Multidisciplinary Care and Nonoperative Management For Rectal Cancer

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I have no disclosures

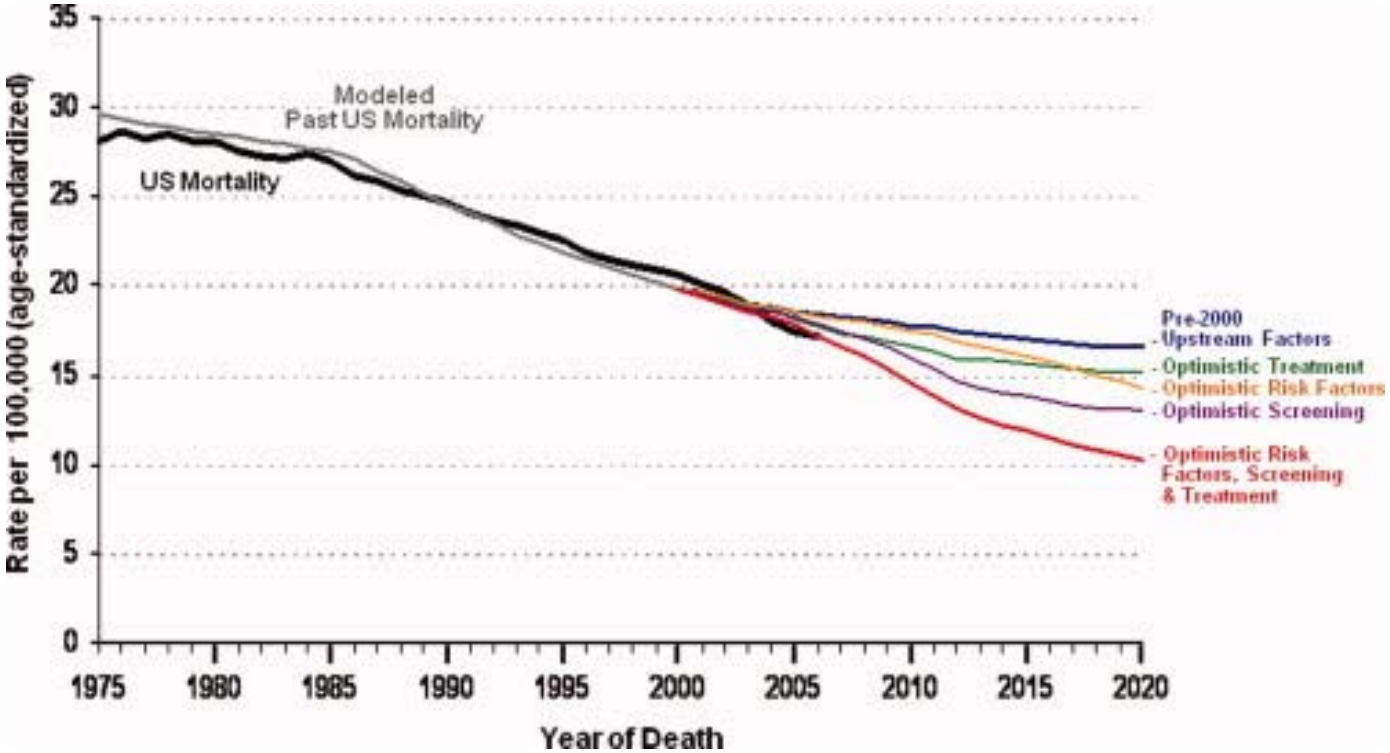
Overview

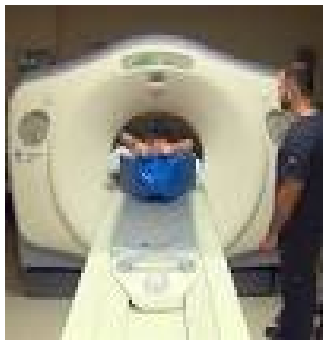
- **Background/Milestones of Rectal Cancer Management**
- **Are all the treatment modalities necessary?**
  - **Radiation, Surgery?**
- **The data on watch-and-wait**
- **What's next and future directions?**

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**
NBCNews.com - Nov 5, 2014
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
CBS News - 10 hours ago

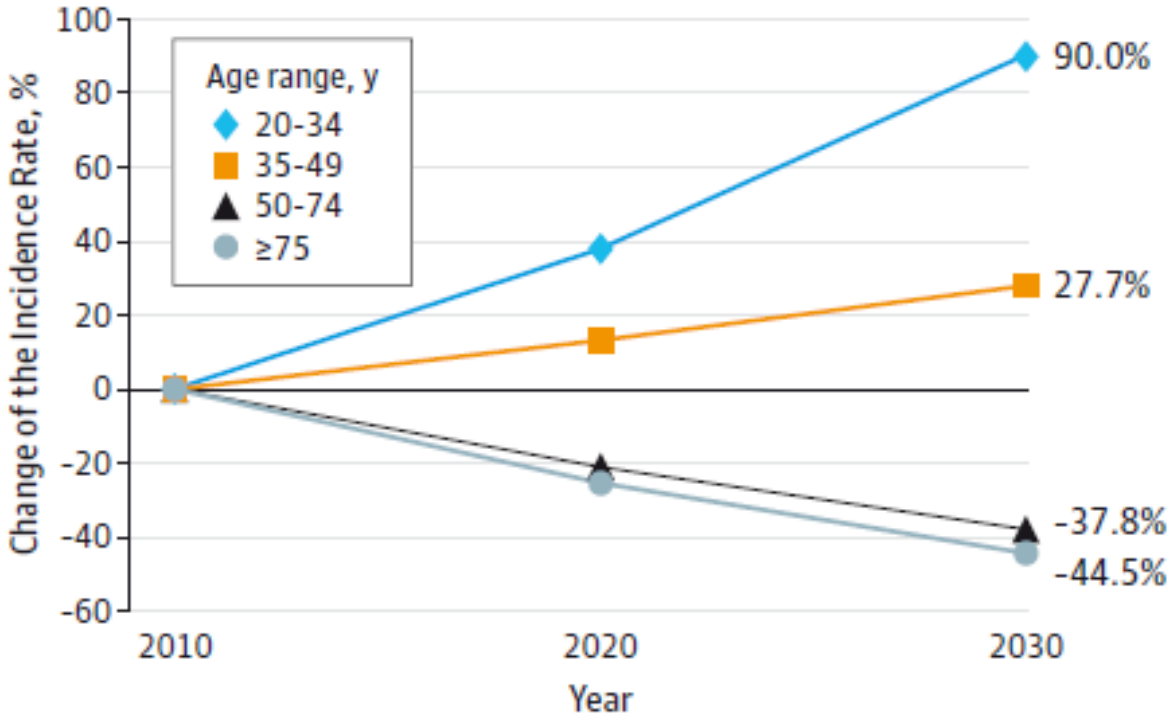
Rate of **colorectal cancer** in **young** adults in the U.S. is rising, study **...**
The Plain Dealer - cleveland.com - 13 hours ago

For Reasons Unknown, **Colon** And Rectal **Cancer** Rates Are Rising **...**
In-Depth - Forbes - 4 hours ago

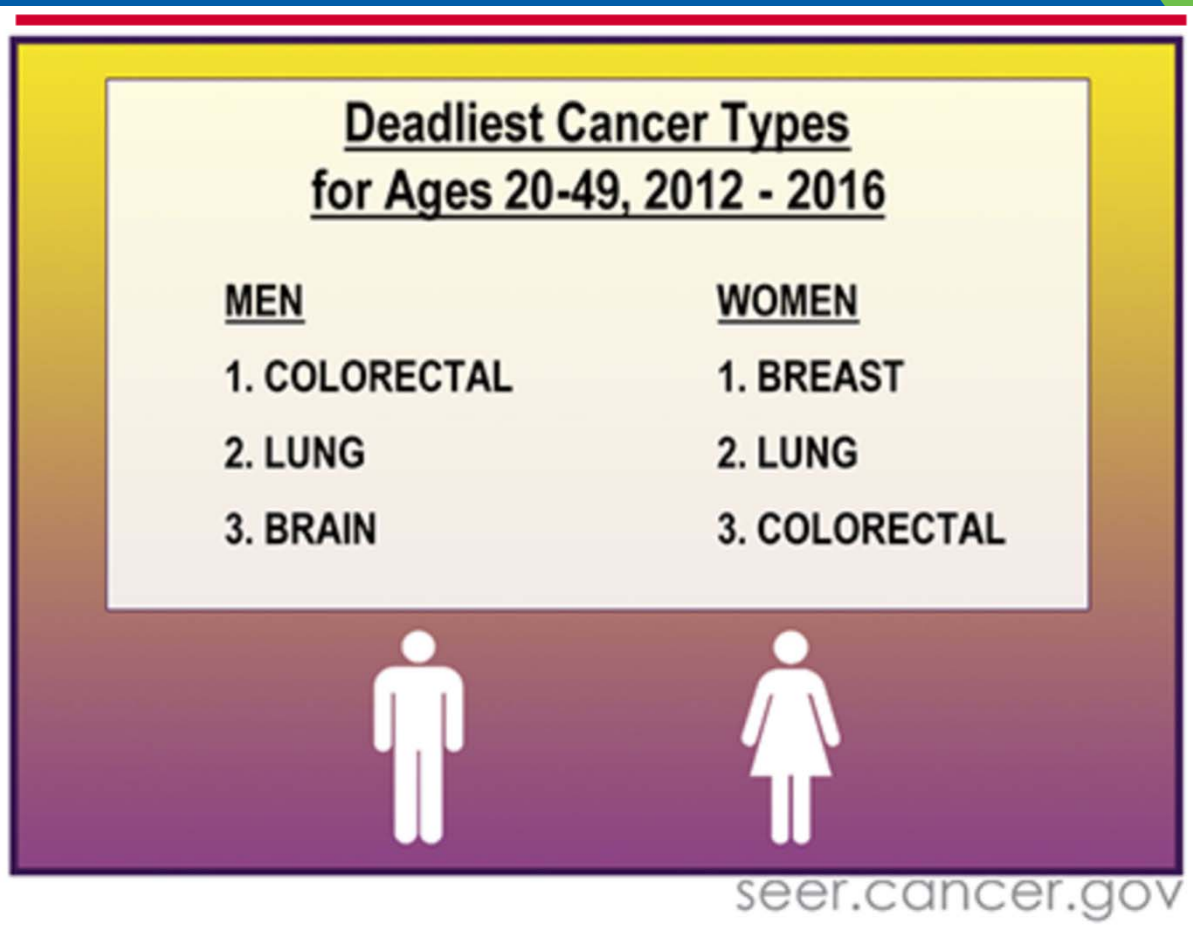
Colon Cancer Rates Rising in **Young** Adults
Blog - New York Times (blog) - 11 hours ago

