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Cancer du rectum: traitement péri-opératoire

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Question

67-year old man, ECOG PS 0, no major comorbidities
cT3dN1M0 EMVI+/CRM+ rectal adenocarcinoma 7 cm from the anal verge

What treatment would you propose?

- A) Neoadjuvant SCRT followed by surgery +/- adjuvant chemo
- B) Neoadjuvant CRT followed by surgery +/- adjuvant chemo
- C) Neoadjuvant FOLFOX/CAPOX followed by surgery +/- adjuvant chemo
- D) Neoadjuvant SCRT followed FOLFOX/CAPOX and surgery
- E) Neoadjuvant mFOLFIRINOX followed by CRT, surgery and adjuvant chemo

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Disclosure

- **Consultancy, advisory role:** Amal Therapeutics, Bayer
- **Research funding:** Amgen, AstraZeneca, Bayer, BMS, Roche, Sanofi
- **Travel grants:** Bayer, Lilly

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Global rectal cancer incidence and mortality

- 8th most common cancer
- 8th most common cause of cancer-related deaths

	CANCER SITE	NO. OF NEW CASES (% OF ALL SITES)		NO. OF NEW DEATHS (% OF ALL SITES)	
	Female breast	2,261,419	(11.7)	684,996	(6.9)
	Lung	2,206,771	(11.4)	1,796,144	(18.0)
	Prostate	1,414,259	(7.3)	375,304	(3.8)
	Nonmelanoma of skin[a]	1,198,073	(6.2)	63,731	(0.6)
61%	Colon	1,148,515	(6.0)	576,858	(5.8)
	Stomach	1,089,103	(5.6)	768,793	(7.7)
	Liver	905,677	(4.7)	830,180	(8.3)
39%	Rectum	732,210	(3.8)	339,022	(3.4)
	Cervix uteri	604,127	(3.1)	341,831	(3.4)
	Esophagus	604,100	(3.1)	544,076	(5.5)

Sung, CA Cancer J Clin 2021 (GLOBOCAN 2020)

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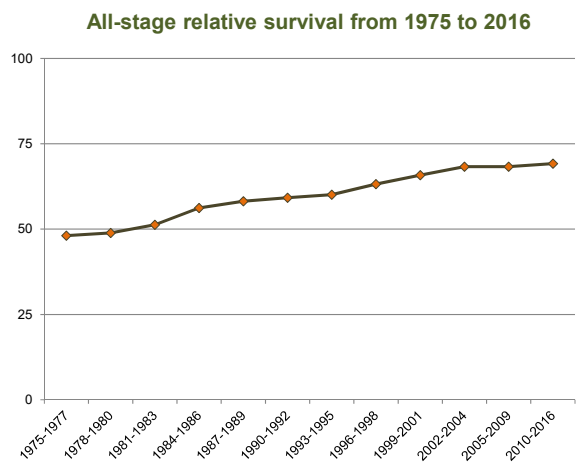
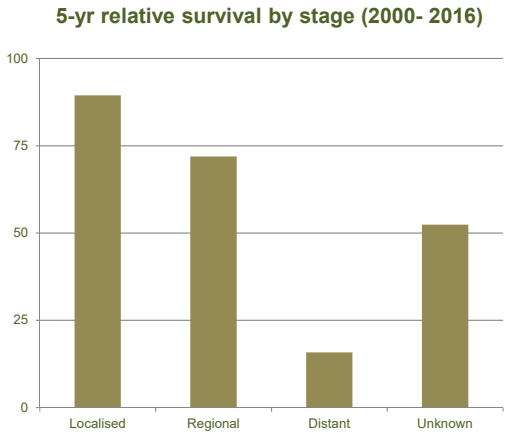
Rectal cancer relative survival over time





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Surveillance, Epidemiology, and End Results (SEER), seer.cancer.gov

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Historical rationale of peri-operative treatment for locally advanced rectal cancer

- High rates of **local recurrence** and overall **poor survival outcomes** after curative resection of rectal cancer (especially before the routine use of total mesorectal excision [TME])
- Local recurrence is associated with a number of **disabling symptoms** including:
  - . pain
  - . fistulation
  - . neurologic deficits
  - . ureteric obstruction
  - . infection
  - . lympho-vascular complications

Source	Number of patients	Local recurrences	Five-year disease-free survival rate
Conventional technique			
Arbman et al., 1996 [9]	134	24%	50%
LSCO*	270	24%	40%
TME			
Arbman et al., 1996 [9]	125	8%	70%
Bjerkeset et al., 1996 [24]	81	4%	85%
Zaheer et al., 1998 [26]	514	7%	79%
Heald et al., 1998 [25]	405	3%	80%

*Lower Silesian Center of Oncology (own data)

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Oncological outcomes of stage II-III rectal cancer patients remain poor despite routine adoption of TME

*Oncologic outcomes following TME surgery alone**

TNM stage	10-year local recurrence	10-year overall survival
I	3%	72%
II	8%	55%
III	19%	37%

* Data from the control group of the Dutch TME trial

van Gjin, Lancet Oncol 2011

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Peri-operative treatment in the pre-TME era

The New England Journal of Medicine

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Volume 312 JUNE 6, 1985 Number 23

Postoperative Adjuvant Chemotherapy or Radiation Therapy for Rectal Cancer: Results From NSABP Protocol R-01[1,2]

Bernard Fisher,[3] Norman Wolmark,[3] Howard Rockette,[3] Carol Redmond,[3] Melvin Deutsch,[3] D. Lawrence Wickerham,[3] Edwin R. Fisher,[3] Richard Caplan,[3] Judith Jones,[3] Harvey Lerner,[2] Philip Gord Sandra Legault-Poisson,[2] Marvin Wexler,[2] Other NSABP Investigators[2,4,*]

Post-op chemo: better DFS/OS
Post-op RT: better local control

PROLONGATION OF THE DISEASE-FREE INTERVAL IN SURGICALLY TREATED RECTAL CARCINOMA

GASTROINTESTINAL TUMOR STUDY GROUP

Post-op CRT: better DFS/OS

Any peri-operative treatment (chemo-, radio- or chemoradio-therapy) either before or after conventional (i.e., non-TME) surgery improves outcomes as compared with surgery alone

ON FOR CARCINOMA OF THE
OID COLON: REPORT OF A
MINISTRATION RANDOMIZED
UDY

HIGGINS, JR, MD,[†] AND ROBERT J. KEEHN[‡]

Pre-op RT: better local control/OS

Preoperative Radiotherapy
in Rectal Cancer

Final Results of a Randomized Study of the European Organization for Research and Treatment of Cancer (EORTC)

Pre-op RT: better local control

ANDRÉ GÉRARD, M.D.,* MARC BUYSE, M.Sc., M.D.A.,† BERNARD NORDLINGER, M.D.,‡ JEAN LOYGUE, M.D.,‡ FRANÇOISE PENE, M.D.,§ PETER HERMF, M.D.,‖ JEAN-FRANÇOIS BOSSET, M.D.,¶ MARC GIGNOUX, M.D.,** JEAN-PIERRE ARNAUD, M.D.,†† CLAUDE DESAIVE, M.D.,‡‡ NICOLE DUEZ, M.Sc.†

ykes' B and C

Carcinoma of the Rectum and Rectosigmoid

A Randomized Multicenter Study

Post-op RT: better local control (stage III)

IB BALSLEV, MD,* MOGENS PEDERSEN, MD,† PETER S. TEGLBJAERG, MD,‡ FINN HANBERG-SOERENSEN, MD, PHD,§ JOERGEN BONE, MD, PHD,‖ NIELS O. JACOBSEN, MD, PHD,‖ JENS OVERGAARD, MD, PHD,# ARNE SELL, MD,# KAMMA BERTELSEN, MD,** ESTHER HAGE, MD, PHD,†† CLAUS FENGER, MD,†† OLE KRONBORG, MD, PHD,‡‡ LISE HANSEN, MSC,§§ HANS HOESTRUP, MD, PHD,¶¶ AND BENT NOERGAARD-PEDERSEN, MD, PHD‖‖

