GASTRIC CANCER: Is there a Role for Adjuvant Radiation Therapy: Yes

David H. Ilson, M.D., Ph.D.
Attending Physician
Memorial Sloan-Kettering Cancer Center
New York
Adjuvant Therapy in Gastric Cancer Modestly Improves OS: 10-15%  

- Survival benefits similar across trials  
- Pre op chemo (Europe/US), D1-2 resection, no RT  
  - ECF, MAGIC: 13% ↑ 5 yr OS  
  - FLOT > ECF  
- Post op chemo (Asia): 4 trials, 3451 pts, D2 resection, no RT  
  - S-1, ACTS-GC: 10% ↑ 5 yr OS  
  - Cape-Oxali, CLASSIC Trial: 9% ↑ 5 yr OS  
  - S-1 + Docetaxel > S-1, Stage III, JACCRO GC-07: 16.4%↑ 3-year RFS  
  - SOX > S-1 Node +, ARTIST 2: 538 pts  
- Post op RT + chemo (U.S.), less than a D1-2 resection  
  - 5FU-LV + RT, INT 116:  
    - 10% ↑ 5 yr OS  

References:  
NEJM 345:725; 2001  
NEJM 355: 11; 2006  
JCO 29: 4387; 2011  
Lancet Oncol 15: 1389; 2014  
J Clin Oncol 36: 2018  
J Clin Oncol 37:4001;2019
What is the role of post op RT?

U.S. Intergroup 116 (SWOG 9008)

Gastric Cancer: Adjuvant 5-FU + RT

- Resected Gastric Cancer
  - No Further Therapy
  - 5 Cycles 5-FU/LV + XRT Cycle 2-3

Macdonald NEJM 345: 725-730; 2001
Overall Survival: INT 116

Macdonald NEJM 345: 725-730; 2001
INT 116: Gastric Cancer

- Biggest impact in decreasing local recurrence
  - 29% ➔ 19% with FU/RT
  - Diffuse cancers did not benefit (39%)
  - HER2 + did not benefit (11% of 258 pts)

- Surgical resection:
  - Only 10% had a D2 resection
  - 54% had less than a D1 resection

- FU/RT: Standard of care for gastric cancer in <D1 resection
- FU/RT: indicated for + Margin resection
INT 113: Esophageal Cancer, Outcome for post op Chemo/RT for Margin Positive Patients

- 467 pts with esophageal AC or SCC
- R1 resection: 43 patients
- 9 (21%) did not recur, all received post op chemo + RT
- Chemo + RT may salvage R1 resection, + margin pts

Kelsen JCO 25: 3719-3725; 2007
Does RT Add to Perioperative Chemotherapy? CRITICS TRIAL

Lancet Oncol 19: 616-628; 2018

Presented By Marcel Verheij at 2016 ASCO Annual Meeting
Results: Overall Survival

- Log-rank p = 0.99

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year OS (%)</td>
<td>40.8</td>
<td>40.9</td>
</tr>
<tr>
<td>Median OS (yrs)</td>
<td>3.5</td>
<td>3.3</td>
</tr>
</tbody>
</table>
DOES RT ADD TO D2 RESECTION?
Adjuvant ChemoRadiotherapy Trial In Stomach Tumors (ARTIST)

• D2 resected gastric adenocarcinoma
• pStage Ib to IV (M0)
• Stratified by (1) stage, (2) type of surgery (STG v TG)

Primary endpoint:
3-y DFS

XP arm (6 cycles of XP)

XPRT arm (2XP/XRT/2XP)

• X: capecitabine 2,000 mg/m²/d D1-D14
• P: cisplatin 60 mg/m² D1
• XRT: capecitabine 1,650 mg/m²/d daily concurrently with RT 45 Gy for 5 weeks


Park JCO 33; 2014
Overall Survival

- 130 death events occurred
- Hazard ratio 1.130 (95% CI, 0.775-1.647)
- $P=0.5272$
Disease-Free Survival: by Lauren Classification

- In 163 patients with intestinal type, 3-y DFS was 94% vs 83% (P=0.01)\(^1\)
Disease-Free Survival: by Lymph Node Status

- In 396 patients with LN+ disease, 3-y DFS was 76% vs 72% (P=0.04)\(^1\)

ATRIST: RT may benefit N+, Intestinal Tumors
What is the role of RT?

