17th ESO-ESMO-EONS Masterclass
Management of rectal cancer

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Leeds Cancer Centre UK

@MontefioreD

+ Razvan Popescu
Summary of topics

- Quality of imaging, surgery and pathology
- Effectiveness of pre-operative radiotherapy
- ESMO treatment guidelines
- Evidence for (C)RT from clinical trials
- Future directions
+ve CRM = microscopic tumour <=1mm from the painted margin
MRI – mesorectal fascia
Role of circumferential margin involvement in the local recurrence of rectal cancer
Adam et al Lancet 1994;344;707-711

- All patients \( n=190 \) LR 29%

- “Curative resections” \( n=141 \) LR 23%
  - CRM+ve (25%) \( n=35 \) LR 66%
  - CRM -ve (75%) \( n=106 \) LR 8%
Local recurrence

- **Muscularis Propria**: 32 events, 154 total
- **Intramesorectal**: 27 events, 398 total
- **Mesorectal**: 19 events, 604 total

<table>
<thead>
<tr>
<th>Events</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>154</td>
</tr>
<tr>
<td>27</td>
<td>398</td>
</tr>
<tr>
<td>19</td>
<td>604</td>
</tr>
</tbody>
</table>

Disease free survival

- **Muscularis Propria**: 45 events, 154 total
- **Intramesorectal**: 100 events, 398 total
- **Mesorectal**: 139 events, 604 total

<table>
<thead>
<tr>
<th>Events</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>154</td>
</tr>
<tr>
<td>100</td>
<td>398</td>
</tr>
<tr>
<td>139</td>
<td>604</td>
</tr>
</tbody>
</table>

**At risk**:

- Mesorectal: 154, 135, 111, 72, 47, 25
- Intramesorectal: 398, 351, 281, 220, 155, 88
- Muscularis propria: 604, 552, 435, 297, 192, 112

**At risk**:

- Mesorectal: 154, 128, 102, 66, 44, 25
- Intramesorectal: 398, 336, 262, 202, 140, 81
- Muscularis propria: 604, 514, 391, 279, 179, 108

*CR07 – Plane of surgical specimen*

*Quirke et al 2009*
## Table 5. Grading of quality and completeness of the mesorectum in a total mesorectal excision specimen according to the plane of surgical excision [2]

<table>
<thead>
<tr>
<th>Plane of Surgery Achieved</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesorectal plane (good plane of surgery achieved)</td>
<td>Intact mesorectum with only minor irregularities of a smooth mesorectal surface; no defect deeper than 5 mm; no coning; and smooth circumferential resection margin on slicing</td>
</tr>
<tr>
<td>Intramesorectal plane (moderate plane of surgery achieved)</td>
<td>Moderate bulk to mesorectum, with irregularities of the mesorectal surface; moderate distal coning; muscularis propria not visible with the exception of levator insertion; and moderate irregularities of circumferential resection margin</td>
</tr>
<tr>
<td>Muscularis propria plane (poor plane of surgery achieved)</td>
<td>Little bulk to mesorectum with defects down onto muscularis propria; very irregular circumferential resection margin; or both</td>
</tr>
</tbody>
</table>

The specimen is examined as a whole (fresh) and as cross-sectional slices (fixed) to make an adequate interpretation. A TME specimen ideally should have a smooth surface, without incisions, defects or cracks, as an indication of successful surgical excision of all mesorectal tissue. ‘Coning’ represents the tendency for the surgeon to cut inwards towards the central tube of the rectum during distal dissection, rather than staying outside the visceral mesorectal fascia. The specimen then shows a tapered, conical appearance representing suboptimal surgical quality.

TME, total mesorectal excision.
Radiotherapy reduces LR for all planes of surgical excision *Quirke et al Lancet 2009*

<table>
<thead>
<tr>
<th></th>
<th>Muscularis propria</th>
<th>Intramesorectal</th>
<th>Mesorectal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>HR (95% CI)</td>
<td>%</td>
</tr>
<tr>
<td>All patients</td>
<td>13%</td>
<td>7% 0.48 (0.25-0.93)</td>
<td>4% 0.32 (0.16-0.64)</td>
</tr>
<tr>
<td>Selective post</td>
<td>16%</td>
<td>10% 0.49 (0.23-1.06)</td>
<td>7% 0.48 (0.23-1.00)</td>
</tr>
<tr>
<td>Pre-op RT</td>
<td>10%</td>
<td>4% 0.52 (0.15-1.79)</td>
<td>1% 0.09 (0.02-0.49)</td>
</tr>
</tbody>
</table>
Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma – Wong et al Cochrane review 2007

