The role of adjuvant chemotherapy in localized rectal cancer

Andrés Cervantes
Disclosures

Consulting and advisory services, speaking or writing engagements, public presentations:

Servier, Merck Serono, Amgen, Roche, Lilly, Bayer, Novartis, Takeda, Beigene

Direct research support to the responsible project lead:

Servier, Roche, Genentech, Bayer, Janssen, Merck Serono, Medimmune
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
Improvement in rectal cancer treatment outcomes in Norway

Distant metastases 4x greater risk than local recurrence


ESMO Preceptorship Program
<table>
<thead>
<tr>
<th>Risk group</th>
<th>TN substage</th>
<th>Therapeutic options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very early</td>
<td>cT1 sm1 (-2?) N0</td>
<td>Local excision (TEM). If poor prognostic signs (sm ≥ 2, high grade, V1), resection (TME) (or possibly CRT)</td>
</tr>
<tr>
<td>Early (good)</td>
<td>cT1-2; cT3a (b) if middle or high, N0 (or cN1 if high), mrf-, no EMVI</td>
<td>Surgery (TME) alone. If poor prognostic signs (crm+, N2) add postop CRT or CT&lt;sup&gt;a&lt;/sup&gt;. (CRT with evaluation, if cCR, wait-and-see, organ preservation)</td>
</tr>
<tr>
<td>Intermediate (bad)</td>
<td>cT2 very low, cT3mrf- (unless cT3a(b) and mid- or high rectum, N1-2, EMVI+, limited cT4aN0)</td>
<td>Preop RT (5 × 5 Gy) or CRT followed by TME. (if CRT and cCR, wait-and-see in high risk patients for surgery)</td>
</tr>
<tr>
<td>Advanced (ugly)</td>
<td>cT3mrf+, cT4a,b, lateral node+</td>
<td>Preop CRT followed by surgery (TME + more extended surgery if needed due to tumour overgrowth). 5 × 5 Gy with a delay to surgery in elderly or in patients with severe comorobidity who cannot tolerate CRT</td>
</tr>
</tbody>
</table>
CURRENT APPROACH TO RECTAL CANCER

- MRI Staging
- MDT discussion
- Preoperative treatment if indicated
- TME Surgical resection
- Pathology assessment and estimation of risk
- Postoperative chemotherapy if indicated
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 American Intergroup* Pooled Analysis

The graph shows survival rates over time for different treatment regimens following surgery.

- Surgery (S) alone
- S + Radiation (RT)
- S + Chemotherapy (CT)
- S + RT + Bolus CT
- S + RT + Infusion CT
- S + RT + Bolus CT (INT 0114)

The $P$ value is less than 0.001.
THE ROLE OF ADJUVANT CHEMOTHERAPY IN LOCALISED RECTAL CANCER: WHAT IS THE EVIDENCE WE HAVE?  
The QUASAR TRIAL

<table>
<thead>
<tr>
<th>UK QUASAR uncertain indication trial</th>
<th>5yr survival</th>
<th>5 yr recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemo</td>
<td>No chemo</td>
</tr>
<tr>
<td>Approx 30% rectal.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole cohort</td>
<td>80.3%</td>
<td>77.4%</td>
</tr>
<tr>
<td>Rectal subgroup</td>
<td>p=0.05</td>
<td></td>
</tr>
</tbody>
</table>

WHAT IS THE EVIDENCE WE HAVE?
The Japanese Society of Cancer of Colon and Rectum Meta-analysis on UFT trials

THE ROLE OF ADJUVANT CHEMOTHERAPY IN LOCALISED RECTAL CANCER: WHAT IS THE EVIDENCE WE HAVE?
The Cochrane Meta-analysis

Postoperative adjuvant chemotherapy in rectal cancer operated for cure. (Review)

