

ONLINE SUPPLEMENT

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Table S1
Clinicopathological characteristics analyzed versus non-responders

	Analyzed (n=453)		Non-responders (n=79)		p-value
Treatment group					0.62
Experimental	243	(53.6)	40	(50.6)	
Standard-care	210	(46.4)	39	(49.4)	
Gender					0.03
Male	285	(62.9)	60	(75.9)	
Female	168	(37.1)	19	(24.1)	
Age at randomization (years) (median, IQR)	63	(55-68)	59	(52-67)	0.005
Distance from anal verge (cm)					0.25†
<5 cm	96	(21.2)	23	(29.1)	
5-10 cm	175	(38.6)	22	(27.8)	
≥10 cm	150	(33.1)	24	(30.4)	
Unknown	32	(7.1)	10	(12.7)	
Type of approach					0.02
Laparoscopic	198	(43.7)	46	(58.2)	
Open	219	(48.3)	25	(31.6)	
Laparoscopic converted to open	36	(7.9)	8	(10.1)	
Type of surgery					0.26
(Low) Anterior resection	269	(59.4)	43	(54.4)	
Abdominoperineal resection	170	(37.5)	35	(44.3)	
Hartmann's procedure	12	(2.6)	-		
Other	2	(0.4)	1	(1.3)	
Pathological T-stage *					0.64
ypT0	138	(30.5)	19	(24.1)	
ypTis	3	(0.7)	-		
ypT1	23	(5.1)	6	(7.6)	
ypT2	104	(23.0)	23	(29.1)	
ypT3	163	(36.0)	27	(34.2)	
ypT4	22	(4.9)	4	(5.1)	
Pathological N-stage *					0.47
ypN0	368	(81.2)	63	(79.7)	
ypN1	63	(13.9)	14	(17.7)	
ypN2	22	(4.9)	2	(2.5)	

Data are presented as n (%). Percentages may not equal 100% due to rounding.

Analyzed represents the number of patients who filled in the questionnaire on time.

† p-value calculated in patients in which the distance to the anal verge was known.

* According TNM5

Table S2

Compliance to pre-operative and post-operative treatment

Experimental	(n=243)
All RT fractions	243 (100)
At least 75% of pre-operative chemotherapy	205 (84.4)
Standard-care without post-operative chemotherapy	(n=111)
At least 45 Gy radiotherapy	108 (97.3)
At least 5 weeks of pre-operative chemotherapy	103 (92.9)
Standard-care with post-operative chemotherapy	(n=99)
At least 45 Gy radiotherapy	99 (100)
At least 5 weeks of pre-operative chemotherapy	93 (93.9)
At least 1 cycle of post-operative chemotherapy	99 (100)
At least 75% of post-operative chemotherapy	58 (58.6)

Data are presented as n (%). Only patients who received at least one cycle of post-operative chemotherapy were included in the standard-care group with post-operative chemotherapy group.

