Gastroesophageal Cancer Role of Radiotherapy

1st Annual Jerome F. Williams Gastric Cancer Program Symposium
Jan 14 2017

Rebecca Wong
Professor, Radiation Oncology
Gastroesophageal cancers

Tumor Location: Esophagus vs gastric
Siewert I,II,III
East versus West
Histology Scc vs adeno
Lauren classification
Genotype: HER2+ vs neg

Aetiology

……

Implications in conducting trials

“Orphan” disease
1 in 2000 people
Changing epidemiology
Importance of adenocarcinoma

Esophagus
Stomach
GEJ

Incidence of adenocarcinoma of the esophagus, GEJ, and stomach 1973-2008, United States

https://seer.cancer.gov/statfacts/
Buas et al Epidemiology and risk factors for gastroesophageal junction tumors: understanding the rising incidence of this disease Semin Radiat Oncol Jan; 23 (1): 3-9, 2013
Heterogeneity – genomics

Adenoca esophagus and gastric intestinal subtype share similar genomic alterations

Comprehensive molecular characterization of gastric adenocarcinoma Nature review 513, 202-209, 2014
Heterogeneity – lymphatics

Esophagus

Tumors of the upper esophagus (n=24)
Tumors of the middle esophagus (n=116)
Tumors of the lower esophagus (n=65)

Stomach

General approach

**Gastroesophageal “Higher risk”**

- **Esophagus**
  - SCC
    - CRTalone
    - Trimodality
  - Adeno
    - Trimodality
    - Perioperative CT
  - Surgeryalone
    - RTalone

- **GEJ**
  - Adeno
    - Trimodality
    - Perioperative CT
  - Surgeryalone
    - CRTalone
    - RTalone

- **Stomach**
  - Adeno
    - Perioperative CT
  - Surgeryalone
    - Postop CRT

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*Princess Margaret Hospital, Toronto*
• Evidence from
  – Esophagus and gastric studies (RCT mostly)
• Special focus on:
  – In patients who are candidates for both definitive chemoradiotherapy and combined modality therapy with surgery, can surgery be avoided?
  – In patients who are candidates for both trimodality and perioperative CT, who should receive RT?
• Factors to consider: from a radiation oncologist’s perspective
**CRT alone - esophagus**

- CRT superior to RT well established

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*Can CRT alone be the treatment of choice?*
Two RCTs –
Role of S in pts treated with CRT

- Induction CT (± use of induction response as a selection factor)
- No detriment to survival
- Reduced local control (HR 2.1, 1.64), reduced toxicity with no S difference
- Practice is heterogeneous
## For SCC: Is CRT enough?

<table>
<thead>
<tr>
<th></th>
<th>Stahl (Germany)</th>
<th>FFCD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response to induction chemo</strong></td>
<td>Single independent prognostic factor for OAS HR 0.3 95%CI 0.19-0.47</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment Related Mortality</strong></td>
<td>13% CRTS vs 4%</td>
<td></td>
</tr>
<tr>
<td><strong>Local Control</strong></td>
<td>HR 2.1(95%CI 1.3-3.5) 56% CRTS vs 41%</td>
<td>HR 1.64 (95%CI 1-2.6) 66% CRTS vs 57%</td>
</tr>
<tr>
<td><strong>Relapse Free Survival</strong></td>
<td>43% CRTS vs 40% ns</td>
<td></td>
</tr>
<tr>
<td><strong>2 y Overall survival</strong></td>
<td>40%CRTS vs 35% ns</td>
<td>34% CRTS vs 40% ns</td>
</tr>
<tr>
<td><strong>Conclusion</strong></td>
<td>Equivalent survival, Reduced toxicity, Inferior local control</td>
<td></td>
</tr>
</tbody>
</table>
Bimodality with S as salvage

- 2001-2005
- N = 99
- 51S, 48 CRT
- Surgery
  - esophagectomy + 2 field node dissection
- CRT
  - 60Gy in 30fr + 5FU/cisplatin
  - 2 cycles adjuvant CT
  - Salvage esophagectomy with residual disease

T1-3N0-1M0 Esophagus ca SCC resectable

Pt choice

S CRT

S

Ariga et al IJROBP 75, 2, 348-356, 2009 Prospective comparison of surgery alone and chemoradiotherapy with selective surgery in resectable squamous cell carcinoma of the esophagus
• CRT group: (13/51) 26% had salvage esophagectomy
• OS not worse (better) in CRT arm
  – OS at 5 yr
• Multivariate analysis shows clinical stage, and treatment approach sig prognostic factors
What is the impact on QoL following trimodality?

