State of the art: Standard(s) of radio/chemotherapy for rectal cancer

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The Royal Marsden Hospital
London & Surrey
Disclosure

• Advisory Board: Sanofi Oncology, Eli-Lilly, Bristol Meyers Squibb, MSD, Bayer, Roche, Five Prime Therapeutics

• Research funding: Eli-Lilly, Janssen-Cilag, Sanofi Oncology, Merck-Serono, Novartis

• Honorarium: Taiho, Pfizer, Amgen, Eli-Lilly
Why are we NOT improving survival with CRT?

Superior local control with surgery alone

Sensitivity and resistance to (C)RT

Reducing distant metastases

Improving efficacy over CRT

Clinical benefit
Why are we NOT improving survival with CRT?

Superior local control with surgery alone
T3 (<5mm) N+ve rectal tumours
Good prognosis rectal cancer managed by surgery alone (no RT) - MERCURY

Disease free survival

T3 <5mm extramural spread, regardless of N stage
Local recurrence 1.7%
5-year DFS: 81%
5-year OS: 67.9%

Overall survival

Taylor et al Ann Surg 2011
Why are we NOT improving survival with CRT?

Superior local control with surgery alone

Reducing distant metastases

Improving efficacy over CRT

Clinical benefit
# Pre-operative CRT: cT3-4 or N+

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Local recurrence</th>
<th>5-year DFS</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>German CAO/ARO/AIO-94</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-op CRT</td>
<td>421</td>
<td>5%</td>
<td>68%</td>
<td>74%</td>
</tr>
<tr>
<td>Post-op CRT</td>
<td>402</td>
<td>9.7%</td>
<td>65%</td>
<td>76%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.048</td>
<td>p=0.80</td>
</tr>
<tr>
<td><strong>FFCD 9203</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Pre-op CRT</td>
<td>375</td>
<td>8.1%</td>
<td>59.4%</td>
<td>67.4%</td>
</tr>
<tr>
<td>Pre-op RT</td>
<td>367</td>
<td>16.5%</td>
<td>55.5%</td>
<td>67.9%</td>
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<tr>
<td></td>
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<td></td>
<td>p=0.004</td>
<td>p=0.684</td>
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<tr>
<td><strong>EORTC 22921</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td>Pre-op CRT</td>
<td>506</td>
<td>7.6-8.7%</td>
<td>56.1%</td>
<td>65.8%</td>
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<tr>
<td>Pre-op RT</td>
<td>505</td>
<td>17.1%</td>
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<td>64.8%</td>
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<td>p=0.002</td>
<td>p=0.84</td>
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### Efficacy of adding oxaliplatin to FP/RT in rectal cancer

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<tr>
<th>Trials</th>
<th>Arms</th>
<th>n</th>
<th>pCR</th>
<th>p</th>
<th>DFS</th>
<th>OS</th>
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<tr>
<td>STAR-01&lt;sup&gt;1&lt;/sup&gt;</td>
<td>FU</td>
<td>379</td>
<td>16%</td>
<td>0.904</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
<td>OX/FU</td>
<td>368</td>
<td>16%</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>ACCORD 12/0405 PRODIGE 2&lt;sup&gt;2&lt;/sup&gt;</td>
<td>CAP</td>
<td>299</td>
<td>13.9%</td>
<td>0.09</td>
<td>67.9%</td>
<td>87.6%</td>
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<td>CAPOX</td>
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<td>German Rectal&lt;sup&gt;3&lt;/sup&gt;</td>
<td>FU</td>
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<td>13%</td>
<td>0.031</td>
<td>71.2%</td>
<td>88.0%</td>
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<td>PETACC-6</td>
<td>CAP</td>
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<td>12%</td>
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*5-year survival rates

# Pre-operative CRT: randomised trials

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<tr>
<th>Study</th>
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<th>Distant metastasis</th>
<th>5-year DFS</th>
<th>5-year OS</th>
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<tr>
<td></td>
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<td>p=0.32</td>
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<td></td>
<td></td>
<td></td>
<td>p=0.52</td>
<td>p=0.84</td>
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</table>

