Watch & Wait - Organ Preservation in Rectal Cancer

Rodrigo O. Perez
Angelita & Joaquim Gama Institute
São Paulo Brazil
Disclosures

I am a colorectal surgeon!
Accidental Watch & Wait
Complete Clinical Response & WW by chance!
Accidental Watch & Wait
Complete Clinical Response & WW by chance!

Staging → High-risk features → nCRT → Accidental cCR

Staging → Low-risk features → nCRT → Intended organ-preservation
Accidental Watch & Wait
Complete Clinical Response & WW by chance!
Complete Clinical Response

Definition

DRE

Smooth, firm but No Irregularities!
Complete Clinical Response

Definition

Sex:  Age:  D. O. Birth:
11/18/2009  17:31:03
CVP:  1  D. F:
&: 5  &: N

Physician:  Comment:
Ruling out extra-rectal/nodal residual disease?
Assessment of Response

MR findings
Assessment of Response
MR findings

Comparison of Magnetic Resonance Imaging and Histopathological Response to Chemoradiotherapy in Locally Advanced Rectal Cancer

Uday Bharat Patel, MBBS1, Gina Brown, FRCP, MD1, Harme Butten, MD, PhD2, Nicholas West, MBChB2, David Sebag-Montefiore, FRCPFRCPath1, Robert Glynn-Jones, FRCP, FRCP1, Eric Reullier, MD3, Marc Peeters, MD, PhD3, Eric Van Cutsem, MD, PhD3, Sergio Ricci, MD, PhD3, Cornelius Van de Velde, MD, PhD3, Penner Kjell1, and Philip Quirke, FRCPath, PhD3
Assessment of Response

PET/CT

Semiquantitative Volumetry by Sequential PET/CT May Improve Prediction of Complete Response to Neoadjuvant Chemoradiation in Patients With Distal Rectal Cancer

SUV
MTV
TLG (combination SUVxMTV)
Assessment of Response
Clinical + Endoscopic + MR + DWI….performs best!

FIG. 3 ROC curves for modalities. Clinical assessment consists of endoscopy, DRE, and biopsy result (if available)
Rectal CA

Not all patients achieve a cCR at the same time!

**ORIGINAL CONTRIBUTION**

**DCR 2019**

Achieving a Complete Clinical Response After Neoadjuvant Chemoradiation That Does Not Require Surgical Resection: It May Take Longer Than You Think!

Angelita Habr-Gama, M.D., Ph.D.1,2 • Guilherme Pagin São Julião, M.D.1
Laura Melina Fernández, M.D.1 • Bruna Borba Vailati, M.D.1 • Andres Andrade, M.D.1
Sérgio Eduardo Alonso Araújo, M.D.2 • Joaquim Gama-Rodrigues, M.D., Ph.D.1,2
Rodrigo Oliva Perez, M.D., Ph.D.1,3

- cCR (never developed regrowth)

<table>
<thead>
<tr>
<th># of Patients achieving complete clinical &amp; endoscopic response</th>
<th>10-16 weeks</th>
<th>&gt;16 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.267</td>
<td>37%</td>
<td>73%</td>
</tr>
</tbody>
</table>

Interval from RT completion (weeks)

- 12 weeks
- 20 weeks
Management of Rectal Cancer
Radical Surgery for all patients after Neoadjuvant CRT?
TME is difficult…

**Original Investigation**

**Effect of Laparoscopic-Assisted Resection vs Open Resection of Stage II or III Rectal Cancer on Pathologic Outcomes**

The ACOSOG Z6051 Randomized Clinical Trial

<table>
<thead>
<tr>
<th></th>
<th>Lap</th>
<th>Open</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Percentage (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRM &gt;1 mm or distance = NA</td>
<td>87.9 (83.8 to 92.0)</td>
<td>92.3 (88.8 to 95.8)</td>
<td>-4.4 (-9.8 to 0.98)</td>
</tr>
<tr>
<td>Distal margin negative</td>
<td>98.3 (96.7 to 99.95)</td>
<td>98.2 (96.5 to 99.95)</td>
<td>-0.1 (-2.3 to 2.5)</td>
</tr>
<tr>
<td>Complete or nearly complete total mesorectal excision</td>
<td>92.1 (88.7 to 95.5)</td>
<td>95.1 (92.2 to 97.9)</td>
<td>-3.0 (-7.4 to 1.5)</td>
</tr>
<tr>
<td><strong>Successful resection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified intent to treat</td>
<td>81.7 (76.8 to 86.6)</td>
<td>86.9 (82.5 to 91.4)</td>
<td>-5.3 (-10.8 to ∞)</td>
</tr>
<tr>
<td>Per protocol</td>
<td>81.7 (76.5 to 86.9)</td>
<td>86.9 (82.5 to 91.4)</td>
<td>-5.3 (-11.0 to ∞)</td>
</tr>
</tbody>
</table>

