



Regione del Veneto

ESMO CONGRESS 2023
Madrid, October 22th 2023

**Can we avoid preoperative (chemo)radiotherapy in
locally advanced rectal cancer patients?**

YES

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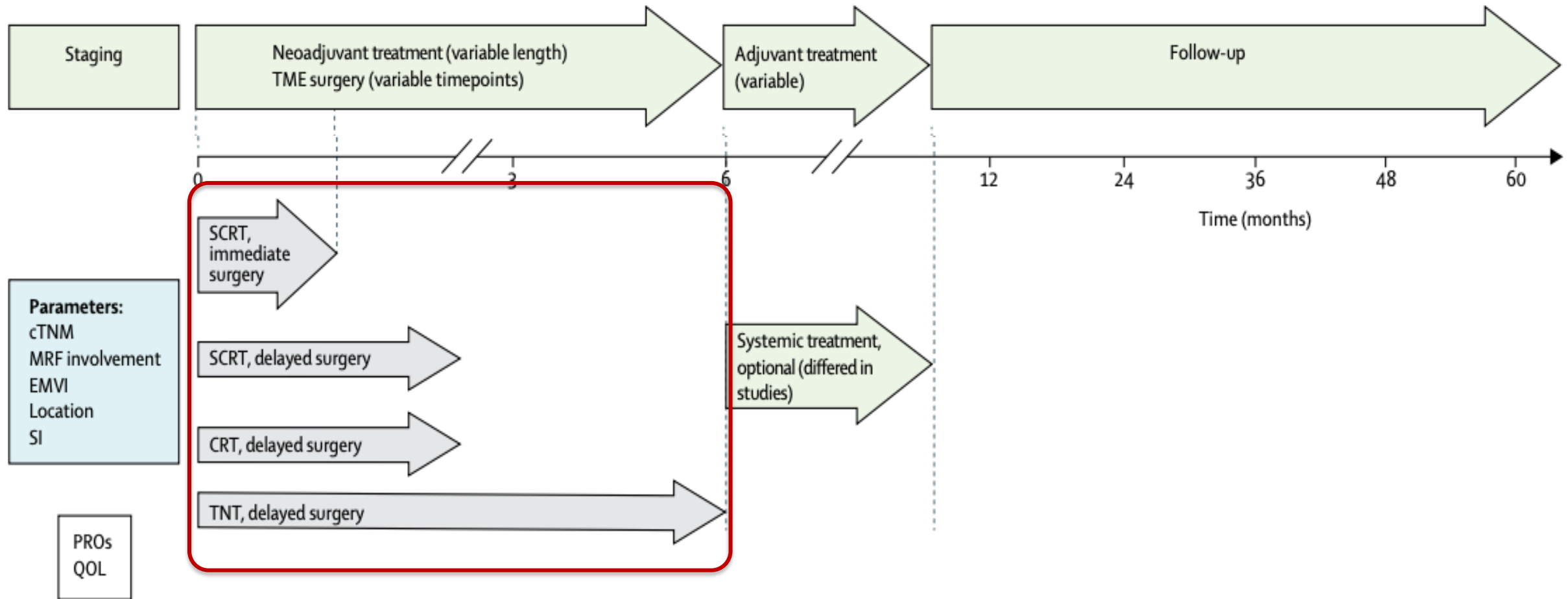
Conflict of Interest Disclosure

Consulting Role or Advisory Board: Amgen, Astellas, Astra Zeneca, Bayer, BMS, Daiichi-Sankyo, GSK, Incyte, Lilly, Merck Serono, MSD, Servier, Takeda

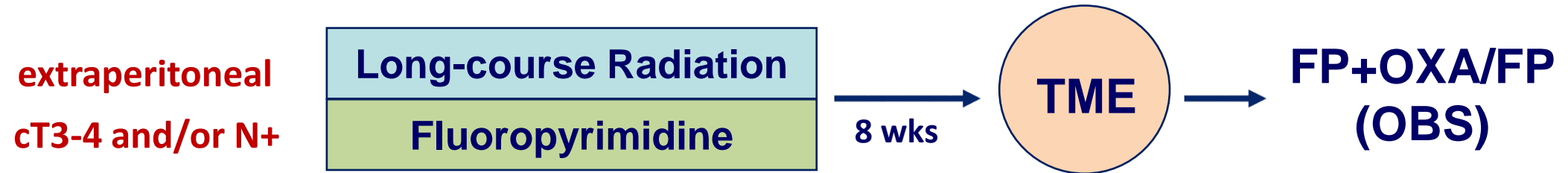
Speakers' Bureau: Amgen, BMS, GSK, Lilly, Merck Serono, Pierre-Fabre, Roche, Servier

Research Funding: Amgen, Astra Zeneca, Bayer, BMS, Lilly, Merck Serono, Roche

LARC: standard treatment



LARC: standard treatment



Outcomes:	pCR	15%
	Local Relapse:	5%
	Distant Metastases:	30%
	5y Disease-Free Survival:	65%
	5y Overall Survival:	75%
	Permanent Stoma:	15%
	G3-4 toxicities:	20%

Not all locally advanced rectal cancer are created equal



THE GOOD THE BAD AND THE UGLY

Not all locally advanced rectal cancer are created equal

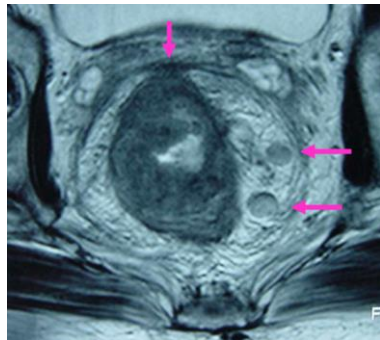


**THE
GOOD**

Main good prognostic factors and how to find them...

...use MRI!

- ✓ At least 1 mm of distance from the mesorectal fascia (CRM-)
- ✓ Extramural spread <5mm (T3a)
- ✓ No extramural vein invasion (EMVI-)
- ✓ Sphincter sparing surgery feasible (no APR predicted)



**Distance to
Mesorectal
Fascia**



**Sphincter
Involvement**



**Venous
Invasion**

Accurate staging, favorable outcome: more than a dream

	MERCURY	OCUM	QUICKSILVER
Completed TME	-	97%	82%
Positive CRM	3%	3%	5%
5y LR	3%	2%	-
5y DFS	67%	76%	-

Taylor, JCO 2013 Ruppert, BJS 2018 Kennedy, JAMA 2019

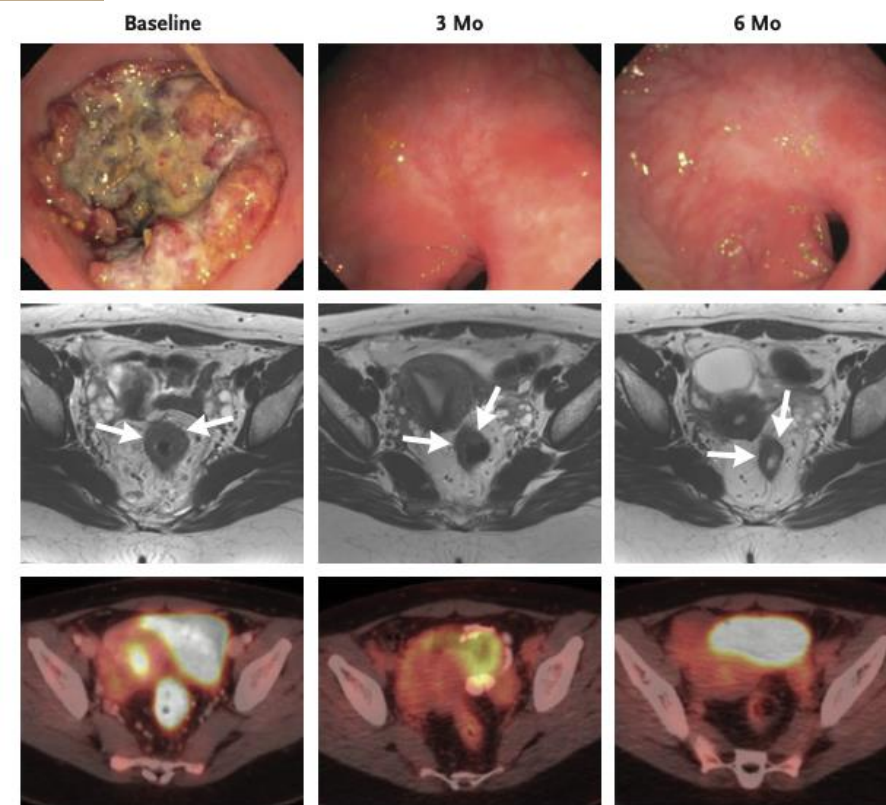
Favorable prognosis for the “good” ones with surgery upfront

Overtreatment risk

~~Chemotherapy~~



And now we have also the SUPERgood...