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Pre-operative radiotherapy improves local control (but no overall survival) even if TME is performed

The Dutch TME trial

Primary endpoint: local control

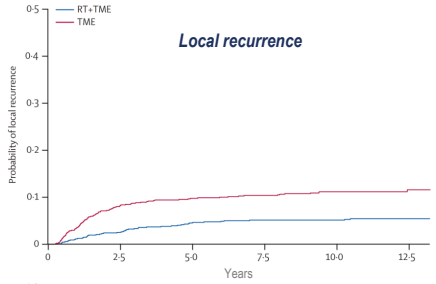
N = 1805 Clinically resectable (stage I-III) → R → **TME** / **SCRT → TME**

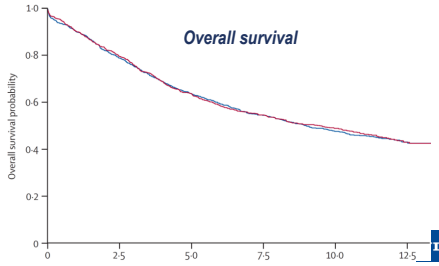
- *SCRT: 25 Gy in 5 fractions*

Median follow-up 11.6 yrs

- **10-yr local relapse: 5% vs 11%, p<0.0001**
- 10-yr distant relapse: 25% vs 28%, p=0.21
- 10-yr OS: 48% vs 49%, p=0.86

Kapiteijn, N Engl J Med 2001; van Gjin, Lancet Oncol 2011





Pre-operative radiotherapy improves local control (but no overall survival) even if TME is performed

The Dutch TME trial

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- 10-yr distant relapse: 25% vs 28%, p=0.21
- 10-yr OS: 48% vs 49%, p=0.86

Kapiteijn, N Engl J Med 2001; van Gjin, Lancet Oncol 2011

Possible survival advantage for stage III patients

	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

Better safety and local control if radiotherapy is given before surgery

The German Rectal Cancer Study Group trial

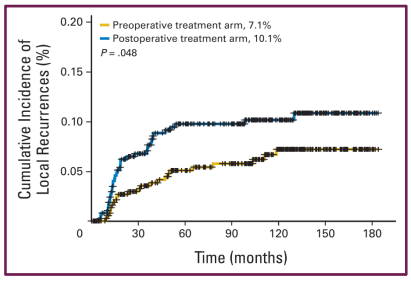
Primary endpoint: 5-yr OS

N = 799
Stage II-III

R → **TME → CRT → ACT**

R → **CRT → TME → ACT**

- *CRT: 50.4 Gy (Pre-op) or 55.8 Gy (Post-op) with 5FU 1000 mg/m2 ci d1-5 q28 x2*
- *CT: FU 500 mg/m2 bolus d1-5 q28 x4*



Median follow-up 11.1 yrs

- **10-yr local relapse: 7.1% vs 10.1%, HR 0.60, p=0.048**
- 10-yr distant relapse: 29.8% vs 29.6%, HR 0.98 p=0.9
- 10-yr OS: 59.6% vs 59.9%, HR 0.98, p=0.85

Table 5. Grade 3 or 4 Toxic Effects of Chemoradiotherapy, According to Actual Treatment Given.[a]

Type of Toxic Effect	Preoperative Chemoradiotherapy (N=399)	Postoperative Chemoradiotherapy (N=237)	P Value
	% of patients		
Acute			
Diarrhea	12	18	0.04
Hematologic effects	6	8	0.27
Dermatologic effects	11	15	0.09
Any grade 3 or 4 toxic effect	27	40	0.001
Long-term			
Gastrointestinal effects†	9	15	0.07
Strictures at anastomotic site	4	12	0.003
Bladder problems	2	4	0.21
Any grade 3 or 4 toxic effect	14	24	0.01

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Sauer, N Engl J Med 2004; Sauer, J Clin Oncol 2012

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Better safety and local control if radiotherapy is given before surgery…but still no survival improvement

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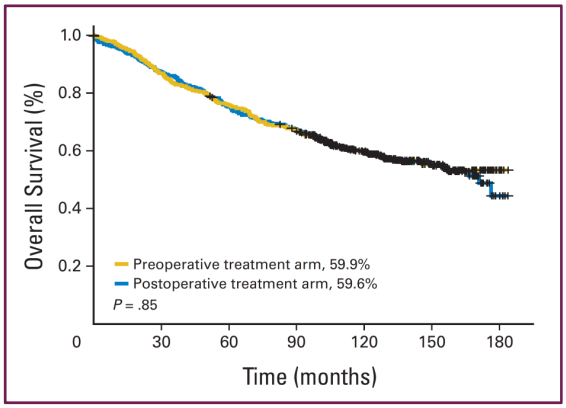

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Sauer, N Engl J Med 2004; Sauer, J Clin Oncol 2012

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Long-course CRT and SCRT + surgery within 1 week are largely equivalent

The Trans-Tasman ROGT 01.04 and Polish trials

Primary endpoint: 3-yr LR

N = 323
T3, N any

R → SCRT → Surg → ACT / CRT → Surg → ACT

- *SCRT: 25 Gy in 5 fractions*
- *LCRT: 50.4 Gy + 5FU 225mg/m²/day*
- *ACT: 5FU 425 mg/m² + FA d1-5 q28 x4 (SCRT) or x6 (CRT)*

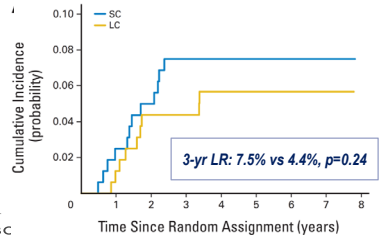
Primary endpoint: Sphincter preservation

N = 312
T3-4, N any, mid-low

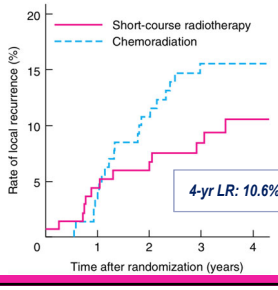
R → SCRT → Surg / CRT → Surg

- *SCRT: 25 Gy in 5 fractions*
- *LCRT: 50.4 Gy + 5FU 325mg/m² +FA d1-5 q28 x2*

LOCAL RECURRENCE



Ngan, J Clin Oncol 2012; Bujko, Br J Surg 2006



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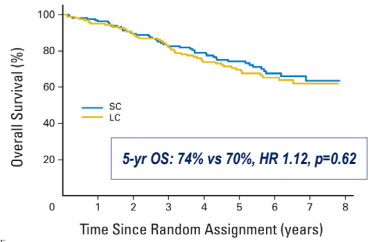
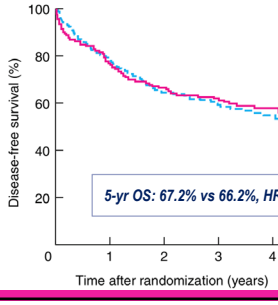
OVERALL SURVIVAL



Ngan, J Clin Oncol 2012; Bujko, Br J Surg 2006



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R
SCRT → Surg
CRT → Surg

- *SCRT: 25 Gy in 5 fractions*
- *LCRT: 50.4 Gy + 5FU 325mg/m² +FA d1-5 q28 x2*

Grade ≥3 late AEs

Late RT Toxicity Type	SC (n = 155) Grade 3	SC (n = 155) Grade 4	LC (n = 158) Grade 3	LC (n = 158) 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

SAFETY

Severe late AEs	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

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Ngan, J Clin Oncol 2012; Bujko, Br J Surg 2006

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Long-course CRT and SCRT + surgery within 1 week are largely equivalent

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N = 323
T3, N any

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- *ACT: 5FU 425 mg/m² + FA d1-5 q28 (CRT)*