Colon Cancer on the Rise for U.S. Adults Under 50
In-Depth - Philly.com - 13 hours ago

Figure 2. Annual Percentage Change–Based Predicted Incidence Rates of Colon Cancer by Age Compared With Incidence Rate in 2010

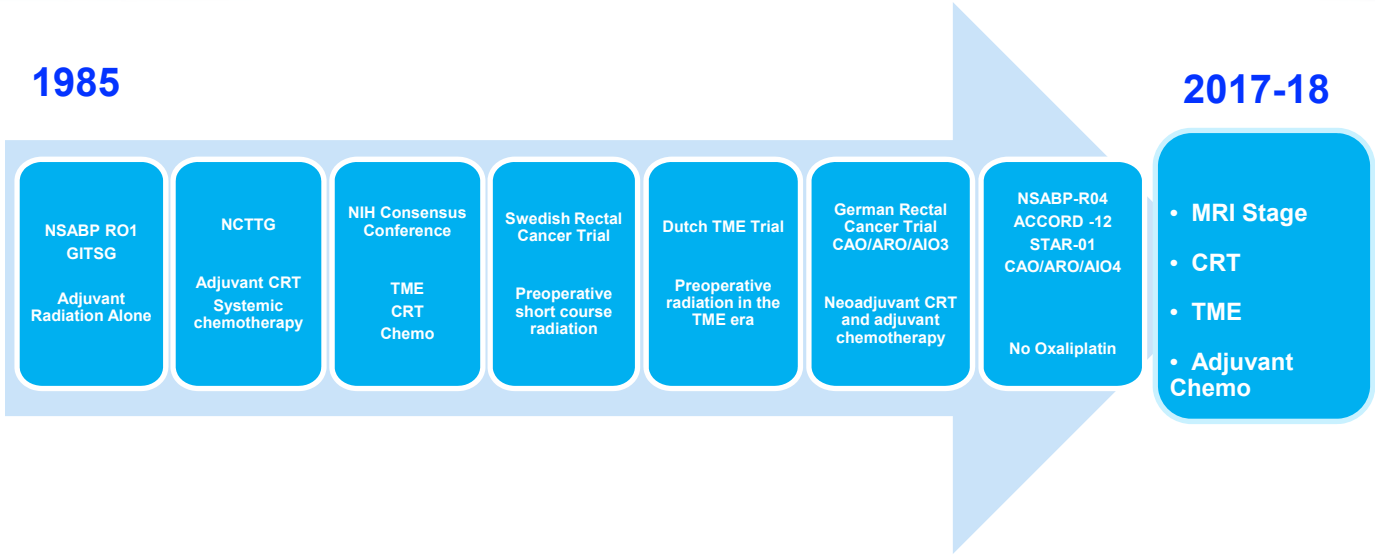


Chang, Jama Surgery 2018



Chang, Jama Surgery 2018

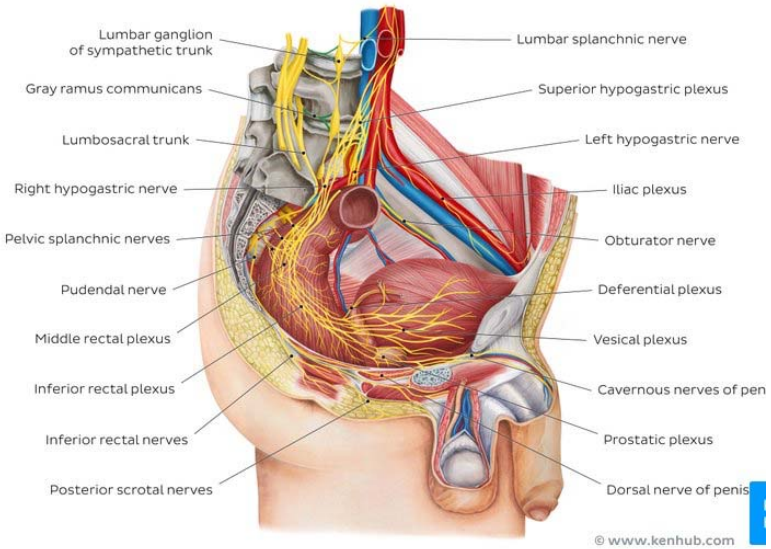
Milestones in the Management of Rectal Cancer



[1]Siegel RL *et al. CA Cancer J Clin 2019*
[2]Siegel RL *et al. CA Cancer J Clin 2017*
[3]*Bailey 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**

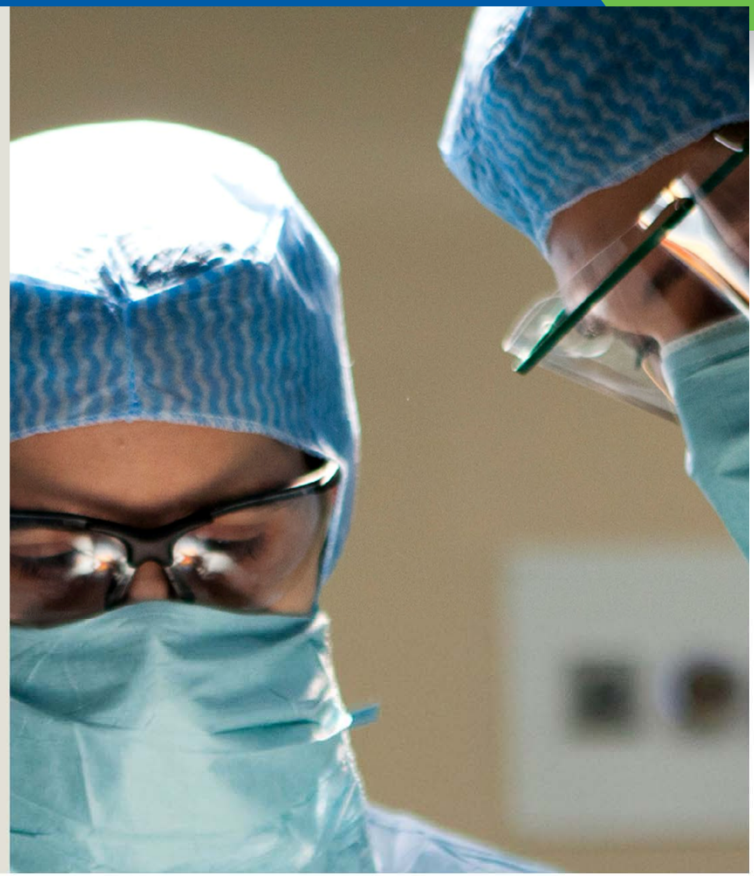


"Poster child" for multidisciplinary care!!

Commission on Cancer®

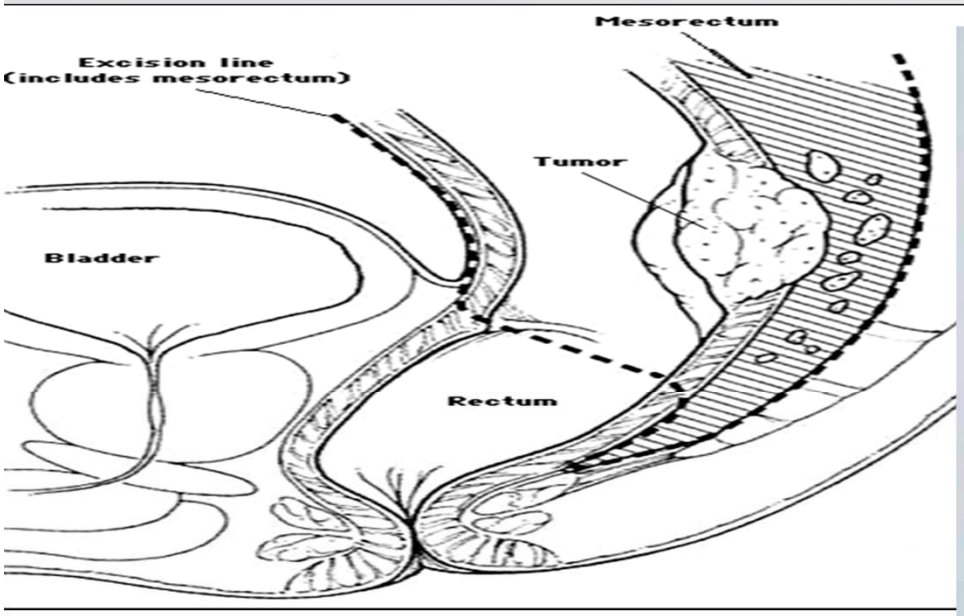
NATIONAL ACCREDITATION PROGRAM FOR RECTAL CANCER

