TRATAMIENTO MULTIDISCIPLINAR DEL CÁNCER DE RECTO AVANZADO

Jaume Capdevila, MD
GI and Endocrine Tumor Unit
Vall d’Hebron University Hospital
Barcelona - Spain
MULTIDISCIPLINARY APPROACH IN THE MANAGEMENT OF RECTAL CANCER

Liver/Lung Surgeon
Colorectal Surgeon
Medical Oncologist
Pathologist
Radiologist
Radiation Oncologist
Nurse
Gastroenterologist

Rectal Cancer Management
20 YEARS VIEW...

Local Relapse:
Previous TME: 25-40%
With TME ≈10%

Line of excision includes mesorectum

Site of tumor deposits

Source: Cancer Control © 2003 H. Lee Moffitt Cancer Center and Research Institute, Inc.
20 YEARS VIEW…

Dworak classification (TRG):
Grade 0: no regression
Grade 1: minor regression (<25% fibrosis over tumor)
Grade 2: moderate regression (25-50% fibrosis)
Grade 3: good regression (fibrosis over tumor)
Grade 4: pathological complete response

20 YEARS VIEW…

High risk rectal cancer
- T4a/T4b
- N2
- >5 mm extramural tissue invasion (T3c-d)
- Extramural vascular invasion
- CRM involved or at risk
- Inguinal lymph nodes
OUTLINE

- Is still necessary CHT-RT with TME?

- Concomitant chemoradiotherapy:
  - 5FU = Capecitabine?
  - Role of Oxaliplatin?
  - Induction Chemotherapy

- Targeted therapies in neoadjuvant treatment
OUTLINE

• Is still necessary CHT-RT with TME?

• Concomitant chemoradiotherapy:
  – 5FU = Capecitabine?
  – Role of Oxaliplatin?
  – Induction Chemotherapy

• Targeted therapies in neoadjuvant treatment
PREOPERATIVE RT ??

PREOPERATIVE RADIOTHERAPY COMBINED WITH TOTAL MESORECTAL EXCISION FOR RESECTABLE RECTAL CANCER

ELLen KAPITEIJN, M.D., CORRIE A.M. MARIJNEN, M.D., IRIS D. NAGTEGAAL, M.D., HEIN PUTTER, PH.D., WILLEM H. STEUP, M.D., PH.D., THEO WIGGERS, M.D., PH.D., HARM J.T. RUTten, M.D., PH.D., LARS PAHLMAN, M.D., PH.D., BENGT GLIMELIUS, M.D., PH.D., J. HAN J.M. VAN KRIEKEN, M.D., PH.D., JAN W.H. LEER, M.D., PH.D., AND CORNELIS J.H. VAN DE VELDE, M.D., PH.D., FOR THE DUTCH COLORECTAL CANCER GROUP*


1861 pts
T1-3, N0-2
Stratification:
Center, surgery
(resection vs APA)
Primary endpoint: OS

RT
5Gyx5d

TME

Kapiteijn et al. NEJM 2001
PREOPERATIVE RT + TME

5-y OS: 64% in both groups

Local relapse rate: 5% vs 10%

M1: 25% vs 28%

Kapiteijn et al. NEJM 2001
RADIOThERAPY SCHEDULE: SHORT vs LONG

• SHORT
RT 5Gy x 5 Sessions (1 week) → Surgery in 1-2 weeks

• LONG
5FU + RT (1.8 Gy x 28 sessions) → Surgery in 6-8 weeks
RADIOTherapy SCHEDULE:
SHORT vs LONG

• **SHORT**
  RT 5Gy x 5 Sessions (1 week) → Surgery in 1-2 weeks

• **LONG**
  5FU + RT (1.8 Gy x 28 sessions) → Surgery in 6-8 weeks

• POLISH

• AUSTRALASIAN
RADIOTHERAPY SCHEDULE: SHORT vs LONG

Randomized (n = 316)
---
Excluded, did not meet inclusion criteria (n = 4)

