Multidisciplinary Care and Nonoperative Management For Rectal Cancer

Steven Nurkin, MS, MD
Associate Professor of Surgery
Department of Surgical Oncology
Roswell Park Comprehensive Cancer Center
I have no disclosures
Overview

- Background/Milestones of Rectal Cancer Management
- Are all the treatment modalities necessary?
  - Radiation, Surgery?
- The data on watch-and-wait
- What’s next and future directions?

Abbreviations:
CRT: chemoradiation
TNT: total neoadjuvant therapy
TME: total mesorectal excision
5-FU/LV: 5-fluorouracil/leucovorin
CapeOx: Capecitabine/Oxaliplatin
FOLFOX: 5-FU, folinic acid and Oxaliplatin
FOLFIRI: 5-FU, folinic acid and irinotecan

Abbreviations:
cCR: clinical complete response
pCR: pathologic complete response
NOM: nonoperative management
W&W or WW: watch & wait
Annual report to the nation on the status of Colorectal Cancer
Impact of interventions (risk factors, screening, and treatment) to reduce future rates
Colon Cancer's New Face: Getting Younger

If the trends continue, they report in the journal *JAMA* Surgery, the number of colon cancer cases in people aged 20 to 34 will spike by nearly ...

Colon cancer on the rise in young adults

Rate of colorectal cancer in young adults in the U.S. is rising, study ...

For Reasons Unknown, Colon And Rectal Cancer Rates Are Rising ...

Colon Cancer Rates Rising in Young Adults

Colon Cancer on the Rise for U.S. Adults Under 50
Figure 2. Annual Percentage Change-Based Predicted Incidence Rates of Colon Cancer by Age Compared With Incidence Rate in 2010

- Age range, y:
  - 20-34
  - 35-49
  - 50-74
  - ≥75

- Change of the Incidence Rate, %:
  - 90.0%
  - 27.7%
  - -37.8%
  - -44.5%

Year:
- 2010
- 2020
- 2030
Deadliest Cancer Types for Ages 20-49, 2012 - 2016

MEN
1. COLORECTAL
2. LUNG
3. BRAIN

WOMEN
1. BREAST
2. LUNG
3. COLORECTAL
Milestones in the Management of Rectal Cancer

1985
- NSABP R01 GITSG
  Adjuvant Radiation Alone
- NCTT
  Adjuvant CRT Systemic chemotherapy
- NIH Consensus Conference
- Swedish Rectal Cancer Trial
  Preoperative short course radiation
- Dutch TME Trial
  Preoperative radiation in the TME era
- German Rectal Cancer Trial
  CAD/ARO/AIO3
- CAO/ARO/AIO4
  Neoadjuvant CRT and adjuvant chemotherapy
- No Oxaliplatin

2017-18
- MRI Stage
- CRT
- TME
- Adjuvant Chemo

1Siegel RL et al. CA Cancer J Clin 2019
2Siegel RL et al. CA Cancer J Clin 2017
3Bailey CE et al JAMA Surg 2015
Smith Adapted
Challenges in Rectal Cancer Treatment

- Difficult surgery (low, male, obese)
- Patients still have local and distant recurrences
- Preservation of quality of life
  - Stoma, Genitourinary dysfunction
- Identifying responders and making treatment more individualized

“Poster child” for multidisciplinary care!!
The “Holy” Mesorectal Plane
Total mesorectal excision reduces local recurrence rates

- 30-40% without TME, 3.7% with TME

- TME varies between surgeons (experience, training, techniques)

Heald *Lancet* 1986; 1(8496)
Heald *Lancet* 1993; 341(8843)
Consequences of radical surgery

**Total mesorectal excision (TME)**

Hospital **mortality**: 1-5%

Complications of CRT + TME
- Anastomotic **leak**: 28%
- Perineal wound **infection**: 37%
- **Readmission** 30 days: 20%

Bowel **obstruction/hernia**: 15%

Urinary **incontinence**: 39%

Sexual **dysfunction**
- women: 29%
- men: 45%

Defecatory problems: 38%

Permanent **stoma**: 30%

---

Peeters et al, JCO 2005   Marijnen et al, JCO 2002
German Rectal Trial - Preop RT

- Reduction in Local Recurrence
- Improved Sphincter Preservation

Sauer NEJM, 2004
Bowel Function 14 Years After Preoperative Short-Course Radiotherapy and Total Mesorectal Excision for Rectal Cancer: Report of a Multicenter Randomized Trial

Chen TY et al., *Clinical Colorectal Cancer* 2015
## Adjuvant Rectal Cancer Trials: Poor Compliance