Pooled analysis of 5 European RCTs (n=2,795)

<table>
<thead>
<tr>
<th></th>
<th>5-year</th>
<th>10-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence</td>
<td>12.9%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>30.8%</td>
<td>34.2%</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>69.6%</td>
<td>57.3%</td>
</tr>
</tbody>
</table>

Valentini et al J Clin Oncol 2011
Selecting patients for the right treatment

CRYS TAL: FOLFIRI ± cetuximab
K-RAS exon 2 mutants
K-RAS wild type
RAS wild type

All comers mCRC

K-RAS exons 2-4
N-RAS exons 2-4 mutants

Are all T3 rectal cancers born equal?

- Circumferential resection margin (CRM)
- Extramural spread (<5mm vs. >5mm)
- T4 tumours
- N0 vs. N1 vs N2
- Extramural venous invasion
- Low lying tumours
Meta-analysis of studies comparing CRM +ve vs. –ve:

Extramural spread (≤5mm vs. >5mm)

T3a

- 5-yr LR 10.4%
- 5-yr OS 85.4%

T3b

- 5-yr LR 26.3%
- 5-yr OS 54.1%

Both p<0.0001

Merkel et al Int J Colorectal Dis 2001
# N0 vs. N1 vs. N2

<table>
<thead>
<tr>
<th>TN staging</th>
<th>Pooled analysis 1&lt;sup&gt;1&lt;/sup&gt; (total n = 2,551)</th>
<th>Pooled analysis 2&lt;sup&gt;2&lt;/sup&gt; (total n = 3,791)</th>
<th>SEER analysis&lt;sup&gt;3&lt;/sup&gt; (total n = 35,829)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>5-yr OS</td>
<td>n</td>
</tr>
<tr>
<td>T3N0</td>
<td>668</td>
<td>74%</td>
<td>1,060</td>
</tr>
<tr>
<td>T3N1</td>
<td>554</td>
<td>61%</td>
<td>887</td>
</tr>
<tr>
<td>T3N2</td>
<td>663</td>
<td>48%</td>
<td>935</td>
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</table>

<sup>1</sup>Gunderson et al Int J Radiat Oncol Biol Phys 2008  
<sup>2</sup>Gunderson et al J Clin Oncol 2004  
<sup>3</sup>Gunderson et al J Clin Oncol 2010
Extramural venous invasion (EMVI): disease free survival n=478

- EMVI was an independent poor prognostic factor on multivariate analyses for
  - stage II rectal cancer HR 2.08 (95% CI 1.10–3.95)
  - Stage III rectal cancer HR 2.74 (95% CI 1.66–4.52)

Chand et al Ann Oncol 2014
Low lying tumours: pooled analysis from 5 (chemo)radiotherapy rectal cancer RCTs

Local recurrence

Overall survival

Cancer specific survival

N
1,353  2,310
CRM +ve
10.6%  5%
5-year LR
19.7%  11.4%
5-yr OS
59.5%  70.1%
5-yr CSS
65.1%  76.6%
All p<0.001

den Dulk et al Eur J Cancer 2009
Are all rectal cancers born equal?

- Circumferential resection margin (CRM)
- Extramural spread (<5mm vs. >5mm)
- T4 tumours
- N0 vs. N1 vs N2
- Extramural venous invasion
- Low lying tumours

Do we have the right tool to detect these high risk features?
Baseline MRI

- Extramural spread threatening anterior circumferential resection margin
- Right pelvic side wall node
- Left pelvic side wall node
Baseline MRI

Extramural venous invasion
## MERCURY

### Circumferential resection margin assessment

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Percentage</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological CRM –ve</td>
<td>354/408</td>
<td>87%</td>
<td>83-90%</td>
</tr>
<tr>
<td>MRI predicted CRM-ve</td>
<td>327/354</td>
<td>92%</td>
<td>90-95%</td>
</tr>
<tr>
<td>MRI prediction CRM-ve</td>
<td>349/408</td>
<td>86%</td>
<td>82-89%</td>
</tr>
<tr>
<td>Histological CRM-ve</td>
<td>27/349</td>
<td>94%</td>
<td>91-96%</td>
</tr>
</tbody>
</table>

