Neoadjuvant Treatment in Rectal cancer

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Neoadjuvant Treatment in Rectal cancer

- Why neoadjuvant treatment is needed in Rectal cancer.
- Preoperative versus Postoperative CRT for Rectal Cancer.
- Preoperative RT with or without CT as Neoadjuvant treatment in Rectal Cancer.
- Capecitabine versus 5-FU based CRT as Neoadjuvant treatment in Rectal Cancer.
- Should Oxaliplatin be added to Preoperative RT plus 5-FU/Capecitabine in locally advanced Rectal cancer?
- Role of addition of Anti EGFR Abs with Preop. CRT in locally advanced Rectal Cancer?
- Role of Total Neoadjuvant Treatment (TNT) in locally advanced rectal cancer.
- Short course RT followed by induction chemotherapy Vs. Long course CRT as Neo-adjuvant treatment in locally advanced rectal cancer.

Neoadjuvant Treatment in Rectal cancer

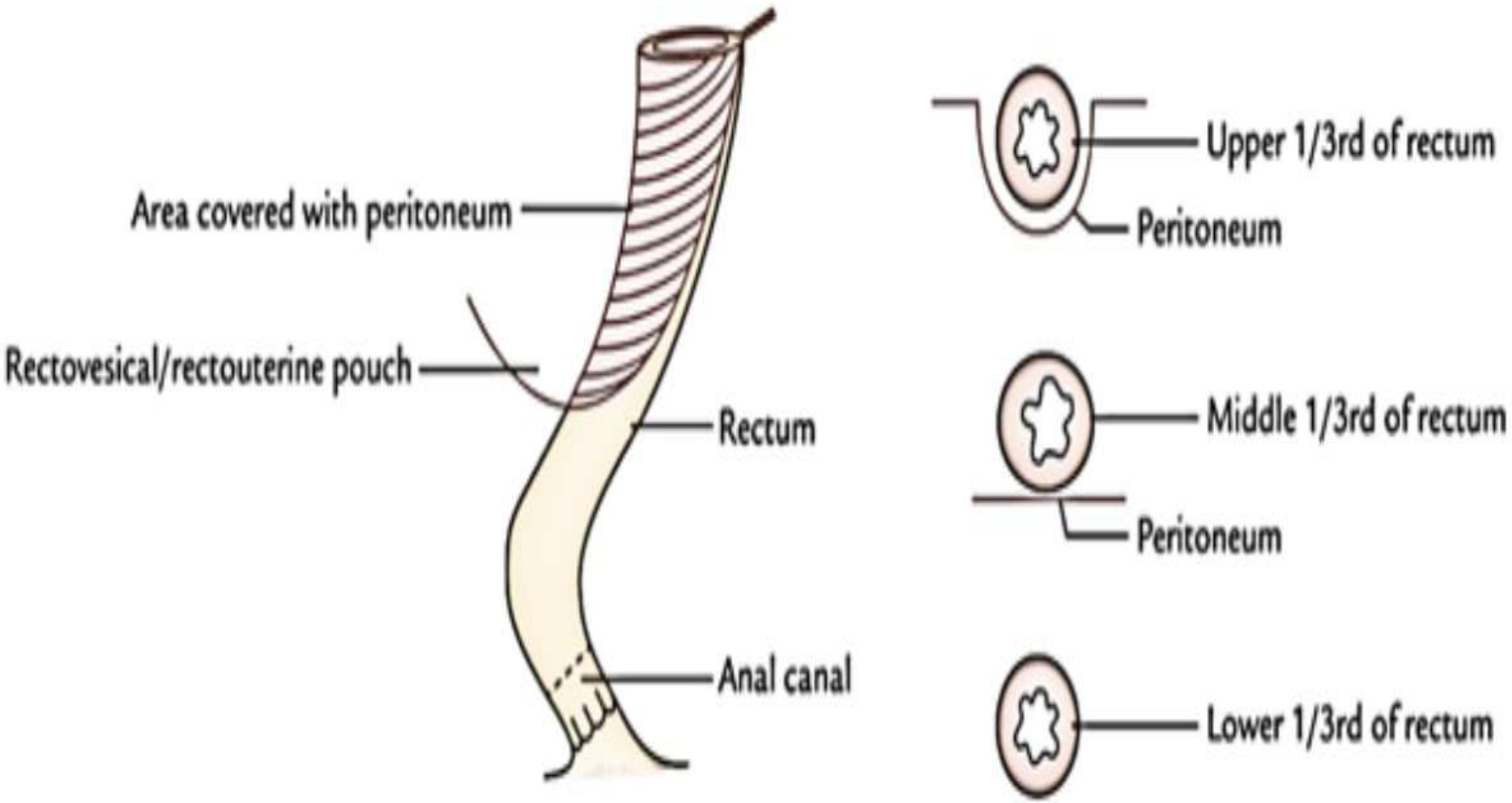
Why neoadjuvant treatment is needed in cancer of rectum?

- Locally advanced cases have high chances of locoregional recurrence after surgical management.
- Anatomical characteristics of Rectum.
- Close proximity of rectum to other pelvic organs.
- Technical difficulties to obtain wide negative margins during surgical resection.

Why neoadjuvant treatment is needed in cancer of rectum?

- Upper 1/3 rectum is covered with peritoneum anteriorly and laterally.
- Middle 1/3 rectum is covered is with peritoneum only anteriorly.
- Lower 1/3 rectum is devoid of peritoneum.
- So mid and lower rectum are very close to nearby structures and it is very difficult for surgeons to obtain surgically negative margins especially circumferential or radial margins.
- So Either Preoperative RT/CT or Postoperative RT/CT are the options to decrease the chances of locoregional recurrence after definitive surgical management.

Why neoadjuvant treatment is needed in cancer of rectum?
Anatomical characteristics of Rectum



Neoadjuvant treatment in Rectal Cancer

Why Preoperative CRT is better than Postoperative CRT ?

Preoperative versus Postoperative CRT for Rectal Cancer (German Rectal Cancer Study Group)

- 421 patients of T3,T4 or N+ rectal cancer were randomly assigned to following groups.

- Preoperative CRT with 50.4 Gy in 28 fractions EBRT with continuous infusion 5-FU 1000 mg/m^2 iv for 120 hours on week 1 & 5 of RT followed by surgery and then 4 cycles of 5 FU based chemotherapy.

- In Postoperative arm same CRT was given postoperatively along with boost RT dose of 540 cGy to the tumor bed followed by 4 cycles of 5-FU based adjuvant chemotherapy.

- Primary end point was over-all survival (OS).

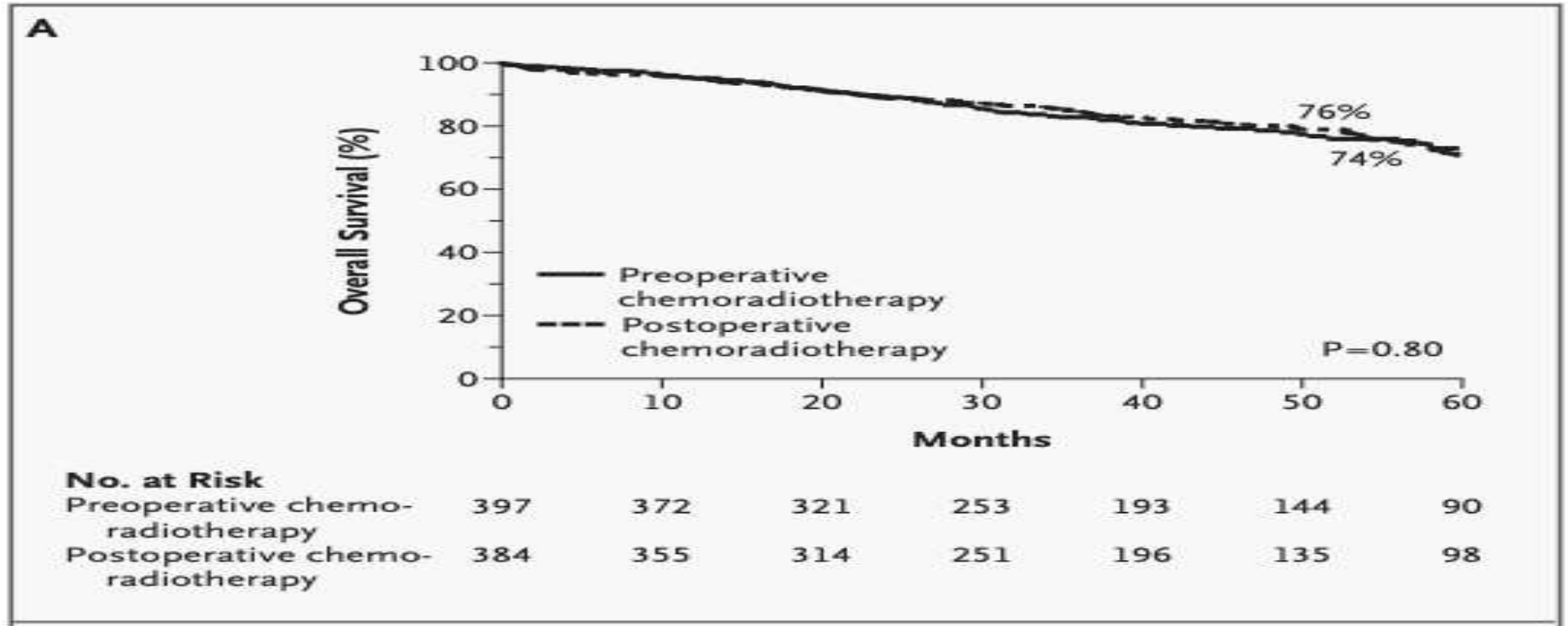
Preoperative versus Postoperative CRT for Rectal Cancer (German Rectal Cancer Study Group)

Variable	Preoperative Chemoradiotherapy	Postoperative Chemoradiotherapy	P Value
Randomly assigned — no.	421	402	
Included in full analysis population — no.	405	394	0.12
Requested change in treatment group — no.	9	19	0.05
Included in treated population — no.	415	384	
Received full dose of radiotherapy — no. (%)	380 (92)	206 (54)	<0.001
Received full dose of chemotherapy — no. (%)	369 (89)	193 (50)	<0.001
Did not receive chemoradiotherapy — no. (%)			
Stage I disease	NA	71 (18)	<0.001
Other reason†	1 (<1)	39 (10)	<0.001
Received radiotherapy with modification — no. (%)‡	19 (5)	31 (8)	0.04
Received chemotherapy with modification — no. (%)‡	23 (6)	26 (7)	0.47
Protocol violations — no. (%)§			
Radiotherapy	13 (3)	33 (9)	0.001
Chemotherapy	15 (4)	49 (13)	<0.001
Missing data — no. (%)			
Radiotherapy	2 (<1)	4 (1)	0.36
Chemotherapy	7 (2)	6 (2)	0.89

Preoperative versus Postoperative CRT for Rectal Cancer (German Rectal Cancer Study Group)

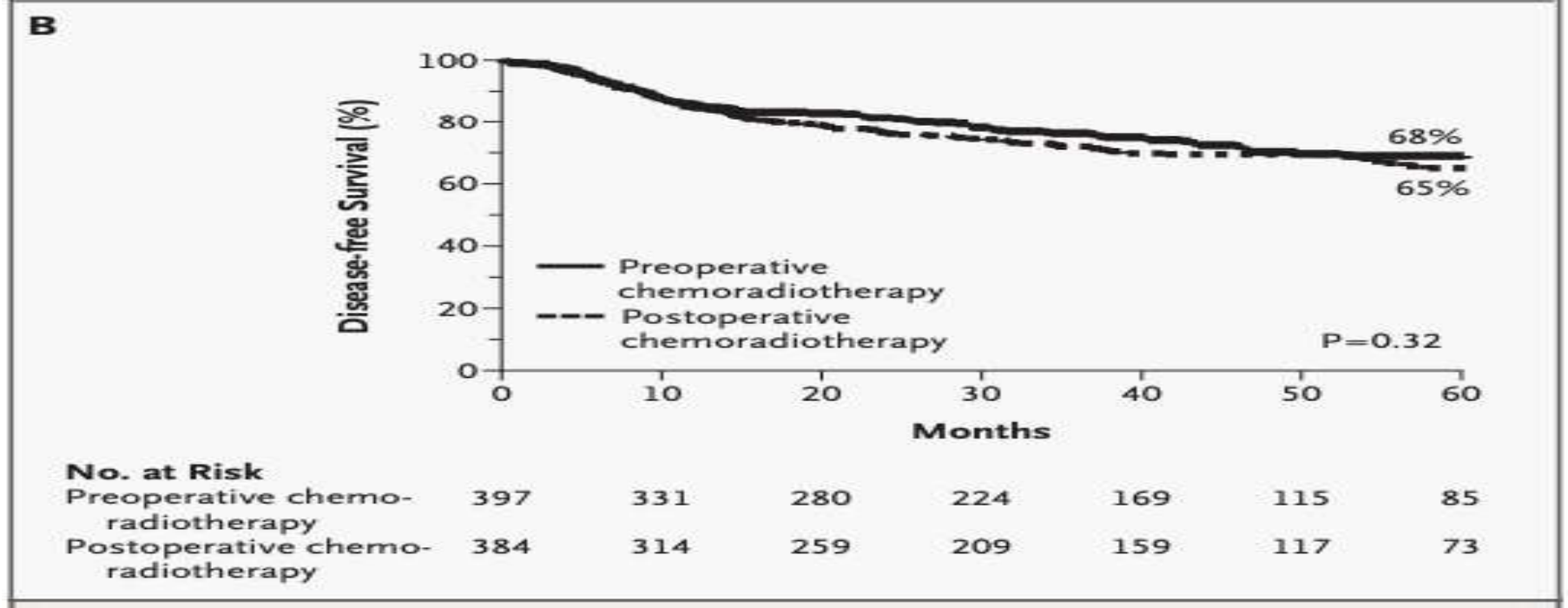
Type of Toxic Effect	Preoperative Chemoradiotherapy (N=399)	Postoperative Chemoradiotherapy (N=237)	P Value
	% of patients		
Acute			
Diarrhea	12	18	0.04
Hematologic effects	6	8	0.27
Dermatologic effects	11	15	0.09
Any grade 3 or 4 toxic effect	27	40	0.001
Long-term			
Gastrointestinal effects†	9	15	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

* All patients who received any preoperative or postoperative radiotherapy according to protocol were included in this



No. at Risk

Preoperative chemoradiotherapy	397	372	321	253	193	144	90
Postoperative chemoradiotherapy	384	355	314	251	196	135	98



No. at Risk

Preoperative chemoradiotherapy	397	331	280	224	169	115	85
Postoperative chemoradiotherapy	384	314	259	209	159	117	73

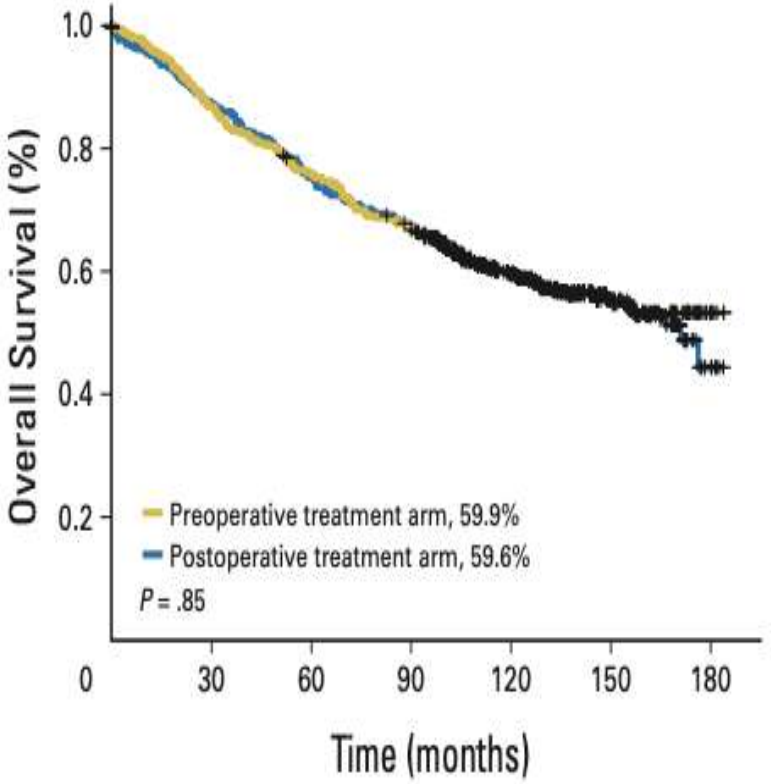
CAO/ARO/AIO-94 Trial

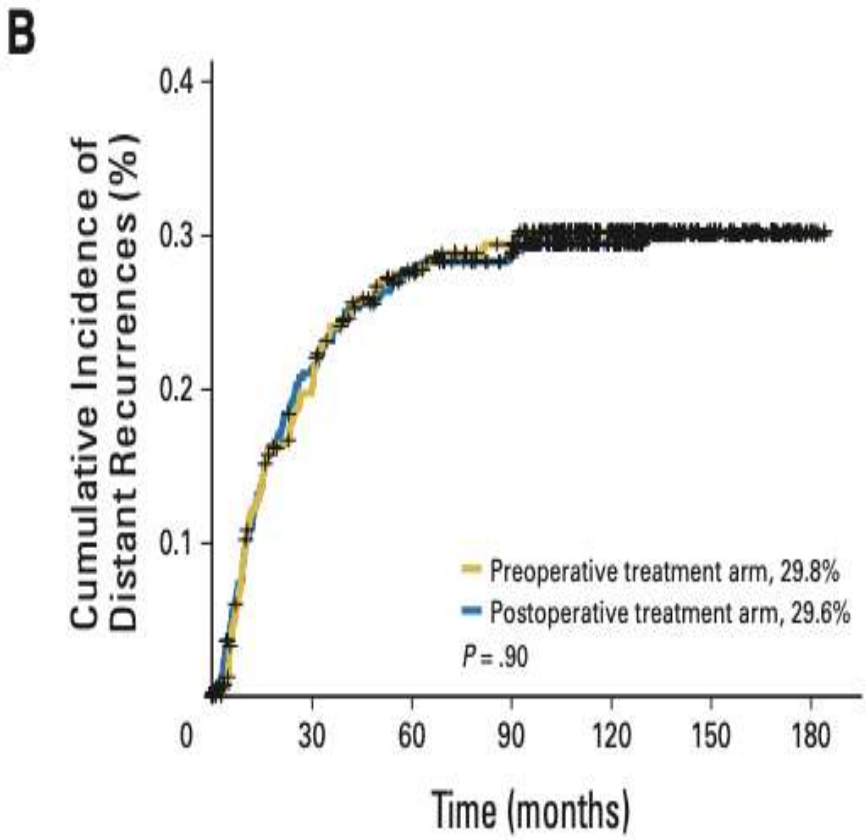
- 823 patients with stage II to III rectal cancer were randomly assigned to preoperative CRT with fluorouracil (FU), followed by TME, and adjuvant FU chemotherapy, or the same schedule of CRT used postoperatively.