Allocated to short-course radiotherapy (n = 155)
- Received allocated intervention (radiotherapy and tumour resection) (n = 143)
- Received chemoradiation (n = 1)
- Did not have radiotherapy (n = 3)
- Did not have surgery (n = 0)
- Laparotomy, no tumour resection (n = 7)
- Did not have both radiotherapy and surgery (n = 1)

Follow-up 48 months (n = 155)
- Analysed (n = 155)

Allocated to chemoradiation (n = 157)
- Received allocated intervention (radiotherapy and tumour resection) (n = 135)
- Received short-course radiotherapy (n = 6)
- Did not have radiotherapy (n = 8)
- Did not have surgery (n = 3)
- Laparotomy, no tumour resection (n = 4)
- Did not have both radiotherapy and surgery (n = 1)

Follow-up 48 months (n = 157)
- Analysed (n = 157)

T1/T2
- 40%
- Adj CHT: 46%

T3/T4
- Adj CHT: 30%

Bujko K, et al. BJS 2006
RADIOTHERAPY SCHEDULE: SHORT vs LONG

Bujko K, et al. BJS 2006
RADIOTherapy SCHEDULE: SHORT vs LONG

Randomly assigned (N = 326)

Allocated to SC RT arm (n = 163)
- Received SC RT (n = 159)
- Received LC RT (n = 2)
- Did not receive RT (n = 2)

Allocated to LC RT arm (n = 163)
- Received LC RT and chemo (n = 159)
- Received LC RT, no chemo (n = 1)
- Did not receive RT (n = 3)

Withdrawn consent; no treatment; data (n = 1)

Analyzed ITT patients analyzed (n = 162)

----

T3 stage

<table>
<thead>
<tr>
<th>N stage</th>
<th>162</th>
<th>100</th>
<th>161</th>
<th>100</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>91</td>
<td>56</td>
<td>90</td>
<td>56</td>
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<tr>
<td>1</td>
<td>59</td>
<td>36</td>
<td>59</td>
<td>37</td>
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<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
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<tr>
<td>X</td>
<td>11</td>
<td>7</td>
<td>10</td>
<td>6</td>
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</table>

Distance of lower border from anal verge, cm

<table>
<thead>
<tr>
<th></th>
<th>0 to &lt; 5</th>
<th>≥ 5 to &lt; 10</th>
<th>≥ 10 to 12</th>
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<tbody>
<tr>
<td>48</td>
<td>30</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>88</td>
<td>54</td>
<td>88</td>
<td>55</td>
</tr>
<tr>
<td>26</td>
<td>16</td>
<td>42</td>
<td>26</td>
</tr>
</tbody>
</table>
RADIOTHERAPY SCHEDULE: SHORT vs LONG

A

Cumulative Incidence (probability)

SC  
LC

Time Since Random Assignment (years)

B

Overall Survival (%)

HR (LC:SC) = 1.12; \( P = .62 \)

0.25 0.5 1 2 4

HR 95% CI

Time Since Random Assignment (years)

Ngan SY et al. JCO 2012
## PERIOPERATIVE CT ??