Table S3
Quality of life scores on the EORTC QLQ-C30 questionnaire

	EXP (n=243)			STD (n=210)			T-test	STD+ (n=99)			STD- (n=111)			ANOVA§
	n*	mean	SD	n*	mean	SD	p-value	n*	mean	SD	n*	mean	SD	p-value
Function scales														
Global health	242	75.1 (19.6)		208	76.6 (20.5)		0.43	99	74.3 (21.5)		109	78.7 (19.4)		0.22
Physical function	243	86.3 (17.9)		210	87.6 (16.4)		0.44	99	87.6 (18.4)		111	87.6 (14.5)		0.74
Role function	243	83.4 (24.6)		210	85.1 (23.0)		0.46	99	85.9 (22.9)		111	84.4 (23.3)		0.69
Emotional function	243	85.8 (19.1)		208	87.6 (15.5)		0.28	99	85.6 (16.3)		109	89.4 (14.6)		0.17
Cognitive function	243	88.3 (17.4)		207	88.6 (15.9)		0.85	98	89.5 (15.2)		109	87.8 (16.6)		0.76
Social function	243	83.8 (22.9)		207	83.8 (22.4)		1.00	98	84.2 (23.6)		109	83.5 (21.3)		0.98
Symptom scales														
Fatigue	243	20.4 (21.0)		210	19.8 (22.6)		0.79	99	20.9 (23.3)		111	18.9 (22.0)		0.76
Nausea and vomiting	243	2.7 (10.5)		210	2.4 (8.6)		0.69	99	3.0 (9.3)		111	1.8 (7.9)		0.61
Pain	243	15.6 (24.0)		210	12.2 (20.7)		0.12	99	13.0 (21.1)		111	11.6 (20.4)		0.26
Dyspnea	243	12.5 (21.1)		210	11.0 (19.3)		0.42	99	12.1 (18.1)		111	9.9 (20.4)		0.53
Insomnia	242	19.7 (26.5)		209	15.2 (24.0)		0.06	98	16.0 (25.0)		111	14.4 (23.2)		0.15
Appetite loss	243	4.5 (14.3)		210	6.5 (18.3)		0.20	99	8.1 (20.8)		111	5.1 (15.7)		0.18
Constipation	243	10.2 (20.7)		209	9.1 (18.7)		0.57	99	10.8 (20.7)		110	7.6 (16.7)		0.44
Diarrhea	243	11.9 (21.0)		207	15.5 (24.1)		0.10	98	18.0 (26.3)		109	13.1 (21.8)		0.08
Financial difficulties	243	9.1 (21.9)		206	9.1 (22.2)		1.00	98	9.5 (24.9)		108	8.6 (19.5)		0.96
Overall QLQ-C30 score ^β		40.6 (4.6)			40.6 (4.5)		0.93		41.2 (4.8)			40.1 (4.1)		0.23

Percentages may not equal 100% due to rounding.

A higher score on the functional scales represents better functioning and a higher score on the single items represents worse symptoms.

EXP experimental; STD standard-care; STD+ standard-care with post-operative chemotherapy; STD- standard-care without post-operative chemotherapy.

* Number of patients who filled in the concerning question(s)

^β Sum score on all variables.

§ p-value represents the difference in mean scores between the EXP, STD+ and STD- groups.

Grey blocks represents small clinical differences (but not statistically significant) in insomnia (in favor of STD-) and diarrhea (in favor of EXP).