Is deferring S for salvage safe?

Esophagectomy Timing After Neoadjuvant Therapy for Distal Esophageal Adenocarcinoma

Jan Franko, MD, PhD, George Voynov, MD, and Charles D. Goldman, MD

Departments of Surgery and Radiation Oncology, Mercy Medical Center, Des Moines, Iowa

• National Cancer Database (US)
• N=4284
• Interval between RT and esophagectomy 7.8 (+ 3.4w)
• 30d and 90d mortality: 2.9% and 7.8%
• 90d mortality: 9w or more: 1.9 95%CI 1.3-2.8; p <0.001)
• Prognostic factors for OS:
  – interval from CRT to S
  – Comorbidities, N status, median household income ($63k) sig

BIAS? Medical comorbidities deferring S

Salvage Surgery After Chemoradiotherapy in the Management of Esophageal Cancer: Is It a Viable Therapeutic Option?

Sheraz Markar, Caroline Gronnier, Alain Duhamel, Arnaud Pasquier, Jérémie Théreaux, Mael Chalret du Rieu, Jérémie H. Lefevre, Kathleen Turner, Guillaume Luc, and Christophe Mariette

### After Matching

<table>
<thead>
<tr>
<th>Variable</th>
<th>SALV (n = 308)</th>
<th>NCRS (n = 308)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality, No. (%)</td>
<td>26 (8.4)</td>
<td>35 (11.4)</td>
<td>0.719 (0.414 to 1.250)</td>
<td>.241</td>
</tr>
<tr>
<td>In-hospital morbidity, No. (%)</td>
<td>196 (63.6)</td>
<td>188 (61.0)</td>
<td>1.117 (0.818 to 1.525)</td>
<td>.506</td>
</tr>
<tr>
<td>Anastomotic leak, No. (%)</td>
<td>53 (17.2)</td>
<td>33 (10.7)</td>
<td>1.732 (1.110 to 2.703)</td>
<td>.015</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>&lt;55Gy</strong></th>
<th><strong>&gt;/=55Gy</strong></th>
<th><strong>p</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>In hospital mortality</td>
<td>4.3%</td>
<td>17.5%</td>
</tr>
</tbody>
</table>

HR, 0.939
95% CI, 0.780 to 1.152
P = .542*
Selective resection - a future reality?

- RTOG 0246
- N = 41 (36 completed CRT)
- Definitive CRT & S salvage
- Adeno (72%)
- 5FU, Cisplatin, Paclitaxel
- 50.4Gy in 28fr
- Salvage esophagectomy 17 (47%)
- 5y OS 37% (95% 22.3-51)
- OS: no difference by histology

CRT alone reserving S for salvage could be a preferred treatment option? – to be confirmed

Trimodality in esophageal cancer - global effort

15 RCTs preoperative CRT globally
1983 Nygaard (France) initiated 1st study
Van Hagen (Netherlands) 2012
Marriet (France) 2014
Total >2000 patients involved
(study sample size ranged from 56 to 364)

CROSS – the trial that consolidated trimodality as treatment of choice

Van de Gaast CROSS group
Netherlands

<table>
<thead>
<tr>
<th></th>
<th>CRT</th>
<th>S alone</th>
<th>HR: 0.66 (95% CI 0.5-0.9) P = 0.003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med S</td>
<td>49m</td>
<td>24m</td>
<td></td>
</tr>
<tr>
<td>5 yS</td>
<td>47%</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>Toxicity ≥Gd 3</td>
<td>12/171 (7%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Postop mortality</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>R0 resection</td>
<td>148/161 (92%)</td>
<td>111/161 (69%)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Van Hagen et al preoperative Chemoradiotherapy for esophageal or junctional cancer NEJM 366,22,2074-2084, 2012
• 12 neoadj CRT, 1854pts
• Mortality HR 0.78 (95% CI 0.7-0.99)
• Similar impact for both histologies
  – SCC HR 0.8 (0.68-0.93)
  – ACC HR 0.75 (0.59-0.95)
HR 0.66 95% CI 0.5-0.9 p=0.003

Median S 26m vs 49m, median FU 32m

Which chemotherapy regimen to use in practice?

van Hagen et al Preoperative Chemoradiotherapyfor Esophageal or Junctional Cancer NEJM 366: 2074-84, 2012
Platinum+Paclitaxel or Platinum+5FU?