<table>
<thead>
<tr>
<th>Study</th>
<th>Treat.</th>
<th>N</th>
<th>CT</th>
<th>TME</th>
<th>pCR</th>
<th>LR</th>
<th>OS (5y)</th>
<th>M1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouliswassif</td>
<td>CT-RT</td>
<td>126</td>
<td>5FU</td>
<td>No</td>
<td>4.8%</td>
<td>15%</td>
<td>54%</td>
<td>30%</td>
</tr>
<tr>
<td>GI Tumor Study Group</td>
<td>IQ RT CT CT-RT</td>
<td>202</td>
<td>5FU</td>
<td>No</td>
<td></td>
<td>55%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PFS*</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.009</td>
<td></td>
</tr>
<tr>
<td>CAA/ARO/AIO (Sauer)</td>
<td>CT-RT post CT RT-pre</td>
<td>394</td>
<td>5FU</td>
<td>Si</td>
<td>0</td>
<td>13%</td>
<td>65%</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>405</td>
<td>5FU</td>
<td></td>
<td>8%</td>
<td>6%</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td>EORTC (Bosset)</td>
<td>RT CT-RT</td>
<td>250</td>
<td>5FULV</td>
<td>35%</td>
<td>2.5%</td>
<td>17%</td>
<td>63%</td>
<td>34%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>750</td>
<td></td>
<td></td>
<td>13.7%</td>
<td>8%</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>FFCD (Gerard)</td>
<td>RT CT-RT</td>
<td>367</td>
<td>5FULV</td>
<td>40%</td>
<td>5.3%</td>
<td>14%</td>
<td>67%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>375</td>
<td></td>
<td></td>
<td>11.4%</td>
<td>5%</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>Buijko</td>
<td>RT CT-RT</td>
<td>155</td>
<td>5FULV</td>
<td>No</td>
<td>3.6%</td>
<td>16%</td>
<td>67%</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>157</td>
<td></td>
<td></td>
<td>16%</td>
<td>14%</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>Ngan</td>
<td>RT CT-RT</td>
<td>163</td>
<td>5FULV</td>
<td>No</td>
<td>1%</td>
<td>5%</td>
<td>74%</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>163</td>
<td></td>
<td></td>
<td>15%</td>
<td>7%</td>
<td>70%</td>
<td>30%</td>
</tr>
</tbody>
</table>
Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer

Table 4. Rates of Sphincter-Sparing Surgery in 194 Patients Determined by the Surgeon before Randomization to Require Abdominoperineal Resection, According to Actual Treatment Given.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative Chemoradiotherapy (N=415)</th>
<th>Postoperative Chemoradiotherapy (N=384)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominoperineal resection deemed necessary — no. (%)</td>
<td>116 (28)</td>
<td>78 (20)</td>
<td></td>
</tr>
<tr>
<td>Sphincter-preserving surgery performed — no./total no. (%)</td>
<td>45/116 (39)</td>
<td>15/78 (19)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Table 5. Grade 3 or 4 Toxic Effects of Chemoradiotherapy, According to Actual Treatment Given.†

<table>
<thead>
<tr>
<th>Type of Toxic Effect</th>
<th>Preoperative Chemoradiotherapy (N=399)</th>
<th>Postoperative Chemoradiotherapy (N=237)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>% of patients</td>
<td>% of patients</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>18</td>
<td>0.04</td>
</tr>
<tr>
<td>Hematologic effects</td>
<td>6</td>
<td>8</td>
<td>0.27</td>
</tr>
<tr>
<td>Dermatologic effects</td>
<td>11</td>
<td>15</td>
<td>0.09</td>
</tr>
<tr>
<td>Any grade 3 or 4 toxic effect</td>
<td>27</td>
<td>40</td>
<td>0.001</td>
</tr>
<tr>
<td>Long-term</td>
<td>% of patients</td>
<td>% of patients</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal effects†</td>
<td>9</td>
<td>15</td>
<td>0.07</td>
</tr>
<tr>
<td>Strictures at anastomotic site</td>
<td>4</td>
<td>12</td>
<td>0.003</td>
</tr>
<tr>
<td>Bladder problems</td>
<td>2</td>
<td>4</td>
<td>0.21</td>
</tr>
<tr>
<td>Any grade 3 or 4 toxic effect</td>
<td>14</td>
<td>24</td>
<td>0.01</td>
</tr>
</tbody>
</table>
ROLE OF PERIOPERATIVE CT-RT

A

Overall Survival (%)

No. at Risk
Preoperative chemoradiotherapy
Postoperative chemoradiotherapy

Months

P = 0.80

B

Disease-free Survival (%)

No. at Risk
Preoperative chemoradiotherapy
Postoperative chemoradiotherapy

Months

P = 0.32

A

Cumulative Incidence of Local Recurrence (%)

