Organ sparing-strategy in rectal cancer

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Actual treatment in rectal cancer

Early rectal cancer (T1, T2, N0)
- TEM/TAE
- TAMIS

Advanced rectal cancer ≥ T3, TxN1
- MRI good
- Neoadjuvant (chemo)radiotherapy

Radical Surgery
- TME +/- proctectomy

MRI good → cCR
"wait and see" organ sparing
Appeal of organ preservation

Minimal perioperative morbidity and mortality (4%)
- bleeding
- anastomotic leak (5%-18%)

Rapid recovery

Preservation of bowel function
- ‘low anterior resection’ syndrome
- permanent colostomy (20%)

Preservation of urogential function

Improved QoL

Reduction in Health care cost
What is the exact role of LE in early rectal cancer?
LNM in pT1 – depth of submucosal invasion

<table>
<thead>
<tr>
<th>depth</th>
<th>n</th>
<th>n (%)N+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sm1</td>
<td>70</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Sm2</td>
<td>120</td>
<td>9 (8%)</td>
</tr>
<tr>
<td>Sm3</td>
<td>154</td>
<td>35 (23%)</td>
</tr>
</tbody>
</table>

Nascimbeni R et al. *Dis Colon Rectum* 2002;45, 200-206
Clinicopathologic features of rectal cancer associated with nodal disease (T1≠T1)

<table>
<thead>
<tr>
<th></th>
<th>pN+(%)</th>
<th>pN-(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor differentiation</td>
<td>84.6%*</td>
<td>15.4%</td>
</tr>
<tr>
<td>LVI</td>
<td>72.4%*</td>
<td>27.6%</td>
</tr>
<tr>
<td>PNI</td>
<td>73.7%*</td>
<td>26.3%</td>
</tr>
</tbody>
</table>

* P<0.001, chi-squared
A predictive model for local recurrence after transanal endoscopic microsurgery for rectal cancer

S. P. Bach¹, J. Hill², J. R. T. Monson³, J. N. L. Simson⁴, L. Lane⁵, A. Merrie⁷, B. Warren⁶ and N. J. McC. Mortensen⁵, on behalf of the Association of Coloproctology of Great Britain and Ireland Transanal Endoscopic Microsurgery (TEM) Collaboration

Risk stratification comes after the local excision and T staging suboptimal (20% understaging uT1)

Br Journal of Surgery 2009;⁹⁶:280-290
Early TME after TEM

UK TEM database, courtesy by Mr C. Cunningham
uT1

TAMIS

Low risk pT1  High risk pT1

average risk patient  high risk patient

Follow-up  Radical Resection  Follow-up

Decision making includes patients characteristics
Effect of neoadjuvant chemo-radiotherapy

may induce significant tumor regression:

- Reduction in tumor size (downsizing)
- Reduction in depth of penetration (downstaging)
- Nodal sterilization
- Pathological complete response (pCR)
TME after neoadjuvant chemoradiation

\( ypT0N0 \) (ypCR)

T2-4, N+ rectal cancer, n = 3105

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>cT2</td>
<td>4%</td>
<td>28%</td>
</tr>
<tr>
<td>cT3</td>
<td>83%</td>
<td>16%</td>
</tr>
<tr>
<td>cT4</td>
<td>12%</td>
<td>12%</td>
</tr>
</tbody>
</table>

TME after neoadjuvant chemoradiation

\( ypT0N0 \) (ypCR)

T2-4, N+ rectal cancer, n = 3105

Can we avoid radical surgery in good responders after chemoradiotherapy?

concept of sustained clinical complete response
n = 265 pts, **distal rectal cancer**

stratification at 8-10 weeks

Local Excision:

n = 22 pts
(8.3%) pT0

wait and see

n = 71 pts
(26.8%)
sustained cCR

---

“wait and see strategy”

1. Timing of response assessment

2. How to assess cCR

3. Early and late failures

4. How to optimise neoadjuvant treatment
Radiation induced necrosis (apoptosis) is time-dependent

Dhadda A.S. *Clinical Oncology* 2009; 21:23-31
12 weeks: the new standard?

Observational

Probst CJ Am Coll Surg 2015;221:430-440
Timing of tumor assessment at 12 w for every one?

Perez RO et al. *Int J Radiation Oncol Biol Phys* 2012
Complete clinical response inter observer variability?