Network meta-analysis approach

N = 10 studies

2 studies Paclitaxel + Platinum
- Lv: SCC only (n=160)
- Hagen: SCC+Adeno (n=366)

Suggest paclitaxel + platinum better
- 0.63 (0.5-0.8) (PaclitaxelPlat)
- 0.79 (0.69-0.92) (plat5FU)
- 0.8 (95% CrI 0.6-1.06) (indirect comparison PaclPlat vs Plat5FU)

Huang et al Systematic review and network meta-analysis: neoadjuvant chemoradiotherapy for locoregional esophageal cancer JJCO 45(11)1923-1028, 2015
Just to complicate our thinking...

- Marriette et al FFCD 9901
  - Early stage
  - 70% SCC
  - CRT arm worse early on

Therapeutic benefit outweighed by early toxicity risks in early stage SCC

Is RT necessary when there is MAGIC?

- **N = 503**
- **ECF**
  - (E 50mg/m², C 60mg /m², F 200mg/m² Cl 21d)
- **3 cycles pre and post op**
- **Lower eso 15%, GE jc 12%**
- **Treatment compliance**
  - 55% (137/250) began postop CT
  - 42% (104/250) of pt assigned to CT completed 6 cycles
- **Outcomes**
  - OAS 5 yr 23 vs 36%
  - OAS HR 0.75 (0.6-0.93; p=0.0009)
  - PFS HR 0.66 (0.53-0.81; p<0.0001)

*Cummingham et al (MRC UK) Perioperative CT vs S alone for resectable GE cancer NEJM 2006*
Preoperative CT vs S

- HR : 0.87 (0.79 – 0.96)
- SCC: 0.92 (0.81-1.04; p = 0.18)
- ACC: 0.83 (0.71-0.5; p = 0.01)
- Indirect comparison between neoadj CRT vs CT
  - 0.88 (0.76-1.01; p = 0.07)
  - Clear advantage of CRT vs CT was not established

The only RCT in GE junction
Preop CT vs Preop CRT (POET)

- XRT
- 5cm sup, 3cm inf, 2cm radial
- L and R cardiac, L gastric, lesser curve, celiac axis, splenic a, hepatic a
- Sample size
- Planned 200
- Superiority trial, 3 y S 25 to 35%
- Slow accrual, stopped at interim with 125 pts (projected final sample size 288)
- FU 21m

Stahl (POET) Phase III comparison of preop CT compared with CRT in patients with locally advanced adenocarcinoma of the esophagogastric junction JCO 27:851-856, 2009
**N = 126 (119 evaluable)**

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>CRT</th>
<th>HR 0.67 CI 0.41-1.07</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3y OAS</strong></td>
<td>27.7%</td>
<td>47.4%</td>
<td>p = 0.07</td>
</tr>
<tr>
<td><strong>Postop death</strong></td>
<td>3.8%</td>
<td>10.2%</td>
<td>p = 0.26</td>
</tr>
<tr>
<td><strong>pCR</strong></td>
<td>2%</td>
<td>15.6%</td>
<td>P = 0.03</td>
</tr>
<tr>
<td><strong>3y Local control</strong></td>
<td>59%</td>
<td>76.5%</td>
<td>p = 0.06</td>
</tr>
</tbody>
</table>

*Stahl Phase III comparison of preop CT compared with CRT in patients with locally advanced adenocarcinoma of the esophagogastric junction JCO 27:851-856, 2009*
Where perioperative CT and trimodality are both appropriate treatment options, who should have trimodality?
### Network Meta-analysis

- 31 trials (CT, RT, CRT, S)
- 3 trials compared CRT and CT

<table>
<thead>
<tr>
<th></th>
<th>Neoadj CRT vs CT</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>3 trials</td>
</tr>
<tr>
<td>N</td>
<td>375</td>
</tr>
<tr>
<td>OS</td>
<td>HR 0.88 (95% CI 0.6-1.2)</td>
</tr>
<tr>
<td>Postop Mortality</td>
<td>OR 2.69 (95% CI 0.6-11.9)</td>
</tr>
<tr>
<td>Locoreg rec.</td>
<td>OR 0.7 (95% CI 0.4-1.2)</td>
</tr>
<tr>
<td>Distant mets</td>
<td>OR 0.79 (95% CI 0.4-1.5)</td>
</tr>
<tr>
<td>Locoreg &amp; dist. mets</td>
<td>OR 0.57 (95% CI 0.15-2.22)</td>
</tr>
</tbody>
</table>

