Neoadjuvant Therapy: Chemo or Chemoradiotherapy?

John V. Reynolds, Dept. of Surgery
St James’s Hospital and Trinity College Dublin
reynoljv@tcd.ie

Relationships with Commercial Interests: (activity/presentation)  NONE

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Speakers Bureau/Honoraria: NONE
LEARNING OBJECTIVES

1. Participants will be up to date on the rationale and status of current international clinical trials comparing neoadjuvant chemotherapy and chemoradiotherapy.

2. Participants will be introduced to an emerging paradigm shift in approach to cancer of the esophagus and junction, and on potential operative risks associated with these approaches.

3. At the conclusion of this activity, participants will be able to discuss the current evidence base in the context of this question.
Neoadjuvant Chemotherapy vs Chemoradiation: Major Current Questions

1. Is multimodal therapy truly the standard of care?

2. Does preoperative chemoradiation significantly increase operative risks?

3. How to approach cN2-3, do we target “local” or “systemic” failure risk as a priority?

4. How to manage ypN1-3, R1 or TRG4/5 after neoadjuvant therapy?

5. Should cT2N0 patients have neoadjuvant therapy?
Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer


METHODS

We randomly assigned patients with resectable tumors to receive surgery alone or weekly administration of carboplatin (doses titrated to achieve an area under the curve of 2 mg per milliliter per minute) and paclitaxel (50 mg per square meter of body-surface area) for 5 weeks and concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days per week), followed by surgery.
Phase III Trial of Trimodality Therapy With Cisplatin, Fluorouracil, Radiotherapy, and Surgery Compared With Surgery Alone for Esophageal Cancer: CALGB 9781

Joel Tepper, Mark J. Krasna, Donna Niedzwiecki, Donna Hollis, Carolyn E. Reed, Richard Goldberg, Krystyna Kiel, Christopher Willett, David Sugarbaker, and Robert Mayer

- RT 50.4 Gy (1.8Gy) - Nth America
Patterns of Recurrence After Surgery Alone Versus Preoperative Chemoradiotherapy and Surgery in the CROSS Trials

<table>
<thead>
<tr>
<th></th>
<th>Surgery alone (%)</th>
<th>CRT plus Surgery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=161</td>
<td>N=213</td>
</tr>
<tr>
<td>Locoregional</td>
<td>9.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>23.6</td>
<td>20.7</td>
</tr>
<tr>
<td>Locoregional and distant</td>
<td>24.2</td>
<td>10.8</td>
</tr>
<tr>
<td>Total</td>
<td>57.1</td>
<td>34.7</td>
</tr>
</tbody>
</table>

Van Hagen et al. NEJM 2012
Van Meerten et al. Br J Cancer 2006
Oppedijk et al. J Clin Oncol 2014
CROSS Trial Data not as compelling for adenocarcinoma as for squamous …

SCC HR 0.45 (CI 0.24-0.84), p=0.011

Adenocarcinoma

HR 0.73

(CI 0.52-0.99), p=0.049

Van Hagen et al. NEJM 2012
### Fully Published Randomized Trials of Preoperative Chemotherapy Compared with Surgery Alone

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Path</th>
<th>Chemotherapy</th>
<th>RO</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC (92-98)</td>
<td>400</td>
<td>SCC/adeno/undiff</td>
<td>CDDP/5-FU</td>
<td>60%</td>
<td>Median (SS) 17 mo</td>
</tr>
<tr>
<td>CT Surgery</td>
<td>402</td>
<td></td>
<td></td>
<td>54%</td>
<td>13 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG 8911 (90-95)</td>
<td>216</td>
<td>SCC/adeno</td>
<td>CDDP/5-FU</td>
<td>63%</td>
<td>Median (NS) 1.3 years</td>
</tr>
<tr>
<td>CT Surgery</td>
<td>227</td>
<td></td>
<td></td>
<td>59%</td>
<td>1.3 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAGIC* (94-02)</td>
<td>250</td>
<td>Adeno</td>
<td>Epirubicin/CDDP/5-FU</td>
<td>NR</td>
<td>5 yr (SS) 36%</td>
</tr>
<tr>
<td>CT Surgery</td>
<td>253</td>
<td></td>
<td></td>
<td></td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFCD* (95-03)</td>
<td>113</td>
<td>Adeno</td>
<td>CDDP/5-FU</td>
<td>84%</td>
<td>5 yr (SS) 38%</td>
</tr>
<tr>
<td>CT Surgery</td>
<td>111</td>
<td></td>
<td></td>
<td>74%</td>
<td>24%</td>
</tr>
</tbody>
</table>