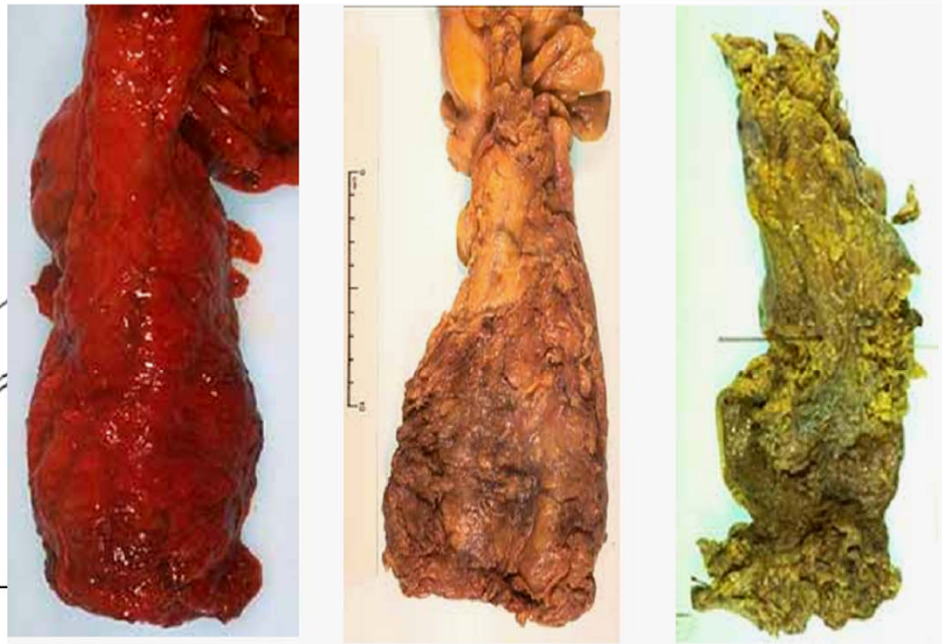
A QUALITY PROGRAM
of the AMERICAN COLLEGE
OF SURGEONS



ROSWELL PARK COMPREHENSIVE CANCER CENTER

The “Holy” Mesorectal Plane





Mesorectal fascia | Intramesorectal | Muscularis propria

Figure 4 Examples of rectal cancer excision specimens showing different surgical excision planes

Quirke Ann Surg. 2002 Apr;235(4):449-57

The Importance of Good TME Surgery

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%

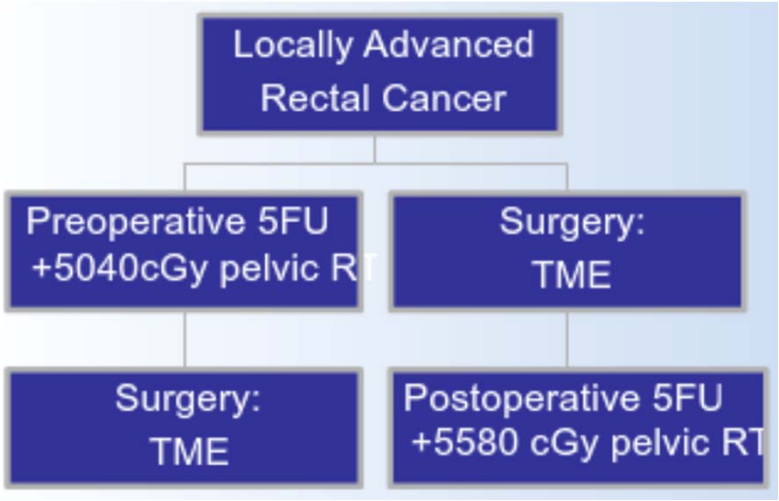
Sexual **dysfunction**
- women: 29%
- men: 45%

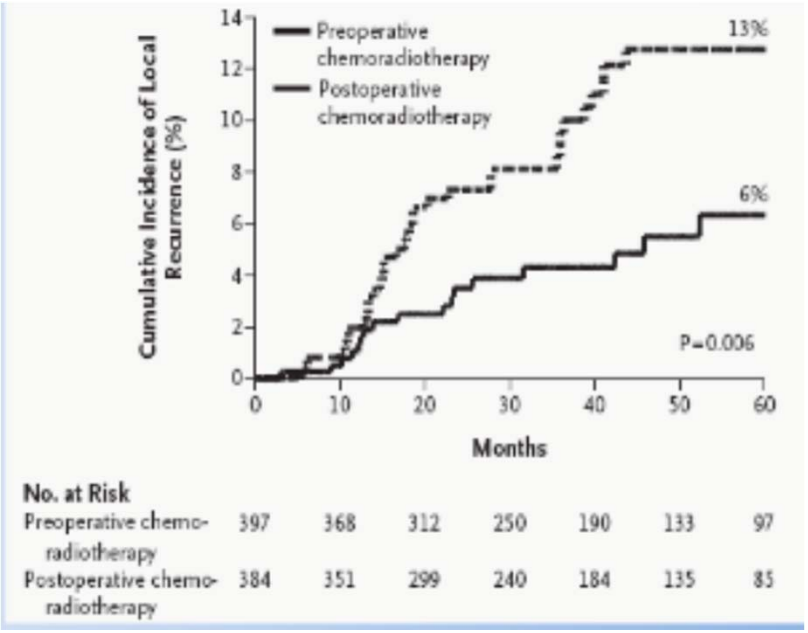
Defecatory problems: 38%

Permanent **stoma**: 30%

Tekkis et al, BMJ 2003
Swellengrebel et al, Ann Surg 2011
Peeters et al, JCO 2005
Marijnen et al, JCO 2002
Peeters et al, JCO 2006
Hendren et al, Ann Surg 2005

