Management of rectal cancer

D Papamichael MD FRCP

Clinical Session – Gastrointestinal Tumours

5th ESO-ESMO Eastern Europe and Balkan Region

Masterclass in Medical Oncology

15-20 June 2018, Belgrade, Serbia
Disclosures

• None
Outline

• Background / historical perspective
• Staging / TME
• Pre-operative RT (and CRT)
• Adjuvant chemotherapy
• Ongoing/future clinical trials
My best hopes from this lecture

- You will understand better short course (SCPRT) / chemoradiation (CRT) for rectal cancer
- You will be able to select patients suitable for short course / long course chemoradiation or surgery alone
- You will rationally decide regarding adjuvant chemotherapy after SCPRT or CRT
- You will be able to tailor the treatment to the individual patient
Outline

- Background / historical perspective
- Staging / TME
- Pre-operative RT (and CRT)
- Adjuvant chemotherapy
- Ongoing/future clinical trials
Targets of therapeutic Management

- Reduction of local recurrence rates
- Increase in overall and disease free survival
- Preservation of anal sphincter
- Preservation of quality of life and sexual function
Postoperative radiochemotherapy


- After a median follow up of 7 years
  - Local recurrence reduction by 46% (p < 0.03)
  - Distant recurrence reduction by 37% (p < 0.01)
Postoperative radiochemotherapy

Disease-free survival

Overall survival

Postoperative radiochemotherapy

HISTORICAL

Disease-free survival

Overall survival

Outline

• Background / historical perspective
• Staging / TME
• Pre-operative RT (and CRT)
• Adjuvant chemotherapy
• Ongoing/future clinical trials
Recommended staging procedures

- TRUS for early T1 cancers – for anatomical detail
- MRI for all cancers (CRM, EMVI, levator assessment, cT substage and cN nodal status)
- CT scan – to image distant spread
- PET/CT for extensive EMVI
- Colonoscopy to rule out synchronous tumours in the colon
- EUA
Relevant factors that need to be imaged

- CRM status
- Extramural Vascular Invasion (EMVI)
- Involvement of levators
- cT substage (cT3c and cT3d)
- cN status
High Quality MRI

- Gives the surgeon a road map for surgery
- Determines need for neoadjuvant chemoradiotherapy or SCPRT
Measuring depth of extramural spread

MERCURY Radiology 2007, 243: 132-9

295/311 (95 %) patients who underwent primary surgery. The mean difference between MRI and histopathology assessment of tumor EMD was -0.046 mm, SD = 3.85 mm, the 95 % CI was -0.487 to 0.395 mm. MRI and histopathology assessment of tumor spread are considered equivalent to within 0.5 mm (\ R).
• Extensive vascular invasion can destroy the vessel wall leaving little evidence of normal venous cellular architecture,

• 10% -50% - underreporting widespread by pathologists

• Poor interobserver agreement for EMVI by pathologists

• Human Pathology, 2012

EMVI -not just T3 tumor

Gross nodular expansion of mesorectal veins

EXTRAMURAL VASCULAR INVASION (EMVI)
DUTCH TME TRIAL (NAGTEGAAL 2002) – UNIRRADIATED GROUP (N= 656)

<table>
<thead>
<tr>
<th>Dutch TME study</th>
<th>3 year local recurrence</th>
<th>p = 0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>+CRM ≤ 2 mm</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>CRM &gt; 2 mm</td>
<td>5.8%</td>
<td>p = 0.0001</td>
</tr>
</tbody>
</table>
potentially involved CRM in 64 patients;
38 /64 relapsed and 32 died.

