State-of-the-art: Radio-/chemotherapy for rectal cancer

Rob Glynne-Jones
Mount Vernon Cancer Centre
My Disclosures: last 5 years

- **Speaker:** Roche, Merck Serono, Sanofi Aventis, Pfizer, AIS

- **Advisory Boards:** Roche, Merck Serono, Sanofi Aventis, Astra Zeneca, Amgen, Servier, Eisai, BMS

- **Funding to attend meetings:** Roche, Merck Serono, Sanofi Aventis

- **Research funding:** Roche, Merck Serono, Sanofi Aventis
My Inherent Bias
Radiotherapy to the pelvis causes substantial permanent late morbidity and functional problems.
The optimal management of localized rectal cancer:

You need

- High quality Magnetic Resonance Imaging (MRI).
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).
Extramural vascular invasion
EMVI and threatened CRM
MRI-EMVI score & Outcome

n=135. Median follow-up=3.12 (0.9-5.7) years.

71% % Relapse-free

32%

MRI-EMVI score= 0-2
MRI-EMVI score= 3-4

p = 0.0015
The optimal management of localized rectal cancer:

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- Surgeons who perform high quality TME
The optimal management of localized rectal cancer:

You need

- High quality Magnetic Resonance Imaging (MRI).
- Surgeons who perform high quality TME
- Pathologists who photograph and score the specimen and can confirm high quality – and feed back
We can judge the quality of the Surgery
## Scoring the Quality of the Mesorectum

<table>
<thead>
<tr>
<th></th>
<th>Mesorectum</th>
<th>Defects</th>
<th>Coning</th>
<th>MRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>Intact, smooth</td>
<td>Not deeper than 5 mm</td>
<td>None</td>
<td>Smooth, regular</td>
</tr>
<tr>
<td>Nearly complete</td>
<td>Moderate bulk, irregular</td>
<td>No visible muscularis propria</td>
<td>Moderate</td>
<td>Irregular</td>
</tr>
<tr>
<td>Incomplete</td>
<td>Little bulk</td>
<td>Down to muscularis propria</td>
<td>Moderate–marked</td>
<td>Irregular</td>
</tr>
</tbody>
</table>

Both the specimen as a whole (fresh) and cross-sectional slices (fixed) are examined in order to make an adequate interpretation.
The optimal management of localized rectal cancer:

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– High quality Magnetic Resonance Imaging (MRI).
– Surgeons who perform high quality TME
– Pathologists who photograph and score the specimen and can confirm high quality – and feed back
– A functional MDT with a good chair
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- To listen to your patient

- And maybe in future immunoscore
CD3 infiltration - immunoscore

The ypTNM downstaging and TRG were used as endpoints to evaluate response to pCRT

- 72% of the biopsies with high infiltration of CD3$^+$ cells responders to CRT (complete or partial response)
- 63% of the biopsies with a low infiltration of CD3$^+$ cells were non-responders to CRT

\[(P = 0.015)\].

Anitei M-G Clin Cancer Res 2014;20:1891
Pre- vs post-operative chemoradiation
CAO/ARO/AIO-94

Locoregional Recurrences

Acute G3/4 adverse events
27% vs 40% (p=0.001)

Long-term G3/4 adverse events
14% vs 24% (p=0.01)

There is a standard for chemoradiation

Different standards

- In different countries
Glimelius
Radiother Oncol 2017
CLINICAL PRACTICE GUIDELINES

Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

R. Glynne-Jones¹, L. Wyrwich², E. Tiret³,⁴, G. Brown⁵, C. Rödel⁶, A. Cervantes⁷ & D. Arnold⁸, on behalf of the ESMO Guidelines Committee*

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org
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NCCN Guidelines Version 3.2017
Rectal Cancer

**Clinical Stage**

- T3, N0 or T any, N1-2 or T4 and/or locally unresectable or medically inoperable

