Evolving Treatment for Rectal Cancer
“Total Neoadjuvant Therapy”

MUSC Postgraduate Course in Surgery,
Charleston, SC
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Chief Section of Colon and Rectal Surgery
Solon and Bettie Gershman Professor of Surgery
Disclosures

- None

The management of rectal cancer is evolving faster than we really understand.

But we are catching up!!!
Outline

• History of the management of rectal cancer
• Evolution of neoadjuvant therapy for rectal cancer
• Total Neoadjuvant therapy
  • The various regimens
  • The future
    • Selection for non-operative management
    • Improving ability to assess pCR
Rectal Cancer Management in 2002

Rectal cancer

Pre-op Staging

T1
Local tx
Radical tx

T2
Radical Sx
Short course XRT

T3-4, N+
Chemo/XRT
Radical Sx

Adjuvant chemotherapy → T3, T4 or N+ pre-op or final pathology
Total Neoadjuvant Therapy

Radiation Therapy

- Long course chemoradiation
  - 5 to 6 weeks of therapy
  - 25 to 28 fractions/treatments
    - 180 cGy per treatment $\rightarrow$ Total 4500-5040 cGY
  - Chemotherapy $\rightarrow$ 5-FU as a sensitizing dose
  - Surgery 8 weeks later

- Short course radiation
  - 5 days of therapy
  - 5 fractions/treatments
    - 500 cGy per treatment $\rightarrow$ Total 2500 cGy
  - Surgery the next week

- Biologically equivalent!
Total Neoadjuvant Therapy
Radiation and Chemotherapy

PREOPERATIVE RADIOThERAPY COMBINED WITH
TOTAL MESORECTAL EXCISION FOR RESECTABLE RECTAL CANCER

ELLEN KAPITELEN, M.D., CORRIE A.M. MARIJNEN, M.D., IRIS D. NAGTEGAAL, M.D., HEIN PUTTER, Ph.D.,
WILLEM H. STEUP, M.D., PH.D., THEO WIGGERS, M.D., PH.D., HARM J.T. RUTTEN, M.D., PH.D.,
LARS PAHLMAN, M.D., PH.D., BENGT GULMELIUS, M.D., PH.D., J. HAN J.M. VAN KRIEKEN, M.D., PH.D.,
JAN W.H. LEER, M.D., PH.D., AND CORNELIS J.H. VAN DE VELDE, M.D., PH.D.,
FOR THE DUTCH COLORECTAL CANCER GROUP*

Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer

Rolf Sauer, M.D., Heinz Becker, M.D., Werner Hohenberger, M.D.,
Claus Rödel, M.D., Christian Wittekind, M.D., Rainer Fietkau, M.D.,
Peter Martus, Ph.D., Jörg Tschmelitsch, M.D., Eva Hager, M.D.,
Clemens F. Hess, M.D., Johann-H. Karstens, M.D., Torsten Liersch, M.D.,
Heinz Schmidberger, M.D., and Rudolf Raab, M.D.,
for the German Rectal Cancer Study Group*

Chemotherapy with Preoperative Radiotherapy in Rectal Cancer

Jean-François Bosset, M.D., Laurence Collette, Ph.D., Gilles Calais, M.D.,
Laurent Mineur, M.D., Philippe Maingon, M.D., Ljiljana Radosovic-Jelic, M.D.,
Alain Daban, M.D., Etienne Bardet, M.D., Alexander Beny, M.D.,
and Jean-Claude Ollier, M.D., for EORTC Radiotherapy Group Trial 22921*

Randomized Trial of Short-Course Radiotherapy Versus Long-Course Chemoradiation Comparing Rates of Local Recurrence in Patients With T3 Rectal Cancer: Trans-Tasman Radiation Oncology Group Trial 01.04

Samuel Y. Ngan, Bryan Barmeister, Richard J. Fisher, Michael Solomon, David Goldstein, David Joseph,
Stephen P. Ackland, David Schache, Bev McClare, Sue-Anne McLachlan, Joseph Kendrick, Trevor Leong,
Cris Hartopamuh, John Zalcberg, and John Mackay