The 5-year OS was 62.2% (95% CI, 56.4% to 68%) in patients with mrCRM clear compared with
42.2% (95% CI, 29.4% to 55%) in patients with predicted mrCRM involved ($P = .01$)
### TME NORTHERN EUROPE: GOOD QUALITY MESORECTAL PLANE: NO RT

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligible</th>
<th>Good Quality Mesorectal</th>
<th>Local Recurrence</th>
<th>Actuarial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedish Rectal Cancer Trial 1997 (574)</td>
<td>T any N any</td>
<td>&lt;10%</td>
<td>150/557</td>
<td>27% &gt;30%</td>
</tr>
<tr>
<td>CR07 overall (592) Quirke 2009</td>
<td>T any N any</td>
<td>51%</td>
<td>59/592</td>
<td>10% 11%</td>
</tr>
<tr>
<td>Dutch TME (180) Nagtegaal 2005</td>
<td>T any N any</td>
<td>56%</td>
<td>Not stated</td>
<td>8.7% at 2 years</td>
</tr>
<tr>
<td>CR07 (301) Quirke 2009</td>
<td>T any N any</td>
<td>100% (MRI not routinely used)</td>
<td>27/301</td>
<td>9% 7% at 3 years</td>
</tr>
<tr>
<td>Mercury* (122) Taylor 2011</td>
<td>T3a/b N any crm-</td>
<td>70%</td>
<td>4/122</td>
<td>3% 3.3% at 5 years</td>
</tr>
</tbody>
</table>

* NB: MRI directed
Total Mesorectal Excision (TME)
What are we trying to stage? Most malignant nodes 3-5mm

7mm benign

Malignant Microscopic focus

Malignant 2mm focus

Malignant Fully replaced

Replaced Extracapsular breach

With thanks to Gina Brown
Outline

• Background / historical perspective
• Staging / TME
• Pre-operative RT (and CRT)
• Adjuvant chemotherapy
• Ongoing/future clinical trials
Preoperative radiotherapy

- Swedish trial, N Engl J Med; 1997

- Short course (25 Gy in one week)

- Surgery (no TME) carried out in the week following radiotherapy

1168 patients
Preoperative radiotherapy

- At 5 years follow up
  - Overall survival was 58% for patients receiving radiotherapy versus 48% (p=0.004)
  - Local recurrence rates were 11% versus 27% respectively (p<0.001)

**Primary endpoint: overall survival**

**Local recurrence rate**
Preoperative radiotherapy

Local Recurrence Rates: median 6y FU

Advantages of pre-operative RT

- Decreased risk for local recurrence
- Decreased risk for early and late toxicity
- Improved therapeutic effect due to increased tumor oxygenation
- Downstaging – Increased rates for sphincter preserving surgery
Pre- versus post-operative radiochemotherapy

Primary endpoint: overall survival

823 patients

Local recurrence rate

EORTC trial

1011 patients

TME in 37%

SCPRT versus CRT: Equivalence in overall survival

Polish trial (Bujko 2006)  Trans-Tasman trial (Ngan 2012)
Benefits and harms of preoperative RT addressed by radiation oncologists in decision consultations

Kunneman M et al Br J Cancer 2015;112:39-43
Rectal cancer therapy (in Sweden) 2016

Early or “good” (30-50%)
Surgery alone

Intermediate or “bad” (40-50%)
Preop RT alone (5x5 Gy)
Locally advanced or “ugly” (10-15%)
Preop CRT (50 Gy with 5-FU)

Locally advanced/ugly: MRI cT3 mrf+, cT4b (downsizing/staging needed)
### Preoperative RT trials: Patterns of failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Local failure</th>
<th>Distant Mets.</th>
<th>5y OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFCD JCO 2006</td>
<td>RT vs. RChT</td>
<td>16%</td>
<td>36%</td>
<td>66%</td>
</tr>
<tr>
<td>EORTC NEJM 2006</td>
<td>RT vs. RChT</td>
<td>17%</td>
<td>32%</td>
<td>65%</td>
</tr>
<tr>
<td>AIO/CAO/ARO NEJM 2004</td>
<td>Pre vs. post</td>
<td>13%</td>
<td>36%</td>
<td>74%</td>
</tr>
<tr>
<td>Marijnen ASCO GI 2005</td>
<td>5x5</td>
<td>11%</td>
<td>n.a.</td>
<td>63%</td>
</tr>
</tbody>
</table>

Despite significant reduction of local relapse, no influence on distant mets. and survival observed.
Outline

• Background / historical perspective
• Staging / TME
• Pre-operative RT (and CRT)
• Adjuvant chemotherapy
• Ongoing/future clinical trials
Chemotherapy for (non-metastatic) rectal cancer