### Extramural tumour spread assessment

<table>
<thead>
<tr>
<th></th>
<th>Mean extramural tumour spread</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>2.80mm (SD 4.60mm)</td>
<td>-0.05mm (95%CI: -0.49mm to 0.40mm)</td>
</tr>
<tr>
<td>Histopathology</td>
<td>2.81mm (SD 4.28mm)</td>
<td></td>
</tr>
</tbody>
</table>

1. MERCURY Study Group BMJ 2006
2. MERCURY Study Group Radiology 2007
Why are we NOT improving survival with CRT?

- Superior local control with surgery alone
- Reducing distant metastases
- Improving efficacy over CRT

Clinical benefit
Clinico-pathological poor risk factors

- Circumferential resection margin involvement (CRM)
- Extramural spread (<5mm vs. >5mm)
- T4 tumours
- N0 vs. N1 vs N2
- Extramural venous invasion
- Low lying tumours
### Serial RMH phase II studies of neoadjuvant chemotherapy, chemoradiation followed by TME

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Recruitment period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemorad(^1)</td>
<td>36</td>
<td>Jan 99 to Aug 01</td>
</tr>
<tr>
<td>EXPERT(^2,3)</td>
<td>105</td>
<td>Nov 01 to Aug 05</td>
</tr>
<tr>
<td>EXPERT-C(^4)</td>
<td>164</td>
<td>Aug 05 to Jul 08</td>
</tr>
</tbody>
</table>

\(^1\)Chau et al Brit J Cancer 2003; \(^2\)Chau et al J Clin Oncol 2006
\(^3\)Chua et al Lancet Oncol 2010; \(^4\)Dewsbury et al J Clin Oncol 2012
Neoadjuvant chemotherapy

Chemoradiation

Post-operative chemotherapy

0 3 6 9 12

18

+12 weeks

Weeks

MRI and CT scans at 12 weeks and after radiotherapy to reassess tumour response

4-6 weeks rest for recovery of acute RT toxicity.

Repeat MRI then TME SURGERY
EXPERT trial schema

OXALIPLATIN 130 mg/m²

CAPECITABINE 2000mg/m²/day for 14 days every 21 days

RT 45Gy in 25# phase 1
9Gy boost phase 2
Capcitabine 1650mg/m²/day continuously

Post operatively
CAPECITABINE 2500mg/m²/day for 14 days every 21 days

4-6 weeks rest for recovery of acute RT toxicity.
Repeat MRI then TME SURGERY

MRI and CT scans at 12 weeks and after radiotherapy to reassess tumour response

EXPERT: Progression free and overall survival (ITT n=105)

Median FU: 55 months

<table>
<thead>
<tr>
<th></th>
<th>3-year</th>
<th>5-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>83%</td>
<td>75%</td>
</tr>
<tr>
<td>PFS</td>
<td>68%</td>
<td>64%</td>
</tr>
</tbody>
</table>

Chua et al Lancet Oncol 2010
EXPERT-C trial design

EXPERT
Neoadjuvant oxaliplatin/capecitabine →
Capecitabine chemoradiation →
Total mesorectal excision →
Adjuvant oxaliplatin/capecitabine

EXPERT-C
Neoadjuvant oxaliplatin/capecitabine/cetuximab →
Capecitabine/cetuximab chemoradiation →
Total mesorectal excision →
Adjuvant oxaliplatin/capecitabine/cetuximab

n=165

• Investigator’s sites in UK, Spain and Sweden
• Recruitment finished in July 2008

Dewdney et al J Clin Oncol 2012
After neoadjuvant chemotherapy plus cetuximab

Baseline

After neoadjuvant chemotherapy
After neoadjuvant chemotherapy plus cetuximab

Baseline

After neoadjuvant chemotherapy
After neoadjuvant chemotherapy plus cetuximab

Baseline

After neoadjuvant chemotherapy
Pathological complete response was achieved on surgical specimen from TME
EXPERT-C trial: 5-year results

Median follow-up = 64 months

Time from randomisation (years)

5-year PFS
CAPOX 67.8% vs. CAPOX+C 75.4%

Time from randomisation (years)

5-year OS
CAPOX 72.3% vs. CAPOX+C 84.3%

Sclafani et al J Nat Cancer Inst 2014
Why are we NOT improving survival with CRT?