- The study was designed to have 80% power to detect non inferiority margin of 10% in 5-year overall survival as the primary end point.

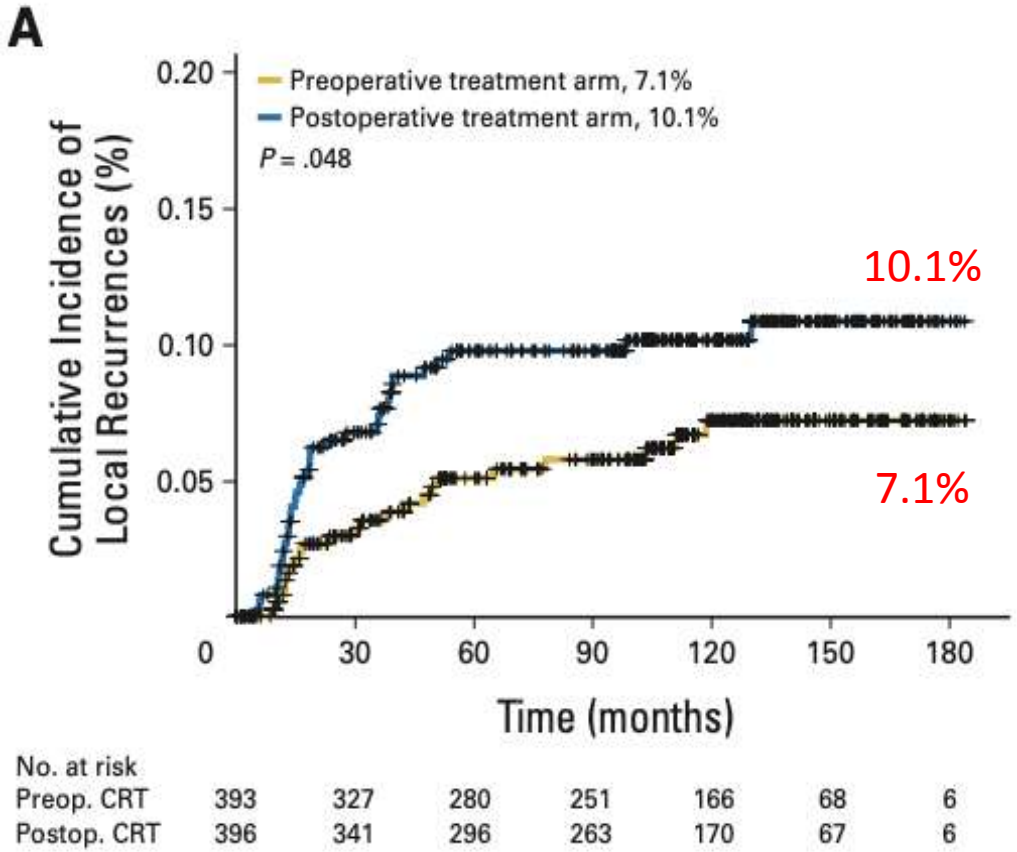
- Secondary end points included the cumulative incidence of local and distant relapses and disease-free survival.

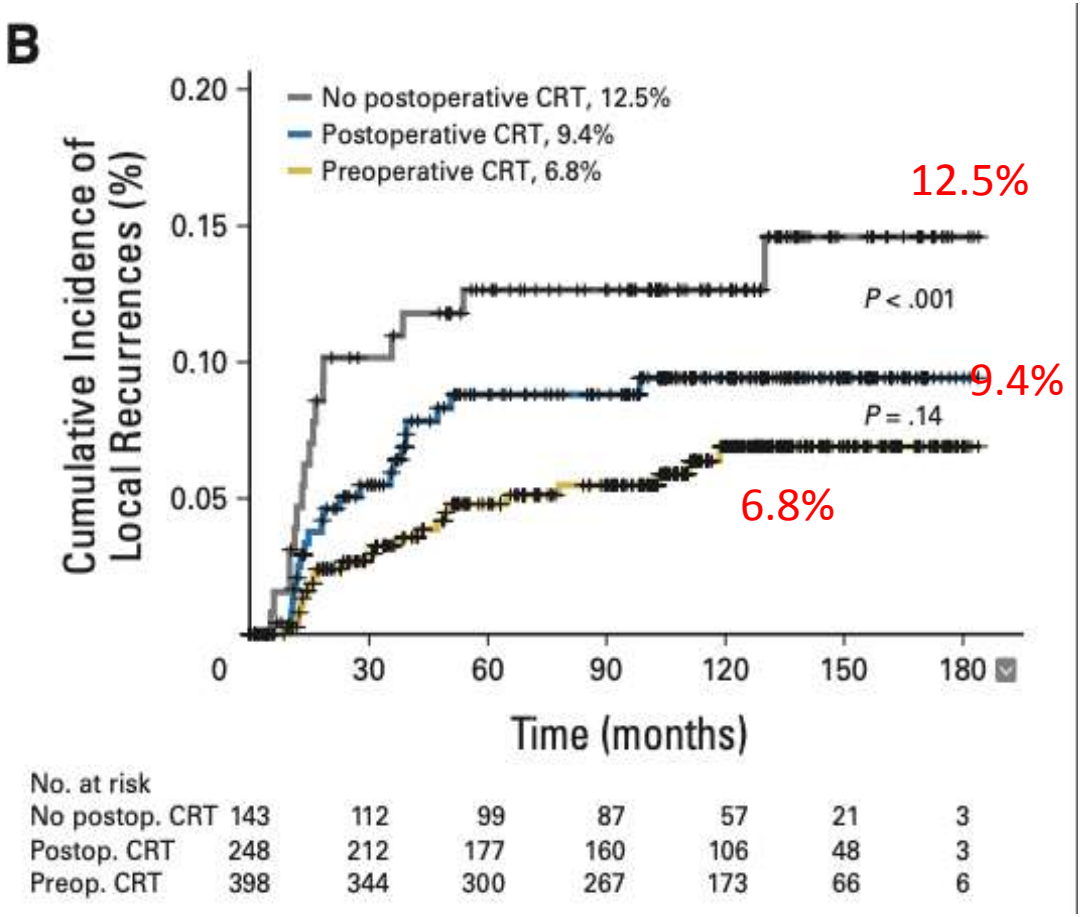
CAO/ARO/AIO-94 Trial



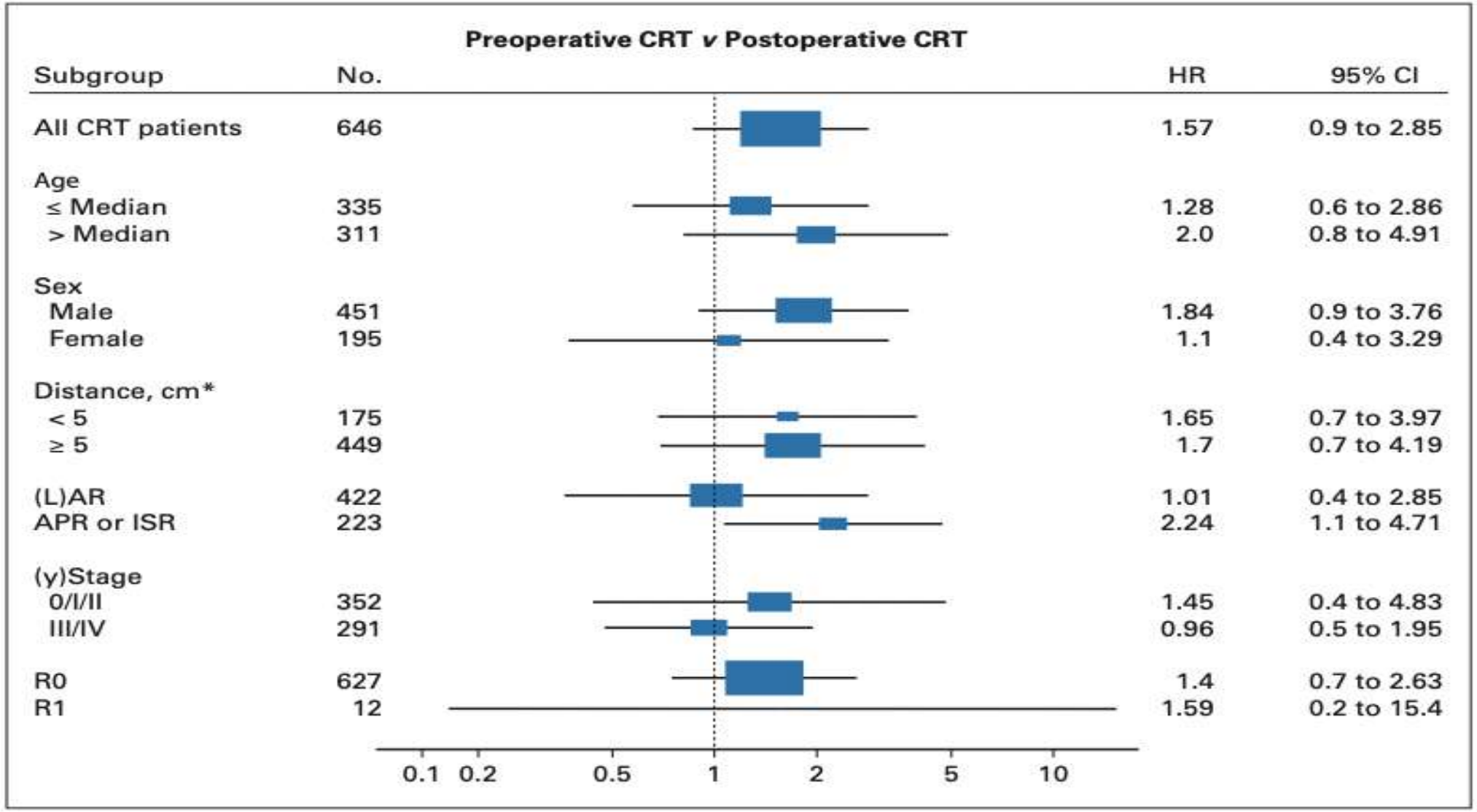


CAO/ARO/AIO-94 Trial





CAO/ARO/AIO-94 Trial
HR of local recurrence for preoperative and postoperative Radiotherapy



Preoperative CRT versus postoperative CRT in Rectal Cancer

- **Preoperative CRT has certain advantages than postoperative CRT**

1. Preoperative CRT results in significant decrease in local recurrence.

2. Preoperative CRT has less toxicity than postoperative CRT (27% vs. 40%; $P = .001$).

3. Improvement in Locoregional control also persisted over 10 years.

4. OS and DFS remains the same with both treatment arms.

5. Increases chances of sphincter preservation.

Preoperative CRT versus postoperative CRT in Rectal Cancer

- **Additional advantages of Preoperative CRT over postoperative RT**

A. Downstaging and facilitates tumor resection.

B. Surgically naïve and better oxygenated tumors are more responsive to preoperative CRT than postoperative CRT.

C. Less injury to small bowel in preoperative CRT

D. Better compliance as compared to postoperative CRT

Preoperative RT with or without CT as Neoadjuvant treatment in Rectal Cancer

Will adding CT to preoperative RT be a better option than Preoperative RT alone ?

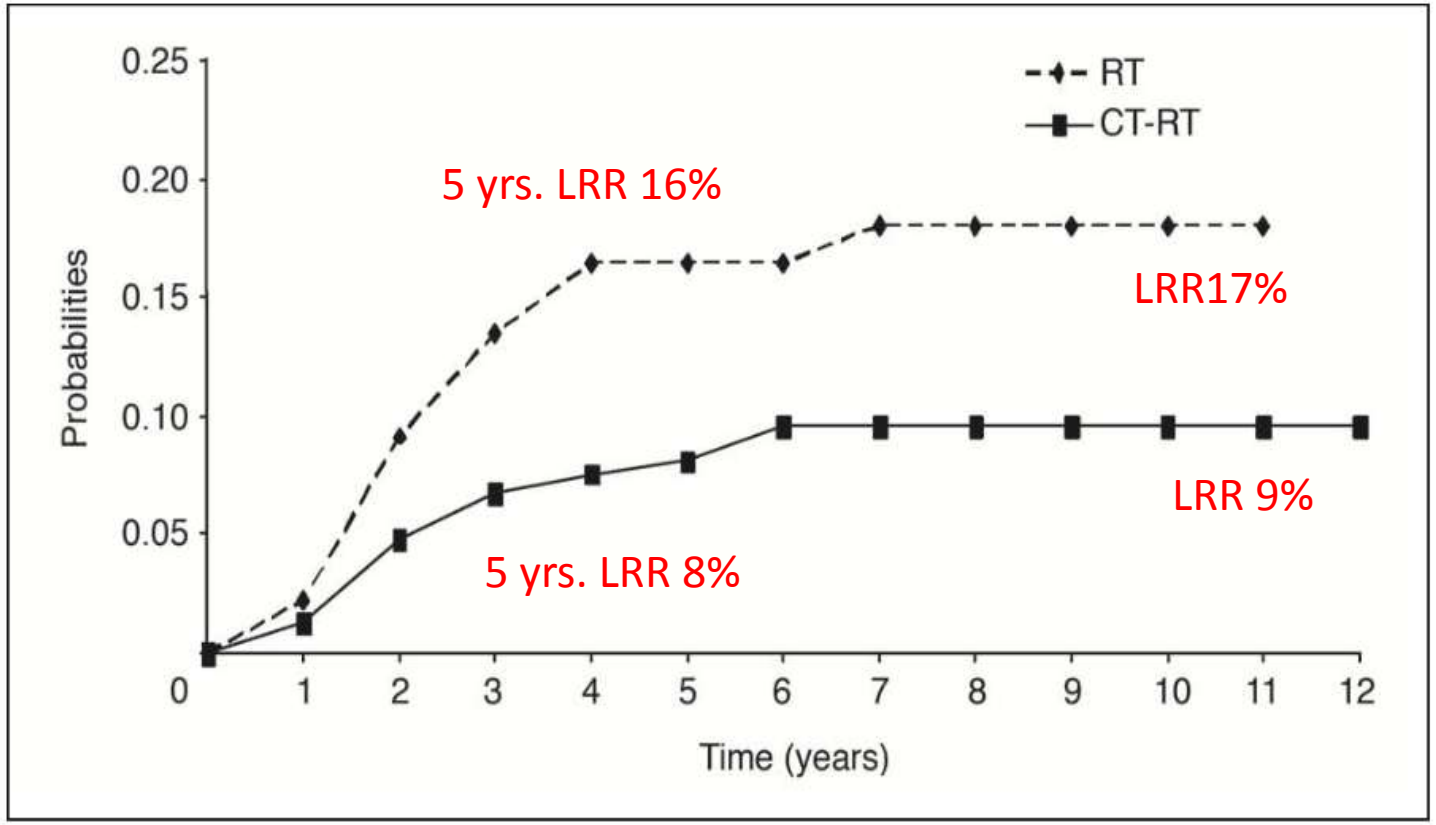
Preoperative RT with or without concurrent CT in T3-4 rectal cancers: FFCD-9203 trial

- 733 Patients having resectable T3-4, Nx, M0 rectal adenocarcinoma accessible to digital rectal examination were included in the study.
- Preoperative radiotherapy with 45Gy/25 fractions/5 weeks was delivered.
- Concurrent chemotherapy with fluorouracil 350 mg/m2/d together with 20 mg/m2/d leucovorin for 5 days was administered during the first and fifth week in the experimental arm.
- Surgery was planned 3 to 10 weeks after the end of radiotherapy. All patients should receive adjuvant chemotherapy with the same fluorouracil/leucovorin regimen.
- The primary end point of the trial was overall survival.

Preoperative RT with or without concurrent CT in T3-4 rectal cancers: FFCD 9203 trial

- Complete sterilization of the operative specimen was more frequent with chemoradiotherapy (11.4% Vs. 3.6%; P < .05).
- The 5-year incidence of local recurrence was lower with chemoradiotherapy (8.1% Vs. 16.5%; P < .05).
- Grade 3 or 4 acute toxicity was more frequent with chemoradiotherapy (14.6% Vs. 2.7%; P < .05).
- Overall 5-year survival in the two groups did not differ.

Cumulative incidence of local recurrence between preoperative radiotherapy (RT) and pre- operative chemotherapy and radiotherapy (CT-RT)



Preoperative RT with or without concurrent CT in resectable T3-4 rectal cancers: EORTC 22921 Trial

- 1011 Patients were allocated to the following four arms:
- Arm 1, preop RT 45 Gy/25f/5 weeks.
- Arm 2, preop RT plus two 5-day CT courses (fluorouracil 350 mg/m2/d and leucovorin 20 mg/m2/d for 5 days) in the first and fifth week of RT.
- Arm 3, preop RT plus four postoperative CT courses.
- Arm 4, preop RT and CT plus postoperative CT.
- Analysis was done regarding differences in tumor size, tumor node stage, number of retrieved nodes, and histologic features such as lymphatic, venous, and perineural invasions, tumor differentiation, and tumor type.