**NeoAdjuvant Therapy**

- Chemotherapy
  - Capcitabine/long-course RT
  - Infusional 5-FU/long-course RT (category 1 and preferred for both)
  - Bolus 5-FU/leucovorin/long-course RT
  - Short-course RT (not recommended for T4 tumors)
- Chemotherapy
  - FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capcitabine

**Primary Treatment**

- Transabdominal resection
  - Resection contraindicated
  - Capecitabine/RT (preferred) or infusional 5-FU/RT (preferred) or bolus 5-FU/leucovorin/RT

**Adjuvant Treatment**

- FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capcitabine
- Surveillance (See REC-8)
- Systemic therapy (See REC-E)
- Surveillance (See REC-8)
- Systemic therapy (See REC-E)

---

1. See Principles of Surgery (REC-B)
2. Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capcitabine or infusional 5-FU.
3. See Principles of Adjuvant Therapy (REC-C)
4. See Principles of Radiation Therapy (REC-D)
5. Imaging (Chest/Abdomen/Pelvis CT with contrast) to be performed prior to adjuvant treatment to assess response to primary therapy or resection.
6. 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.
9. FOLFOXIRI is not recommended in this setting.
Major Milestones in rectal cancer management

- **1985**: NSABP R-01 and GITSG: Adjuvant CRT improves outcomes vs. surgery alone
- **1995**: NIH consensus: Adjuvant CRT is LARC standard of care
- **2005**: Dutch TME: NA-CRT improves LRR vs. surgery alone
- **2015**: NSABP R-04: capecitabine non-inferior to 5-FU as NA-CRT; addition of oxaliplatin no benefit

**NCCTG: Adjuvant CRT improves outcomes vs. RT alone**

**German Rectal CAO/ARO/AIO-94 and NSABP R-03**: NA-CRT vs. adjuvant becomes standard of care

**TNT approach (GCR3 & NRG-Gl002 studies):**
- Selective RT elimination (N1048/PROSPECT)
- Selective surgery elimination ("watchful waiting")
- Organ preservation
- Imaging & biomarker driven clinical response assessments
- Optimizing NA-CRT (RAPIDO)
Preoperative Options to influence outcomes in rectal cancer

- Radiotherapy (5 x 5Gy)
- Chemoradiation (with fluoropyrimidines)
- Neoadjuvant chemotherapy +/- Biologicals
- (now Immunotherapy)

- Different combinations and sequences of the above (4 x 3 x 2 x 1 = 24)

- (Post-op CRT as adjuvant)
5 Options for chemotherapy in locally advanced rectal cancer

- **Induction** - pre RT (Short-course (SCPRT) or chemoradiation (CRT))
- **Concurrent** - With RT (CRT)
- **Consolidation** - post CRT or SCPRT if waiting 6-12 weeks before surgery
- **Neoadjuvant alone without RT**
- **Post-op adjuvant**
“An important aim is to treat so that the risk of residual disease in the pelvis, frequently causing a disabling local recurrence, is very low. This risk should preferably be less than about 5% in the population in whom curative treatment is intended”

Bengt Glimelius
What is the risk of metastatic disease for cT3N1?
Rectal Cancer: ESMO Clinical Practice Guidelines  
Guidelines in Annals of Oncology 2013

**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 Followed by surgery (25Gy in 5F Elderly or severe comorbidity)**
The optimal management of localized rectal cancer

- Could you select on a more individual basis?

- ie is preventing local recurrence your only objective?
Fig. 2. Radiotherapy (RT) for all patients diagnosed with rectal cancer in Sweden and Norway from 1996 to 2012.
Pre- vs post-operative chemoradiation
CAO/ARO/AIO-94
At two years, overall survival was 82.0 percent in the group assigned to radiotherapy and surgery and 81.8 percent in the group assigned to surgery alone (P=0.84).
SCPRT versus CRT: no difference in local control

14.4% vs 18.6% P = 0.17

Polish Trial (Bujko 2006)

7.5% vs 4.4% P = 0.24)