German Rectal Trial - Preop RT

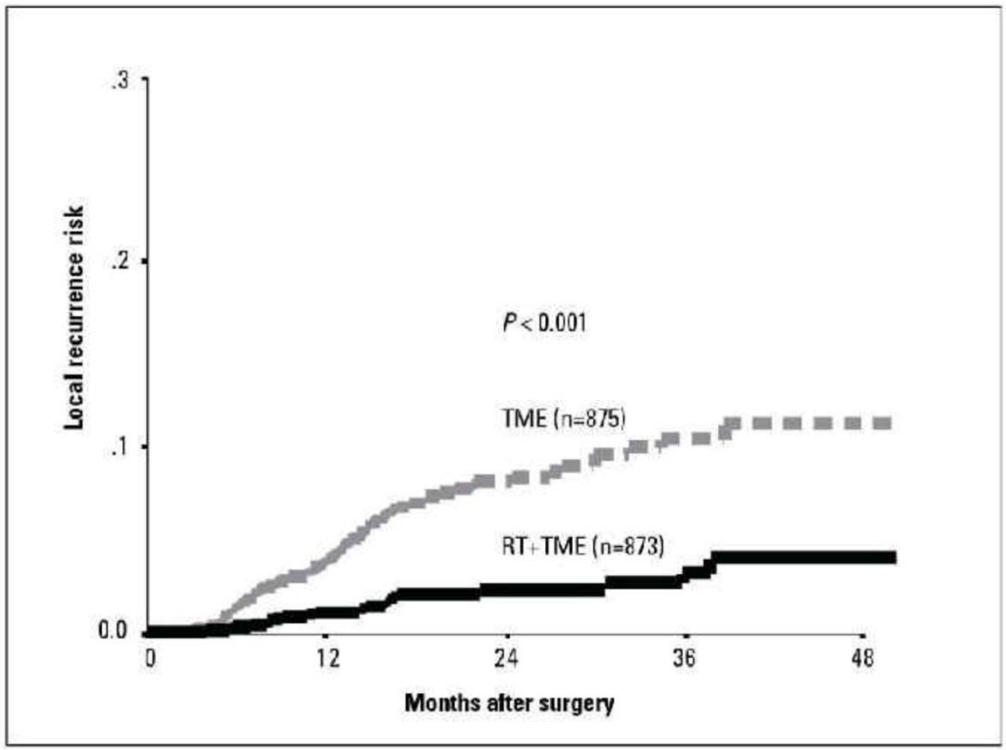




- Reduction in Local Recurrence
- Improved Sphincter Preservation

Sauer NEJM, 2004

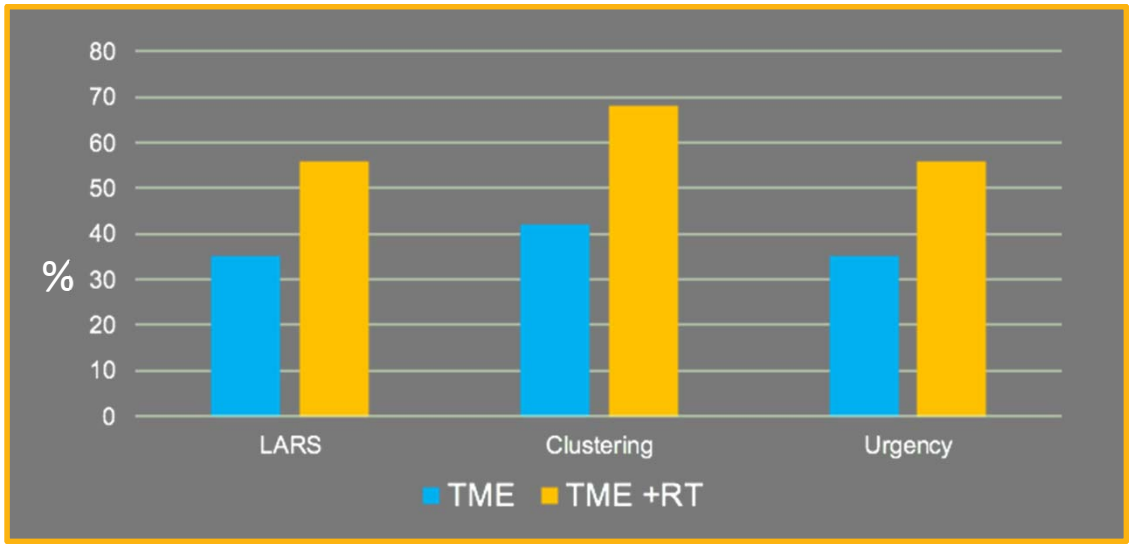
Dutch TME Trial - Pre Op RT/TME



Van De Velde Lancet Oncol. 2011 Jun;12(6

Original Study

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

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

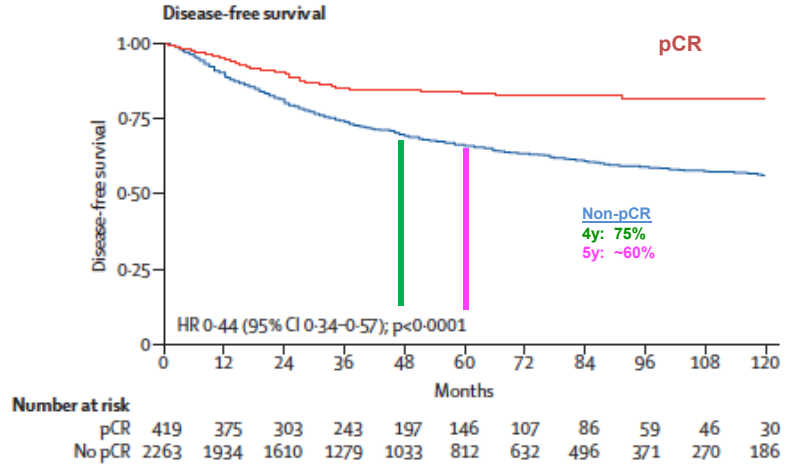
Presented By Cathy Eng at 2018 ASCO Annual Meeting
Adapted by JJ Smith 16 June 2018

Existing Paradigm of Treatment for Locally Advanced Rectal Cancer

Diagnosis → Staging → NCRT → TME → Adjuvant Chemotherapy

2019:
>44,000 new cases
(US alone)[1]

5-FU based nCRT
6 weeks



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

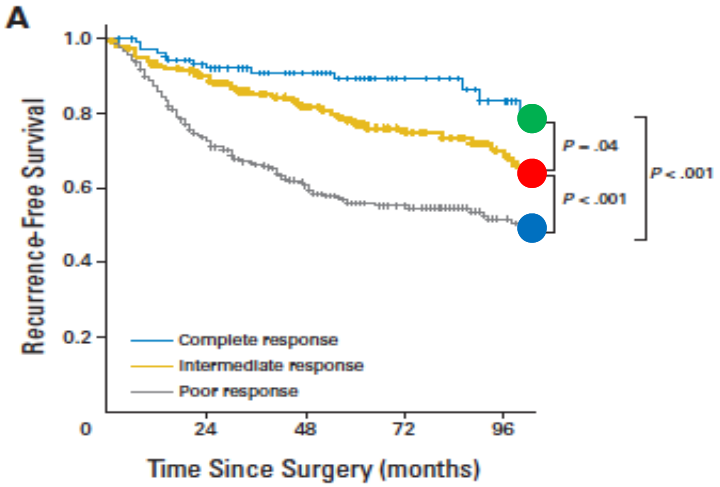
2nd line:
FOLFIRI

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

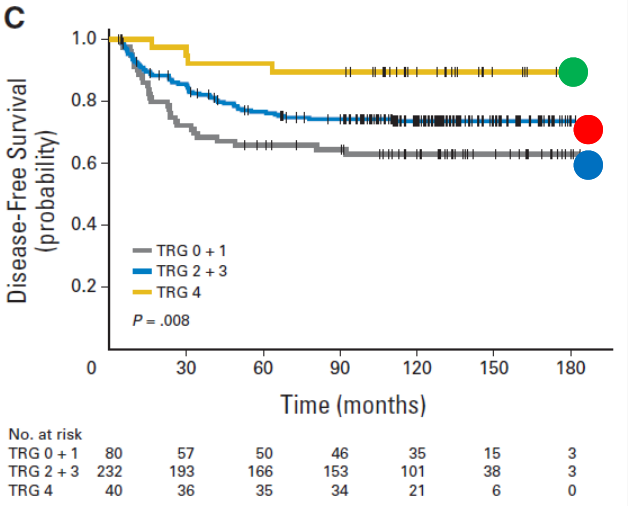
[1]Siegel RL *et al. CA Cancer J Clin 2019*

Maas M et al, *The Lancet Oncol* 2010; 11(9): 835-844

Recurrence-free survival by response



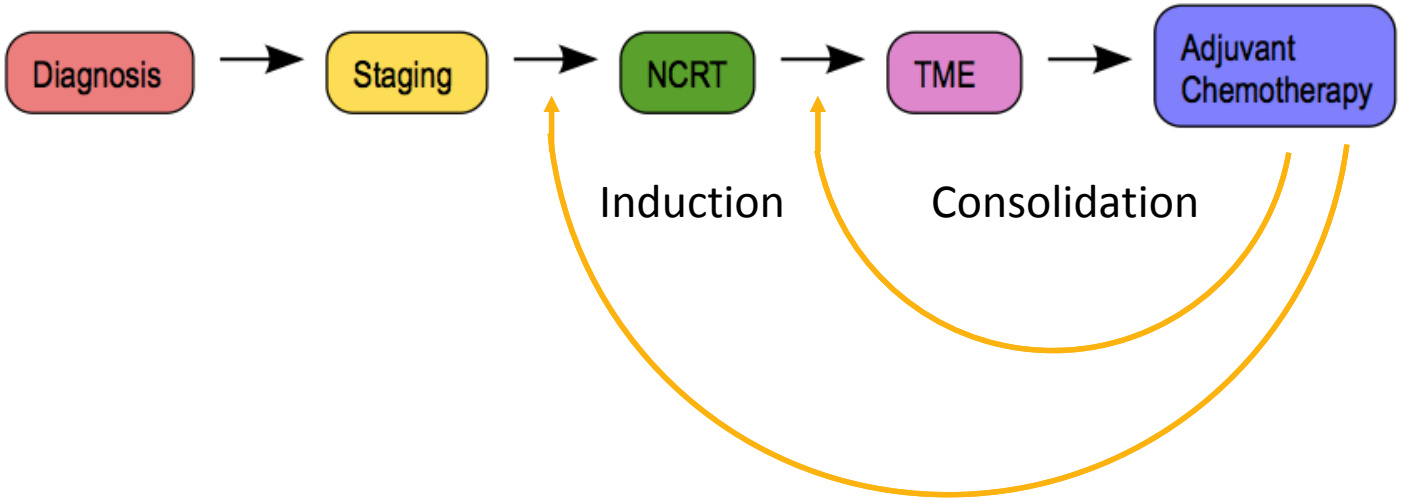
Park I J et al. *J Clin Oncol* 2012;30:1770-1776



Fokas E et al. *J Clin Oncol* 2014;32:1554-1562

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

Total Neoadjuvant Therapy (TNT)