No. at Risk
Preoperative chemoradiotherapy
Postoperative chemoradiotherapy

Months

P = 0.006

B

Cumulative Incidence of Distant Recurrence (%)

No. at Risk
Preoperative chemoradiotherapy
Postoperative chemoradiotherapy

Months

P = 0.84
Chemotherapy with Preoperative Radiotherapy in Rectal Cancer

Jean-François Bosset, M.D., Laurence Collette, Ph.D., Gilles Calais, M.D., Laurent Mineur, M.D., Philippe Maingon, M.D., Ljiljana Radojevic-Jelic, M.D., Alain Daban, M.D., Etienne Bardet, M.D., Alexander Beny, M.D., and Jean-Claude Ollier, M.D., for EORTC Radiotherapy Group Trial 22921*

1011 pts
T3-4
Stratification: Center, gender, T, distance to anal margin
Primary endpoint: OS

Bosset et al. NEJM 2006
**ROLE OF PERIOPERATIVE CT**

**Figure 3.** Progression-free Survival According to Postoperative Treatment or No Postoperative Treatment.

- **Progression-free Survival (%)**
  - No postoperative chemotherapy: 52.2%
  - Postoperative chemotherapy: 58.2%

- **Overall Survival (%)**
  - No postoperative chemotherapy: 63.2%
  - Postoperative chemotherapy: 67.2%

**HR: 0.87** (0.72-1.04; P=0.13)  
**HR: 0.85** (0.68-1.04; P=0.12)

Bosset et al. NEJM 2006
ROLE OF PERIOPERATIVE CT

RT: 17%
Preop CT-RT: 9%

RT + postop CT: 9%
Preop CT-RT + postop CT: 7%

TME ~ 35%
372 patients

Bosset et al. NEJM 2006
ROLE OF PERIOPERATIVE CT

5-y progression-free survival rate: 76% vs 65%
(HR: 0.64, P=0.013)
ROLE OF PERIOPERATIVE CT

Limitations
- 30% did not start adj CHT
- Dose dense: 45%
- >70% pN0
- Low quality of surgery
- Possible overstaging (only staging by CT scan)

## Local Recurrence Rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CRT</th>
<th>RT</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosset 2006</td>
<td>22 Events, 253 Total</td>
<td>43 Events, 252 Total</td>
<td>0.46 [0.27, 0.80]</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Boullis-Wassif 1984</td>
<td>19 Events, 120 Total</td>
<td>16 Events, 121 Total</td>
<td>1.02 [0.51, 2.04]</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Gerard 2006</td>
<td>30 Events, 375 Total</td>
<td>61 Events, 367 Total</td>
<td>0.44 [0.27, 0.69]</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>754 Total</strong></td>
<td><strong>740 Total</strong></td>
<td><strong>0.53 [0.39, 0.72]</strong></td>
<td><strong>M-H, Fixed, 95% CI</strong></td>
</tr>
</tbody>
</table>

Total events: 71 CRT, 122 RT

Heterogeneity: $\chi^2 = 4.24, df = 2 (p = 0.12); I^2 = 53\%$

Test for overall effect: $Z = 4.03 (p < 0.0001)$

## Overall Survival

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI</th>
<th>Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosset 2006</td>
<td>45.4%</td>
<td>1.02 [0.63, 1.26]</td>
<td></td>
</tr>
<tr>
<td>Boullis-Wassif 1984</td>
<td>15.0%</td>
<td>1.16 [0.60, 1.66]</td>
<td></td>
</tr>
<tr>
<td>Bujko 2006</td>
<td>13.8%</td>
<td>0.99 [0.68, 1.45]</td>
<td></td>
</tr>
<tr>
<td>Gerard 2006</td>
<td>25.8%</td>
<td>0.96 [0.73, 1.27]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>1.02 [0.89, 1.17]</strong></td>
<td><strong>M-H, Fixed, 95% CI</strong></td>
</tr>
</tbody>
</table>

Total events: 71 CRT, 122 RT

Heterogeneity: $\chi^2 = 0.66, df = 3 (p = 0.88); I^2 = 0\%$

Test for overall effect: $Z = 0.26 (p = 0.79)$
OUTLINE

• Is still necessary CHT-RT with TME?