TROG-01 Trial (Ngan 2012)
SCPRT versus CRT: Equivalence in overall survival

Polish trial (Bujko 2006)  
Trans-Tasman trial (Ngan 2012)
- Short course (5x5 Gy) and immediate Surgery
- Short course (5x5 Gy) and wait 6-8 weeks (or even longer)
STOCKHOLM III

Resectable Rectal AdenoCa

RANDOMISE

25 Gy in 5 F → Surgery

50 Gy in 25 F

Surgery (delayed)

Primary endpoint: sphincter preservation rate

Pettersson et al  BJS  2010/ Erlandsson 2017
Stockholm III trial: Overall Survival

Graph showing overall survival over time since randomisation (in years). The survival rates are compared between SRT, SRT-delay, and LRT-delay groups. The p-value for the comparison is 0.61.

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>SRT</th>
<th>SRT-delay</th>
<th>LRT-delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>129 (0)</td>
<td>112 (0)</td>
<td>128 (0)</td>
</tr>
<tr>
<td>1</td>
<td>112 (0)</td>
<td>92 (11)</td>
<td>92 (14)</td>
</tr>
<tr>
<td>2</td>
<td>92 (14)</td>
<td>43 (52)</td>
<td>43 (52)</td>
</tr>
<tr>
<td>3</td>
<td>42 (51)</td>
<td>22 (68)</td>
<td>22 (68)</td>
</tr>
<tr>
<td>4</td>
<td>19 (65)</td>
<td>18 (72)</td>
<td>18 (72)</td>
</tr>
<tr>
<td>5</td>
<td>12 (70)</td>
<td>18 (72)</td>
<td>11 (74)</td>
</tr>
<tr>
<td>6</td>
<td>12 (70)</td>
<td>18 (72)</td>
<td>11 (74)</td>
</tr>
<tr>
<td>7</td>
<td>12 (70)</td>
<td>18 (72)</td>
<td>11 (74)</td>
</tr>
<tr>
<td>8</td>
<td>12 (70)</td>
<td>18 (72)</td>
<td>11 (74)</td>
</tr>
<tr>
<td>9</td>
<td>12 (70)</td>
<td>18 (72)</td>
<td>11 (74)</td>
</tr>
<tr>
<td>10</td>
<td>12 (70)</td>
<td>18 (72)</td>
<td>11 (74)</td>
</tr>
</tbody>
</table>
Stockholm III trial: Recurrence Free Survival

**Graph:**
- **SRT**
- **SRT-delay**
- **LRT-delay**

**Table: Number at risk (censored)**

<table>
<thead>
<tr>
<th></th>
<th>Time since randomisation (years)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0</td>
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</tr>
</tbody>
</table>

**P-value:** p=0.92
RT selected on the basis of

- Involved LN
Fokas 2014  Updated Results of the CAO/ARO/AIO-94 Trial for CRT

<table>
<thead>
<tr>
<th>Preop N category</th>
<th>No at risk</th>
<th>10-Year Cumulative Incidence of Local Recurrence (%)</th>
<th>No at risk</th>
<th>10-Year Cumulative Incidence of Distant Mets (%)</th>
<th>No at risk</th>
<th>10-Year DFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>391</td>
<td>6.9</td>
<td>406</td>
<td>30.2</td>
<td>361</td>
<td>73</td>
</tr>
<tr>
<td>cN0</td>
<td>161</td>
<td>7.7</td>
<td>169</td>
<td>31.2</td>
<td>152</td>
<td>71.6</td>
</tr>
<tr>
<td>cN+</td>
<td>213</td>
<td>6.9</td>
<td>220</td>
<td>28.9</td>
<td>193</td>
<td>74.7</td>
</tr>
<tr>
<td>unknown</td>
<td>17</td>
<td></td>
<td>17</td>
<td></td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

In German trial defining LN status on ultrasound did not predict DFS or OS or LR!
## Clinical Lymph node staging

