxicity with Multi-Fraction SABR

- 12-month ≥ grade 2 GI toxicity rates
  - Single-fraction: 26.1%
  - Multi-fraction: 7.8%

*No significant difference in ≥G3 GI toxicity in single (12.3%) vs. multi-fraction (5.6%) SABR
NCDB Analysis

Multi-agent chemotherapy associated with improved survival

SBRT associated with improved survival vs. multi-agent chemotherapy

Figure 3. Kaplan-Meier survival curves: (A) single-agent CT alone versus multi-agent CT alone and (B) SBRT combined with multi-agent CT versus multi-agent CT alone. CT indicates chemotherapy; SBRT, stereotactic body radiotherapy.
Phase 2 Multi-institutional Trial Evaluating Gemcitabine and Stereotactic Body Radiotherapy for Patients With Locally Advanced Unresectable Pancreatic Adenocarcinoma

Joseph M. Herman, MD; Daniel T. Chang, MD; Karyn A. Goodman, MD; Avani S. Dholakia, MD; Siva P. Raman, MD; Amy Hacker-Prietz, PA-C; Christine A. Iacobuzio-Donahue, MD; Mary E. Griffith, RN; Timothy M. Pawlik, MD; Jonathan S. Pai, BA; Eileen O’Reilly, MD; George A. Fisher, MD; Aaron T. Wild, MD; Lauren M. Rosati, BS; Lei Zheng, MD; Christopher L. Wolfgang, MD; Daniel A. Lacheru, MD; Laurie A. Columbo, RN; Elizabeth A. Sugar, PhD; and Albert C. Koong, MD, PhD

Figure 2. Kaplan-Meier estimates of the survival function for (A) overall survival and (B) progression-free survival are shown. The 95% confidence intervals are included as dotted lines.

Med OS 13.9 mos
Current Study: Pancreatic Cancer Research Study (PanCRS)

Induction Chemotherapy: mFOLFIRINOX x 4 cycles

- Restage
- Progression
- Stable or Better Disease

Randomize

Arm 1
- mFOLFIRINOX

Arm 2
- SBRT+mFOLFIRINOX
- Off Study

Participating Institutions:
- Stanford, MDACC, UCSF, Loyola, PMH, UTSW, MUSC, Swedish
Summary

• Systemic chemotherapy should be first initial treatment in patients with locally advanced pancreatic cancer.

• Chemoradiotherapy contributes to local control and chemotherapy-free interval.
Thank You!