

Pre-operative Radiotherapy

Short Course

or

Long Course?

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Overview

- Efficacy

- Stage

- Location

- Upper / Middle / Distal

- Sphincter-sparing

- Meso-rectal Fascia / Circumferential Resection Margin ~ CRM

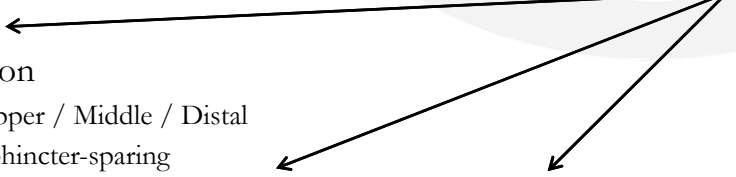
- Toxicity

- Guidelines

- Time, Timing & Cost

- Recommendations

Down-staging





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Overview

- Area of controversy
 - Literature
 - Guidelines
 - Own practice



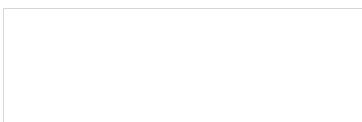
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Study Populations

• Short Course

* selected post-operative RT
selected post-op chemoradiation

	Groups	Inclusions	Staging
Dutch	RT + TME vs TME*	Resectable (<i>not fixed</i>) ≤ 15 cm Below S1-2	DRE
MRC- NCIC	RT + TME vs TME#	Resectable (<i>not fixed</i>) ≤ 15 cm	DRE



Study Populations

•Short Course

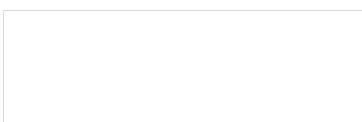
* selected post-operative RT
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	Groups	Inclusions	Staging
Dutch	RT + TME vs TME*	Resectable (<i>not fixed</i>) ≤ 15 cm Below S1-2	DRE <i>1/3rd stage I</i>
MRC-NCIC	RT + TME vs TME#	Resectable (<i>not fixed</i>) ≤ 15 cm	DRE
Polish	SC vs LC	Palpable Resectable T3-4 No sphincter invasion on DRE	<i>ypT1-2</i> <i>ypN0 SC arm</i> 39.5% 37.6
Australian	SC vs LC	T3 anyN ≤ 12 cm	27% 60% MRI or ERUS

Study Populations

•Long Course

	Groups	Inclusions	Staging
German	LC Pre vs Post-op	T3-4 or N+ Resectable ≤ 16 cm	CT & ERUS
NSABP	LC Pre vs Post-op	T3-4 or N+ ≤ 15 cm	ERUS optional



Study Populations

• Long Course

	Groups	Inclusions	Staging
German	LC Pre vs Post-op	T3-4 or N+ Resectable ≤ 16 cm	18% $pT1-2N0$ UK ERUS optional
NSABP	LC Pre vs Post-op	T3-4 or N+ ≤ 15 cm	
Polish	SC vs LC	Palpable Resectable T3-4 No sphincter invasion on DISE	$\gamma pT1-2$ $\gamma pN0$ SC arm 39.5% 37.6
Australian	SC vs LC	T3 anyN ≤ 12 cm	27% 60% MRT or ERUS

Dutch

• 12YLR

- RT + TME 5%
- TME 11%

	10-year local recurrence				10-year overall survival					
	n	RT+TME (%)	TME (%)	p	Interaction	n	RT+TME (%)	TME (%)	p	Interaction
All eligible patients					p=0.312					p=0.262
TNM I	507	<1%	3%	0.027	..	507	65%	72%	0.321	..
TNM II	491	5%	8%	0.212	..	496	50%	55%	0.242	..
TNM III	622	9%	19%	<0.0001	..	624	39%	37%	0.526	..
Patients with a negative CRM					p=0.15					p=0.027
TNM I	497	<1%	3%	0.027	..	497	65%	72%	0.293	..
TNM II	421	4%	7%	0.355	..	421	51%	57%	0.213	..
TNM III	435	5%	17%	<0.0001	..	435	50%	40%	0.032	..

Data are shown for patients for whom the TNM stage was known. RT=radiotherapy. TME=total mesorectal excision. CRM= circumferential resection margin.

Table 3: Local recurrence and survival in patients specified per TNM stage and treatment group

+CRM

•Dutch

CRM involvement	RT + TME	TME
No	729 (81%)	729 (80%)
Yes	143 (16%)	148 (16%)

Table 2. Relationship between circumferential margin involvement and local recurrences over treatment arms

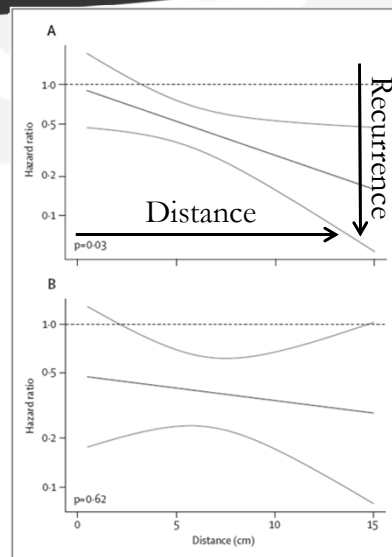
	TME		RT + TME		Total		p value
	n	LR (%)	n	LR (%)	n	LR (%)	
>2 mm	483	5.8	504	0.9	987	3.3	<0.0001
1-2 mm	52	14.9	47	0	100	8.5	0.02
≤1 mm	120	16.4	107	9.3	227	13.1	0.08
Postoperative RT	56	17.3	—	—	—	—	—
No postoperative RT	64	15.7	—	—	—	—	—
Total	656	8.4	662	2.1	1318	5.2	<0.0001