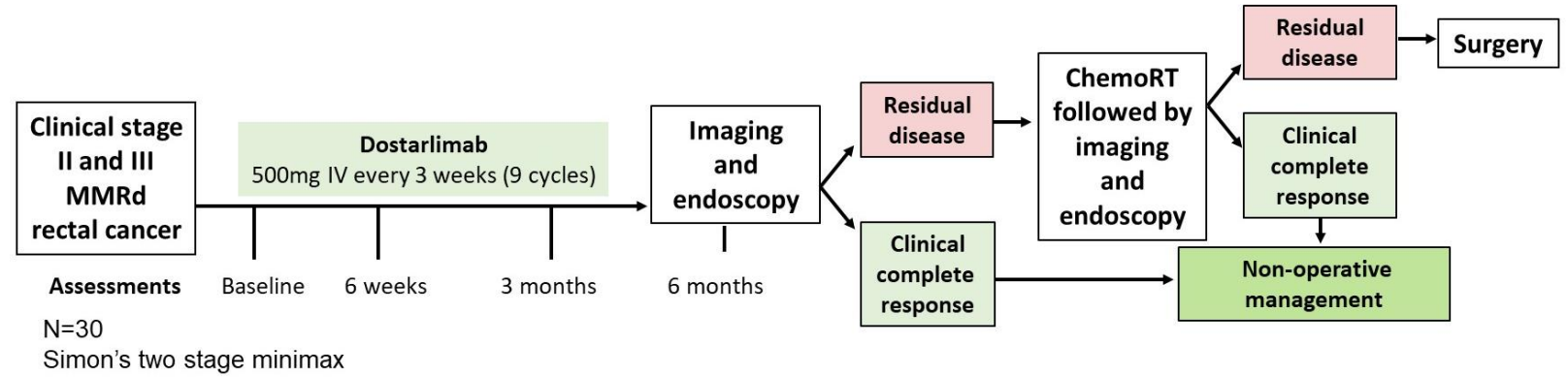
MSI-H Rectal cancer: dostarlimab neoadjuvant treatment

ORIGINAL ARTICLE

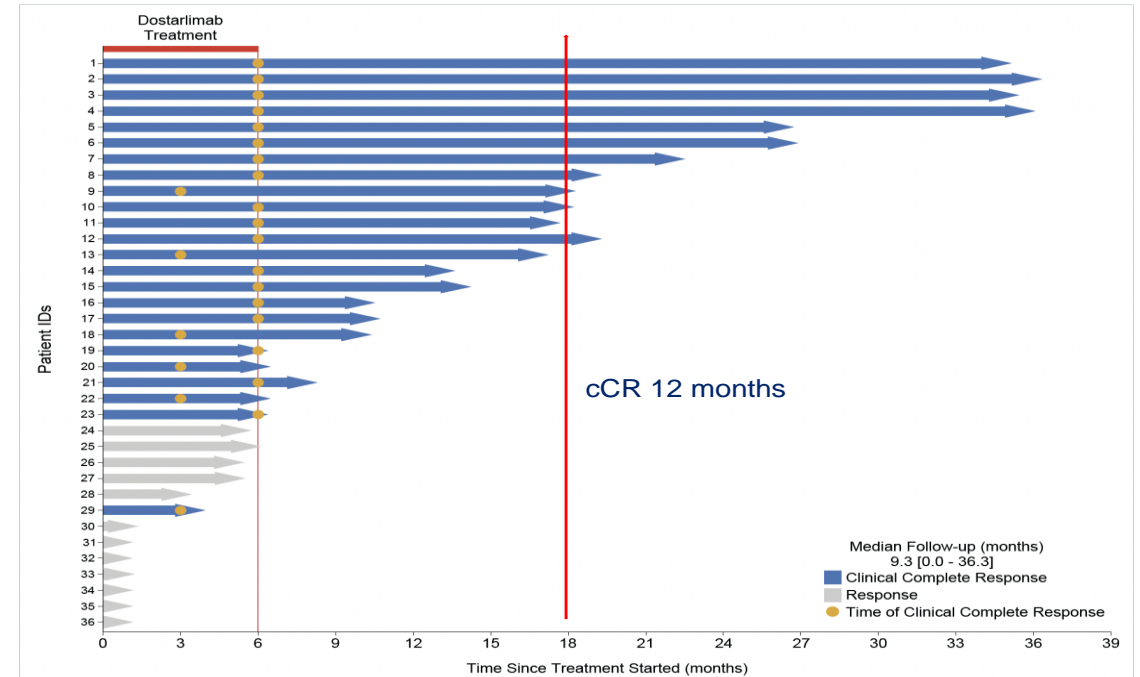
PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.

ABSTRACT



ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response
1	38	T4	N+	23.8	CR	CR	CR	cCR
2	30	T3	N+	20.5	CR	CR	CR	cCR
3	61	T1/2	N+	20.6	CR	CR	CR	cCR
4	28	T4	N+	20.5	CR	CR	CR	cCR
5	53	T1/2	N+	9.1	CR	CR	CR	cCR
6	77	T1/2	N+	11.0	CR	CR	CR	cCR
7	77	T1/2	N+	8.7	CR	CR	CR	cCR
8	55	T3	N+	5.0	CR	CR	CR	cCR
9	68	T3	N+	4.9	CR	CR	CR	cCR
10	78	T3	N-	1.7	CR	CR	CR	cCR
11	55	T3	N+	4.7	CR	CR	CR	cCR
12	27	T3	N+	4.4	CR	CR	CR	cCR
13	26	T3	N+	0.8	CR	CR	CR	cCR
14	43	T3	N+	0.7	CR	CR	CR	cCR



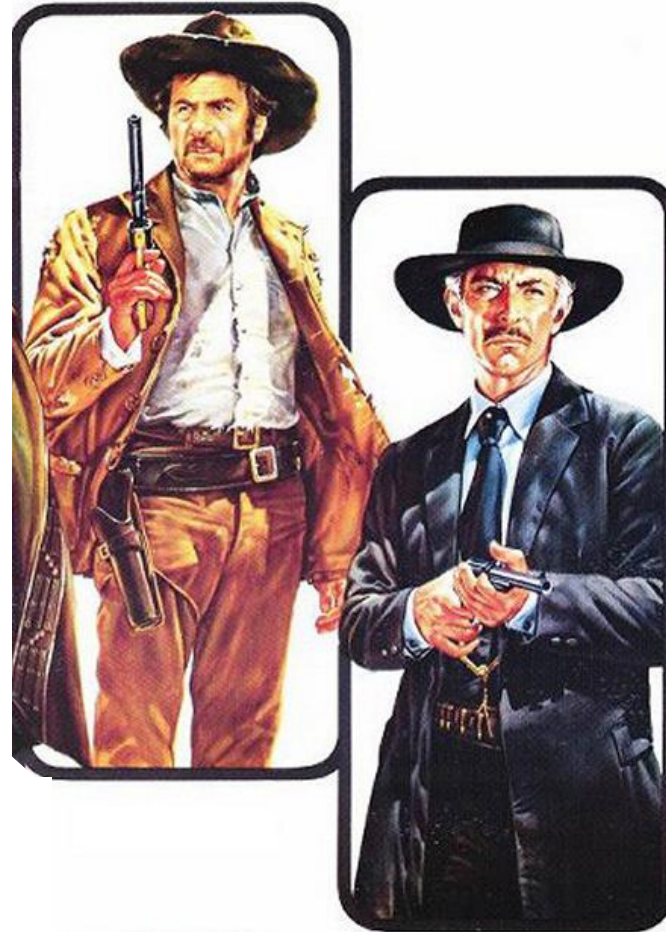
Not all locally advanced rectal cancer are created equal



