THE ROLE OF CHEMOTHERAPY IN LOCALIZED RECTAL CANCER:

Andrés Cervantes
Professor of Medicine
CONFLICT OF INTEREST DISCLOSURE

Employment:  None;  Stock Ownership:  None

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

Research Funding:  Genentech, Merck Serono, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda, Astelas, Fibrogen, Amcure, Sierra Oncology, Astra Zeneca, Medimmune, BMS, MSD, Pierre Fabre

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.
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

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?

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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 Neuro Tox</th>
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<tbody>
<tr>
<td>MOSAIC(^1)</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>
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<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>
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<tr>
<td>XELOXA(^3)</td>
<td>1886</td>
<td>FULV Mayo</td>
<td>CAPEOX</td>
<td>III</td>
<td>0.80 0.0038</td>
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<tr>
<td>XELOXA³</td>
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<td>CAPEOX</td>
<td>III</td>
<td>0.80 0.0038</td>
<td>0.83 0.04</td>
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<td>11%</td>
</tr>
<tr>
<td>AIO04⁴</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>
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<tr>
<td>NSABP R04⁵</td>
<td>128</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>
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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
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  - For R0 resection
  - For cCR
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).

POLISH PHASE III TRIAL CRT VS 5X5 AND FOLFOX

RT+5FU LV wk1,5
Ox weekly

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

Locally advanced
Unresectable
Locally recurrent

Primary end point R0 resection

5x5
FOLFOX 4 x 3

Primary end point R0 resection

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 RACOMIZED 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
Q5: What treatment would you recommend next?

1. 4 months of adjuvant 5-FU/FA or capecitabine  
   - 24.6%

2. 3 months of adjuvant capecitabine and oxaliplatin (i.e., CAPOX)  
   - 28.9%

3. 4 to 6 months of adjuvant 5-FU and oxaliplatin (i.e., FOLFOX)  
   - 22.8%

4. Observation  
   - 22.8%

5. Other  
   - 0.9%
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