Best chances of an optimal specimen: Open Surgery!
# Management of Rectal Cancer

**Radical Surgery for all?**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Morbidity</td>
<td>38%</td>
</tr>
<tr>
<td>Mortality</td>
<td>2-3%</td>
</tr>
<tr>
<td>Urinary Dysfunction</td>
<td>20%</td>
</tr>
<tr>
<td>Sexual Dysfunction</td>
<td>15%</td>
</tr>
<tr>
<td>Fecal Incontinence</td>
<td>20%</td>
</tr>
<tr>
<td>APR requirement</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>Stoma (temporary)</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Recurrence</td>
<td>8-40%</td>
</tr>
</tbody>
</table>

[Image of medical procedure]
Treatment of Rectal Cancer
Patients’ Expectations

Patient values post-surgery

Sum of responses

- Not applicable/no response
- Not important
- Somewhat important
- Important
- Most Important

#1: AVOIDING A STOMA!!!
The risk of definitive stoma formation at 10 years after low and ultralow anterior resection for rectal cancer

B. Celerier*, Q. Denost††, B. Van Geluwe††, A. Pontallier†† and E. Rullier††

*Department of Digestive Surgery, CHU Bordeaux, Saint André Hospital, Bordeaux, France and ††Université Bordeaux Segalen, Bordeaux, France

Received 9 January 2015; accepted 15 May 2015; Accepted Article online 21 September 2015

starts at 8%....ends at 22% in 10 years!
Risk of disability pension in patients following rectal cancer treatment and surgery

L. Chen¹, I. Glimelius¹, M. Neovius¹, S. Eloranta¹, S. Ekberg¹, E. Martling², and K. E. Smedby¹

Disability pension in patients with rectal cancer

Risk of being out of work is quite significant!
Management of a cCR

**Watch & Wait**

[Diagram]

- **Watch & Wait Protocol**
  - No Lesion
  - OEA
  - 3D ERUS
  - MRI
  - PET/CT

- **Reassess every 1-2 mo**

**DRE**

**Rigid Proctoscopy**

**Radiology q3mo**
Watch & Wait Local Recurrences

**Meta-Analysis**

Oncological and Survival Outcomes in Watch and Wait Patients With a Clinical Complete Response After Neoadjuvant Chemoradiotherapy for Rectal Cancer

*A Systematic Review and Pooled Analysis*

*N=692*

**Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study**


*N=880*

3yr Local Regrowth Rate: 22%
Regrowth
Relevance of Baseline Stage

Regrowth-free Survival (1yr)

cT2: 96% @ 1yr
cT3/4: 69% @ 1yr

cT2 are less likely to recur after initial cCR!
Regrowth
Relevance of Baseline Stage

N=602 patients
11 studies

Factors affecting local regrowth after watch and wait for patients with a clinical complete response following chemoradiotherapy in rectal cancer (InterCoRe consortium): an individual participant data meta-analysis


Lancet 2018

Risk of Regrowth

p=0.03

ctT1/T2: 19%
cT3: 31%
cT4: 37%

ctT stage increase: 10% Increase in local regrowth risk!
Regrowth
Relevance of Baseline Stage N-Stage

Organ Preservation Among Patients With Clinically Node-Positive Rectal Cancer: Is It Really More Dangerous?

Angelita Habr-Gama, M.D., Ph.D.1,2 • Guilherme Pagin São Julião, M.D.1 • Bruna Borba Vailati, M.D.1 • Laura Melina Fernandez, M.D.1 • Cinthia Denise Ortega, M.D.3
• Nuno Figueiredo, M.D.4 • Joaquim Gama-Rodrigues, M.D., Ph.D.1,2 • Rodrigo Oliva Perez, M.D., Ph.D.1,2,5

Surgery-free Survival

p = 0.8836

No. at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>N-</th>
<th>N+</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12</td>
<td>102</td>
<td>47</td>
</tr>
<tr>
<td>13-24</td>
<td>80</td>
<td>41</td>
</tr>
<tr>
<td>25-36</td>
<td>72</td>
<td>32</td>
</tr>
<tr>
<td>37-48</td>
<td>66</td>
<td>23</td>
</tr>
<tr>
<td>49-60</td>
<td>54</td>
<td>17</td>
</tr>
<tr>
<td>61-72</td>
<td>44</td>
<td>14</td>
</tr>
<tr>
<td>73-84</td>
<td>39</td>
<td>12</td>
</tr>
<tr>
<td>85-96</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>97-108</td>
<td>26</td>
<td>7</td>
</tr>
<tr>
<td>109-120</td>
<td>15</td>
<td>6</td>
</tr>
</tbody>
</table>

cN stage: No increased risk for local regrowth!
Conditional Survival in Patients With Rectal Cancer and Complete Clinical Response Managed by Watch and Wait After Chemoradiation