Pathological characteristics after Preoperative RT versus Preop. RT + CT in Rectal cancer: EORTC 22921

Characteristic	RT Group (n = 476)		RT-CT Group (n = 473)		P
	No. of Patients	%	No. of Patients	%	
Tumor size, mm					
Median	30.0		25.0		< .0001
90% range	10.0-70.0		8.0-110.0		
Tumor stage					
0	25	5.3	65	13.7	< .001
1	36	7.6	49	10.4	
2	141	29.6	156	33.0	
3	233	48.9	175	37.0	
4	25	5.3	18	3.8	
Missing	16	3.4	10	2.1	
Nodes					
Total examined, No.					
Mean	9		7		.046
Range	0.0-45.0		0.0-39		
N0	288	60.5	340	71.9	
N1	108	22.7	84	17.8	
N2	57	12.0	34	7.2	< .001
Missing	23	4.8	15	3.2	
Positive in all patients, No.					
Mean	1.52		0.86		< .0001
SD	0.16		0.10		
Metastases status at surgery					
M0	442	92.9	436	92.2	
M1	20	4.2	22	4.7	
Missing	14	2.9	15	3.2	

pCR

pCR

Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer : Cochrane meta-analysis

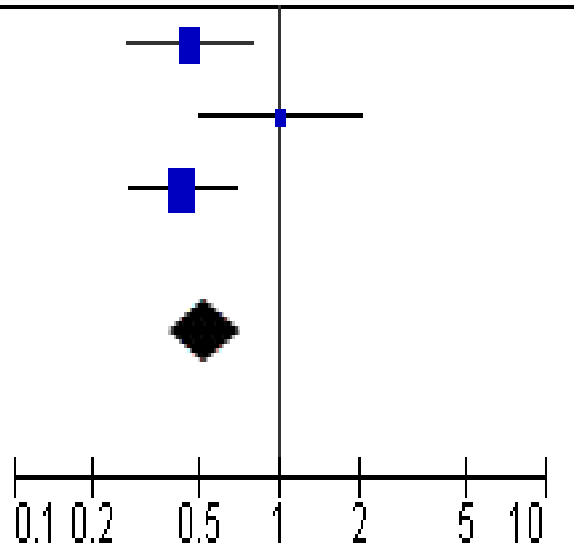
- This meta-analysis has summarized the results of five studies that compared preoperative RT alone with preoperative CRT in rectal cancer patients.
- All of these studies were randomized.
- Preoperative CRT is more effective in causing tumour shrinkage (downstaging), and in preventing local recurrence of the disease.
- However, addition of chemotherapy did not result in more sphincter preserving surgeries, and did not affect the overall survival in rectal cancer patients.
- Compared to RT alone, preoperative CRT leads to increased side effects during treatment.

Cochrane meta-analysis: OR of Local recurrence comparing Preop. RT versus preop. CRT in rectal cancer

Study or Subgroup	CRT Events	CRT Total	RT Events	RT Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bosset 2006	22	253	43	252	35.2%	0.46 [0.27, 0.80]
Boulis-Wassif 1984	19	126	18	121	14.0%	1.02 [0.51, 2.04]
Gerard 2006	30	375	61	367	50.8%	0.44 [0.27, 0.69]
Total (95% CI)		**754**		**740**	**100.0%**	**0.53 [0.39, 0.72]**
Total events	71		122			

Heterogeneity: $Chi^2 = 4.24$, $df = 2$ ($P = 0.12$); $I^2 = 53\%$

Test for overall effect: $Z = 4.03$ ($P < 0.0001$)



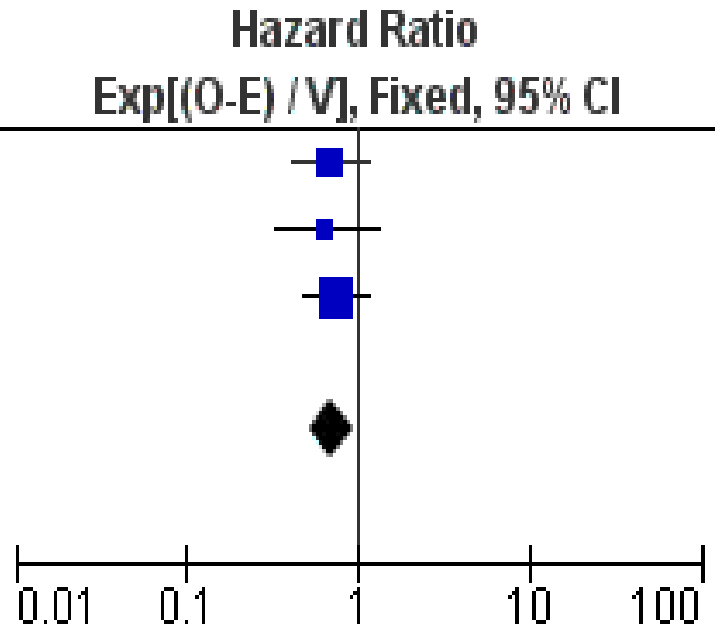
Cochrane meta-analysis: HR of Local recurrence comparing Preop. RT versus preop. CRT in rectal cancer

Study or Subgroup	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Bosset 2006	34.1%	0.69 [0.41, 1.15]
Bujko 2006	18.7%	0.65 [0.33, 1.30]
Gerard 2006	47.1%	0.74 [0.48, 1.15]
Total (95% CI)	**100.0%**	**0.71 [0.52, 0.95]**

Total events

Heterogeneity: $Chi^2 = 0.12$, $df = 2$ ($P = 0.94$); $I^2 = 0\%$

Test for overall effect: $Z = 2.28$ ($P = 0.02$)

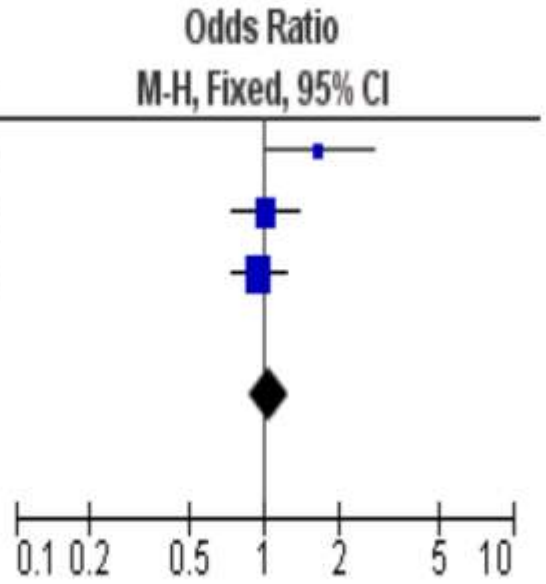


Cochrane meta-analysis: odds ratio of Overall Survival comparing Preop. RT versus preop. CRT in rectal cancer

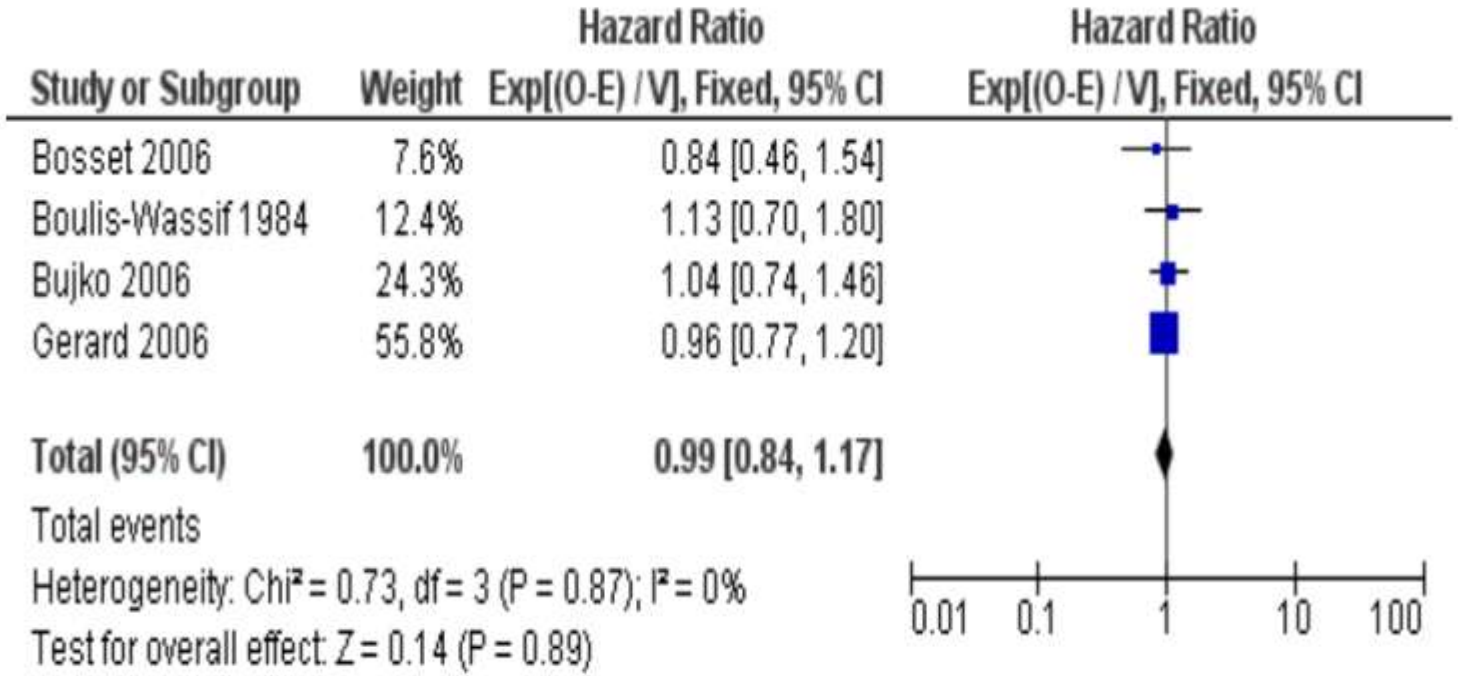
Study or Subgroup	CRT Events	CRT Total	RT Events	RT Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Boulis-Wassif 1984	68	126	50	121	10.6%	1.66 [1.01, 2.75]	1984
Gerard 2006	122	375	118	367	36.4%	1.02 [0.75, 1.38]	2006
Bosset 2006	173	506	178	505	53.0%	0.95 [0.74, 1.24]	2006
Total (95% CI)		**1007**		**993**	**100.0%**	**1.05 [0.88, 1.27]**	
Total events	363		346				

Heterogeneity: $Chi^2 = 3.78$, $df = 2$ ($P = 0.15$); $I^2 = 47\%$

Test for overall effect: $Z = 0.55$ ($P = 0.58$)



Cochrane meta-analysis: HR of DFS comparing Preop. RT versus preop. CRT in rectal cancer

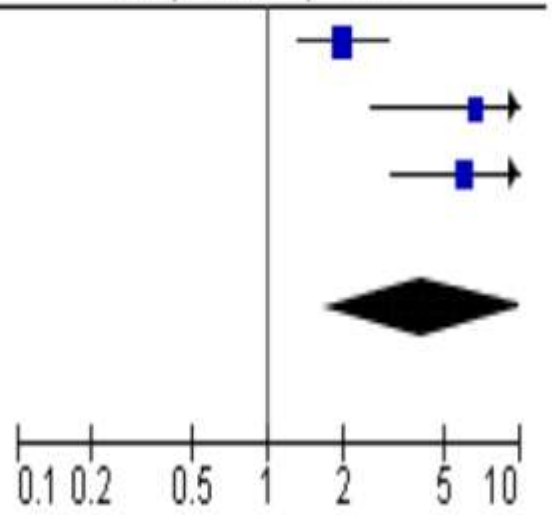


Cochrane meta-analysis: odds ratio of grade III/IV toxicity comparing Preop. RT versus preop. CRT in rectal cancer

Study or Subgroup	CRT Events	CRT Total	RT Events	RT Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosset 2006	67	483	37	495	38.4%	1.99 [1.31, 3.04]
Bujko 2006	29	157	5	155	28.0%	6.80 [2.56, 18.07]
Gerard 2006	55	375	10	367	33.6%	6.14 [3.08, 12.24]
Total (95% CI)		**1015**		**1017**	**100.0%**	**4.10 [1.68, 10.00]**
Total events	151		52			

Heterogeneity: $Tau^2 = 0.49$; $Chi^2 = 10.57$, df = 2 (P = 0.005); $I^2 = 81\%$

Test for overall effect: Z = 3.10 (P = 0.002)

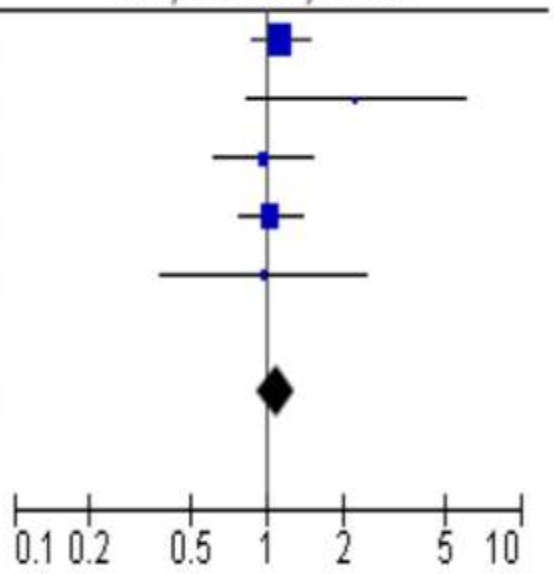


Cochrane meta-analysis: odds ratio of sphincter preservation comparing Preop. RT versus preop. CRT in rectal cancer

Study or Subgroup	CRT Events	CRT Total	RT Events	RT Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosset 2006	263	473	249	475	45.0%	1.14 [0.88, 1.47]
Boulis-Wassif 1984	13	124	6	121	2.9%	2.24 [0.82, 6.11]
Bujko 2006	87	157	87	155	14.7%	0.97 [0.62, 1.52]
Gerard 2006	188	357	185	357	34.1%	1.03 [0.77, 1.39]
Latkauskas 2011	32	46	26	37	3.3%	0.97 [0.38, 2.49]
Total (95% CI)		**1157**		**1145**	**100.0%**	**1.09 [0.92, 1.30]**
Total events	583		553			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.54$, $df = 4$ ($P = 0.64$); $I^2 = 0\%$

Test for overall effect: $Z = 1.00$ ($P = 0.32$)



Preoperative RT with or without CT as Neoadjuvant treatment in Rectal Cancer

- **Preoperative CRT is better than preoperative RT alone**

1. Significantly decreased chances of local recurrence.
2. Significantly increased chances of pCR.
3. Significantly increased chances of grade III/IV toxicity.
4. Early handling of micro-metastasis.
5. There is no statistically significant difference in 5 yrs. OS and DFS between both arms.
6. No much effect on sphincter preservation.

Capecitabine versus 5-FU based chemotherapy with RT as Neoadjuvant treatment in Rectal Cancer

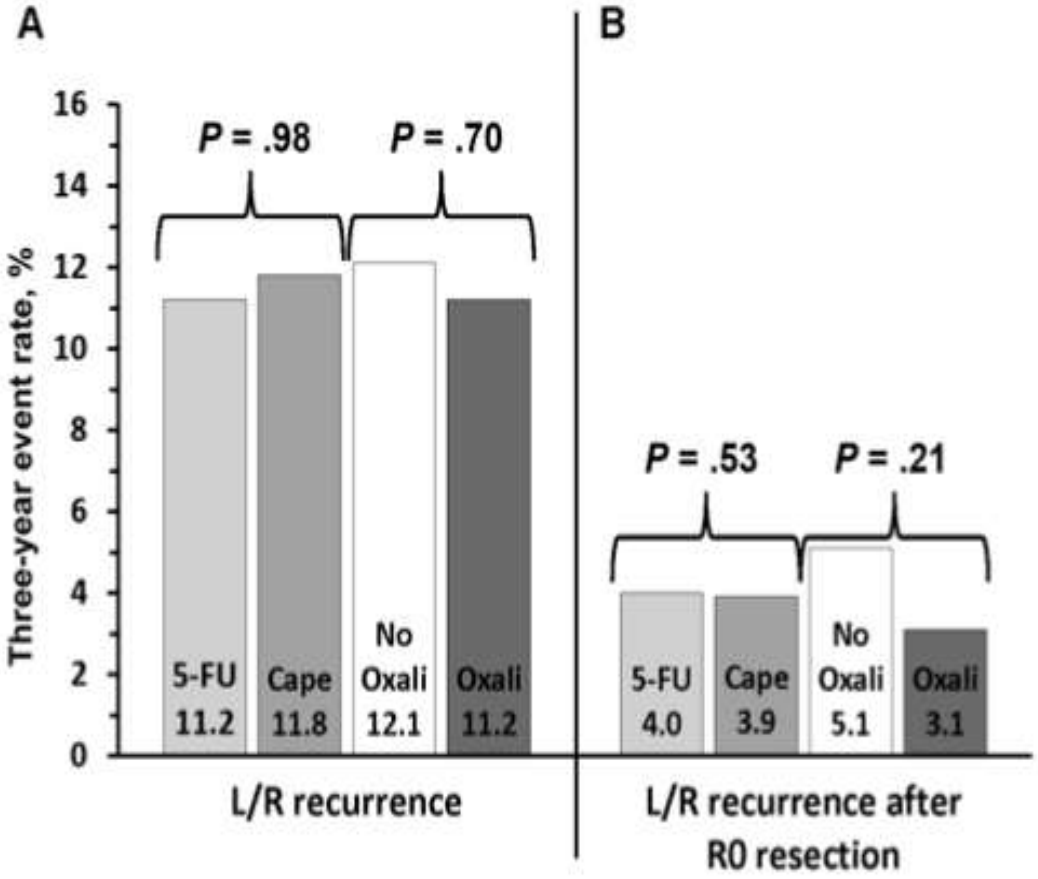
Whether Capecitabine may be used in place of 5-FU/LV based chemotherapy concurrently with RT?

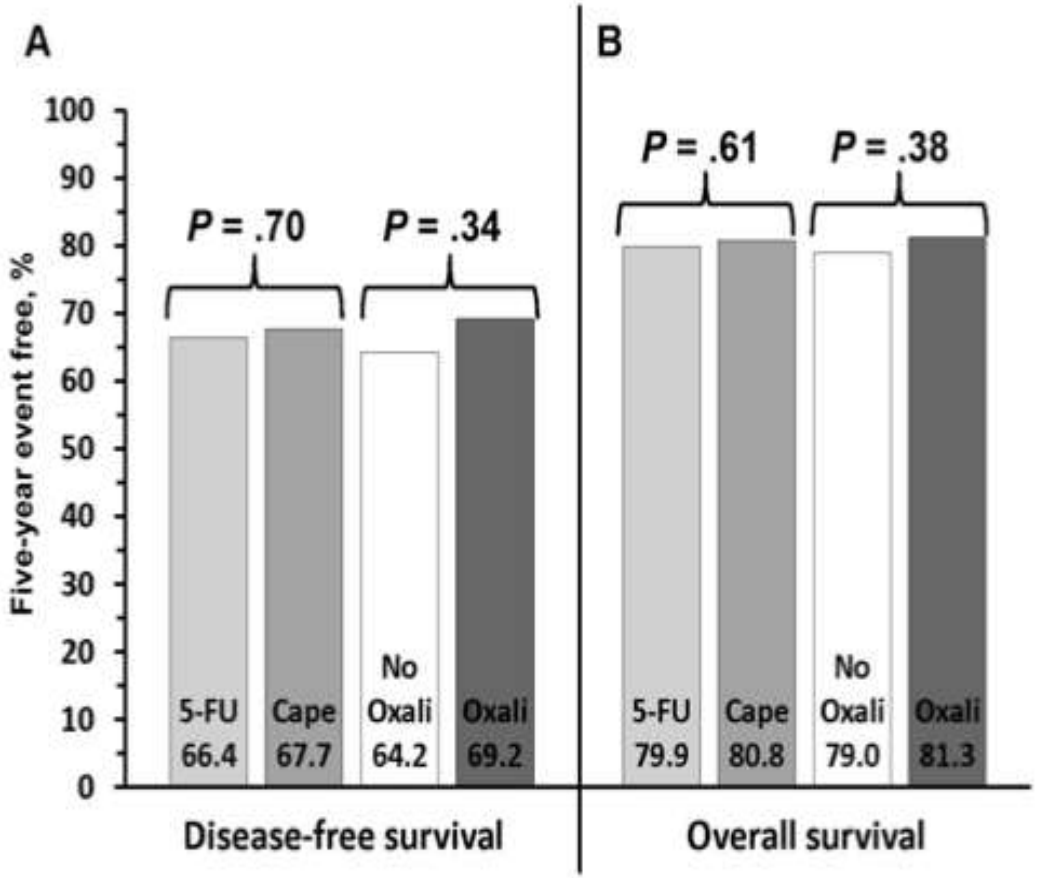
Neoadjuvant 5-FU or Capecitabine Plus RT With or Without Oxaliplatin in Rectal Cancer Patients: NSABP-R4 trial

Patients with clinical stage II or III rectal cancer undergoing preoperative radiation were randomly assigned to one of four chemotherapy regimens in a 2x2 design:

- Central Venous Infusion 5-FU or oral capecitabine with or without oxaliplatin.
- The primary endpoint was loco-regional tumor control at 3 years.
- The secondary endpoints of this study were overall survival (OS), disease-free survival (DFS), and time to loco-regional recurrence (TLRR).
- Time-to-event endpoint distributions were estimated using the Kaplan-Meier method.
- Hazard ratios were estimated from Cox proportional hazard models.