Primary endpoint: Sphincter preservation

SCRT → Surg
CRT → Surg

Long-course CRT is the preferred option when tumour downstaging is needed (at least in the pre-TNT era…)

Treatment					R1 resection
SCRT	1%	28%	SCRT	1%	13%
CRT	15%	45%	CRT	16%	4%

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Ngan, J Clin Oncol 2012; Bujko, Br J Surg 2006

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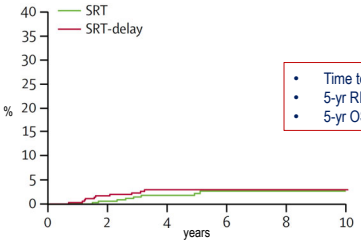
Delaying surgery after SCRT increases pathological tumour regression

The Stockholm III trial

Primary endpoint: time to LR (non-inferiority)

N = 840 Resectable → R → SCRT → Surg (<1w) / SCRT → Surg (4-8w) / RT → Surg (4-8w)

- *SCRT: 25 Gy in 5 fractions*
- *RT: 50 Gy in 25 fractions*



- Time to recurrence 33.4 vs 19.3 (NS)
- 5-yr RFS: 65% vs 68%
- 5-yr OS: 76% vs 77%

	SRT (n = 234)	SRT-delay (n = 228)	P‖
Tumour stage			0·001
ypo	4 (1·7)	27 (11·8)	
ypI	69 (29·5)	76 (33·3)	
ypII	71 (30·3)	53 (23·2)	
ypIII	74 (31·6)	55 (24·1)	
ypIV	5 (2·1)	6 (2·6)	
ypx†	11 (4·7)	11 (4·8)	
Tumour category			< 0·001
ypT0	5 (2·1)	27 (11·8)	
ypT1	12 (5·1)	27 (11·8)	
ypT2	74 (31·6)	60 (26·3)	
ypT3‡			
ypT3ab	88 (37·6)	67 (29·4)	
ypT3cd	41 (17·5)	26 (11·4)	
ypT3x	3 (1·3)	1 (0·4)	
ypT4‡			
ypT4a	1 (0·4)	5 (2·2)	
ypT4b	3 (1·3)	3 (1·3)	
ypTx†	7 (3·0)	12 (5·3)	
Node category			0·059
ypN0	149 (63·7)	163 (71·5)	
yp N1	52 (22·2)	41 (18·0)	
ypN2	28 (12·0)	19 (8·3)	
ypNx†	5 (2·1)	5 (2·2)	
Tumour regression*			< 0·001
Grade 0	17 (7·3)	15 (6·6)	
Grade 1	165 (70·5)	104 (45·6)	
Grade 2	41 (17·5)	64 (28·1)	
Grade 3	2 (0·9)	11 (4·8)	
Grade 4	4 (1·7)	23 (10·1)	
Grade x†	5 (2·1)	11 (4·8)	
Circumferential resection margin§	n = 170	n = 150	1·000#
Positive (≤ 1 mm)	11	9	
Negative (> 1 mm)	159	141	

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Pettersson, Br J Surg 2015; Erlandsson, Lancet Oncol 2017

SCRT and delayed surgery may be the best option for elderly patients

The NACRE trial

Primary endpoints (hierarchical):
1. *R0 resection (non-inferiority)*
2. *Autonomy preservation (superiority)*

N = 103 Age ≥75 ≥T3, or low T2 → R → CRT → Surg (6-8 wks later)

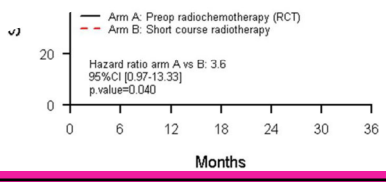
- *SCRT: 25 Gy in 5 fractions*
- *LCRT: 50 Gy + Cape 1600 mg/m²/d.*

CLOSED

Poor recruitment (~25% of the planned accrual)

CAUTION HANDLE WITH CARE

All pre-op tox		
≥G3 pre-op tox		
All post-op tox	50%	65%
≥G3 post-op tox	7%	2%



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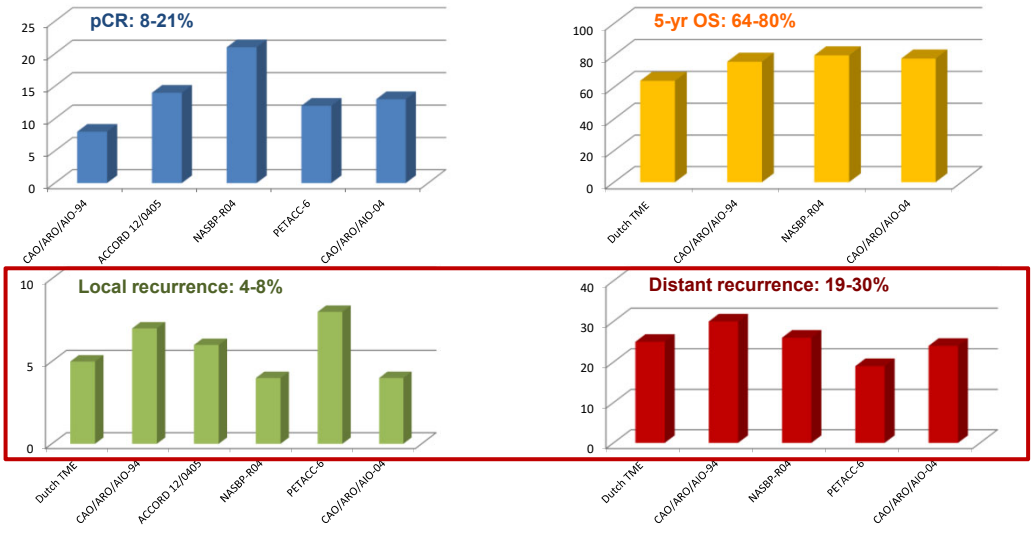
Pernot, GI ASCO 2021

Rectal cancer outcomes with neoadjuvant (C)RT and TME surgery: distant failure is now the main issue!



Van Gijn, Lancet Oncol 2011; Sauer, J Clin Oncol 2012; Gérard, J Clin Oncol 2012; Allegra, J Natl Cancer Inst 2015; Rödel, Lancet Oncol 2015; Schmoll, ASCO 2018

As simple as that…

Watson, how can we reduce distant recurrence in rectal cancer…?!?

Elementary, my dear Watson…give some adjuvant chemotherapy…

Phase III trials of adjuvant chemotherapy vs observation following pre-operative (chemo)radiotherapy

Study	Period	Accrual	Staging modality	Adj CT regimen	Primary endpoint	5-yr DFS (%)	5-yr OS (%)
I-CNR-RT	1992-2003	100%	DRE, rigid rectoscopy, CT AP, chest X-ray, (ERUS optional)	bolus 5-FU-LV	5-yr OS	62.8^ **HR 0.98** 65.3^	70.0^ **HR 1.04** 69.1^
EORTC 22921	1993-2003	100%	DRE, rigid rectoscopy, CT AP, chest X-ray, (ERUS optional)	bolus 5-FU-LV	5-yr OS	52.2 **HR 0.87** 58.2	63.2 **HR 0.85** 67.2
PROCTOR/ SCRIPT	2000 - 2013	52%	NA (inclusion after surgery)	bolus 5-FU-LV/ Nordic/Cape	5-yr OS	55.4 **HR 0.80** 62.7	79.2 **HR 0.93** 80.4
CHRONICLE	2004 - 2008	14%	NA (inclusion after surgery) CT TAP before Adj CT	CAPOX	3-yr DFS	71.3* **HR 0.80** 77.5*	87.8* **HR 1.18** 88.8*

^ Survival outcomes in the resected population
** 3-yr survival rates*

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Sainato, Radiot Oncol 2014; Bosset, N Engl J Med 2006; Breugom, Ann Oncol 2015; Glynne-Jones, Ann Oncol 2014

ULB iris

Phase III trials of adjuvant chemotherapy vs observation following pre-operative (chemo)radiotherapy…and caveats