- Post-op – after surgery

- In the context of CRT/pre-op

- Adjuvant chemotherapy / following resection
  - To eradicate micro-metastatic disease and prevent distant recurrences
  - When is it indicated
    (what is the benchmark: pre-op staging, post-op histopathology report or both)
### NCCN Guidelines Version 1.2018
### Rectal Cancer

#### CLINICAL STAGE
- **T3, N any with clear circumferential margin (CRM) (by MRI):**
  - **T1-2, N1-2**

#### NEOADJUVANT THERAPY
- **Chemo/RT**
  - Capcitabine/long-course RT* or infusional 5-FU/long-course RT* (category 1 and preferred for both) or
  - Bolus 5-FU/leucovorin/long-course RT* or
  - Short-course RT* or
- **Chemotherapy**
  - FOLFOX (preferred) or CAPEOX (preferred) or
  - 5-FU/leucovorin or capcitabine

#### PRIMARY TREATMENT
- **Consider restaging**
- **Transabdominal resection**
  - CT3, N0 before chemo/RT
  - CT1-3, N1-2 before chemo/RT

#### ADJUVANT TREATMENT
- 5-FU/leucovorin or capcitabine or CAPEOX (preferred)
- Surveillance (See REC-11)
- FOLFOX or CAPEOX
- Surveillance (See REC-11)

#### ADJUVANT TREATMENT (6 MO PERIOPERATIVE TREATMENT PREFERRED)
- Systemic therapy (See REC-F)

---

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

---

*See Principles of Imaging (REC-A).*

*See Principles of Surgery (REC-C).*

*CRM measured at the closest distance of the tumor to the mesorectal fascia. Clear CRM: Greater than 1 mm from mesorectal fascia, levator muscles and not invading into the intersphincteric plane.

*Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capcitabine or infusional 5-FU.*

*See Principles of Adjuvant Therapy (REC-D).*

*See Principles of Radiation Therapy (REC-E).*

*Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for down-staging and the possibility of long-term toxicity.*

*If patient treated with short course RT, surgery should be within 1 week or delayed 6-8 weeks.*

*In those patients who achieve a complete clinical response with no evidence of residual disease on digital rectal examination, rectal MRI, and direct endoscopic evaluation, a “watch and wait,” nonoperative management approach may be considered in centers with experienced multidisciplinary teams. The degree to which risk of local and/or distant failure may be increased relative to standard surgical resection has not yet been adequately characterized. Decisions for non-operative management should involve a careful discussion with the patient of his/her risk tolerance.*

*FOLFOXIRI* is not recommended in this setting.
# NCCN Guidelines Version 1.2018
## Rectal Cancer

### Clinical Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Neoadjuvant Therapy</th>
<th>Primary Treatment</th>
<th>Adjuvant Treatment</th>
</tr>
</thead>
</table>
| T3, N any with involved CRM (by MRI) or T4, N any or Locally unresectable or medically inoperable | **Chemo/RT**  
- Capecitabine/long-course RT or infusional 5-FU/long-course RT (category 1 and preferred for both) or Bolus 5-FU/leucovorin/long-course RT or | **Chemotherapy**  
12-16 weeks  
- (FOLFOX or CAPEOX) (preferred) or 5-FU/leucovorin or capecitabine | (FOLFOX or CAPEOX) (preferred) or 5-FU/leucovorin or Capetitabine |

| | Involved CRM or bulky residual disease | **Restaging**  
6 weeks post completion of RT | **Transabdominal Resection**  
(12-16 weeks)  
- (FOLFOX or CAPEOX) (preferred) or 5-FU/leucovorin or Capetitabine |

| | Restaging | **Transabdominal Resection**  
(12-16 weeks)  
- (FOLFOX or CAPEOX) (preferred) or 5-FU/leucovorin or Capetitabine |

### Surveillance (See REC-11)

- In those patients who achieve a complete clinical response with no evidence of residual disease on digital rectal examination, rectal MRI, and direct endoscopic evaluation, a "watch and wait", nonoperative management approach may be considered in centers with experienced multidisciplinary teams. The degree to which risk of local and/or distant failure may be increased relative to standard surgical resection has not yet been adequately characterized. Decisions for nonoperative management should involve a careful discussion with the patient of his/her risk tolerance.