Neoadjuvant 5-FU or Capecitabine Plus RT With or Without Oxaliplatin in Rectal Cancer Patients: NSABP-R4 trial

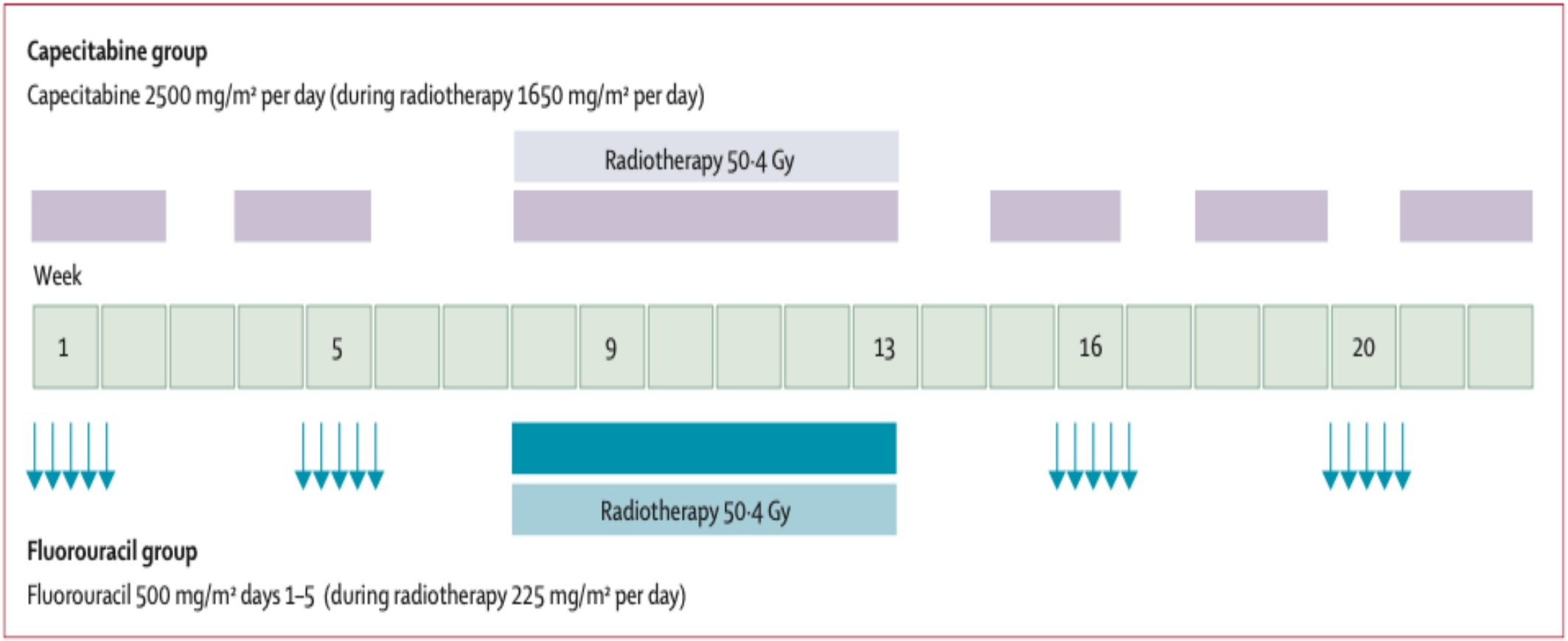




CRT with capecitabine versus 5-FU for locally advanced rectal cancer: multicentric, non-inferiority, phase III RCT

- Patients aged 18 years or older with pathological stage II–III locally advanced rectal cancer from 35 German institutions were enrolled into the study.
- Patients were randomly assigned to treatment group in a 1:1 ratio using permuted blocks, with stratification by centre and tumour stage.
- The primary endpoint was overall survival.
- Analyses were done based on all patients with post-randomisation data.
- Non-inferiority of capecitabine was tested with a 12·5% margin in terms of 5-year overall survival.

CRT with capecitabine versus 5-FU for locally advanced rectal cancer: multicentric, non-inferiority, phase III RCT



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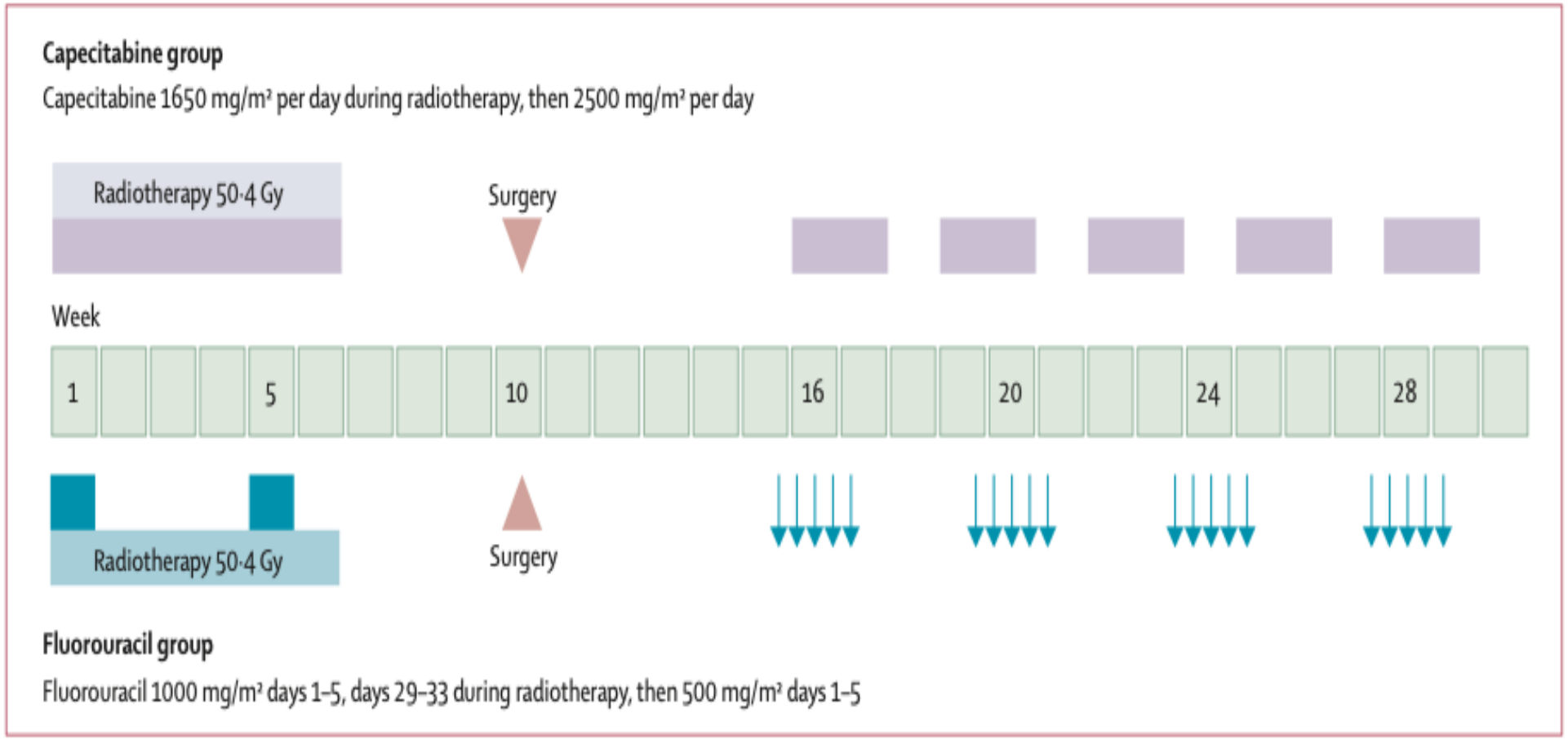
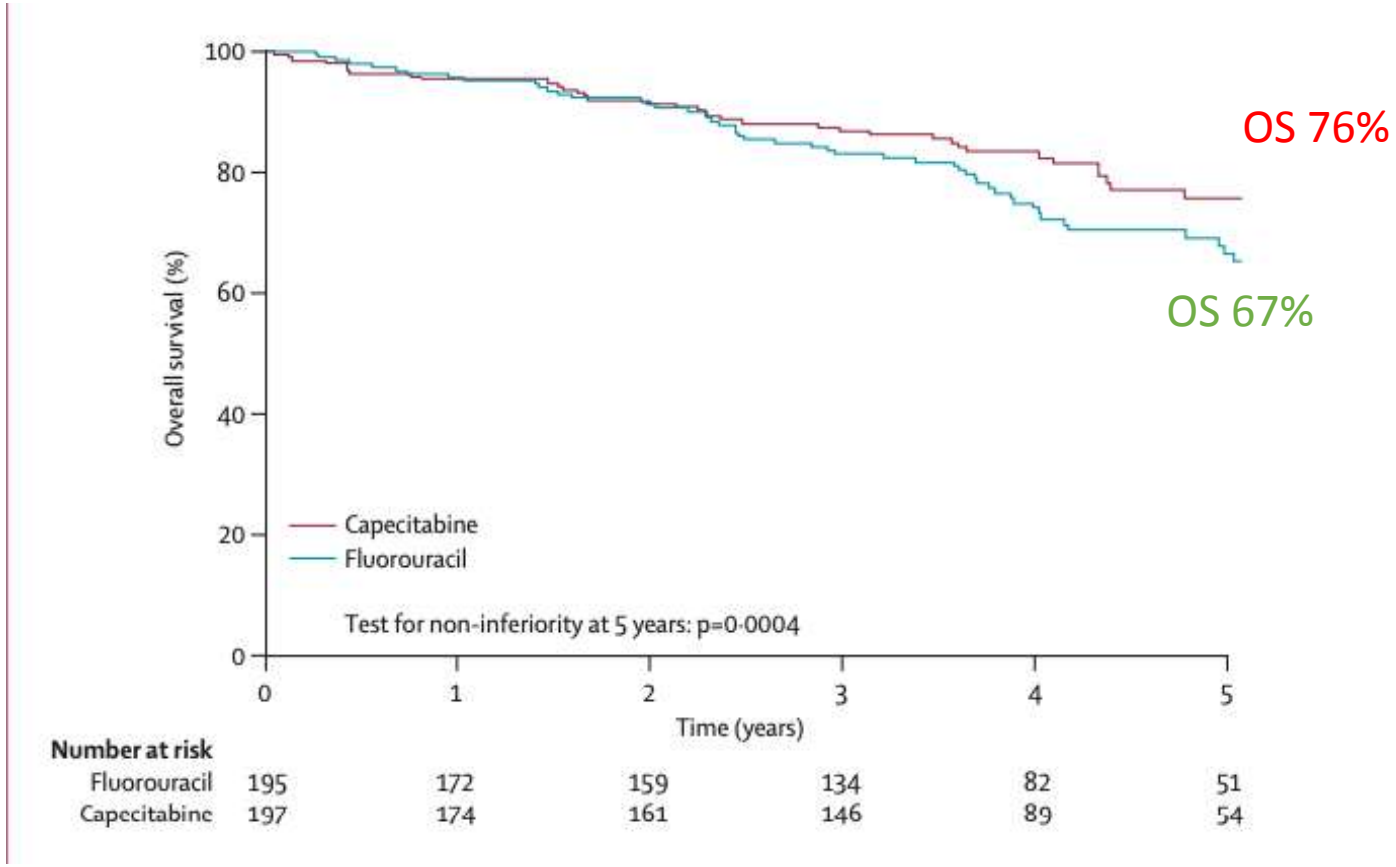


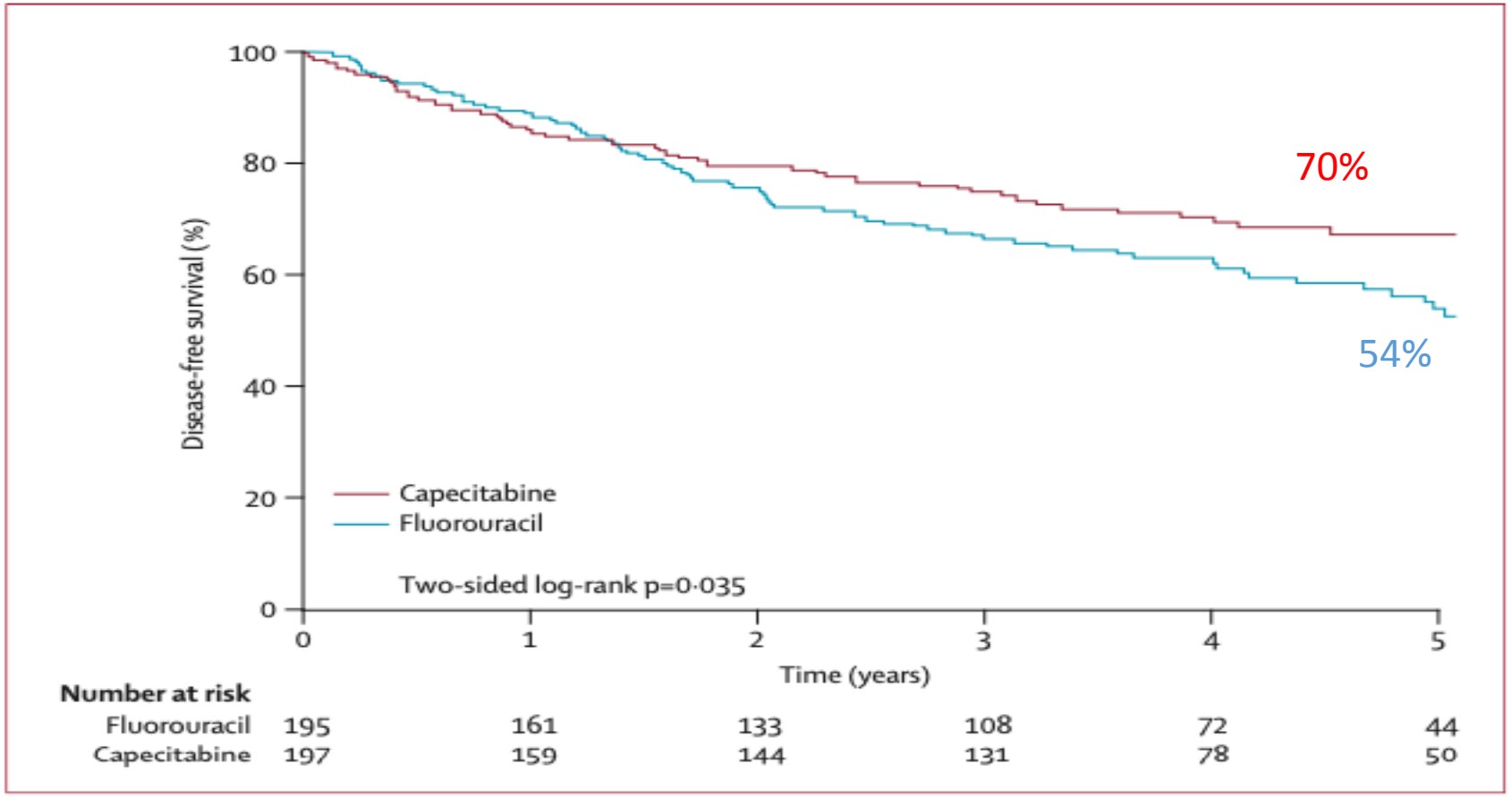
CRT with capecitabine versus 5-FU for locally advanced rectal cancer: multicentric, non-inferiority, phase III RCT



OS 76%

OS 67%

CRT with capecitabine versus 5-FU for locally advanced rectal cancer: multicentric, non-inferiority, phase III RCT



Capecitabine versus 5-FU based chemotherapy with RT as Neoadjuvant treatment in Rectal Cancer

- **Why Capecitabine may be used in place of 5-FU/LV based chemotherapy concurrently with RT ?**

1. Better compliance for patients.
2. Equivalent or better LRCR.
3. Equivalent or better OS and DFS (statistically insignificant)
4. Less toxicity.

Should Oxaliplatin be added to Preoperative RT plus Capecitabine in locally advanced Rectal cancer?

Primary Tumor Response to Preoperative CRT with or without Oxaliplatin in Locally Advanced Rectal Cancer: STAR-01 trial

- 747 patients with resectable, locally advanced (cT3-4 and/or cN1-2) adenocarcinoma of the mid-low rectum were randomly assigned to receive:

- Pelvic radiation (50.4 Gy in 28 daily fractions) and concomitant infused fluorouracil (225 mg/m2/d) either alone (arm A, n- 379) or combined with oxaliplatin (60 mg/m2 weekly X 6; arm B, n- 368).

- Overall survival was the primary end point.