*Included patients with gastric cancer. Abbreviations: RO, complete resection; CT, Chemotherapy; SCC, squamous cell carcinoma; adeno, adenocarcinoma; undiff, undifferentiated; CDDP, cisplatin; 5-FU, 5-fluorouracil; SS, statistically significant; mo, months; NS, not statistically significant; NR, not reported.
Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. Lordick¹, C. Mariette², K. Haustermans³, R. Obermannová⁴ & D. Arnold⁵ on behalf of the ESMO Guidelines Committee*

¹University Cancer Centre Leipzig, University Hospital Leipzig, Leipzig, Germany; ²Department of Digestive and Oncological Surgery, University Hospital Claude Huriez, Lille, France; ³Department of Radiation Oncology, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium; ⁴Clinic of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute and Faculty of Medicine, Masaryk University, Brno, Czech Republic; ⁵Instituto CUF de Oncologia, Lisbon, Portugal

- **cTNM staging (endoscopy, EUS, MS-CT, FDG-PET)**
  - **Functional assessment** (symptoms, comorbidity, nutritional status, patient preferences)

**Limited disease** (cT1-T2 cN0 M0)

- Squamous cell cancer³
  - Neoadjuvant chemoradiotherapy
  - Restaging (exclusion of M1)
  - Resection

**Locally advanced disease** (cT3-T4 or cN1-3 M0)

- Adenocarcinoma⁴
  - Neoadjuvant chemoradiotherapy
  - Restaging (exclusion of M1)
  - Resection

- Squamous cell cancer³
  - Definitive chemoradiotherapy
  - Follow-up (every 3 months)
  - Salvage resection⁴

- Adenocarcinoma⁴
  - Perioperative chemotherapy
  - Restaging (exclusion of M1)
  - Reoperation
POET TRIAL

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>R0</th>
<th>pCR</th>
<th>N0</th>
<th>Median Survival</th>
<th>3 yr OS</th>
<th>Local Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>59</td>
<td>70%</td>
<td>2%</td>
<td>37%</td>
<td>21 mos</td>
<td>28%</td>
<td>59%</td>
</tr>
<tr>
<td>Chemo RT</td>
<td>60</td>
<td>72%</td>
<td>16%</td>
<td>64%</td>
<td>33 mos</td>
<td>47%</td>
<td>77% P = 0.07</td>
</tr>
</tbody>
</table>

- EUS, laparoscopy staged pts
- Siewart I-III, T3-4 adrenocarcinoma
- TTE, THE and gastrectomy allowed

Stahl, JCO 2009
Neo-AEGIS –
CROSS vs Pre and Postoperative Chemotherapy

Adenocarcinoma
Esophageal and GEJ
AEG I-III
cT2-3N0-3M0
PS0-2

N=594

Primary endpoint:
Overall survival
Secondary endpoints:
pCR, complications,
PFS, AE, QOL etc.

Modified MAGIC
EOX×3 Surgery EOX×3
Peri-CTx

CROSS
Neo CRT wCP-RT(41.4Gy)+Surgery

Reynolds JV. BMC Cancer 2017; 17: 401 (NCT 01726452)
Neo AEGIS Accrual

Accrual Target: 594 originally, now 628 patients
Accrual Time: Approx. 7 years. Study scheduled to close to recruitment 31-Dec-2019
Accrual: 280/628 patients recruited as of 12th of September 2018.
Sites: 25 Active sites in UK (17), Ireland (6), DK (1) and France (1)
FLOT erupts on to the scene
Adeno (75%)
cT2-4/cNany
Gastric and
AEG 1-III
No prior Tx
Central Path of
TRG (Becker)

FLOT-4-AIO: Phase II

FLOTx4 –surgery-FLOT x4 (n=128)

ECF/ECX x3 –surgery- ECF/ECX x3
N=137

• PHASE II results
• 2010-2
• pCR (20/128 (16%) FLOT vs (8/126 (6%) ECF(X): P=0.02

(pCR rate with chemotherapy alone to rival nCRT)