Randomized clinical trial

Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer

K. Bujko¹, M. P. Nowacki², A. Nasierowska-Guttmejer³, W. Michalski⁴, M. Bebenek⁵ and M. Kry⁶
for the Polish Colorectal Study Group
Total Neoadjuvant Therapy
Surgical Therapy

Rectal Cancer: The Basingstoke Experience of Total Mesorectal Excision, 1978-1997
Richard J. Heald, MChir, FRCS; Brendan J. Moran, MCh, FRCS; Roger D. H. Ryall, FRCR

Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomised controlled trial
Seung-Yong Jeong, Ji Won Park, Byung Ho Nam, Sohee Kim, Sung-Bum Kang, Seok-Byung Lim, Hyo Seong Choi, Duck-Woo Kim, Hee Jin Chang, Dae Yong Kim, Kyung Hae Jung, Tae-You Kim, Gyeong Hoon Kang, Eui Kye Chie, Sun Young Kim, Dae Kyung Sohn, Dae-Hyun Kim, Jae-Sung Kim, Hye Seung Lee, Jae Hyun Kim, Jae Hwan Oh

A Randomized Trial of Laparoscopic versus Open Surgery for Rectal Cancer
H. Jaap Bonjer, M.D., Ph.D., Charlotte L. Deijen, M.D., Gabor A. Abis, M.D., Miguel A. Cuesta, M.D., Ph.D., Martijn H.G.M. van der Pas, M.D., Elly S.M. de Lange-de Klerk, M.D., Ph.D., Antonio M. Lacy, M.D., Ph.D., Willem A. Beemelman, M.D., Ph.D., John Andersson, M.D., Eva Angelene, M.D., Ph.D., Jacob Rosenberg, M.D., Ph.D., Alois Fuerst, M.D., Ph.D., and Eva Haglind, M.D., Ph.D., for the COLOR II Study Group

Effect of Laparoscopic-Assisted Resection vs Open Resection on Pathological Outcomes in Rectal Cancer
The ALaCaRT Randomized Clinical Trial
Andrew R. L. Stevenson, MB BS, FRACS; Michael J. Solomon, MB BS, MSc; Mark B. F. Choy, FRCS, FRACS; John W. Lumley, MB BS, FRACS; Peter Hawatt, MB BS; Andre B. Clouton, MB BS, FRACS; Vol J. Gebel, MB BS, FACS; Peter Busuttil, MB BS, MSc; Wendy Hage, MBBS, MPhD; Joanne Ruhmann, MB BS, FRACS; MD. for the ALaCaRT Investigators

Effect of Laparoscopic-Assisted Resection vs Open Resection of Stage II or III Rectal Cancer on Pathologic Outcomes
The ACOSOG Z6051 Randomized Clinical Trial
James Fleshman, MD; Megan Branda, MS; Daniel J. Sargent, PhD; Anne Marie Bollett, MD; Virgil C. George, MD; Maher Abbas, MD; Walter R. Peters Jr, MD; Dipen M. Mais, MD; George Chang, MD; Alan Herline, MD; Alessandro Fichera, MD; Matthew Mutic, MD; Steven Wexner, MD; Mari Whitelock, MD; John Marks, MD; Ella Bimbaim, MD; David Margolin, MD; David Larson, MD; Peter Marcello, MD; Mitchell Posner, MD; Thomas Read, MD; John Monson, MD; Sherry M. Wien, MD; Peter W. T. Pisters, MD; Heidi Nelson, MD

COLOR III: a multicentre randomised clinical trial comparing transanal TME versus laparoscopic TME for mid and low rectal cancer
Charlotte L. Deijen1 · Simone Velthuis2 · Alice Tsi3 · Stella Mavrogeni3 · Elly S.M. de Lange-de Klerk1 · Colin Sietsema2 · Jurriaan B. Tuynman1 · Antonio M. Lacy3 · George B. Hanna5 · H. Jaap Bonjer1

Washington University in St. Louis • School of Medicine
Department of Surgery
Section of Colon and Rectal Surgery
Total Neoadjuvant Therapy
The Short Comings

