NON-SURGICAL MANAGEMENT OF EARLY STAGE RECTAL CANCER

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WHAT IS NON-SURGICAL MANAGEMENT OF RECTAL CANCER?

• Accurately identifying patients who have had a complete clinical response to neoadjuvant therapy
• Following a surveillance protocol to identify recurrences early so that survival is not compromised
• Other names:
  – Non-operative management
  – Watch-and-Wait strategy
DEFINITION OF COMPLETE CLINICAL RESPONSE (cCR)

- No evidence of disease after neoadjuvant therapy
  - Digital rectal exam (DRE)
    - Flat mucosa without mass or nodularity
  - Endoscopy
    - Flat white scar with or without telangiectasias and lack of ulceration or nodularity
  - MRI
    - No detectable tumour or lymph node

CCR, complete clinical response; MRI, magnetic resonance imaging
THE HISTORY OF THE ‘WATCH-AND-WAIT’ STRATEGY
PIVOTAL STUDY: HABR-GAMA 2004

• Published a study reporting a ‘watch-and-wait’ (W&W) approach
  – Retrospective study of from 1991-2002: 93 patients (71 with cCR and 22 with pCR at surgery)
    • 80% with T3/T4 lesions
    • 22.5% with node + disease
  – 27% cCR to neoadjuvant therapy
  – 3% local recurrence rate
  – 4% distal recurrence rate
  – 92% DFS at 5 years
  – 100% OS at 5 years

• Suggested W&W may be a feasible approach for patients

• Since then, there have been multiple W&W strategy studies published

• A review of several prospective studies follows...

cCR, clinical complete response; DFS, disease-free survival; Gy, gray; OS, overall survival; pCR, pathologic complete response; T, tumour; W&W, watch-and-wait
MAASTRICHT UNIVERSITY STUDY

- **100 patients with cCR or near cCR**
  - 85 patients → NOM
  - 15 patients underwent TEM

- Median follow-up = 3.4 years

- **3-year OS** = 97%
- **3-year DMFS** = 97%

Martens MH et al. JNCI 2016;108(12):1-10

cCR, clinical complete response; DMFS, distant metastases-free survival; NOM, non-operative management; OS, overall survival; TEM, transanal endoscopic microsurgery
DANISH PROSPECTIVE STUDY: HIGH-DOSE CRT

- 55 patients with distal rectal cancer, cT2-3, N0-1
- IMRT 60 Gy/30 fx to tumour, 50 Gy/30 fx to pelvis + concurrent oral tegafur-uracil
- Endorectal brachytherapy boost: 5 Gy
- 6 weeks post-CRT: endoscopy + MRI
- **78% cCR observed**
  - 2-year LR = 26%
  - All salvaged with R0 surgery
  - No increase in surgical complications
- **Low rate (<10%) G3+ acute/late toxicity**

cCR, complete clinical response; CRT, chemoradiation; cT, clinical tumour stage; fx, fractions; G, grade; Gy, gray; IMRT, intensity-modulated radiotherapy; LR, local recurrence; MRI, magnetic resonance imaging; N, node; R, residual tumour
HABR-GAMA PROSPECTIVE STUDY

- 70 patients with T2-4 N0-2M0 distal rectal cancer
- Neoadjuvant chemoradiotherapy included 54 Gy and 5FU/LV delivered in 6 cycles every 21 days
- 47 (68%) patients had initial cCR
  - 27% local recurrence
  - most (17%) within first 12 months
  - 4 patients (10%) >12 months of follow-up
- 35 patients (50%) avoided surgery
- 3-year OS = 90%

5FU, fluorouracil; cCR, complete clinical response; Gy, gray; M, metastasis; LV, leucovorin; N, node; OS, overall survival; T, tumour
Habr-Gama A et al. Dis Colon Rectum 2013;56(10):1109-17
• Pooled data from 23 studies, 867 patients with rectal adenocarcinoma managed by W&W after cCR to neoadjuvant chemoradiation