- 19 trials >8000 patients

**Overall mortality**

- Total (95% CI)
  - Heterogeneity: $\chi^2 = 18.29, df = 13 (P = 0.15); I^2 = 29$
  - Test for overall effect: $Z = 2.06 (P = 0.039)$
  - Test for subgroup differences: Not applicable

- Overall mortality: 100.0 % 0.93 [0.87, 1.00]

**Cause specific mortality**

- Total (95% CI)
  - Heterogeneity: $\chi^2 = 8.70, df = 4 (P = 0.07); I^2 = 54$
  - Test for overall effect: $Z = 2.40 (P = 0.016)$
  - Test for subgroup differences: Not applicable

- Cause specific mortality: 100.0 % 0.87 [0.78, 0.98]

**Local recurrence**

- Total (95% CI)
  - Heterogeneity: $\chi^2 = 68.71, df = 11 (P<0.00001); I^2 = 84$
  - Test for overall effect: $Z = 6.76 (P < 0.00001)$
  - Test for subgroup differences: Not applicable

- Local recurrence: 100.0 % 0.71 [0.64, 0.78]
Pre-operative chemoradiation for non-metastatic locally advanced rectal cancer—Caluwe Cochrane review 2012

• 5 trials >2000 patients

Overall Survival

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Chemoradiation Events</th>
<th>Total</th>
<th>Radiotherapy Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosset 2006</td>
<td>173</td>
<td>506</td>
<td>178</td>
<td>505</td>
<td>45.2%</td>
<td>0.95 [0.74, 1.24]</td>
</tr>
<tr>
<td>Buijko 2006</td>
<td>53</td>
<td>157</td>
<td>52</td>
<td>155</td>
<td>13.4%</td>
<td>1.01 [0.63, 1.61]</td>
</tr>
<tr>
<td>Gerard 2006</td>
<td>128</td>
<td>375</td>
<td>124</td>
<td>367</td>
<td>31.8%</td>
<td>1.02 [0.75, 1.38]</td>
</tr>
<tr>
<td>Boulis-Wassif 1984</td>
<td>49</td>
<td>126</td>
<td>40</td>
<td>121</td>
<td>9.6%</td>
<td>1.29 [0.77, 2.17]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1164</strong></td>
<td><strong>1148</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>101</strong></td>
<td>0.91 [0.85, 1.20]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>403</strong></td>
<td><strong>394</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 1.02, df = 3 (P = 0.80); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.15 (P = 0.88)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Local Recurrence

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Chemoradiation Events</th>
<th>Total</th>
<th>Radiotherapy Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosset 2006</td>
<td>22</td>
<td>253</td>
<td>43</td>
<td>252</td>
<td>30.0%</td>
<td>0.46 [0.27, 0.80]</td>
</tr>
<tr>
<td>Boulis-Wassif 1984</td>
<td>19</td>
<td>124</td>
<td>18</td>
<td>121</td>
<td>11.8%</td>
<td>1.04 [0.51, 2.08]</td>
</tr>
<tr>
<td>Buijko 2006</td>
<td>13</td>
<td>155</td>
<td>21</td>
<td>157</td>
<td>14.6%</td>
<td>0.59 [0.29, 1.23]</td>
</tr>
<tr>
<td>Gerard 2006</td>
<td>25</td>
<td>375</td>
<td>49</td>
<td>375</td>
<td>34.9%</td>
<td>0.48 [0.29, 0.79]</td>
</tr>
<tr>
<td>Ngan 2010</td>
<td>7</td>
<td>163</td>
<td>12</td>
<td>163</td>
<td>8.8%</td>
<td>0.56 [0.22, 1.47]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1070</strong></td>
<td><strong>1068</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>100</strong></td>
<td>0.56 [0.42, 0.75]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>86</strong></td>
<td><strong>143</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 3.86, df = 4 (P = 0.43); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.98 (P &lt; 0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pre-operative chemoradiation for non-metastatic locally advanced rectal cancer - Caluwe Cochrane review 2012