• Despite significant advances in surgical technique and neoadjuvant therapy
  • Improved local recurrence rates
  • Variable utilization of neoadjuvant therapy
  • Significant variation in surgical outcomes
  • No improvement in disease free survival
  • The greatest risk of tumor recurrence remained distant metastasis
    • 25% for Stage II
    • 40% for Stage III
Total Neoadjuvant Therapy
A Call to Action

Failure of Evidence-Based Cancer Care in the United States
The Association Between Rectal Cancer Treatment, Cancer Center Volume, and Geography

John R. T. Monson, MD,* Christian P. Probst, MD,* Steven D. Wexner, MD,† Feza H. Remzi, MD,‡
James W. Fleshman, MD,§ Julio Garcia-Aguilar, MD,¶ George J. Chang, MD,|| and David W. Dietz, MD‡;
On behalf of The Consortium for Optimizing the Treatment of Rectal Cancer (OSTRiCh)

- National Cancer Data Base (NCDB) patients with Stage II and III rectal cancer
  - 74% received some form of neoadjuvant therapy
  - Utilization was associated with
    - Urban location
    - Comprehensive cancer center
    - Volume >10 cases/year

Total Neoadjuvant Therapy
A Call to Action

High Rate of Positive Circumferential Resection Margins Following Rectal Cancer Surgery
A Call to Action

Aaron S. Rickles, MD,* David W. Dietz, MD,† George J. Chang, MD,‡ Steven D. Wexner, MD,§
Mariana E. Berho, MD,★ Feza H. Remzi, MD,† Frederick L. Greene, MD,∥ James W. Fleshman, MD,**
Maher A. Abbas, MD,†† Walter Peters, MD,‡‡ Katia Noyes, PhD,* John R. T. Monson, MD,*
and Fergal J. Fleming, MD*;
on behalf of the Consortium for Optimizing the Treatment of Rectal Cancer (OSTRiCh)

• Review of NCDB data – 2010-2011
• + CRM → 17.2% (2859 of 16,619 pts)
• Risk factors:
  • T3, N1, tumor size, histology

Total Neoadjuvant Therapy
A Call to Action

Association Between Time to Initiation of Adjuvant Chemotherapy and Survival in Colorectal Cancer
A Systematic Review and Meta-analysis

Conclusion
In a meta-analysis of the available literature on time to AC, longer time to AC was associated with worse survival among patients with resected colorectal cancer.

Ideally within 8 weeks of surgery
Total Neoadjuvant Therapy
As Call to Action

• Total Mesorectal Excision (TME)
• Measurement of quality of surgery via specific pathologic assessment
• Appropriate pre-therapy staging
• Routine utilization of Multi-disciplinary teams
• Utilization of patient specific neo-adjuvant and adjuvant therapies
• Appropriate timing of adjuvant therapy
Total Neoadjuvant Therapy

“Old time” Neoadjuvant therapy

Initiation CRT
1-2 wks

Chemoradiation
5-6 weeks

Waiting
6-8 weeks

Recovery
4-8 weeks

Systemic Chemo
6 months

Surgery

Diagnosis

Best case scenarios – Chemo – 5.5 months from Dx
-- Completion of therapy – 11.5 months

Complete pathologic response rate – 16-20%
Total Neoadjuvant Therapy
Systemic Chemo with XRT

- No improvement in complete pathologic response
- Significant increase in Grade 3 and 4 toxicity
- Variable improvement of Disease-Free Survival
Total Neoadjuvant Therapy
Systemic Chemo after XRT

Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial


- All patients treated with 5040cGy and F-FU
  - Surgery 6-8 weeks later
  - Received 2 cycles of FOLFOX with surgery 4 weeks later
  - Received 4 cycles of FOLFOX with surgery 4 weeks later
  - Received 6 cycles of FOLFOX with surgery 4 weeks later
Total Neoadjuvant Therapy
Systemic Chemo after XRT