98% probability neoadj CRT the best treatment re survival compared with neadj CT or RT

Kelvin Chan et al presented Sunnybrook Health Sciences Centre ASCO 2016 manuscript in prep
# Trimodality vs CT

## Key outcomes

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>OS</strong></td>
<td>Possible adv with CRT based on NW-MA</td>
</tr>
<tr>
<td><strong>Post op mortality</strong></td>
<td>Higher postop mortality CRT based on NW-MA</td>
</tr>
<tr>
<td><strong>Duration of therapy</strong></td>
<td>4.5w vs 9w x 2</td>
</tr>
</tbody>
</table>

## Tumor factors

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Resectability</strong></td>
<td>RT has greater downstaging effect</td>
</tr>
<tr>
<td><strong>Volume requiring XRT</strong></td>
<td>N+ location, size of tumor, lymphatic stations at risk</td>
</tr>
</tbody>
</table>

## Patient factors

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Cardiopulmonary reserve</strong></td>
<td>RT has potentially greater cardiopulmonary risks</td>
</tr>
<tr>
<td><strong>Surgical risks</strong></td>
<td>Individual assessment</td>
</tr>
</tbody>
</table>
Radiotherapy details

• Gross disease
  – GTV, Nodes,
• Rationale & design of CTV
• Normal tissues
• RT plan design/ technique/Quality
• Translating multimodality findings to the planning CT
**Choice of CTV – microscopic extent**

- 34 SCC esophagus, 32 adeno GEJ

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>% &lt;3cm</th>
<th>%&lt;4cm</th>
<th>%&lt;5cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC</td>
<td>10.6±11</td>
<td>94</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td>GEJ</td>
<td>14.5±13.4</td>
<td>83</td>
<td>86</td>
<td>93</td>
</tr>
</tbody>
</table>

**Balance between Risk and toxicity**


Huang pattern of lymph node metastases and its implications in radiotherapeutic CTV in patients with thoracic esophageal SCC: a report of 1077 cases Rad Onc 95: 229-233, 2010
Classical esophagus vs proximal stomach fields

Toxicity
Factors: nodes at risk, nodes involved, length, bulky
Radiotherapy side effects

• Acute and late reaction tissues
• Dose tolerance criteria:
  – TD5/5, Volumetric (V5, V20, Mean, Max…)
• Serial (spinal cord) versus parallel organs

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Vx Conditions</th>
<th>Mean</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal canal</td>
<td>-</td>
<td>-</td>
<td>≤45Gy†</td>
</tr>
<tr>
<td>Lung</td>
<td>V5 &lt;60%*</td>
<td>&lt;18Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V20 &lt;30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>V40 &lt;60%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>Qualitative assessment</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>V30 ≤30%</td>
<td>&lt;30Gy</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>V22.5 &lt; 33%</td>
<td>18Gy</td>
<td></td>
</tr>
</tbody>
</table>

Emami Tolerance of normal tissues to therapeutic radiation reports of radiotherapy and oncology 2013
Pulmonary toxicity V5, VS5...

- 16.4% (serious) postoperative complications
- 1% (2/110) death due to progressive pneumonia
- Multivariate analysis
  - VS5 significant (volume of lung spared from low doses of radiation)

- Criteria: Volume receiving 5Gy (V5) <60%

PET in esophageal cancer RT

Symptomatic cardiac toxicity is predicted by dosimetric and patient factors rather than changes in $^{18}$F-FDG PET determination of myocardial activity after chemoradiotherapy for esophageal cancer☆

Andre Konski a,*, Tianyu Li b, Michael Christensen a, Jonathan D. Cheng b, Jian Q. Yu b, Kevin Crawford a, Oleh Haluszka d, Jeffrey Tokar b, Walter Scott b, Neal J. Meropol c, Steven J. Cohen b, Alan Maurer d, Gary M. Freedman e

a Wayne State University School of Medicine, Detroit, MI; b Fox Chase Cancer Center, Philadelphia, PA; c Case Western Reserve University, Cleveland, OH, USA; d Temple University School of Medicine; and e University of Pennsylvania, Philadelphia, PA, USA

• N = 12/102 (6 symptomatic)
• Threshold recommendations: V20 (70%), V30 (65%), V40 (60%)
• 127 gastric cancer
• 45Gy in 25 fr with 5FU CT
• Lipase and amylase deficiencies found in 48% and 20% of pts
• Age and pretreatment activities influence risk
Inter-observer variation in target definition

Fig. 1. Anteroposterior and posteroanterior views of a gastric cancer planning target volume. Red demonstrates large interobserver variability and blue small variability.