Acute Toxicity

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Chemoradiation</th>
<th>Radiotherapy</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Bosset 2004</td>
<td>137</td>
<td>400</td>
<td>69</td>
</tr>
<tr>
<td>Bujko 2006</td>
<td>29</td>
<td>157</td>
<td>5</td>
</tr>
<tr>
<td>Gerard 2006</td>
<td>55</td>
<td>375</td>
<td>10</td>
</tr>
<tr>
<td>Ngan 2007</td>
<td>46</td>
<td>163</td>
<td>3</td>
</tr>
</tbody>
</table>

Total (95% CI)

- Total events: 267, 87
- Heterogeneity: Chi² = 17.82, df = 3 (P = 0.0005); I² = 83%
- Test for overall effect: Z = 10.06 (P < 0.00001)

Late Toxicity

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Chemoradiation</th>
<th>Radiotherapy</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Bujko 2006</td>
<td>11</td>
<td>157</td>
<td>16</td>
</tr>
<tr>
<td>Ngan 2010</td>
<td>14</td>
<td>163</td>
<td>12</td>
</tr>
</tbody>
</table>

Total (95% CI)

- Total events: 25, 28
- Heterogeneity: Chi² = 1.04, df = 1 (P = 0.31); I² = 4%
- Test for overall effect: Z = 0.45 (P = 0.65)
Mean extramural spread MRI 2.8mm = Mean extramural spread path 2.81mm

- ESMO Guidelines statement

“……. rectal MRI for all tumours, including the earliest ones, is required in order to select patients for preoperative treatment and extent of surgery.”
MERCURY results

• MRI assessment of the CRM predicts DFS and LR

• Comparison of MR and Histopath response to CRT

• MRI detected tumour response for locally advanced rectal cancer predicts survival outcomes

• Preop High-resolution MRI Can Identify Good Prognosis Stage I, II, and III Rectal Cancer Best Managed by Surgery Alone
MRI – Selection for pre-op (C)RT

Margin at risk = Pre-op CRT

Options
- Surgery alone
- Surgery then post-op CRT
- Pre-op SCPRT then surgery
Local recurrence by T3 substage
Sebag-Montefiore et al ESTRO 2012

- T3a ≤1mm: 3% vs 6%
- T3b >1-5mm: 3% vs 10%
- T3c >5-15mm: 10% vs 22%

N=150

N=309
### MRI findings

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>A threatened (&lt;1 mm) or breached resection margin or low tumours encroaching onto the inter-sphincteric plane or with levator involvement</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>Any cT3b or greater, in which the potential surgical margin is not threatened <em>or</em> any suspicious lymph node not threatening the surgical resection margin <em>or</em> the presence of extramural vascular invasion</td>
</tr>
<tr>
<td>Low risk</td>
<td>T1 or cT2 or cT3a and <strong>no lymph node involvement</strong></td>
</tr>
</tbody>
</table>
Rectal Cancer: ESMO Clinical Practice Guidelines
Annals of Oncology 2017

**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)

MR stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2N0</td>
<td>57</td>
</tr>
<tr>
<td>T3aN0</td>
<td>24</td>
</tr>
<tr>
<td>T3bN0</td>
<td>19</td>
</tr>
<tr>
<td>T2N+</td>
<td>7</td>
</tr>
<tr>
<td>T3a N+</td>
<td>6</td>
</tr>
<tr>
<td>T3bN+</td>
<td>9</td>
</tr>
</tbody>
</table>

Complete data (Surgery MRI and Pathology) n=477

Consented to follow up n=386

Complete data with FU n=374

MRI defined good prognosis n=141

MRI defined bad prognosis n=234

Surgery alone n=122

Pre operative radiotherapy n=19

LR 4/122 (3%) 5yr DFS 85%
Rectal and sexual function is worse after preoperative radiotherapy and TME compared with TME alone: Results from many randomised studies

- Peeters K, J Clin Oncol 2015;25:6199
- Dahlberg M, Dis Colon Rectum 1998;41:543
- Stephens RJ, J Clin Oncol 2010;28:4233
- Marijnen CAM, J Clin Oncol 2005;23:1847
- Lundby L, Lancet 1997;350:564
- Lange MM, Br J Surg 2007;94:1278
Clinically operable adenocarcinoma of the rectum <15cm from anal verge; no metastases

n = 1350

PRE

Pre-operative RT
25Gy / 5F

Surgery

Pathology

SEL POST

Surgery

Pathology

CRM-ve

No CRT

CRM+ve

Post-op (C)RT
Dutch RT
CR07 CRT

Adjuvant chemotherapy given as per local policy – CR07
### CR07 and Dutch TME trial data