<table>
<thead>
<tr>
<th></th>
<th>Colon cancer without neoadjuvant treatment</th>
<th>Rectal cancer without neoadjuvant treatment</th>
<th>Rectal cancer with 5x5 Gy RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=21,629)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>40</td>
<td>38</td>
<td>57</td>
</tr>
<tr>
<td>Specificity</td>
<td>84</td>
<td>87</td>
<td>66</td>
</tr>
<tr>
<td>PPV</td>
<td>59</td>
<td>57</td>
<td>47</td>
</tr>
<tr>
<td>NPV</td>
<td>72</td>
<td>76</td>
<td>74</td>
</tr>
</tbody>
</table>

Brouwe NPM, Brouwer M, Stijns RCH, et al., Clinical lymph node staging by imaging in colorectal cancer: A flip of the coin? J Clin Oncol 35, 2017 (suppl; abstr e15160)
Even Gina Brown did not find that defining LN status on MRI predicted DFS or OS or LR!
Local Recurrence rates in CRO7 according the plane of surgery

<table>
<thead>
<tr>
<th>TNM stage</th>
<th>Muscularis propria</th>
<th>Intra-mesorectal</th>
<th>Mesorectal</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>8%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>II</td>
<td>6%</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>III</td>
<td>20%</td>
<td>14%</td>
<td>6%</td>
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<td><strong>20%</strong></td>
<td><strong>14%</strong></td>
<td><strong>6%</strong></td>
</tr>
</tbody>
</table>
Pathologically defined Lymph nodes only affect your local recurrence rate if you leave them inside the patient!
Novel Options
**NSABP R04 (5FU vs Capecitabine- +/- oxaliplatin)**

<table>
<thead>
<tr>
<th>1608 patients</th>
<th>PVI 5FU 225 mg/m², 5 days per week</th>
<th>Capecitabine 825 mg/m² BID 7 days per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>138/777 (17.8%)</td>
<td>161/779 (20.7%)</td>
</tr>
<tr>
<td>G3-5 diarrhoea</td>
<td>11.7%</td>
<td>11.7%</td>
</tr>
<tr>
<td>3 three-year local-regional event rates</td>
<td>11.2%</td>
<td>11.8%</td>
</tr>
<tr>
<td>5 Year DFS</td>
<td>66.4%</td>
<td>67.7%</td>
</tr>
<tr>
<td>5 year OS</td>
<td>79.9%</td>
<td>80.8%</td>
</tr>
<tr>
<td>Endpoint</td>
<td>STAR-01</td>
<td>ACCORD 12/0405</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>----------------</td>
</tr>
<tr>
<td>PCR</td>
<td>16% both arms</td>
<td>14% vs 19%</td>
</tr>
<tr>
<td>CRM</td>
<td>4% vs 7%</td>
<td>8% vs 13%</td>
</tr>
<tr>
<td>Node + (stage III)</td>
<td>29% vs 26%</td>
<td>30% vs 26%</td>
</tr>
</tbody>
</table>

Oxaliplatin Phase III trials: Control arm in red
## Phase III Chemoradiotherapy trials with or without Oxaliplatin