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Chemotherapy</th>
<th>Comments</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 22921</td>
<td>1011</td>
<td>2x2: Atypical 5-FU (Days 1-5)</td>
<td>37% underwent TME 27% did NOT initiate adjuvant CTX ONLY 43% received planned post-op CTX</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LARC</td>
<td>655</td>
<td>Obs vs 5-FU/LV</td>
<td>28% did NOT initiate adjuvant CTX 58.4% received 3-6 of proposed 6 cycles CRT or 5x5 28% did NOT complete adjuvant CTX</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PROCTOR/SCRIPT (closed prematurely)</td>
<td>470 / 840</td>
<td>Obs vs. 5-FU/Cape</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Chronicle (closed prematurely)</td>
<td>113 / 800</td>
<td>Obs. vs. XELOX x 6</td>
<td>52% did NOT complete planned CTX</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>ADORE</td>
<td>321</td>
<td>5-FU vs. FOLFOX x 8</td>
<td>Based on yp staging R0 resection 38m f/u 96% completion of CTX p=0.05</td>
<td>NS (ITT)</td>
<td>FOLFOX&gt;F L (DFS)</td>
</tr>
</tbody>
</table>

Presented By Cathy Eng at 2018 ASCO Annual Meeting
Adapted by JJ Smith 16 June 2018
Existing Paradigm of Treatment for Locally Advanced Rectal Cancer

**Diagnosis**
- 2019: >44,000 new cases (US alone)\(^1\)

**Staging**

**NCRT**
- 5-FU based nCRT 6 weeks

**TME**

**Adjuvant Chemotherapy**

- 1st line: 5-FU or FOLFOX 16-18 weeks
- 2nd line: FOLFIRI

**Targeted therapy:**
- No clear role for locally advanced rectal cancer patients (e.g., Cetuximab)

\(^1\)Siegel RL et al. CA Cancer J Clin 2019

Maas M et al, The Lancet Oncol 2010; 11(9): 835-844
Recurrence-free survival by response

- Best response (TRG 4 or pCR)
- Intermediate response (TRG 2-3)
- Worst response (TRG 0-1)

Fokas E et al. *J Clin Oncol* 2014;32:1554-1562
Total Neoadjuvant Therapy (TNT)

- Diagnosis
- Staging
- NCRT
- TME
- Adjuvant Chemotherapy

Induction → Consolidation
TNT is associated with higher pCR rates

<table>
<thead>
<tr>
<th>Treatment Groupa</th>
<th>All Patients, No.</th>
<th>All Patients, Sustained cCR, No. (%)b</th>
<th>Surgery Within 12 Months, No.</th>
<th>Surgery Within 12 Months, pCR, No. (%)b</th>
<th>Complete Response (pCR and Sustained cCR) at 12 Months, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChemoRT with planned adjuvant chemotherapy</td>
<td>94</td>
<td>9 (9.6)</td>
<td>82</td>
<td>14 (17.1)</td>
<td>23 (24.5)</td>
</tr>
<tr>
<td>Stage II</td>
<td>226</td>
<td>10 (4.4)</td>
<td>214</td>
<td>35 (16.4)</td>
<td>45 (19.9)</td>
</tr>
<tr>
<td>Total</td>
<td>320</td>
<td>19 (5.9)</td>
<td>296</td>
<td>49 (16.6)</td>
<td>68 (21.3)</td>
</tr>
</tbody>
</table>

- TNT

| Stage II         | 43               | 23 (53.5)                            | 20                          | 0                                      | 23 (53.5)                                   |
| Stage III        | 265              | 44 (16.6)                            | 215                         | 43 (20.0)                             | 87 (32.8)                                   |
| Total            | 308              | 67 (21.8)                            | 235                         | 43 (18.3)                             | 110 (35.7)                                  |

Cercek A et al, *JAMA Oncology*, March 22, 2018
Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial

Systemic Chemotherapy Before Surgery
(Total Neoadjuvant Therapy – TNT)

Potential Advantages

• Earlier treatment of subclinical *micrometastasis*

• Improves treatment *compliance* and ensures efficacy

• *Reduces the time* to ileostomy closure

• *Enhances response* of the primary tumor

• Can be given before (induction) or after (consolidation) CRT
Do all rectal cancer patients require this aggressive multimodality approach?

Can we do the same or more with less?
“Pick Your Poison”

Chemotherapy
Radiation
Surgery
Do All Rectal Cancer Patients need CRT?

The Prospect Trial

From Franke et al, Clinical Colorectal Cancer 2017
Based on Schrag D et al, J Clin Oncol. 2014
What if the tumor disappears after Neoadjuvant therapy?

Routine: **CRT → TME**

- **TME** has toxicity

- **pCR**
  - Occurs in 12-38% of patients
  - 85-95% 4-yr and 5-yr DFS

- **clinical complete response (cCR)**
  - pCR associated with cCR

Maas M et al. *Lancet Oncol* 2010 Sep;11(9):835-44
265 resectable LOW rectal cancer patients s/p CRT

- **cCR** → WW (n = 71)
- non-cCR → Resection (n = 194; 22 had **pCR**)

- **cCR** = possible cure
- **Deferral of surgery** = safe
- **Surgical salvage** = effective
- **OS** = no significant difference

*Habr-Gama A et al., Ann Surg 2004; 240 (4):711-7*
International W&W Registry

- 880 patients entered in W&W protocols
- 47 centers
- 15 countries
- From 1991 to 2015
- Denominator unknown
- Most patients already published in other series

van der Valk et al, The Lancet 2018;391:2537-45
International W&W Registry: Results