Al-Batran SE Lancet Oncol 2016; 17: 1697
FLOT regimen with Docetaxel ……

• Improved median survival from 35 to 50 months (HR; 0.77; p=0.012)
• Improved PFS 18-30 months (HR; 0.75; p=0.004)
• 94% vs 87% progressed to surgery (p=0.001)
• FLOT increased neutropenia (51% vs 39%); p = 0.002
• FLOT increased infections (18% vs 9%); p < 0.001

ESOPEC – FLOT versus CROSS

ESOPEC: prospective randomized controlled multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (NCT02509286)

- Endpoint: Overall survival
- 223/438 randomized (13.8.2018)
- 25 active sites
- Start 2016
- Timeline 2016 – 2023

Hoeppner et al.; J BMC Cancer (2016)
Amended TopGear Protocol

Adenocarcinoma
Gastric /GEJ
AEG II and III (NOT AEG1)
cT3N0-3M0

N=620

450 RANDOMIZED

TopGear amendment, 2017. Leong T
Modified Neo-AEGIS Trial

Adenocarcinoma
Oesophageal and GOJ
AEG I-III
cT2-3N0-3M0
PS0-2
No prior therapy

N=628

Primary endpoint:
Overall survival
Secondary endpoint: pCR, complications, PFS,AE, QOL etc.

“Best - evidenced chemotherapy”
EOXx3
Or FLOT x 4
Surgery
Peri-CTx
EOXx3
or FLOT x4

“Best CRT regimen – CROSS”
Neo CRT
wCP-RT(41.4Gy)+Surgery

New design based on non-inferiority, and 3 year survival 53% in both groups
The addition of RT to neo-CTX results in higher pCR rate, without significantly affecting survival.

## What we know re Chemo vs Chemoradiation

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparison</th>
<th>OS Arm A</th>
<th>OS Arm B</th>
<th>RO</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POET (n=119)</strong></td>
<td>CF/w x 14 vs plus 30Gy + EPx1</td>
<td>24% 5 yr</td>
<td>40% 5yr</td>
<td>79% vs 88%</td>
<td>2% vs 12%</td>
</tr>
<tr>
<td>RCT</td>
<td></td>
<td></td>
<td></td>
<td>P=0.0055</td>
<td>P=0.03</td>
</tr>
<tr>
<td><strong>AUSTRALIA (n=75)</strong></td>
<td>CF/q21d x2 vs plus 35Gy</td>
<td>36% 5 yr</td>
<td>45% 5yr</td>
<td>88% vs 100%</td>
<td>0 vs 13%</td>
</tr>
<tr>
<td>RCT</td>
<td></td>
<td></td>
<td></td>
<td>29/33 vs 33/33</td>
<td>0/36 vs 5/39</td>
</tr>
<tr>
<td><strong>NEORES (n=181)</strong></td>
<td>CF/q21d x 3 vs plus 40Gy</td>
<td>49% 3 yr</td>
<td>47% 3yr</td>
<td>74% vs 87%</td>
<td>8% vs 24%</td>
</tr>
<tr>
<td>RCT 72% Adeno</td>
<td></td>
<td></td>
<td></td>
<td>58/78 vs 68/78</td>
<td>7/91 vs 22/90</td>
</tr>
<tr>
<td><strong>MAGIC VS CROSS (n=313)</strong></td>
<td>ECF (nonrandomized) vs CROSS protocols</td>
<td>51% 3 yr</td>
<td>55% 3yr</td>
<td>92% vs 93%</td>
<td>7% vs 15%</td>
</tr>
<tr>
<td>Non-randomized</td>
<td></td>
<td></td>
<td></td>
<td>120/131 vs 160/172</td>
<td>9/137 vs 26/176</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P=0.002</td>
<td>P=0.007</td>
</tr>
</tbody>
</table>
Multimodality treatment for Esophageal Adenocarcinoma: multi-center propensity-score matched study


10 European Centres with Established Prospective Registries
2001-2012
608 pt with Stage II/III tumours: 301 nCT and 307 nCRT
Propensity score matching and Cox regression analysis

ypT0: 27% vs 5% ; p < 0.001
ypN0 63% vs 32% ; p < 0.001: FAVOURING nCRT
R1/R2 8% vs 22% ; p < 0.001