Superior local control with surgery alone

Reducing distant metastases

Improving efficacy over CRT

Clinical benefit
Balancing survival with quality of life

- Short term toxicities
- Long term complications
- Permanent sequelae
- Local recurrence
- Distant metastases
- Cure

Clinical benefit
What constitutes a good response after CRT?

Pathological complete response\(^1\)

- pCR seen in 16%
- Significant more T1/2 achieved

pCR

Do T1/2 tumours need pCR to have better survival?

Pathological Tumour regression grade\(^2\)

\(^1\)Maas et al Lancet Oncol 2010; \(^2\)Fokas et al J Clin Oncol Oncol 2014
## Efficacy of adding oxaliplatin to FP/RT in rectal cancer

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<th>Trials</th>
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*5-year survival rates

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Disease free survival good vs. poor responders: Pathology and MRI

Despite a lack of 100% agreement between pathology and MRI, assessment of T stage by either MRI or pathology show equal performance in the prediction of survival

# mrTRG vs. pTRG

<table>
<thead>
<tr>
<th>Description</th>
<th>mrTRG</th>
<th>Grade</th>
<th>pTRG</th>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>No regression (intermediate signal intensity, same appearances as original tumour)</td>
<td></td>
<td>mrTRG 5</td>
<td>pTRG 0</td>
<td></td>
<td>No regression</td>
</tr>
<tr>
<td>Slight regression (little areas of low signal intensity fibrosis or mucin but mostly tumour)</td>
<td></td>
<td>mrTRG 4</td>
<td>pTRG 1</td>
<td></td>
<td>Dominant tumour mass with obvious fibrosis and/or vasculopathy</td>
</tr>
<tr>
<td>Moderate regression (low signal intensity fibrosis predominaes but there are obvious areas of intermediate signal intensity)</td>
<td></td>
<td>mrTRG 3</td>
<td>pTRG 2</td>
<td></td>
<td>Dominantly fibrotic changes with few tumour cells or groups (easy to find)</td>
</tr>
<tr>
<td>Good regression (predominant low signal intensity fibrosis with no obvious residual tumour signal)</td>
<td></td>
<td>mrTRG 2</td>
<td>pTRG 3</td>
<td></td>
<td>Very few (difficult to find microscopically) tumour cells in fibrotic tissue with or without mucous substance</td>
</tr>
<tr>
<td>Complete regression (absence of tumour signal and barely visible treatment related scar)</td>
<td></td>
<td>mrTRG 1</td>
<td>pTRG 4</td>
<td></td>
<td>No tumour cells, only fibrotic mass (total regression or response)</td>
</tr>
</tbody>
</table>

Abbreviations: mrTRG = magnetic resonance tumour regression grade; pTRG = pathological tumour regression grade.
MERCURY: MRI post-CRT TRG

Based on similar principles to Dworak’s pathologic TRG

- mrTRG 5: no fibrosis evident; tumour signal visible only
- mrTRG 4: predominantly tumour signal intensity with minimal fibrotic low-signal intensity
- mrTRG 3: mixed areas of low-signal fibrosis and intermediate signal intensity present but without predominance of tumour signal
- mrTRG 2: in-between mrTRG1 and 3
- mrTRG 1: absence of any tumour signal

Unfavourable: TRG 4-5
Favourable: TRG 1-3

Patel et al J Clin Oncol 2011
Correlation between mrTRG and pTRG

<table>
<thead>
<tr>
<th>pTRG&lt;sup&gt;b&lt;/sup&gt;</th>
<th>5</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>17</td>
<td>20</td>
<td>13</td>
<td>2</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>12</td>
<td>19</td>
<td>23</td>
<td>4</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>6</td>
<td>8</td>
<td>24</td>
<td>4</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>12</td>
<td>4</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>44</td>
<td>56</td>
<td>73</td>
<td>14</td>
<td>191</td>
</tr>
</tbody>
</table>

Abbreviations: mrTRG = magnetic resonance tumour regression grade; pTRG = pathological tumour regression grade.