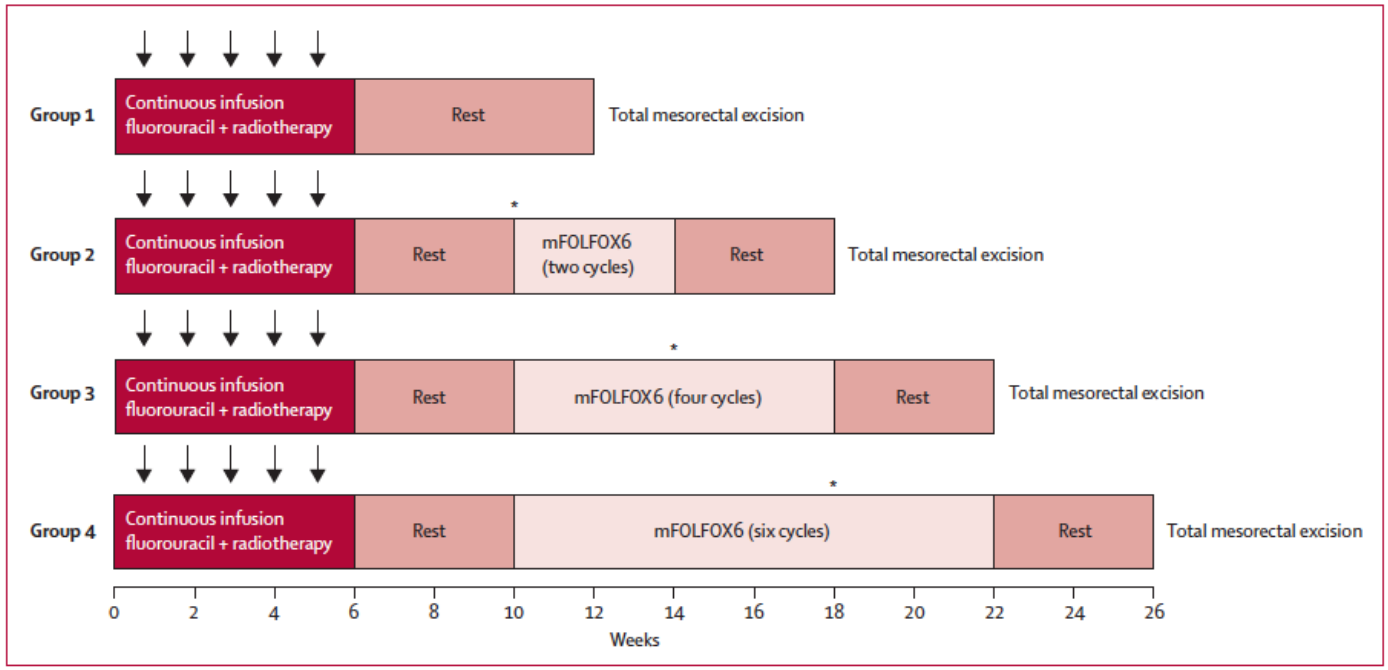


TNT is associated with higher pCR rates

Treatment Group[a]	All Patients, No.	All Patients, Sustained cCR, No. (%)[b]	Surgery Within 12 Months, No.	Surgery Within 12 Months, pCR, No. (%)[b]	Complete Response (pCR and Sustained cCR) at 12 Months, No. (%)
ChemoRT with planned adjuvant chemotherapy					
Stage II	94	9 (9.6)	82	14 (17.1)	23 (24.5)
Stage III	226	10 (4.4)	214	35 (16.4)	45 (19.9)
Total	320	19 (5.9)	296	49 (16.6)	68 (21.3)
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



ypT0: 18%

ypT0: 25%

ypT0: 30%

ypT0: 38%

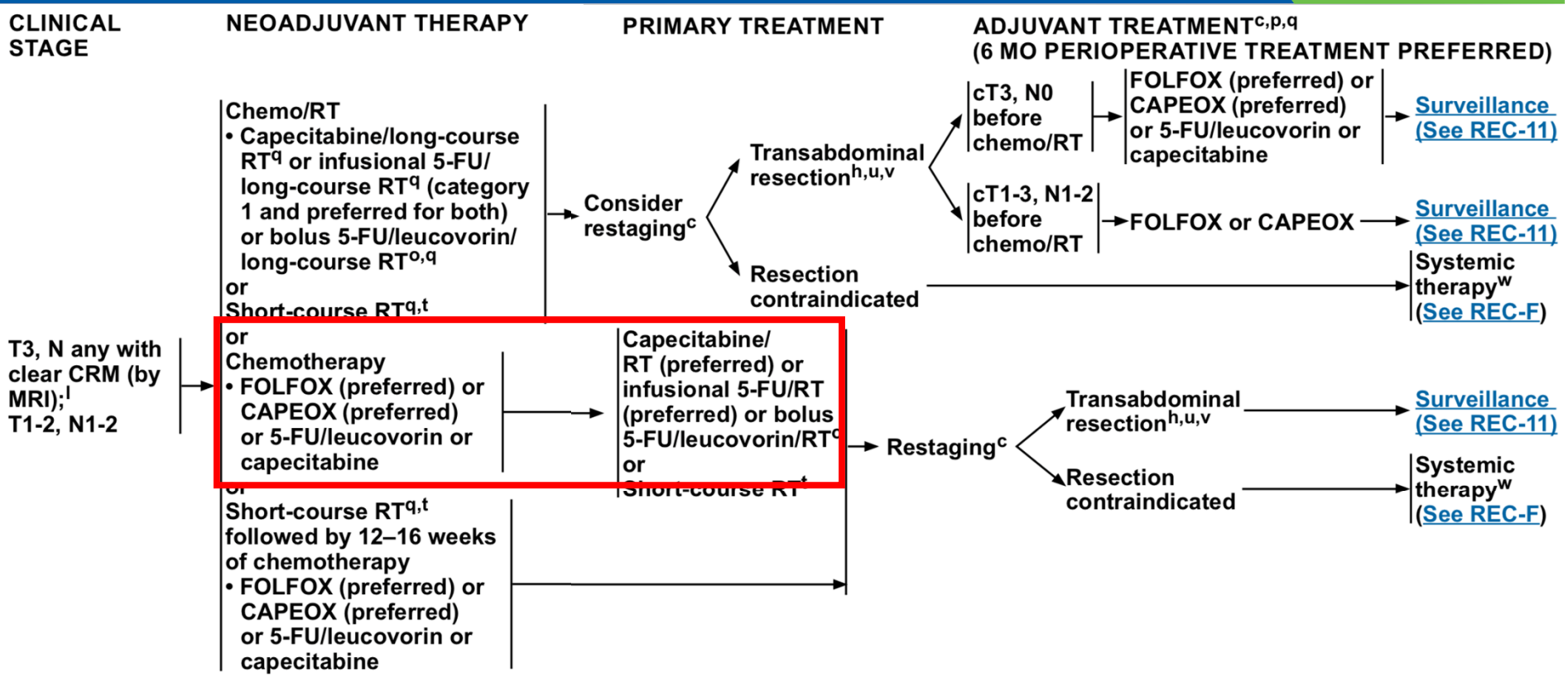
Garcia-Aguilar et al, *The Lancet Oncology*, Volume 16, Issue 8, 2015.

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

NCCN 2019


CLINICAL STAGE
NEOADJUVANT THERAPY
PRIMARY TREATMENT
ADJUVANT TREATMENT[c,p,q] (6 MO PERIOPERATIVE TREATMENT PREFERRED)
T3, N any with clear CRM (by MRI);[l] T1-2, N1-2
Chemo/RT
• Capecitabine/long-course RT[q] or infusional 5-FU/ long-course RT[q] (category 1 and preferred for both) or bolus 5-FU/leucovorin/ long-course RT[o,q]
or
Short-course RT[q,t]
or
Chemotherapy
• FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capecitabine
or
Short-course RT[q,t] followed by 12–16 weeks of chemotherapy
• FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capecitabine
Consider restaging[c]
Capecitabine/ RT (preferred) or infusional 5-FU/RT (preferred) or bolus 5-FU/leucovorin/RT[o]
or
Short-course RT[t]
Restaging[c]
Transabdominal resection[h,u,v]
Resection contraindicated
Transabdominal resection[h,u,v]
cT3, N0 before chemo/RT
FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capecitabine
Surveillance (See REC-11)
cT1-3, N1-2 before chemo/RT
FOLFOX or CAPEOX
Surveillance (See REC-11)
Systemic therapy[w] (See REC-F)
Resection contraindicated
Surveillance (See REC-11)
Systemic therapy[w] (See REC-F)

Do all rectal cancer patients require this aggressive multimodality approach?

Can we do the same or more with less?

“Pick Your Poison”