Toxicity comparison between Arm A and Arm B STAR-01 trial

Table 3. Acute Toxicity on All Subjects Receiving at Least One Dose of Study Drugs (safety population)

	Grade 1-2				Grade 3-4				
	RT and FU (n = 379)		Oxaliplatin Plus RT and FU (n = 352)		RT and FU (n = 379)		Oxaliplatin Plus RT and FU (n = 352)		
Toxicity	No.	%	No.	%	No.	%	No.	%	*P*
Diarrhea	167	44	165	47	16	4	54	15	< .001
Nausea	65	17	125	36	0	0	6	2	.012
Vomiting	19	5	80	23	0	0	4	1	.054
Abdominal pain	61	16	87	25	0	0	6	2	.012
Anemia	72	19	80	23	2	0.5	0	0	.500
Radiation dermatitis	150	40	126	36	7	2	16	5	.037
Neurosensory	2	0.5	124	35	0	0	5	1	.026
Dysuria	106	28	95	27	2	0.5	3	1	.677
Asthenia	75	20	109	31	0	0	11	3	< .001
Fever	16	4	80	23	0	0	4	1	.054
Overall	291	77	244	69	29	8	85	24	< .001

Pathologic Findings on TME Specimens From Patients Treated With Preoperative Chemoradiation- STAR-01 trial

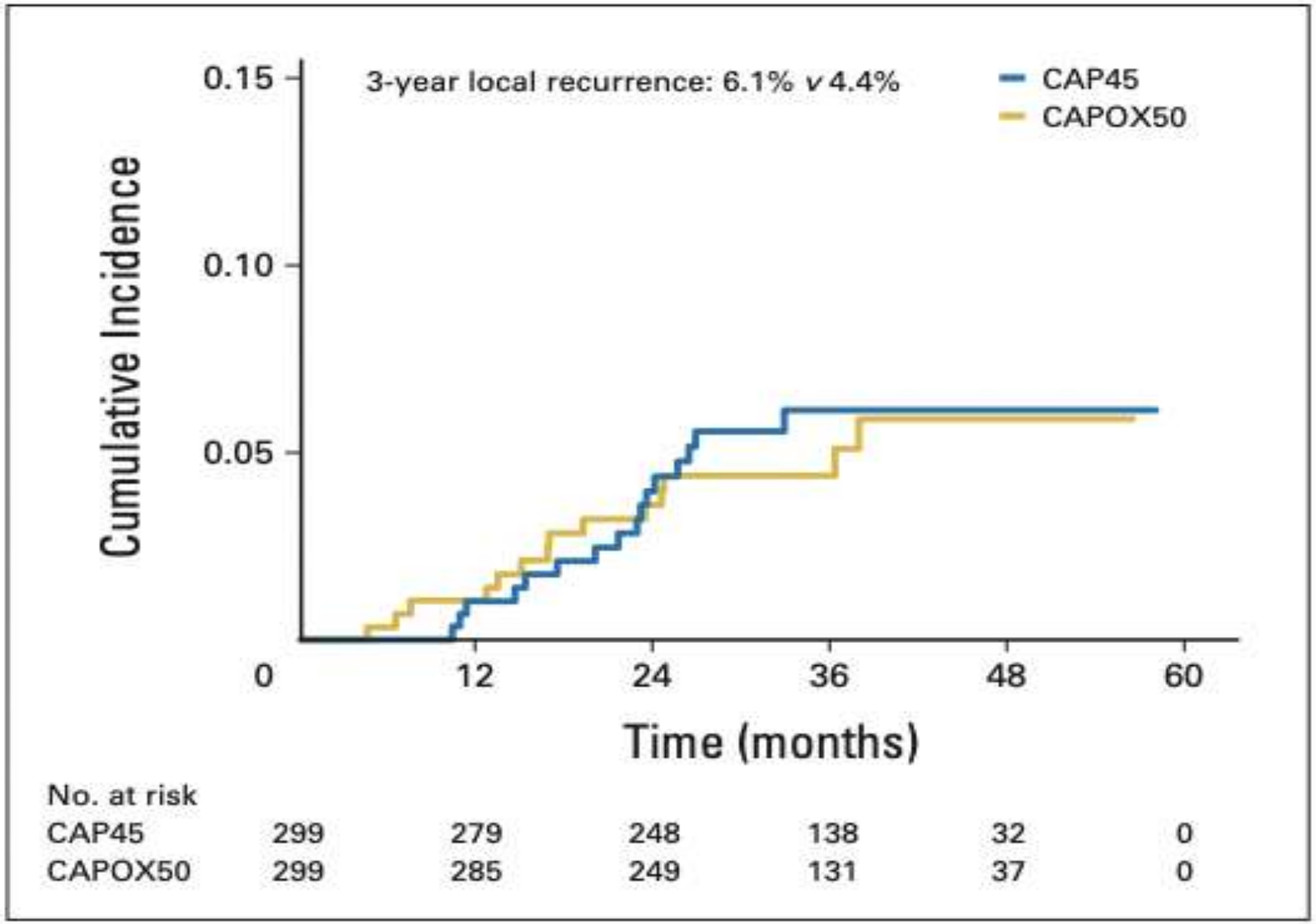
Table 5. Pathologic Findings on TME Specimens From Patients Treated With Preoperative Chemoradiation

Pathologic Finding	RT and FU (n = 358) No.	RT and FU (n = 358) %	Oxaliplatin Plus RT and FU (n = 347) No.	Oxaliplatin Plus RT and FU (n = 347) %	P
Tumor diameter, mm*					
Median	25		20		.195
Range	1-100		2-80		
Missing	23		23		
ypT-stage					
0	64	18	65	19	.578
1	25	7	35	10	
2	106	30	94	27	
3	152	42	140	40	
4	11	3	13	4	
Examined lymph nodes					
Median	12		11		.013
Range	0-47		0-42		
ypN-stage					
0	264	74	247	71	.630
1	63	18	63	18	
2	31	9	37	11	
Tumor regression grade†					
0-1-2	146	41	119	34	.170
3	140	39	157	45	
4	62	17	60	17	
Missing/undetermined	10	3	11	3	
Resection status					
R0	335	94	335	97	.070‡
R1	6	2	7	2	
R2a	5	1	4	1	
R2b	12	3	1	0.3	
CRM status					
Positive (≤ 1 mm)	15	7	9	4	.239
Negative	203	93	202	96	
Missing	140		136		

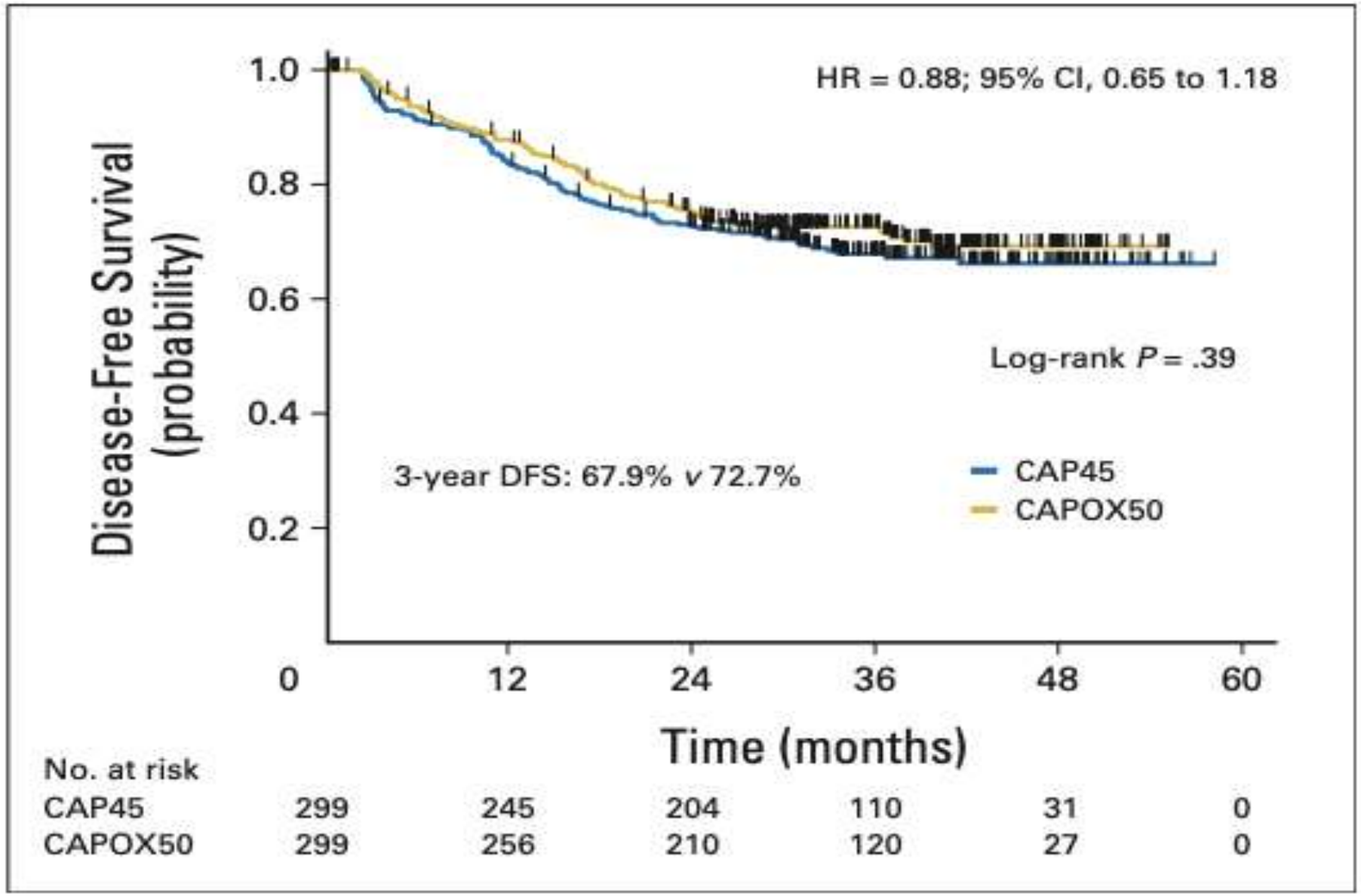
Clinical Outcome of the ACCORD 12/0405 PRODIGE 2 RCT in Rectal Cancer

- 598 patients were randomly assigned to:
- Preoperative CT-RT with CAP45 (45-Gy RT for 5 weeks with concurrent capecitabine)- Arm A
- CAPOX50 (50-Gy RT for 5 weeks with concurrent capecitabine and oxaliplatin)- Arm B
- Total meso-rectal excision was planned 6 weeks after CT-RT.

Clinical Outcome of the ACCORD 12/0405 PRODIGE 2 RCT in Rectal Cancer



Clinical Outcome of the ACCORD 12/0405 PRODIGE 2 RCT in Rectal Cancer



Overview of four RCTs regarding neoadjuvant treatment with or without Oxaliplatin

Trial	No. of Patients	Treatment		Early Grade 3 to 4 Toxicity (%)	ypCR (%)	Sphincter-Saving Surgery (%)
		Regimen	No. of Patients			
ACCORD 12[6]	598					
Control arm		CAP45	299	11	13.9	75
Experimental arm		CAPOX50	299	25	19.2	76
P				< .001	.09	
STAR-01[9]	747					
Control arm		RT 50.4 Gy + FU	379	8	16	78
Experimental arm		RT 50.4 Gy + FU + OX	368	24	16	79
P				< .001		
NSABP R-04[10*]	1,608					
Control arm		RT + FU ± OX RT 45 Gy + (0.8 to 5.4 Gy)		6†	19.1†	62
Experimental arm		Capecitabine ± OX		15 (diarrhea)‡	20.9‡	62
P				< .05		
CAO/ARO 04[11,12§]	1,265					
Control arm		RT + FU	637	21	13.1†	88
Experimental arm		RT + FU + OX	628	22.9	17.6‡	88
P					.033	

So there is no role of adding Oxaliplatin to Preoperative RT plus Capecitabine as this combination leads to

- Very high grade 3,4 toxicity.
- No improvement in ypCR.
- No improvement in sphincter preservation.
- No improvement in OS or DFS.

Is there any role of addition of Anti EGFR antibodies with Preoperative RT Plus CT in locally advanced Rectal Cancer?

Neoadjuvant Oxaliplatin, Capecitabine, and Preoperative Radiotherapy With or Without Cetuximab Followed by TME in High-Risk Rectal Cancer: EXPERT-C Trial

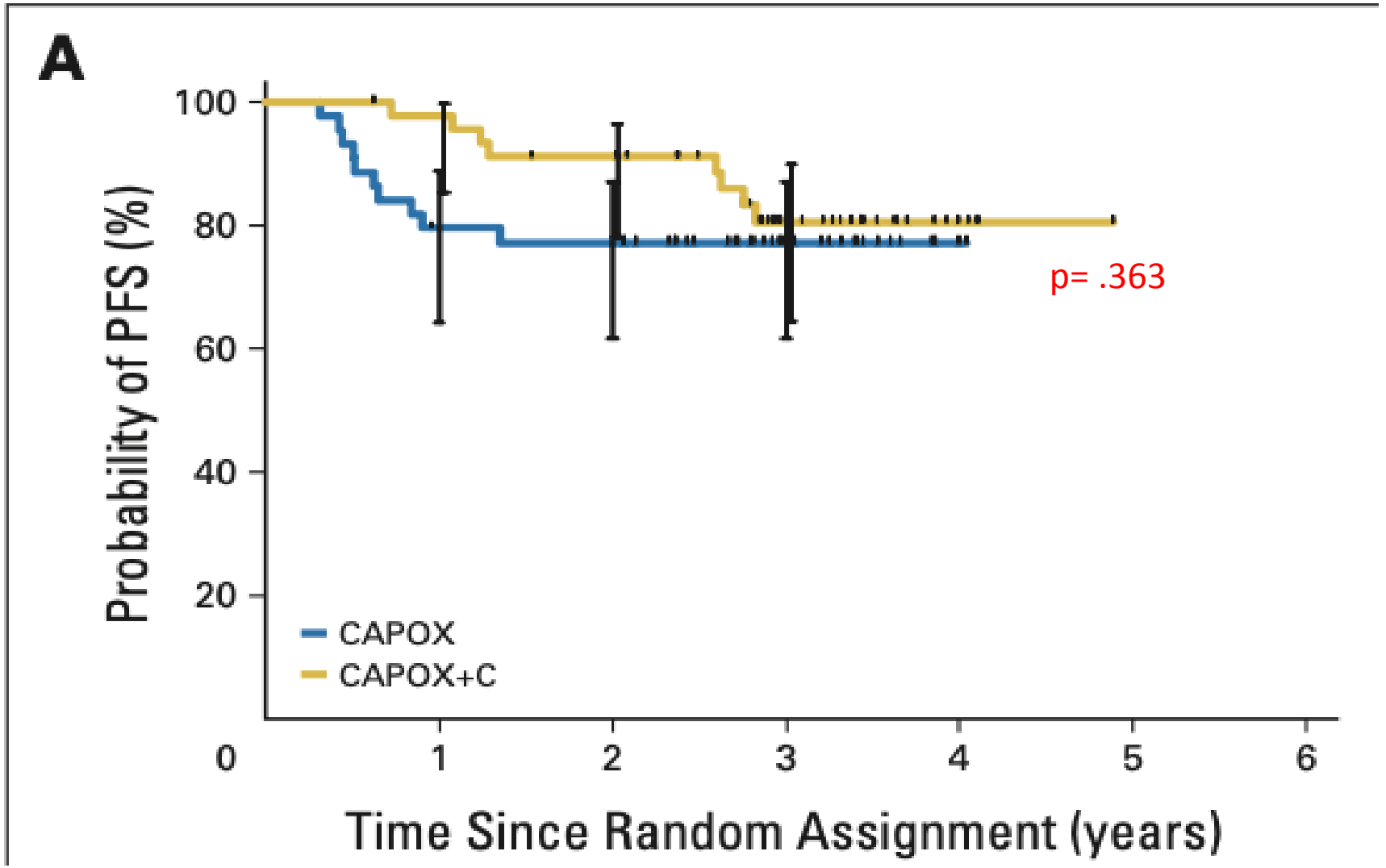
- Patients with operable MRI defined high-risk rectal cancer received four cycles of capecitabine/oxaliplatin (CAPOX) followed by capecitabine based chemoradiotherapy, surgery, and adjuvant CAPOX (four cycles) - Arm A

- Same regimen as in Arm A plus weekly cetuximab (CAPOX-C)- Arm B.

- Primary end point was complete response.

- Secondary end points were radiologic response (RR), progression-free survival (PFS).

PFS in Arm A versus Arm B



Radiological Response rates in Arm A versus Arm B

Table 3. Radiologic Response

	Wild-Type Patients					All Treated Patients				
	CAPOX (n = 44)		CAPOX+C (n = 46)			CAPOX (n = 81)		CAPOX+C (n = 83)		
Response	No.	%	No.	%	*P*	No.	%	No.	%	*P*
Neoadjuvant chemotherapy										
CR	1	2	5	11		2	3	6	8	
PR	21	48	27	59		38	51	43	56	
SD	20	46	12	26		33	44	27	35	
PD	1	2	0	0		2	3	1	1	
Unknown*	1	2	2	4		6	7	6	7	
Overall response†	22	51	32	71	.038	40	54	49	64	.41
Chemoradiation										
CR	2	5	7	16		7	9	9	11	
PR	30	70	34	77		50	66	55	72	
SD	6	14	3	7		14	19	11	14	
PD	4	9	0	0		4	5	1	1	
Unknown*	1	2	2	4		6	8	7	8	
Overall response†	32	75	41	93	.065	57	76	64	84	.23

Toxicities in Arm A versus Arm B

Toxicity*	CAPOX (n = 81) No. of Patients	%	CAPOX+C (n = 83) No. of Patients	%
During neoadjuvant chemotherapy	81		83	
Febrile neutropenia	1	1	1	1
Diarrhea	7	9	7	8
Lethargy	8	10	7	10
Nausea and vomiting	2	2	2	2
Hand-foot syndrome	1	1	3	4
Stomatitis	0	0	1	1
Neuropathy	0	0	2	2
Rash	0	0	8	10
During chemoradiotherapy	75		78	
Diarrhea	1	1	8	10
Rash	0	0	7	9
Hand-foot syndrome	1	1	3	4
During adjuvant chemotherapy	52		65	
Febrile neutropenia	0	0	0	0
Diarrhea	3	6	10	16
Lethargy	1	2	7	12
Nausea and vomiting	0	0	1	2
Hand-foot syndrome	0	0	2	3
Stomatitis	0	0	1	2
Neuropathy	5	10	3	5
Rash	1	2	6	10

Neoadjuvant CRT with or without panitumumab in wild-type KRAS, locally advanced rectal cancer (LARC): RCT SAKK 41/07

- Patients with wild-type KRAS, T3-4 and/or N+ LARC were randomly assigned to receive CRT with or without Panitumumab (6 mg/kg).
- The primary end-point was pCR.
- Panitumumab (6 mg/kg every 2 weeks for 4 cycles) was administered i.v. over 60 min. Capecitabine (825 mg/m2) was taken twice daily orally throughout RT. RT was given in dose of 45 Gy /25 fractions of 1.8 Gy over 5 weeks, starting from 7 days after the first panitumumab administration (P + CRT arm).
- Surgery was planned 6 weeks after completion of CRT. TME with sphincter preservation was carried out whenever feasible.

