State-of-the-art: Standards of care in preoperative treatment 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
Accepted wisdom: Preoperative Options in resectable rectal cancer

- **Short Course Preoperative Radiotherapy** (SCPRT - 5 x 5Gy) usually given in Nordic countries, the UK and The Netherlands

- **Long Course Chemoradiation (with fluoropyrimidine)** 45-50Gy usually given in most of Central and Southern Europe
Preoperative Options to influence outcomes in rectal cancer

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

- Different combinations and sequences of the above (4 x 3 x 2 x 1 = 24)
NCCN Guidelines Version 1.2018
Rectal Cancer

CLINICAL STAGE  NEOADJUVANT THERAPY  PRIMARY TREATMENT  ADJUVANT TREATMENT

T3, N any with clear circumferential margin (CRM) (by MRI):1
T1-2, N1-2

Chemo/RT
- Capecitabine/long-course RT\textsuperscript{1} or infusional 5-FU/long-course RT\textsuperscript{1} (category 1 and preferred for both) or
- Bolus 5-FU/leucovorin/long-course RT\textsuperscript{0,4}

or
- Short-course RT

Consider restaging\textsuperscript{c}

Transabdominal resection\textsuperscript{h,u,v}
Resection contraindicated

C3, N0 before chemo/RT

5-FU/leucovorin or capecitabine or FOLFOX (preferred) or CAPEOX (preferred)

Surveillance
(See REC-11)

CT1-3, N1-2 before chemo/RT

FOLFOX or CAPEOX

Surveillance
(See REC-11)

Systemic therapy\textsuperscript{w}
(See REC-F)

Capecitabine/RT (preferred) or infusional 5-FU/RT (preferred) or bolus 5-FU/leucovorin/RT\textsuperscript{3} or Short-course RT\textsuperscript{t}

Restaging\textsuperscript{c}

Transabdominal resection\textsuperscript{h,u}
Resection contraindicated

Systemic therapy\textsuperscript{w}
(See REC-F)

\textsuperscript{c}See Principles of Imaging (REC-A).
\textsuperscript{h}See Principles of Surgery (REC-C).
\textsuperscript{1}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.
\textsuperscript{0}Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
\textsuperscript{3}See Principles of Adjuvant Therapy (REC-D).
\textsuperscript{4}See Principles of Radiation Therapy (REC-E).
\textsuperscript{1}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.
\textsuperscript{w}If patient treated with short course RT, surgery should be within 1 week or delayed 6-8 weeks.
\textsuperscript{2}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.
\textsuperscript{w}FOLFOXIRI 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.
US Intergroup phase III trial
ACOSOG, Z9062, CALGB, E81001

LARC stage II/III
MRI: CRM -ve

R

5FU CRT
FOLFOX #6

PR/SD?

T
M
E

PD?

R0?
R1/2?

5FU CRT

FOLFOX #8
FOLFOX #6

N planned: >11201° endpoint: 3y DFS
2° toxicity, local failures, OS,
Some European Guidelines for Rectal Cancer

EURECCA colorectal: Multidisciplinary management: European consensus conference colon & rectum

Cornelis J.H. van de Velde, Petra G. Boelens, Josep M. Borras, Jan-Willem Coebergh, Lennart Blomqvist

DOI 10.1007/s12094-016-1591-0

SEOM Clinical Guideline of localized rectal cancer (2016)

K. Gonzalez-Flores • F. Lusa • C. Preluca • E. Pah • S. Roselló • M. J. Safont • R. Vera • J. Aparicio • M. T. Caño • C. Fernandez-Martos


Practice parameters for early rectal cancer management: Italian Society of Colorectal Surgery (Societá Italiana di Chirurgia Colo-Rettale; SICCR) guidelines

A. Arezzo, F. Bianco, F. Arienti, C. Cozzi, R. Falietti, F. Khusaib, G. Rotondaro, G. A. Santoro, N. Verri, S. De Franciscis, A. Ball, G. M. Rocchetti

Changes in nationwide use of preoperative radiotherapy for rectal cancer after revision of the national colorectal cancer guideline

ESMO Rectal Cancer Guidelines 2017

CLINICAL PRACTICE GUIDELINES

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

R. Glynne-Jones¹, L. Wyrwicz², E. Tirt³,⁴, G. Brown⁵, C. Rödel⁶, A. Cervantes⁷ & D. Arnold⁸ on behalf of the ESMO Guidelines Committee

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

†Approved by the ESMO Guidelines Committee: August 2002, last update May 2017. This publication supersedes the previously published version—Ann Oncol 2013; 24 (Suppl. 6):v81–v88.