- FOLFOX is not recommended in this setting.

---

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
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. Tret³,⁴, G. Brown⁵, C. Rödel⁶, A. Cervantes⁷ & D. Arnold⁸, on behalf of the ESMO Guidelines Committee*
‘Summarising, it is reasonable to consider adjuvant ChT in rectal cancer patients after preoperative CRT/RT with yp stage III (and ‘high-risk’ yp stage II). The level of scientific evidence for sufficient benefit is much lower than in colon cancer and is probably limited to DFS rather than toOS [II, C]. Hence, the decision on postoperative ChT (fluoropyrimidine 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.’
Adjuvant chemotherapy

- Cochrane report 2012, CD004078
  - 9221 patients from 21 trials
  - Trials run through multiple decades, great heterogeneity (stage, treatment, setting)
  - HR for OS 0.88 (0.76-0.91), for DFS 0.75 (0.68-0.83), small but statistically significant gain

- “Modern” trials
Adjuvant chemotherapy

- Cochrane report 2012, CD004078
  - 9221 patients from 21 trials
  - Trials run through multiple decades, great heterogeneity (stage, treatment, setting)
  - HR for OS 0.88 (0.76-0.91), for DFS 0.75 (0.68-0.83), small but statistically significant gain

- “Modern” trials
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 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] 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] 1988</td>
</tr>
<tr>
<td>Thomas 1988 (GTSG)</td>
<td>-0.198</td>
<td>0.225</td>
<td>3.4%</td>
<td>0.82 [0.53, 1.28] 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] 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] 1991</td>
</tr>
<tr>
<td>Matsuda 1991 (SGACCS)</td>
<td>-0.128</td>
<td>0.118</td>
<td>7.4%</td>
<td>0.87 [0.70, 1.11] 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] 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] 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] 1995</td>
</tr>
<tr>
<td>Kornek 1996</td>
<td>-0.821</td>
<td>0.4</td>
<td>1.3%</td>
<td>0.44 [0.20, 0.96] 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] 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] 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] 1998</td>
</tr>
<tr>
<td>Taal 2001 (NACCP)</td>
<td>-0.105</td>
<td>0.165</td>
<td>5.2%</td>
<td>0.90 [0.65, 1.24] 2001</td>
</tr>
<tr>
<td>Kato 2002 (TACSG)</td>
<td>-0.068</td>
<td>0.265</td>
<td>2.6%</td>
<td>0.38 [0.23, 0.64] 2002</td>
</tr>
<tr>
<td>Cañiero 2003</td>
<td>0.086</td>
<td>0.14</td>
<td>6.3%</td>
<td>1.09 [0.83, 1.43] 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] 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] 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] 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] 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); ι² = 41%
Test for overall effect: Z = 5.95 (P < 0.00001)
Figure 1. Forest plot of comparison: Adjuvant vs No Adjuvant ALL, outcome: Overall Survival

<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>-0.892</td>
<td>0.366</td>
<td>1.4%</td>
<td>0.41 [0.20, 0.84]</td>
<td>1981</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>
</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>
</tr>
<tr>
<td>Hafström 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>
</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>
</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>
</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>
</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>
</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>
</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>
</tr>
<tr>
<td>Ito 1996 (TSGHCFU)</td>
<td>0.285</td>
<td>0.341</td>
<td>1.6%</td>
<td>1.33 [0.68, 2.59]</td>
<td>1996</td>
</tr>
<tr>
<td>Yasutomi 1997 (JFMT C-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>
</tr>
<tr>
<td>Kodaira 1998 (JFMT C-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>
</tr>
<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>
</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>
</tr>
<tr>
<td>Cafiero 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>
</tr>
<tr>
<td>Watanabe 2004 (JFMTC 15-2)</td>
<td>-0.128</td>
<td>0.222</td>
<td>3.3%</td>
<td>0.88 [0.57, 1.36]</td>
<td>2004</td>
</tr>
<tr>
<td>Glimelius 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>
</tr>
<tr>
<td>Sakamoto 2007 (JFMTC 15-1)</td>
<td>-0.094</td>
<td>0.165</td>
<td>5.2%</td>
<td>0.91 [0.66, 1.26]</td>
<td>2007</td>
</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>
</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>
</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
Adjuvant chemotherapy