- careful digital examination

- proctoscopy
  - whitening of mucosa
  - teleangiectasia
  - loss of plicability of rectal wall

Habr-Gama et al. *Dis of Colon Rectum* 2010;53:1692-1698
Predictive value of clinical complete response (ccR)

n = 488 patients
Memorial Sloan Kettering

ccR = 19%

cpR = 10%

ccR = predictive factor for cpR

but:

75% of ccR : residual foci of tumor:
Maastricht (Dutch) criteria for multimodal assessment of response

- substantial downsizing: no residual tumor, only fibrosis (low signal on high b-value DW-MRI)

- no suspicious lymph nodes on MRI

- no residual tumor at endoscopy (residual scar)

- normal biopsies from the scar

- no palpable tumor

diagnostic performance of MRI for the prediction of complete response (ypT0)

<table>
<thead>
<tr>
<th></th>
<th>Standard MRI</th>
<th>MRI + DWI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0-40%</td>
<td>52-64%</td>
</tr>
<tr>
<td>Specificity</td>
<td>92-98%</td>
<td>89-97%</td>
</tr>
<tr>
<td>PPV</td>
<td>0-56%</td>
<td>62-81%</td>
</tr>
<tr>
<td>NPV</td>
<td>79-85%</td>
<td>88-90%</td>
</tr>
<tr>
<td>AUC</td>
<td>0.58-0.76</td>
<td>0.78-0.80*</td>
</tr>
<tr>
<td>(\kappa) – IO agreement</td>
<td>0.2-0.32</td>
<td>0.51-0.58</td>
</tr>
</tbody>
</table>

Positive posttest probability

- Clinical: 90%
- T2-MRI / DWI MRI: 75%
- All: 98%

Negative posttest probability

- Clinical: 20%
- T2-MRI / DWI MRI: 26%
- All: 15%

patient not eligible for wait and see
near complete response: minimal residual disease
Can biopsies rule out persisting cancer in incomplete clinical response?

\[ \text{PPV} = 100\% \quad \text{NPV} = 21\% \]

\[ \text{accuracy} = 71\% \]

<table>
<thead>
<tr>
<th>Biopsy finding</th>
<th>Incomplete histopathological response</th>
<th>Complete histopathological response</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Negative</td>
<td>11</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>3</td>
<td>39</td>
</tr>
</tbody>
</table>

Perez RO et al. *Colorectal Dis* 2012
Response is heterogeneous in the tumor

Significant no of advanced cancers do not have residual cancer cells in mucosa, submucosa after chemoradiation
LE after chemoradiation in good responders?

What margins margins?

= excisional biopsy to further tailor treatment
(avoid to jeopardise CRM if completion is needed)
# Morbidity TEM after neoadjuvant chemoradiation therapy

<table>
<thead>
<tr>
<th></th>
<th>Study group (neoadjuvant CRT) N=23</th>
<th>Control group N = 13</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I morbidity</td>
<td>52%</td>
<td>13%</td>
<td>0.030</td>
</tr>
<tr>
<td>Grade II/III</td>
<td>56%</td>
<td>23%</td>
<td>0.050</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>70%</td>
<td>23%</td>
<td>0.030</td>
</tr>
<tr>
<td>Hospital readmission</td>
<td>43%</td>
<td>7%</td>
<td>0.020</td>
</tr>
<tr>
<td>Late complications</td>
<td>4%</td>
<td>15%</td>
<td>0.25</td>
</tr>
<tr>
<td>Interval to healing</td>
<td>8 (5-12) weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Perez RO et al. *Dis Colon Rectum 2011; 54*: 545-551
Nodal metastasis in relation to ypT

<table>
<thead>
<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ypT0</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>ypT1</td>
<td>4</td>
<td>8</td>
<td>7</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>ypT2</td>
<td>23</td>
<td>26</td>
<td>20</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td>ypT3</td>
<td>47</td>
<td>55</td>
<td>36</td>
<td>37</td>
<td>40</td>
</tr>
</tbody>
</table>
What about lymph nodes?

TME: ypT0N1
### Actual series on non-operative treatment after chemoradiation and cCR

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>cCR</th>
<th>FU (mo)</th>
<th>Local failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habr Gama 2006 (1991-2005)</td>
<td>361</td>
<td>99 (27.4%)</td>
<td>60</td>
<td>5 (5.0%)</td>
</tr>
<tr>
<td>Habr Gama 2011 (1991-2011)</td>
<td>173</td>
<td>67 (38.7%)</td>
<td>65</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Maas 2011</td>
<td>192</td>
<td>21 (10.9%)</td>
<td>25</td>
<td>1 (4.7%)</td>
</tr>
<tr>
<td>Yu 2011</td>
<td>22</td>
<td>17.8</td>
<td></td>
<td>9 (41%)</td>
</tr>
<tr>
<td>Dalton 2012</td>
<td>49</td>
<td>12 (24%)</td>
<td>25</td>
<td>6 (50%)</td>
</tr>
</tbody>
</table>
Improving local control in rectal cancer