• Concomitant chemoradiotherapy:
  – 5FU = Capecitabine?
  – Role of Oxaliplatin?
  – Induction Chemotherapy

• Targeted therapies in neoadjuvant treatment
COLON CANCER = RECTAL CANCER?

Gunderson et al. ASCO 2008
Different relapse patterns??

COLON

LOCAL
< 5%

DISTANT
32%

RECTUM

LOCAL
~5%

DISTANT
30-35%

Andre et al. ASCO 2007
Kapiteijn et al. NEJM 2001
Bosset et al. Lancet Oncol 2014
ROLE FOR OXALIPLATIN?

- STAR-01
- ACCORD 12/0405
- CAO/ARO/AIO-04
- NSABP R-04
- PETACC-6
STAR-01

STUDY OUTLINE

RT 50.4 Gy
FU 225 mg/m²/day PVI

RT 50.4 Gy
FU 225 mg/m²/day PVI
OXA 60 mg/m² weekly x 6

Primary endpoint: overall survival

FU/LV (bolus or CI, center choice)

6-8 wks

Primary endpoint: overall survival

Aschele et al. JCO 2011
ACCORD 12

**Cape**: 800 mg/m²/bid
- 45 Gy/1.8 Gy SD

**Oxaliplatin**: 50 mg/m²/week
- Cape: 800 mg/m²/bid
- 50 Gy/2.0 Gy SD

**Adjuvant Chemotherapy** (local policy)

Gérard JP et al. JCO 2012
CAO/ARO/AIO-04

Best arm of CAO/ARO/AIO-94:

**RT 50.4 Gy + 5-FU**
1000 mg/m² days 1-5 + 29-33

Based on phase I/II trials:

**RT 50.4 Gy + 5-FU/OX**
Ox: 50 mg/m² d 1, 8, 22, 29
5-FU: 250 mg/m² d 1-14 + 22-35

**5-FU**
500 mg/m² d 1-5, q29
4 cycles (4 months)

**mFOLFOX6**
Oxaliplatin: 100 mg/m² d1,q15
Folinic Acid: 400 mg/m² d1
5-FU: 2400 mg/m² d1-2
8 cycles (4 months)
NSABP R-04

Group 1
5FU (CVI 225mg/m² 5d/week) +
4600cGy + 540-1080cGy

Group 2
5FU (CVI 225mg/m² 5d/week) +
Oxaliplatin 50 mg/m²/week X 5 +
4600cGy + 540-1080cGy

Group 3
Capecitabine 825 mg/m² PO BID +
4600cGy + 540-1080cGy

Group 4
Capecitabine 825 mg/m² PO BID +
Oxaliplatin 50 mg/m²/week X 5 +
4600cGy + 540-1080cGy