<table>
<thead>
<tr>
<th>Trial</th>
<th>No of patients</th>
<th>Regimens</th>
<th>DFS</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAO/ARO/AIO-04 Rodel Lancet Oncology 2015</td>
<td>1236</td>
<td>CRT + Ox 60mg Plus OX adjuvant</td>
<td>71.2% vs 75.9%</td>
<td>+4.7% (HR 0.79)</td>
</tr>
<tr>
<td>NSABP R-04 JNCI 2016</td>
<td>1606</td>
<td>CRT + Ox 60mg</td>
<td>64.2% vs 69.2%</td>
<td>+5%</td>
</tr>
<tr>
<td>ACCORD 12 updated 2016 GI ASCO</td>
<td>598</td>
<td>CRT + Ox 60mg + RT 50Gy</td>
<td>67.9% v 72.7%</td>
<td>+4.3%</td>
</tr>
<tr>
<td>STAR-01 WGICC 2016</td>
<td>747</td>
<td>CRT + Ox 60mg</td>
<td>5 year 66.3% vs 69.2 %</td>
<td>+2.9% (HR 0.89)</td>
</tr>
<tr>
<td>PETTAC-6</td>
<td>1090</td>
<td>CRT + Ox 60mg Plus OX adjuvant</td>
<td>75% vs 74%</td>
<td>-0.6% outlier</td>
</tr>
<tr>
<td>Chinese Trial Jiao 2015</td>
<td>208</td>
<td>CRT + Ox 60mg All received adjuvant FOLFOX 6–8 cycles</td>
<td>3-year DFS 69.9% vs 80.6% (P&gt;0.05)</td>
<td>+10.6%</td>
</tr>
</tbody>
</table>
Adjuvant trials in colon cancer using oxaliplatin in the novel arm.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient No</th>
<th>Path Stage</th>
<th>Treatment arms</th>
<th>Median Age</th>
<th>Compliance to planned cycles</th>
<th>5 year DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOSAIC (Andre 2004 updated 2015)</td>
<td>2246</td>
<td>II, III</td>
<td>LV5FU2, FOLFOX4</td>
<td>60, 61</td>
<td>86.5%, 74.7%</td>
<td>67.5% vs 73.2% +5.7%</td>
</tr>
<tr>
<td>NSABP C07 (Kuebler 2007 updated 2011)</td>
<td>2407</td>
<td>II, III</td>
<td>FULV, FLOX</td>
<td>59, 59</td>
<td>Not stated, Not stated</td>
<td>64.2% vs 69.4% +5.2%</td>
</tr>
<tr>
<td>NO16968 (Haller 2011)</td>
<td>1886</td>
<td>III</td>
<td>FULV, XELOX</td>
<td>61, 62</td>
<td>83%, 69%</td>
<td>3-year DFS 70.9% vs 66.5% +4.4%</td>
</tr>
</tbody>
</table>
US Intergroup phase III trial
ACOSOG, Z9062, CALGB, E81001

LARC stage II/III
MRI: CRM -ve

R

5FU CRT

FOLFOX #6

PR/SD?

T

ME

R0?

R1/2?

PD

FOLFOX #8

FOLFOX #6

5FU CRT

5FU CRT

N planned: > 800
1° endpoint: 3y DFS
2° toxicity, local failures, OS,
Prospect

- Selective use of chemoradiation in patients with cT2N1 and cT3N0-1 rectal cancer undergoing sphincter-sparing low anterior resection.
Prospect

- Selective use of chemoradiation in patients with cT2N1 and cT3N0-1 rectal cancer undergoing sphincter-sparing low anterior resection.

- The 3-year DFS and freedom from LR for PROSPECT-eligible patients were 79.1% and 97.4%.

RAPIDO Trial

N = 885 patients

Primary endpoint 3 year DFS
## RAPIDO Results: Pathology

<table>
<thead>
<tr>
<th>TNM5</th>
<th>Operated patients (n=792)</th>
<th>TNM5</th>
<th>Operated patients (n=796)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ypT0</td>
<td>183</td>
<td>ypN0</td>
<td>567</td>
</tr>
<tr>
<td>ypTis</td>
<td>5</td>
<td>ypN1</td>
<td>157</td>
</tr>
<tr>
<td>ypT1</td>
<td>33</td>
<td>ypN2</td>
<td>72</td>
</tr>
<tr>
<td>ypT2</td>
<td>161</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypT3</td>
<td>350</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypT4</td>
<td>59</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- ypT0: 23.1% (183/792)  
- ypTis: 0.6% (5/792)    
- ypT1: 4.2% (33/792)    
- ypT2: 20.3% (161/792)  
- ypT3: 44.2% (350/792)  
- ypT4: 7.4% (59/792)    
- ypN0: 71.2% (567/796)  
- ypN1: 19.7% (157/796)  
- ypN2: 9.0% (72/796)
N = 540, randomized 1:1
cT4 or fixed at DRE cT3
M0
ECOG 0-2
Treatment length and total oxaliplatin dose were balanced.
Primary end-point [n=515]