Distance from Anal Verge

•Dutch

•Not accounting for +CRM →

•Accounting for +CRM →






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Results

• **MRC-NCIC**



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	Preoperative radiotherapy (n=674)	Selective postoperative chemoradiotherapy (n=676)	HR (95% CI)
Disease-related events			
Local recurrence criteria			
Intraluminal tumour			
Positive biopsy	2	23	--
No biopsy	0	2	--
Not intraluminal tumour			
Positive imaging	15	25	--
Positive biopsy	4	18	--
Eq imaging, CEA+ve, M0	3	2	--
Missing data	3	2	--
Local recurrence (total)	27 (4%)	72 (11%)	--
Distant metastases	128 (19%)	139 (21%)	--
Disease-related death	89 (13%)	102 (15%)	--
Kaplan-Meier results*			
Local recurrence	--	--	0.39 (0.27-0.58); p=0.0001
2 year	3.4%	8.3%	--
3 year	4.4%	10.6%	--
5 year	4.7%	11.5%	--
Disease-free survival	--	--	0.76 (0.62-0.94); p=0.013
2 year	82.5%	77.6%	--
3 year	77.5%	71.5%	--
5 year	73.6%	66.7%	--
Overall survival	--	--	0.91 (0.73-1.13); p=0.40
2 year	86.1%	84.8%	--
3 year	80.3%	78.6%	--
5 year	70.3%	67.9%	--



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+CRM

• **MRC-NCIC**

- RT + TME 4.7%
- TME 11.5%

	RT + TME	TME
Circumferential resection margin*		
Involved	5 (10%)	7 (12%)
Not involved	533 (89%)	541 (88%)
Missing	30	28

Effects in subgroups	RT + TME	TME	
3-year local recurrence by CRM involvement†			
Involved (positive)	13.8%	20.7%	0.64 (0.25-1.64)
Not involved (negative)	3.3%	8.9%	0.36 (0.23-0.57)
3-year local recurrence by tumour position (cm)‡			
>10-15	1.2%	6.2%	0.19 (0.07-0.47)
>5-10	5.0%	9.8%	0.50 (0.28-0.90)
0-5	4.8%	10.4%	0.45 (0.23-0.88)
3-year local recurrence by TNM stage§			
I	1.9%	2.8%	0.68 (0.16-2.81)
II	1.9%	6.4%	0.29 (0.12-0.67)
III	7.4%	15.4%	0.46 (0.28-0.76)



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Long Course

- German
 - 10YLR
 - Pre 7.1%
 - Post 10.1% $p < 0.05$
 - ypCR 9%
 - +CRM
 - Pre 2%
 - Post 3%

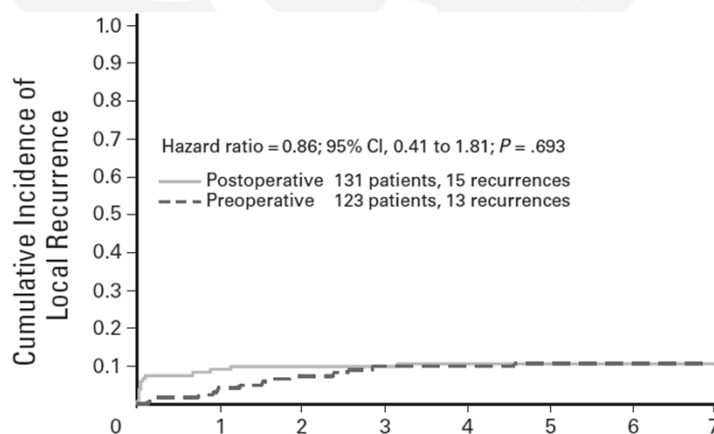
Table 2. Influence on Local Recurrence Risk of Different Covariables Based on the Received Therapy

Variable	Preoperative CRT			Postoperative CRT			No Postoperative CRT		
	No. at Risk	Cumulative Local Recurrence Rate (%)		No. at Risk	Cumulative Local Recurrence Rate (%)		No. at Risk	Cumulative Local Recurrence Rate (%)	
		At 5 Years	At 10 Years		At 5 Years	At 10 Years		At 5 Years	At 10 Years
Overall	398	4.7	6.8	248	8.8	9.4	143	12.5	12.5
Age, years									
≤ Median	198	6.3	7.1	137	8.8	8.8	60	16.3	16.3
> Median	200	3.0	6.6	111	8.8	10.2	83	9.7	9.7
Sex									
Male	287	3.7	6.6	164	9.5	10.5	90	16.8	16.8
Female	111	7.2	7.2	84	7.5	7.5	53	5.9	5.9
Distance from anal verge, cm									
0 < 5	116	10.1	10.1	59	16.1	16.1	27	4.5	4.5
5 < 10	185	1.2	4.9	102	7.8	9.3	64	18.7	18.7
10-16	83	2.5	4.3	79	2.7	2.7	45	10.4	10.4
Type of resection									
Low anterior	253	2.6	4.7	169	3.9	3.9	104	15.2	15.2
Intersphincteric	36	2.8	6.0	18	23	23	5	40	40
Abdominoperineal	108	10.4	12.3	61	18.2	20.7	33	0	0
(y)TNM stage									
pCR/0	36	2.9	2.9	0			2	0.0	0.0
yI/I	111	1.0	3.4	2	50	50	73	6.1	6.1
yII/II	116	2.8	4.2	87	3.6	3.6	28	20	20
yIII/III	102	9.5	11.0	146	10.9	12	20	32.0	32.0
yIV/IV	30	18.7	45.8	13	16.7	16.7	19	6.7	6.7
Completeness of local resection									
R0	387	4.6	6.7	240	7.7	8.3	141	12	12
R1	4	25.0	—	8	48.6	48.6	0		

Abbreviations: CRT, chemoradiotherapy; pCR, pathologic complete response.

Results

- NSABP R-03
 - 5YLR 10.7% each
 - ypCR 15%



No. at risk								
Postoperative	131	105	93	84	75	68	57	48
Preoperative	123	103	94	84	80	75	72	63

Sphincter-Sparing

• German

Table 4. Rates of Sphincter-Sparing Surgery in 194 Patients Determined to Require Abdominoperineal Resection, According to Actual Treatment Given.^a

Variable
Abdominoperineal resection deemed necessary — no. (%)
Sphincter-preserving surgery performed — no./total no. (%)

Table 3. Postoperative Pathological Tumor Stage, Type of Surgery, and Completeness of Resection, According to Actual Treatment Given.^a

Variable	Preoperative Chemoradiotherapy (N=415)	Postoperative Chemoradiotherapy (N=384)	P Value
Histopathological finding (%)			<0.001
Complete response	8	0	
TNM stage			
I	25	18	
II	29	29	
III	25	40	
IV	6	7	
Unknown	6	6	
Type of resection (%)			0.45
Low anterior resection	69	71	
APR	23	2	
Other	3	3	0.69
With distant metastasis	2	4	
Incomplete†			
Without distant metastasis	3	3	
With distant metastasis	3	4	