3 year OS: 58% vs 53% p = 0.391 NO DIFFERENCE
3 year DFS: 53% vs 49% p = 0.660

Higher mean lymph node harvest (27 vs 14) in nCT group, suggesting that surgical QA may be important, and demanding further research in both cohorts
Neoadjuvant Chemotherapy
Old and New
OEO2 vs OEO 5

4 cycles ECX no better than 2 CF
17% ECX vs 6% CF for TRG 1 or 2

Alderson D et.al, Lancet Oncology 2017
If current RCTs are negative for the primary end point what secondary end points [Operative Complications; Toxicity (early and late); Cost] may be “practice changing”?
nCRT and operative risks

- Lung
- Heart
- Conduit
- Hepatic
<table>
<thead>
<tr>
<th>Organ at Risk</th>
<th>Dose Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord</td>
<td>D 0.1cc &lt; 45Gy</td>
</tr>
<tr>
<td>Spinal Cord PRV</td>
<td>D1cc &lt; 40Gy</td>
</tr>
<tr>
<td>Combined Lungs</td>
<td>V20Gy &lt; 25%</td>
</tr>
<tr>
<td>Heart</td>
<td>V40Gy &lt; 30%, V25Gy &lt; 50%</td>
</tr>
<tr>
<td>Liver</td>
<td>V30Gy &lt; 30%</td>
</tr>
<tr>
<td>Individual Kidneys</td>
<td>V20Gy &lt; 70% with contralateral kidney V20Gy &lt; 30%</td>
</tr>
<tr>
<td>Combined Kidneys</td>
<td>V20Gy &lt; 50%</td>
</tr>
<tr>
<td>Stomach</td>
<td>Defined as Region of Interest rather than Organ at Risk</td>
</tr>
</tbody>
</table>

**RT Treatment Plan Optimisation for Organs at Risk**  
*(Neo-AEGIS Trial; CROSS vs MAGIC in adenocarcinoma)*
What Are the Major Complications:

**CROSS TRIAL:**
Van Hagen, NEJM, 2012; 366:22

<table>
<thead>
<tr>
<th></th>
<th>Surgery alone</th>
<th>CRT + Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year survival</td>
<td>44%</td>
<td>58%</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>44%</td>
<td>46%</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>17%</td>
<td>21%</td>
</tr>
<tr>
<td>Chylothorax</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>Mediastinitis</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td><em>Anastomotic leak</em></td>
<td>25%</td>
<td>22%</td>
</tr>
<tr>
<td>In hospital mortality</td>
<td>7 (3.8%)</td>
<td>6 (3.4%)</td>
</tr>
</tbody>
</table>
Meta-analysis of postoperative morbidity and perioperative mortality in patients receiving neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal and gastro-oesophageal junctional cancers