SG1
CRT(6 weeks) 6 weeks

SG2
CRT(6 weeks) 4 wk 2 wk 3-5 wks

SG3
CRT(6 weeks) 4 wk 2 wk 2 wk 2 wk 3-5 wks

SG4
CRT(6 weeks) 4 wk 2 wk 2 wk 2 wk 2 wk 2 wk 3-5 wks

Lancet Oncol 2015;16(8):957-66
Total Neoadjuvant Therapy
Systemic Chemo only

PROSPECT

- Preoperative Radiation or Selective Preoperative radiation and Evaluation before Chemotherapy and TME

- MSK, prospective pilot study
  - Stage II/III rectal ca (best actors)
  - 6 cycles FOLFOX
  - TME 3-6 weeks after chemo

*JCO (2014) 32:513*
Total Neoadjuvant Therapy
Systemic Chemo only

Results
- pCR 25%
- 4y Loc Rec 0%
- 4y DFS 84%

Conclusion – Neoadjuvant chemotherapy alone does not compromise outcomes in selected patients

JCO (2014) 32:513
Total Neoadjuvant Therapy
Systemic Chemo only

PROSPECT

- **Response ≥ 20%**
  - TME
  - FOLFOX x 6

- **Response < 20%**
  - Re-stage
  - ChemoRT
  - TME
  - FOLFOX x 4

**Randomize 1:1**

- ChemoRT
  - TME
  - FOLFOX x 8
Total Neoadjuvant Therapy
Short course XRT + Chemotherapy

RAPIDO

Total Neoadjuvant Therapy
*Short course XRT + Chemotherapy*

Five Fractions of Radiation Therapy Followed by 4 Cycles of FOLFOX Chemotherapy as Preoperative Treatment for Rectal Cancer

Robert J. Myerson, MD, PhD, * Benjamin Tan, MD, † Steven Hunt, MD, ‡ Jeffrey Olsen, MD, * Elisa Birnbaum, MD, † James Fleshman, MD, ‡ Feng Gao, MD, § Lannis Hall, MD, MPH, * Ira Kodner, MD, † A. Craig Lockhart, MD, MHS, ‡ Matthew Mutch, MD, † Michael Naughton, MD, † Joel Picus, MD, † Caron Rigden, MD, † Bashar Safar, MBBS, MRCS, ‡ Steven Sorscher, MD, † Rama Suresh, MD, † Andrea Wang-Gillam, MD, PhD, † and Parag Parikh, MD *

- 76 patients with Stage II or III rectal cancer
- End points
  - T stage downstaging
  - Grade 3+ GI toxicity

*Int J Radiat Oncol Biol Phys 2014;88(4):829*
Total Neoadjuvant Therapy

Short course XRT + Chemotherapy

- T stage downstaging
  - T0 → 28% (16% p=0.21)
  - T2 or < → 70% (41% p<0.001)
  - N+ to N0 → 78% to 32%
- Grade 3+ GI toxicity
  - 9%
- Tolerance of therapy
  - 95% or 72 of 76 patients complete all therapy

*Int J Radiat Oncol Biol Phys 2014;88(4):829*
Total Neoadjuvant Therapy
Short course XRT + Chemotherapy