More pts in pre-op group who were initially considered for sphincter-sparing ended up having an APR



Sphincter-Sparing

• NSABP R-03

• ypCR 15%

Table 2. Characteristics of Eligible Patients in NSABP R-03 Trial

Characteristic	Preoperative (n = 123)		Postoperative (n = 131)	
	No.	%	No.	%
Age, years				
≤ 60	53	43.1	59	45.0
> 60	70	56.9	72	55.0
Sex				
Male	85	69.1	89	67.9
Female	38	30.9	42	32.1
Intended procedure				
SSS	43	35.0	44	32.8
Non-SSS	80	65.0	88	67.2
Multiple tumors				
Yes	4	3.3	1	0.8
No	119	96.8	130	99.2
Palpable tumor*				
Yes	94	79.0	111	85.4
No	25	21.0	19	14.6

Abbreviations: NSABP R-03, National Surgical Adjuvant Breast and Bowel Project R-03; SSS, sphincter-saving surgery.
*Excludes patients with multiple tumors.



Results

•Polish	<u>SC</u>	<u>LC</u>	
•Compliance	98%	62%	$p < 0.05$
•4Y LR	10.6%	15.6%	NS
• <u>+CRM</u>	<u>12.9%</u>	<u>4.4%</u>	$p < 0.05$
•ypCR	0.7%	16.1%	$p < 0.05$
• <u>Sphincter-sparing</u>	<u>61%</u>	<u>58%</u>	NS

With *Down Staging* never really know what the true stage was
 Important to Medical Oncologist → *risk of systemic relapse*

Results

•Australian	<u>SC</u>	<u>LC</u>	
•4Y Local Recurrence	7.5%	5.7%	NS
• <u>+CRM</u>	<u>3%</u>	<u>3%</u>	NS
•ypT0-2	28%	45%	$p < 0.05$
• <u>Sphincter-sparing</u>	<u>63%</u>	<u>69%</u>	NS

•No relationship with location in rectum

Toxicity

Polish

• Acute

- SC 3.2%
- LC 18.2% $p < 0.05$

• Late

- SC 28.3%
- LC 27%

Table 2 Intention-to-treat analysis of severe late toxic effects in 279 patients*

	Short-course radiotherapy (n = 138)	Chemoradiation (n = 141)
Small/large intestine†	7 (5-1)	2 (1-4)
Urinary bladder	2 (1-4)	1 (0-7)
Skin (non-healing perineal wound)	0	4 (2-8)
Urether	1 (0-7)	1 (0-7)
Nerves: motor function	3 (2-2)	2 (1-4)
Nerves: sensory function	1 (0-7)	1 (0-7)
Nerves: pain	0	1 (0-7)
Postoperative hernia requiring surgery	1 (0-7)	1 (0-7)
Fracture of femoral neck	1 (0-7)	0
Total complications	16 in 14 patients	13 in 10 patients

Australian

• Acute 2007 abstract

- | | SC | LC |
|--------------------------|------|------|
| • Grade 3 $p < 0.05$ | | |
| • Dermatitis | 0 | 5.5% |
| • Proctitis | 0% | 3.7% |
| • Nausea | 0% | 3.1% |
| • Fatigue | 0% | 3.7% |
| • Grade 3-4 $p < 0.05$ | | |
| • Diarrhea | 1.3% | 14% |
| • Surgical Complications | 51% | 49% |

• Late

- SC 5.8%
- LC 8.2% NS

Table 4. Late RT Toxicities by Worst Grade

Late RT Toxicity Type	SC (n = 155)		LC (n = 158)	
	Grade 3	Grade 4	Grade 3	Grade 4
Skin, pelvic	0	1	0	1
Subcutaneous tissue	0	1	0	1
Small or large intestine	2	3	6	2
Bladder	3	0	2	0
Other*	2	1	3	0
Any toxicity	6	3	10	3

NOTE. The maximum grade (RTOG/EORTC Late Radiation Morbidity Scoring Scheme) for each type and each patient was determined. Only grades 3 or 4 late toxicities are tabulated. Of the total number of patients evaluable for late RT toxicity analysis, 155 patients received SC and 158 patients received LC.

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; LC, long course; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; SC, short course.

*Other reported toxicities for SC included vesicocutaneous fistula (grade 4), anastomotic stricture requiring dilatations (grade 3), and proctalgia (grade 3). Other toxicities for LC included deep venous thrombosis (grade 3), perianal pain (grade 3), and presacral abscess (grade 3). The crude rates of late RT toxicity were 5.8% (nine of 155 patients) for SC and 8.2% (13 of 158 patients) for LC ($P = .53$).

Polish QoL Study

•EORTC QLQ-C30 7m post-op

- Global scale
- 5 functional scales } $\uparrow \text{score} = \uparrow \text{QoL}$
- 3 symptom scales
- 6 symptom single items } $\downarrow \text{score} = \downarrow \text{symptoms}$

•Con't

- 2 stool frequency
- 2 global eval. of anorectal function

•Anorectal functions *not validated*

- 2 urgency
- 3 constipation & diarrhea
- 2 residual stool
- 5 faecal & gas incontinence
- 1 differentiation between stool & gas
- 2 abdominal pain

•Sexual function *not validated*

“Did your health status &/or treatment cause your sexual life to decline?”

- 1 – Never
- 2 – Sometimes
- 3 – Often
- 4 – Very often

Table 1
Characteristics of the patients who filled in the QLQ-C30 questionnaire

	Short-course radiotherapy N = 111	Chemoradiation N = 110	P-value
Numbers of responders/number of eligible patients	111/132 (84)	110/124 (89)	0.28
Median age (range), years	62 (35–75)	60 (34–73)	0.27
Male	67 (61)	72 (65)	0.43
Female	44 (39)	38 (34)	
Median distance from anal verge to the lower tumour edge (range), cm	6 (2–10)	6 (2–9)	0.68
Median time from surgery to answering (range), months	12 (3–57)	11 (5–65)	0.69
Postoperative chemotherapy			
Yes	53 (48)	30 (27)	0.002
No	58 (52)	80 (73)	
Permanent stoma			
Yes	56 (51)	49 (44)	0.38
No	55 (49)	60 (56)	

Data are expressed as number (%) of patients unless otherwise stated.