TME
PETACC-6

Cape: 825 mg/m²/bid
RADIOTHERAPY

TME
Adjuvant Capecitabine

Oxaliplatin: 50 mg/m²/week
Cape: 825 mg/m²/bid
RADIOTHERAPY

TME
Adjuvant Cape+Oxaliplatin

Schmoll HJ, et al. ASCO 2014
<table>
<thead>
<tr>
<th>Summary</th>
<th>STAR-01</th>
<th>ACCORD 12/0405</th>
<th>CAO/ARO/AIO-04</th>
<th>NSABP R-04</th>
<th>PETACC-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of Pts</td>
<td>747</td>
<td>598</td>
<td>1265</td>
<td>1608</td>
<td>1094</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>OS</td>
<td>pCR</td>
<td>DFS</td>
<td>LR relapse</td>
<td>DFS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(71% vs 76%, HR:0.79, p=0.03)</td>
<td></td>
<td>(74% in both arms)</td>
</tr>
<tr>
<td>Pathology</td>
<td>pCR not improved (16% both arms)</td>
<td>pCR n.s. improved (14% vs 19%)</td>
<td>pCR n.s. improved (13% vs 18%)</td>
<td>pCR not improved</td>
<td>pCR not improved</td>
</tr>
<tr>
<td></td>
<td>More tox with Ox</td>
<td>More tox with Ox</td>
<td>No more tox</td>
<td>5FU/CPC (18% vs 21%)</td>
<td>(13 vs 15%)</td>
</tr>
<tr>
<td>Adjuvant Chemo</td>
<td>FU/LV</td>
<td>Center choice</td>
<td>mFOLFOX6</td>
<td>Center choice</td>
<td>CPC vs CPC-OXL</td>
</tr>
<tr>
<td>Compliance adj CHT</td>
<td>NA</td>
<td>42%</td>
<td>60%</td>
<td>NA</td>
<td>69% vs 57%</td>
</tr>
</tbody>
</table>
ROLE FOR CAPECITABINE INSTEAD OF 5FU?

- NSABP R-04
- MARGIT
NSABP R-04

RANDOMIZATION

Group 1
5FU (CVI 225mg/m² 5d/week) + 4600cGy + 540-1080cGy

Group 2
5FU (CVI 225mg/m² 5d/week) + Oxaliplatin 50 mg/m²/week X 5 + 4600cGy + 540-1080cGy

Group 3
Capecitabine 825 mg/m² PO BID + 4600cGy + 540-1080cGy

Group 4
Capecitabine 825 mg/m² PO BID + Oxaliplatin 50 mg/m²/week X 5 + 4600cGy + 540-1080cGy

TME

MARGIT

Treatment regimen
Neoadjuvant stratum S I

Arm A
Capecitabine 2,500mg/m²/day (during radiotherapy 1,650mg/m²/day)

Radiotherapy 50.4 Gy

Week
1 5 10 16 20 24 28

Radiotherapy 50.4 Gy

5-FU 500mg/m² day 1 – 5 (during radiotherapy 1000 mg/m² d 1 – 5, d 29 – 33)

Arm B
## Summary

<table>
<thead>
<tr>
<th></th>
<th>MARGIT</th>
<th>NSABP-R04</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N of pts</strong></td>
<td>392</td>
<td>1608</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>5-y OS (non-inferiority. $\beta$: 20%)</td>
<td>LR relapse</td>
</tr>
<tr>
<td><strong>Preop CRT</strong></td>
<td>5-FU + 50.4 Gy vs Cape 1650 mg/m$^2$ + 50.4 Gy</td>
<td>5-FU + 50.4 Gy vs 5-FU/Ox + 50.4 Gy vs Cape 1650 mg/m$^2$ + Ox 50 mg/m$^2$ weekly</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td>pCR improved (13.2% vs 5.4%)</td>
<td>pCR not improved 5FU/CPC (18% vs 21%) OXL/No (19% vs 18%)</td>
</tr>
</tbody>
</table>
LOW COMPLIANCE OF ADJUVANT CHEMOTHERAPY

Compliance to (neo-) adjuvant CAPOX

- Cycle 1: 100% Cap, 100% Ox
- Cycle 2: 95% Cap, 96% Ox
- Cycle 3: 65% Cap, 70% Ox
- Cycle 4: 62% Cap, 62% Ox
- Cycle 5: 57% Cap, 57% Ox
- Cycle 6: 53% Cap, 52% Ox

Percent of patients by cycle:
- Cycle 1: 91.4% received, 61.7% no adj. therapy, 57.5% missing
- Cycle 2: 56.8%, 47.5%, 43.8%
- Cycle 3: 49.4%, 40.0%
- Cycle 4: 45.7%
- Cycle 5: 50.0%
- Cycle 6: 50.0%
INDUCTION CHEMOTHERAPY