THE AND THE
BAD UGLY

Not all locally advanced rectal cancer are created equal

**cT3>5mm
cN0/+
predicted CRM-
EMVI+**



THE BAD AND THE UGLY

**cT4
cN0/+
predicted CRM+
low-lying tumors**

Not all locally advanced rectal cancer are created equal

**cT3>5mm
cN0/+
predicted CRM-
EMVI+**



**PROSPECT
FOWARC
CONVERT**

**FOWARC
CONVERT**

**cT4
cN0/+
predicted CRM+
low-lying tumors**

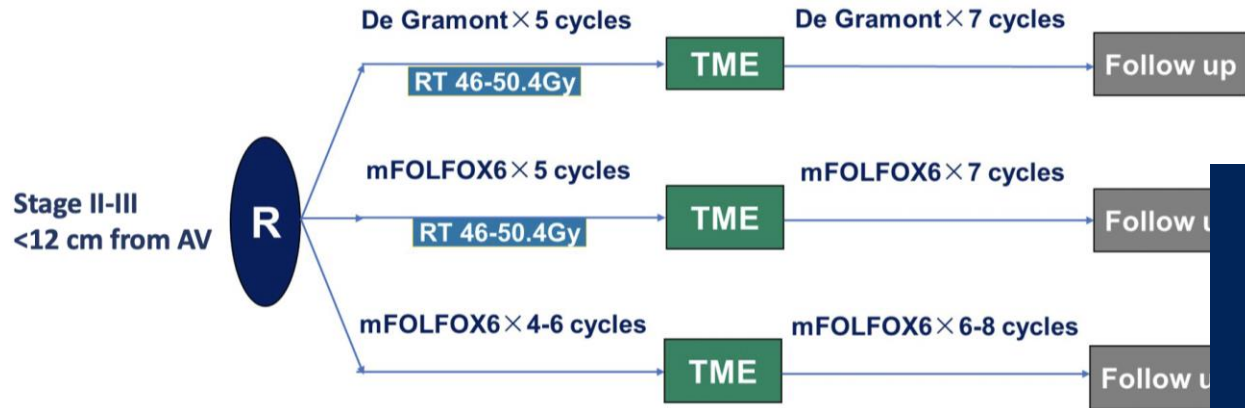
Radiotherapy added value

1. Increases tumor shrinkage:
 - more sphincter preservation
2. Increases cCR:
 - more non-operative management
3. Increases pCR probability
4. Reduces local relapses
5. Impacts on DFS and OS

...are we sure?!

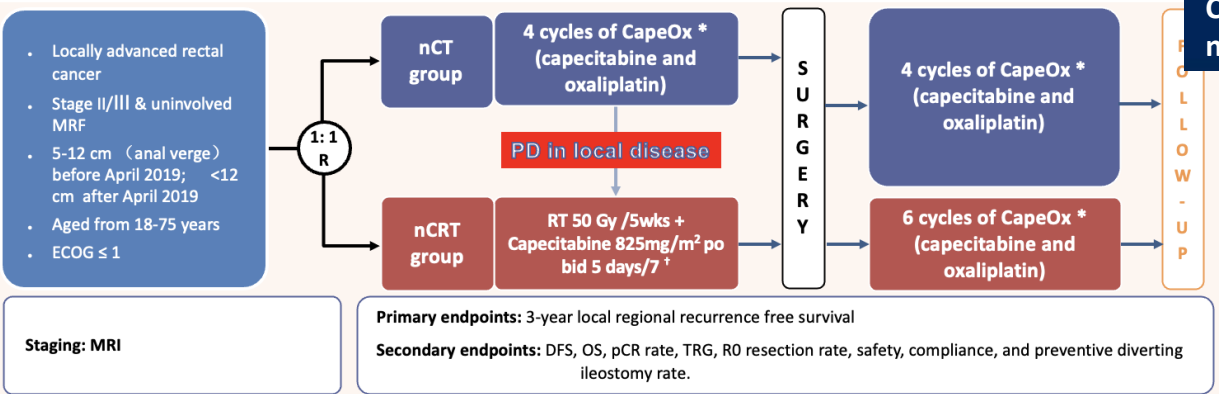
Studies on RT avoidance or RT adaptive introduction

FOWARC



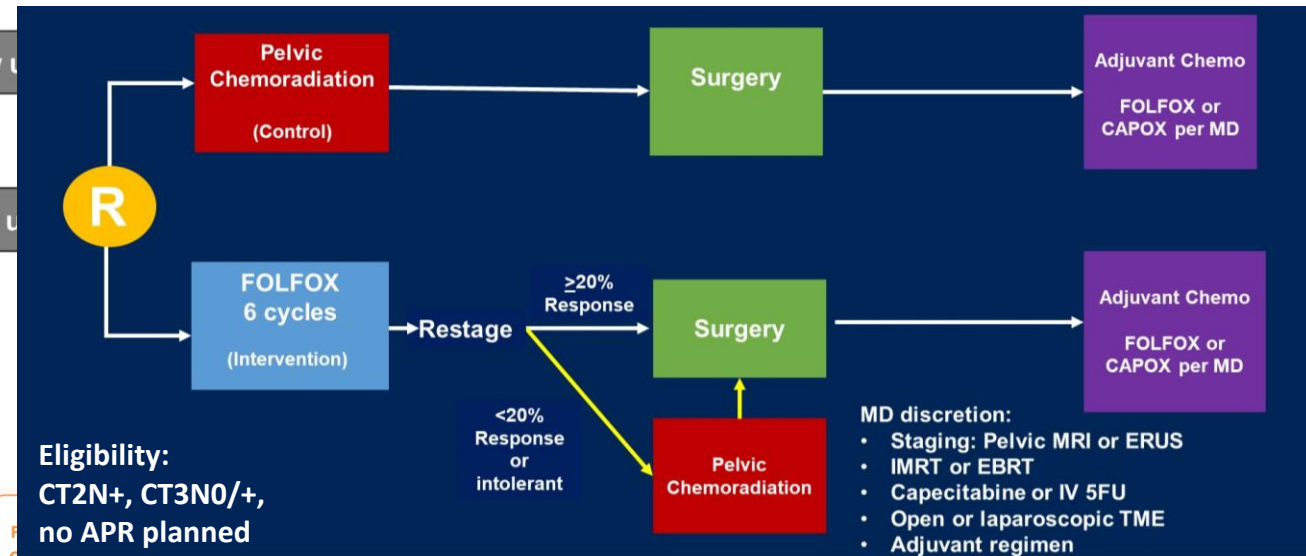
Deng Y et al, J Clin Oncol 2019

CONVERT



Ding PR et al, ESMO Congress 2023

PROSPECT



Schrag D et al, N Engl J Med 2023

Clinical and pathological outcome

ypStage 0-1: 36% vs 37%



	FOWARC		PROSPECT		CONVERT		
	CT	CRT	CT	CRT	CT	CRT	
Surgery performed	93%	89%	92%	94%	83%	79%	✓
R0 resection	89%	91%	99%	97%	100%	100%	✓
Anal preservation	90%	84%	98%	98%	95%	94%	✓
pCR	7%	14%	22%	24%	11%	13%	✗