• 2-year local recurrence rate: 15.7%
  – 95% had salvage surgeries

• NOM vs. surgery with cCR or pCR
  – No difference in OS or cancer-specific mortality
SURGERY WITH PCR VS CCR MANAGED BY W&W

A. Disease-free survival for patients treated by surgery with pCR vs W&W

<table>
<thead>
<tr>
<th></th>
<th>W&amp;W</th>
<th>Surgery with pCR</th>
<th>Weight (%)</th>
<th>HR IV, random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Araujo et al (2015)</td>
<td>23/42</td>
<td>22/69</td>
<td>77.4</td>
<td>0.47 (0.26-0.84)</td>
</tr>
<tr>
<td>Smith et al (2012)</td>
<td>N/A/32</td>
<td>N/A/57</td>
<td>10.1</td>
<td>0.29 (0.06-1.43)</td>
</tr>
<tr>
<td>Maas et al (2011)</td>
<td>1/21</td>
<td>4/20</td>
<td>5.5</td>
<td>1.39 (0.15-12.41)</td>
</tr>
<tr>
<td>Smith et al (2015)</td>
<td>2/18</td>
<td>2/30</td>
<td>6.9</td>
<td>0.42 (0.06-2.98)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>113/176</td>
<td></td>
<td>100</td>
<td>0.47 (0.28-0.78)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2=0.00; \quad \text{DF}=3 (p=0.73); \quad I^2=0$

Test for overall effect: Z=2.89, $p=0.004$

B. Overall survival for patients treated by surgery with pCR vs W&W

<table>
<thead>
<tr>
<th></th>
<th>W&amp;W</th>
<th>Surgery with pCR</th>
<th>Weight (%)</th>
<th>HR IV, random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Araujo et al (2015)</td>
<td>8/42</td>
<td>10/69</td>
<td>59.6</td>
<td>0.62 (0.24-1.58)</td>
</tr>
<tr>
<td>Smith et al (2012)</td>
<td>N/A/32</td>
<td>N/A/57</td>
<td>23.5</td>
<td>0.61 (0.14-2.74)</td>
</tr>
<tr>
<td>Maas et al (2011)</td>
<td>0/21</td>
<td>2/20</td>
<td>6.9</td>
<td>5.50 (0.34-88.03)</td>
</tr>
<tr>
<td>Gossedge et al (2012)</td>
<td>1/15</td>
<td>1/13</td>
<td>6.8</td>
<td>0.23 (0.01-3.81)</td>
</tr>
<tr>
<td>Smith et al (2015)</td>
<td>0/18</td>
<td>1/30</td>
<td>3.3</td>
<td>6.89 (0.12-395.98)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>128/189</td>
<td></td>
<td>100</td>
<td>0.73 (0.35-1.51)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2=0.01; \quad \text{DF}=4 (p=0.40); \quad I^2=1$

Test for overall effect: Z=0.85, $p=0.40$

cCR, complete clinical response; CI, confidence interval; DF, degrees of freedom; HR, hazard ratio; IV, inverse variance; pCR, pathologic complete response; W&W, watch-and-wait.
AMONG THOSE WITH cCR, SURGERY VS W&W

A. Disease-free survival for patients treated by surgery with cCR vs W&W

<table>
<thead>
<tr>
<th></th>
<th>W&amp;W</th>
<th>Surgery with cCR</th>
<th>Weight (%)</th>
<th>HR IV, random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al (2015)</td>
<td>3</td>
<td>10</td>
<td>65.6</td>
<td>0.65 (0.18-2.36)</td>
</tr>
<tr>
<td>Lai et al (2016)</td>
<td>2</td>
<td>3</td>
<td>34.4</td>
<td>0.43 (0.07-2.56)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5</td>
<td>13</td>
<td>100</td>
<td>0.56 (0.20-1.60)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2=0.00$; $X^2=0.13$, DF=1 ($p=0.71$); $I^2=0\%$
Test for overall effect: $Z=1.08$, $p=0.28$

