MANAGEMENT OF EARLY RECTAL CANCER: Any role for adjuvant chemotherapy?

Andrés Cervantes
Professor of Medicine
CONFLICT OF INTEREST DISCLOSURE

Sub-title

Employment: None; Stock Ownership: None

Consultant or Advisory Role: Merck Serono, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda, Astelas.

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Speaking: Merck Serono, Roche, Angem, Bayer, Servier, Foundation Medicine. Grant support: Merck Serono, Roche.

Others: Executive Board member of ESMO, Chair of Education ESMO, General and Scientific Director INCLIVA, Associate Editor: Annals of Oncology and ESMO Open, Editor in chief: Cancer Treatment Reviews.
CURRENTS CONCEPTS IN RECTAL CANCER DIAGNOSIS AND THERAPY

- TME surgery
- Optimal staging by MRI
- Pathological assessment of the quality of surgery
- Preoperative radiation or chemoradiation
- Integration of knowledge in a multidisciplinary team approach
- Selective approach for preoperative treatment
- Non surgical “watch and see” approach for patients achieving a cCR
CURRENT APPROACH TO RECTAL CANCER

- MRI Staging
- MDT discussion
- Preoperative treatment if indicated
- TME Surgical resection vs wait and see approach
- Pathology assessment and estimation of risk
- Postoperative chemotherapy if indicated
Distant metastases 4x greater risk than local recurrence

CLINICAL PRACTICE GUIDELINES

Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

R. Glynne-Jones¹, L. Wyrwicz², E. Tiret³, G. Brown⁵, C. Rödel⁶, A. Cervantes⁷ & D. Arnold⁸, on behalf of the ESMO Guidelines Committee.

ESMO Guidelines

“....... pelvic MRI for all tumours, including the earliest ones, is required in order to select patients for preoperative treatment and extent of surgery.”


ESMO PRECEPTORSHIP PROGRAM
Afectación de la fascia mesorectal
Invasión venosa extramural
Afectación del puborectal
ESMO Rectal Cancer Guidelines: Staging

Key Messages

SoC
TME alone
AVOID RT

TME alone if high quality or plus SCPRT/CRT

SCPRT or CRT
Then TME

CRT or SCPRT + FOLFOX then TME

THE ROLE OF ADJUVANT CHEMOTHERAPY IN LOCALISED RECTAL CANCER: WHAT IS THE EVIDENCE WE HAVE?

• The pre-TME/preoperative RT or ChRT data
• The TME/preoperative RT or ChRT data
• How to integrate ChT in patients with locally advanced disease?
THE ROLE OF ADJUVANT CHEMOTHERAPY IN LOCALISED RECTAL CANCER: WHAT IS THE EVIDENCE WE HAVE IN THE PRE-TME PRE-RT/CHRT PREOPERATIVE ERA?

- American Intergroup
- Quasar
- Japanese Society of Colon and Rectal Meta-analysis on individual data
- Cochrane Meta-analysis on individual data
THE ROLE OF ADJUVANT CHEMOTHERAPY IN LOCALISED RECTAL CANCER: WHAT IS THE EVIDENCE WE HAVE?

- The pre-TME/preoperative RT or ChRT data
- The TME/preoperative RT or ChRT data
- How to integrate ChT in patients with locally advanced disease?
THE ROLE OF ADJUVANT CHEMOTHERAPY IN LOCALISED RECTAL CANCER: WHAT IS THE EVIDENCE WE HAVE IN THE TME/PREOPERATIVE RT OR CHRT ERA?