RISK ADAPTIVE STRATEGIES
ESMO guidelines: Risk adaptive strategies

Rectal cancer: treatment

Very early disease
cT1, sm1 cN0

Local RT may be used as an alternative to local surgery (+/- CRT)

TEM if pT1 and no adverse features
TEM plus perioperative CRT if adverse features present
TME if adverse histopathology (sm ≥2, G3, V1, L1)

Early disease
cT1-cT2; cT3a (b if middle or high) cN0 (cN1 if high), MRF clear, no EMVI

CRT or ‘watch-and-wait’ for fragile, high-risk patients or those rejecting radical surgery
MRI to re-evaluate tumour

TME in most cases (plus photographic record of specimen and assessment of TME quality)
Postoperative CRT/chemotherapy (fluoropyrimidine+/oxaliplatin) considered if poor prognostic signs on histopathology (CRM+, extranodal/N2)

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

SCPRT or CRT if good-quality mesorectal resection not assured
MRI to re-evaluate tumour

TME in most cases (plus photographic record of specimen and assessment of TME quality)

Locally advanced disease
cT3c,d or very low, levators threatened, MRF clear cT3c,d mid-rectum, cN1-N2 (extranodal), EMVI+, limited cT4aN0

SCPRT or CRT

MRI to re-evaluate tumour

‘Watch-and-wait’ may be considered in high-risk patients if cCR achieved with CRT

TME (plus photographic record of specimen and assessment of TME quality)

Locally advanced disease
cT3c,d mid-rectum, cN0-N1, MRF threatened

SCPRT plus FOLFOX and delay to surgery

MRI to re-evaluate tumour

‘Watch-and-wait’ may be considered in high-risk patients if cCR achieved with CRT

TME (plus photographic record of specimen and assessment of TME quality)

Advanced disease
cT3 with any MRF involved, any cT4a,b, lateral node+

CRT

Further surgery if needed due to tumour overgrowth

notes:
cCR, clinical complete response; CRM, circumferential resection margin; CRT, chemoradiotherapy; EMVI, extramural vascular invasion; FOLFOX, leucovorin/fluorouracil/oxaliplatin; MRF, mesorectal fascia; RT, radiotherapy; SCPRT, short-course preoperative RT; TEM, transanal endoscopic microsurgery; TME, total mesorectal excision
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

What we know

1. CRT /SCPRT reduce local recurrence
What we know

1. CRT /SCPRT reduce local recurrence

Swedish Rectal Cancer trial, German CAO/ARO/AIO trial, Dutch TME trial, CR07 etc..
Pre- vs post-operative chemoradiation
CAO/ARO/AIO-94

Overall Survival (%)

Time (months)

No. at risk
Preop. CRT  404  351  305  268  174  67  6
Postop. CRT 395  342  295  262  172  70  6

Preoperative treatment arm, 59.9%
Postoperative treatment arm, 59.6%
P = .85
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)
What we know

1. CRT /SCPRT reduce local recurrence
2. CRT (45 Gy/25/33 days) gives more down-staging than RT alone (45 Gy/25/33 days) [EORTC 22921]---pCR
What we know

1. CRT /SCPRT reduce local recurrence
2. CRT (45 Gy/25/33 days) gives more down-staging than RT alone (45 Gy/25/33 days) [EORTC 22921]
3. Post-op adjuvant 5FU alone does not reduce metastatic disease or improve outcomes (after CRT/SCPRT)

But poor compliance and delay to start
So shift to Neoadjuvant chemotherapy
NCCTG/Mayo 794751

Semustine
Bolus 5-FU

68% pN+

204 patients

Graphs showing disease-free survival and overall survival.

Impact on overall survival of 6 methods of treatment in rectal cancer pooled analysis

- Surgery (S) alone
- S+Radiation (RT)
- S+Chemotherapy (CT)
- S+RT+Bolus CT
- S+RT+Infusion CT
- S+RT+Bolus CT (INT 0114)

*pNode negative 1171
pNode positive 2573 (69%)

Stage II if $\geq 12$ LNs examined, TTR significantly prolonged in newer- versus older trials.