B. Overall survival for patients treated by surgery with cCR vs W&W

<table>
<thead>
<tr>
<th></th>
<th>W&amp;W</th>
<th>Surgery with cCR</th>
<th>Weight (%)</th>
<th>HR IV, random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al (2015)</td>
<td>0</td>
<td>3</td>
<td>53.5</td>
<td>4.50 (0.33-62.28)</td>
</tr>
<tr>
<td>Lai et al (2016)</td>
<td>2</td>
<td>3</td>
<td>46.5</td>
<td>3.33 (0.20-55.69)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2</td>
<td>6</td>
<td>100</td>
<td>3.91 (0.57-26.72)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2=0.00$; $X^2=0.02$, DF=1 ($p=0.88$); $I^2=0\%$
Test for overall effect: $Z=1.39$, $p=0.16$

cCR, complete clinical response; CI, confidence interval; DF, degrees of freedom; HR, hazard ratio; IV, inverse variance; W&W, watch-and-wait.
### SUMMARY OF NOM RECTAL CANCER STUDIES

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>cT3-4 (%)</th>
<th>cN+ (%)</th>
<th>CRT</th>
<th>cCR (%)</th>
<th>F/u (y)</th>
<th>LR (%)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maastricht, Netherlands</td>
<td>21</td>
<td>71</td>
<td>71</td>
<td>50.4 Gy + cape</td>
<td>11</td>
<td>2.1</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>75</td>
<td>74</td>
<td>50.4 Gy + cape</td>
<td>---</td>
<td>3.4</td>
<td>15</td>
<td>97</td>
</tr>
<tr>
<td>Sao Paulo, Brazil</td>
<td>70</td>
<td>71</td>
<td>39</td>
<td>54 Gy + 5FU/LV → 5FU/LV</td>
<td>68</td>
<td>4.7</td>
<td>27</td>
<td>90</td>
</tr>
<tr>
<td>Denmark</td>
<td>40</td>
<td>47</td>
<td>45</td>
<td>60 Gy + 5 Gy brachy + tegafur-uracil</td>
<td>78</td>
<td>2.0</td>
<td>26 (2y)</td>
<td>100</td>
</tr>
<tr>
<td><strong>Retrospective studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sao Paulo, Brazil</td>
<td>99</td>
<td>82</td>
<td>28</td>
<td>50.4 Gy + 5FU</td>
<td>27</td>
<td>5.0</td>
<td>6</td>
<td>93</td>
</tr>
<tr>
<td>MSKCC, USA</td>
<td>113</td>
<td>80</td>
<td>66</td>
<td>45 – 54 Gy + FP +/- FOLFOX</td>
<td>11</td>
<td>3.6</td>
<td>21 (5y)</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90% DSS</td>
</tr>
<tr>
<td>Manchester, UK</td>
<td>129</td>
<td>76</td>
<td>65</td>
<td>45 Gy + cape</td>
<td>---</td>
<td>2.8</td>
<td>38 (3y)</td>
<td>96</td>
</tr>
<tr>
<td>IWWD</td>
<td>880</td>
<td>54</td>
<td>50</td>
<td></td>
<td>---</td>
<td>3.3</td>
<td>25 (2y)</td>
<td>85</td>
</tr>
</tbody>
</table>

5FU, fluorouracil; brachy, brachytherapy; cape, capecitabine; cCR, complete clinical response; cN, clinical lymph node stage; CRT, chemoradiation therapy; cT, clinical tumour stage; DSS, disease-specific survival; FOLFOX, folinic acid, fluorouracil and oxaliplatin; F/u, follow-up; Gy, gray; IWWD, International Watch and Wait Database; LR, local recurrence; LV, leucovorin; MSKCC, Memorial Sloan Kettering Cancer Center; NOM, non-operative management; OS, overall survival; y, year.