- Cochrane report 2012, CD004078
  - 9221 patients from 21 trials
  - Trials run through multiple decades, great heterogeneity (stage, treatment, setting)
  - HR for OS 0.88 (0.76-0.91), for DFS 0.75 (0.68-0.83), small but statistically significant gain

- “Modern” trials
“modern" adjuvant rectal trials

- EORTC 22921 – (Bosset Lancet Oncol 2014)
- Italian – (Cionini Radiother Oncol 2014)
- Chronicle – (Glynne-Jones Ann Oncol 2014)
- Dutch - (Breugom Ann Oncol 2015)

Meta-analysis

- Breugom (Lancet Oncol 2015)

None of the above are positive
Progression-free survival (PFS) and overall survival (OS) from the date of surgery by adjuvant treatment.

Laurence Collette et al. JCO 2007;25:4379-4386
Kaplan-Meier curve of disease-free survival after surgery by adjuvant treatment and pathological down staging to ypT0-2.

Laurence Collette et al. JCO 2007;25:4379-4386
EORTC 22921

With a 10.4 year median follow-up (Bosset et al Lancet Oncol 2014) no difference in:

- Study designed and powered to show an absolute 10% OS benefit
- OS
- PFS
- Cumulative incidence of distant spread

But

- Chemotherapy arms showed lower LR
- Benefit of adj. chemo seen in first analysis for ypT0-2 disappeared
- Chemotherapy given as a bolus regimen in the Mayo Clinic schedule but with a dose reduction
“Italian” trial

- 655 pts with cT3-4 rectal cancer undergoing CRT randomised after surgery to 6# cycles of 5FU vs observation
- Chemotherapy: “lower” dose 5FU/LV
- No difference in:
  - OS
  - Local control
  - Distant spread
Patients who received CRT were then randomly assigned: CapeOx vs observation

- Poor accrual; 113 patients randomised
- Observation group had higher number of node+ve patients, but no suggestion of benefit for the chemotherapy arm
- Results are difficult to interpret due to small numbers

R Glynne-Jones et al Ann Oncol 2014
“Dutch” study

- Pre-op RT or CRT followed by TME
- 470 patients randomly assigned to receive chemotherapy or observation
- More than 80% of patients had ypTNM stage III disease

No difference in terms of:
- OS
- DFS

Breugom et al Ann Oncol 2015
Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data

Anne J Breugom*, Marlies Swets*, Jean-François Bosset, Laurence Collette, Aldo Sainati, Luca Cionini, Rob Glynne-Jones, Nicholas Coussell, Esther Bastiaannet, Collette B M van den Broek, Gerrit-Jan Liefters, Hein Putter, Cornelis J H van de Velde

Figure 4: Cumulative incidence of distant recurrences

What about adding oxaliplatin?

- CRT +/- oxaliplatin
  - ACCORD 12/0405 PRODIGE 2
  - STAR – 01
  - German CAO/ARO/AIO-04
  - PETACC 6

- ADORE
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%

<table>
<thead>
<tr>
<th>Time (in years)</th>
<th>5-FU</th>
<th>5-FU/OX</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</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>
<td>364</td>
</tr>
<tr>
<td>4</td>
<td>233</td>
<td>230</td>
</tr>
<tr>
<td>5</td>
<td>114</td>
<td>110</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Overall Survival: Intention-to-treat analysis

Mixed-effects Cox model:
HR = 0.96; 95% CI = (0.72, 1.26)
P-value = 0.752
3-year OS: 88.0% vs. 88.7%
5-year OS: 78.3% vs. 78.0%

<table>
<thead>
<tr>
<th>Time (in years)</th>
<th>5-FU</th>
<th>5-FU/OX</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>623</td>
<td>613</td>
</tr>
<tr>
<td>1</td>
<td>572</td>
<td>559</td>
</tr>
<tr>
<td>2</td>
<td>530</td>
<td>512</td>
</tr>
<tr>
<td>3</td>
<td>446</td>
<td>430</td>
</tr>
<tr>
<td>4</td>
<td>286</td>
<td>268</td>
</tr>
<tr>
<td>5</td>
<td>142</td>
<td>123</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
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; 15:1245-1253
The Adore trial

![Graph showing disease-free survival with FOLFOX group and fluorouracil plus leucovorin group, with hazard ratio (HR) 0.657 (95% CI 0.434-0.994; p=0.047).]