Receiving RT in chemotherapy arm:

- PROSPECT: 9%

- CONVERT: 1%

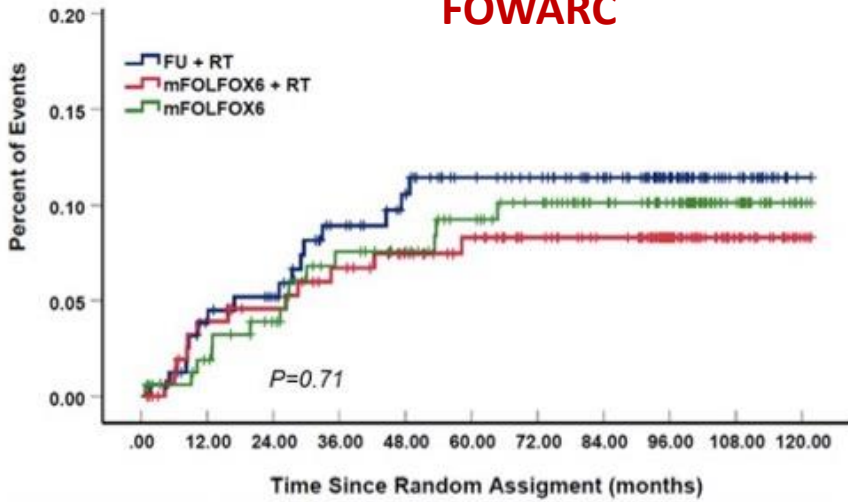
Deng et al, J Clin Oncol 2019

Schrag D et al, N Engl J Med 2023

Ding et al, ESMO Congress 2023

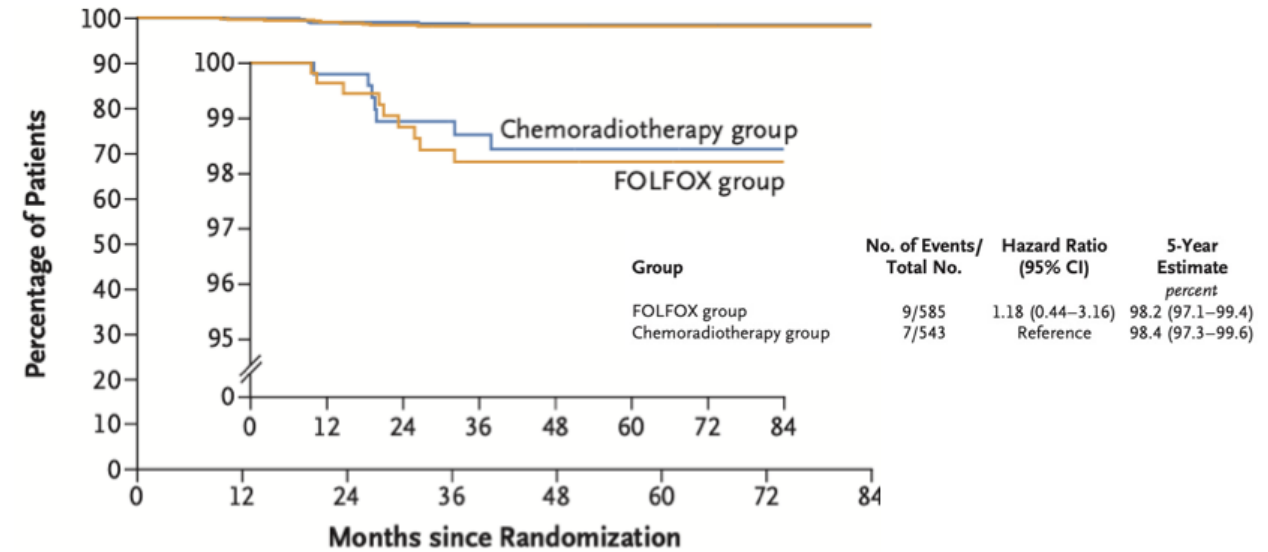
Locoregional Relapse

FOWARC

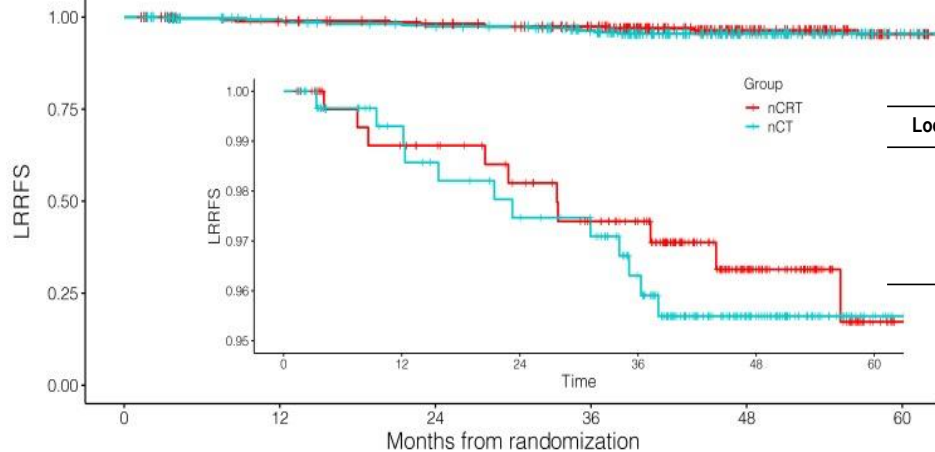


Treatment	5y-LR(%)	10y-LR (%)	HR (95% CI)
FU-RT	10.8	10.8	Ref
FOLFOX	8.8	9.6	0.800 (0.37-1.75)

PROSPECT



CONVERT



Deng Y et al, ASCO Annual Meeting 2023

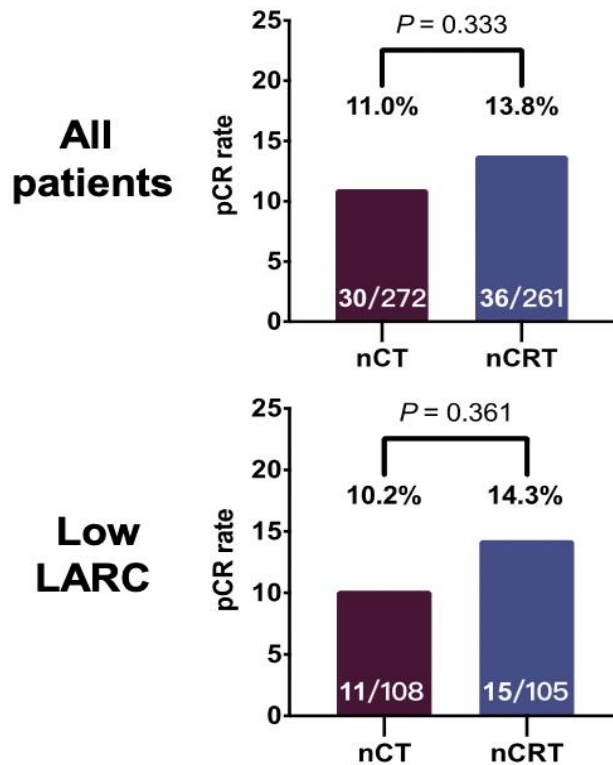
Schrag D et al, N Engl J Med 2023

Ding PR et al, ESMO Congress 2023

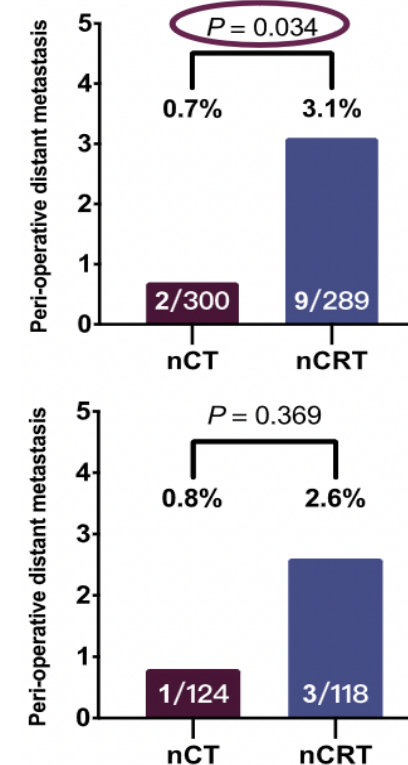
How these early response outcomes impact on survival end-points?