- Radio-chemotherapy
- Resting period

- Radio-chemotherapy
- Resting period

- Radio-chemotherapy
  - Resting period
  - Chemotherapy
  - Resting period

Higher radiation dose
Effective radiation sensitization

Increasing interval to surgery
Neoadjuvant chemotherapy
Additional chemotherapy during resting period

**TABLE 1. Patient’s demographics and clinical features**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>29</td>
<td>100</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57.6 ± 12.2</td>
<td></td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>21/8 (72.4/27.6)</td>
<td></td>
</tr>
<tr>
<td>Distance anal verge (cm)</td>
<td>3.76 ± 1.58</td>
<td></td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>3.80 ± 0.89</td>
<td></td>
</tr>
<tr>
<td>Initial staging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>(17.2)</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>(82.8)</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>25</td>
<td>(86.2)</td>
</tr>
<tr>
<td>N+</td>
<td>4</td>
<td>(13.8)</td>
</tr>
<tr>
<td>Initial disease staging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>5</td>
<td>(17.2)</td>
</tr>
<tr>
<td>II</td>
<td>20</td>
<td>(69.0)</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>(13.8)</td>
</tr>
</tbody>
</table>

Values presented in parentheses are percentages.

Habr-Gama A. *Dis Colon Rectum* 2009;52(12):1927-1934
Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial


- **Group 1**: Continuous infusion fluorouracil + radiotherapy → Rest → Total mesorectal excision (ypT0N0) 18%
- **Group 2**: Continuous infusion fluorouracil + radiotherapy → Rest → mFOLFOX6 (two cycles) → Rest → Total mesorectal excision 25%
- **Group 3**: Continuous infusion fluorouracil + radiotherapy → Rest → mFOLFOX6 (four cycles) → Rest → Total mesorectal excision 30%
- **Group 4**: Continuous infusion fluorouracil + radiotherapy → Rest → mFOLFOX6 (six cycles) → Rest → Total mesorectal excision 38%

no increased morbidity in delayed TME group
Danish Prospective Observational Study

- 51 Stage I-III low rectal cancer patients (< 6m from anal verge)
- EBR 60 Gy + Brachytherapy boost 6Gy + Tagefur/Uracyl 300 mg/m²

\[ \text{cCR} \quad 40 \text{ pts (78%)} \]

At median FU 23.9 m

- 9 regrowth (22%) : all salvaged, all R0
- 3 DM

\[ \text{NO cCR} \quad 0 \text{ recurrence after TME} \]
Danish Prospective Observational Study
Cumulative local recurrence in the cCR group

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


The next best evidence?

prospective randomised trials unlikely to happen

Lancet Oncol 2016
Tumour regrowth:
n=109 :28% at 1 yr. (95% endoluminal)
Regrowth in near complete response
Stringent and prolonged FU needed

Y 1 – Y 2  clinical / 2mo
MRI/ 4mo

Y 3 – Y 5  clinical/ 4mo
MRI/ 6mo

Y 5 – Y 10  clinical/ 6mo
MRI/ 1 yr
Colostomy-free survival

A Colostomy-free survival

B Colostomy-free survival difference (RP model)

Number at risk

- cCR and watch and wait: 109
- Surgical resection: 109

Time since start of CRT (months)

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT</td>
<td>90</td>
<td>68</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>CRT</td>
<td>56</td>
<td>53</td>
<td>20</td>
<td>26</td>
</tr>
</tbody>
</table>
A  Non-regrowth disease-free survival

Time-varying HR 0.497 (95% CI 0.25–0.98); p=0.043

B  Overall survival

Time-varying HR 0.321 (95% CI 0.12–0.86); p=0.024

Number at risk
- cCR and watch and wait 102 80 55 109
- Surgical resection 104 86 33 109

Survival (%)
Functional outcome should be monitored also for wait and see.
"clinical" complete response after chemo-radiation and long interval

- "wait and see"
- TAE/TEM (excisional biopsy)
  - early regrowth
  - sustained cCR
  - ypT0
  - yp≥T1
- close follow-up
- delayed radical surgery
- radical surgery

late failures
“wait and see protocols”

- lack of clarity to **define** clinical complete response (cCR)
  - clinical criteria
  - imaging
  - punch biopsy – TEM (excisional biopsy)

- 20% - 30% fail the first year (**early regrowth**)
  - outcome early salvage

- uncertainty in regard to long-term efficacy (**late failure**)
  - rational, consistent follow-up programme
  - selection of patients
  - outcome late salvage
Conclusion

non-operative treatment **not accepted paradigm yet** (but appealing)

optimal neoadjuvant therapy to be determined

**multimodal-defined cCR** improves accuracy

**longer follow-up** needed (>5 yrs.)