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PROCTOR/ SCRIPT	2000 - 2013	52%	NA (inclusion after surgery)	bolus 5-FU-LV/ Nordic/Cape	+10% in 5-yr OS	94.5%	73.6%
CHRONICLE	2004 - 2008	14%	NA (inclusion after surgery) CT TAP before Adj CT	CAPOX	+10.5% in 3-yr DFS	92.6%	48.1%

Old studies, long recruitment period

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Sainato, Radiot Oncol 2014; Bosset, N Engl J Med 2006; Breugom, Ann Oncol 2015; Glynne-Jones, Ann Oncol 2014

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Poor accrual

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Sainato, Radiot Oncol 2014; Bosset, N Engl J Med 2006; Breugom, Ann Oncol 2015; Glynne-Jones, Ann Oncol 2014

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Old studies, long recruitment period | Poor accrual | Inadequate staging modalities | Sub-optimal chemo regimens | Unrealistic statistical hypothesis | Poor compliance with chemotherapy

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Sainato, Radiot Oncol 2014; Bosset, N Engl J Med 2006; Breugom, Ann Oncol 2015; Glynne-Jones, Ann Oncol 2014

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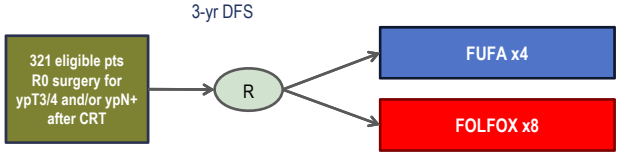
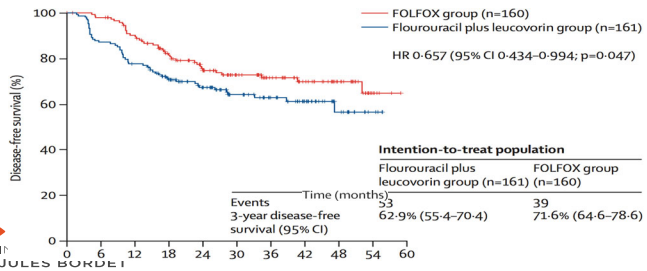
Single agent 5FU vs oxaliplatin-based adjuvant chemotherapy following pre-operative chemoradiotherapy

The ADORE trial

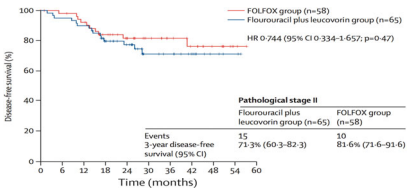
Primary endpoint:
3-yr DFS



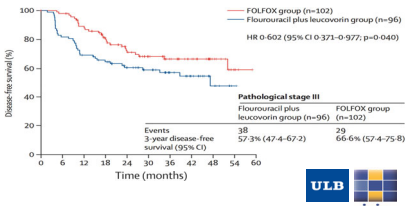
All patients



ypStage II patients



ypStage III patients



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Hong, Lancet Oncol 2014

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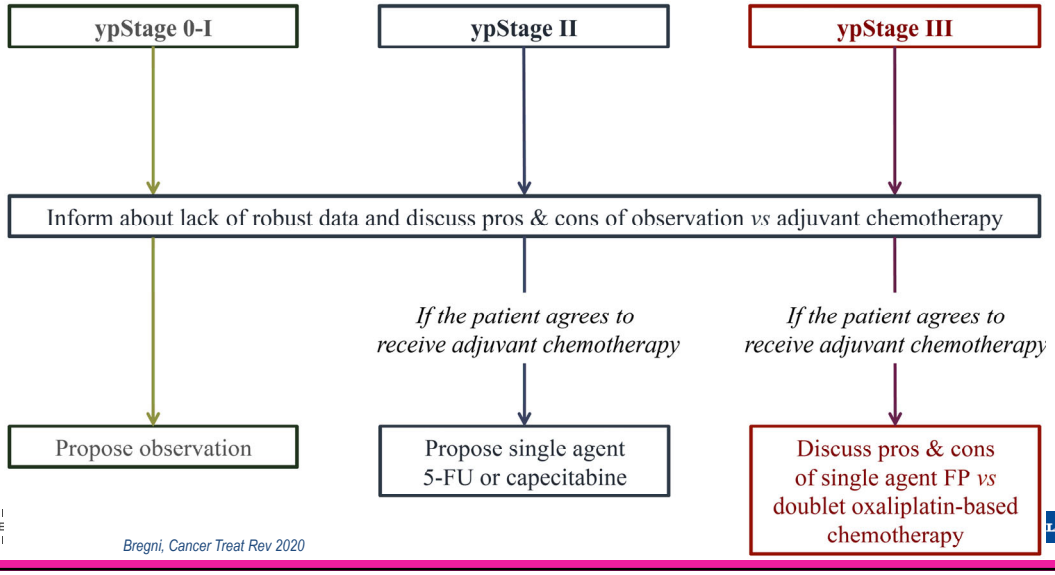
My recommendations for adjuvant chemotherapy following pre-operative (chemo)radiotherapy



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Bregni, Cancer Treat Rev 2020

ULB iris

Adding oxaliplatin to long-course CRT does not improve outcomes

Trial	N	Treatment	Primary endpoint	ypCR	3/5-yr DFS	3/5-yr OS
STAR	747	5FU + RT 5FU-Ox60 + RT	5-yr OS	16% 16%	66.3% 69.2%	77.6% 80.4%
ACCORD PRODIGE 2	598	Cape + 45 Gy Cape-Ox50 + 50 Gy	ypCR	13.9% 19.2%	67.9% 72.7%	76.4% 81.9%
NSABP-R04	1608	5FU/Cape + RT 5FU/Cape-Ox50 + RT	3-yr local control	17.8% 19.5%	64.2% 69.2%	79.0% 81.3%
CAO/ARO/AIO-04	1265	5FU + RT 5FU-Ox50 + RT	3-yr DFS	13.0%† 17.0%†	71.2%† 75.9%†	88.0% 88.7%
PETACC-6	1094	Cape + RT Cape-Ox50 + RT	3-yr DFS	11.3% 13.3%	71.3% 70.5%	83.1% 80.1%
FOWARC	312	5FUFA + RT mFOLFOX6 + RT	3-yr DFS	14.0%† 27.5%†	76.4% 77.8%	93.7% 92.0%

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Aschele, J Clin Oncol 2011; Aschele, ASCO 2016; Gerard, J Clin Oncol 2010; Gerard J, Clin Oncol 2012; Allegra, J Natl Cancer Inst 2015; Rödel, Lancet Oncol 2012; Rödel, Lancet Oncol 2015; Schmoll, ASCO 2014; Schmoll, ASCO 2018; Deng, J Clin Oncol 2016; Deng, ASCO 2018

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Adding irinotecan to long-course CRT The jury is still out...