Table 3
Characteristics of patients who filled in the questionnaire of anorectal and sexual function

	Short-course radiotherapy N = 58	Chemoradiation N = 60	P-value
Numbers of responders/number of eligible patients	58/69 (84)	60/68 (88)	0.28
Mean age (range), years	63 (35–75)	61 (34–72)	0.62
Male	31 (53)	37 (62)	0.37
Female	27 (46)	23 (38)	
Mean time from surgery to answering (range), months	14 (4–74)	10.5 (5–47)	0.32
Mean distance from anal verge to the lower tumour edge (range), cm	7 (3–10)	7 (4–9)	0.89
Postoperative chemotherapy			
Yes	26 (45)	15 (25)	0.019
No	32 (55)	45 (75)	

Data are expressed as number (%) of patients unless otherwise stated.

Polish QoL Study

•QLQ-C30 Validated

Table 2
Mean scores of QLQ-C30 questionnaire in the two treatment-assigned groups

	Short-course radiotherapy N = 111	Chemoradiation N = 110	P-value
Global Health	57	61	0.22
<i>Functional scales</i>			
Physical function	76	75	0.78
Role function	74	73	0.76
Emotional function	66	67	0.69
Cognitive function	77	76	0.72
Social function	75	73	0.58
Symptoms Scales			
<i>Symptom scales/items</i>			
Fatigue	34	36	0.67
Nausea and vomiting	8	5	0.03
Pain	28	31	0.73
Dyspnoea	18	18	0.64
Insomnia	36	34	0.62
Appetite loss	13	14	0.88
Constipation	23	19	0.34
Diarrhoea	23	18	0.19
Financial difficulties	33	38	0.20

Polish QoL

•Ano-rectal & Sexual *not validated*

Table 6
Answers to question "Did your health status and/or treatment cause your sexual life to decline?" in the two treatment-assigned groups

	Short-course radiotherapy N = 58	Chemoradiation N = 60
Male		
No, not at all	6 (19)	11 (31)
A little bit	9 (29)	10 (28)
A lot	16 (51)	15 (42)
No data	0	1
Female		
No, not at all		
A little bit		
A lot		
No data		

Table 5
Global evaluation of anorectal function during the preceding week

	Short-course radiotherapy N = 58	Chemoradiation N = 60	P-value
Anorectal functions caused a worsening of quality of life			
No, not at all	20 (35)	17 (29)	0.52
A little bit	28 (49)	26 (44)	
A lot	9 (16)	16 (27)	
No data	1	1	
Scoring of anorectal functions			
Very good/good	23 (41)	21 (37)	0.52
Bad but acceptable	33 (59)	34 (60)	
Unacceptable, I regret that a stoma was not performed	0 (0)	2 (4)	
No data	2	3	

Answers to the questionnaire in the two treatment-assigned groups. Data are expressed as number of patients (%).

Table 4
Anorectal function as perceived during the week preceding evaluation

	Short-course radiotherapy N = 58 Incidence of symptom [Incidence of severe symptom]	Chemoradiation N = 60 Incidence of symptom [Incidence of severe symptom]	P-value†
Stool frequency per day, median (range)	4 (1-10)	5 (1-20)	0.35
No data	2	3	
Anti-diarrhoeal drugs			
Yes† (very often)	28 (49%) [3 (5%)]	24 (40%) [6 (10%)]	
No	29 (51%)	36 (60%)	0.38
No data	1	0	
Constipation			
Yes (very often)	34 (60%) [4 (7%)]	31 (52%) [3 (5%)]	0.31
No	23 (40%)	29 (48%)	
No data	1	0	
Need of taking medicines for constipation			
Yes (very often)	15 (27%) [2 (4%)]	17 (29%) [0 (0%)]	0.33
No	41 (73%)	42 (71%)	
No data	2	1	
Enema usage			
Yes (very often)	3 (5%) [0 (0%)]	7 (12%) [1 (2%)]	0.38
No	55 (95%)	52 (88%)	
No data	0	0	
Incontinence of gas			
Yes (very often)	44 (78%) [10 (17%)]	45 (75%) [11 (19%)]	0.81
No	14 (24%)	15 (25%)	
No data	0	1	
Incontinence of loose stool			
Yes (very often)	42 (72%) [5 (8%)]	40 (66%) [7 (11%)]	0.65
No	16 (28%)	20 (33%)	
No data	0	0	
Incontinence of solid stool			
Yes (very often)	23 (40%) [4 (7%)]	29 (50%) [4 (6%)]	0.66
No	1 (2%)	29 (50%)	
No data	0	2	
Rectal bleeding			
Yes (very often)	1 (2%) [0 (0%)]	40 (66%) [4 (6%)]	0.99
No	1 (2%)	20 (33%)	
No data	0	0	
Rectal pain			
Yes (very often)	1 (2%) [0 (0%)]	24 (40%) [10 (16%)]	0.96
No	1 (2%)	35 (59%)	
No data	0	1	
Stoma			
Yes (very often)	1 (2%) [0 (0%)]	53 (88%) [7 (11%)]	0.78
No	1 (2%)	7 (12%)	
No data	0	0	
Stoma			
Yes (very often)	1 (2%) [0 (0%)]	56 (93%) [6 (9%)]	0.33
No	1 (2%)	4 (7%)	
No data	0	0	
Stoma			
Yes (very often)	1 (2%) [0 (0%)]	38 (63%) [5 (8%)]	0.48
No	1 (2%)	21 (36%)	
No data	0	1	
Stoma			
Yes (very often)	1 (2%) [0 (0%)]	32 (54%) [6 (9%)]	0.79
No	1 (2%)	27 (46%)	
No data	0	1	
Stoma			
Yes (very often)	1 (2%) [0 (0%)]	38 (63%) [6 (9%)]	0.27
No	1 (2%)	19 (33%)	
No data	0	3	

(continued on next page)

Polish & Australian

- Short Course

- ↓ acute toxicity
- ↑ protocol adherence

- Long Course

- ↑ down-staging
- ↑ ypCR
- ↓ +CRM

- No difference

- LR, DM, DFS, OS
- Overall & G3-4 late toxicity
- QLQ-C30, anorectal & sexual function