R0 resection rates (surgery performed & pathologic R0 status):
- 77% for SCPRT with 3 cycles of chemotherapy
- 71% for CRT (control arm)
- (p=0.081)

Secondary end-points

<table>
<thead>
<tr>
<th></th>
<th>SCRPT + FOLFOX4</th>
<th>CRTx</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall acute toxicity</td>
<td>75%</td>
<td>83%</td>
<td>p= 0.006</td>
</tr>
<tr>
<td>Grade III/IV toxicities</td>
<td>23%</td>
<td>21%</td>
<td>NS</td>
</tr>
<tr>
<td>pCR rate</td>
<td>16%</td>
<td>12%</td>
<td>p= 0.17</td>
</tr>
</tbody>
</table>
Polish-2: Secondary end-points

Overall survival

Disease-free survival

p=0.046

p=0.85

chemoradiation

short-course radiotherapy with consolidating chemotherapy

[median follow-up: 36 months]
Conclusions

- CRT with capecitabine is a standard
- QA is essential
- We probably should be more selective for RT
- We need oncological outcomes/results of RAPIDO? Better paradigm
- We may need to consider immune markers
Thank you
Transcriptomic classification of four consensus molecular subtypes

- **CMS1**, called MSI-like, contains most microsatellite instable (MSI) tumors and enriched for tumors with a CpG-island methylator phenotype (CIMP) and mutations in the BRAF oncogene (14%).
- **CMS2**, called canonical, with high chromosomal instability (CIN) and activation of the Wnt and MYC pathways (37%).
- **CMS3**, called metabolic - enriched in KRAS mutations and shows a disruption of metabolic pathways (13%).
- **CMS4**, called mesenchymal, has a mesenchymal phenotype and frequent CIMP phenotype (23%) stratifies CRC into intrinsic subtypes with different prognosis.

### MRI FINDINGS

<table>
<thead>
<tr>
<th></th>
<th>T2, T3a, T3b &lt;4mm</th>
<th>T3b &gt;4mm</th>
<th>T3d &gt;15mm, T4a (resectable)</th>
<th>T3c, T3d, T4b</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRM not threatened</td>
<td>CRM not threatened</td>
<td>CRM not</td>
<td>CRM not threatened</td>
<td>CRM breached</td>
</tr>
<tr>
<td>(predicted margin ≥2mm)</td>
<td>(predicted</td>
<td>threatened</td>
<td>(predicted margin ≥2mm)</td>
<td>or threatened</td>
</tr>
<tr>
<td>N0</td>
<td>margin ≥2mm)</td>
<td>N2</td>
<td>N: Any</td>
<td>(predicted</td>
</tr>
<tr>
<td>EMVI: Negative</td>
<td>EMVI: Negative</td>
<td>EMVI:</td>
<td>EMVI: Any</td>
<td>margin &lt;1mm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive</td>
<td></td>
<td>N: Any</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EMVI: Any</td>
</tr>
</tbody>
</table>

### MRI RISK STRATIFICATION

#### LOW RISK

- Low risk local recurrence
- Low risk of metastases

#### INTERMEDIATE RISK

- Moderate risk of local recurrence
- High risk of metastases

#### HIGH RISK

- High risk of local recurrence
- High risk of metastases

### MRI DIRECTED CLINICAL MANAGEMENT

- **Surgery alone**
  - If able to perform good quality RO resection, RT may be omitted

- **SCPRT or CRT**
  - SCPRT or CRT depending on whether shrinkage of tumour required