Petersen SH, Harling H, Kirkeby LT, Wille-Jørgensen P, Mocellin S

THE COCHRANE COLLABORATION®
Figure 8. Forest plot of comparison: 1 Adjuvant vs No Adjuvant ALL, outcome: 1.2 Disease Free Survival (DFS).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grage 1981</td>
<td>-0.562</td>
<td>0.278</td>
<td>2.4%</td>
<td>0.57 [0.33, 0.98]</td>
<td>1981</td>
</tr>
<tr>
<td>Fisher 1988 (NSABP)</td>
<td>-0.342</td>
<td>0.121</td>
<td>7.3%</td>
<td>0.71 [0.56, 0.90]</td>
<td>1988</td>
</tr>
<tr>
<td>Thomas 1988 (GTSO)</td>
<td>-0.198</td>
<td>0.225</td>
<td>3.4%</td>
<td>0.82 [0.53, 1.28]</td>
<td>1988</td>
</tr>
<tr>
<td>Hafström 1990</td>
<td>-0.446</td>
<td>0.236</td>
<td>3.2%</td>
<td>0.64 [0.40, 1.02]</td>
<td>1990</td>
</tr>
<tr>
<td>Krook 1991 (NCCTG)</td>
<td>-0.416</td>
<td>0.144</td>
<td>6.1%</td>
<td>0.66 [0.50, 0.87]</td>
<td>1991</td>
</tr>
<tr>
<td>Matsuda 1991 (SGACCS)</td>
<td>-0.128</td>
<td>0.118</td>
<td>7.4%</td>
<td>0.88 [0.70, 1.11]</td>
<td>1991</td>
</tr>
<tr>
<td>Bosset 2006 (EORTC)</td>
<td>-0.139</td>
<td>0.094</td>
<td>8.9%</td>
<td>0.87 [0.72, 1.05]</td>
<td>1993</td>
</tr>
<tr>
<td>QUASAR 2007</td>
<td>-0.386</td>
<td>0.134</td>
<td>6.6%</td>
<td>0.68 [0.52, 0.88]</td>
<td>1994</td>
</tr>
<tr>
<td>CCCSGJ 1995</td>
<td>-0.462</td>
<td>0.108</td>
<td>8.0%</td>
<td>0.63 [0.51, 0.78]</td>
<td>1995</td>
</tr>
<tr>
<td>Kornak 1996</td>
<td>-0.821</td>
<td>0.4</td>
<td>1.3%</td>
<td>0.44 [0.20, 0.96]</td>
<td>1996</td>
</tr>
<tr>
<td>Ito 1996 (TSGHCFU)</td>
<td>-0.105</td>
<td>0.374</td>
<td>1.5%</td>
<td>0.90 [0.43, 1.87]</td>
<td>1996</td>
</tr>
<tr>
<td>Yasutomi 1997 (JFMTC 7-2)</td>
<td>-0.117</td>
<td>0.12</td>
<td>7.3%</td>
<td>0.89 [0.70, 1.13]</td>
<td>1997</td>
</tr>
<tr>
<td>Kodaira 1998 (JFMTC 7-1)</td>
<td>-0.329</td>
<td>0.112</td>
<td>7.8%</td>
<td>0.72 [0.58, 0.90]</td>
<td>1998</td>
</tr>
<tr>
<td>Taal 2001 (NACC)</td>
<td>-0.105</td>
<td>0.165</td>
<td>5.2%</td>
<td>0.90 [0.65, 1.24]</td>
<td>2001</td>
</tr>
<tr>
<td>Kato 2002 (TACSG)</td>
<td>-0.968</td>
<td>0.265</td>
<td>2.6%</td>
<td>0.38 [0.23, 0.64]</td>
<td>2002</td>
</tr>
<tr>
<td>Caffaro 2003</td>
<td>0.086</td>
<td>0.14</td>
<td>6.3%</td>
<td>1.09 [0.83, 1.43]</td>
<td>2003</td>
</tr>
<tr>
<td>Watanabe 2004 (JFMTC15-2)</td>
<td>-0.288</td>
<td>0.189</td>
<td>4.4%</td>
<td>0.75 [0.52, 1.09]</td>
<td>2004</td>
</tr>
<tr>
<td>Sakamoto 2007 (JFMTC15-1)</td>
<td>-0.117</td>
<td>0.155</td>
<td>5.6%</td>
<td>0.89 [0.66, 1.21]</td>
<td>2007</td>
</tr>
<tr>
<td>Koda 2009</td>
<td>-1.022</td>
<td>0.528</td>
<td>0.8%</td>
<td>0.36 [0.13, 1.01]</td>
<td>2009</td>
</tr>
<tr>
<td>Hamaguchi 2011</td>
<td>-0.416</td>
<td>0.196</td>
<td>4.1%</td>
<td>0.66 [0.45, 0.97]</td>
<td>2011</td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.75 [0.68, 0.83]