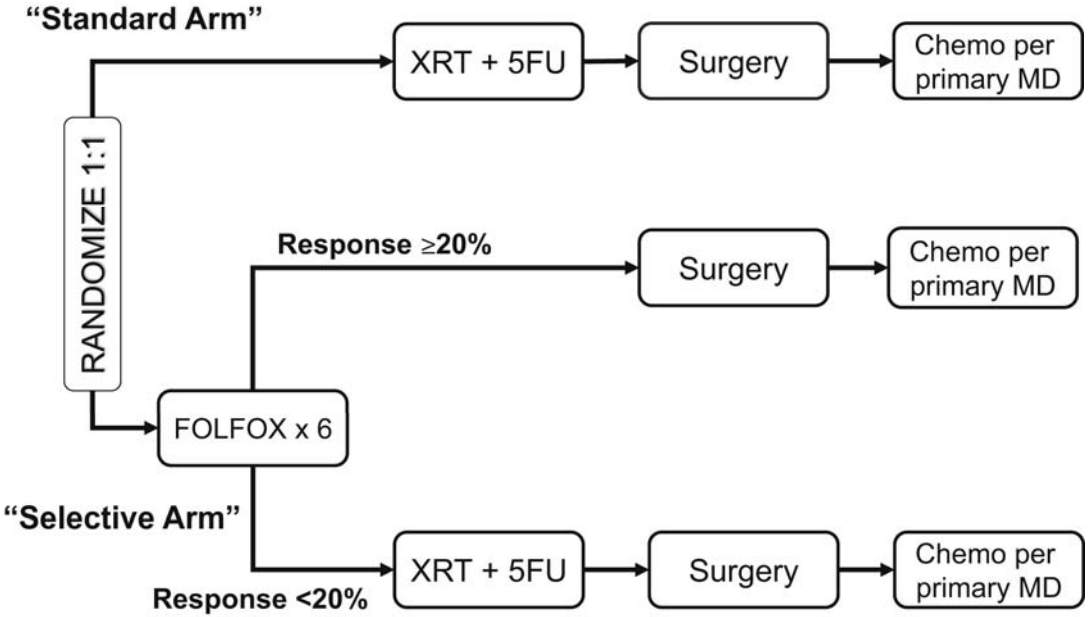
Chemotherapy

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

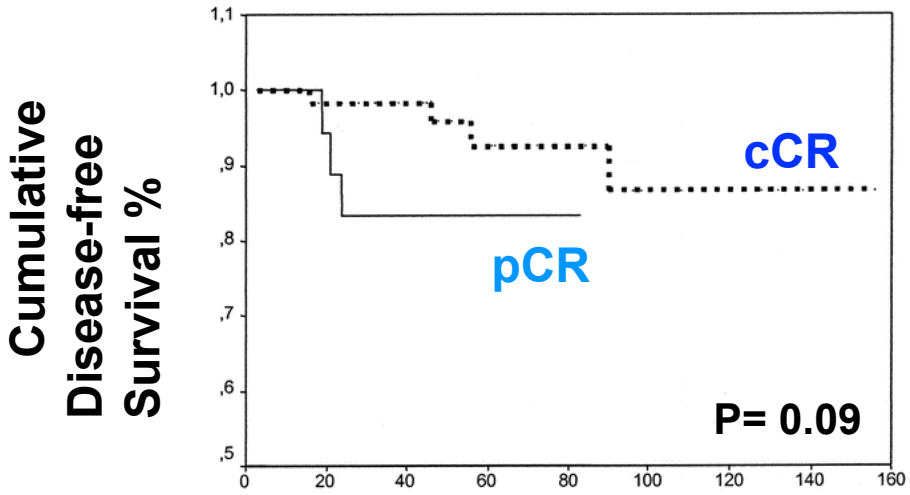
- **clinical complete response (cCR)**
  - pCR associated with cCR

Maas M et al. *Lancet Oncol* 2010 Sep;11(9):835-44

Professor Habr-Gama, São Paulo, Brazil

265 resectable LOW rectal cancer patients s/p CRT

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



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

cCR = possible cure

Deferral of surgery = safe

Surgical salvage = effective

OS = no significant difference

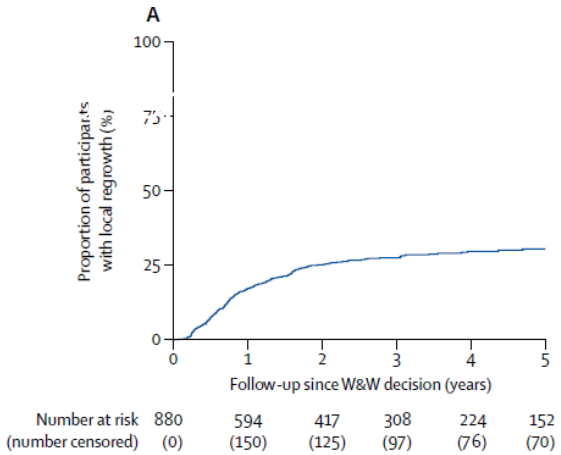
International W&W Registry

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

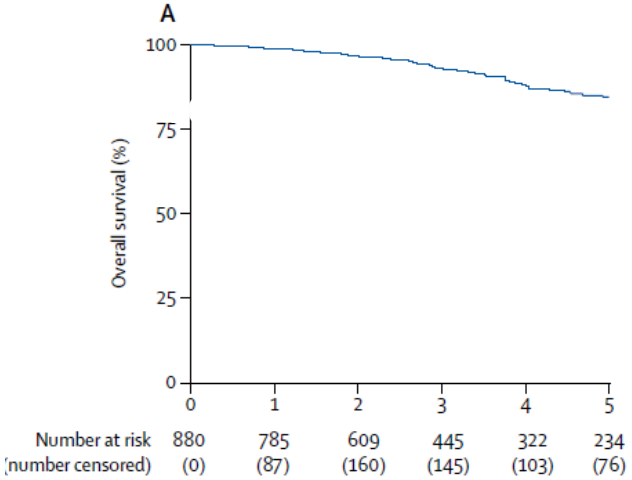
van der Valk et al, *The Lancet* 2018;391:2537-45

International W&W Registry: Results

Tumor Regrowth



Overall Survival



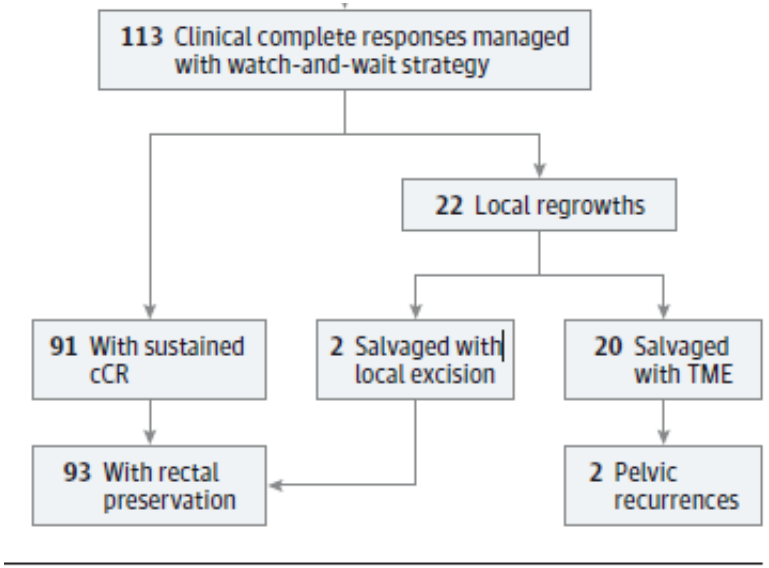
Salvage Surgery

Missing data in 31%

TME in 54%

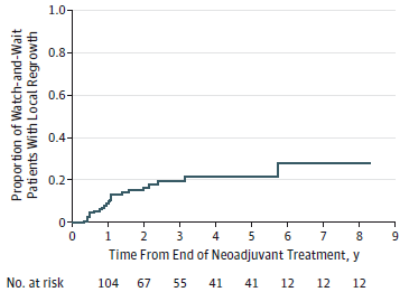
van der Valk et al, *The Lancet* 2018;391:2537-45