<table>
<thead>
<tr>
<th>PRE</th>
<th>SEL POST</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch TME trial Lancet Oncology 2011</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage I</th>
<th>&lt;1%</th>
<th>3%</th>
<th>10 yr eligible</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC CR07 ESTRO 2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage I</th>
<th>3%</th>
<th>5%</th>
<th>5 yr ITT</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 or less</td>
<td>5%</td>
<td>7%</td>
<td>5yr ITT</td>
<td>50</td>
</tr>
<tr>
<td>T3a</td>
<td>3%</td>
<td>6%</td>
<td>5 yr ITT</td>
<td>33</td>
</tr>
</tbody>
</table>
Dutch TME and MRC CR07 trials
Van Gijn et al Lancet Oncology 2011
Sebag-Montefiore et al Lancet 2009

Dutch TME trial

MRC CR07
TROG AGIT LSSANZ RACS trial
Ngan et al JCO 2012

N=326

Short course
Pre op (25Gy in 5F)

CRT – 5FU 225mg/m2 cont
50.4Gy CRT

5FU/LV x 4

5FU/LV x 6
TROG AGIT LSSANZ RACS trial
Ngan et al JCO 2012

Cumulative Incidence (probability)

Time Since Random Assignment (years)

No. at risk 323 301 274 250 198 144 94 42 0

SCPRT
CRT

Leeds Institute of Cancer and Pathology
Radiation Therapeutics

17th ESO-ESMO Masterclass in Clinical Oncology
Rectal Cancer: ESMO Clinical Practice Guidelines
Annals of Oncology 2017

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

Surgery (TME alone)

Advanced (ugly)
- cT3 MRF +ve
- cT4a,b
- Lateral node +ve

25Gy in 5F
or
CRT
Followed by TME
Rectal Cancer: ESMO Clinical Practice Guidelines Annals of Oncology 2017

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
- ? Neoadjuvant Chemo
- Followed by TME
<table>
<thead>
<tr>
<th>Risk group</th>
<th>TN substage</th>
<th>Possible therapeutic options</th>
<th>Further considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very early</td>
<td>cT1 sm1 N0 (on ERUS and MRI)</td>
<td>Local excision (TEM)</td>
<td>Alternatively, in the case of adverse features on pathology, TEM plus salvage (or adjuvant) CRT in perioperative high-risk patients (but unproven benefit—with high risk of local recurrence for pT2)</td>
</tr>
<tr>
<td>Early (Good)</td>
<td>cT1–cT2; cT3a/b if middle or high, N0 (or also cN1 if high), MRF clear, no EMVI</td>
<td>Surgery (TME) alone is standard. If unexpected poor prognostic signs on histopathology (CRM+, extranodal/N2), consider postoperative CRT/CT (see postoperative recommendations in Table 2)</td>
<td>For fragile, high-risk patients or those rejecting radical surgery (CRT with evaluation, local excision or if achieving cCR, ‘watch-and-wait’, organ preservation)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>cT3a/b very low, levators clear, MRF clear or cT3a/b in mid- or high rectum, cN1–2 (not extranodal), no EMVI</td>
<td>Surgery (TME) alone is a standard only if good-quality mesorectal resection assured (and local recurrence ≤0.5% or, if not, preoperative SCPRT (5×5 Gy) or CRT followed by TME</td>
<td>If CRT is given and cCR is achieved, ‘watch-and-wait’ in high-risk patients for surgery may be considered</td>
</tr>
<tr>
<td>Bad</td>
<td>cT3c/d or very low localisation levators threatened, MRF clear, cT3c/d mid-rectum, cN1–N2 (extranodal), EMVI+, limited cT4aN0</td>
<td>Preoperative SCPRT (5×5cGy) or CRT followed by TME, depending on need for regression</td>
<td>If CRT and cCR achieved, ‘watch-and-wait’ in high-risk patients may be considered</td>
</tr>
<tr>
<td>Advanced (Ugly)</td>
<td>cT3 with any MRF involved, any cT4a/b, lateral node+</td>
<td>Preoperative CRT followed by surgery (TME and more extended surgery if needed due to tumour overgrowth), or preoperative SCPRT (5×5 Gy) plus FOLFOX and delay to surgery</td>
<td>Alternatively, 5×5 Gy alone with a delay to surgery in fragile/elderly or in patients with severe comorbidity who cannot tolerate CRT</td>
</tr>
</tbody>
</table>
Pre-operative Chemoradiotherapy regimen

