Which neo-adjuvant treatment in rectal cancer?

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Disclosures

• None
Which neoadjuvant treatment

• What is the standard of care?

• Intensification of concurrent CRT

• Addition of NAC to standard of care?

• Can we use NAC instead of (C)RT?
## NICE and ESMO guidelines

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>NICE</th>
<th>ESMO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk</strong></td>
<td>A threatened (&lt;1 mm) or breached resection margin or low tumours encroaching onto the inter-sphincteric plane or with levator involvement</td>
<td>cT3 mrf+ cT4 with invasion of organs not readily resectable</td>
</tr>
<tr>
<td><strong>Moderate risk</strong></td>
<td>Any cT3b or greater, in which the potential surgical margin is not threatened or any suspicious lymph node not threatening the surgical resection margin or the presence of extramural vascular invasion</td>
<td>cT2 very low cT3 (b) c/d mrf- N1-2, EMVI + limited cT4 (vaginal or peritoneal involvement) N+</td>
</tr>
<tr>
<td><strong>Low risk</strong></td>
<td>T1 or cT2 or cT3a and no lymph node involvement</td>
<td>cT1-T2, some early T3a(-b) and clear mrf N0</td>
</tr>
</tbody>
</table>

www.nice.org.uk  
Annals of Oncology 2013  
24 S6 vi81-88
NICE and ESMO guidelines

Pelvic MRI

Risk of local recurrence

Early (good) → SCPRT
Intermediate (bad) → CRT
Advanced (ugly) → Surgery
Standard of care

• Avoid radiotherapy in good prognosis patients

• 25Gy in five fractions for intermediate risk
  – with delay is an option for frail “unfit” patients

• Fluoropyrimidine CRT (5FU/Capecitabine)
  – Radiotherapy dose varies
  – Intermediate and High risk
CAO/ARO/AIO-94 Trial
JCO 2012 30:1926-1933

- Distant metastases remains a big problem
Which neoadjuvant treatment

• What is the standard of care?

• **Intensification of concurrent CRT**

• Addition of NAC to standard of care?

• Can we use NAC instead of (C)RT?
## Phase III trials Investigating Oxaliplatin - DFS

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Result</th>
<th>DFS end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAO/ARO/AIO-04</td>
<td>1236</td>
<td><strong>5FU</strong> CRT + Adj 5FU vs Ox <strong>5FU</strong> CRT + Adj Ox5FU</td>
<td>+ve Primary end point 4.7% improvement (Lancet Oncology in press)</td>
</tr>
<tr>
<td>NSABP R04</td>
<td>1606</td>
<td>PVI 5FU vs Cape +/- Oxaliplatin</td>
<td>Secondary end point Approx 5% (presented)</td>
</tr>
<tr>
<td>ACCORD 12</td>
<td>598</td>
<td>Cape CRT 45 vs Ox Cap <strong>50</strong> Non trial adj chemo (minority)</td>
<td>Secondary end point 4.8% improvement for +Ox</td>
</tr>
<tr>
<td>STAR – 01</td>
<td>747</td>
<td>PVI 5FU CRT +/- Ox5FU Non trial adjuvant 5FU recommended</td>
<td>Data awaited</td>
</tr>
<tr>
<td>PETTAC 6</td>
<td>1090</td>
<td>Cape CRT + adj cape vs Cape Ox CRT + adj Cape Ox</td>
<td>-ve Primary end point -0.6% for +Ox (abstract)</td>
</tr>
</tbody>
</table>
CAO/ARO/AIO-4 Trial n=1265

<table>
<thead>
<tr>
<th></th>
<th>5FU RT</th>
<th>Ox 5FU RT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>R0 resection</td>
<td>95%</td>
<td>95%</td>
<td>NS</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>4.6%</td>
<td>2.9%</td>
<td></td>
</tr>
<tr>
<td>Distant mets</td>
<td>22.4%</td>
<td>18.5%</td>
<td></td>
</tr>
<tr>
<td>3yr DFS</td>
<td>71.2%</td>
<td>75.9%</td>
<td>HR 0.79 (0.64-0.98)</td>
</tr>
<tr>
<td>3yr OS</td>
<td>88.0%</td>
<td>88.7%</td>
<td>HR 0.96 (0.72-1.26)</td>
</tr>
<tr>
<td></td>
<td>5FU RT</td>
<td>Ox 5FU RT</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>Acute Gd3/4</td>
<td>20%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>GI Gd 3/4</td>
<td>15%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy Interruption</td>
<td>7%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy dose reduction</td>
<td>3%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Concurrent chemo dose</td>
<td>21%</td>
<td>15%</td>
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</tbody>
</table>