Table S4
Quality of life scores on the EORTC QLQ-CR29 questionnaire

	EXP (n=243)			STD (n=210)			T-test <i>p</i> -value	STD+ (n=99)			STD- (n=111)			ANOVA§ <i>p</i> -value
	n*	mean	SD	n*	mean	SD		n*	mean	SD	n*	mean	SD	
Function scales														
Urinary frequency	238	70.4 (24.9)	206	70.5 (24.0)	0.97	98	68.0 (23.2)	108	72.7 (24.7)	0.40				
Blood and mucus in stool	243	97.0 (7.4)	209	97.2 (7.6)	0.75	98	96.9 (8.7)	111	97.4 (6.4)	0.84				
Stool frequency, non-stoma	118	67.2 (21.9)	91	65.2 (21.8)	0.51	45	64.1 (23.6)	46	66.3 (20.0)	0.71				
Stool frequency, stoma	122	82.9 (21.5)	118	86.3 (18.6)	0.20	51	84.3 (20.1)	67	87.8 (17.3)	0.28				
Body image	243	78.9 (24.9)	210	78.1 (24.1)	0.73	99	80.9 (21.6)	111	75.7 (26.0)	0.29				
Sexual items														
Sexual activity (male)	138	71.0 (24.4)	144	67.8 (24.9)	0.25	68	68.1 (24.4)	76	67.5 (25.5)	0.51				
Sexual functioning (male) ^a	76	59.4 (20.8)	83	52.4 (21.2)	0.04	39	55.6 (20.6)	44	49.6 (21.1)	0.05				
Sexual activity (female)	92	85.7 (17.4)	65	82.1 (20.5)	0.23	30	77.8 (19.2)	35	85.7 (21.6)	0.12				
Sexual functioning (female) ^a	34	58.5 (27.1)	22	58.7 (27.9)	0.98	13	48.1 (29.5)	9	74.1 (16.9)	0.09				
Single items														
Urinary incontinence	240	12.9 (19.6)	205	13.7 (21.6)	0.71	97	12.0 (18.7)	108	15.1 (23.8)	0.52				
Dysuria	239	3.9 (12.0)	206	3.2 (12.3)	0.56	98	2.7 (10.3)	108	3.7 (13.9)	0.72				
Abdominal pain	243	10.3 (21.0)	210	12.5 (20.8)	0.25	98	11.1 (19.6)	111	13.8 (21.8)	0.34				
Buttock pain	242	10.6 (20.2)	208	12.5 (22.3)	0.35	99	12.9 (23.8)	110	12.1 (21.0)	0.62				
Bloating abdomen	243	13.4 (21.9)	209	15.5 (21.7)	0.33	98	16.8 (23.0)	110	14.2 (20.4)	0.43				
Dry mouth	242	16.5 (24.5)	210	15.2 (23.3)	0.57	99	14.1 (21.9)	111	16.2 (24.6)	0.70				
Hair loss	243	4.3 (13.7)	209	3.2 (12.7)	0.40	99	1.7 (8.8)	111	4.5 (15.2)	0.22				
Taste loss	243	7.7 (18.8)	210	4.9 (13.9)	0.08	98	4.4 (14.0)	111	5.5 (13.9)	0.20				
Anxiety	243	28.7 (27.4)	208	27.1 (24.0)	0.52	98	29.6 (23.9)	110	24.8 (24.1)	0.34				
Weight	243	14.1 (24.7)	210	16.0 (21.4)	0.39	99	15.8 (20.9)	111	16.2 (22.0)	0.68				
Single items, non-stoma patients														

Flatulence	118	41.8 (28.0)	90	43.3 (31.0)	0.71	43	37.2 (31.9)	47	48.9 (29.4)	0.15
Fecal incontinence	118	19.2 (24.4)	90	21.1 (25.2)	0.58	44	19.7 (26.2)	46	22.5 (24.4)	0.75
Sore skin	117	14.8 (23.8)	91	16.1 (24.0)	0.70	44	13.6 (25.2)	47	18.4 (22.9)	0.59
Embarrassment	118	27.9 (31.8)	92	28.6 (28.6)	0.83	45	23.0 (27.4)	47	34.0 (29.1)	0.21
Single items, stoma patients										
Stoma care problems	117	4.0 (15.3)	114	2.9 (10.5)	0.54	47	2.1 (8.2)	67	3.5 (11.8)	0.72
Flatulence	124	30.1 (26.0)	120	30.6 (26.8)	0.90	50	33.3 (26.9)	70	28.6 (26.8)	0.62
Fecal incontinence	123	18.4 (23.1)	117	16.0 (20.3)	0.38	51	14.4 (18.0)	66	17.2 (22.1)	0.54
Sore skin	123	16.5 (24.3)	117	15.7 (21.7)	0.66	50	16.7 (22.6)	67	14.9 (21.1)	0.88
Embarrassment	123	29.0 (31.4)	118	22.3 (25.8)	0.07	51	25.5 (24.6)	67	19.9 (26.6)	0.12

Percentages may not equal 100% due to rounding.

A higher score on the functional scales represents better functioning and a higher score on the single items represents worse symptoms.

EXP experimental; *STD* standard-care; *STD+* standard-care with post-operative chemotherapy; *STD-* standard-care without post-operative chemotherapy.

^a Sexual functioning items only apply to sexually active patients.

* Number of patients who filled in the concerning question(s).

§ p-value represents the difference in mean scores between the EXP, STD+ and STD- groups.

Grey blocks represent clinical differences (which are not statistically significant).