	24	28	<.001
			<.001
Adherence to the protocol (%)			
PS	98	69	
AS	100	77	
Severe surgical complications (%)			
PS	10	11	0.85
AS	7.1	3.5	0.26
Overall surgical complications (%)			
PS	27	21	0.27
AS	51	49	
Sphincter preservation (%)			
PS	61	58	0.57
Pathologic complete response (%)			
PS	1	15	<.001
ypT0-2 (%)			
PS	40	62	<.001
ypN0 (%)			
PS	52	68	0.007
Positive circumferential margin (%)			
PS	13	4	0.017
Local recurrence rate (%)			
PS at 4 years	10.6	15.6	0.21
AS at 3 years	7.5	4.4	0.24
Distant metastases (%)			
PS crude rates	31.4	34.6	0.54
AS at 5 years	28	31	0.85
Overall survival (%)			
PS at 4 years	67.2	66.2	0.96
AS at 5 years	74	70	0.56
Disease-free survival (%)			
PS at 4 years	58.4	55.6	0.82
Grade III-IV late toxicity (%)			
PS crude rates	10.1	7.1	0.36
AS crude rates	7.6	8.8	0.84
Overall late toxicity (%)			
PS crude rates	28.3	27	0.81
QLQ-C30 global health status*			
PS mean scores	57	61	0.22
Poor anorectal function (%)			
PS	59	64	0.52
Decline in sexual function (%)			
PS male	80	69	0.56
PS female	41	52	0.1

Abbreviations: PS, Polish study; AS, Australian study; QLQ, quality of life questionnaire.

Lack of data in the table indicates some data were not published.

*The differences in the scores of all other scales or single items of QLQ were also insignificant.



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- EURECCA 2013 *European Registration of Cancer Care*

- uT3 anyN

‘... achieved moderate consensus (for) Short Course followed by immediate surgery or Long Course with delayed surgery for a (-)CRM presentation in any localization.’

- CRM+ anyT anyN

- Long Course

- uT4 anyN

- Long Course

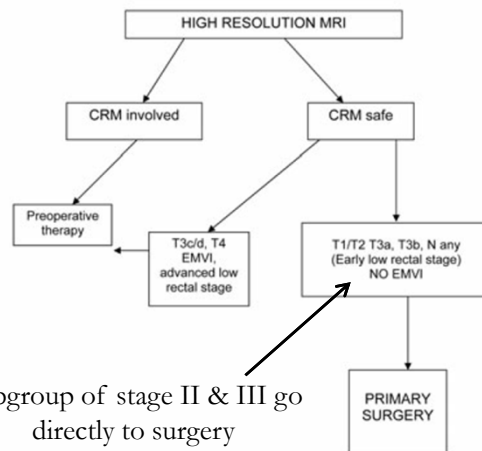
- **ESMO 2013**
 - **MERCURY**
 - Prospective study
 - **TNM 7**
 - sub-classification including MRI findings
 - *Not validated*

TNM	Extension to
Tis	Carcinoma <i>in situ</i> : intraepithelial or invasion of lamina propria
T1	Submucosa
T2	Muscularis propria
T3	Subserosa/perirectal tissue
	T3a ^a <1 mm
	T3b 1–5 mm
	T3c 5–15 mm
	T3d 15+ mm
T4	Perforation into visceral peritoneum (a) or invasion to other organs (b) ^b
N1	1–3 regional nodes involved
N1a	1 lymph node
N1b	2–3 lymph nodes
N1c	Small deposits in the fat
N2	4 or more regional nodes involved
N2a	4–6 lymph nodes
N2b	7 or more lymph nodes
M1	Distant metastases
M1a	One distant organ or set of lymph nodes
M1b	More than one organ or to the peritoneum

MRI feature	Good prognosis	Poor prognosis
CRM	>1mm clear	<1mm involved
Low rectal <5cm	intersphincteric plane clear of tumor	intersphincteric plane involved by tumor
T stage	T1/T2, T3a<1mm, T3b, 1-5mm extramural spread	T3c>5mm extramural spread, T4
EMVI	negative	positive
N stage	any	any

- **CRM**
 - >1mm = 'Good'
 - <1mm = 'Poor'
- **T-stage**
 - T1-3b = 'Good'
 - T3cd-4 = 'Poor'
- **Distal**
 - +ISP/LA* = 'Poor'
 - -ISP/LA = 'Good'
- **EMVI** *extra-mural venous invasion*
 - Yes = 'Poor'
 - No = 'Good'

*Inter-sphincteric plane / Levators



Subgroup of stage II & III go directly to surgery

FIGURE 2. Treatment plans according to MRI prognosis.

• **Early** → TME *post-op if +CRM or N2*

- -CRM
- T1-3b
- -EMVI
- Mid / Upper
- N1 if Upper

• **Intermediate** → SC or LC

- -CRM
- Distal T2, T3cd4 mid / upper, N1-2
- +EMVI

• **Advanced** → LC

- +CRM, T4, lateral nodes

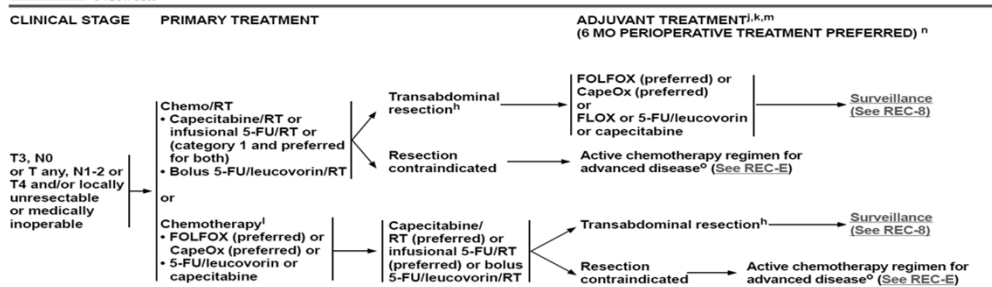
Table 6. Choice of treatment according to risk category for primary rectal cancer without distant metastases