• GRUPO CANCER DE RECTO 3 STUDY

• THE TIMING OF RECTAL CANCER RESPONSE TO CHEMORADIATION CONSORTIUM
INDUCTION CHEMOTHERAPY

Grupo Cáncer de Recto 3 Study

MRT-defined Poor Risk: ≤ 2mm to mesorectal fascia, low-lying T3, T3N+, T4

RT 50.4 Gy + Cape/Oxaliplatin

TME

CAPOX 4#, q21

R

CAPOX 4#, q21

RT 50.4 Gy + Cape/Oxaliplatin

TME

Fernandez-Martos C et al. JCO 2012
## INDUCTION CHEMOTHERAPY

<table>
<thead>
<tr>
<th></th>
<th>CRT+TME+ adjuvant CAPOX N=52</th>
<th>Induction-CAPOX + CRT + TME N=56</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0 resection rates</td>
<td>87%</td>
<td>86%</td>
<td>n.s.</td>
</tr>
<tr>
<td>pCR</td>
<td>13%</td>
<td>14%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Compliance 4 X CAPOX</td>
<td>54%</td>
<td>91%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Toxicity (Grad 3/4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPOX-RT</td>
<td>29%</td>
<td>23%</td>
<td>0.36</td>
</tr>
<tr>
<td>CAPOX</td>
<td>54%</td>
<td>19%</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Fernandez-Martos C et al. JCO 2012
INDUCTION CHEMOTHERAPY

Radiotherapy - radiation 5 days/week, total 45 Gy (min. boost of 54 Gy, max. boost +36 Gy).

Chemotherapy - 5-FU 225 mg/m²/day as 7-day continuous infusion.

Resting Period

Assessment of tumor response - by proctoscopic exam; TME if indicated by stable disease.

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) (modified FOLFOX-6).

Surgery - Total Mesorectal Excision (TME).
INDUCTION CHEMOTHERAPY

<table>
<thead>
<tr>
<th>Pathologic tumor response</th>
<th>SG1 (n = 60)</th>
<th>SG2 (n = 67)</th>
<th>SG3 (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologic complete response (pCR)</td>
<td>11 (18%)</td>
<td>17 (25%)</td>
<td>17 (29%)</td>
</tr>
<tr>
<td>Pathologic partial response (pPR)</td>
<td>43 (72%)</td>
<td>50 (75%)</td>
<td>39 (66%)</td>
</tr>
<tr>
<td>Stable disease (pSD)</td>
<td>6 (10%)</td>
<td>0 (0%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

pCR rate SG1-SG3

Garcia-Aguilar J et al. ASCO 2012
OUTLINE

• Is still necessary CHT-RT with TME ?

• Concomitant chemoradiotherapy:
  – 5FU = Capecitabine ?
  – Role of Oxaliplatin ?
  – Induction Chemotherapy

• Targeted therapies in neoadjuvant treatment
BEVACIZUMAB-BASED CHEMORADIATION

• Preclinical models have demonstrated the synergy of bevacizumab and radiation therapy\(^1\).

• VEGF-targeted therapy may sensitize tumors to radiation by normalizing the tumor vasculature increasing the oxygenation and the cytotoxicity of radiation\(^2\).

• A phase I study established the safety of bevacizumab in the neoadjuvant chemoradiotherapy\(^3\). Bevacizumab at 5 mg/Kg every 2 weeks in combination with 5-FU and radiotherapy did not show any DLT or perioperative morbidity/mortality.

• Phase II clinical trial with the combination of bevacizumab, capecitabine and radiation therapy has demonstrated a pCR rate 32% and 24% had < 10% viable tumor cells in the specimen\(^1\). No grade 3 toxicities were observed. No perioperative complications were reported.

• Bevacizumab + Capecitabine: Spanish TTD randomized phase II trial\(^2\).