Rectal cancer patients (N=1070) who underwent neoadjuvant therapy (diagnosed from 1/1/06 to 1/31/15)

<table>
<thead>
<tr>
<th></th>
<th>cCR → W&amp;W</th>
<th>TME with pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>113 (11%)</td>
<td>136 (13%)</td>
</tr>
<tr>
<td>Median age</td>
<td>67</td>
<td>57</td>
</tr>
<tr>
<td>Median distance from anal verge</td>
<td>5.5 cm</td>
<td>7.0 cm</td>
</tr>
<tr>
<td>5-year DFS</td>
<td>75%</td>
<td>92%</td>
</tr>
<tr>
<td>5-year OS</td>
<td>73%</td>
<td>94%</td>
</tr>
<tr>
<td>DSS</td>
<td>90%</td>
<td>98%</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>8%</td>
<td>4%</td>
</tr>
</tbody>
</table>

cCR, complete clinical response; DFS, disease-free survival; DSS, disease-specific survival; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival; pCR, pathologic complete response; TME, total mesorectal excision; W&W, watch-and-wait
Smith JJ et al. JAMA Oncology 2019;5(4):e185896
• **22 patients (20%) in the W&W group had local regrowth**
  – Median time to regrowth 11.2 months
  – All had salvage surgery
  – 20 (91%) of patients remained free of pelvic disease

• **5-year rectal preservation rate with W&W was 79%**

• **Among W&W patients who experienced local regrowth, distant metastases 36% vs. 1% who did not**
  – Difference in disease biology?
WHAT IS THE APPROPRIATE FOLLOW-UP FOR PATIENTS WITH A cCR?

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 3 months</td>
<td>1</td>
</tr>
<tr>
<td>Every 4 months</td>
<td>2</td>
</tr>
<tr>
<td>Every 6 months</td>
<td>3-5</td>
</tr>
<tr>
<td>Every 12 months</td>
<td>5+</td>
</tr>
</tbody>
</table>

cCR, complete clinical response
Smith JJ et al. ASCO GI 2015 (Abstract 509)
IMPORTANT POINTS ON cCR

• Does NOT equal pCR
• As pCR improves, it is likely more patients will be identified with a cCR
• The trend toward moving more therapy upfront (as in the TNT approach) may lead to more patients with a cCR

**cCR, complete clinical response; pCR, pathologic complete response; TNT, total neoadjuvant therapy**
## SURVIVAL FOR RECTAL CANCER WITH STANDARD OF CARE

<table>
<thead>
<tr>
<th></th>
<th>5 years (N=421)</th>
<th>10 years (N=404)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>76%</td>
<td>59.6%</td>
</tr>
<tr>
<td>Local relapse</td>
<td>6%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>36%</td>
<td>29.8%</td>
</tr>
</tbody>
</table>

- Total TNT approach has also become an option:
**TNT APPROACH**

- A single-institution retrospective analysis
  - T3/4 or node-positive rectal cancer

<table>
<thead>
<tr>
<th></th>
<th>Traditional CRT (n= 320)</th>
<th>TNT (n = 308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>21%</td>
<td>36%</td>
</tr>
</tbody>
</table>

- CR = pCR or cCR for 12+ months
- Patients in the TNT group received a greater percentage of the planned chemotherapy dose vs. the CRT with adjuvant chemotherapy group

CR, complete response; cCR, complete clinical response; CRT, chemoradiotherapy; pCR, pathologic complete response; T, tumour; TNT, total neoadjuvant therapy
Cercek A et al. JAMA Oncology 2018;4(6):e180071
SURGERY TIMING STUDY