• Chronicle trial
• Proctor/script trial
• Meta-analysis by Breugom on individual data from 4 trials and 1200 pts
• Adore trial
• CAO/ARO/AIO-04 trial
PROCTOR/SCRIPT TRIAL: ASSESSING THE VALUE OF ADJUVANT CHEMOTHERAPY IN THE TREATMENT OF RECTAL CANCER AFTER PREOPERATIVE CHEMORADIATION OR 5X5 RADIATION

- Target population 840 pts
- Primary end point: OS at 5 years improved from 60 to 70%
- Accrued nr. Patients 437 over 14 years
- Underpowered to detect any potential benefit of Chemotherapy
- 5 year OS for observation: 79.2%
- 5 year OS for adj therapy: 80.4%

- HR for DFS: 0.80 (95% CI: 0.60-1.07; p:0.13)
- HR for OS: 0.93 (95% CI: 0.61-1.29; p:0.73)

Breugom et al, Ann Oncol 2015; 26:696-701
WHAT IS THE EVIDENCE WE HAVE?
The Breugom’s Meta-analysis

## Adding Oxaliplatin to 5-FU based adjuvant therapy in localised colon/rectal cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Control</th>
<th>Exp.</th>
<th>Stage</th>
<th>DFS HR P value</th>
<th>OS HR P value</th>
<th>Absolute Gain in OS</th>
<th>G3 Neurotox</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOSAIC¹</td>
<td>2246</td>
<td>FULV2</td>
<td>FOLFOX4</td>
<td>II/III</td>
<td>0.80 0.003</td>
<td>0.84 0.046</td>
<td>4.2% at 6 y stage III</td>
<td>12%</td>
</tr>
<tr>
<td>NSABP-C07²</td>
<td>2407</td>
<td>FULV Roswell</td>
<td>FLOX</td>
<td>II/III</td>
<td>0.80 0.0034</td>
<td>0.82 0.002</td>
<td>2.7 at 5 y Stage III</td>
<td>8.2%</td>
</tr>
<tr>
<td>XELOXA³</td>
<td>1886</td>
<td>FULV Mayo</td>
<td>CAPEOX</td>
<td>III</td>
<td>0.80 0.0038</td>
<td>0.83 0.04</td>
<td>6 % at 7 y</td>
<td>11%</td>
</tr>
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Adding Oxaliplatin to 5-FU based adjuvant therapy in localised colon/rectal cancer

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<tr>
<td>MOSAIC(^1)</td>
<td>224</td>
<td>FULV2</td>
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<td>0.84 0.046</td>
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<td>12%</td>
</tr>
<tr>
<td>NSABP-C07(^2)</td>
<td>240</td>
<td>FULV Roswell</td>
<td>FLOX</td>
<td>II/III</td>
<td>0.80 0.0034</td>
<td>0.82 0.002</td>
<td>2.7 at 5 y Stage III</td>
<td>8.2%</td>
</tr>
<tr>
<td>XELOXA(^3)</td>
<td>188</td>
<td>FULV Mayo</td>
<td>CAPEOX</td>
<td>III</td>
<td>0.80 0.0038</td>
<td>0.83 0.04</td>
<td>6 % at 7 y</td>
<td>11%</td>
</tr>
<tr>
<td>AIO04(^4)</td>
<td>123</td>
<td>FU</td>
<td>mFOLFOX6</td>
<td>II/III</td>
<td>0.79 0.030</td>
<td>0.96 NS</td>
<td>0.7 at 3 y</td>
<td>9%</td>
</tr>
<tr>
<td>NSABP R04(^5)</td>
<td>128</td>
<td>FU/Cape</td>
<td>+ Oxali</td>
<td>II/III</td>
<td>0.94 NS</td>
<td>0.94 NS</td>
<td>NR</td>
<td>6%</td>
</tr>
<tr>
<td>PETACC6(^6)</td>
<td>898</td>
<td>Cape</td>
<td>+ Oxali</td>
<td>II/III</td>
<td>1.04 NS</td>
<td>NR</td>
<td>NR</td>
<td>8%</td>
</tr>
</tbody>
</table>

THE ROLE OF ADJUVANT CHEMOTHERAPY IN LOCALISED RECTAL CANCER: WHAT IS THE EVIDENCE WE HAVE?
THE ADORE TRIAL

Rectal Cancer patients who completed preoperative Long course chemoradiation and Surgery with free margins ypT3-4N0 or anyTN1-2