**Intention-to-treat population**

<table>
<thead>
<tr>
<th>Group</th>
<th>Events</th>
<th>3-year disease-free survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flourouracil plus leucovorin group (n=161)</td>
<td>53</td>
<td>62.9% (55.4-70.4)</td>
</tr>
<tr>
<td>FOLFOX group (n=160)</td>
<td>39</td>
<td>71.6% (64.6-78.6)</td>
</tr>
</tbody>
</table>

Hong YS et al. Lancet Oncol 2014; 15:1245-1253
The Adore trial

**Intention-to-treat population**

<table>
<thead>
<tr>
<th></th>
<th>Flourouracil plus leucovorin group (n=161)</th>
<th>FOLFOX group (n=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>3-year overall survival (95% CI)</td>
<td>85.7% (80.3–91.1)</td>
<td>95.0% (91.6–98.4)</td>
</tr>
</tbody>
</table>

**Number at risk**

<table>
<thead>
<tr>
<th></th>
<th>Flourouracil plus leucovorin group</th>
<th>FOLFOX group</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 months</td>
<td>161</td>
<td>160</td>
</tr>
<tr>
<td>54 months</td>
<td>147</td>
<td>146</td>
</tr>
<tr>
<td>48 months</td>
<td>144</td>
<td>145</td>
</tr>
<tr>
<td>42 months</td>
<td>132</td>
<td>131</td>
</tr>
<tr>
<td>36 months</td>
<td>109</td>
<td>104</td>
</tr>
<tr>
<td>30 months</td>
<td>79</td>
<td>83</td>
</tr>
<tr>
<td>24 months</td>
<td>58</td>
<td>65</td>
</tr>
<tr>
<td>18 months</td>
<td>38</td>
<td>47</td>
</tr>
<tr>
<td>12 months</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>6 months</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>0 months</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
ADORE (Adjuvant Oxaliplatin in Rectal Cancer)

- 5FU/LV vs FOLFOX for 4 months
- Primary end-point: DFS
- ITT: 3 yr DFS 71.6% vs 62.9% p=.047, 3yr OS 95% vs 85.7% p=0.036
- When benefit evaluated by post-CRT pathologic stage only yp stage III patients had DFS benefit
- No observational arm
- Randomised phase II study with 80% power
So what have these trials shown us?

- All Oxaliplatin trials used low dose oxaliplatin as a radiosensitizer with CRT
- 2 trials mandated oxaliplatin also as postoperative adjuvant (so if benefit which component?)
- Some of these trials did not mandate TME
Why these negative results?

- Impact of adjuvant chemotherapy may be over-estimated in the “modern” era due to stage migration, better surgery and other mitigating factors.

- Difference between “clinical” stage II-III may be too broad; therefore looking for a 10% difference may be an error. Some patients at least will have stage II disease.

- Timing of adjuvant chemotherapy:
  
  - CRT: 6 weeks
  - Surgery wait: 6-8 weeks
  - Recovery from surgery: 4-6 weeks
  
  Total: 16-20 weeks
Increase in **Time to Adjuvant Chemotherapy** was associated with a **decrease in overall survival**
Adjuvant chemotherapy in rectal cancer

- After SCRT (and immediate surgery) – should treat as colon cancer according to histology (hardly evidence – based !)