93% v. 93%

83% v. 66%

# Total Neoadjuvant Therapy

*Short course XRT + Chemotherapy*

## Table 2: Preoperative chemotherapy delivery

<table>
<thead>
<tr>
<th>Preoperative chemotherapy timing and delivery</th>
<th>Target interval (weeks)</th>
<th>Achieved interval (weeks) average ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset of chemotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interval from last radiation treatment to day 1, cycle 1 of chemotherapy</td>
<td>1.6-2.6</td>
<td>2.3 ± 0.6</td>
</tr>
<tr>
<td>Number of cases delayed ≥2 weeks beyond target</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Delivery of chemotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration: Interval from day 1, cycle 1 to day 1, last cycle chemotherapy</td>
<td>6</td>
<td>6.4 ± 1.2</td>
</tr>
<tr>
<td>Number of cases delayed ≥2 weeks beyond target duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose: Number of cases with chemotherapy dose reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases with dose reduction and/or any delay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1 week delay alone allowed for first instance of grade 3 neutropenia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Timing of surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interval from day 1, last cycle chemotherapy to surgery</td>
<td>4.9</td>
<td>7.7 ± 2.8</td>
</tr>
<tr>
<td>Number of cases delayed ≥2 weeks beyond target from last cycle chemotherapy to surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interval from day 1 radiation therapy to surgery</td>
<td>13-18</td>
<td>17.3 ± 2.9</td>
</tr>
<tr>
<td>Number of cases delayed ≥2 weeks beyond target from day 1 radiation therapy to surgery</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Int J Radiat Oncol Biol Phys 2014;88(4):829*
Total Neoadjuvant Therapy
Short vs Long XRT + Chemotherapy

- Comparison of neoadjuvant regimens for tumor response
  - Data from Wash U and Memorial Sloan-Kettering
  - Compared: (912 total patients)
    - Traditional CRT → 498 patients
    - Short course–XRT -TNT → 96 patients
    - Long course–XRT – TNT → 318 patients
- Primary outcome -- Neoadjuvant Rectal score (NAR)

Unpublished data
# Total Neoadjuvant Therapy

## Short vs Long XRT + Chemotherapy

<table>
<thead>
<tr>
<th>NAR Score</th>
<th>Low NAR 0 - 7.9</th>
<th>Mid NAR 8 - 15.9</th>
<th>High NAR &gt; 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>CRT</td>
<td>498</td>
<td>131 (26)</td>
<td>236 (48)</td>
</tr>
<tr>
<td>SC-TNT</td>
<td>96</td>
<td>39 (41)</td>
<td>34 (35)</td>
</tr>
<tr>
<td>LC-TNT</td>
<td>318</td>
<td>136 (43)</td>
<td>118 (37)</td>
</tr>
</tbody>
</table>

## Odds Ratio of Achieving NAR<8

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC-TNT vs. CRT</td>
<td>1.95</td>
</tr>
<tr>
<td>LC-TNT vs. CRT</td>
<td>2.09</td>
</tr>
<tr>
<td>LC-TNT vs. SC-TNT</td>
<td>1.08</td>
</tr>
</tbody>
</table>

*Unpublished data*
Modernization of Rectal Cancer Care

The Future

- Prospective population based clinical trial of traditional vs total neoadjuvant therapy
  - Long-course chemoradiation → surgery → systemic chemotherapy
  - Short-course radiation → systemic chemotherapy → surgery

1 week 2 weeks 16 weeks 4 weeks 6 weeks 8 wks
XRT Wait Period Systemic Chemo Surgery Wait Period Recovery Systemic Chemo

6 weeks 8 weeks 6 weeks 26 weeks
Chemoradiation Waiting period Surgery Recovery Systemic Chemo

46 wks

37 wks
Modernization of Rectal Cancer Care

The Future

• Primary endpoint
  • Complete pathologic response rate

• Secondary endpoints
  • Patient reported outcomes related to therapy
    • Level of functioning
    • Time away from work
  • Timing and completeness of completion of therapy
  • Cost – will CMS claims data
  • Long term cancer related outcomes
Modernization of Rectal Cancer Care

The Future

- 10% morbidity
  - 5 days (XRT)
  - 2 weeks (Wait Period)
- 5% morbidity
  - 16 weeks (Systemic Chemo)
  - 4 weeks (Wait Period)
  - 4-6 weeks (Recovery from surgery)
  - 8 weeks (Systemic Chemo)
- 15% morbidity
  - 5-6 weeks (Chemoradiation)
  - 6-8 weeks (Waiting period)
  - 4-6 weeks (Recovery from surgery)
  - 6 months (Systemic Chemo)

89.5% completion
90% completion

Unpublished data from the STELLAR Trial
Total Neoadjuvant Therapy
The Future

- Long-course chemoradiation → systemic chemotherapy → surgery

- Short-course radiation → systemic chemotherapy → surgery

Who really needs surgery?
• A complete pathologic response (pCR) is associated with improved outcomes
  • Ranges from 18-35%
  • Increases with less depth of invasion
  • Surgeons ability to determine is poor