Intra-fraction organ motion

Median 5.6mm
Range 0-52
90th percentile 15

Treatment technique

Jansen et al Interobserver variation of clinical target volume delineation in gastric cancer IJROBP 77, 4, 1166-1170, 2010
Interfraction and respiratory organ motion during conformal radiotherapy in gastric cancer IJROBP 77, 1, 53-59, 2010
Wo et al Gastric lymph node contouring atlas: a tool to aid in clinical target volume definition in 3 –dimensional treatment planning for gastric cancer Practical Radiation Oncology 3, e11-19, 2013
“Postop CRT” The first adjuvant for gastric cancer – what about it?

- Postoperative CRT (MacDonald) was the first study to show survival benefit beyond S alone

- Rapidly “taken” over by Perioperative CT (MAGIC)

- Postoperative CRT
  - Difficult to deliver
  - Postoperative volumes
  - Radiobiological principles predict less efficient use of RT

Can RT be more efficiently used in gastric cancer?
CRITICS

Perioperative CT [postop RT] did not improve survival compared with periop CT alone

63% started postop treatments, 50% completed the entire treatment

Ongoing analyses may identify specific subgroups more likely to benefit

PFS: 5yr 38.5% CT, 39.5% CRT

ASCO 2016 presented by Marcel Verheij
How effective is the state of the art surgery in securing local control?

- Control arms (S) in RCTs
- Local recurrence rates ranged from 21 to 72% with surgery alone

<table>
<thead>
<tr>
<th>RCTs</th>
<th>Study</th>
<th>N</th>
<th>Local regional recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham 2005</td>
<td>Preop CT</td>
<td>S 250 vs 253</td>
<td>14% 21% §</td>
</tr>
<tr>
<td>Hartgrink 2004</td>
<td>D2 D1</td>
<td>331 vs 380†</td>
<td>32% 42%*</td>
</tr>
<tr>
<td>MacDonald 2002</td>
<td>Post CRT</td>
<td>S 120 vs 177</td>
<td>65%∫ 72%</td>
</tr>
<tr>
<td>Zhang 1998</td>
<td>Preop RT</td>
<td>S 171 vs 199</td>
<td>39% 52%</td>
</tr>
</tbody>
</table>

†, Number achieving curative resection; *, denominator equals total treated curatively minus postoperative deaths; §, denominator equals patients assigned to the group; ∫, patients could have relapses at multiple sites, total number of relapses greater than number of patients.

What is local control in our practice environment?
A better way of using RT – Preop?

Table 5 Randomized trials comparing preoperative RT vs. surgery alone—outcomes

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N¹</th>
<th>FU</th>
<th>OS²</th>
<th>Regional RFS</th>
<th>Toxicity³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skoropad</td>
<td>2002</td>
<td>77 [51]</td>
<td>NA</td>
<td>5-year: 59%, 10-year: 32%</td>
<td>NA</td>
<td>Percentage with complications: 57%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75 [51]</td>
<td>NA</td>
<td>5-year: 30%, 10-year: 18%</td>
<td>NA</td>
<td>Percentage with complications: 49%</td>
</tr>
<tr>
<td>Skoropad</td>
<td>2000</td>
<td>59 [40]</td>
<td>NA</td>
<td>5-year: 50%</td>
<td>NA</td>
<td>Percentage with complications: 35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53 [38]</td>
<td>NA</td>
<td>5-year: 50%</td>
<td>NA</td>
<td>Percentage with complications: 50%</td>
</tr>
<tr>
<td>Zhang</td>
<td>1998</td>
<td>171</td>
<td>199</td>
<td>10.6 years</td>
<td>5-year: 30%, 10-year: 20%</td>
<td>5-year: 20%, 10-year: 13%</td>
</tr>
<tr>
<td>Shchepton</td>
<td>1994</td>
<td>98</td>
<td>100</td>
<td>5-year: 45% (preoperative RT), 51% (preoperative RTHT)</td>
<td>5-year: 30%</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Wong et al Postoperative chemoradiotherapy vs preoperative chemoradiotherapy for locally advanced (operable) gastric cancer: Clarifying the role and technique of radiotherapy JGO 6(1): 89-107, 2015
Preoperative CRT

- Ajani 2004
- N = 34
- 2 cycles 5FU, LV, cisplatin + CRT (45Gy+ 5FU)
- pCR 30%
- pCR S 64m vs < pPR 12.6m p = 0.03

- Ajani 2006 (RTOG 9904)
- N = 49
- 2 cycles of 5FU, LV, cisplatin + CRT
- pCR 26%

- Acute toxicities
  - Gd 4 21% Gd 5 0
- Late radiation toxicities
  - Gd 3 5%
- Postoperative complications
  - Gd 3 10%
  - Hemorrhage, respiratory, sepsis, abscess, infection
Preop RT for gastric cancer?