Suggests undetected 20-30% stage III disease in older trials even if 12 LNs examined.

Shi Q et al  J Clin Oncol 31:3656-3663
EORTC 22921 – Overall Survival - 25% ypN+

10 year OS 51.8% vs 48.4%  (HR 0.91- 95% CI 0.77–1.09; p=0.32)
Data from the PROCTOR SCRIPT trial
Swets M et al Eur J cancer 2018;89:1-8

<table>
<thead>
<tr>
<th>biomarker</th>
<th>patients / event</th>
<th>HR</th>
<th>95%CI</th>
<th>p-value</th>
<th>P for interaction</th>
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<tbody>
<tr>
<td>Lymphatic invasion</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>present</td>
<td>120 / 40</td>
<td>1.15</td>
<td>(0.62-2.14)</td>
<td>0.66</td>
<td>0.99</td>
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<tr>
<td>absent</td>
<td>100 / 22</td>
<td>1.12</td>
<td>(0.49-2.60)</td>
<td>0.78</td>
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<tr>
<td>PNI</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>present</td>
<td>19 / 13</td>
<td>0.96</td>
<td>(0.31-2.90)</td>
<td>0.96</td>
<td>0.89</td>
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<td>1.11</td>
<td>(0.64-1.93)</td>
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<td>present</td>
<td>62 / 26</td>
<td>0.78</td>
<td>(0.36-1.69)</td>
<td>0.52</td>
<td>0.31</td>
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<tr>
<td>absent</td>
<td>159 / 37</td>
<td>1.35</td>
<td>(0.71-2.59)</td>
<td>0.36</td>
<td></td>
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<tr>
<td>IMVI</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>present</td>
<td>38 / 13</td>
<td>0.99</td>
<td>(0.30-3.23)</td>
<td>0.99</td>
<td>0.72</td>
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<tr>
<td>absent</td>
<td>182 / 49</td>
<td>1.17</td>
<td>(0.67-2.06)</td>
<td>0.58</td>
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<tr>
<td>Tumor budding</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>present</td>
<td>99 / 36</td>
<td>1.20</td>
<td>(0.63-3.32)</td>
<td>0.58</td>
<td>0.65</td>
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<tr>
<td>absent</td>
<td>119 / 26</td>
<td>0.93</td>
<td>(0.43-2.01)</td>
<td>0.86</td>
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<td>Combination of biomarkers</td>
<td></td>
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<tr>
<td>&lt; 2 biomarkers</td>
<td>118 / 20</td>
<td>1.46</td>
<td>(0.59-3.56)</td>
<td>0.41</td>
<td>0.55</td>
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<tr>
<td>≥ 2 biomarkers</td>
<td>103 / 43</td>
<td>1.08</td>
<td>(0.59-1.97)</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>221 / 63</td>
<td>1.12</td>
<td>(0.68-1.81)</td>
<td>0.65</td>
<td></td>
</tr>
</tbody>
</table>

- Favours chemotherapy
- Favours observation

Overall survival for all patients and by patients subgroups, comparing observation and adjuvant chemotherapy.
So

- 5FU ?not going to improve survival for stage II
- Difficult to select preoperatively for CRT or for NACT!
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>
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<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>
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<td>cN+</td>
<td>213</td>
<td>6.9</td>
<td>220</td>
<td>28.9</td>
<td>193</td>
<td>74.7</td>
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<td>unknown</td>
<td>17</td>
<td></td>
<td>17</td>
<td></td>
<td>16</td>
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</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>Parameters of clinical lymph node staging in %.</th>
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<tbody>
<tr>
<td>Colon cancer without neoadjuvant treatment</td>
</tr>
<tr>
<td>(n=21,629)</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>PPV</td>
</tr>
<tr>
<td>NPV</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)
The Mercury Study

Even Gina Brown did not find that defining LN status on MRI predicted DFS or OS or LR!
What we know

1. CRT /SCPRT reduce local recurrence
2. CRT (45 Gy/25/33 days) gives more down-staging than RT alone (45 Gy/25/33 days)
3. Post-op adjuvant 5FU alone does not reduce metastatic disease or improve outcomes (after CRT/SCPRT)
4. Good quality TME improves outcomes
ESMO guidelines 2017