<sup>a</sup>mrTRG 1 and mrTRG 5 indicate complete radiological regression and no radiological regression, respectively.

<sup>b</sup>pTRG 4 and pTRG 0 indicate complete pathological regression and no pathological regression, respectively.

Sclafani et al Br J Cancer 2017
Combining pTRG and mrTRG to predict survival

Sclafani et al Br J Cancer 2017
TRIGGER: mrTRG as biomarker for stratified management of rectal cancer patients

RANDOMISATION
Consent (PIS STEP 2) during last cycle of CRT
1:2 randomisation ratio

Control Arm
MRI scan
Within 4–6 weeks of CRT completion
CONTROL ARM POST-CRT MRI CRF
mrTRG NOT reported

Intervention arm
MRI scan
Within 4–6 weeks of CRT completion
INTERVENTION ARM POST-CRT MRI CRF
mrTRG reported

mrTRG I & II
Good response
Consolidation Chemotherapy
24 weeks

Deferral of surgery
SURVEILLANCE PROTOCOL
Follow-up every 3 mths for two years and every 6 mths for further 3 years
Protocol section 11.3.1
Suspicion of clinical or radiological local regrowth or pelvic relapse
Follow Regrowth pathway
Protocol section 2.2.2

If mrTRG II
Adjuvant Chemotherapy
24 weeks

Chemotherapy
12 weeks
Repeat MRI scan
Surgery

Surgery
Annual clinical follow up visits for 3 years
Disease status at 5 years

Adjuvant Chemotherapy
24 weeks

ClinicalTrials.gov NCT02704520
“Responding to response – challenging the paradigm”

What is the optimal time for surgery?

To wait (a long time) seems better
Low-lying rectal cancer
Watch & Wait/ Deferral of Surgery with post CRT complete clinical response

- Initially triumphed by Habr-Gama et al
- A number of retrospective institutional series and registry data supported this approach

Actuarial local regrowth rates in patients with clinical complete response to CRT managed by watch & wait

34% had tumour local regrowth
Of whom 88% had salvage therapy with surgery (76%) and contact RT (12%)
Renehan et al Lancet Oncol 2016
Royal Marsden Deferral of Surgery Prospective Study

- MRI defined complete response: mrTRG1-2: low signal intensity fibrotic scar tissue only seen at MRI performed 4 weeks after long-course CRT, confirmed at 8-12 week MRI

<table>
<thead>
<tr>
<th>Clinical follow-up</th>
<th>1M, 2M, 3Mly – 1-2 yrs, 6Mly – 3-4 yrs, then annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>1M, 2M, 3Mly – 1st yr, 6Mly – 2nd yr, annually</td>
</tr>
<tr>
<td>PET</td>
<td>2M, 4M, 1 yr</td>
</tr>
<tr>
<td>Sigmoidoscopy</td>
<td>3Mly – Yr 1, 6Mly – Yr 2, annually</td>
</tr>
<tr>
<td>CT &amp; colonoscopy</td>
<td>As per current NICE guidelines</td>
</tr>
</tbody>
</table>

- Primary endpoint: Local Failure
  - Powered for unacceptable failure rate – 80% power <15% local recurrence at 2 years
- Safe deferral
  - 90% power – ≥10% defer – expected to be at least 25%
  - Success ≥11 of 59 patients safely defer surgery at 2 years

NCT01047969
“Responding to response – challenging the paradigm”

What is the optimal time for surgery?

To wait (longer) seems better
Timing after CRT? When is maximum response reached?