- Non-randomised Phase 2 Trial, Stage 2 and 3 rectal cancer

<table>
<thead>
<tr>
<th>GROUP 1</th>
<th>Continuous infusion fluorouracil + radiotherapy</th>
<th>Rest</th>
<th>Total mesorectal excision</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP 2</td>
<td>Continuous infusion fluorouracil + radiotherapy</td>
<td>Rest</td>
<td>mFOLFOX6 (two cycles)</td>
</tr>
<tr>
<td>GROUP 3</td>
<td>Continuous infusion fluorouracil + radiotherapy</td>
<td>Rest</td>
<td>mFOLFOX6 (four cycles)</td>
</tr>
<tr>
<td>GROUP 4</td>
<td>Continuous infusion fluorouracil + radiotherapy</td>
<td>Rest</td>
<td>mFOLFOX6 (six cycles)</td>
</tr>
</tbody>
</table>

**Outcome** | **Group 1 (n=60)** | **Group 2 (n=67)** | **Group 3 (n=67)** | **Group 4 (n=65)**
--- | --- | --- | --- | ---
Sphincter-sparing surgery | 77% | 75% | 75% | 68%
pCR | 18% | 25% | 30% | 38%

mFOLFOX6, folinic acid, fluorouracil and oxaliplatin; pCR, pathological complete response
NOM FOR RECTAL CANCER: SUMMARY

- **cCR rates: vary depending on approach**
  - Traditional NAT, 21%
  - Possibly higher with TNT approach

- **With NOM: approximate 25% local recurrence**

- **95% can be salvaged with TME**

- **Short-term survival does not appear to be compromised**
  - More data on long-term survival needed
ONGOING STUDIES
*Patients with tumour progression at the interval evaluation will be treated according to standard of care:

CapeOX, oxaliplatin and capecitabine; CNCT, consolidation neoadjuvant chemotherapy; CRT, chemoradiation therapy; DFS, disease-free survival; DRE, digital rectal examination; EBRT, external beam radiotherapy; FOLFOX, folinic acid, fluorouracil and oxaliplatin; fx, fractions; Gy, gray; INCT, induction neoadjuvant chemotherapy; MRI, magnetic resonance imaging; NOM, non-operative management; TME, total mesorectal excision.


Stage II-III rectal cancer
N=202
EBRT: 56 Gy/28 fx
Primary endpoint: 3 years DFS
Arm considered promising if 3-year DFS ≥ 85%
Phase III Study objectives:

- Primary objective is to compare 3-year DFS in the control arm vs the mrTRG-directed management arm
- OS, CFS, DR and LR in the control arm vs the mrTRG-directed management arm, and tumour regrowth rates in patients treated with deferral of surgery

Brachy, brachytherapy; cape, capecitabine; CFS, colostomy-free survival; cT, clinical tumour stage; DFS, disease-free survival; DR, distant recurrence; EBRT, external beam radiotherapy; fx, fractions; Gy, gray; LC CRT, long-course chemoradiation therapy; LR, local recurrence; mrTRG, magnetic resonance tumour regression grade; NOM, non-operative management; R, randomisation; OS, overall survival

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5576102/
https://clinicaltrials.gov/ct2/show/NCT02704520
IS NON-OPERATIVE MANAGEMENT OR WATCH-AND-WAIT STRATEGY APPROPRIATE FOR OUR PATIENTS?

There are varying opinions!
• For patients who achieve a cCR
  – DRE, rectal MRI, and endoscopic evaluation
• A watch-and-wait, non-operative management approach may be considered in centres 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 characterised
• Decisions for non-operative management should involve a careful discussion with the patient of his/her risk tolerance
WHAT PATIENTS WOULD BE APPROPRIATE FOR NOM STRATEGY?

- **cCR** – determined at a tertiary care centre
  - DRE, MRI, endoscopy
- Patients who are **not candidates for a sphincter preserving operation**
  - For those who will not end up with a permanent ostomy, not worth the risk
- Patients at **high risk for morbidity/mortality from any surgical resection**
- Patients who **will be compliant with a strict surveillance schedule**
- Patients who are **well informed, willing to accept unknown risks**

*cCR, complete clinical response; DRE, digital rectal examination; MRI, magnetic resonance imaging; NOM, non-operative management*
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