1:1 Randomization

BOLUS 5FU-LV
Mayo Clinic Schedule

FOLFOX

Hong YS et al. Lancet Oncol 2014
THE ROLE OF ADJUVANT CHEMOTHERAPY IN LOCALISED RECTAL CANCER: WHAT IS THE EVIDENCE WE HAVE?
THE ADORE TRIAL

- No observational arm
- Randomised phase II trial 80% Power
- Unilateral hypothesis
- Target population 320 pts
- Primary end point: DFS at 3 years improved by 8% from 70 to 78%
- Accrued nr. Patients 322 over 3.5 years

Hong YS et al. Lancet Oncol 2014
ADORE TRIAL: ADJUVANT CHEMOTHERAPY IN STAGE II/III RECTAL CANCER AFTER PREOPERATIVE CHEMORADIATION
DISEASE FREE AND OVERALL SURVIVAL

Hong YS et al. Lancet Oncol 2014
THE ROLE OF ADJUVANT CHEMOTHERAPY IN LOCALISED RECTAL CANCER: WHAT IS THE EVIDENCE WE HAVE?

- The pre-TME/preoperative RT or ChRT data
- The TME/preoperative RT or ChRT data
- How to integrate ChT in patients with locally advanced disease?
  - For R0 resection
  - For cCR
NEOADJUVANT CT PLUS CT-RT VERSUS CT-RT FOLLOWED BY SURGERY AND ADJUVANT CT IN MRI DEFINED HIGH RISK RECTAL CANCER: THE PHASE II RANDOMIZED VALENCIAN EXPERIENCE

MRI defined Locally advanced Rectal Cancer patients N=108

1:1 Randomization

Concurrent CRT with CAPOX

CAPOX x 4

Concurrent CRT with CAPOX

S

Adjuvant CAPOX

POLISH PHASE III TRIAL CRT VS 5X5 AND FOLFOX

- RT+5FU LV wk1,5
- Ox weekly

Locally advanced
Unresectable
Locally recurrent

Primary end point R0 resection

5x5

FOLFOX 4 x 3

- MRI defined 66%
- Oxaliplatin became optional
- Short duration FOLFOX
- Weekly Ox single agent wk 2,3,4

POLISH TRIAL: OVERALL SURVIVAL FAVORS PREOPERATIVE SCPRT + CHRT VERSUS PREOPERATIVE CHEMORADIATION IN LOCALLY ADVANCED RECTAL CANCER

HR: 0.73 p: 0.046

THE WAY FORWARD: THE PHASE III RANDOMIZED RAPIDO TRIAL

MRI defined Locally advanced Rectal Cancer patients N=920

1:1 Randomization

CRT with CAPECITABINE Week 1-6

Surgery Week 12

Adjuvant CT OPTIONAL

5x5 RT Week 1

Neoadjuvant XELOX x6 Week 3-16

Surgery Week 24-28

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

PI: Prof. C. van de Velde
THE ROLE OF ADJUVANT CHEMOTHERAPY IN LOCALISED RECTAL CANCER: CONCLUSIONS

- Adjuvant Chemotherapy is not standard of care for all localized rectal cancer patients
- Adjuvant Chemotherapy should be considered for patients at risk after direct surgery without neoadjuvant therapy
- Adjuvant Chemotherapy should be also considered after neoadjuvant Chemoradiation for patients with stage ypIII and high risk stage ypII. LoE: II GoR: C
- The decision on postoperative Chemotherapy (FU alone or combined with oxaliplatin) should be risk balanced, taking into account both the predicted toxicity for a particular patient and the risk of relapse, and should be made jointly by the individual and the clinician.
FACTORS FAVORING HIGHER ypCR Rate IN RECTAL CANCER

- **Clinical Stage**
  - T1: 57%
  - T2: 28%
  - T3: 16%
  - T4: 12%

- **Interval between CRT and surgery**
  - Patients undergoing surgery ≥8 weeks after CRT had a higher pCR rate (30.8% vs. 16.5%, p = 0.03) and decreased 3-year local recurrence rate (1.2% vs. 10.5%, p = 0.04).