Response assessment in Arm A versus Arm B

	No. of patients	Percent[a]	95% CI (exact)
Pathological near-complete or complete tumor response (pNC/CR)			
Panitumumab + chemoradiotherapy (CRT)	21/40	53	(36, 69)%
CRT	09/28	32	(16, 52)%
Total	30/68	44	(32, 57)%
R0 resection[b]			
Panitumumab + CRT	33/39	85	(70, 94)%
CRT	25/27	93	(76, 99)%
Total	58/66	89	(78, 95)%
Sphincter preservation			
Panitumumab + CRT	27/39	69	(52, 83)%
CRT	19/27	70	(50, 86)%
Total	46/66	70	(57, 80)%
Downstaging of primary tumor or lymph nodes			
Panitumumab + CRT	34/39	87	(73, 96)%
CRT	23/27	85	(66, 96)%
Total	57/66	86	(76, 94)%
Downstaging of primary tumor and lymph nodes			
Panitumumab + CRT	16/39	41	(26, 58)%
CRT	08/27	30	(14, 50)%
Total	24/66	36	(25, 49)%

Toxicity profile in Arm A versus Arm B

	Grade 3–4		Grade 1–2	
	Panitumumab + chemoradiotherapy (CRT; $n = 40$)	CRT ($n = 28$)	Panitumumab + CRT ($n = 40$)	CRT ($n = 28$)
Diarrhea	4 (10%)	1 (4%)	29 (73%)	15 (54%)
Hand-foot syndrome	1 (2%)	0 (0%)	6 (15%)	4 (14%)
Fatigue	1 (2%)	0 (0%)	18 (45%)	9 (32%)
Acneiform skin rash	1 (2%)	0 (0%)	14 (35%)	0 (0%)
Nausea	0 (0%)	0 (0%)	10 (25%)	6 (21%)
Anastomotic leakage	6 (15%)	1 (4%)	1 (3%)	1 (4%)

Addition of anti-EGFR antibodies (Cetuximab/Panitumumab) with preoperative CRT leads to

No statistically improvement in pCR.

Increased grade 3 or 4 toxicity

Slight improvement in OS or PFS was due to TNT approach in Expert-C trial

Leading to better compliance to neoadjuvant chemotherapy.

So, anti-EGFR antibodies are not recommended to combine with preoperative CRT.

Is there any role of Chemotherapy alone and selective chemoradiation as neoadjuvant treatment in locally advanced Rectal Cancer?

Preoperative Chemotherapy with or without chemoradiation in rectal cancer: FOWARC trial

- 495 patients with locally advanced stage II/III rectal cancer to three treatments:

- Arm A: Five 2-week cycles of infusional 5-FU (leucovorin 400 mg/m2, 5-FU 400 mg/m2, and 5-FU 2.4 g/m2 over 48 h) plus radiotherapy (46.0 to 50.4 Gy delivered in 23 to 28 fractions during cycles 2 through 4) followed by surgery.

- Arm B: seven cycles of mFOLFOX6 plus RT(46.0 to 50.4 Gy delivered in 23 to 28 fractions during cycles 2 through 4) followed by surgery.

- ARM C: four to six cycles of mFOLFOX6 followed by surgery and six to eight cycles of mFOLFOX6.

- The primary end point was 3-year disease-free survival. Secondary end points of histopathologic response and toxicity are reported.

Pathological response to various Neoadjuvant treatments

Table 3. Postsurgery Pathologic Response

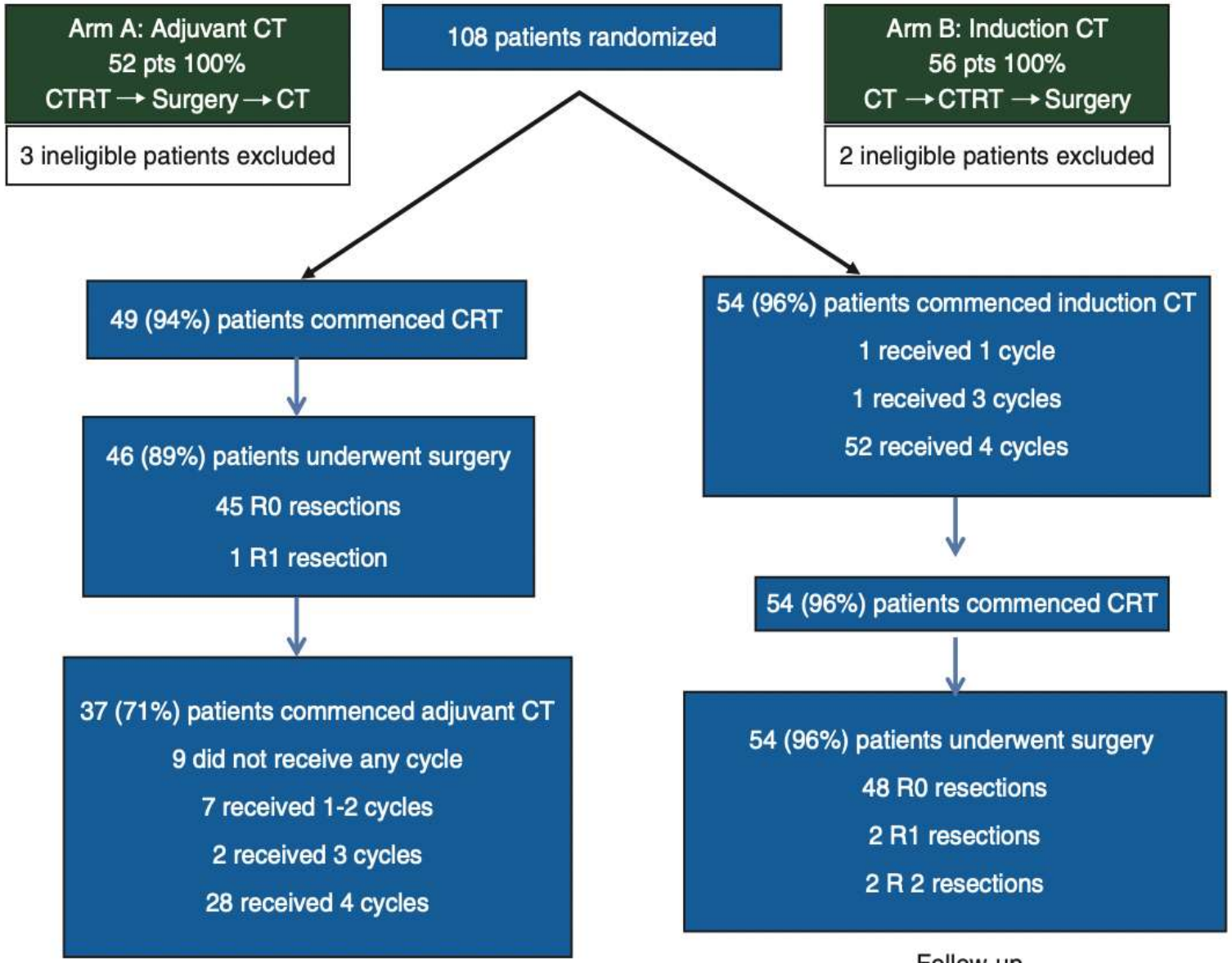
Characteristic	Treatment Group, No. (%)		
	Fluorouracil- Radiotherapy	mFOLFOX6-Radiotherapy	mFOLFOX6
No. of patients	143*	149	152
pCR†	20 (14.0)	41 (27.5)	10 (6.6)
OR (95% CI)‡	1	0.428 (0.237 to 0.776)	2.309 (1.041 to 5.121)
ypStage			
0-I	53 (37.1)	84 (56.4)	54 (35.5)
OR (95% CI)‡	1	0.453 (0.283 to 0.726)	1.093 (0.679 to 1.759)
II-IV	90 (62.9)	65 (43.6)	98 (64.5)
OR (95% CI)‡	1	2.201 (1.376 to 3.520)	0.964 (0.599 to 1.552)
TRG§			
0-1	70 (49.0)	102 (68.5)	50 (32.9)
OR (95% CI)‡	1	0.431 (0.266 to 0.697)	2.032 (1.264 to 3.267)
2-3	71 (49.7)	46 (30.9)	102 (67.1)
OR (95% CI)‡	1	2.335 (1.448 to 3.765)	0.511 (0.319 to 0.819)

Total Neoadjuvant Treatment (TNT)

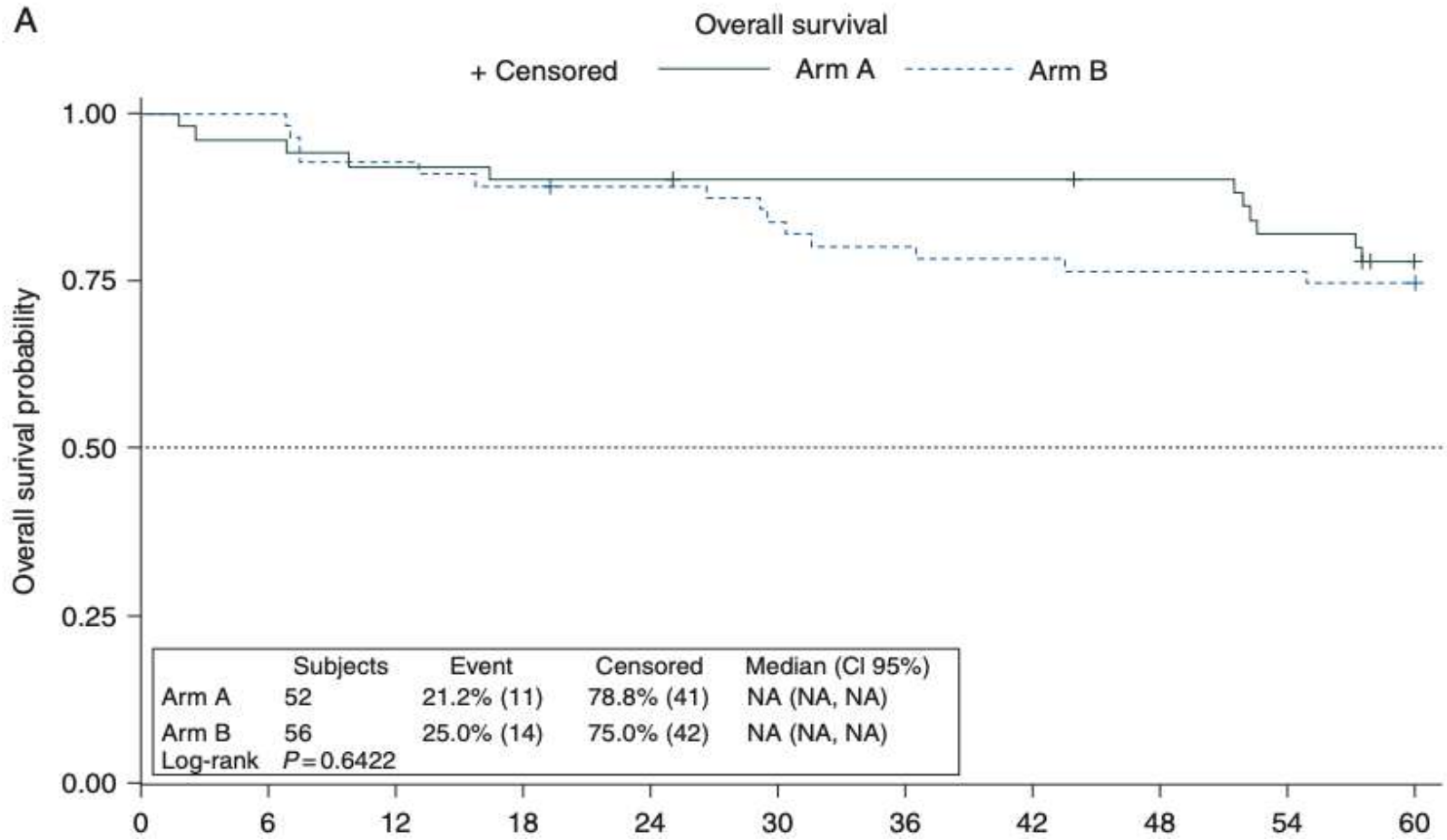
- TNT refers to the strategy in which the preoperative chemoradiotherapy and chemotherapy are given as neoadjuvant treatment before definitive surgery in locally advanced rectal cancer.

- This treatment strategy has been tested by many phase III trials and has now become the standard of care in locally advanced rectal cancers.

Spanish GCR Trial



5 years OS in Arm A versus Arm B

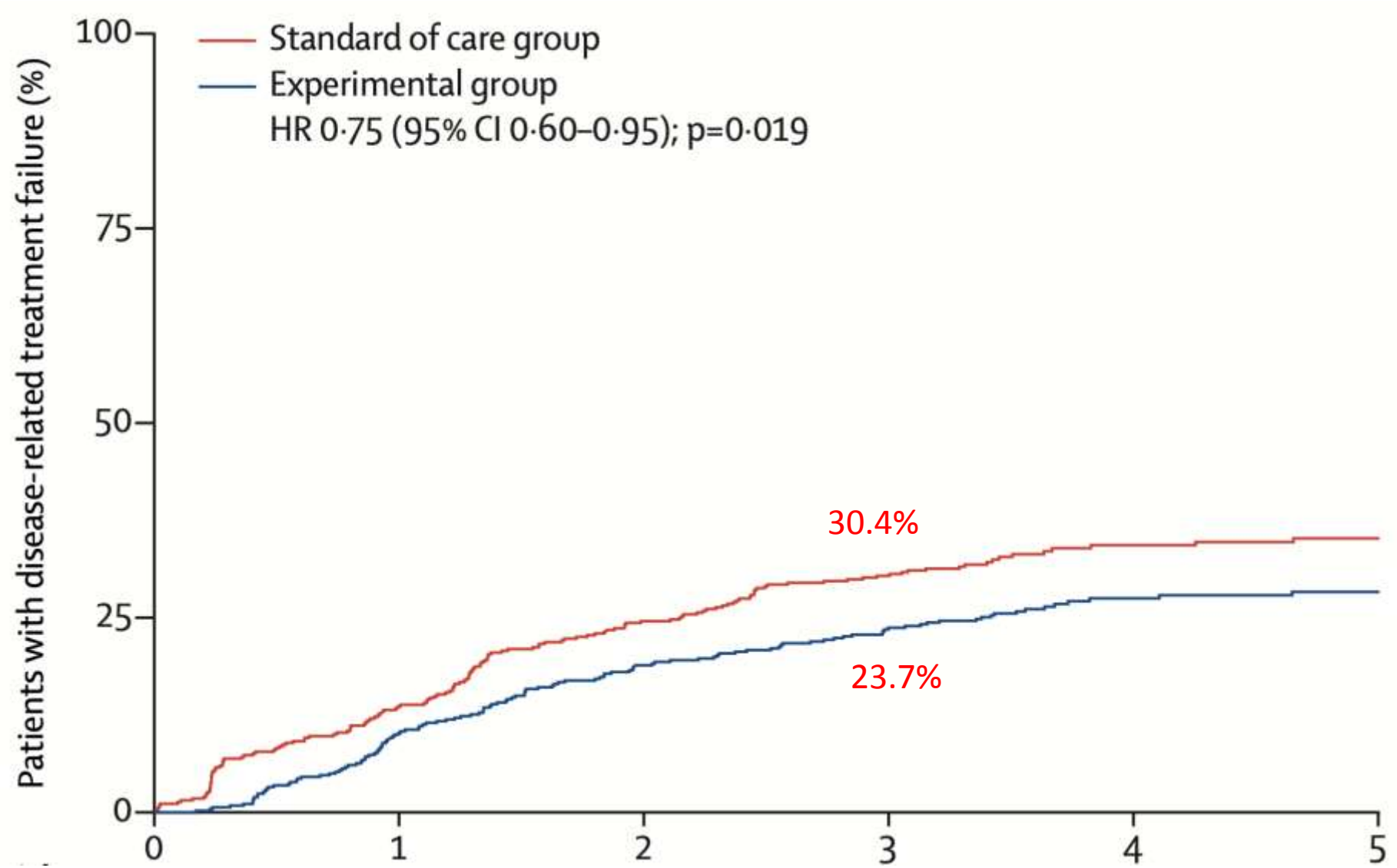


78% with Arm A versus 75% with Arm B

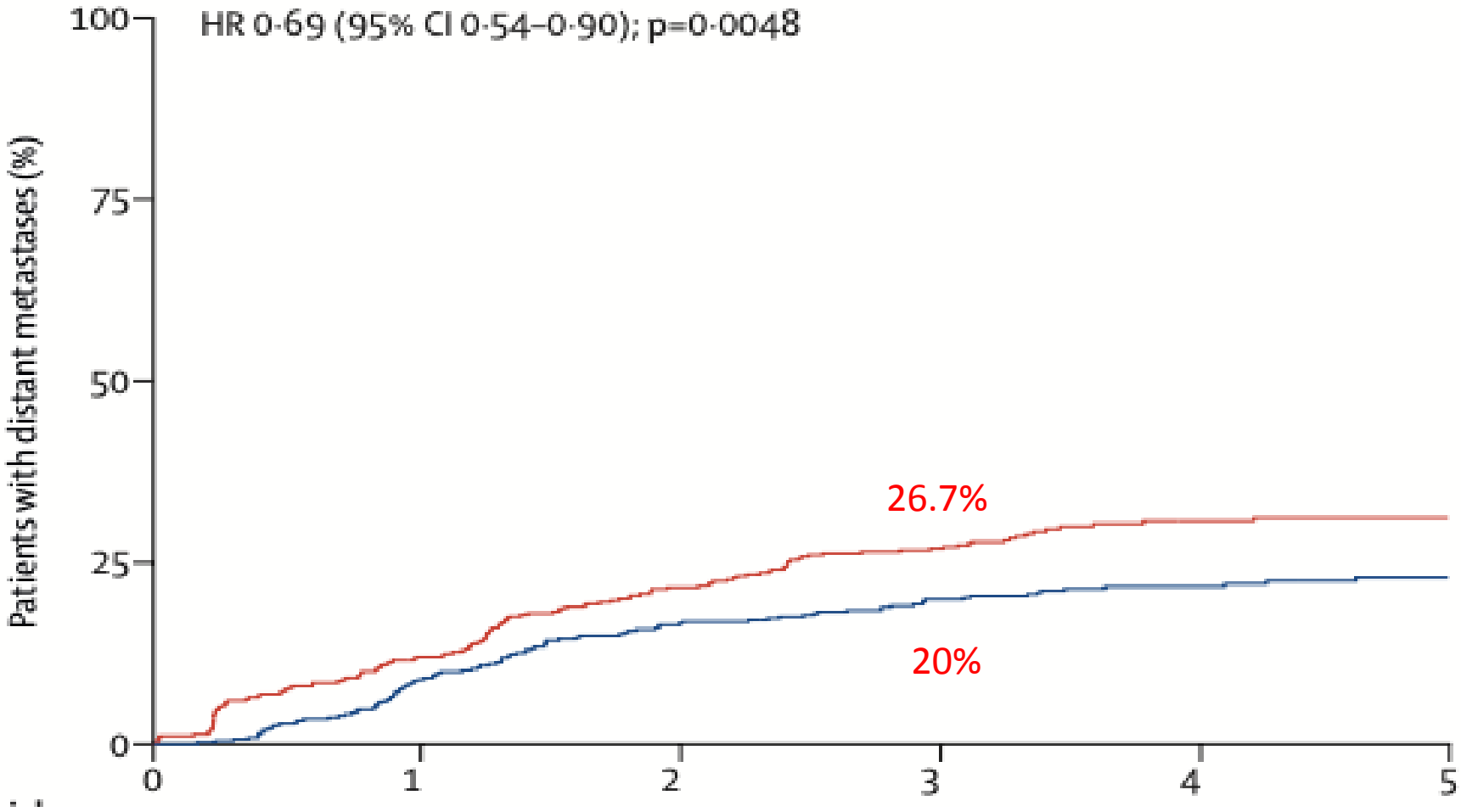
Rapido Trial

- Patients of locally advanced rectal cancer (T3, T4, N1, N2) and high risk MRI pelvis were divided into two Arms:
- Arm A: Short course RT (25 Gy/5F/1.3 weeks) followed by 6 cycles of Capox or 9 cycles of Folfox4 and then TME was done.
- Arm B: 50 to 50.4 Gy in 25 to 28 fractions along with Tab Capecitabine followed by surgery and then adjuvant chemotherapy with 8 cycles of Capox or 12 cycles of Folfox4 were given.
- The primary endpoint was 3-year disease-related treatment failure, defined as the first occurrence of locoregional failure, distant metastasis, new primary colorectal tumour, or treatment-related death.