Risk group	TN substage	Therapeutic options
Very early	cT1 sm1 (-?) N0	Local excision (TEM). If poor prognostic signs (sm ≥ 2, high grade, V1), resection (TME) (or possibly CRT)
Early (good)	cT1-2; cT3a (b) if middle or high, N0 (or cN1 if high), mrf-, no EMVI	Surgery (TME) alone. If poor prognostic signs (crm+, N2) add postop CRT or CT ^a . (CRT with evaluation, if cCR, wait-and-see, organ preservation)
Intermediate (bad)	cT2 very low, cT3mrf- (unless cT3a(b) and mid- or high rectum, N1-2, EMVI+, limited cT4aN0	Preop RT (5 × 5 Gy) or CRT followed by TME. (if CRT and cCR, wait-and-see in high risk patients for surgery)
Advanced (ugly)	cT3mrf+, cT4a,b, lateral node+	Preop CRT followed by surgery (TME + more extended surgery if needed due to tumour overgrowth). 5 × 5 Gy with a delay to surgery in elderly or in patients with severe comorbidity who cannot tolerate CRT


• **NCCN**

National Comprehensive Cancer Network® **NCCN Guidelines Version 1.2015 Rectal Cancer**

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^hSee Principles of Surgery (REC-B).
ⁱSee Principles of Adjuvant Therapy (REC-C).
^jSee Principles of Radiation Therapy (REC-D).
^kFernandez-Martos C, Pericay C, Aparicio J, et al: Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. *J Clin Oncol* 2010;28:859-868.
^lCercek A, Goodman KA, Hajj C, et al: Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. *J Natl Compr Canc Netw*. 2014;12:513-519.
^mPostoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results.
ⁿTotal duration of perioperative chemotherapy, inclusive of chemotherapy and radiation therapy, should not exceed 6 months.
^oFOLFOXIRI is not recommended in this setting.



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PRINCIPLES OF RADIATION THERAPY

- Radiation therapy fields should include the tumor or tumor bed, with a 2-5 cm margin, the presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures.
- Multiple radiation therapy fields should be used (generally a 3- or 4-field technique). Positioning and other techniques to minimize the volume of small bowel in the fields should be encouraged.
- For postoperative patients treated by abdominoperineal resection, the perineal wound should be included within the fields.
- Intensity-modulated radiation therapy (IMRT) should only be used in the setting of a clinical trial or in unique clinical situations including re-irradiation of recurrent disease after previous radiotherapy.
- Radiation doses:
 - ▶ 45-50 Gy in 25-28 fractions to the pelvis.
 - ▶ For resectable cancers, after 45 Gy a tumor bed boost with a 2 cm margin of 5.4 Gy in 3 fractions could be considered for preoperative radiation and 5.4-9.0 Gy in 3-5 fractions for postoperative radiation.
 - ▶ Small bowel dose should be limited to 45 Gy.
- Intraoperative radiation therapy (IORT), if available, should be considered for very close or positive margins after resection, as an additional boost, especially for patients with T4 or recurrent cancers. If IORT is not available, 10-20 Gy external beam radiation and/or brachytherapy to a limited volume could be considered soon after surgery, prior to adjuvant chemotherapy.
- For unresectable cancers, doses higher than 54 Gy may be required, if technically feasible.
- 5-fluorouracil-based chemotherapy should be delivered concurrently with radiation therapy.
- In patients with a limited number of liver or lung metastases, radiotherapy can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3-D conformal radiotherapy, IMRT, or stereotactic body radiation therapy (SBRT). (category 3)
- Side effect management:
 - Female patients should be considered for vaginal dilators and instructed on the symptoms of vaginal stenosis.
 - Male patients should be counseled on infertility risks and given information regarding sperm banking.
 - Female patients should be counseled on infertility risks and given information regarding oocyte, egg or ovarian tissue banking prior to treatment.


→ Surveillance
(See REC-8)

→ Surveillance
(See REC-8)

emotherapy regimen for
I disease^a (See REC-E)

o receive preoperative therapy,
sive of chemotherapy and

Chen Y, Sun J, Wang H, et al. Neoadjuvant chemotherapy plus, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Canc Netw. 2014;12:513-519.



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EBS 2-4- Version 2

Evidence-Based Series #2-4 Version 2: Section 1

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

**Preoperative or Postoperative Therapy for the Management of
Patients with Stage II or III Rectal Cancer:**
Guideline Recommendations

R Wong, S Berry, K Spithoff, M Simunovic, K Chan, O Asgoola, B Dingle,
RB Rumble, B Cummings, and the Gastrointestinal Cancer Disease Site Group

Report Date: July 15, 2008
This report replaces previous versions of
Practice Guidelines #2-3 and #2-13

RECOMMENDATIONS

Preoperative Therapy

- Preoperative chemoradiotherapy (CRT) is preferred, compared to preoperative RT (standard fractionation: longer course: 45-50.4Gy in 25-28 fractions) alone, to decrease local recurrence.


These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: published guideline was

2. What is the role of postoperative RT and/or CT for patients with resected stage II or III rectal cancer who have not received preoperative RT, in terms of improving survival and delaying local recurrence?

TARGET POPULATION
These recommendations apply to adult patients with clinically resectable or resected stage II or III rectal cancer.

RECOMMENDATIONS
Preoperative Therapy

- Preoperative chemoradiotherapy (CRT) is preferred, compared to preoperative RT (standard fractionation: longer course: 45-50.4Gy in 25-28 fractions) alone, to decrease local recurrence.
- Preoperative CRT is preferred, compared with a postoperative approach, to decrease local recurrence and adverse effects.



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•Saskatchewan



Provincial Colorectal Cancer Treatment Guidelines

As per consensus at the Provincial Colorectal Cancer Meeting, June 17, 2011

- Surgery alone
 - Stage I
 - Consider for proximal T3N0 MSI-H after interdisciplinary discussion
- Long Course
 - Distal T2N0 for consideration of sphincter preservation
 - Stage II-III
- Short Course
 - Stage II-III who are not candidates for Long Course



•Alberta

- SC or LC
 - Stage II-III
 - Amenable to surgery
- LC
 - Not amenable to surgery

Table 2. Recommendations for Treatment of Patients with Rectal Cancer Amenable to Resection.