Local relapse is not an issue, and systemic recurrence is the problem..

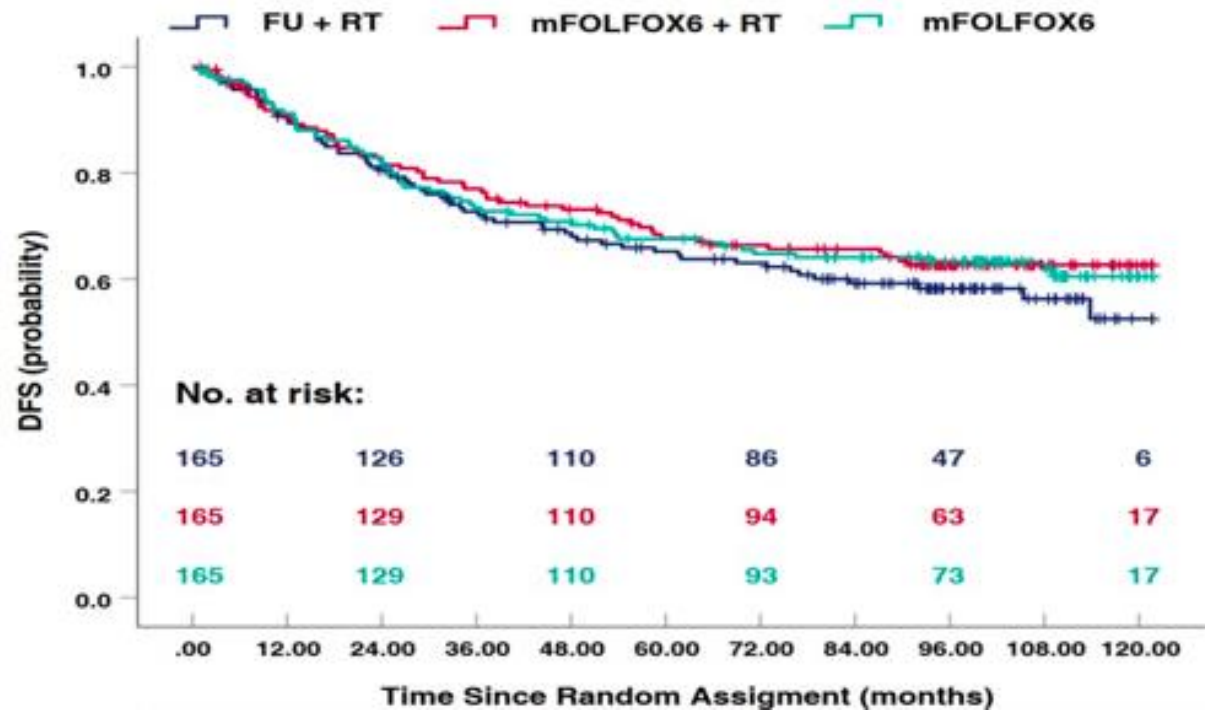
Similar pCR



Lower peri-operative distant mets with CT

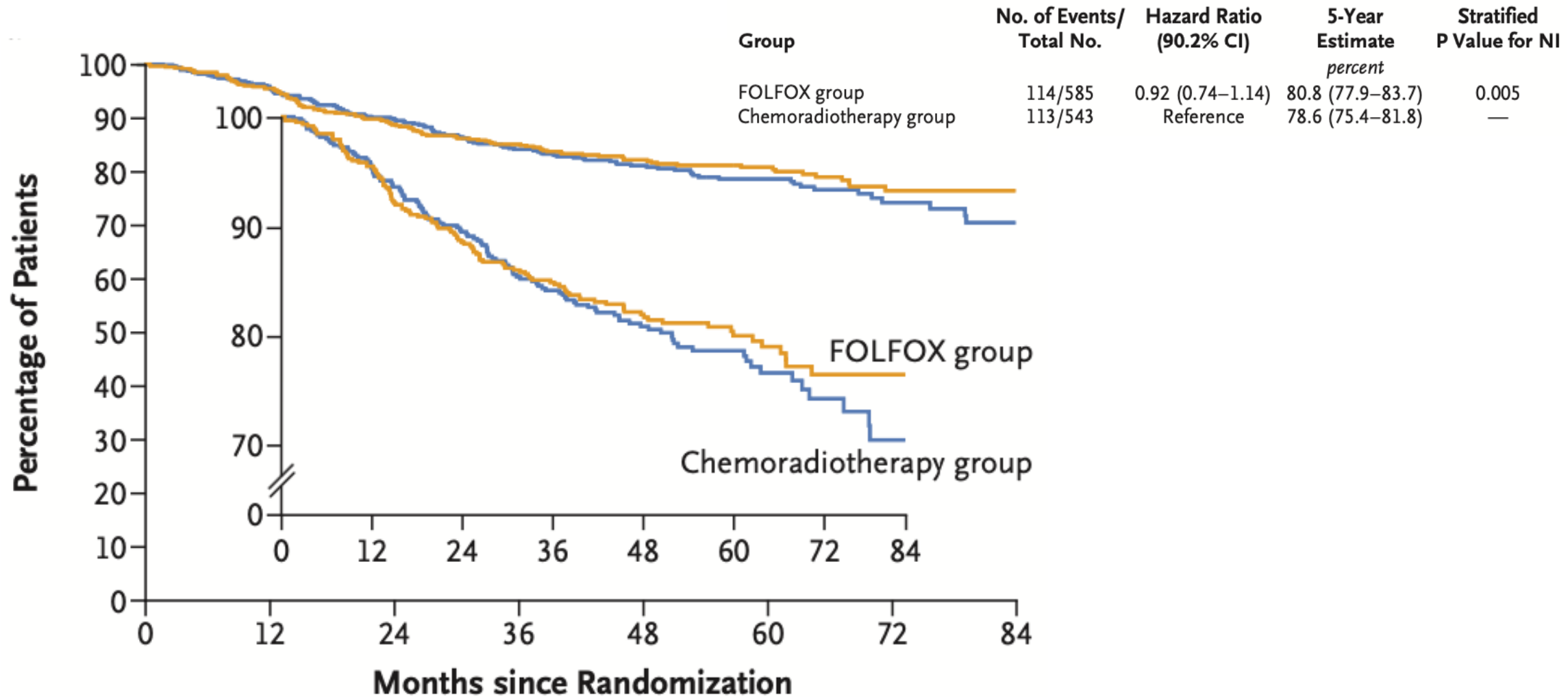


Disease-Free Survival: FOWARC Trial

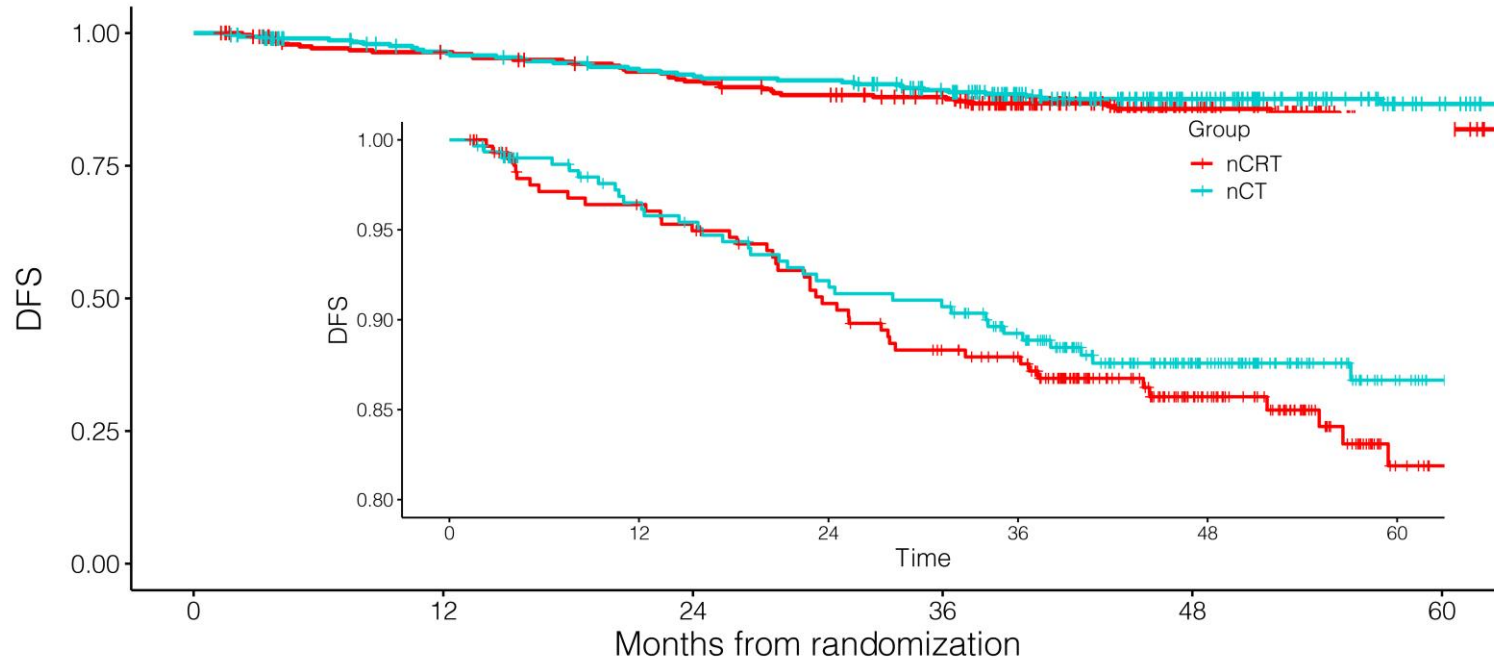


Treatment	5y-DFS	10y-DFS	HR (95% CI)
FU-RT	65.2%	52.5%	Ref
FOLFOX	67.5%	60.5%	0.86 (0.60-1.23)