## STAGE II/III RECTAL CANCER TREATED WITH PRE-OP FLUOROPYRIMIDINES + RT +/- OXALIPLATIN: ypCR Rate

<table>
<thead>
<tr>
<th>Study</th>
<th># Pts</th>
<th>ChemoRT Regimen</th>
<th>ypCR Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD 12 (JCO 2010)</td>
<td>291</td>
<td>Cape+RT</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>293</td>
<td>Cape + Oxali 50mg/m2 wkly+RT</td>
<td>19 (p=0.09)</td>
</tr>
<tr>
<td>STAR-01 (JCO 2011)</td>
<td>379</td>
<td>FU CI+RT</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>368</td>
<td>FU CI + Oxali 60mg/m2 wkly+RT</td>
<td>16</td>
</tr>
<tr>
<td>German AIO-04 (Lancet 2012)</td>
<td>623</td>
<td>FU CI+RT</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>613</td>
<td>FU CI + Oxali 50mg/m2 wkly+RT</td>
<td>17 (p=0.038)</td>
</tr>
<tr>
<td>PETAAC-6 (PASCO, 2013)</td>
<td>547</td>
<td>Cape+RT</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>547</td>
<td>Cape + Oxali 50mg/m2 wkly+RT</td>
<td>13 (p=0.031)</td>
</tr>
<tr>
<td>NSABP R-04 (PASCO, 2012)</td>
<td>636</td>
<td>FU/Cape+RT</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>640</td>
<td>FU/Cape + Oxali 50mg/m2 wkly+RT</td>
<td>20 (p=0.42)</td>
</tr>
</tbody>
</table>
TOTAL NEOADJUVANT TREATMENT VS PREOPERATIVE NEOADJUVANT CRT

811 Nonmetastatic resectable LARC evaluated in surgical clinic

- 13 Surgery alone (1%)\textsuperscript{a} 
- 320 chemoRT with adjuvant CT 
- 410 TNT 
- 68 Chemotherapy alone

Cercek A, et al. JAMA Oncol 2018; 4:e180071
QRT NEOADYUVANTE Y CIRUGÍA VS TRATAMIENTO NEOADYUVANTE TOTAL: DIFERENCIAS EN RCp

### Table 2. Responses to Treatment

<table>
<thead>
<tr>
<th>Treatment Groupa</th>
<th>All Patients, No.</th>
<th>All Patients, Sustained cCR, No. (%)b</th>
<th>Surgery Within 12 Months, No.</th>
<th>Surgery Within 12 Months, pCR, No. (%)b</th>
<th>Complete Response (pCR and Sustained cCR) at 12 Months, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChemoRT with planned adjuvant chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>94</td>
<td>9 (9.6)</td>
<td>82</td>
<td>14 (17.1)</td>
<td>23 (24.5)</td>
</tr>
<tr>
<td>Stage III</td>
<td>226</td>
<td>10 (4.4)</td>
<td>214</td>
<td>35 (16.4)</td>
<td>45 (19.9)</td>
</tr>
<tr>
<td>Total</td>
<td>320</td>
<td>19 (5.9)</td>
<td>296</td>
<td>49 (16.6)</td>
<td>68 (21.3)</td>
</tr>
<tr>
<td>TNT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>43</td>
<td>23 (53.5)</td>
<td>20</td>
<td>0</td>
<td>23 (53.5)</td>
</tr>
<tr>
<td>Stage III</td>
<td>265</td>
<td>44 (16.6)</td>
<td>215</td>
<td>43 (20.0)</td>
<td>87 (32.8)</td>
</tr>
<tr>
<td>Total</td>
<td>308</td>
<td>67 (21.8)</td>
<td>235</td>
<td>43 (18.3)</td>
<td>110 (35.7)</td>
</tr>
</tbody>
</table>

