OLD APPROACH TO RECTAL CANCER

- Surgical resection
- Pathology assessment and estimation of risk
- Treatment based upon classical TNM factors
- Postoperative concurrent chemoradiation

NIH consensus conference.
Adjuvant therapy for patients with colon and rectal cancer
JAMA, Sep 1990; 264: 1444 - 1450.
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
CURRENT APPROACH TO RECTAL CANCER

- MRI Staging
- MDT discussion
- Preoperative chemoradiation 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?

IF NO PREOPERATIVE CHRT OR RT IS GIVEN...

- American Intergroup data
- Quasar data
- 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

* NSABP, NCCTG and US-GI Intergroup

### 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>Approx 30% rectal.</td>
<td>Chemo</td>
<td>No chemo</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>19.6%</td>
</tr>
</tbody>
</table>

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

Petersen et al, Cochrane Data Base of Systematic Rev 2012; CD004078
Figure 1. Forest plot of comparison: I Adjuvant vs No Adjuvant\footnote{ALL, outcome: I.1 Overall Survival.}

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Year</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grage 1981</td>
<td>-0.892</td>
<td>0.366</td>
<td>1.4%</td>
<td>0.41 [0.20, 0.84]</td>
<td>1981</td>
<td></td>
</tr>
<tr>
<td>Thomas 1988 (GTSG)</td>
<td>-0.288</td>
<td>0.215</td>
<td>3.5%</td>
<td>0.75 [0.49, 1.14]</td>
<td>1988</td>
<td></td>
</tr>
<tr>
<td>Fisher 1988 (NSABP)</td>
<td>-0.236</td>
<td>0.134</td>
<td>6.8%</td>
<td>0.79 [0.61, 1.03]</td>
<td>1988</td>
<td></td>
</tr>
<tr>
<td>Hafrström 1990</td>
<td>-0.342</td>
<td>0.255</td>
<td>2.6%</td>
<td>0.71 [0.43, 1.17]</td>
<td>1990</td>
<td></td>
</tr>
<tr>
<td>Krook 1991 (NCCTG)</td>
<td>-0.342</td>
<td>0.134</td>
<td>6.8%</td>
<td>0.71 [0.55, 0.92]</td>
<td>1991</td>
<td></td>
</tr>
<tr>
<td>Matsuda 1991 (SGACCS)</td>
<td>-0.03</td>
<td>0.119</td>
<td>7.8%</td>
<td>0.97 [0.77, 1.23]</td>
<td>1991</td>
<td></td>
</tr>
<tr>
<td>Bosset 2006 (EORTC)</td>
<td>-0.163</td>
<td>0.105</td>
<td>8.9%</td>
<td>0.85 [0.69, 1.04]</td>
<td>1993</td>
<td></td>
</tr>
<tr>
<td>QUASAR 2007</td>
<td>-0.261</td>
<td>0.13</td>
<td>7.0%</td>
<td>0.77 [0.60, 0.99]</td>
<td>1994</td>
<td></td>
</tr>
<tr>
<td>CCCSGJ 1995</td>
<td>-0.416</td>
<td>0.122</td>
<td>7.6%</td>
<td>0.66 [0.52, 0.84]</td>
<td>1995</td>
<td></td>
</tr>
<tr>
<td>Kornek 1996</td>
<td>-0.868</td>
<td>0.464</td>
<td>0.9%</td>
<td>0.42 [0.17, 1.04]</td>
<td>1996</td>
<td></td>
</tr>
<tr>
<td>Ito 1996 (TSCHCFU)</td>
<td>0.285</td>
<td>0.341</td>
<td>1.6%</td>
<td>1.33 [0.68, 2.59]</td>
<td>1996</td>
<td></td>
</tr>
<tr>
<td>Yasutomi 1997 (JFMTC 7-2)</td>
<td>-0.051</td>
<td>0.133</td>
<td>6.9%</td>
<td>0.95 [0.73, 1.23]</td>
<td>1997</td>
<td></td>
</tr>
<tr>
<td>Kodaira 1998 (JFMTC 7-1)</td>
<td>-0.073</td>
<td>0.125</td>
<td>7.4%</td>
<td>0.93 [0.73, 1.19]</td>
<td>1998</td>
<td></td>
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<tr>
<td>Taal 2001 (NACCP)</td>
<td>-0.051</td>
<td>0.184</td>
<td>4.4%</td>
<td>0.95 [0.66, 1.36]</td>
<td>2001</td>
<td></td>
</tr>
<tr>
<td>Kato 2002 (TACSG)</td>
<td>-0.416</td>
<td>0.327</td>
<td>1.7%</td>
<td>0.66 [0.35, 1.25]</td>
<td>2002</td>
<td></td>
</tr>
<tr>
<td>Cafferero 2003</td>
<td>0.285</td>
<td>0.198</td>
<td>4.0%</td>
<td>1.33 [0.90, 1.96]</td>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>Watanabe 2004 (JFMTC15-2)</td>
<td>-0.128</td>
<td>0.222</td>
<td>3.3%</td>
<td>0.88 [0.57, 1.36]</td>
<td>2004</td>
<td></td>
</tr>
<tr>
<td>Gimmelius 2005 (NGTATG)</td>
<td>-0.1</td>
<td>0.101</td>
<td>9.2%</td>
<td>0.90 [0.74, 1.10]</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>Sakamoto 2007 (JFMTC15-1)</td>
<td>-0.094</td>
<td>0.165</td>
<td>5.2%</td>
<td>0.91 [0.66, 1.26]</td>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>Koda 2009</td>
<td>-1.309</td>
<td>0.845</td>
<td>0.3%</td>
<td>0.27 [0.05, 1.42]</td>
<td>2009</td>
<td></td>
</tr>
<tr>
<td>Hamaguchi 2011</td>
<td>-0.511</td>
<td>0.239</td>
<td>2.9%</td>
<td>0.60 [0.38, 0.96]</td>
<td>2011</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.83 [0.76, 0.91]