<table>
<thead>
<tr>
<th></th>
<th>Arm A: RT+CAP+BVZ</th>
<th>Arm B: RT+CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery performed</td>
<td>43 (98%)</td>
<td>46 (100%)</td>
</tr>
<tr>
<td>pCR (ypT0N0)</td>
<td>7 (16%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>R0 resection rates</td>
<td>42 (95.45%)</td>
<td>44 (96%)</td>
</tr>
<tr>
<td>Downstaging (lower pT compared with the pretreatment cT)</td>
<td>26 (59%)</td>
<td>18 (39%) (p: 0.0429)</td>
</tr>
<tr>
<td>Sphincter saving surgery**</td>
<td>26 (59%)</td>
<td>30 65%) (p: 0.82)</td>
</tr>
</tbody>
</table>

\(^1\)Crane CH, et al. Int J Radiat Oncol Biol Phys. 2010

\(^2\)Martinez M, et al. ASCO 2012
A pilot study has demonstrated the safety of cetuximab on combination with standard neoadjuvant 5-FU and radiotherapy in patients with locally advanced rectal cancer. Up to 6 phase I/II studies of cetuximab in combination with 5FU/Capecitabine +/- Oxaliplatin or Irinotecan have been reported, with disappointing pCR (9-15%).

CETUXIMAB-BASED CHEMORADIATION

**EXPERT-C TRIAL DESIGN**

- **CAPOX** n=81
  - Neoadjuvant CAPOX x4
  - Neoadjuvant CAPOX x4 with Cetuximab
- **CAPOX + C** n=83
  - CRT with Capecitabine
  - CRT with Capecitabine & Cetuximab
- **Adjuvant CAPOX x 4**
  - TME
  - Adjuvant CAPOX x4 with Cetuximab

**Wild Type Population**

- 15 insufficient tissue for analysis
- 164 patients
- 149 patients

- 90 wild type (60%)
- 59 mutant (40%)

<table>
<thead>
<tr>
<th>Primary endpoint- wild type population</th>
<th>CAPOX n=44</th>
<th>CAPOX + C n=46</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>4 (9%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>pCR</td>
<td>3 (7%)</td>
<td>5 (11%)</td>
</tr>
</tbody>
</table>

CETUXIMAB-BASED CHEMORADIATION

**Progression free survival – wild type population**

- **CAPOX +C**
- **CAPOX**

HR = 0.62 95%CI (0.24 – 1.57), p=0.308
3 yr PFS 77% vs 80%

**Overall survival – wild type population**

- **CAPOX +C**
- **CAPOX**

HR = 0.27 95% CI (0.07 - 0.99) p=0.035
3 yr OS 81% vs 96%

ANSWERS AND MORE QUESTIONS!

• Is still necessary CHT-RT with TME:
  – Yes… but currently ongoing studies with induction chemotherapy showed promising pCR.

• Concomitant chemotherapy:
  – 5FU = Capecitabine: Yes (at least…)
  – Role of Oxaliplatin: No in concomitant CHRT, but may be in adjuvant/induction therapy…
  – Increasing interest in more intensive induction therapy

• Targeted therapies in neadjuvant treatment:
  – Poor results with anti-EGFR and anti-VEGF in pCR endpoint. Need for a better patient selection ?? (RAS, EGFR, VEGF mRNA¹…) or better endpoints ?? (survival ??)

¹Vallbohmer D, et al. ASCO 2010
… AND MORE QUESTIONS …

- Insufficient clinical and radiological criteria for patient’s selection (TNM, MRI, …)
  - Need for prognostic and predictive factors.

*Gene expression profiling

Das et al. Cancer 2007
Ghadimi et al. JCO 2007
Watanabe et al. Cancer Res 2006

- The real problem is distance recurrence !!
  - Induction CT ?
  - More intense adjuvant CT ?
  - Addition of targeted therapies to CT ?
GRACIAS POR VUESTRA ATENCIÓN

jacapdevila@vhebron.net
jcapdevila@onco.cat