Trial	N	Treatment	Primary endpoint	ypCR	3/5-yr DFS	3/5-yr OS
CINCLARE	356	Cape + RT → CAPOX x1 CAPIRI + RT → CAPIRI x1*	pCR	15% 30%	na	na
ARISTOTLE	598	Cape + 45 Gy Cape-Ox50 + 50 Gy	DFS	17% 20%	na	na

** Irinotecan dose: 80 mg/m2 q1w for UGT1A1*1*1 and 65 mg/m2 q1w for UGT1A1*1*28*
*** Irinotecan dose: 60 mg/m2 q1w for all patients*

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Zhu, J Clin Oncol 2020; Sebag-Montefiore, ASCO 2020

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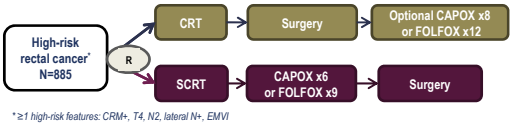
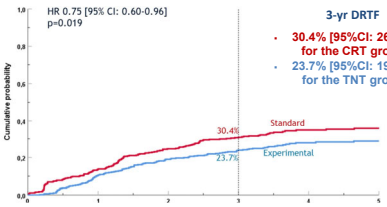
Total neoadjuvant therapy: RAPIDO and PRODIGE 23

RAPIDO



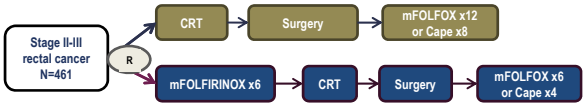
*≥1 high-risk features: CRM+, T4, N2, lateral N+, EMVI

Treatment	pCR	p value
Standard	14.3%	<0.001
TNT	28.4%	

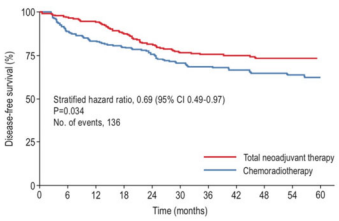


3-yr DRTF
- 30.4% [95%CI: 26.1-34.6] for the CRT group
- 23.7% [95%CI: 19.8-27.6] for the TNT group

PRODIGE 23



Treatment	pCR	p value
Standard	12.1%	<0.001
TNT	27.8%	



3-yr DFS
- 75.7% [95%CI: 69.4-80.8] for the TNT group
- 68.5% [95%CI: 61.9-74.2] for the CRT group

Bahadoer, Lancet Oncol 2020; Conroy, Lancet Oncol 2021

RAPIDO vs PRODIGE 23
Safety and compliance

Safety and compliance measures	RAPIDO		PRODIGE 23	
	TNT arm	Standard arm	TNT arm	Standard arm
(Chemo)radiotherapy compliance	100% (RT)	93% (CRT)	98% (RT)	99% (RT)
Chemotherapy compliance	85% (neoadj)	67% (adj)	92% (neoadj)	75% (adj)
Grade ≥3 AEs during neoadjuvant tx	**48%**	**25%**	**46% + 37%**	**36%**
Grade ≥3 AEs during adjuvant tx	**-**	**35%**	**44% (3m)**	**74% (6m)**
Surgery	92%	89%	92%	95%
Post-op complication	50%	47%	29%	31%
Treatment-related deaths	3%	3%	NR	NR

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Van der Valk, Radiot Oncol 2020; Bahadoer, Lancet Oncol 2020; Conroy, Lancet Oncol 2021

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RAPIDO vs PRODIGE 23
Eligibility criteria and baseline patient characteristics

Demographics/PS	RAPIDO Age ≥18 yrs, ECOG PS 0-1	PRODIGE 23 Age ≤75, WHO PS 0-1
Median age	62 yrs	61 yrs
"Elderly"	40% (≥65 yrs)	13% (≥70 yrs)
PS 0/1	81% / 19%	79% / 21%

High-risk features (MRI)	RAPIDO* ≥1 high-risk features (T4, N2, EMVI+, MRF+, lateral N+)	PRODIGE 23 Stage II/III
T4	31%	17%
N2	65%	unk (N+ 90%)
EMVI +	30%	unk
MRF +	61%	27%
Lateral N+	15%	unk

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* 65% of patients had at least 2 high-risk features

Van der Valk, Radiot Oncol 2020; Bahadoer, Lancet Oncol 2020; Conroy, Lancet Oncol 2021

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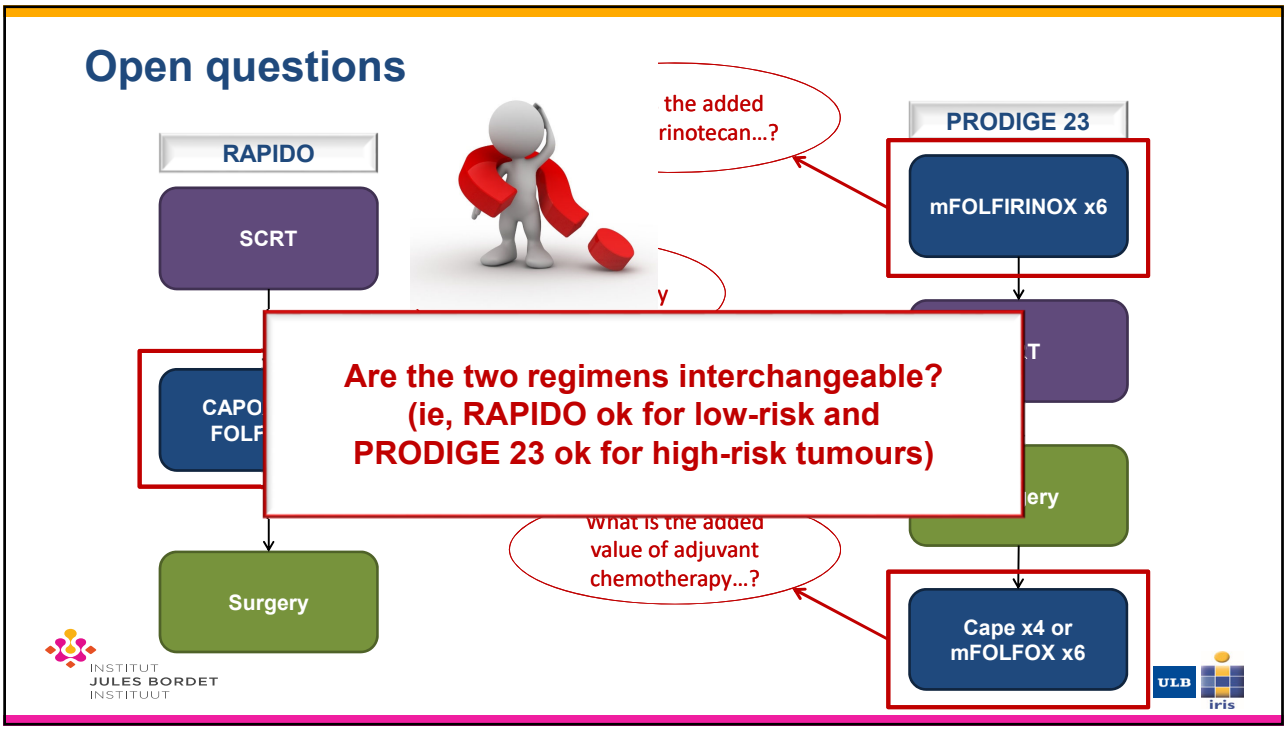
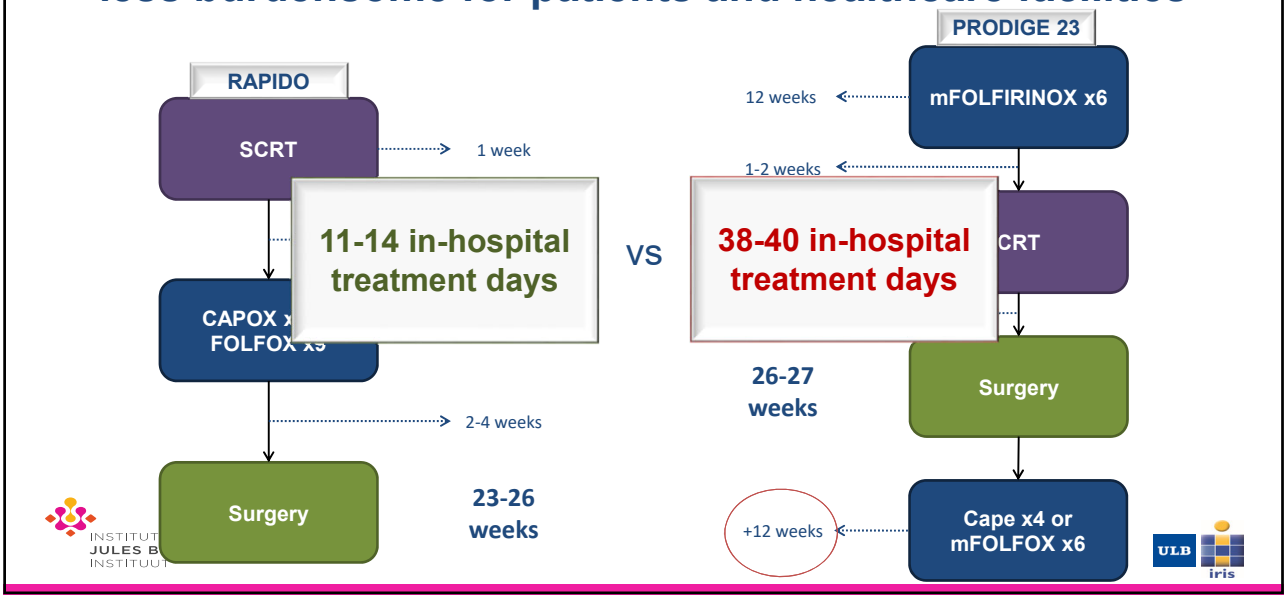
Open questions