- Fluorpyrimidine
  - 5FU bolus or as continuous infusion
  - Oral Capecitabine

- Radiotherapy dose
  - ESMO guidelines
    - 45-50.4Gy intermediate risk
    - 50.4Gy advanced

- Radiotherapy target volume
  - External iliac nodes not routinely included
  - In intermediate risk superior limit can be lowered to S2/3
  - Low level evidence for the role of boost in advanced
Intensification of CRT

• Addition of drug or targeted therapy to CRT
  – Disappointing (0xaliplatin ph III, VEGF/EGFR ph II)
  – Clinical trials

• Neoadjuvant chemotherapy + pre-op CRT
  – More evidence (encouraging ph II eg EXPERT)

• Short course radiotherapy + neoadjuvant chemotherapy
  – RAPIDO trial ongoing

• Neoadjuvant chemotherapy
  – PROSPECT trial ongoing

• Radiotherapy dose escalation
  – Clinical trials
Summary of doublet and triplet CRT

- Oxaliplatin
  - Phase III disappointing

- Irinotecan
  - ARISTOTLE trial recruiting

- EGFR
  - Single arm phase II – inferior early pathological end points

- Vascular targeted
  - Limited data
RAPIDO Ph III Trial n=940
Hospers et al ECCO 2017

MRI defined Locally advanced

Standard of care control arm

RT+CAPE

5.5 weeks 6-8 weeks

CAPE + OXALIPLATIN

6-8 weeks 24 weeks

14 weeks

Overall ypT0 = 23%

Variable use by country Differing Standards of Care

Use of 5x5

1 week 1 week 18 weeks 2-4 weeks

18 weeks NAC

MRI defined cT4a,cT4b,cN2, EMVI+, Lat LN+
Intensification of treatment using neoadjuvant chemo separate from RT

SELECTION FOR NEOADJUVANT CHEMOTHERAPY

- Extensive EMVI
- Disease breaching/outside the mesorectal fascia

- NEO-ADJUVANT BEFORE CRT
- IN THE INTERVAL BETWEEN CRT AND TME OP
Intensification of treatment using neoadjuvant chemo separate from RT

NEO-ADJUVANT CHEMO BEFORE CRT

EXPERT, EXPERT-C Trials

<table>
<thead>
<tr>
<th>Clinical Response after NACT</th>
<th>ITT population n=269</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>11</td>
<td>4.1</td>
</tr>
<tr>
<td>Partial response</td>
<td>157</td>
<td>58.4</td>
</tr>
<tr>
<td>Stable disease</td>
<td>76</td>
<td>28.3</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3</td>
<td>1.1</td>
</tr>
<tr>
<td>Unassessable/not known</td>
<td>22</td>
<td>8.2</td>
</tr>
</tbody>
</table>
Intensification of treatment using neoadjuvant chemo separate from RT

Radiotherapy was given 5 days per week for 5 weeks for a total of 45 Gy with a minimum boost of 5.4 Gy. Fluorouracil was given as a 225 mg/m² per day continuous infusion for 7 days/week during radiation therapy for 5-6 weeks, depending on the number of radiation boosts given.

mFOLFOX6 was given in 2-week cycles of leucovorin 200 mg/m² or 400 mg/m² and oxaliplatin 85 mg/m² in a 2-h infusion, bolus fluorouracil 400 mg/m² on Day 1, and a 46-h infusion of fluorouracil 2400 mg/m².

*Interim assessments were done by proctoscopic examination; total mesorectal excision was done if the patient had stable or progressive disease.
<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 (60) SG1</th>
<th>Cohort 2 (67) SG2</th>
<th>Cohort 3 (67) SG3</th>
<th>Cohort 4 (65) SG3</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>11 (18%)</td>
<td>17 (25%)</td>
<td>20 (30%)</td>
<td>25 (38%)</td>
</tr>
<tr>
<td>Post CRT Chemo</td>
<td>None</td>
<td>2 cycles</td>
<td>4 cycles</td>
<td>6 cycles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FOLFOX</td>
<td>FOLFOX</td>
<td>FOLFOX</td>
</tr>
<tr>
<td>Interval to surgery</td>
<td>8 weeks</td>
<td>11 weeks</td>
<td>15 weeks</td>
<td>19 weeks</td>
</tr>
<tr>
<td>N0/N+</td>
<td>75%/25%</td>
<td>75%/25%</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
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**Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial**