- After CRT
  - if pCR, perhaps no benefit
  - if PR, then chemo indicated, but uncertain benefit?
  - if no response, then clearly indicated, but benefit unlikely.
Adjuvant chemotherapy in rectal cancer

- After SCRT (and immediate surgery) – should treat as colon cancer according to histology

- After CRT
  - if pCR, perhaps no benefit
  - if PR, then chemo indicated, but uncertain benefit?
  - if no response, then clearly indicated, but benefit unlikely.
POLISH PHASE III TRIAL CRT VS 5X5 AND FOLFOX

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

Locally advanced
Unresectable
Locally recurrent

RT+5FU LV wk1,5
Ox weekly

5x5
FOLFOX 4 x 3

Primary end point R0 resection
<table>
<thead>
<tr>
<th></th>
<th>5x5 + FOLFOX N=261</th>
<th>CRT N=254</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HISTOPATHOLOGY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R0 Resection</td>
<td>77%</td>
<td>71%</td>
<td>P=0.07</td>
</tr>
<tr>
<td>pCR</td>
<td>16%</td>
<td>12%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>CANCER OUTCOME</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3yr Local failure</td>
<td>22%</td>
<td>21%</td>
<td>NS</td>
</tr>
<tr>
<td>3yr Distant mets</td>
<td>30%</td>
<td>27%</td>
<td>NS</td>
</tr>
<tr>
<td>3yr DFS</td>
<td>52%</td>
<td>53%</td>
<td>NS</td>
</tr>
<tr>
<td>3yr OS</td>
<td>73%</td>
<td>65%</td>
<td>P=0.046</td>
</tr>
<tr>
<td><strong>LATE TOXICITY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>8%</td>
<td>5%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Median follow up 35 months
Conclusions

- Adjuvant chemotherapy should not be standard of care for all fully resected localised rectal cancer patients
- Should be considered for patients at risk, who did not receive neo-adjuvant therapy for whatever reason
- Should be considered for yp stage III disease after neo-adjuvant therapy
- Joint decision between patient and clinician balancing risks and benefits
- (and I have not even started to consider the elderly!)
Outline

• Background / historical perspective
• Staging / TME
• Pre-operative RT (and CRT)
• Adjuvant chemotherapy
• Ongoing/future clinical trials
Questions: Total Neoadjuvant: Yes/No? Adjuvant Cth: Yes/No? Long versus Short Course?

The Rapido Rectal Cancer RCT Currently Accruing:

- Intervention arm includes total neoadjuvant therapy
- Also compares short vs. long course XRT
- Hypothesis is that intervention improves DFS by 10%
Can we Omit Radiation From NAT?

PROSPECT: N1048 is ongoing Selective Use of Pelvic XRT

Stage II/III rectal cancer

5FUXRT → TME → Chemo per MD/patient

Restaging MRI and colonoscopy response:

FOLFOX x 6

>=20%

<=20%

5FUXRT

Chemo per MD/patient

Phase II: N=366 patients R0 resection is primary endpoint
Phase III N=1060 patients Time to local and distant recurrence are co-primary endpoints
Non-inferiority design
Proposed CREATE trial
UK, Australia, Sweden

A. Standard arm
Operable rectal cancer on pretreatment MRI >T3b or N+ or EMVI+

B. Experimental arm

Randomise

MDT defined: Surgery/CRT/SCRT
12 weeks post op OxDmG or CapOx chemo

12 weeks neoadjuvant OxDmG or CapOx chemo
MDT defined: Surgery/CRT/SCRT

Co primary end point: Distant mets and 3 yr DFS
Stratified by MDT defined pelvic treatment
Organ Preservation in Rectal Cancer After Neoadjuvant Therapy With CR: Results

Kaplan-Meier estimates at 4 yrs

- Rectal preservation: 72%
- Local tumor regrowth: 26%
  - Pelvic recurrence after salvage: 1.5%

Organ Preservation in Rectal Cancer After Neoadjuvant Therapy With CR: Survival

Current Wisdom

- Pre-operative CRT better than post-op
- Improves Local recurrence but not OS
- If CRM threatened on MRI needs response so CRT – if still CRM +ve, consider further systemic chemo pre-op
- Low rectal cancers (below the levators) always have threat to CRM
- T1/T2N0 mid/upper rectum don’t usually need RT or CRT unless if you want to avoid radical surgery
- CRT helps preserve sphincters
- Adjuvant chemo: uncertainty possibly due to “inaccurate” initial staging. Ongoing trials to establish value of “total” tx up front
- Greatest advances: surgery/TME, staging/MRI
Thank you