Rapido Trial- 3 years DRTFR



3 years cumulative DM rate



	Experimental group	Standard of care group	p value
All eligible patients			
Surgery with curative intent within 6 months after the end of preoperative treatment			
Yes	426/462 (92%)	400/450 (89%)	0·086*
No	36/462 (8%)	50/450 (11%)	..
Disease-related treatment failure, first occurring	128 (23·7%)†	152 (30·4%)†	0·019†
Locoregional failure			
Local progression, unresectable tumour	1/128 (1%)	1/152 (1%)	..
R2 resection	0	0	..
Local recurrence	22/128 (17%)	13/152 (10%)	..
Locoregional failure and distant metastasis‡			
Local progression, unresectable tumour	4/128 (3%)	2/152 (1%)	..
R2 resection	1/128 (1%)	0	..
Local recurrence	7/128 (5%)	4/152 (3%)	..
Distant metastasis	86/128 (67%)	123/152 (81%)	..
New primary colorectal tumour	3/128 (2%)	5/152 (3%)	..
Treatment-related death	4/128 (3%)	4/152 (3%)	..
Patients with a resection within 6 months after the end of preoperative treatment			
Residual tumour classification			
R0 >1 mm	382/423 (90%)	360/398 (90%)	0·87*
R1 ≤1 mm	38/423 (9%)	37/398 (9%)	..
R2	3/423 (1%)	1/398 (<1%)	..
Circumferential resection margin			
>1 mm	385/423 (91%)	363/398 (91%)	0·92*
≤1 mm	38/423 (9%)	35/398 (9%)	..
Differentiation grade during pathological assessment			
Well differentiated	62/423 (15%)	82/398 (21%)	0·09*§
Moderately differentiated	167/423 (39%)	189/398 (47%)	..
Poorly differentiated	44/423 (10%)	35/398 (9%)	..
No tumour	129/423 (30%)	69/398 (17%)	..
Not assessed	21/423 (5%)	23/398 (6%)	..
Pathological complete response			
Yes	120/423 (28%)	57/398 (14%)	<0·0001*
No	303/423 (72%)	341/398 (86%)	..
Pathological T stage¶			
ypT0	129/423 (30%)	69/398 (17%)	<0·0001*
ypTis	2/423 (<1%)	1/398 (<1%)	..
ypT1	17/423 (4%)	17/398 (4%)	..
ypT2	82/423 (19%)	96/398 (24%)	..

UNICANCER-PRODIGE 23 Trial

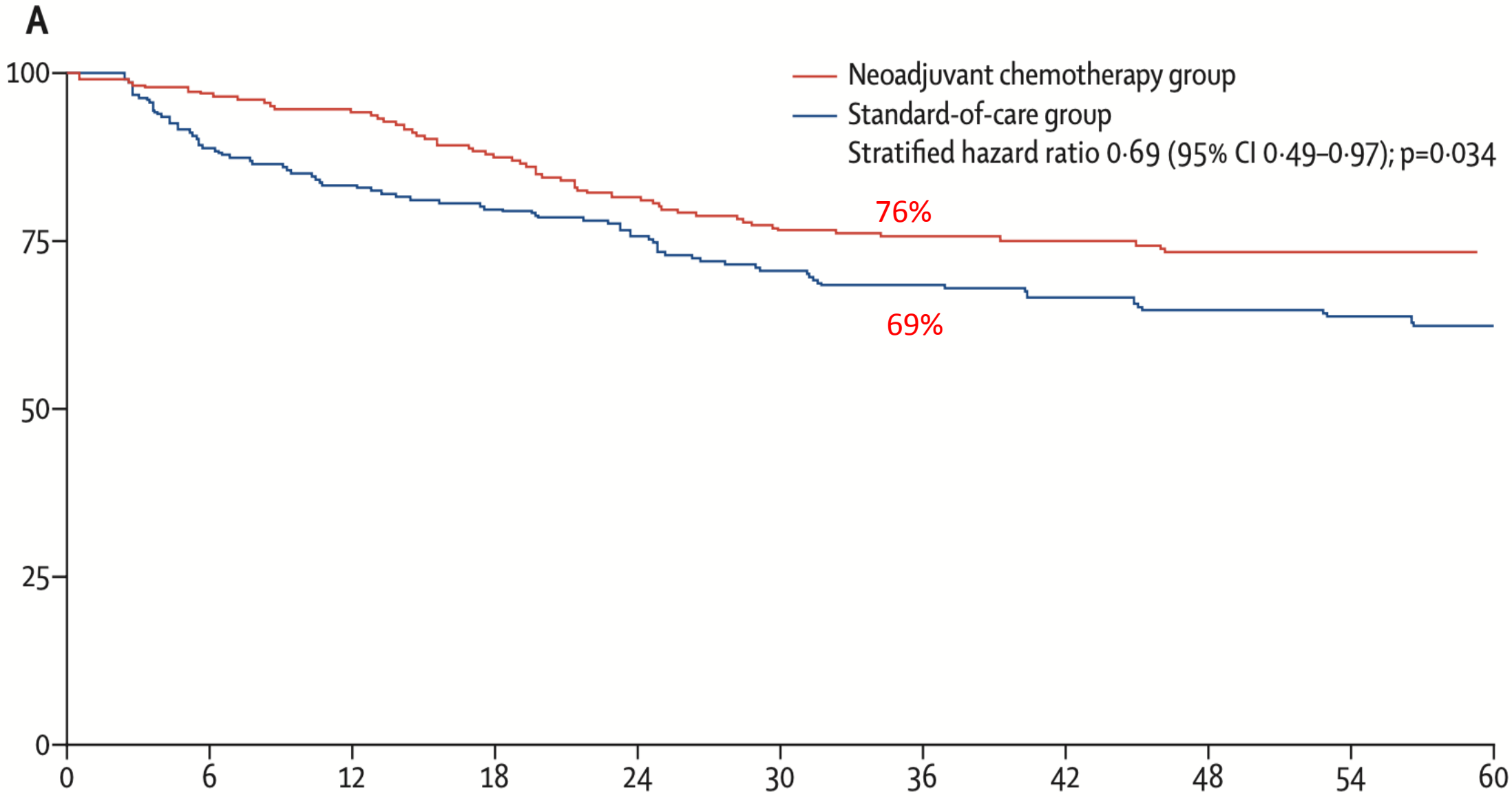
- Patients of locally advanced rectal cancer (T3, T4, M0) were divided into two Arms:

- Arm A: Received neoadjuvant chemotherapy (FOLFORINOX) followed by CRT(50 Gy during 5 weeks and concurrent oral capecitabine twice daily for 5 days per week) and then TME and adjuvant chemotherapy.

- Arm B: Received chemoradiotherapy, TME, and adjuvant chemotherapy for 6 months.

- The primary endpoint was 3-year Disease free survival (DFS). Safety analysis was also done on treated patients.

3 years DFS for Arm A versus Arm B



	Neoadjuvant chemotherapy group (n=231)	Standard-of-care group (n=230)	p value
Surgery			
Yes	213 (92%)	218 (95%)	0·26
No	18 (8%)	12 (5%)	..
Primary tumour resection			
Yes	213 (100%)	215 (99%)	0·25
No	0	3 (1%)	..
Quality of mesorectal resection			0·17
Grade 1	14/185 (8%)	9/188 (5%)	..
Grade 2	17/185 (10%)	11/188 (6%)	..
Grade 3	136/185 (81%)	156/188 (89%)	..
Missing	46	42	..
Grade 2 or 3	153/185 (92%)	167/188 (95%)	0·23
Circumferential resection margin, mm			0·72
≤1	8/175 (5%)	11/196 (6%)	..
>1	149/175 (95%)	173/196 (94%)	..
Missing	56	34	..
Median number of regional lymph nodes retrieved (IQR)	13 (8–18)	15 (10–19)	0·019
Missing	2	4	..
ypT			0·0018
ypT0	60/212 (28%)	27/215 (13%)	..
ypTis	3/212 (1%)	2/215 (1%)	..
ypT1	11/212 (5%)	17/215 (8%)	..
ypT2	57/212 (27%)	62/215 (29%)	..
ypT3	77/212 (36%)	103/215 (48%)	..
ypT4	4/212 (2%)	4/215 (2%)	..
Missing	1	3	..
ypN			0·0010
ypN0	175/212 (83%)	145/215 (67%)	..
ypN1	30/212 (14%)	49/215 (23%)	..
ypN2	7/212 (3%)	20/215 (9%)	..
ypNx	0	1/215 (1%)	..
Missing	1	3	..
Pathological complete response rate (ypT0N0)			<0·0001
Yes	59/212 (28%)	26/215 (12%)	..
No	153/212 (72%)	189/215 (88%)	..

Total Neoadjuvant Treatment (TNT) versus standard neoadjuvant preoperative RT+CT followed by surgery & adjuvant CT

- TNT is a better option due to following reasons

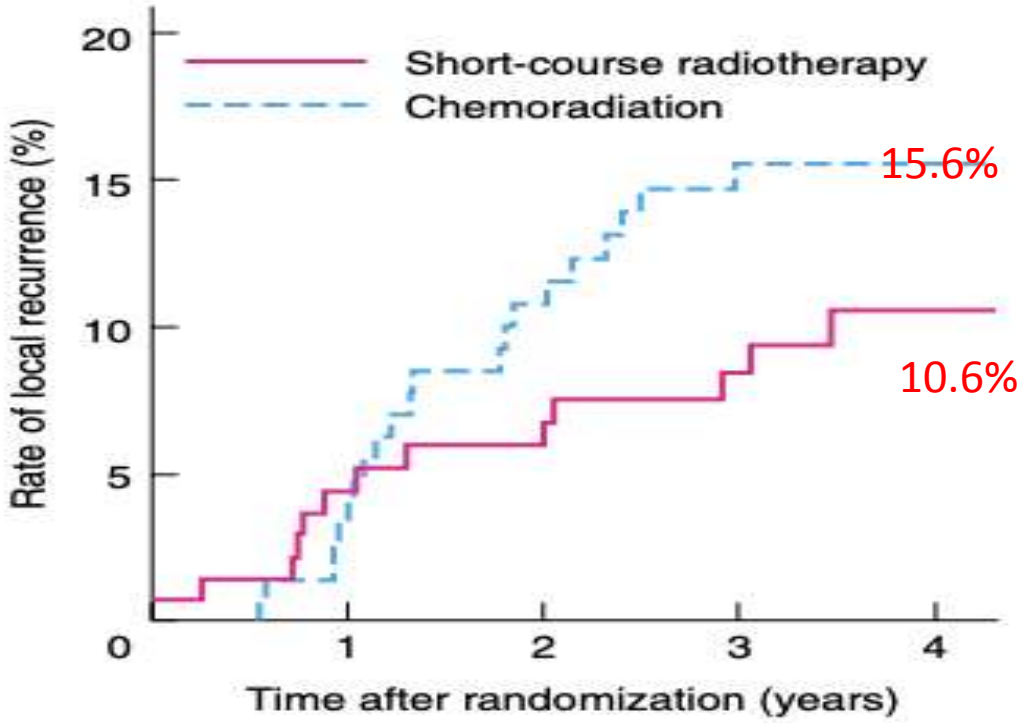
  - early control of micro-metastasis.
  - better compliance.
  - less toxicity.
  - increased pCR.
  - facilitates resection.
  - decreases time for patient living with ileostomy tube.

Short course RT followed by induction chemotherapy Versus Long course CRT as Neo-adjuvant treatment in locally advanced rectal cancer

Short versus Long course RT+CT (Polish Trial)

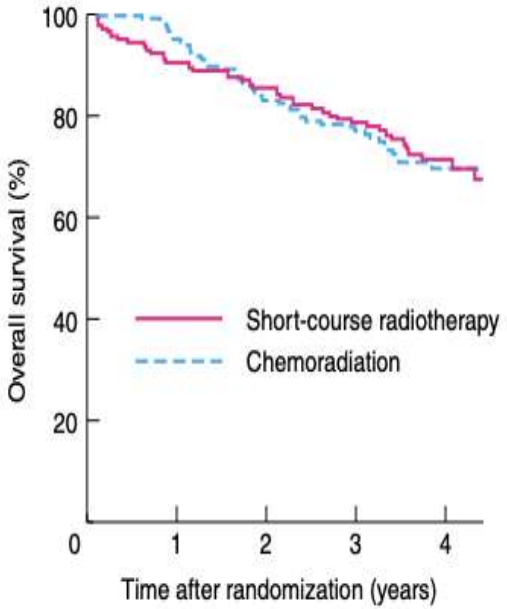
- Patients with locally advanced rectal cancer (T3,4) without sphincter involvement on digital rectal examination, were included into the study.
- Arm A: Received preoperative RT (five fractions of 5 Gy) with total mesorectal excision (TME) performed within 7 days.
- Arm B: CRT (50·4 Gy in 28 f of 1·8 Gy per fraction), plus bolus 5- FU and leucovorin) and TME 4–6 weeks later.
- The primary endpoint was 3-year Disease free survival (DFS). Safety analysis was also done on treated patients.

Local Control rates in CRT versus SCRT



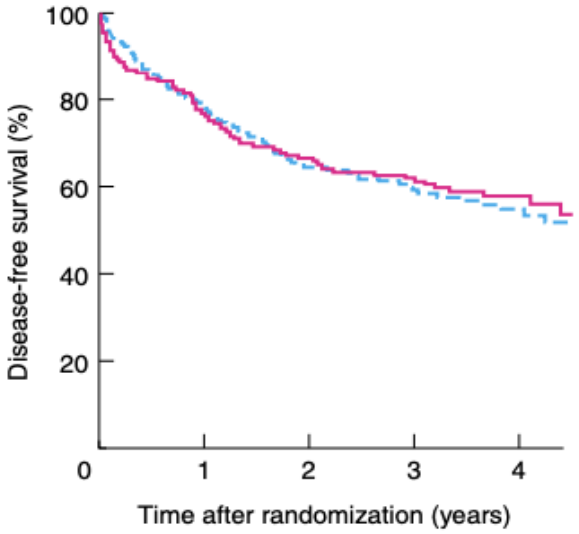
No. at risk					
Short-course radiotherapy	146	125	118	100	46
Chemoradiation	149	136	116	98	53

4 years OS & DFS with CRT versus SCRT



66.2%
vs.
67.2%

risk



58.4%
Vs.
55.6%

	Short-course radiotherapy ($n = 155$)	Chemoradiation ($n = 157$)
Deaths		
Yes	52 (33·5)	53 (33·8)
Deaths related to rectal cancer	35	46
Deaths from treatment complications*	5	5
Deaths from causes not related to rectal cancer	8	1
Deaths from unknown causes	4	1
No	103 (66·5)	104 (66·2)
Local recurrences alone or with distant metastases†		
Yes	13 (9·0)	21 (14·2)
Local recurrences alone	2 (1·4)	9 (6·1)
No	131 (91·0)	127 (85·8)
Non-applicable, tumour not resected	8	8
Non-applicable, R2 surgery	1	0
No data	2	1
Distant metastases alone or with local recurrence		
Yes	48 (31·4)	54 (34·6)
Distant metastases alone	36 (23·5)	42 (26·9)
No	105 (68·6)	102 (65·4)
No data	2	1
Late complications		
Yes	39 (28·3)	38 (27·0)
Severe late complications	14 (10·1)	10 (7·1)
No	99 (71·7)	103 (73·0)
Non-applicable (tumour not resected or death within 30 days of surgery)	11	8
No data	6	8
Late permanent stoma		
Yes	87 (56·9)	81 (51·6)
Stoma after abdominoperineal resection	52	58
Stoma for palliation of uncontrolled local disease	9	10
Temporary stoma not reversed‡	18	9
Stoma because of late morbidity or poor anorectal function§	8	4
No	66 (43·1)	76 (48·4)
No data	2	0

Short versus Long course RT+CT (TROG Trial)