K. Kumagai¹, I. Rouvelas¹, J. A. Tsai¹, D. Mariosa², F. Klevebro¹, M. Lindblad¹, W. Ye², L. Lundell¹ and M. Nilsson¹

<table>
<thead>
<tr>
<th>Reference</th>
<th>Risk ratio</th>
<th>Risk ratio</th>
<th>Respiratory complication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NACR + surgery</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>SCC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nygaard et al.³⁴</td>
<td>1-62 (0-40, 4-33)</td>
<td>10 of 47</td>
<td>5 of 38</td>
</tr>
<tr>
<td>Aapro et al.³¹</td>
<td>1-01 (0-20, 8-68)</td>
<td>2 of 26</td>
<td>2 of 34</td>
</tr>
<tr>
<td>Le Prise et al.³⁰</td>
<td>1-50 (0-44, 5-16)</td>
<td>5 of 35</td>
<td>4 of 42</td>
</tr>
<tr>
<td>Bosset et al.²⁵</td>
<td>12-91 (0-73, 22-90)</td>
<td>6 of 138</td>
<td>0 of 137</td>
</tr>
<tr>
<td>Lee et al.³⁷</td>
<td>0-27 (0-03, 2-25)</td>
<td>1 of 35</td>
<td>5 of 48</td>
</tr>
<tr>
<td>Natsugoe et al.³⁹</td>
<td>0-77 (0-14, 4-14)</td>
<td>2 of 20</td>
<td>3 of 23</td>
</tr>
<tr>
<td>Lv et al.⁵²</td>
<td>7-00 (0-37, 13-36)</td>
<td>3 of 80</td>
<td>0 of 80</td>
</tr>
<tr>
<td>Subtotal (I² = 5-5%, P = 0-385)</td>
<td>1-42 (0-76, 2-67)</td>
<td>29 of 361</td>
<td>19 of 402</td>
</tr>
<tr>
<td>AC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walsh et al.³⁸</td>
<td>0-94 (0-68, 1-32)</td>
<td>28 of 51</td>
<td>32 of 55</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0-94 (0-68, 1-32)</td>
<td>28 of 51</td>
<td>32 of 55</td>
</tr>
<tr>
<td>AC and SCC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burmeister et al.²⁶</td>
<td>0-76 (0-49, 1-19)</td>
<td>25 of 112</td>
<td>36 of 123</td>
</tr>
<tr>
<td>Tepper et al.²⁶</td>
<td>1-14 (0-49, 2-69)</td>
<td>8 of 26</td>
<td>7 of 26</td>
</tr>
<tr>
<td>van Hagen et al.⁴³</td>
<td>1-05 (0-84, 1-32)</td>
<td>78 of 168</td>
<td>82 of 186</td>
</tr>
<tr>
<td>Subtotal (I² = 0-0%, P = 0-421)</td>
<td>0-99 (0-81, 1-21)</td>
<td>111 of 306</td>
<td>123 of 335</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bagheri et al.²⁹</td>
<td>1-00 (0-07, 14-90)</td>
<td>1 of 20</td>
<td>1 of 20</td>
</tr>
<tr>
<td>Subtotal</td>
<td>1-00 (0-07, 14-90)</td>
<td>1 of 20</td>
<td>1 of 20</td>
</tr>
<tr>
<td>Overall (I² = 0-0%, P = 0-573)</td>
<td>1-01 (0-85, 1-19)</td>
<td>169 of 758</td>
<td>177 of 812</td>
</tr>
</tbody>
</table>

Favours NACR Favours surgery alone
# Neoadjuvant chemoradiation and postoperative pulmonary morbidity and mortality

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Pulmonary morbidity</th>
<th>Postoperative Mortality</th>
<th>3 year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>nCT</td>
<td>nCRT</td>
<td>nCT</td>
</tr>
<tr>
<td><strong>NeoRes</strong></td>
<td>Cisplatin/5FU ± 40Gy/20Fr</td>
<td>13%</td>
<td>22%</td>
</tr>
<tr>
<td><strong>POET</strong></td>
<td>PLF ± Cisplatin Etoposide 30Gy/15Fr</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>CROSS</strong></td>
<td>Carboplatin Paclitaxel 41.4Gy/23Fr</td>
<td>44%</td>
<td>46%</td>
</tr>
<tr>
<td><strong>FFCD 9901</strong></td>
<td>Cisplatin/5-FU 45Gy/25Fr</td>
<td>53%</td>
<td>40%</td>
</tr>
</tbody>
</table>
NeoRes (Sweden): Chemo vs. CRT 2016

12 month mortality unrelated to disease:
- nCRT = 11 of 90 (12%)
- nCT = 3 of 91 (3%)

$p = 0.036$
Study population

- Consecutive patients treated with neoadjuvant therapy for locally advanced esophageal cancer 2010 – 2016

- Exclusion:
  - Salvage

Elliott JA, et al, submitted for publication
Radiation and pulmonary function: Cellular mechanisms

- Radiation
  - Fibroblast
  - Fibrocyte
  - Myofibroblast
  - Interstitial Fibrosis
  - Collagens
  - Fibronectin
  - ECM proteins

- EMT
  - Injured alveolar epithelial cell
  - Mesenchymal cell

- Alveolar epithelial cell apoptosis
- Alveolar epithelial cell

- Pro-inflammatory cytokines
- Anti-inflammatory cytokines

- Monocyte
- Lymphocyte
- Neutrophil
- Macrophage
- M2 Macrophage

- Radiation Pneumonitis
**Methods**

Assessment of pulmonary function and HR-QL

- **Vmax® Encore PFT system**
  
  *FEV1, FVC, DLCO*

- **Global Lung Function Initiative equations**
  
  *Age, sex, height and ethnicity specific reference values*

- **EORTC Common Toxicity Criteria**
  
  *Radiation-induced lung injury (RILI)*

- **EORTC QLQ C30 and OG25**
  
  *Disease-free at last follow-up*
What is the impact of neoadjuvant chemoradiation on pulmonary function?