CAO/ARO/AIO-4 Trial n=1265

Phase III trials investigating Ox – pCR

<table>
<thead>
<tr>
<th>Trial</th>
<th>5FU</th>
<th>Oxs5FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIO</td>
<td></td>
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<tr>
<td>R04</td>
<td></td>
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<tr>
<td>ACCORD 12</td>
<td></td>
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<tr>
<td>PETTAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAR 01</td>
<td></td>
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</tbody>
</table>

p-values:
- p=0.03
- p=0.14
- p=0.09
- p=0.31
- NS
ARISTOTLE – NCRI phase III

MRI defined locally advanced rectal cancer
No metastases

Declare proposed post-op chemotherapy policy

N =600

Capectabine CRT
(Cape 900mg/m2 5 days/week)

SURGERY (8-10 weeks)
Proposed post-op policy

Irinotecan Capecitabine CRT
(Capecitabine 650mg/m2 5d/wk
Irinotecan 60mg/m2 wk 1-4)

SURGERY (8-10 weeks)
Proposed post-op policy

Primary end point – 3yr DFS
Summary of Phase III CRT intensification trials

• No change in standard of care

• Phase III published data awaited

• Problems with interpretation
  - Differences in the “platform”
    • RT dose; 5FU between arms
  - Trial design
    • Mix of CRT + adjuvant and CRT intensification
  - Case mix
    • Lack of MRI; a lot of intermediate risk
  - Experimental arms
    • Toxicity and radiotherapy compliance
Which neoadjuvant treatment

- What is standard of care?
- Intensification of concurrent CRT
- Addition of NAC to standard of care?
- Can we use NAC instead of (C)RT?
Rationale for NAC

• Advantages
  - Full dose systemic chemotherapy earlier
  - Reduced toxicity and better compliance
  - Earlier reversal of defunctioning stoma
  - “Platform” for future biomarker and novel therapies

• Disadvantages
  - Selection – risk of overtreatment
  - Delay to curative surgery
  - No phase III trial evidence
Neoadjuvant Ct Plus Ct-rt In MRI Defined High Risk Rectal Cancer: The Panex Experience
Scalfani et al ASCO 2014
# Neoadjuvant Ct Plus Ct-rt In MRI Defined High Risk Rectal Cancer: The Panex Experience

Scalfani et al ASCO 2014

<table>
<thead>
<tr>
<th>ITT population (N=269)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response after NACT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>11</td>
<td>4.1</td>
</tr>
<tr>
<td>Partial response</td>
<td>157</td>
<td>58.4</td>
</tr>
<tr>
<td>Stable disease</td>
<td>76</td>
<td>28.3</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3</td>
<td>1.1</td>
</tr>
<tr>
<td>Unknown/Not assessable</td>
<td>22</td>
<td>8.2</td>
</tr>
<tr>
<td><strong>Response after CRT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>31</td>
<td>11.5</td>
</tr>
<tr>
<td>Partial response</td>
<td>183</td>
<td>68.0</td>
</tr>
<tr>
<td>Stable disease</td>
<td>30</td>
<td>11.2</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5</td>
<td>1.9</td>
</tr>
<tr>
<td>Unknown/Not assessable</td>
<td>20</td>
<td>7.4</td>
</tr>
<tr>
<td><strong>Median time (wks) from CRT to surgery (range)</strong></td>
<td>6.6</td>
<td>3.4 - 44.6</td>
</tr>
</tbody>
</table>

**Surgery**
- R0 resection | 233 | 86.6 |
- R1 resection | 7 | 2.6 |
- R2 resection | 4 | 1.5 |
- Not completed | 5 | 1.9 |
- Not performed | 20 | 7.4 |
- AR/APR (n=244) | 140/104 | 57.4/42.6 |