Recurrence Risk Over Time

Gialherme P. São Julião, MD,* Georgios Karakounis, MD,† Laura M. Fernandez, MD,‡ Angelita Habr-Gama, MD, PhD,*§ Bruna B. Vailati, MD,* Mit Dattani, FRCS,** Matthew F. Kalady, MD,† and Rodrigo O. Perez, MD, PhD*§

Ann Surg 2019

Local recurrence free survival

100%  88%  82%  78%
Conditional Survival in Patients With Rectal Cancer and Complete Clinical Response Managed by Watch and Wait After Chemoradiation

Recurrence Risk Over Time

Giaillherme P. S. Julião, MD,* Georgios Karagounis, MD,† Laura M. Fernandez, MD,‡ Angelita Habr-Gama, MD, PhD,§ Bruna B. Vailati, MD,* Mitali Dattani, FRCS,** Matthew F. Kalady, MD,† and Rodrigo O. Perez, MD, PhD*§

Ann Surg 2019

...provided a patient survived 1yrs without recurrence...
Conditional Survival... Conditional Survival... Conditional Survival...

Local recurrence free survival improves!

Most powerful risk-factor (protective) is achieving and sustaining a cCR over time...
Rectal Cancer Management

Watch & Wait

Recurrences after cCR

Nearly all (90%) had an endoluminal component
Rectal Cancer Management

Watch & Wait

Recurrences after cCR

Nearly all (90%) had an endoluminal component
Rectal Cancer Management

Watch & Wait

primary complete response… exclusive nodal recurrence…
Watch & Wait
Local Recurrences

Are they Salvageable?

Clinical Investigation
Local Recurrence After Complete Clinical Response and Watch and Wait in Rectal Cancer After Neoadjuvant Chemoradiation: Impact of Salvage Therapy on Local Disease Control
Angelita Habr-Gama, MD, PhD, Joaquim Gama-Rodrigues, MD, PhD, Guilherme P. Sáo Julião, MD, Igor Proscurshim, MD, Charles Sabbagh, MD, Patricio B. Lynn, MD, and Rodrigo O. Perez, MD, PhD

7%
93%
YES
Watch & Wait
Local Recurrences

Are they Salvageable?
Is sphincter (or organ) preservation possible?
Treatment of Rectal Cancer

Watch & Wait

CLINICAL INVESTIGATION

INTERVAL BETWEEN SURGERY AND NEOADJUVANT CHEMORADIATION THERAPY FOR DISTAL RECTAL CANCER: DOES DELAYED SURGERY HAVE AN IMPACT ON OUTCOME?

Angelita Habr-Gama, M.D., Ph.D., Rodrigo Oliva Perez, M.D., Ph.D.,
Igor Procurshim, M.S., Rafael Miyashiro Nunes dos Santos, M.S.,
Desiderio Kiss, M.D., Ph.D., Joaquim Gama-Rodrigues, M.D., Ph.D.

Overall Survival

Disease-Free Survival

p = 0.96

p = 0.76

5yr OS

Suspected cCR 85%
Others 84%

Mean FU 46.0 mo

5yr DFS

Suspected cCR 52%
Others 58%

Mean FU 46.0 mo

Delayed Surgery = No Oncological Compromise

Int J Rad Oncol 2008
Watch & Wait

Recurrences

What about Systemic Recurrences?
Incidence of metastases

**FIGURE 5.** Pooled 5-year incidence of metastases in Watch and Wait patients.

*No difference!*
Incidence of metastases

8-12%
Watch & Wait vs Surgery
Systematic Review

Incidence of metastases

<table>
<thead>
<tr>
<th>WW (80%)</th>
<th>WW+ Regrowth (20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distant Metastases</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>36%</td>
</tr>
</tbody>
</table>

Majority of distant mets among those with local regrowths!
## Overall Survival

**Extended nCRT & WW**

**Assessment of a Watch-and-Wait Strategy for Rectal Cancer in Patients With a Complete Response After Neoadjuvant Therapy**

<table>
<thead>
<tr>
<th></th>
<th>pCR</th>
<th>WW</th>
<th>WW+ Regrowth</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distant Metastases</strong></td>
<td>4%</td>
<td>1%</td>
<td>36%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*JAMA Oncology | Original Investigation*

JAMA 2019
### Overall Survival

Extended nCRT & WW

<table>
<thead>
<tr>
<th></th>
<th>pCR</th>
<th>WW</th>
<th>WW+ Regrowth</th>
<th>p</th>
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<td>4%</td>
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<td>36%</td>
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**True complete Responders**
### Overall Survival