Stage	Recommendations
Stage 0	<ul style="list-style-type: none"> • Perform local or transanal excision.⁴ • No adjuvant systemic therapy is indicated.
Stage I	<ul style="list-style-type: none"> • If sufficient rectum distal to the cancer permits a colorectal or coloanal anastomosis, perform a radical en bloc excision of the rectum by low anterior resection. Otherwise, perform an abdominoperineal resection. • To precisely dissect the rectum and para-rectal lymph nodes within the mesorectal envelope and to obtain an optimal circumferential radial margin, surgery should only be performed by a surgeon experienced with the total mesorectal excision technique.¹⁴ • In a carefully selected patient with low-risk T₁ disease who accepts an increased risk of tumor recurrence, a prolonged period of post-operative surveillance, and a decreased success after salvage surgery, consider transanal excision.^{4,7} A T₁ rectal cancer is considered "low-risk" if (1) it is T_{1sm} or T_{1ms} (invasion into the superficial or middle third of the submucosa). • No adjuvant systemic therapy is indicated.
Stage II and Stage III	<ul style="list-style-type: none"> • Patients with rectal cancer not immediately amenable to surgical resection as well as patients with clinical stage II and III disease¹⁵ should be offered long-course pre-operative radiotherapy (4,500 to 5,400 cGy in twenty-five to thirty fractions) with either protracted venous infusion 5-Fluorouracil (225 mg/m² per day by ambulatory infusion pump during the entire period of radiation therapy)¹⁶ or Capecitabine (825 mg/m² po BID).¹⁷ If sufficient rectum distal to the cancer permits a colorectal or coloanal anastomosis, perform a radical en bloc excision of the rectum by low anterior resection. Otherwise, perform an abdominoperineal resection. Either surgery should be performed six to eight weeks after having completed the course of radiation.¹⁵ • Patients with rectal cancer amenable to surgical resection can be offered short-course pre-operative radiotherapy (2,500 cGy in five fractions).^{15,18} If sufficient rectum distal to the cancer permits a colorectal or coloanal anastomosis, perform a radical en bloc excision of the rectum by low anterior resection. Otherwise, perform an abdominoperineal resection. Either surgery should be performed within one week of having completed the course of radiation. • Pre-operative chemoradiotherapy is associated with a lower rate of grade 3/4 acute toxicities, long-term toxicities, and local recurrence, but no difference in five-year overall survival when compared to post-operative chemoradiotherapy.¹⁹ • To precisely dissect the rectum and para-rectal lymph nodes within the mesorectal envelope and to obtain an optimal circumferential radial margin, surgery should only be performed by a surgeon experienced with the total mesorectal excision technique.¹⁴ • A total of six months of chemotherapy is recommended for adjuvant chemotherapy options extrapolated from colon cancer; see the Clinical Practice Guideline for Early-Stage Colon Cancer. • If a patient with rectal cancer undergoes a low anterior resection or an abdominoperineal resection without pre-operative radiotherapy, offer two months of adjuvant chemotherapy (as for colon cancer), then radiotherapy (4,500 to 5,400 cGy in twenty-five to thirty fractions) with either concurrent protracted venous infusion 5-Fluorouracil (225 mg/m² per day by ambulatory infusion pump)¹⁶ or Capecitabine (825 mg/m² po BID)¹⁷, and then two additional months of adjuvant chemotherapy (as for colon cancer).^{15,17} • As long as resection of a metachronous polyp, second colorectal cancer, or metastasis to liver or lung is appropriate, surveillance is recommended (see Clinical Practice Guideline for Colorectal Cancer Surveillance).
Locally Recurrent Cancer	<ul style="list-style-type: none"> • Care should be directed by the Multidisciplinary Gastrointestinal Tumor Team. • If the recurrence is not amenable to surgical resection, see Clinical Practice Guideline for Metastatic Colorectal Cancer.
Stage IV	<ul style="list-style-type: none"> • Consider palliative radiotherapy for local symptoms. • See Clinical Practice Guideline for Metastatic Colorectal Cancer.



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Gastrointestinal
6. Rectum
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• 6.2 Diagnostic and Staging Work-Up
• 6.3 Primary Surgical Therapy
• 6.4 Pathology
• 6.5 Staging
• 6.6 Treatment Options by Stage
• 6.6a Liver-Limited Metastatic Colorectal
• 6.7 Follow-up and Surveillance of Rectal Cancer Patients Treated with Curative Intent
• 6.8 Appendix - Colorectal Cancer Care Map for Physicians

6.6 Treatment Options by Stage

Print this Page

Revised 16 October 2012

The tumor stage may be clinical (c) or pathological (p). A "yp" stage refers to tumors treated with pre-operative chemo-, radiation-, or chemo-radiation therapy which has the potential of therapy decisions are based on clinical stage with stage 0/I rectal tumors treated with surgery alone and stage III/IV tumors treated with surgery, pre-operative radiation/chemoradiation + therapy.

Stage 0 cancer is limited to mucosa without invasion of the lamina propria

- Local, transanal excision or endoscopic polypectomy with clear margins
- Transabdominal resection (Anterior Resection, Low Anterior Resection, Abdomino Perineal Resection) for larger lesions not amenable to local excision.

Stage I T1-2, N0, M0

- Transabdominal resection (AR, LAR, APR) with no requirement for neoadjuvant or adjuvant radiation therapy remains standard of care.
- In patients whose medical comorbidities preclude formal transabdominal resection or who refuse major surgery despite counseling, local, transanal excision may be considered. Endoscopic Microsurgery) be offered in experienced centers only and should consider clinical as well as pathologic criteria (T1 lesion, well or moderate differentiation, size less and ability to achieve negative deep margin of at least 3mm). Postoperative radiation therapy is generally considered after local excision has been carried out.

Stage II T3, N0, M0

- Referral to Radiation/Medical Oncology for neoadjuvant (preoperative) radiation therapy (with or without chemotherapy) is recommended.
- For non-fixed tumours in the upper two-thirds of the rectum: neoadjuvant short-course radiation therapy (2500cGy in five fractions) to be followed by LAR or APR within approx clear radial margins may not benefit from radiation).
- For any fixed rectal tumours, rectal tumours approaching the mesorectal margin, and for tumours in the distal third of rectum: neoadjuvant long-course radiation therapy (4500cG followed by LAR or APR six to ten weeks following the completion of neoadjuvant therapy.
- Adjuvant capecitabine is given for 6 months following short-course radiation therapy (GIBCAE) or for 4 months following long-course chemoradiation therapy (GIBCRT).
- Adjuvant chemotherapy should start as close to four weeks post-op as possible.
- Patients treated with upfront resection and with pathologic Stage II rectal cancer should be referred to BCCA medical oncology and radiation oncology for postoperative adjuvant
- See Stage III adjuvant chemotherapy recommendations for patients with ypN+ disease
- Consider treatment in a clinical trial, if available.