Tumor Regrowth

Overall Survival

Salvage Surgery
Missing data in 31%
TME in 54%

van der Valk et al, *The Lancet* 2018;391:2537-45
Recent MSK results with W&W

Smith JJ et al, JAMA Oncology 2018
W&W Outcomes

Overall Survival

Disease-specific survival

Smith JJ et al, JAMA Oncology 2018

>60% died of other causes
Rate of local regrowth in patients after apparent clinical complete response

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Metastasis</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local re-growths</td>
<td>22</td>
<td>8/22</td>
<td>36%</td>
</tr>
<tr>
<td>No Local re-growths</td>
<td>91</td>
<td>1/91</td>
<td>1%</td>
</tr>
</tbody>
</table>

21% local regrowth (95% CI 12–30)

Smith JJ et al, *JAMA Oncology* 2018
• Use of a WW approach carries some risk—whether that risk would have been mitigated with upfront TME after neoadjuvant therapy is unknown

• Identification of those who will completely respond to neoadjuvant therapy and who are optimal candidates for WW approaches is as of yet unknown

• Use of a WW approach in the context of a cCR is likely best done in the context of a clinical trial (if possible)
Nonoperative management after neoadjuvant therapy for rectal cancer: A single institution experience over 5 years

Strode, M. Nurkin S. et. al Surgical Oncology Volume 28, March 2019
Review from a prospectively collected database, of patients with rectal cancer at Roswell Park from 2012 – 2016.

- 29 patients experienced a cCR after neoadjuvant therapy
- 80% low tumors
- 45% N1,2+
- 65% TNT
# Tumor Response Assessment

## Complete Response
- Flat, white scar
- Telangiectasia
- No ulcer
- No nodularity

## Near Complete Response
- Small mucosal nodules or
  minor mucosal abnormality
- Superficial ulceration
- Mild persisting erythema of
  the scar

## Incomplete response
- Visible tumor

### Endoscopy
- Normal
- Only dark T2 signal, no intermediate T2 signal
- No visible lymph nodes
- No visible tumor on B800-B1000 signal
- Lack of or low signal on ADC map
- Uniform, linear signal in wall above tumor bed

### MRI-T2W
- Only dark T2 signal, no intermediate T2 signal
- No visible lymph nodes
- No visible tumor on B800-B1000 signal
- Lack of or low signal on ADC map

**Smith JJ et al., BMC Cancer, 2015.**

**Habr-Gama et al. DCR 53:12 (2010)**
## Post-cCR follow-up

**Typical surveillance and intervals:**

<table>
<thead>
<tr>
<th></th>
<th>Yr1</th>
<th>Yr2</th>
<th>Yr3-5</th>
<th>&gt;Yr5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endoscopy</strong></td>
<td>q3m</td>
<td>q4m</td>
<td>q6m</td>
<td>q12m</td>
</tr>
<tr>
<td><strong>DRE</strong></td>
<td>q3m</td>
<td>q4m</td>
<td>q6m</td>
<td>q12m</td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td>q6m</td>
<td>q6m</td>
<td>q6-12</td>
<td>-</td>
</tr>
<tr>
<td><strong>CT/MRI/EUS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2 patients with local recurrence, 5 distant recurrence
4 of 6 were salvaged with surgical management
• Median follow-up – 27.6 months

No mortalities
What we don’t know…

• How to **predict** response?
• How to **maximize** tumor response?
• When is the best time to **assess** response?
• How to **identify** true responders?
• How often to **survey** these patients?
• Will tumors **re-grow**? Will they be **salvageable**?
• Can **occult cancer cells** metastasize?

**Are we putting some patients at risk?**
Conclusions

• Neoadjuvant treatment strategies, like TNT, may facilitate durable rates of cCR.

• Continued responses after these treatments could possibly enable more patients to undergo nonoperative management.

• We believe nonoperative management can be offered to those seeking rectal preservation, but more research is required to select the appropriate patients.

• For those patients experiencing recurrence, the majority of patients can be salvaged surgically.
Pre-operative TNT followed by selective W & W approach will not compromise DFS comparing to historical controls who received standard of care treatment.
RAPIDO Trial – Ongoing
Summary

• Rectal cancer is a difficult disease to treat, and its management is evolving

• Tumor response to neoadjuvant therapies are variable, and it is unclear if all modalities are really needed

• TME is effective but associated with significant morbidity

• Like anal cancer, some patients can be CURED WITH CHEMOTHERAPY AND RADIATION!
  • But who are they?
• Nonoperative management may be feasible in a select group of patients, that achieve a complete clinical response
• Clinical trials are still needed to address many of the unanswered questions
Thank you!

Patrick Boland  David Mattson  Matthew Strode  Jill Willard  Heather Sabadasz

Sarbajit Mukherjee  Joshua Smith - MSK

ROSWELL PARK COMPREHENSIVE CANCER CENTER