- After completing CRT, patients undergoing surgery with a delay ≥8 weeks are 3x more likely to undergo T downstaging than patients <8 weeks (OR, 3.79; CI: 1.11 –12.99; P<0.03).

pCR: 17.8% in delayed group; 5.5% in standard group

Evans et al Dis Colon Rectum 2011
RCT Optimal timing for surgery after pre-operative CRT (6 vs. 12 weeks)

MRI-defined poor risk rectal cancer:
- CRM <1mm
- Low-lying tumour
- T3 (>5mm extramural spread)
- EMVI +ve
- N2

Primary endpoint: Tumour downstaging rates as defined as the proportion of patients downstaged by T staging seen on post CRT MRI

To detect ↑ in mrT downstaging from an expected 40% in the 6 weeks’ arm to 60% in the 12 weeks’ arm, 218 patients would be required (80% power; 2-sided \( \alpha =0.0492 \))

Evans et al ESCP, ESMO 2016
RCT Optimal timing for surgery after pre-operative CRT (6 vs. 12 weeks)

Recruited from 22 centres from UK, Brazil, Canada and Cyprus between Oct 09 and Dec 14

<table>
<thead>
<tr>
<th></th>
<th>6 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>122</td>
<td>115</td>
</tr>
<tr>
<td>Primary endpoint:</td>
<td>mrT-downstaging</td>
<td></td>
</tr>
<tr>
<td></td>
<td>52 (43%)</td>
<td>67 (58%)</td>
</tr>
</tbody>
</table>

Relative Risk: 1.4; 95% CI: 1.1, 1.8; p=0.019
RCT Optimal timing for surgery after pre-operative CRT (6 vs. 12 weeks)

<table>
<thead>
<tr>
<th>mrTRG</th>
<th>6 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7 (6%)</td>
<td>21 (22%)</td>
</tr>
<tr>
<td>2</td>
<td>31 (28%)</td>
<td>29 (30%)</td>
</tr>
<tr>
<td>3</td>
<td>45 (41%)</td>
<td>81 (39%)</td>
</tr>
<tr>
<td>4</td>
<td>22 (20%)</td>
<td>31 (15%)</td>
</tr>
<tr>
<td>5</td>
<td>6 (5%)</td>
<td>8 (4%)</td>
</tr>
</tbody>
</table>

Differences in mrTRG between the two arms were significant (p=0.0006)
## RCT Optimal timing for surgery after pre-operative CRT (6 vs. 12 weeks) Pathological findings

<table>
<thead>
<tr>
<th></th>
<th>6 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>ypCR</td>
<td>11 (11%)</td>
<td>23 (24%)</td>
</tr>
<tr>
<td>ypT0</td>
<td>9 (9%)</td>
<td>23 (24%)</td>
</tr>
<tr>
<td>ypN0</td>
<td>48 (50%)</td>
<td>62 (65%)</td>
</tr>
<tr>
<td>ypCRM +ve</td>
<td>8 (8%)</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Specimen grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 complete</td>
<td>68 (71%)</td>
<td>65 (68%)</td>
</tr>
<tr>
<td>2 near complete</td>
<td>14 (15%)</td>
<td>13 (14%)</td>
</tr>
<tr>
<td>3 incomplete</td>
<td>4 (4%)</td>
<td>10 (10%)</td>
</tr>
</tbody>
</table>

Evans et al ESCP, ESMO 2016
# RCT Optimal timing for surgery after pre-operative CRT (6 vs. 12 weeks)

<table>
<thead>
<tr>
<th></th>
<th>6 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Post-operative complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>25 (45%)</td>
<td>35 (48%)</td>
</tr>
<tr>
<td>Wound infection/</td>
<td>14 (25%)</td>
<td>13 (18%)</td>
</tr>
<tr>
<td>Delayed healing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>6 (11%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Medical (MI, PE etc)</td>
<td>2 (4%)</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (18%)</td>
<td>20 (27%)</td>
</tr>
</tbody>
</table>

Differences in post-operative complications between the two arms were non-significant (p=0.48)
Summary of 6 vs. 12 trial

6 weeks

12 weeks

↑ Favourable mrTRG

↑ pCR, pT0

↑ mrT-downstaging

↔ Post-operative complications

Clinical benefit
Balancing survival with quality of life

- Short term toxicities
- Permanent sequelae
- Long term complications

Clinical benefit

- Local recurrence
- Distant metastases
- Cure

Permanent sequelae
Acknowledgement

National Health Service funding to the National Institute for Health Research Biomedical Research Centre