- **Gastric Cancer: Extent of Surgery Dictates Need for RT**
- **Post op RT + 5-FU/LV:** less than a D1 resection
  - Indicated for + margin patients
- **Gastric Cancer: Periop or Post op Chemo with D1-D2 resection**
  - RT does not add a survival benefit
  - ? Post Op RT improved outcome after D2 in N+, Intestinal tumors (ARTIST)
- **ARTIST 2: ASCO 2019, role of post op RT**
  - S-1 x 1 year
  - S-1 + Oxali x 6 months
  - S-1 + Oxali, + RT, 6 months
  - Node +, intestinal or diffuse allowed, Stage II-III
Adjuvant chemoRadioTherapy In Stomach Tumor 2

- 900 patients with D2 resected gastric adenocarcinoma
- pStage II to III, LN+
- Stratified by (1) stage, (2) type of surgery (STG vs TG), (3) Lauren classification

Randomization:
- Adjuvant Chemotherapy with S-1 (S-1 for one year)
- Adjuvant Chemotherapy with SOX (S-1/oxaliplatin for 6 mo)
- Adjuvant Chemoradiotherapy (SOX x2 → S-1/RT → SOX x4)

- Primary endpoint: DFS
- S-1: 40-60 mg bid 4/2 wks q6wks
- SOX: 5-1 40 mg/m² bid 2/1 wks q3wks + oxaliplatin 130 mg/m² D1
- S-1/RT: S-1 40 mg bid daily concurrently with RT 45 Gy for 5 wks

1 ClinicalTrials.gov, NCT0176146

J Clin Oncol 37: 4001; 2019

Presented By Se Hoon Park at 2019 ASCO Annual Meeting
ARTIST 2 Disposition of Study Treatment

Recruited between Feb 2013 and Feb 2018
This interim results included those who completed or prematurely discontinued study treatments.
Data cutoff date: Jan 17, 2018

S-1
180 allocated
180 treated
129 (72%) completed
51 (28%) prematurely discontinued
• AEs: 9
  Withdrawal: 23
  Recurrence: 15
  Violation/NA: 4

SOX
180 allocated
179 treated
153 (85%) completed
26 (15%) prematurely discontinued
• AEs: 10
  Withdrawal: 9
  Recurrence: 6
  Violation/NA: 1

SOXRT
178 allocated
177 treated
148 (84%) completed
29 (16%) prematurely discontinued
• AEs: 9
  Withdrawal: 14
  Recurrence: 6
  Violation/NA: 0
## ARTIST 2 Baseline Characteristics: Patient

<table>
<thead>
<tr>
<th></th>
<th>Total (n=538)</th>
<th>S-1 (n=180)</th>
<th>SOX (n=180)</th>
<th>SOXRT (n=178)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>61 (27-85)</td>
<td>63 (32-85)</td>
<td>60 (31-79)</td>
<td>62 (27-77)</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td>350 (65%)</td>
<td>121 (67%)</td>
<td>112 (62%)</td>
<td>117 (66%)</td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>295 (55%)</td>
<td>93 (52%)</td>
<td>93 (52%)</td>
<td>109 (61%)</td>
</tr>
<tr>
<td>1</td>
<td>241 (45%)</td>
<td>86 (48%)</td>
<td>85 (48%)</td>
<td>68 (39%)</td>
</tr>
<tr>
<td>2</td>
<td>2 (0%)</td>
<td>1 (0%)</td>
<td>1 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Type of surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total gastrectomy</td>
<td>194 (36%)</td>
<td>65 (36%)</td>
<td>62 (34%)</td>
<td>67 (38%)</td>
</tr>
<tr>
<td>Subtotal gastrectomy</td>
<td>344 (64%)</td>
<td>115 (64%)</td>
<td>117 (66%)</td>
<td>110 (62%)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>161 (30%)</td>
<td>55 (31%)</td>
<td>51 (28%)</td>
<td>55 (31%)</td>
</tr>
<tr>
<td>III</td>
<td>377 (70%)</td>
<td>125 (69%)</td>
<td>128 (72%)</td>
<td>122 (69%)</td>
</tr>
</tbody>
</table>
## ARTIST 2 Baseline Characteristics: Tumor