Disease-Free Survival: PROSPECT Trial



Disease-Free Survival: CONVERT Trial



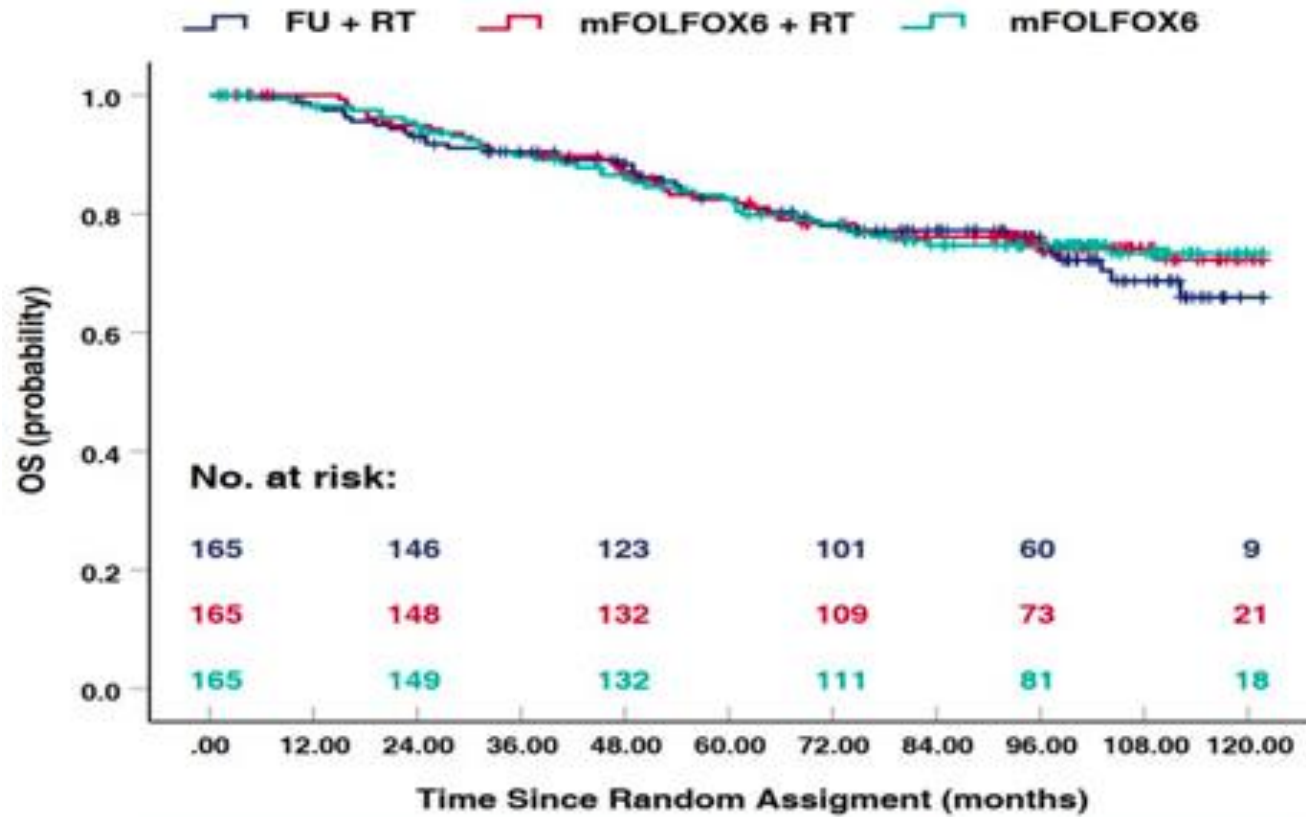
Number at risk

Group	0	12	24	36	48	60
nCRT	289	265	247	225	134	65
nCT	300	269	255	234	147	82

Months from randomization

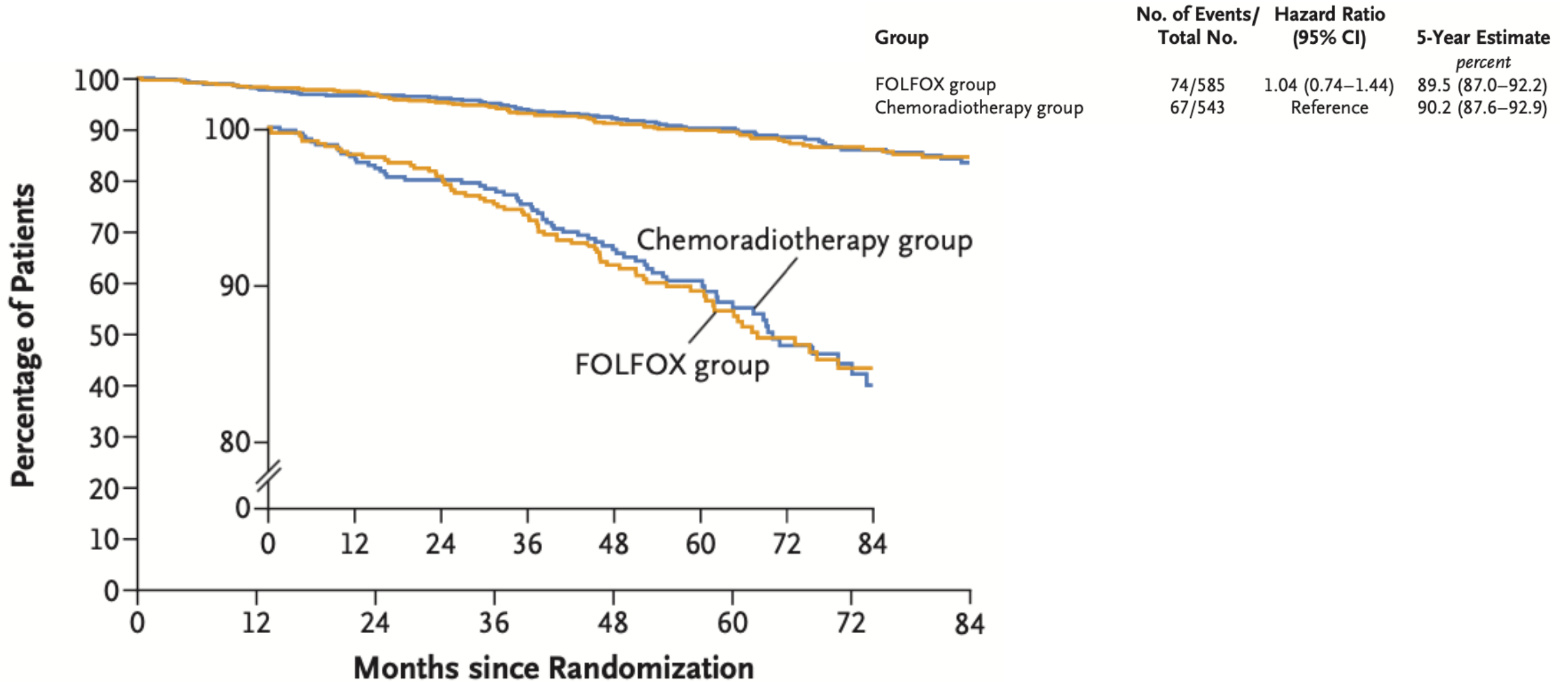
Disease-free survival rates at 3 years	
nCRT	nCT
87.9 (84.1-91.8)	89.2 (85.6-92.9)
Hazard ratio: 0.88 (0.54-1.44)	

Overall Survival: FOWARC Trial

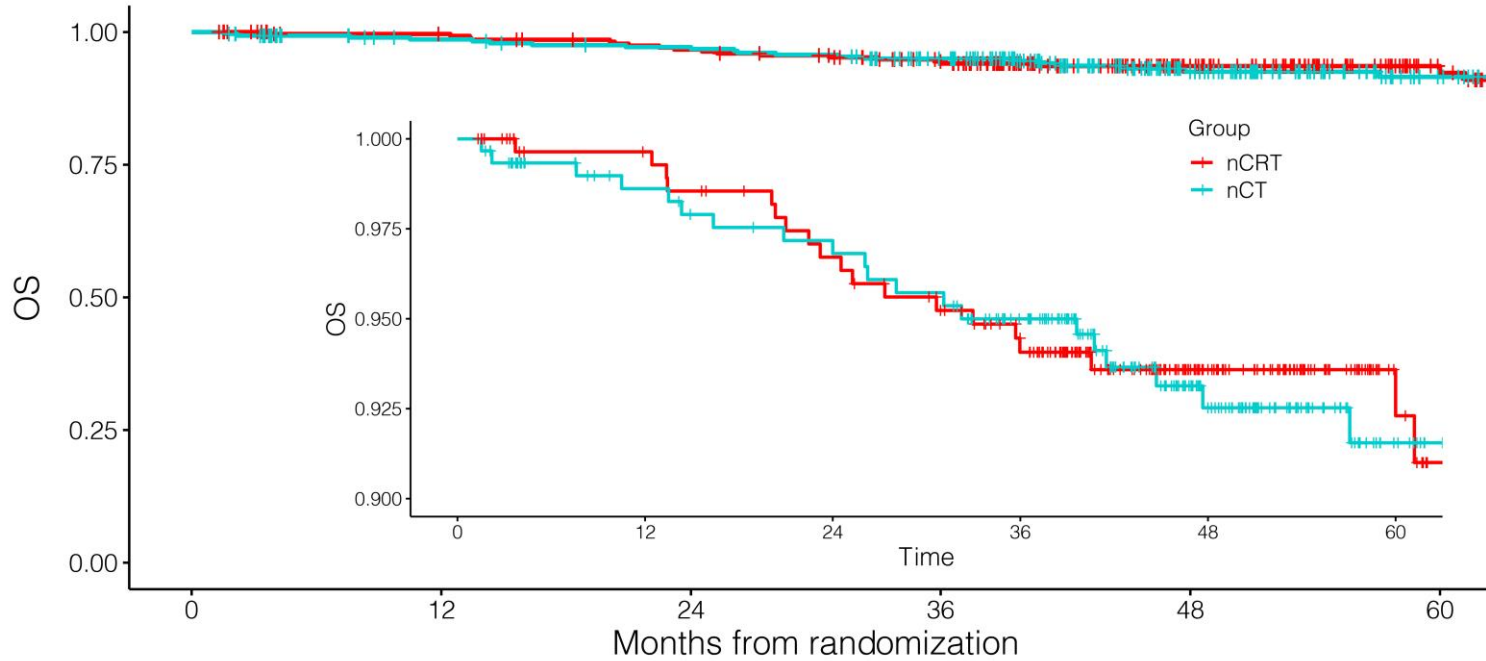


Treatment	5y-OS	10y-OS	HR (95% CI)
FU-RT	82.5%	65.9%	Ref
FOLFOX	81.8%	73.4%	0.91 (0.58-1.41)

Overall Survival: PROSPECT Trial



Overall Survival: CONVERT Trial



Number at risk

Group	0	12	24	36	48	60
nCRT	289	274	263	240	143	73
nCT	300	275	268	247	151	83

Months from randomization

Overall Survival rates at 3 years	
nCRT	nCT
94.1 (91.3-96.9)	95.0 (92.4-97.5)
Hazard ratio: 0.86 (0.42-1.76)	

So what?

If survival outcomes are comparable, why to prefer neoadjuvant chemotherapy over chemoradiation?

Radiation acute and late toxicities

Radiation Oncology

CORE IM | 5 PEARLS

Common Radiation Sites & Side Effects

Radiation effects are **location, depth, & timeframe** specific



Location

What are the nearby structures?



Depth

Is this radiation shallow or deep?