Recent MSK results with W&W

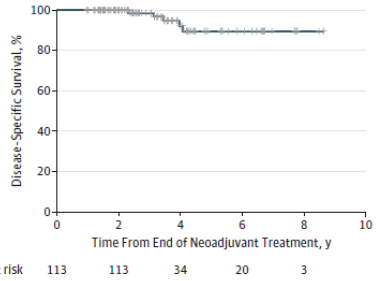


Smith JJ et al, *JAMA Oncology* 2018

Tumor Regrowth

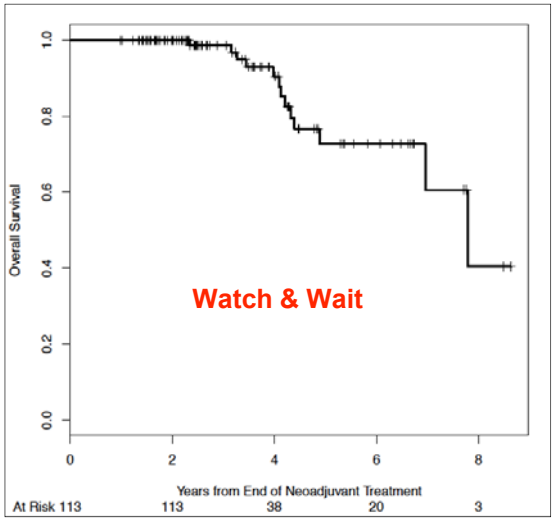


Disease Specific Survival



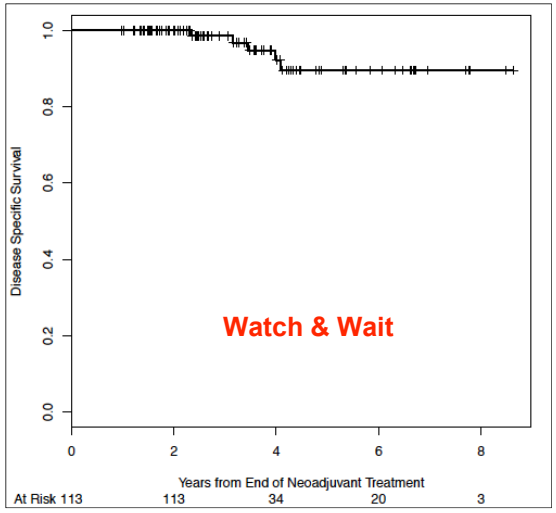
W&W Outcomes

Overall Survival



73%

Disease-specific survival

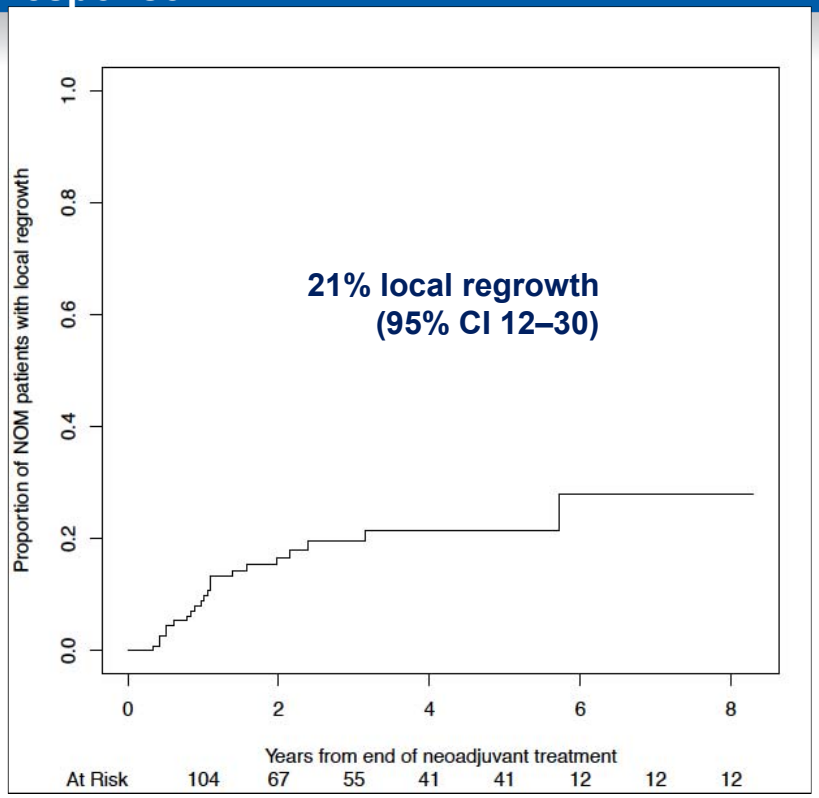


90%

>60% died of other causes

Smith JJ et al, *JAMA Oncology* 2018

Rate of local regrowth in patients after apparent clinical complete response



	n	Metastasis	%
Local re-growths	22	8/22	36%
No Local re-growths	91	1/91	1%

Smith JJ et al, *JAMA Oncology* 2018

MSK - Conclusions

- 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)

Roswell Park Experience

Surgical Oncology 28 (2019) 116–120

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Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

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

Table 1
Patient demographics and tumor information.

		Overall
Overall	N	29 (100%)
Age at Diagnosis	Mean/Std/N	67.4/14.3/29
	Median/Min/Max	69.8/41.3/92.3
Gender	Male	13 (44.8%)
	Female	16 (55.2%)
Coronary Artery Disease	Yes	7 (24.1%)
Hypertension	Yes	15 (51.7%)
Diabetes	Yes	6 (20.7%)
Body Mass Index (BMI)	Mean/Std/N	28.3/4.8/29
	Median/Min/Max	27.2/19.0/38.2
Baseline CEA	Mean/Std/N	2.2/1.5/26
	Median/Min/Max	1.7/0.5/5.1
Pathology	Well	5 (17.2%)
	Moderate	21 (72.4%)
	Poorly	2 (6.9%)
	Unknown	1 (3.4%)
Location in rectum from anal verge	Lower < 7 cm	23 (79.3%)
	Middle 7–11 cm	5 (17.2%)
	Upper 12–15 cm	1 (3.4%)
T Stage	T2	5 (17.2%)
	T3	24 (82.8%)
N Stage	N0	14 (48.3%)
	N1,2+	13 (44.8%)
	Unknown	2 (6.9%)
Chemotherapy (induction and consolidation)	None	11 (37.9%)
	Induction	7 (24.1%)
	Consolidation	11 (37.9%)

- 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

Strode, M. Nurkin S. et. al Surgical Oncology Volume 28, March 2019

Tumor Response Assessment

	Complete Response	Near Complete Response	Incomplete response
Endoscopy	• Flat, white scar • Telangiectasia • No ulcer • No nodularity	• Small mucosal nodules or minor mucosal abnormality • Superficial ulceration • Mild persisting erythema of the scar	• Visible tumor
Digital Rectal Exam	• Normal	• Smooth induration or minor mucosal abnormalities	• Palpable tumor nodules
MRI-T2W	• Only dark T2 signal, no intermediate T2 signal AND • No visible lymph nodes	• Mostly dark T2 signal, some remaining intermediate signal AND/OR • Partial regression of lymph nodes	• More intermediate than dark T2 signal, no T2 scar AND/OR • No regression of lymph nodes
MRI-DW	• No visible tumor on B800-B1000 signal AND/OR • Lack of or low signal on ADC map • Uniform, linear signal in wall above tumor is ok	• Significant regression of signal on B800-B1000 AND/OR • Minimal or low residual signal on ADC map	• Insignificant regression of signal on B800-B1000 AND/OR • Obvious low signal on ADC map

**Habr-Gama et al. DCR 53:12 (2010)

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

Post-cCR follow-up

Typical surveillance and intervals:

	Yr1	Yr2	Yr3-5	>Yr5
Endoscopy	q3m	q4m	q6m	q12m
DRE	q3m	q4m	q6m	q12m
Imaging CT/MRI/EUS	q6m	q6m	q6-12	-

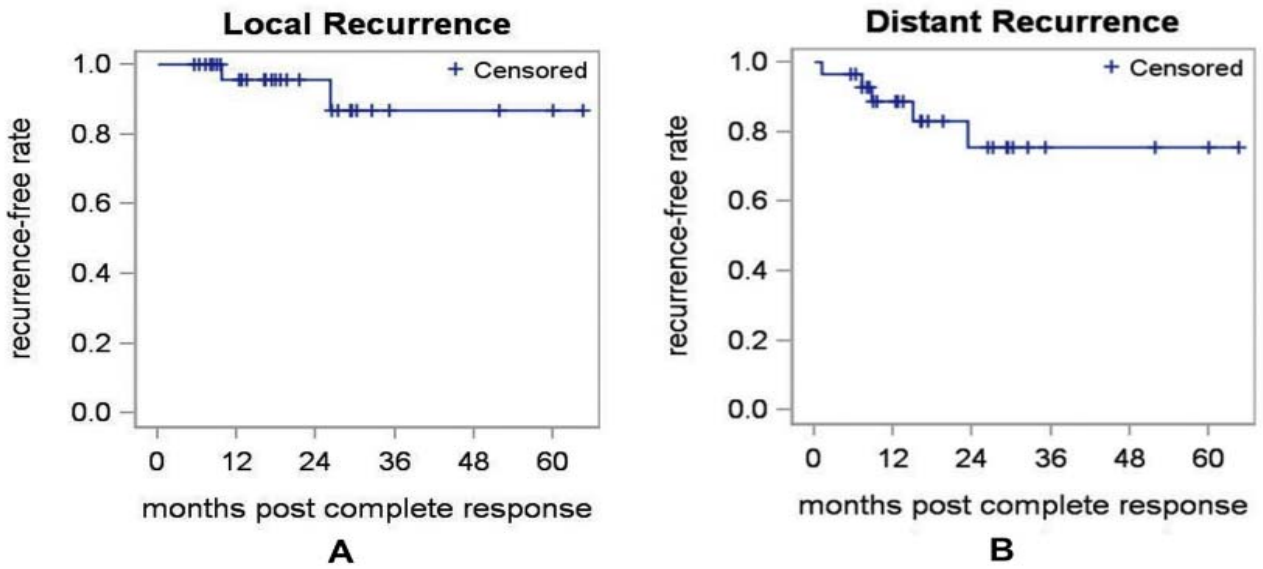
Table 2

Patient staging and treatment Outcomes.

Patient	Sex	Age	Location of tumor	TNM staging	Pre-therapy CT staging results	CRT (50Gy)	Chemo? Consolidation or induction	Local Recurrence	Distant Recurrence after cCR	Alive	Alive with disease	Treatment of recurrence
1	Male	78	Low	cT3N0	no mets	CRT with Capecitabine	no	none	none	yes		
2	Female	78	Low	cT3N1	no mets	CRT with Capecitabine	no	none	none	yes		
3	Female	51	High	cT3N1	no mets	CRT with 5 FU	Consolidation chemo with FOLFIRI (4 cycles)	none	none	yes		
4	Female	88	Low	cT3N1	no mets	CRT with 5 FU	Consolidation chemo with 5 FU, Leucovorin (8 cycles)	none	none	yes		
5	Male	79	Low	cT3N1	no mets	CRT with Capecitabine	Consolidation chemo with FOLFOX (8 cycles)	none	Lung, 15 months	yes		Lung metastasectomy
6	Female	44	Low	cT2N0	no mets	CRT with 5 FU	Consolidation chemo with 5 FU, Leucovorin (8 cycles)	none	none	yes		
7	Female	78	Low	cT3N1	no mets	CRT with Capecitabine	Consolidation chemo with Capecitabine (6 cycles)	none	none	yes		
8	Female	89	Low	cT3N0	no mets	CRT with Capecitabine	no	none	none	yes		
9	Female	78	Middle	cT3N0	no mets	CRT with Capecitabine	Consolidation chemo with Capecitabine (6 cycles)	none	none	Yes		
10	Female	79	Low	cT3N1	no mets	CRT with Capecitabine	no	none	none	Yes		
11	Female	79	Low	cT2N0	no mets	CRT with Capecitabine	no	none	Lung, 7 months	yes	yes	Additional chemotherapy
12	Male	59	low	cT3N2	no mets	CRT with 5 FU	***Induction FOLFOX followed by CRT***	none	none	yes		
13	Male	64	Low	cT2N0	no mets	CRT with Capecitabine	no	Yes, 2.5 years	none	yes		Salvage surgery scheduled
14	Female	48	Low	cT3N1	no mets	CRT with Capecitabine	***Induction FOLFOX followed by CRT***	none	none	yes		
15	Male	82	Middle	cT2N0	no mets	CRT with 5 FU	no	none	none	yes		
16	Male	71	Low	cT2N0	no mets	CRT with Capecitabine	no	none	none	yes		
17	Male	60	Low	cT3N1	no mets	CRT with Capecitabine	***Induction FOLFOX followed by CRT***	none	none	yes		
18	Female	55	Middle	cT3N0	no mets	CRT with 5 FU	Consolidation chemo with FOLFOX (8 cycles)	none	none	yes		
19	Female	49	Low	cT3N1	no mets	CRT with 5 FU	Consolidation chemo with FOLFOX (8 cycles)	none	none	yes		
20	Male	70	Low	cT3N1	no mets	CRT with Capecitabine	Consolidation chemo with CAPOX (1 cycle)	yes	Liver + local, 13 months	yes		Salvage APR and Liver resection followed by 5-FU and Bevacizumab
21	Male	91	Low	cT3N1	no mets	CRT with 5 FU	no	none	none	yes		
22	Male	54	Low	cT3N2	no mets	CRT with Capecitabine	***Induction FOLFOX followed by CRT***	none	Isolated aortocaval node, 3 years	yes	yes	Additional chemotherapy and SBRT
23	Female	94	Low	cT3N0	no mets	CRT with 5 FU	no	none	none	no	no	Deceased due to other causes
24	Male	76	Middle	cT3N0	no mets	CRT with 5-FU	no	none	Liver, 9 months	yes		FOLFOX and Bevacizumab followed by liver resection
25	Male	66	Middle	cT3N0	no mets	CRT with Capecitabine	***Induction FOLFOX followed by CRT***	none	none	yes		
26	Male	76	Low	cT3N1	no mets	CRT with Capecitabine	***Induction FOLFOX followed by CRT***	none	none	yes		
27	Female	47	Low	cT3N0	no mets	CRT with Capecitabine	***Induction FOLFOX followed by CRT***	none	none	yes		
28	Female	71	Low	cT3N1-2	no mets	CRT with Capecitabine	Consolidation chemo with FOLFOX (8 cycles)	none	none	yes		
29	Female	67	Low	cT3N0	no mets	CRT with Capecitabine	Consolidation chemo with FOLFOX (8 cycles)	none	none	yes		