Why the RAPIDO schema may be the preferred choice: less burdensome for patients and healthcare facilities

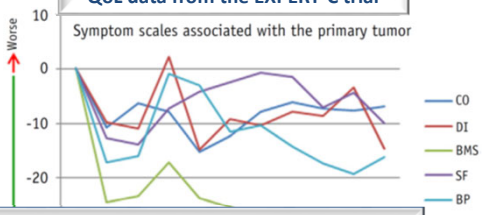


Why the PRODIGE schema may be the preferred choice: easier to start and rapid symptom control

Tumour response by RAS/BRAF status following induction therapy with CAPOX +/- cetuximab (EXPERT-C trial)

	CAPOX		CAPOX-C		*p* Value
	N	%	*N*	%	
Neoadjuvant chemotherapy[a]					
KRAS[b]/*BRAF* wild-type	22/43	51.2	32/44	72.7	0.038
RAS wild-type	21/39	53.8	28/36	77.8	0.030
Chemoradiotherapy[a]					
KRAS[b]/*BRAF* wild-type	32/42	76.2	40/45	88.9	0.117
RAS wild-type	30/38	78.9	32/37	86.5	0.290
Complete					
KRAS[b]/					
RAS wi					

QoL data from the EXPERT-C trial



The PRODIGE 23 strategy may be a good option for bulky/symptomatic tumours (and pragmatic solution if no rapid access to radiotherapy is available)

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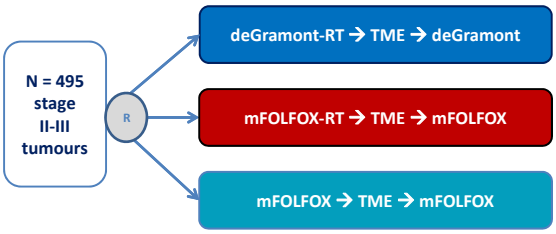
Sclafani, Eur J Cancer 2014; Sclafani, Int J Radiat Oncol Biol Phys 2015

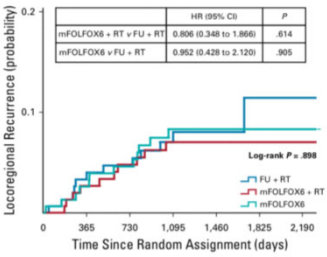
Why the PRODIGE schema may be the preferred choice: building on recent data on radiotherapy-free strategies

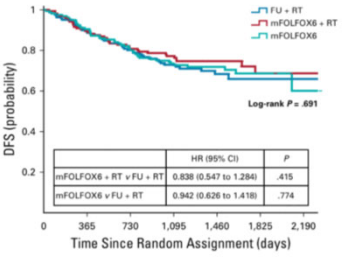
The FOWARC trial



Primary endpoint
3-year DFS
- mFOLFOX6-RT vs de Gramont-RT
- mFOLFOX6 vs deGramont-RT

Better safety profile and long-term QoL without radiotherapy





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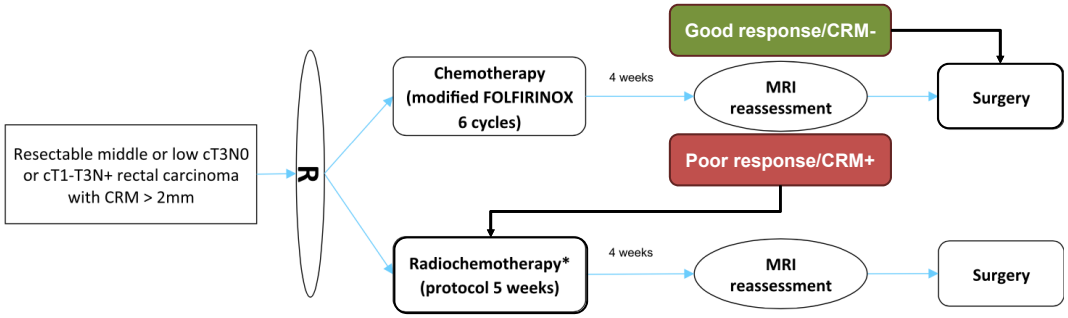
Deng, J Clin Oncol 2016; Deng, J Clin Oncol 2019

Why the PRODIGE schema may be the preferred choice: building on recent data on radiotherapy-free strategies

The NORAD01-GRECCAR 16 trial ...and, potentially, the future neoadjuvant treatment paradigm



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Brouquet, BMC Cancer 2020

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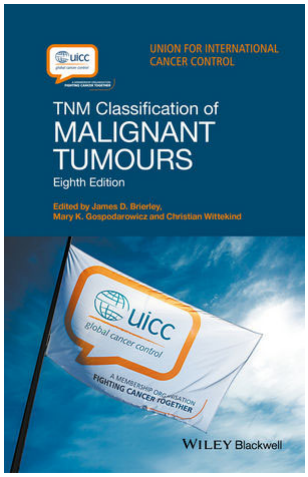
Making treatment decisions: the TNM-based old-fashioned approach



- ❑ Stage I → upfront surgery
- ❑ Stage II-III → neoadjuvant therapy

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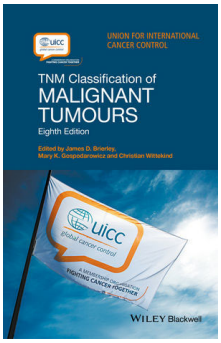
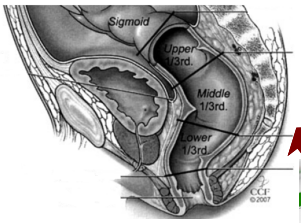
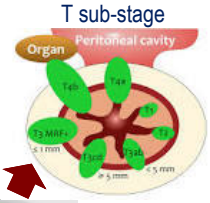
Making treatment decisions: TNM is not enough anymore...!



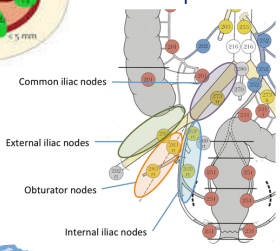
Tumour location



T sub-stage

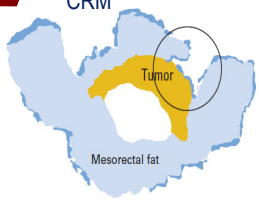


Lateral pelvic N+



EMVI

CRM



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Nougaret, Radiology 2013; Nagtegaal, J Clin Oncol 2008; Smith, Br J Surg 2008; Horvat, RadioGraphics 2019

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Stage II-III rectal cancers

Low risk
T3a/b high-mid tumours
N0, EMVI-, CRM-

Discussion with patient about pros & cons of CRT/SCRT vs upfront surgery

Intermediate risk
T3 low tumours, T3c/d high-mid tumours, N1, EMVI-, CRM-

High risk
T4, N2, lateral N+, EMVI+, CRM+
levator muscles threatened/involved

Discussion with patient about pros & cons of CRT/SCRT vs TNT

yes — Decline CT? Unfit for CT? — no

yes — Fit for triplet CT? Age ≤ 75 yrs? — no

yes — Symptomatic disease requiring immediate control? Expected delays in starting RT? — no