Timeframe

Acute inflammation vs chronic fibrotic changes

Brain

Acute & Chronic

Fatigue
Memory loss

Lung

Acute	Chronic
Pneumonitis	Pulmonary fibrosis
Esophagitis	Esophageal strictures
Acute pericarditis	Myocardial fibrosis

Breast

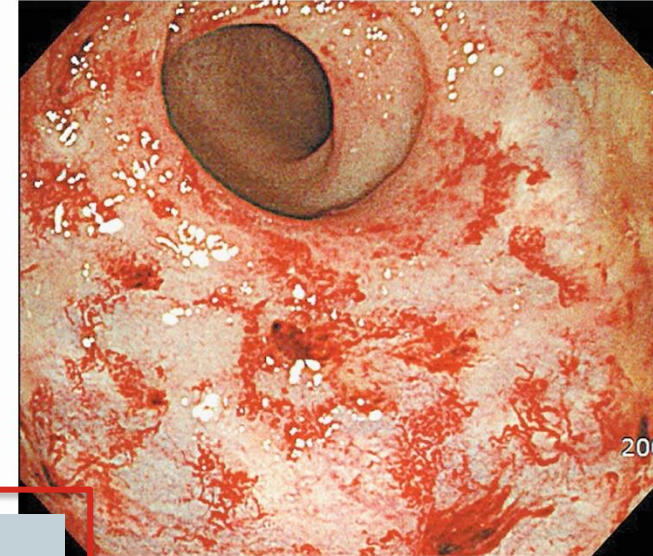
Acute	Chronic
Dermatitis	Scarring and fibrosis

Abdomen/Pelvis

Acute	Chronic
Enteritis	Strictures
Proctitis	Detrusor dysfunction
Colitis	Sexual dysfunction
Cystitis	Infertility

Key Points:

These exist on a spectrum
Many are diagnosis of exclusion



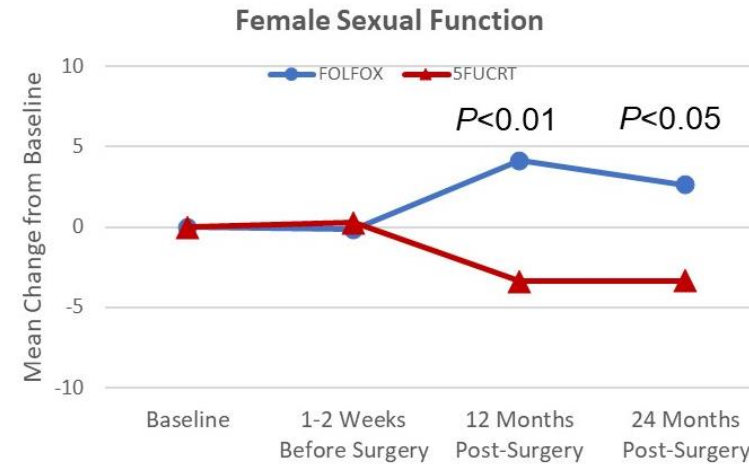
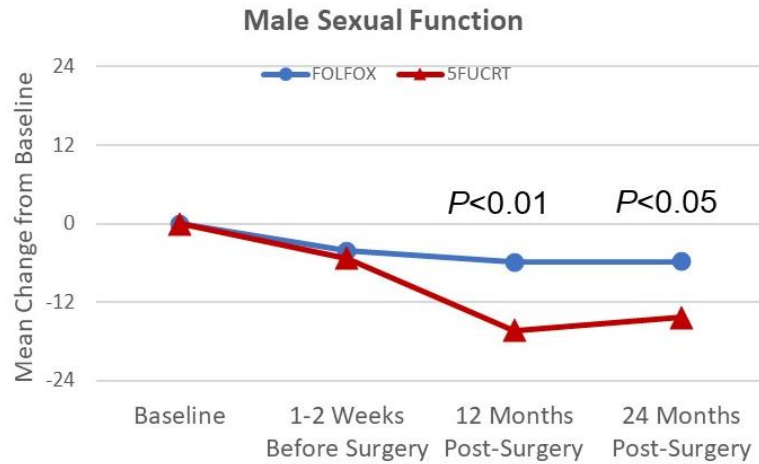
Grade 3-4 Toxicities

	Neoadjuvant Phase		Adjuvant Phase	
	CT	CRT	CT	CRT
PROSPECT	41%	23%	25%	39%
CONVERT	12%	8%	5%	9%

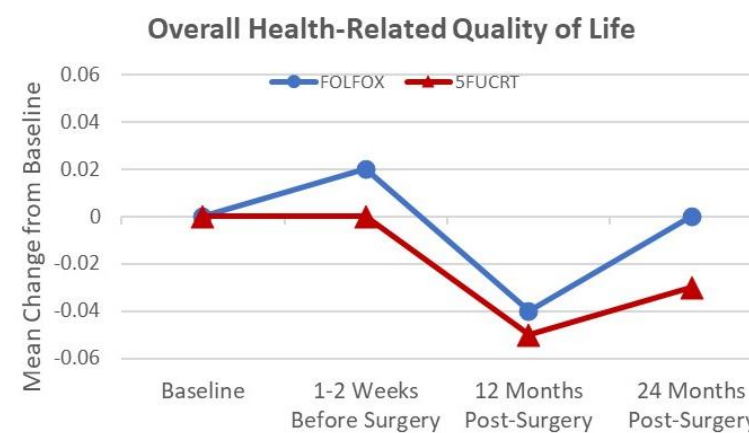
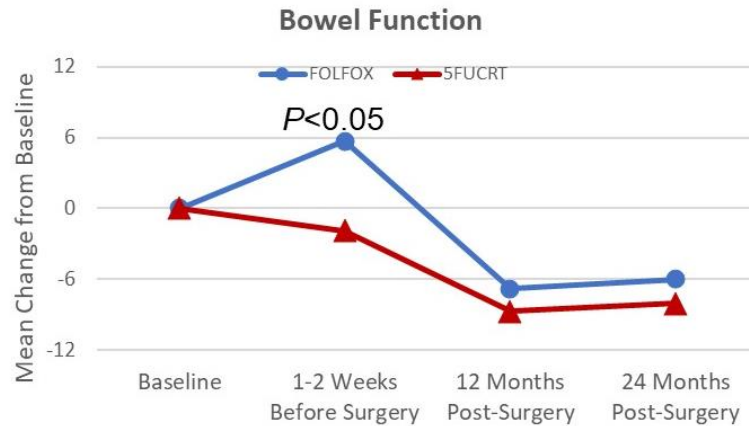
**More acute toxicity in CT arm during the neoadjuvant phase,
but more late toxicity at the end of the whole treatment in CRT arm**

..but what do patients say?

PROSPECT Trial: patient-reported outcomes (PROs)



Sexual and Bowel function favour FOLFOX group



Overall Health-related QoL not significant trend in favour of FOLFOX group

Better long term bowel function without RT

FOWARC Trial: better bowel and anal function in FOLFOX treated

Finding	Fluorouracil Plus Radiotherapy	mFOLFOX	P*
No. of patients	61	89	
Stool frequency, per day			.000
0-3	24 (39.3)	64 (71.9)	
4-5	17 (27.9)	10 (11.2)	
6-9	12 (19.7)	14 (15.7)	
≥ 10	8 (13.1)	1 (1.1)	
Wexner score > 8	25 (41)	16 (18)	.005
Solid incontinence	18 (29.5)	6 (6.7)	.001
Liquid incontinence	20 (32.8)	7 (7.9)	.000
Gas incontinence	10 (16.4)	2 (2.2)	.006
Day incontinence	24 (39.3)	20 (22.5)	.068
Night incontinence	20 (32.8)	8 (9.0)	.001
Anal blood loss	2 (3.3)	3 (3.4)	.252
Use of pads	19 (31.1)	8 (9.0)	.002

What can further improve patients outcome?

TOLERABILITY

Toxicity

QoL

Functionality



EFFICACY

pCR

DFS

OS

The Good, the Bad and the Ugly

The Good:
avoid overtreatment
and go for surgery upfront



The Ugly:
we need more
systemic efficacy

**The Bad: adaptive strategy with RT
only to who needs it**

Any room for efficacy improvement?

- ✓ **Chemotherapy anticipation: TNT Strategy**
- ✓ **Chemotherapy intensification: FOLFOXIRI** (ph III FAVORE, ph III GRECCAR16)
- ✓ **Checkpoint inhibitors:**
 - **MSI-H** (dostarlimab: ph II AZUR-1)
 - **MSS** (camrelizumab: ph III UNION; durvalumab: ph II NSABP FR2, ph II PANDORA; ph II avelumab: AVANA)
- ✓ **New target therapies? RAS inhibitors, BRAF inhibitors..?**

In the meantime, we can only work to reduce adverse effects..

...and the adaptive PROSPECT trial strategy, giving RT only to patients who really need it, it's perfect for us!



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