<table>
<thead>
<tr>
<th></th>
<th>Total (n=538)</th>
<th>S-1 (n=180)</th>
<th>SOX (n=180)</th>
<th>SOXRT (n=178)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intestinal type disease</strong></td>
<td>162 (30%)</td>
<td>52 (29%)</td>
<td>58 (32%)</td>
<td>52 (29%)</td>
</tr>
<tr>
<td><strong>pT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>42 (8%)</td>
<td>14 (8%)</td>
<td>13 (7%)</td>
<td>15 (8%)</td>
</tr>
<tr>
<td>2</td>
<td>90 (17%)</td>
<td>32 (18%)</td>
<td>29 (16%)</td>
<td>29 (16%)</td>
</tr>
<tr>
<td>3</td>
<td>214 (39%)</td>
<td>79 (44%)</td>
<td>60 (33%)</td>
<td>73 (41%)</td>
</tr>
<tr>
<td>4</td>
<td>192 (36%)</td>
<td>55 (31%)</td>
<td>77 (43%)</td>
<td>60 (34%)</td>
</tr>
<tr>
<td><strong>pN, median (range)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissected no. of LNs</td>
<td>43 (12-101)</td>
<td>42 (16-99)</td>
<td>45 (12-95)</td>
<td>43 (20-101)</td>
</tr>
<tr>
<td>Positive no. of LNs</td>
<td>5 (1-66)</td>
<td>6 (1-33)</td>
<td>4 (1-42)</td>
<td>6 (1-66)</td>
</tr>
<tr>
<td>LN ratio</td>
<td>0.13 (0.01-0.91)</td>
<td>0.13 (0.01-0.91)</td>
<td>0.10 (0.02-0.83)</td>
<td>0.15 (0.01-0.71)</td>
</tr>
</tbody>
</table>

- **Lymphovascular invasion**: 409 (76%), 130 (72%), 145 (81%), 134 (75%)
- **Perineural invasion**: 329 (61%), 110 (61%), 110 (61%), 109 (61%)
- **HER2+ (2+/ISH+ or 3+)**: 30 (6%), 9 (5%), 8 (4%), 13 (7%)
ARTIST 2 Primary Endpoint

- Median f/u: 37 mo
- DFS events: 161 (30%)

<table>
<thead>
<tr>
<th>Arm</th>
<th>Median DFS, mo</th>
<th>3-y DFS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-1</td>
<td>58.4</td>
<td>64</td>
</tr>
<tr>
<td>SOX</td>
<td>Not reached</td>
<td>78</td>
</tr>
<tr>
<td>SOXRT</td>
<td>Not reached</td>
<td>73</td>
</tr>
</tbody>
</table>

---

Presented By Se Hoon Park at 2019 ASCO Annual Meeting
ARTIST 2 Subgroup Analysis of DFS

- S-1 v SOX/SOXRT

- S-1/SOX v SOXRT

HR 0.648 (95% CI 0.467-0.898; P=0.009)

HR 0.859 (95% CI 0.602-0.1.226; P=0.401)
ARTIST 2 Subgroup Analysis of DFS

- S-1 v SOX/SOXRT
- S-1/SOX v SOXRT
Ongoing Randomized Trials of Preop Chemo + / - RT

- **TOPGEAR (NCT 01924819)**
  - Perioperative ECF/X, FLOT
  - + / - Preoperative RT
  - GEJ and Gastric cancer, 752 pts

- **ESOPEC (NCT 92509286)**
  - FLOT vs CROSS, Eso and GEJ, 438 pts

- **NEO-Aegis (NCT 0172645)**
  - ECF/X, FLOT vs CROSS, Eso and GEJ, 366 pts

- **CRITICS 2: CROSS vs DOC vs DOC ➔ Chemo/RT**
Adjuvant RT in Gastric Cancer: Yes

- Adjuvant RT improves OS post < D1 resection
  - Reduces Local Recurrence
- Role for improving survival for + margin pts
- ARTIST
  - RT may benefit N+, Intestinal tumors
- ARTIST 2
  - Could not validate benefit for RT in N+
  - Trial did not complete accrual
  - Only one third of patients had intestinal tumors, no clear RT benefit
Fig 2. Disease-free survival. XP, capecitabine plus cisplatin; XFRP, concurrent chemoradiotherapy with capecitabine plus cisplatin.

Fig 3. Overall survival. XP, capecitabine plus cisplatin; XFRP, concurrent chemoradiotherapy with capecitabine plus cisplatin.

141 recurrence events occurred
Hazard ratio 0.745 (95% CI, 0.530 to 1.060)
P = .2922

130 death events occurred
Hazard ratio 1.130 (95% CI, 0.775 to 1.647)
P = .3072