Cercek A, et al. JAMA Oncol 2018; 4:e180071
PROLONGING NEOADJUVANT CT IN RECTAL CANCER AFTER CRT

### PROSPECTIVE STUDIES ASSESSING ORGAN PRESERVATION IN EARLY RECTAL CANCER AFTER CRT FOLLOWED BY LOCAL EXCISION AND WATCH AND WAIT

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Therapy</th>
<th>Timing of surgery (weeks)</th>
<th>Organ Preservation</th>
<th>All recurrence (local + distant)</th>
<th>Isolated local recurrence</th>
<th>Salvage surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOSOG Z6041</td>
<td>79</td>
<td>CRT</td>
<td>9-13</td>
<td>72 (91%)</td>
<td>8/79 (10%)</td>
<td>3/79 (4%)</td>
<td>2/3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxaliplatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARTS</td>
<td>55</td>
<td>CRT</td>
<td>8-10</td>
<td>41/55 (74%)</td>
<td>7/55 (12%)</td>
<td>2/55 (3%)</td>
<td>2/2</td>
</tr>
<tr>
<td>TREC</td>
<td>27</td>
<td>SCRT</td>
<td>8-10</td>
<td>19 (70%)</td>
<td>3/27 (11%)</td>
<td>1 (4%)</td>
<td>0/1*</td>
</tr>
<tr>
<td>TREC</td>
<td>61</td>
<td>SCRT</td>
<td>8-10</td>
<td>56 (92%)</td>
<td>9/61 (14%)</td>
<td>4 (6%)</td>
<td>-</td>
</tr>
<tr>
<td>GRECCAR 2</td>
<td>73</td>
<td>CRT</td>
<td>13</td>
<td>47 (64%)</td>
<td>11/73 (15%)</td>
<td>5 (5%)</td>
<td>4/5 *</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>295</td>
<td></td>
<td></td>
<td><strong>235 (79%)</strong></td>
<td><strong>38 (12%)</strong></td>
<td><strong>15 (5%)</strong></td>
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LONG TERM OUTCOMES FOR RECTAL CANCER PATIENTS AND cCR AFTER NEOADJUVANT TREATMENT WITHOUT SURGERY: “WACHT AND WAIT” LOCAL AND DISTANT RELAPSES AT 5 YEARS

MEDIAN FOLLOW-UP 3.5 YEARS
N: 880

Van der Valk MJM et al. Lancet 2018; 391:2537-2545
LONG TERM OUTCOMES FOR RECTAL CANCER PATIENTS AND cCR AFTER NEOADJUVANT TREATMENT WITHOUT SURGERY OS AND DFS AT 5 YEARS

Van der Valk MJM et al. Lancet 2018; 391:2537-2545
Conclusions

1. MULTIDISCIPLINARY DISCUSSION ESSENTIAL
2. DEFINE AIMS OF THERAPY AND OPTIMAL TREATMENT
3. SELECTIVE APPROACH ACCORDING TO MRI IF R0 RESECTION IS THE AIM
   - T1-T3a-b. SURGERY ALONE
   - LOW LOCAL RISK I: 5X5 RT VS SURGERY ALONE
   - IF MODERATE LOCAL RISK: RT 5x5 VS LONG COURSE CRT
Conclusions-2

- TREAT ACCORDING TO AIM: R0 RESECTION vs cCR
- IF AIMING AT cCR A MORE INTENSIVE TREATMENT COULD BE JUSTIFIED AS AN EXPERIMENTAL APPROACH
- IN HIGH RISK MRI DEFINED PATIENTS:
  - MESORECTAL FASCIA INVOLVED OR CLOSED, EMVI+, N2, o LATERAL NODES.
  - A MORE INTENSIVE MULTIMODAL APPROACH MAY BE JUSTIFIED
  - TOTAL NEOADJUVANT TREATMENT SHOULD BE CONSIDERED AS EXPERIMENTAL
Thank you