Heterogeneity: Tau² = 0.01; Chi² = 28.73, df = 20 (P = 0.09); I² = 30%
Test for overall effect: Z = 4.11 (P < 0.0001)

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?

IF PREOPERATIVE CHRT OR RT 5x5 IS GIVEN...

- Chronicle trial/Proctor/Script trial
- Meta-analysis on single patient data of 4 trials
- Adore trial
- CAO/ARO/AIO-04 trial
- PETACC 6 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 observation: 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
THE ROLE OF ADJUVANT CHEMOTHERAPY IN LOCALISED RECTAL CANCER: WHAT IS THE EVIDENCE WE HAVE?
A single patient data Meta-analysis of 4 RCTs

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 CAO/ARO/AIO-04 TRIAL

• No observational arm
• Randomised phase III trial 80% Power
• Bilateral hypothesis
• Target population 1200 pts
• Primary end point: DFS at 3 years improved by 7% from 75 to 82%
• Accrued nr. Patients 1265 over 3.7 years
• MRI mandatory

Rödel et al. ASCO 2014 abstract
Phase III: 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

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

Based on phase I/II trials:

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

Note: Chemo gap during 3rd week of RT

mFOLFOX6
Oxaliplatin: 100 mg/m² d1,q15
Folinic acid: 400 mg/m² d1
5-FU: 2400 mg/m² d1-2
8 cycles (4 months)
Disease-free Survival: Intention-to-treat analysis

Mixed-effects Cox Model:
HR = 0.79; 95% CI = (0.64, 0.98)
P-value = 0.030
3-year DFS: 71.2% vs. 75.9%
5-year DFS: 64.3% vs. 68.8%

N at risk
<table>
<thead>
<tr>
<th></th>
<th>5-FU</th>
<th>5-FU/OX</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>623</td>
<td>613</td>
</tr>
<tr>
<td>1</td>
<td>509</td>
<td>522</td>
</tr>
<tr>
<td>2</td>
<td>441</td>
<td>447</td>
</tr>
<tr>
<td>3</td>
<td>363</td>
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<td>4</td>
<td>233</td>
<td>230</td>
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<tr>
<td>5</td>
<td>114</td>
<td>110</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Presented By Claus Rodel at 2014 ASCO Annual Meeting
Disease-free survival: primary analysis (ITT) follow up 31 months (2.6-5.6 years)

Cox model adjusted for stratification factors (except center)
HR = 1.04 (0.81-1.33)
P = 0.78
3-year DFS: 74.5% Cape
73.9% Cape+Oxali

Presented By Hans-Joachim Schmoll at 2014 ASCO Annual Meeting
DOWNSTAGING AFTER NEOADJUVANT TREATMENT: NEOADJUVANT RECTAL SCORE

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

DOWNSTAGING AFTER NEOADJUVANT TREATMENT: NEOADJUVANT RECTAL SCORE

NEoadjuvant Rectal Score
A Series of 158 Locally Advanced Rectal Cancer Patients Treated with CT-RT

Funciones de supervivencia

Log Rang Test  p: 0.004
(Mantel Cox)

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 should be considered for patients at risk after direct surgery.
- **Adjuvant Chemotherapy (oxaliplatin based) should be given after neoadjuvant Chemoradiation for patients at high risk.**
- Adjuvant Chemotherapy could be also selectively considered for locally advanced patients with intermediate response to Chemoradiation.