Elliott JA, et al, submitted for publication

<table>
<thead>
<tr>
<th>Metric</th>
<th>Baseline</th>
<th>Preoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (L)</td>
<td>97 ± 18%</td>
<td>92 ± 20%</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>105 ± 16%</td>
<td>98 ± 20%</td>
</tr>
<tr>
<td>DLCO (mol/min/kPa)</td>
<td>98 ± 21%</td>
<td>82 ± 20%</td>
</tr>
</tbody>
</table>
What is the differential effect of nCRT vs chemotherapy?

Independent predictors of %ΔDLCO:

Chemoradiation \((P=0.018)\)

Smoking \((P=0.003)\)

\[7.3 \pm 14.9\% \text{ versus } 14.0 \pm 13.8\%\]

Elliott JA, submitted for publication
# Chemotherapy or Multimodal: Is there a standard of care?

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparison</th>
<th>5 yr OS Arm A</th>
<th>5 yr OS Arm B</th>
<th>R0</th>
<th>pCR Adeno</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLOT (n=368)</td>
<td>FLOT vs MAGIC</td>
<td>45% projected</td>
<td>36% projected</td>
<td>84% vs 77%</td>
<td>16% vs 6%*</td>
</tr>
<tr>
<td>2017 EAC 56%; gastric 44%</td>
<td></td>
<td>(57% 3 yr)</td>
<td>48% 3 yr</td>
<td>300/356 vs 276/360</td>
<td>20/128 vs 8/137 in Phase 2</td>
</tr>
<tr>
<td>CROSS (n = 368)</td>
<td></td>
<td></td>
<td></td>
<td>P=0.011</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EAC 75% Carbo / Taxol +41Gy vs Surgery</td>
<td></td>
<td>92% vs 69%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAGIC (n=503)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006 EAC 26%; gastric 74%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECF x 3 pre and post vs Surgery</td>
<td></td>
<td>69% vs 66%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OEO 5 (n = 897)</td>
<td>CF x 2 pre vs ECX x 4</td>
<td>42% 3 yr ECX</td>
<td>39% 3 yr CF</td>
<td>70% vs 62%</td>
<td>7% ECX vs 1% CF</td>
</tr>
<tr>
<td>2017 EAC 100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NO!** A standard of care requires at least one and ideally more than one high-quality RCT that addresses the question.
Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*

F. Lordick¹, C. Mariette², K. Haustermans³, R. Obermannová⁴ & D. Arnold⁵ on behalf of the ESMO Guidelines Committee*

¹University Cancer Centre Leipzig, University Hospital Leipzig, Leipzig, Germany; ²Department of Digestive and Oncological Surgery, University Hospital Claude Huriez, Lille, France; ³Department of Radiation Oncology, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium; ⁴Clinic of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute and Faculty of Medicine, Masaryk University, Brno, Czech Republic; ⁵Instituto CUF de Oncologia, Lisbon, Portugal

cTNM staging (endoscopy, EUS, MS-GI, FDG-PET)
Functional assessment (symptoms, comorbidity, nutritional status, patient preferences)

Limited disease (cT1-T2 cN0 M0)
Locally advanced disease (cT3-T4 or cN1-3 M0)

Squamous cell cancer³
- Neoadjuvant chemoradiotherapy
- Restaging (exclusion of M1)
- Resection¹,²

Definitive chemoradiotherapy
- Follow-up (every 3 months)
- Salvage resection⁴

Adenocarcinoma⁴
- Perioperative chemotherapy
- Restaging (exclusion of M1)
- Resection

- Neoadjuvant chemoradiotherapy
- Restaging (exclusion of M1)
- Resection
Conclusions

1. Is radiation required? Unknown in 2018, may not know for 5 years

2. Current trials – Esopec, NeoAEGIS, TOPGEAR, not mutually exclusive, of major clinical importance and provide opportunities for translational science

3. If primary outcome equivalent, attention on “real world” secondary outcomes

4. Need for trials focused on systemic failure cN2/3, y(p)N2/3, TRG 4/5

5. FLOT – is it a true elixir, hype or real, careful study required in esophageal cases
Thank you very much (reynoljv@tcd.ie)