SCRT / CRT

mFOLFIRINOX → CRT
(PRODIGE 23 strategy)

SCRT → CAPOX / FOLFOX4
(RAPIDO strategy)

TME
W&W (if cCR) or local excision (if ycT1), but only in highly specialised centres

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What the peri-operative management of rectal cancer may look like in the next future…

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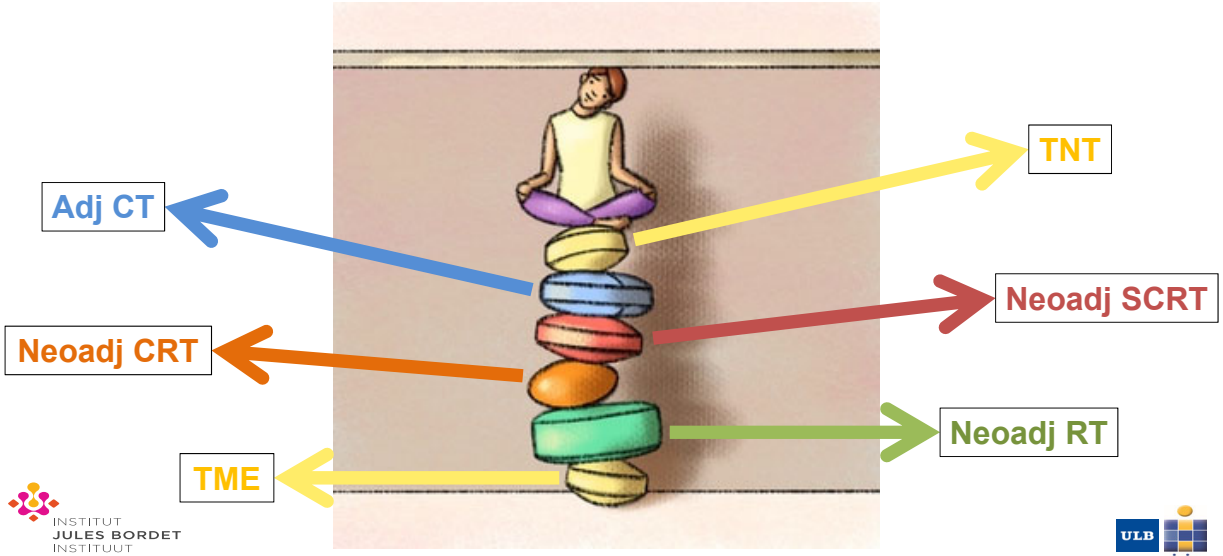
The "treatment ceiling effect" in rectal cancer



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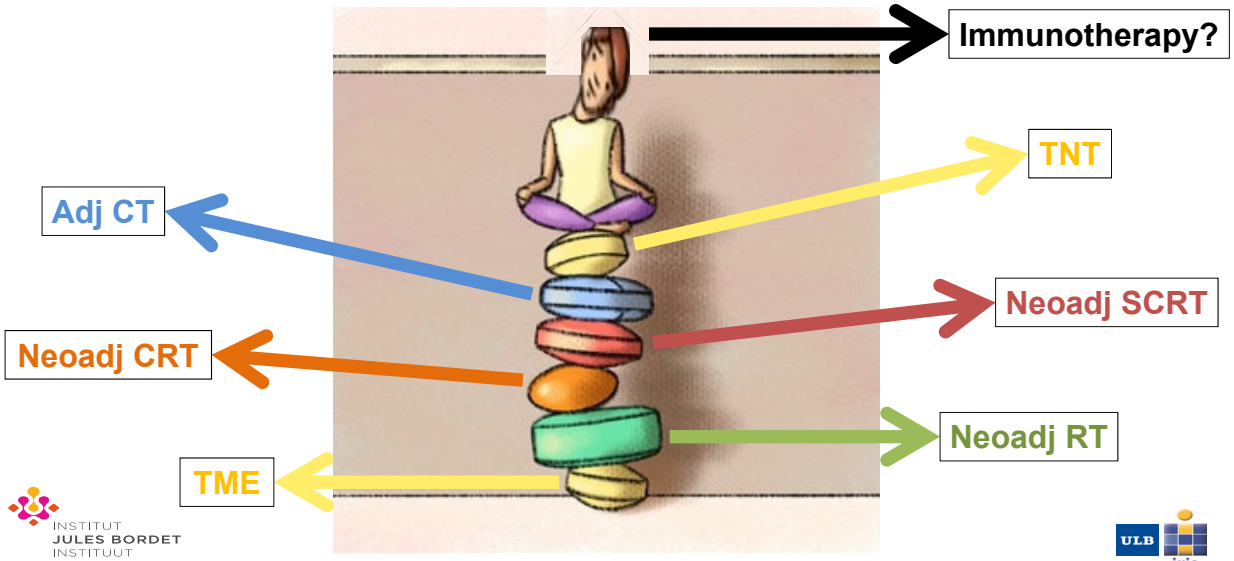
The “treatment ceiling effect” in rectal cancer



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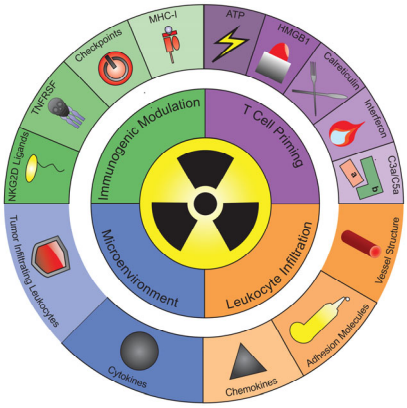
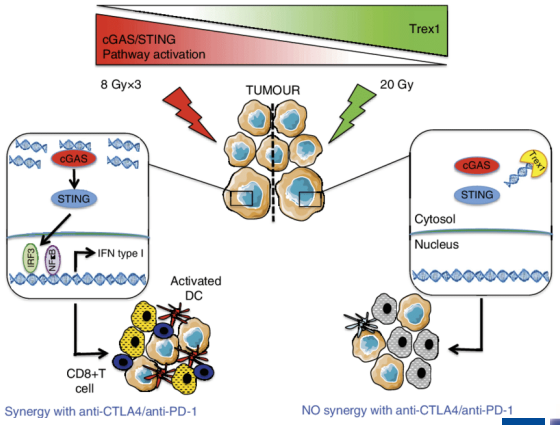
Why immunotherapy for rectal cancer?

- The vast majority of rectal cancers are MSS/MMRp, but…
- The immunomodulatory effects of RT may increase the therapeutic potential of ICIs





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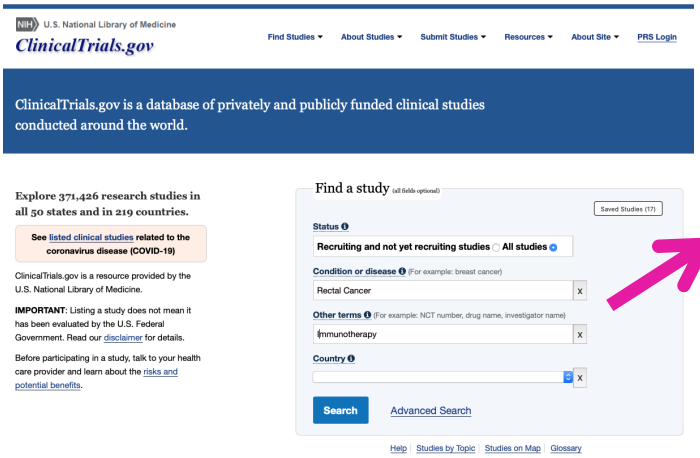
Walle, Ther Adv Med Oncol 2018; Vanpouille-Box, Nat Comm 2017

Immunotherapy for rectal cancer is now a hot topic



About 30 ongoing/planned clinical trials (ie, >1700 pts) with ICIs or other immuno-modulatory agents