**Pathologic complete response**
- 48 | 17.8 |

**Tumour downstaging at surgery (n=244)**
- T downstaging | 137 | 56.1 |
- N downstaging | 135 | 55.3 |
- T or N downstaging | 195 | 79.9 |

**Median time (wks) from surgery to ACT (range)**
- 8.0 | 4.1 - 26.4 |

**After NAC**
- **CR** 4.1%
- **PR** 58.4%

**pCR 17.8%**
Neoadjuvant Ct Plus Ct-rt In MRI Defined High Risk Rectal Cancer: The Panex Experience

Scalfani et al ASCO 2014

5-yr local PFS 94.6%
95% CI: 91.7% - 97.5%

5-yr PFS 69.7%
95% CI: 64.2% - 75.2%

* Scalfani et al. ASCO 2014; abstract 3575
<table>
<thead>
<tr>
<th></th>
<th>NAC n=56</th>
<th>Adjuvant n=52</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>14.3%</td>
<td>13.5%</td>
<td>NS</td>
</tr>
<tr>
<td>R0</td>
<td>86%</td>
<td>87%</td>
<td>NS</td>
</tr>
<tr>
<td>Gd 3,4 during chemo</td>
<td>19%</td>
<td>54%</td>
<td>P=0.0004</td>
</tr>
<tr>
<td>Gd 3/4 during CRT</td>
<td>23%</td>
<td>29%</td>
<td>NS</td>
</tr>
<tr>
<td>RT compliance</td>
<td>85%</td>
<td>80%</td>
<td>NS</td>
</tr>
</tbody>
</table>
Spanish GCR-3 phase II
Fernandez-Martos Annals of Oncology 2015 epub May 8

Local recurrence

Distant recurrence

Log-rank $P=0.3470$

Log-rank $P=0.8489$
RAPIDO Ph III Trial  n=885

RT+CAPE

5.5 weeks  6-8 weeks

5x5

CAPE + OXALIPLATIN

6-8 weeks  24 weeks

MRI defined cT4a,cT4b,cN2, EMVI+, Lat LN+

1 week  1 week  18 weeks  2-4 weeks

DFS at 3 years improve by 10% from 50 to 60%

n=650
Proposed CREATE trial
UK, Australia, Sweden

A. Standard arm
Operable rectal cancer on pretreatment MRI >T3b or N+ or EMVI+

Randomise

B. Experimental arm
12 weeks neoadjuvant OxMdG or CapOx chemo

MDT defined:-
Surgery/CRT/SCRT

12 weeks post op OxMdG or CapOx chemo

MDT defined:-
Surgery/CRT/SCRT

Co primary end point: Distant mets and 3 yr DFS
Stratified by MDT defined pelvic treatment
Which neoadjuvant treatment

• What is standard of care?

• Intensification of concurrent CRT

• Addition of NAC to standard of care?

• Can we use NAC instead of (C)RT?
## Neoadjuvant chemotherapy prior to Surgery

*Sclafani F, Cunningham D. Future Oncol 2014; 10:2243-2257.*

<table>
<thead>
<tr>
<th>Author</th>
<th>No</th>
<th>Patient selection</th>
<th>Poor risk features</th>
<th>Treatment</th>
<th>R0 rate</th>
<th>pCR Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schrag et al. (2014)</td>
<td>32</td>
<td>T2N1, T3 any N, No N2, No lower third</td>
<td>T4:0% CRM:0%</td>
<td>FOLFOX-BEV</td>
<td>100%</td>
<td>25%</td>
</tr>
<tr>
<td>Fernandez-Martos et al. (2014)</td>
<td>46</td>
<td>T3 midd rectum, no CRM+</td>
<td>T4:0% CRM:0%</td>
<td>CAPOX-BEV</td>
<td>95,6%</td>
<td>20%</td>
</tr>
<tr>
<td>Uehara et al. (2013)</td>
<td>32</td>
<td>T3c-d-T4, N2, CRM+</td>
<td>T4a: 28% T4b: 31% CRM: NR</td>
<td>CAPOX-BEV</td>
<td>84,3%</td>
<td>12,5%</td>
</tr>
<tr>
<td>Ishii et al. (2010)</td>
<td>26</td>
<td>T3-4 any N, within 12 cm of anal verge</td>
<td>T4:12% CRM NR</td>
<td>IFL</td>
<td>100%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Cercek et al. (2010)</td>
<td>6</td>
<td>T2-3, N1</td>
<td>T4: 0% CRM NR</td>
<td>FOLFOX</td>
<td>100%</td>
<td>33%</td>
</tr>
</tbody>
</table>
PROSPECT trial n=1060