- **CRT required**
  - CRT required or SCPRT + chemo
The FOWARC trial – Design

Endpoints
Primary endpoint: 3 yr DFS

*D Patients recruited from 15 Chinese Centres 2010-2015

Deng, J Clin Oncol 2016
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fluorouracil-Radiotherapy</th>
<th>mFOLFOX6-Radiotherapy</th>
<th>mFOLFOX6</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>143*</td>
<td>149</td>
<td>152</td>
</tr>
<tr>
<td>pCR†</td>
<td>20 (14.0)</td>
<td>41 (27.5)</td>
<td>10 (6.6)</td>
</tr>
<tr>
<td>OR (95% CI)‡</td>
<td>1</td>
<td>0.428 (0.237 to 0.776)</td>
<td>2.309 (1.041 to 5.121)</td>
</tr>
<tr>
<td>ypStage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>53 (37.1)</td>
<td>84 (56.4)</td>
<td>54 (35.5)</td>
</tr>
<tr>
<td>OR (95% CI)‡</td>
<td>1</td>
<td>0.453 (0.283 to 0.726)</td>
<td>1.093 (0.679 to 1.759)</td>
</tr>
<tr>
<td>II-IV</td>
<td>90 (62.9)</td>
<td>65 (43.6)</td>
<td>98 (64.5)</td>
</tr>
<tr>
<td>OR (95% CI)‡</td>
<td>1</td>
<td>2.201 (1.376 to 3.520)</td>
<td>0.964 (0.599 to 1.552)</td>
</tr>
<tr>
<td>TRG§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>70 (49.0)</td>
<td>102 (68.5)</td>
<td>50 (32.9)</td>
</tr>
<tr>
<td>OR (95% CI)‡</td>
<td>1</td>
<td>0.431 (0.266 to 0.697)</td>
<td>2.032 (1.264 to 3.267)</td>
</tr>
<tr>
<td>2-3</td>
<td>71 (49.7)</td>
<td>46 (30.9)</td>
<td>102 (67.1)</td>
</tr>
<tr>
<td>OR (95% CI)‡</td>
<td>1</td>
<td>2.335 (1.448 to 3.765)</td>
<td>0.511 (0.319 to 0.819)</td>
</tr>
</tbody>
</table>

Abbreviations: mFOLFOX6, modified infusional fluorouracil, leucovorin, and oxaliplatin; OR, odds ratio; pCR, pathologic complete response; TRG, tumor regression grading.

*Includes two patients with progressive disease who did not undergo surgery.
†pCR was evaluated independently by two pathologists blinded to treatment groups.
‡ORs were calculated compared with the fluorouracil-radiotherapy group by using logistical regression.
§TRG was evaluated semiquantitatively on a scale of 0 to 3 (complete to poor response, respectively).
<table>
<thead>
<tr>
<th>Regimens</th>
<th>Number of patients</th>
<th>G3/G4 toxicity Diarrhea</th>
<th>Interval to surgery (median in days)</th>
<th>ypN+</th>
<th>pCR</th>
<th>TRG0-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Gramont RT 46-50.4Gy</td>
<td>165</td>
<td>7.7%</td>
<td>53</td>
<td>19.1%</td>
<td>14%</td>
<td>49%</td>
</tr>
<tr>
<td>FOLFOX RT 46-50.4Gy</td>
<td>165</td>
<td>14.5%</td>
<td>52</td>
<td>12.6%</td>
<td>27.5%</td>
<td>68.5%</td>
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<tr>
<td>FOLFOX alone</td>
<td>165</td>
<td>7.3%</td>
<td>Not stated</td>
<td>Not stated</td>
<td>6.6%</td>
<td>32.9%</td>
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</table>
## FOWARC

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Number of patients</th>
<th>MRI staging</th>
<th>Good quality TME</th>
<th>G3/G4 toxicity diarrhea</th>
<th>Interval to surgery (median in days)</th>
<th>pCR</th>
<th>TRG0-1</th>
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</thead>
<tbody>
<tr>
<td>De Gramont RT 46-50.4Gy</td>
<td>165</td>
<td>95%</td>
<td>80%</td>
<td>7.7%</td>
<td>53</td>
<td>14%</td>
<td>49%</td>
</tr>
<tr>
<td>FOLFOX RT 46-50.4Gy</td>
<td>165</td>
<td></td>
<td></td>
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