**Extended nCRT & WW**

<table>
<thead>
<tr>
<th></th>
<th>pCR</th>
<th>WW</th>
<th>WW+ Regrowth</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>Distant Metastases</strong></td>
<td>4%</td>
<td>1%</td>
<td>36%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**False complete Responders**
Overall Survival
Sustained cCR x Regrowths

Baseline T Classification Predicts Early Tumor Regrowth After Nonoperative Management in Distal Rectal Cancer After Extended Neoadjuvant Chemoradiation and Initial Complete Clinical Response

DCR 2017

No. at risk
- WW
- Local regrowth or recurrence
- WW without local relapse

<table>
<thead>
<tr>
<th>Mo</th>
<th>WW</th>
<th>Local regrowth or recurrence</th>
<th>WW without local relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>57</td>
<td>16</td>
<td>41</td>
</tr>
<tr>
<td>24</td>
<td>49</td>
<td>13</td>
<td>36</td>
</tr>
<tr>
<td>36</td>
<td>42</td>
<td>9</td>
<td>33</td>
</tr>
<tr>
<td>48</td>
<td>39</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>60</td>
<td>28</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>72</td>
<td>23</td>
<td>4</td>
<td>19</td>
</tr>
</tbody>
</table>

93% True
86% False
63%

p=0.03
Overall Survival
Extended nCRT & WW

Assessment of a Watch-and-Wait Strategy for Rectal Cancer in Patients With a Complete Response After Neoadjuvant Therapy

<table>
<thead>
<tr>
<th>Distant Metastases</th>
<th>pCR (4%)</th>
<th>WW (1%)</th>
<th>WW+ Regrowth (36%)</th>
<th>p (&lt;0.001)</th>
</tr>
</thead>
</table>

Incomplete Responders operated after nCRT
Treatment of Rectal Cancer

Watch & Wait

**Clinical Investigation**

Interval between surgery and neoadjuvant chemoradiation therapy for distal rectal cancer: does delayed surgery have an impact on outcome?

Angelita Habr-Gama, M.D., Ph.D., Rodrigo Olivera Perez, M.D., Ph.D.,
Igor Procurshim, M.S., Rafael Miyashiro Nunes dos Santos, M.S.,
Desiderio Kiss, M.D., Ph.D., Joaquim Gama-Rodrigues, M.D., Ph.D.

**Overall Survival**

- Delayed due to suspected cCR
- Delayed for other reasons

\[ p = 0.96 \]

**Disease-Free Survival**

- Delayed due to suspected cCR
- Delayed for other reasons

\[ p = 0.76 \]

<table>
<thead>
<tr>
<th></th>
<th>5yr OS</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susp cCR</td>
<td>85%</td>
<td>84%</td>
</tr>
<tr>
<td>Mean FU 46.0 mo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Delayed Surgery = No Oncological Compromise**

Int J Rad Oncol 2008
Overall survival at 3 years

3-year overall survival: 93.5% (95% CI: 90.2–96.2)

No adjuvant chemo!
Overall survival in pCR patients

Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data

3yr OS 90.1%

40% adjuvant chemotherapy!
Old Standard
Complete Clinical Response & WW by chance!

Staging → High-risk features → nCRT → Accidental Organ Preservation

Staging → Low-risk features → nCRT → Intended organ-preservation
New Possibilities
There is a chance for organ-preservation in advanced and early stage disease!
New Standard
There is a chance for organ-preservation in advanced and early stage disease!

cT2N0
@ level of anorectal ring
Maximizing complete tumor response

RT Dose escalation

Radiation dose-response model for locally advanced rectal cancer after pre-operative chemoradiotherapy

Ane L. Appet, M.Sc.¹,², John Plon, M.D.¹, Ivan R. Vogelius, Ph.D.³, Søren M. Bentzen, Ph.D., D.Sc.⁴, and Anders Jakobsen, D.M.Sc.¹,²

More RT = Increased Response
Maximizing complete tumor response
Consolidation Chemo

More Chemo = Increased Response

<table>
<thead>
<tr>
<th>Interval</th>
<th>% pCR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>18%</td>
<td>0.03</td>
</tr>
<tr>
<td>12 weeks</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>18 weeks</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>24 weeks</td>
<td>38%</td>
<td></td>
</tr>
</tbody>
</table>

Lancet Oncol 2015
cT2 rectal cancer
Standard vs Extended nCRT?
cT2 rectal cancer
Standard vs Extended nCRT (All)

Surgery-free Survival

- Extended CRT: 62% (p=0.005)
- Standard CRT: 32%

No. at risk

Months

- Extended CRT: 32, 28, 24, 20, 16, 13, 10, 8, 3, 1
- Standard CRT: 23, 16, 14, 11, 9, 6, 5, 5, 4, 4
"A good surgeon knows HOW to operate;
A better surgeon knows WHEN to operate;
The best surgeon knows when NOT to operate"
21 a 23 de Novembro de 2019
Sheraton São Paulo WTC Hotel