TOPGEAR

Resectable adenoca
stomach, GEJ
T1N1-T3-4N+

Randomize
Stratify

ECF(X) x3

Preop CRT
45Gy + CI 5FU(X)

S

ECF(X) x3

ECF(X) x3

World’s largest hot wheel loop
• CTV to include “D2” lymph node regions
• 45Gy in 25fr
• ECF(X)
• Pre treatment QA
Interim analysis

- Sep 2009-Jul 2014
- 120 pts/ 51 sites

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Age ≥70</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>Male</td>
<td>75%</td>
<td>77%</td>
</tr>
<tr>
<td>GEJ</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>Lower third</td>
<td>27%</td>
<td>25%</td>
</tr>
<tr>
<td>other</td>
<td>47%</td>
<td>48%</td>
</tr>
<tr>
<td>T1-2</td>
<td>17%</td>
<td>13%</td>
</tr>
<tr>
<td>&gt;T2</td>
<td>83%</td>
<td>87%</td>
</tr>
<tr>
<td>N0</td>
<td>47%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Accrual to date: 324/750 target sample size
## Compliance and $\geq\text{Gd 3}$ toxicities

<table>
<thead>
<tr>
<th>Compliance (%)</th>
<th>CT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop CT</td>
<td>93</td>
<td>98</td>
</tr>
<tr>
<td>Preop RT</td>
<td>90</td>
<td>92</td>
</tr>
<tr>
<td>Surgery</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>Completed S: Receiving post op CT</td>
<td>64</td>
<td>50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gd$\geq3$ toxicity (%)*</th>
<th>CT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>6.7</td>
<td>8.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11.7</td>
<td>16.7</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>8.3</td>
<td>10</td>
</tr>
</tbody>
</table>
## Surgery related adverse events Gd 3+ interim analysis N = 120

<table>
<thead>
<tr>
<th>Surgical complications Gd 3+</th>
<th>CT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastomotic leak</td>
<td>5.6</td>
<td>7.8</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Infection (chest)</td>
<td>9.3</td>
<td>9.8</td>
</tr>
<tr>
<td>Infection (intraabdominal)</td>
<td>7.4</td>
<td>5.9</td>
</tr>
<tr>
<td>Infection (wound)</td>
<td>3.7</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac arrythmia</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac ischemia/infractio/angina</td>
<td>1.9</td>
<td>0</td>
</tr>
<tr>
<td>Thrombosis/embolism</td>
<td>1.9</td>
<td>2</td>
</tr>
<tr>
<td>Chyle leak</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
## Rationale in favor of preop RT

<table>
<thead>
<tr>
<th>Factor</th>
<th>Preoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient population</td>
<td>Decision based on clinical staging</td>
<td>Decision based on pathological staging</td>
</tr>
<tr>
<td>Toxicity burden</td>
<td>Toxicity of preoperative therapy may preclude</td>
<td>Toxicity of surgery may preclude the use of postoperative therapy</td>
</tr>
<tr>
<td></td>
<td>surgery</td>
<td></td>
</tr>
<tr>
<td>Timing of surgery</td>
<td>Need to be delayed until completion of surgery</td>
<td>For all patients as first modality</td>
</tr>
<tr>
<td>Treatment volume</td>
<td>Generally smaller</td>
<td>Generally larger</td>
</tr>
<tr>
<td>Dose effect</td>
<td>Require less dose for the same local control benefit</td>
<td>Require more dose for the same local control benefit</td>
</tr>
</tbody>
</table>

Table 2: Pros and cons of pre vs. postoperative radiotherapy
Take Home Message

• RT has a important role to play in the curative management of esophageal cancers
  – Future role of radical CRT and selective salvage surgery as preferred strategy

• In patients where trimodality and perioperative CT are both suitable options
  – choice dependent of morbidity of RT

• In patients gastric and GEJ pts
  – perioperative CT[preopRT] with tailored RT volumes is being actively tested in global trial

• RT design important in personalizing decision making