Stage III or T4N0: T4 or Tany, N+1, M0

- Referral to Radiation/Medical Oncology for neoadjuvant (preoperative) radiation therapy (with or without chemotherapy) is recommended.
- For mobile, non-fixed tumours in the upper two-thirds of the rectum: neoadjuvant short-course radiation therapy (2500cGy in five fractions of the first day of radiation) to be followed by LAR or APR six to ten weeks following the completion of neoadjuvant therapy.
- For any fixed rectal tumours, rectal tumours or lymph nodes approaching the mesorectal margin, and for tumours in the distal third of rectum: neoadjuvant long-course radiation chemotherapy to be followed by LAR or APR six to ten weeks following the completion of neoadjuvant therapy.
 - Adjuvant chemotherapy is given for 6 months following short-course radiation therapy or for 4 months following long-course chemoradiation therapy. Standard of ca operative systemic therapy. There is some evidence that patients who achieve good downstaging (T0-2, N0) benefit from adjuvant 5-FU based therapy. Capecitabine + mFOLFOS is considered for patients with ypTanyN+ disease as these patients are known to be at high risk of distant relapse.
 - Patients presenting with advanced clinical stage (bulky T or N stage, T4 or N2) who achieve good downstaging may be considered for either capecitabine or FOLFIRI.
 - Please refer to current treatment protocols for indications, dosing and eligibility criteria.
- Adjuvant chemotherapy should start as close to four weeks post-op as possible.
- Patients treated with upfront resection and with pathologic Stage III rectal cancer should be referred to BCCA medical oncology and radiation oncology for postoperative adjuvant
- Consider treatment in a clinical trial, if available.



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•Short Course

- CRM not threatened on imaging
- uT3 anyN
- Non-fixed
- Proximal uT3 with -CRM may consider no RT

•Long Course

- CRM threatened on imaging
- uT4
- Clinically fixed rectal tumours
- Distal

•Distal

•Subgroup analysis ~ *Australian*

- 79 distal tumours LR
 - SC 6/48 12.5%
 - LC 1/31 0.03% $p = 0.26$

•Overall Local Recurrence did not differ depending on

- Distance from anal verge OR
- Distance from anal verge and treatment received

•Resectable


•Short Course $n = 181$

	≤ 5 cm	6-10 cm	11- 15 cm
	R0 / R1	R0 / R1 / R?	R0 / R1 / R?
LAR	5 / 1	89 / 4 / 1	14 / 1 / 1
APR	26 / 13	26 / 0	0 / 0

•Overall +CRM 14%

- 14/19 R1 occurred distally

•Long Course all R0 $n = 9$



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BMJ

Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study

MERCURY Study Group

- uT2N0 → T1ME
- MRI
 - Standardized technique and reporting
 - Reinforced by training workshops
 - Question remains
 - ‘... whether such results can be reproduced by other centers.’
 - Recommend

- Workshop training
 - Standardization of reporting
 - Strict adherence to the scanning technique and reporting criteria



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Staging

- BCCA - Fraser Valley Cancer Centre
 - MRI *5 facilities*
 - No/few GI trained sub-specialists
 - No known internal QA process
 - ERUS *2 facilities*
 - 1 gastroenterologist
 - 1 gastroenterologist & 1 radiologist
 - No known QA process

- Australian Retrospective ~ 31% of uT1-2 under-staged

CRM relationship

Nodal status

Rad Onc

CRM status

TN

Med Onc

TN

Understaging in the Community

- uT2N0
 - Consider Short Course
 - 5 days RT alone \checkmark
 - 5 weeks of Post-op Chemoradiation
 - Less effective & more toxic than Pre-op Chemoradiation
 - Is it less effective & more toxic than *Short Course*?
 - Co-morbidities that may make post-op chemoradiation less safe
 - Compliance issues

Time, Timing & Cost

- Time
 - Short Course *is short* 12 vs 77 days
 - Self-employed patients / Patients without benefits
 - Compliance
 - Co-morbidities
- Timing
 - OR availability 7-10 days after completion of short course
- Cost
 - 5 days RT alone vs 25-28 days + capecitabine

Recommendations ✓

	Short	Long
uT2 N0	+/-	-

Recommendations ✓

	Short	Long
uT2 N0	+/-	-
uT3 N0	+++	++

Recommendations ✓

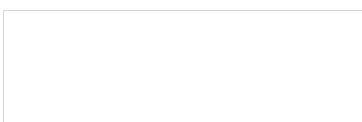
	Short	Long
uT2 N0	+/-	-
uT3 N0	+++	++
uT4 anyN	-	+++

Recommendations ✓

	Short	Long
uT2 N0	+/-	-
uT3 N0	+++	++
uT4 anyN	-	+++
anyT N+	+++	++

Recommendations ✓

	Short	Long
uT2 N0	+/-	-
uT3 N0	+++	++
uT4 anyN	-	+++
anyT N+	+++	++
Threatened CRM	-	+++



Recommendations ✓

	Short	Long
uT2 N0	+/-	-
uT3 N0	+++	++
uT4 anyN	-	+++
anyT N+	+++	++
Threatened CRM	-	+++
Distal T2	+/-	++ sphincter sparing*

*Explicit goal; appropriate surgical expertise

Recommendations ✓

	Short	Long
uT2 N0	+/-	-
uT3 N0	+++	++
uT4 anyN	-	+++
anyT N+	+++	++
Threatened CRM	-	+++
Distal T2	+/-	++ sphincter sparing*
Distal T3	++	++ sphincter sparing*

*Explicit goal; appropriate surgical expertise

Pre-operative Radiotherapy

Short Course

or

Long Course?

Chad R Lund MSc MD FRCPC
Radiation Oncology

Sept 5, 2014