<table>
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<td>Interval to surgery</td>
<td>8 weeks</td>
<td>11 weeks</td>
<td>15 weeks</td>
<td>19 weeks</td>
</tr>
<tr>
<td>Pelvic Fibrosis (1-10)</td>
<td>2.4</td>
<td>3.4</td>
<td>4.4</td>
<td>3.9 p=0.0001</td>
</tr>
<tr>
<td>Technical difficulty (1-10)</td>
<td>4.6</td>
<td>4.9</td>
<td>5.1</td>
<td>4.8 (p=0.8)</td>
</tr>
</tbody>
</table>

Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial

SUMMARY

- Preoperative CRT better than postop
- SCPRT=CRT for resectable cancers
- SCPRT/CRT improves local recurrence but not DFS or OS
- If CRM threatened on MRI needs response so CRT
- Low rectal cancers (below the levators) often have threat to CRM and may have LPLN
**ESMO Rectal Cancer Guidelines**


**Key Messages**

- **SoC**
  - TME alone
  - AVOID RT

- **TME alone if high quality or plus SCPRT/CRT**

- **SCPRT or CRT Then TME**

- **CRT or SCPRT + FOLFOX then TME**

**SoC**

- TME alone if middle or high cN0 (cN1 if high) MRF clear; no EMVI

**TME alone if high quality or plus SCPRT/CRT**

- cT1-2; cT3a/b if middle or high cN0 (cN1 if high) MRF clear; no EMVI

**SCPRT or CRT Then TME**

- cT3a/b very low levators clear. MRF clear, cT3a/b in mid or high rectum, cN1-2 (not extranodal), no EMVI

**CRT or SCPRT + FOLFOX then TME**

- cT3 with MRF involved cT4b, levators threatened, lateral node +ve
Organ Preservation

Organ preservation trials
Allows intensification

- Low risk
  - (C)RT
  - CCR W+W
  - TEM
  - Contact

- Moderate risk
  - Consider
  - SCPRT

- High risk
  - Consider
  - CRT

(C)RT
- Highly selected
- CRT not changed
- Surgery plan changed
- Intensive FU for LR

CCR W+W
- RT not given
- Intensification poss
- “Double jeopardy”
- Highest CCR
- Intensive FU for LR

17th ESO-ESMO Masterclass in Clinical Oncology
Habr Gama data
IJROBP 2014 88:822-8

CRT n=183

CCR n=90

Early regrowth n=17
FTLE n=5
AR n=7
APER n=4
Unres n=1

Unres n=2

Late regrowth n=11
FTLE n=2
Brachy n=1
AR n=0
APER n=7
Unres n=1
Unres n=2

Organ preservation n= 70
Unresectable pelvic disease n=6
Organ Preservation – Key publications

**Wait-and-See Policy for Clinical Complete Responders After Chemoradiation for Rectal Cancer**


See accompanying editorial doi: 10.1200/JCO.2011.38.1336; listen to the podcast by Dr Kachnic at www.jco.org/podcast

**Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis**


**Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial**

Eric Rullier, Philippe Rouanet, Jean-Jacques Tuchet, Alain Valverde, Bernard Lelong, Michel Riviere, Jean-Luc Faucheron, Mehrdad Jafari, Guillaume Portier, Bernard Meunier, Igor Sileznjek, Michel Prudhomme, Frederic Marchal, Marc Pocard, Denis Pezet, Anne Rullier, Véronique Vendrely, Quentin Denost, Julien Asselineau, Adelaïde Doussau
TREC - Study Design

- Feasibility – yes 63 randomised
- Early information on OP
Deferral of rectal surgery study
Royal Marsden Study – gina.brown@rmh.nhs.uk

Rectal cancer receiving CRT and agrees to surgery in needed

MRI 4 weeks post CRT + MDT discussion

- No visible tumour
- Visible tumour good PR
- Stable disease

CONSIDERATION OF TRIAL

MRI and FDG PET at 8 weeks

- No visible tumour or further regression
- No further regression / growth of disease

Protocol defined follow up

Surgical resection

17th ESO-ESMO Masterclass in Clinical Oncology
STARTREC – Study design
Phase II/III clinical trial

Week 1-5

Radical Surgery
- TME

Organ preservation
- 5x5 Gy
- CRT
- Evaluation

Week 11-13 – Central review

Little or no residual disease
- CCR
- W&W

Week 16-20 – Central review

Good response: residual disease
- Not CCR
- TEM

Poor/inadequate response
- TME

high risk conversion TME

TME