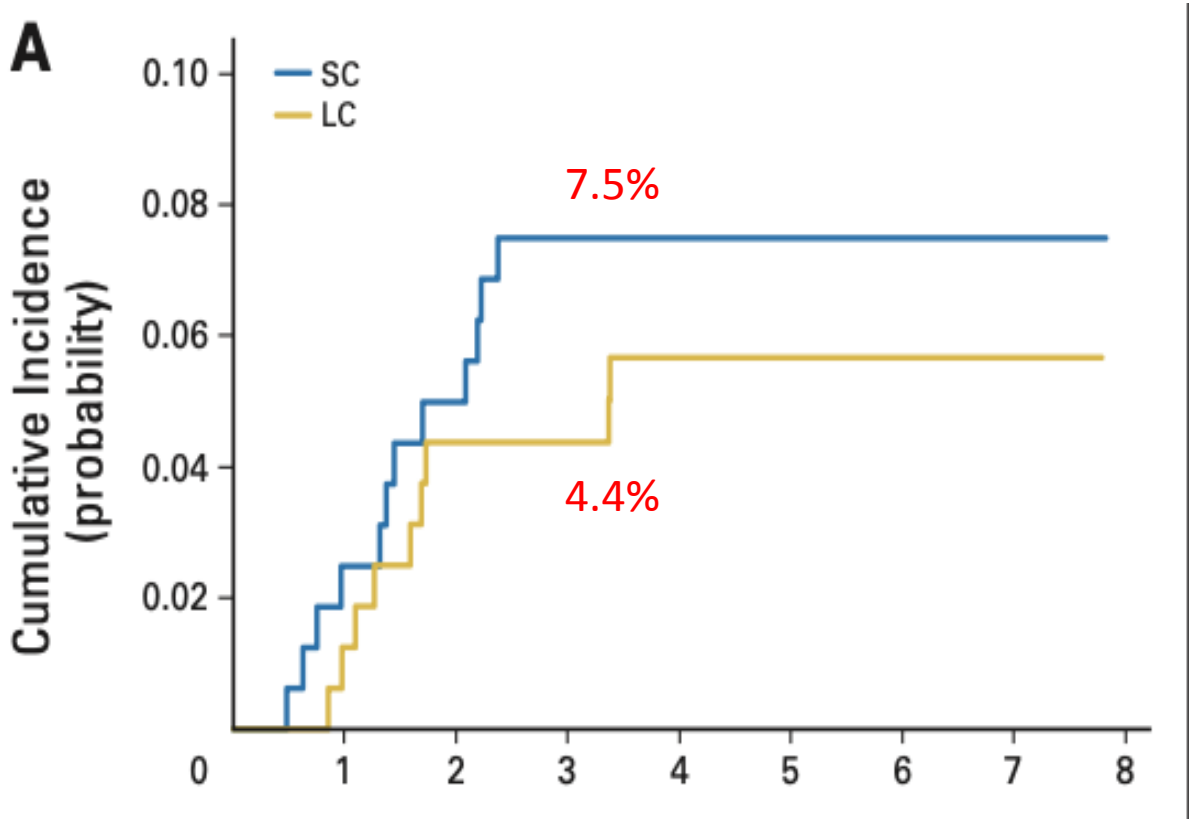
- 326 Patients with locally advanced rectal cancer (T3,N0-2M0) within 12 cm from anal verge, were included into the study.

- Arm A: pelvic radiotherapy 5 fractions of 5 Gy in 1 week, early surgery, and six courses of adjuvant chemotherapy.

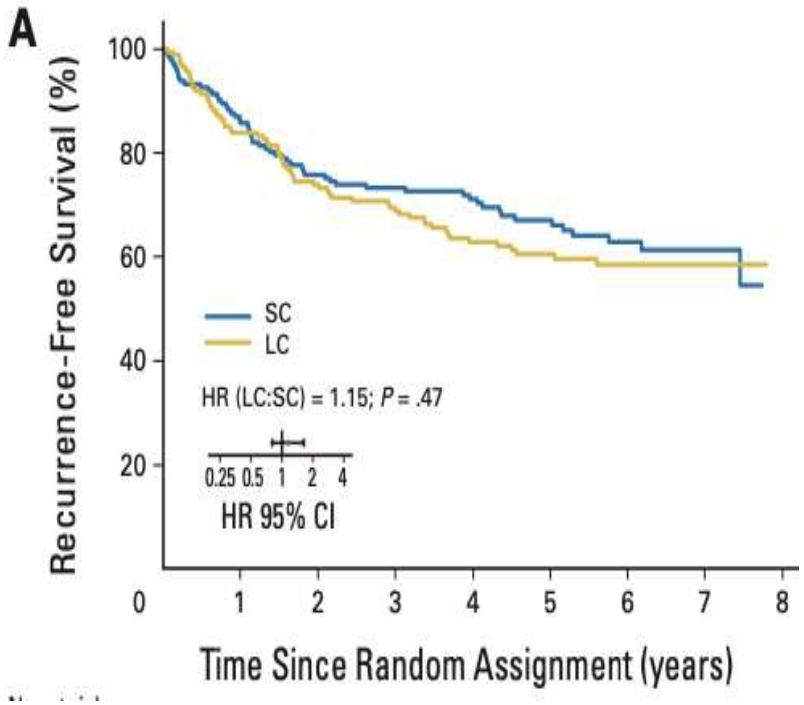
- Arm B: 50.4 Gy, 1.8 Gy/fraction, in 5.5 weeks, with continuous infusional 5-FU 225 mg/m2 per day, surgery in 4 to 6 weeks, and four courses of chemotherapy.

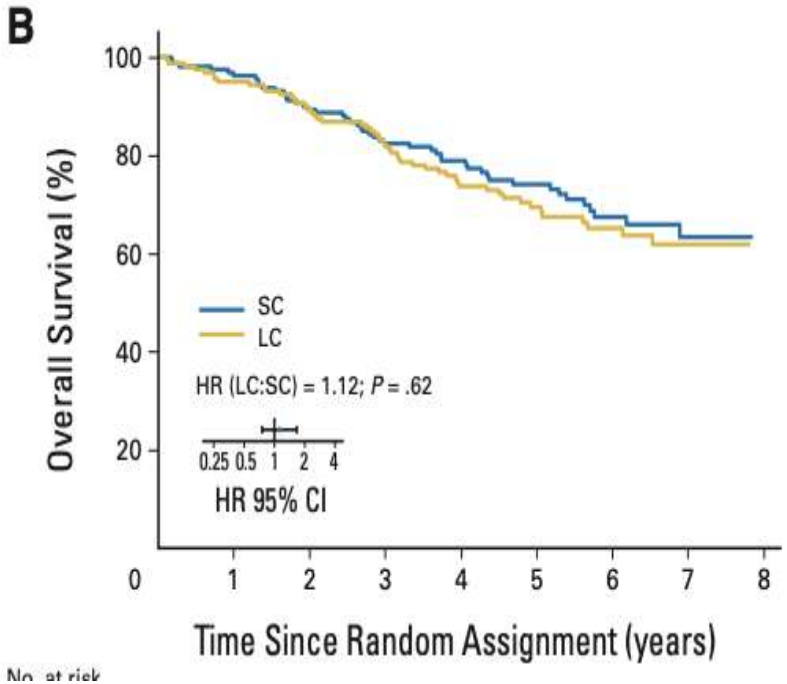
- The primary endpoint was 3-year Disease free survival (DFS). Safety analysis was also done on treated patients.

Local Recurrence rate with 3 Years LCRT Vs. SCRT



5 yrs. RFS and OS with LCRT versus SCRT





5 yrs. OS
74% with LC
versus 70%
SC

Short versus Long course RT+CT (Stellar Study)

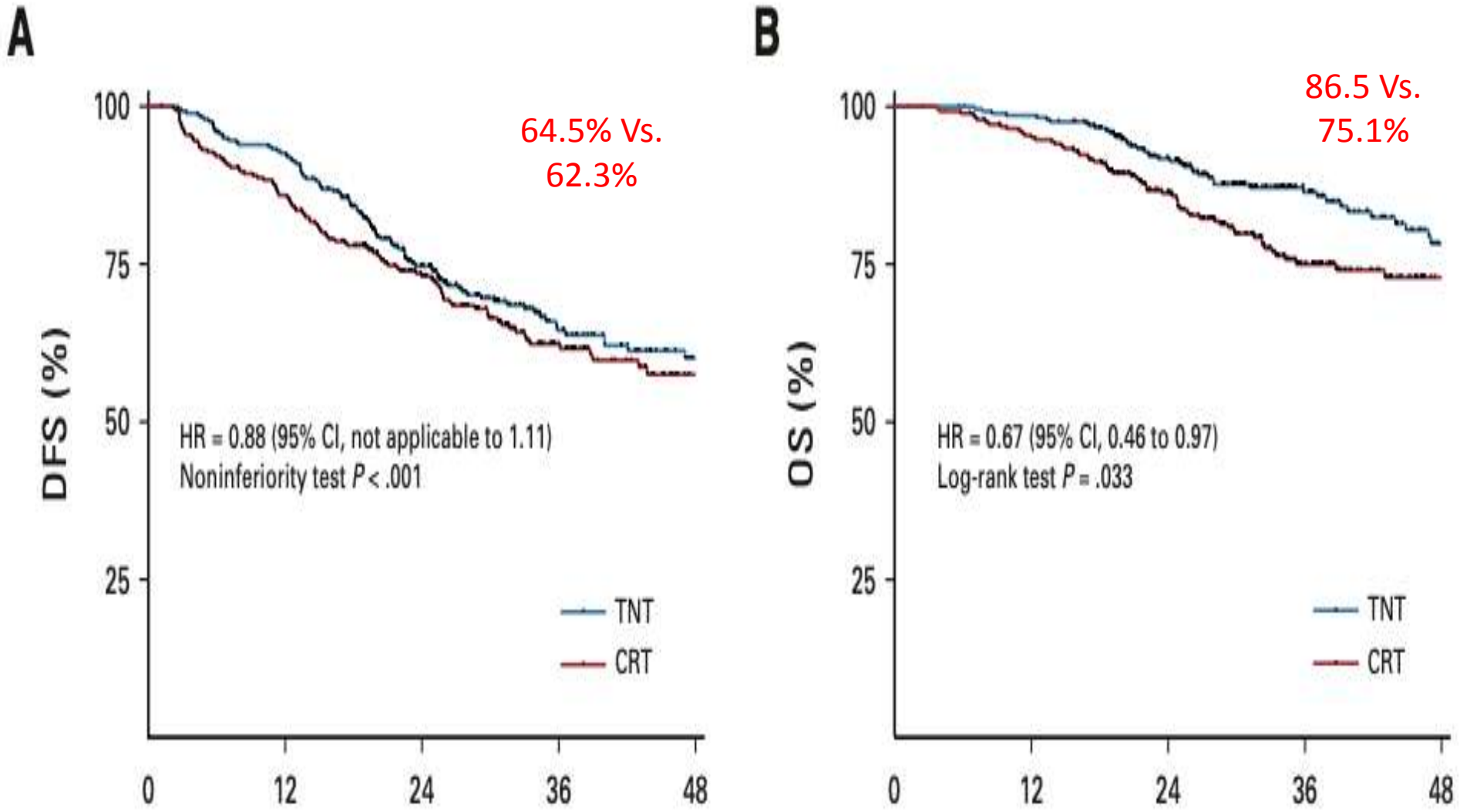
- 599 Patients with locally advanced rectal cancer (T3,T4,N+) of middle or distal 1/3rd rectal cancers were randomly assigned to following arms.

- Arm A: Pelvic radiotherapy 5 fractions of 5 Gy (25Gy) in 1 week followed by 4 cycles of chemotherapy (TNT) and then surgery (SC-TNT).

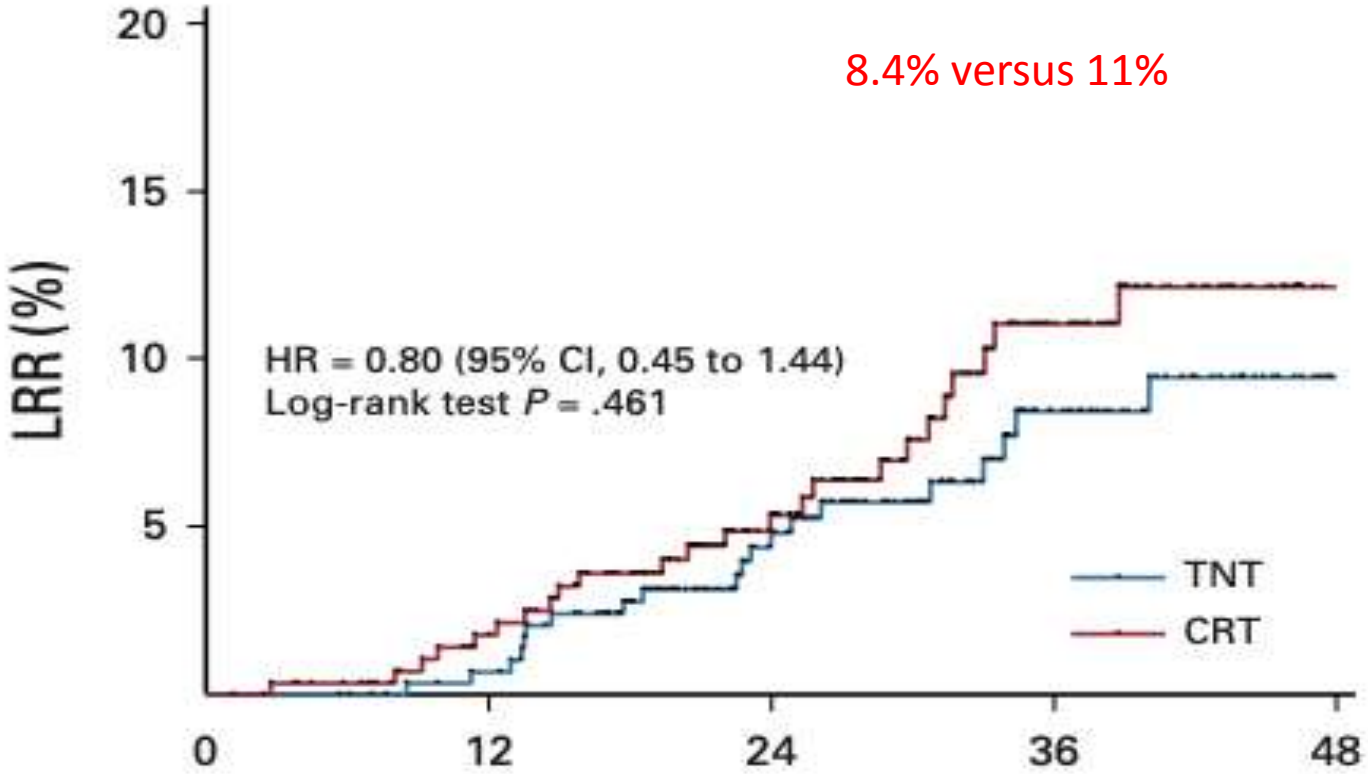
- Arm B: 50 Gy, 2Gy/fraction, in 5 weeks, with concurrent Capecitabine followed by TME and then adjuvant chemotherapy (LC-CRT).

- The primary endpoint was 3-year Disease free survival (DFS).

3 Yrs. DFS & OS with SC-TNT versus LC-CRT



3 Yrs. LRR with SC-TNT versus LC-CRT



8.4% versus 11%

TABLE 3. Summary of Randomized Controlled Trials Comparing TNT and CRT Followed by Surgery in Patients With Locally Advanced Rectal Cancer

			Stage		TNT					Surgery	Postoperative	3-Year	3-Year	3-Year	3-Year
Study	Eligibility (total number)	Treatment Schedules	cT4, %	N+, %	RT	CRT	Regimen	Completion, %	≥ 3 Toxicity, %	% of ITT	Chemotherapy	DFS, %	OS, %	DM, %	LRR, %
STELLAR	cT3-4 or N+ (n = 599)	TNT: 298	15.9	84.8	5 Gy × 5f	—	4 CAPOX	82.6	26.5	77.8	2 CAPOX	64.5	86.5[a]	22.8	8.4
		CRT: 293	12.8	83.5	50 Gy/25f	CAP	—	95.2	12.6	77.4	6 CAPOX	62.3	75.1[a]	24.7	11.0
RAPIDO[16]	cT4 or N2/+	TNT: 462	32	91	5 Gy × 5f	—	8 CAPOX/12 FOLFOX	84.6	47.6	92	—	23.7[b]	89.1	20.0[a]	8.3
	EMVI/MRF+ (n = 912)	CRT: 450	30	92	50 Gy/25f	CAP	—	90.0	24.7	89	8 CAPOX/12 FOLFOX	30.4[b]	88.8	26.8[a]	6.0
Polish II[15]	Fixed cT3, cT4 (n = 515)	TNT: 256	63	–	5 Gy × 5f	—	3 FOLFOX	72	24.2	84	—	53	73[a]	30	22
		CRT: 259	64		50 Gy/25f	CAPOX	—	64	23.5	81	—	52	65[a]	27	21
PRODIGE 23[14]	cT3-4 or N+ (n = 461)	TNT: 231	18	90	50 Gy/25f	CAP	6 FOLFIRINOX	89.6	46.9	92	6 mFOLFOX6/4 CAP	76[a]	91	17[a]	4
		CRT: 230	16	90	50 Gy/25f	CAP	—	98.7	35.6	95	12 mFOLFOX6/8 CAP	69[a]	88	25[a]	6

Abbreviations: c, clinical; CAP, capecitabine; CAPOX, capecitabine, oxaliplatin; CRT, chemoradiotherapy; DFS, disease-free survival; DM, distant metastasis; EMVI, extramural vascular invasion; FOLFIRINOX, oxaliplatin, irinotecan, leucovorin, fluorouracil; FOLOX, fluorouracil, oxaliplatin; ITT, intention-to-treat; LRR, locoregional recurrence; mFOLFOX6, modified FOLFOX6, oxaliplatin, leucovorin, fluorouracil or capecitabine; MRF, mesorectal fascia; N, regional lymph node; OS, overall survival; RT, radiotherapy; T, primary tumor; TNT, total neoadjuvant therapy.

[a]$P < .05$.

[b]Three-year disease-related treatment failure.

- Short Course RT and Long course RT are equally effective as neoadjuvant treatment in terms of local control rates and overall survival in locally advanced rectal cancer.

- Short course RT with immediate surgery has limited effect on tumor shrinkage and downstaging.

- Short course RT with a delay of surgery at least 8 weeks results in better tumor shrinkage and increased pCR as compared with immediate surgery.

- Short course RT is more effective if used as a part of TNT approach as shown by Rapido and Stellar trials.

- Acute effects are more common with LCRT than short course RT.

- Permanent stoma & Anastomotic leakage are more common with short course RT.

- Need for downstaging and long term toxicities should be discussed comprehensively when considering short course RT as a part of neoadjuvant management in locally advanced rectal cancer.

Thanks