“For patients with LARC, treatment decisions regarding neoadjuvant therapy should be based on preoperative,
- MRI-predicted CRM (≤1 mm),
- EMVI
- and more advanced T3 sub-stages (T3c/T3d)

which define the risk of both local recurrence and/or synchronous and subsequent metastatic disease (Hunter 2012)”

We didn’t specify nodes
Oncological outcome after MRI-based selection for neoadjuvant chemoradiotherapy in the OCUM Rectal Cancer Trial

R. Ruppert¹, T. Junginger², H. Ptok⁴, J. Strassburg⁵, C. A. Maurer¹⁰, P. Brosi¹¹, J. Sauer⁷, J. Baral⁸, M. Kreis⁶, D. Wollschlaeger³, P. Hermanek⁹ and S. Merkel⁹, on behalf of the OCUM group

¹Department of General and Visceral Surgery, Endocrine Surgery and Coloproctology, Municipal Hospital of Munich-Neuperlach, Munich, ²Department of General and Abdominal Surgery and ³Institute of Medical Biostatistics, Epidemiology and Informatics, University Medical Centre, Johannes Gutenberg University, Mainz, ⁴Department of Surgery, Carl-Thiem-Klinik, Cottbus, ⁵Department of General and Visceral Surgery, Vivantes Klinikum im Friedrichshain, and ⁶Department of Surgery, Campus Benjamin Franklin, Charité, University Medicine Berlin, Berlin, ⁷Department of General, Visceral and Minimally Invasive Surgery, Arnsberg, ⁸Department of General and Visceral Surgery, Municipal Hospital, Karlsruhe, and ⁹Department of Surgery, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany, and ¹⁰Hirslanden Private Hospital Group, Clinic Beau-Site, Berne, and ¹¹Department of Surgery and Transplantation, University Hospital Zurich, Zurich, Switzerland

Correspondence to: Professor T. Junginger, Department of General and Abdominal Surgery, University Medical Centre Mainz, Langenbeckstrasse 1, D 55131 Mainz, Germany (e-mail: junginger@uni-mainz.de)

Background: It is not clear whether all patients with rectal cancer need chemoradiotherapy. A restrictive use of neoadjuvant chemoradiotherapy (nCRT) based on MRI findings for rectal cancer was investigated in this study.
Only 4/228 predicted negative CRM were $\leq 1$ mm
Local Recurrence

5 year local recurrence rate for 428 patients (per protocol) = 2.7%

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
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<tbody>
<tr>
<td>Primary surgery</td>
<td>254</td>
<td>239</td>
<td>229</td>
<td>218</td>
<td>177</td>
<td>127</td>
</tr>
<tr>
<td>Surgery after nCRT</td>
<td>174</td>
<td>163</td>
<td>156</td>
<td>139</td>
<td>118</td>
<td>83</td>
</tr>
<tr>
<td>Surgery only instead of surgery after nCRT or nRT</td>
<td>44</td>
<td>40</td>
<td>36</td>
<td>31</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>Surgery after nCRT or nRT instead of primary surgery</td>
<td>71</td>
<td>68</td>
<td>65</td>
<td>61</td>
<td>49</td>
<td>38</td>
</tr>
</tbody>
</table>
What we don’t know

- Does neoadjuvant or post-op adjuvant 5FU and oxaliplatin reduce metastatic disease?
- Shift to NACT because more down-staging
The standard of care for localized rectal cancer:

You need

- High quality Magnetic Resonance Imaging (MRI).
The optimal management of localized rectal cancer:

You need

- High quality Magnetic Resonance Imaging (MRI).
- 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
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>
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<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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</table>
Local Recurrence rates in CRO7 according the plane of surgery

<table>
<thead>
<tr>
<th>TNM stage</th>
<th>Plane of Surgery</th>
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<tbody>
<tr>
<td>I</td>
<td>Muscularis propria</td>
<td>Intra-mesorectal</td>
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<tr>
<td>I</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>II</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>III</td>
<td>20%</td>
<td>14%</td>
</tr>
</tbody>
</table>
Pathologically defined Lymph nodes only affect your local recurrence rate if you leave them inside the patient!
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.
- A functional MDT with a good chair.
Conclusions

- CRT with capecitabine is a standard
- QA is essential
- We probably should be more selective for RT
- No evidence that we benefit stage II with chemotherapy ? stage III (if we could define)
- We need oncological outcomes/results of RAPIDO ? Better paradigm
Thank you