Total Neoadjuvant Therapy
The Future
Total Neoadjuvant Therapy
Nonoperative Management

Non-Operative Management of Rectal Cancer
Watch and Wait

The Data

Operative Versus Nonoperative Treatment for Stage 0 Distal Rectal Cancer Following Chemoradiation Therapy

Long-term Results

Angelita Habr-Gama, MD,* Rodrigo Oliva Perez, MD,* Wladimir Nadalin, MD,† Jorge Sabbaga, MD,‡ Ulysses Ribeiro Jr, MD,‡ Afonso Henrique Silva e Sousa Jr, MD,* Fábio Guilherme Campos, MD,* Desidério Roberto Kiss, MD,* and Joaquim Gama-Rodrigues, MD‡

A

Observation group (n=71)

Resection group (n=22)

P=0.003

Overall Survival

B

Observation group (n=71)

Resection group (n=22)

P=0.09

Disease-Free Survival
Watch and Wait
The Data

- Clinical and endoscopic findings of a Complete Response
  - Treatment was 5040 cGy + 5-FU
  - Follow-up
    - 8 weeks after chemo/XRT → DRE, endoscopy and CEA
    - 1st yr → DRE, endoscopy, and CEA every 1-2 months
    - 2nd yr → every 3 months
    - 3rd yr → every 6 months
Watch and Wait

The Data

Complete Clinical Response

Incomplete Response

8 weeks after treatment

Dis Colon Rectum 2010 53(12):1692-1698
Watch and Wait

The Data

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. São Julião, MD, * † Igor Proscurshim, MD, * Charles Sabbagh, MD, *
Patricio B. Lynn, MD, * and Rodrigo O. Perez, MD, PhD * , +

![Flowchart Diagram]

- Neoadjuvant CRT
  - 183 patients
  - 8 week hiatus
- Response Assessment
- Persistent Tumor
- Incomplete Response
  - Radical Surgery
  - 93 patients
- Complete Clinical Response
  - 90 patients
- Non-Operative Management
  - Median follow-up of 60 mo
  - 62 patients
- Salvageable Local Failures
  - (Early + Late Failures)
  - 22 patients
- Unresectable Local Failures
  - 6 patients
Watch and Wait
The Data

- Recurrence in 28 patients
  - Median time to recurrence → 9.5 mos (3-64)
    - 17 early recurrences
    - 11 late recurrences
  - Operation
    - FTLE → 7
    - APR → 11
    - Sphincter saving → 7
    - Brachy XRT → 1
    - Unresectable → 2
  - Re-recurrence
    - Local only → 4
    - Distant only → 5

Free of local recurrence
After salvage
All watch & wait
P<0.001

## Watch and Wait
### The Data

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Tx</th>
<th>Pts</th>
<th>F/U</th>
<th>LR</th>
<th>2-yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habr-Gama et al</td>
<td>2004</td>
<td>W&amp;W</td>
<td>71</td>
<td>57</td>
<td>7%</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resect</td>
<td>22</td>
<td>48</td>
<td>0%</td>
<td>83%</td>
</tr>
<tr>
<td>Maas M et al</td>
<td>2011</td>
<td>W&amp;W</td>
<td>21</td>
<td>25</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resect</td>
<td>20</td>
<td>35</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Smith JD et al</td>
<td>2012</td>
<td>W&amp;W</td>
<td>32</td>
<td>28</td>
<td>20%</td>
<td>88%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resect</td>
<td>57</td>
<td>28</td>
<td>0%</td>
<td>98%</td>
</tr>
<tr>
<td>Ayloor Seshadri et al</td>
<td>2013</td>
<td>W&amp;W</td>
<td>23</td>
<td>72</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resect</td>
<td>10</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Habr-Gama et al</td>
<td>2013</td>
<td>W&amp;W</td>
<td>47</td>
<td></td>
<td></td>
<td>50%</td>
</tr>
</tbody>
</table>

J Clin Oncol 2011 29(35):4633-4640
Hepatogastroenterology 2013 60(123):410-414
Dis Colon Rectum 2013 56(10):1109-1117*
Watch and Wait
Prospective Randomized Trial

- Prospective observational study
  - 20 sites in the US and Canada
  - Cross-over design for stages II and III
- Follow-up
  - After each therapy
  - DRE and CEA q3 months
  - MRI q6 months

*Patients with tumor progression at the interval evaluation will be treated according to standard of care.