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Results of immunotherapy trials in rectal cancer… not looking so good (at least for MMRp/MSS tumours)

Trial	N	Eligibility	Treatment	Primary endpoint	pCR
VOLTAGE	39	Stage II-III	CRT → **Nivolumab** x5	pCR	30% (MSS, n=37) 100% (MSI, n=2)
NRG-GI002	185	High-risk stage II-III	FOLFOX x8 → CRT FOLFOX x8 → CRT + **Pembrolizumab** x6	NAR score	29.4% 31.9%
NCT04231552	27	Stage II-III	SCRT → CAPOX + **Camrelizumab** x2	pCR	46% (MSS, n=26) 100% (MSI, n=1)
NCT03503630	13	Stage II-III	SCRT → FOLFOX + **Avelumab** x6	pCR	25%

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Yoshino, ASCO 2019; Rahma, GI ASCO 2021; Lin, GI ASCO 2021; Shamseddine, Radiat Oncol 2020

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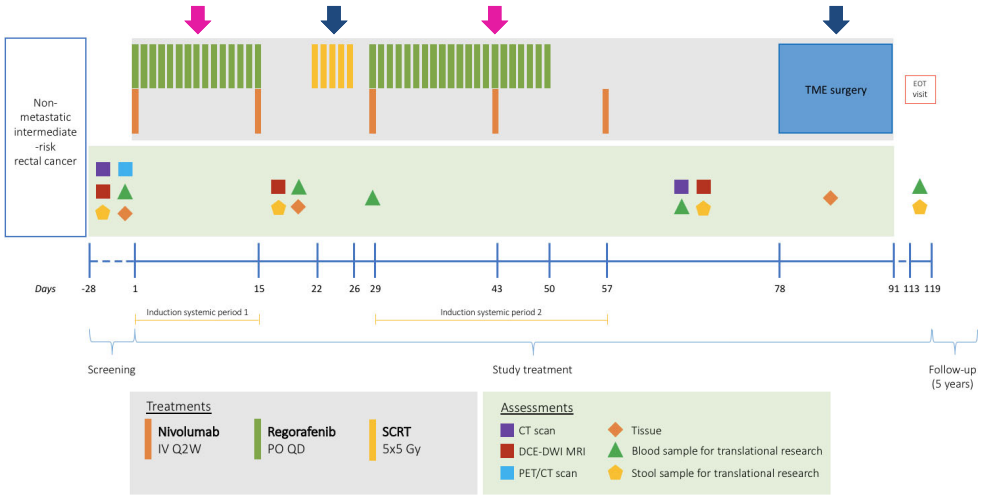
REGorafenib and nIvolumab iN rectAl cancer (REGINA)

- Single-arm phase II study
- Simon's two-stage design + early safety analysis
- Primary endpoint: pCR
- Sample size: max 60 pts
- H0=12%, H1=24% α=5%, β=20%
- Sponsor: Institut Jules Bordet
- Supported by Bayer
- PI: Dr F. Sclafani



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Bregni, Acta Oncol 2011

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The potential of ctDNA as a decision tool in non-metastatic rectal cancer: still a long way to go…

Table 1 Characteristics of all included studies on reporting an association between circulating DNA and localized rectal cancer

Author	Year	*N*	Design	Treatment	CfDNA	Response	Recurrence	Survival
Zitt	2008	26	Single arm	LCCR	qPCR total cfDNA quantification	Responders with significant decrease in cfDNA ($p=0.006$)	NA	NA
Agostini	2011	67	Single arm	LCCR	qPCR Integrety index (Alu 247/115 ratio)	Decreased integrity index in responders ($p=0.0009$)	NA	NA
Sun	2013	34	Single arm	LCCR	qPCR 100 and 400 bp fragments	Decreased 400/100 bp ratio in responders ($p<0.01$)	NA	NA
Carpinetti	2015	4	Single arm	LCCR	ctDNA by patient-specific genome sequencing	One patient with pCR had no detectable ctDNA	Two patients with distant met increased ctDNA	NA
Boysen	2017	75	Single arm	LCCR ($n=12$) SCRT ($n=63$)	Total cfDNA ddPCR target B2 M gene	NA	Higher cfDNA if recurrence ($p=0.08$)	NA
Schou	2017	123	Single arm	LCCR ICT (CAPOX, ($n=52$)	Total cfDNA Direct fluorescent assay	No difference by baseline cfDNA	Increased risk of recurrence by 75q	High cfDNA associated with decreased DFS ($p=0.015$)
Sclafani	2017	97	Single arm	ICT (CAPOX) LCCR ± cetuximab	qPCR KRAS/BRAF in baseline sample	No difference with baseline ctDNA ($p=0.57$)	NA	No difference in PFS ($p=0.43$) or OS ($p=0.6$)
Tie	2018	159	Single arm	LCCR	Personalized assay to quantify ctDNA	pCR not associated with change from +ctDNA to %ctDNA	ctDNA post-op highly predictive for recurrence ($p<0.001$)	Worse DFS if ctDNA detected post-op ($p<0.001$)
Li[a]	2017	30	Single arm	LCCR	ctDNA by 61-gene NGS panel	Prediction accuracy of ctDNA 70%	NA	NA

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Boysen, Clin Transl Oncol 2019

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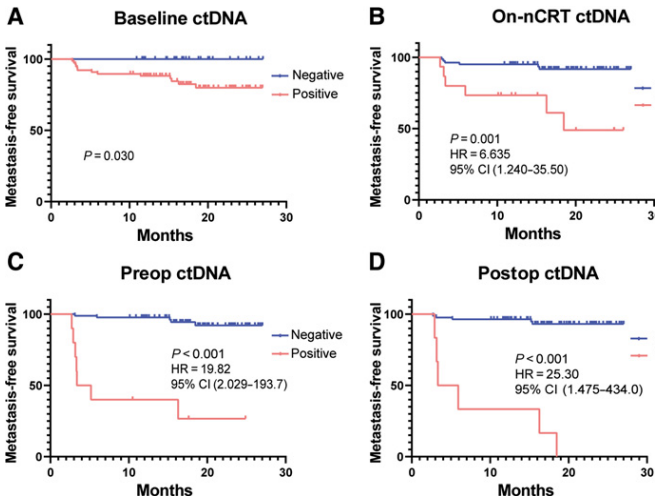
The value of ctDNA in non-metastatic rectal cancer appears to be time-point dependent

- 106 LARC pts treatred with neoadjuvant CRT
- Serial ctDNA analysed by NGS at
  - Baseline (ctDNA+ 75%)
  - During CRT (ctDNA+ 16%)
  - Pre-surgery (ctDNA+ 11%)
  - Post-surgery (ctDNA+ 7%)



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Zhou, Clin Cancer Res 2021

Question

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67-year old man, ECOG PS 0, no major comorbidities
cT3dN1M0 EMVI+/CRM+ rectal adenocarcinoma 7 cm from the anal verge

What treatment would you propose?

- A) Neoadjuvant SCRT followed by surgery +/- adjuvant chemo
- B) Neoadjuvant CRT followed by surgery +/- adjuvant chemo
- C) Neoadjuvant FOLFOX/CAPOX followed by surgery +/- adjuvant chemo
- D) Neoadjuvant SCRT followed FOLFOX/CAPOX and surgery
- E) Neoadjuvant mFOLFIRINOX followed by CRT, surgery and adjuvant chemo

Question

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Conclusions

- The management of non-metastatic rectal cancer has evolved over time, and it is still evolving
- Total neoadjuvant therapy (either according to the RAPIDO or PRODIGE-23 trial) should be considered as a new standard of care for fit, high-risk stage II, or stage III patients
- A multidisciplinary approach is key (now more than ever!)
- Alternative management strategies including better risk stratification tools (ctDNA analysis?) and therapies (immune checkpoint inhibitors?) are currently under investigation, and may further shape the future treatment paradigm

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THANKS

For any queries, please contact

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