Heterogeneity: Tau² = 0.02; Chi² = 32.41, df = 19 (P = 0.03); I² = 41%
Test for overall effect: Z = 5.95 (P < 0.00001)
Figure 1. Forest plot of comparison: 1 Adjuvant vs No Adjuvant ALL, outcome: 1.1 Overall Survival

Petersen et al, Cochrane Data Base of Systematic Rev 2012; CD004078
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
Patients with locally advanced rectal cancer

Pre-operative chemoradiation
Min 45Gy and fluoropyrimidine based

RO resection achieved

RANDOMISE

Follow-up only

Capecitabine + Oxaliplatin
6 courses

WHAT IS THE EVIDENCE WE HAVE?
The Chronicle trial

- Target population 800 pts
- Primary end point: DFS at 3 years (HR:0.75)
- Accrued nr. Patients 113
- Underpowered to detect any potential benefit of Chemotherapy

- HR for DFS: 0.80 (95% CI: 0.38-1.69; p:0.56)
- HR for OS: 1.18 (95% CI: 0.43-3.26; p:0.75)

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>
<tr>
<td>AIO04⁴</td>
<td>1233</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 R04⁵</td>
<td>1284</td>
<td>FU/Cape + Oxali</td>
<td>II/III</td>
<td>0.94 NS</td>
<td>0.94 NS</td>
<td>NR</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>PETACC6⁶</td>
<td>898</td>
<td>Cape + Oxali</td>
<td>II/III</td>
<td>1.04 NS</td>
<td>NR</td>
<td>NR</td>
<td>8%</td>
<td></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

BOLUS 5FU-LV Mayo Clinic Schedule

1:1 Randomization

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 TRAIL: 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?
**RECTAL CANCER: ESMO CLINICAL PRACTICE GUIDELINES**

**ANNALS OF ONCOLOGY 2013**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
</table>
| Early (good) | $cT1-2; cT3a$  
            $T3 (b)$ if mid or high  
            $N0$ (or $cN1$ if high)  
            $MRF$ --ve; $EMVI$ --ve |
| Intermediate (bad) | $cT2$ very low,  
                      $cT3$ mrf --ve (unless  
                      $cT3a(b)$ and mid or high rectum,  
                      $N1-2$, $EMVI$ +ve,  
                      limited $cT4aN0$ |
| Advanced (ugly) | $cT3$ MRF +ve  
                    $cT4a,b$  
                    Lateral node +ve |

- **Surgery (TME alone)**
- **25Gy in 5F or CRT Followed by TME**
- **CRT Followed by surgery**  
  (25Gy in 5F  
  Elderly or severe co-morbidity)

DOWNSTAGING AFTER NEOADJUVANT TREATMENT: NEOADJUVANT RECTAL SCORE

\[ NAR = \frac{[5 \ pN - 3(cT - pT) + 12]^2}{9.61} \]

NEOADJUVANT RECTAL SCORE
A SERIES OF 158 LOCALLY ADVANCED RECTAL CANCER PATIENTS TREATED WITH CT-RT

Log Rang Test  p: 0.004
(Mantel Cox)

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

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

Primary end point R0 resection


- 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
ADJUVANT THERAPY FOR LOCALIZED RECTAL CANCER

CLINICAL PRACTICE GUIDELINES

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

R. Glynne-Jones¹, L. Wyrwicz², E. Tiret³,⁴, G. Brown⁵, C. Rödel⁶, A. Cervantes⁷ & D. Arnold⁸, on behalf of the ESMO Guidelines Committee*

MULTIDISCIPLINARY TEAM FOR COLORECTAL CANCER
BIOMEDICAL RESEARCH INSTITUTE INCLIVA
UNIVERSITY HOSPITAL VALENCIA

- **MRI**: Salvador Campos
- **Pathology**: Samuel Navarro, Carolina Martínez
- **Surgery**: Alejandro Espí, Estephanie García-Botello, Vicente Plá, David Moro, José Martín Arévalo.
- **Radiation Oncology**: Esther Jordá
- **Medical Oncology**: Susana Roselló, Desam Roda, Noelia Tarazona, Tania Fleitas, Marisol Huerta, Isabel Chirivella (Family Cancer Unit), Andrés Cervantes
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.
Thank you