BMC Cancer 2015 15:767
**Watch and Wait**

**Prospective Randomized Trial**

**Table 2: Memorial Sloan Kettering Regression Schema**

<table>
<thead>
<tr>
<th></th>
<th>Complete Response</th>
<th>Near Complete Response</th>
<th>Incomplete Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endoscopy</strong></td>
<td>Flat, white scar</td>
<td>Irregular mucosa</td>
<td>Visible tumor</td>
</tr>
<tr>
<td></td>
<td>Telangiectasia</td>
<td>Small mucosal nodules or minor mucosal abnormality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No ulcer</td>
<td>Superficial ulceration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No nodularity</td>
<td>Mild persisting erythema of the scar</td>
<td></td>
</tr>
<tr>
<td><strong>Digital Rectal Exam</strong></td>
<td>Normal</td>
<td>Smooth induration or minor mucosal abnormalities</td>
<td>Palpable tumor nodules</td>
</tr>
<tr>
<td><strong>MRI-T2W</strong></td>
<td>Only dark T2 signal, no intermediate T2 signal</td>
<td>Mostly dark T2 signal, some remaining intermediate signal</td>
<td>More intermediate than dark T2 signal, no T2 scar</td>
</tr>
<tr>
<td></td>
<td>AND/AND</td>
<td>AND/AND</td>
<td>AND/AND</td>
</tr>
<tr>
<td></td>
<td>No visible lymph nodes</td>
<td>Partial regression of lymph nodes</td>
<td>No regression of lymph nodes</td>
</tr>
<tr>
<td><strong>MRI-DW</strong></td>
<td>No visible tumor on B800-B1000 signal</td>
<td>Significant regression of signal on B800-B1000</td>
<td>Insignificant regression of signal on B800-B1000</td>
</tr>
<tr>
<td></td>
<td>AND/AND</td>
<td>AND/AND</td>
<td>AND/AND</td>
</tr>
<tr>
<td></td>
<td>Lack of or low signal on ADC map</td>
<td>Minimal or low residual signal on ADC map</td>
<td>Obvious low signal on ADC map</td>
</tr>
</tbody>
</table>

*BMC Cancer 2015 15:767*
Total Neoadjuvant Therapy Nonoperative Management

Aluminum surfaces

Transvaginal PAT/US probe

Optical fibers

Laser and optical system

Probe sheath

PAT/US image

PAT/US real time system
Total Neoadjuvant Therapy
Nonoperative Management

Approach: PAT/US imaging

In vivo US image

In vivo PAT/US image

PAT image

Transvaginal ultrasound
In vivo Imaging of human ovaries

Before surgery

Ex vivo Imaging

Cancer is early stage T1c on the surface

Histology

Malignant ovary

H&E

Washington University in St. Louis • School of Medicine

Department of Surgery
Section of Colon and Rectal Surgery
Total Neoadjuvant Therapy

Rectal cancer
Pre-op Staging

T1
- Local tx
- Chemo/XRT

T2
- Radical Sx
- Short course XRT
- Chemo/XRT

Stage 2/3
- Chemo
- Watch & wait
- Radical Sx
Watch and Wait
Who, How and Why

- Who?
  - T3,Nx
  - Tx,N+
  - Can we expand to earlier cancers?
- How?
  - Radiation therapy – preferably short course
  - Chemotherapy – FOLFOX – complete course
  - Surveillance
- Why?
  - Highly motivated patient
  - Avoid a permanent colostomy
  - Medically unfit for surgery
  - Avoid functional impact of proctectomy
Total Neoadjuvant Therapy

Thank-you