T2N1, T3N0,T3N1, T1-3 N2
DRE, CT and either ERUS/pelvic MRI
Sphincter sparing surgery planned

Co primary end points ph III
- Time to LR
- DFS
mFOLFOX6 Following Chemoradiation - Tumor Response and Surgical Complications in Patients With Locally Advanced Rectal Cancer (NCT00335816)

SG1: CI 5-FU + XRT, Rest, TME
N=60

SG2: CI 5-FU + XRT, Rest, mFOLFOX-6 (2 cycles), Rest, TME
N=67

SG3: CI 5-FU + XRT, Rest, mFOLFOX-6 (4 cycles), Rest, TME
N=67

SG4: CI 5-FU + XRT, Rest, mFOLFOX-6 (6 cycles), Rest, TME
N=65

↓ XRT - Radiotherapy 5 days/week, total 45 Gy with minimum boost of 5.4 Gy
■ CI 5-FU - Continuous infusion 5-fluorouracil 225 mg/m²/day, 7 days/week during radiation therapy
☐ mFOLFOX-6 - 2 week cycles of LV 200 mg/m² or 400 mg/m² (2h infusion), oxaliplatin 85 mg/m² (2h infusion), 5-FU 400 mg/m² (bolus), and a 5-FU 2,400 mg/m² (46h infusion)
* Interim Evaluation - by proctoscopic exam; TME performed if stable or progressive disease
TME - Total Mesorectal Excision

## NCT00335816 - Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>SG1</th>
<th>SG2</th>
<th>SG3</th>
<th>SG4</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Patients</strong></td>
<td>60</td>
<td>67</td>
<td>67</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>57 (34-87)</td>
<td>56 (32-84)</td>
<td>56 (21-76)</td>
<td>58 (33-72)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>23 (38%)</td>
<td>30 (45%)</td>
<td>30 (45%)</td>
<td>24 (37%)</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>ECOG 0</strong></td>
<td>55 (92%)</td>
<td>60 (90%)</td>
<td>56 (84%)</td>
<td>51 (78%)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Clinical Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>II</td>
<td>19 (32%)</td>
<td>12 (18%)</td>
<td>15 (22%)</td>
<td>18 (28%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>41 (68%)</td>
<td>55 (82%)</td>
<td>57 (78%)</td>
<td>47 (72%)</td>
<td></td>
</tr>
<tr>
<td><strong>Local Staging</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>ERUS</td>
<td>57 (95%)</td>
<td>55 (82%)</td>
<td>60 (89%)</td>
<td>47 (72%)</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>7 (12%)</td>
<td>15 (22%)</td>
<td>16 (23%)</td>
<td>26 (40)</td>
<td></td>
</tr>
<tr>
<td><strong>Distance Anal Verge (cm)</strong></td>
<td>6.9 (3.0)</td>
<td>6.2 (3.1)</td>
<td>7.1 (2.9)</td>
<td>6.7 (3.4)</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Size (cm)</strong></td>
<td>4.6 (1.5)</td>
<td>5.0 (2.0)</td>
<td>4.6 (1.8)</td>
<td>5.3 (2.1)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

NCT00335816 - Pathologic Tumor Response

Conclusions

• No change in Standard of Care

• Selection to avoid overtreatment

• NAC approaches ph II data promising

• Phase III trial data is required
FOWARC Trial
Deng et al ASCO 2015

Stage II/III
N-165
Each arm

De Gramont×5 cycles
RT

mFOLFOX6×5 cycles
RT

mFOLFOX6×4-6 cycles
S

De Gramont×7 cycles
S

mFOLFOX6×7 cycles
S

mFOLFOX6×6-8 cycles

pCR
19/133
14%

40/143
28%

9/148
6%