- 2 patients with local recurrence, 5 distant recurrence
- 4 of 6 were salvaged with surgical management

- Median follow-up – 27.6 months



No mortalities

	1-yr Rate (95% CI)	3-yr Rate (95% CI)
LOCAL	0.95 (0.72, 0.99)	0.87 (0.54, 0.97)
DISTANT	0.89 (0.69, 0.96)	0.76 (0.49, 0.90)
Any Recurrence	0.89 (0.69, 0.96)	0.68 (0.40, 0.85)

What we don’t know…

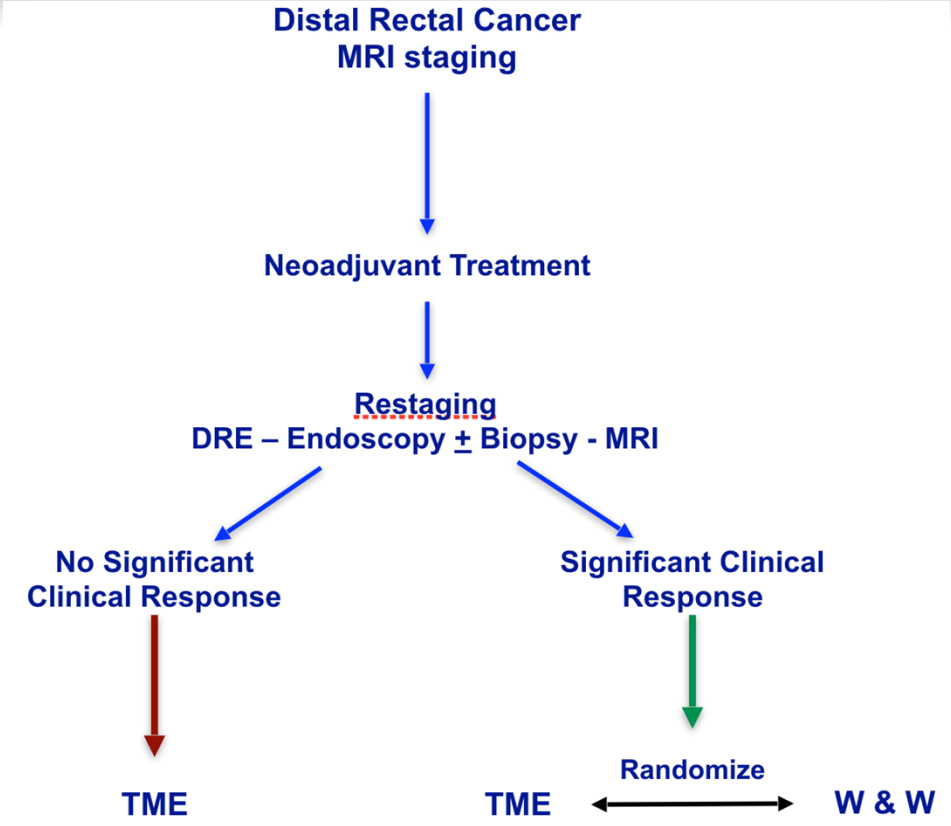
- How to **predict** response?
- How to **maximize** tumor response?
- When is the best time to **assess** response?
- How to **identify** true responders?
- How often to **survey** these patients?
- Will tumors **re-grow**? Will they be **salvageable**?
- Can **occult cancer cells** metastasize?

Are we putting some patients at risk?

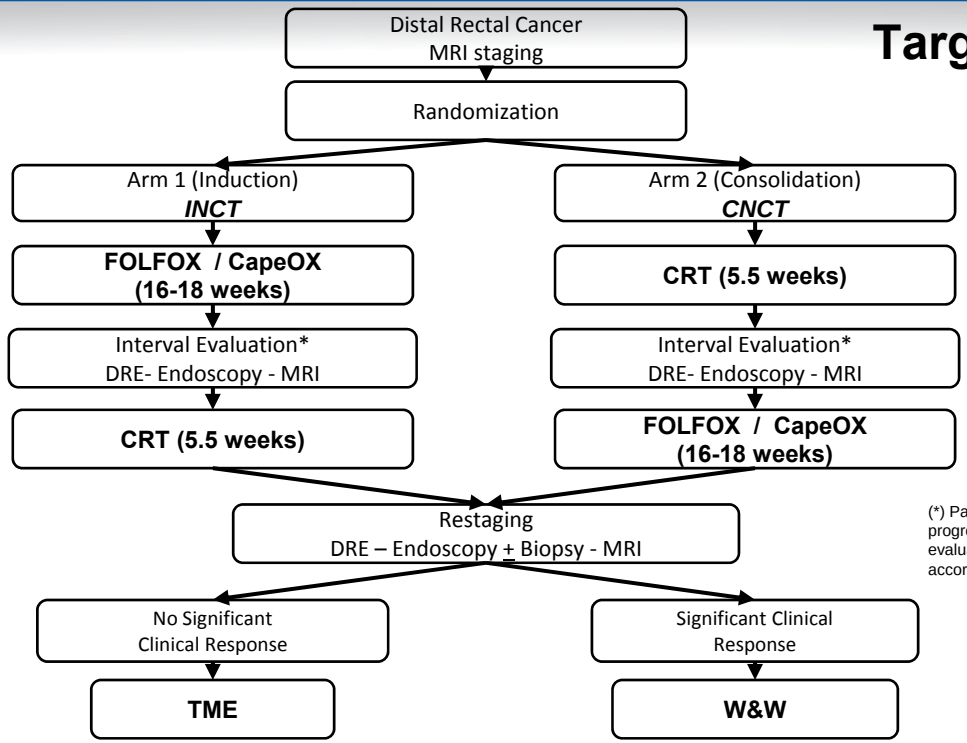
Conclusions

- 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.

Optimal Design for a W&W Trial



OPRA Trial - Protocol Schema



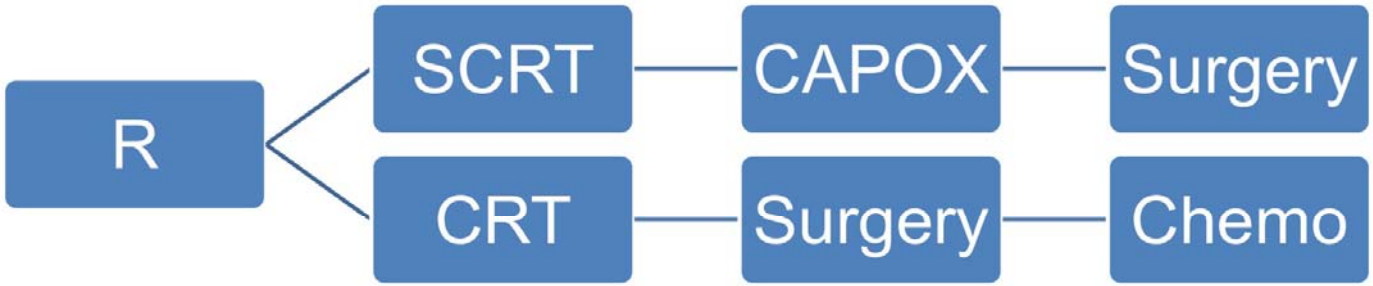
Target accrual: 221

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

Pre-operative TNT followed by selective W & W approach will not compromise DFS comparing to historical controls who received standard of care treatment

Smith JJ et al, *BMC Cancer*. 2015

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!

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