- Differences **between EXP and STD** in favor of **STD**: embarrassment stoma (small)
- Differences **between EXP and STD-** in favor of **STD-**: female sexual functioning (moderate), embarrassment stoma (small)
- Differences **between EXP and STD+** in favor of **EXP**: female sexual functioning (moderate)
- Differences **between STD+ and STD-** in favor of **STD+**: flatulence non-stoma (moderate), embarrassment non-stoma (small)
- Differences **between STD+ and STD-** in favor of **STD-**: female sexual activity (small), female sexual functioning (large), embarrassment stoma (small)

Table S5
Quality of life scores on the EORTC QLQ-CIPN20 questionnaire

	EXP (n=243)			STD (n=210)			T-test <i>p</i> -value	STD+ (n=99)			STD- (n=111)			ANOVA§ <i>p</i> -value
	n*	mean	SD	n*	mean	SD		n*	mean	SD	n*	mean	SD	
Sensory scale		20.1 (18.9)		11.0 (13.7)		<0.0001		15.8 (15.9)		6.6 (9.4)		<0.0001		
Tingling fingers or hands	238	21.3 (28.0)	208	14.4 (23.7)	0.005	99	19.9 (27.3)	109	9.5 (18.8)	<0.0001				
Tingling toes or feet	238	42.7 (37.3)	207	20.3 (28.8)	<0.0001	98	32.7 (32.5)	109	9.2 (19.2)	<0.0001				
Numbness fingers or hands	238	16.9 (25.4)	207	12.2 (22.0)	0.04	98	18.0 (26.3)	109	7.0 (15.8)	<0.0001				
Numbness toes or feet	238	34.5 (37.4)	208	17.8 (27.8)	<0.0001	99	27.9 (31.8)	109	8.6 (19.5)	<0.0001				
Pain fingers or hands	238	6.9 (19.0)	207	4.3 (15.0)	0.12	99	5.4 (17.0)	108	3.4 (12.8)	0.22				
Pain toes or feet	236	20.2 (33.4)	208	6.4 (18.0)	<0.0001	99	9.8 (22.5)	109	3.4 (12.0)	<0.0001				
Trouble standing or walking	236	19.8 (30.7)	207	9.3 (21.5)	<0.0001	98	14.3 (25.8)	109	4.9 (16.0)	<0.0001				
Trouble distinguishing temperature	238	5.5 (17.1)	206	2.3 (11.7)	0.02	99	3.0 (12.7)	107	1.6 (10.6)	0.06				
Trouble hearing	237	13.1 (24.2)	204	11.4 (21.2)	0.47	98	10.2 (18.8)	106	12.6 (23.2)	0.57				
Motor scale		11.7 (13.6)		8.5 (12.2)	0.11		10.8 (14.1)		6.3 (9.8)	0.002				
Cramps fingers or hands	238	9.7 (20.4)	208	7.5 (19.2)	0.26	99	9.4 (22.4)	109	5.8 (15.6)	0.22				
Cramps toes or feet	238	19.3 (28.9)	206	15.9 (25.0)	0.18	99	18.5 (26.6)	107	13.4 (23.3)	0.16				
Trouble holding a pen	238	4.5 (14.6)	207	3.4 (12.0)	0.39	99	4.7 (14.3)	108	2.2 (9.4)	0.28				
Trouble handling small objects	238	15.3 (25.2)	208	10.7 (19.3)	0.03	99	14.5 (20.8)	109	7.3 (17.2)	0.008				
Weakness in hands	238	11.9 (21.9)	208	10.6 (20.9)	0.51	99	12.5 (20.5)	109	8.9 (21.1)	0.39				
Feet dropped downwards	238	6.3 (19.2)	208	3.0 (14.1)	0.04	99	3.0 (15.1)	109	3.1 (13.3)	0.13				
Weakness in legs	238	14.8 (26.1)	205	11.4 (20.9)	0.05	98	12.6 (22.7)	107	8.4 (18.9)	0.07				
Trouble using the pedals	198	6.6 (18.0)	167	3.2 (14.7)	0.05	77	4.8 (17.7)	90	1.9 (11.6)	0.08				
Autonomic scale		7.9 (13.9)		7.2 (14.6)	0.61		8.8 (16.4)		5.7 (12.6)	0.25				
Dizziness	238	9.1 (19.0)	204	8.8 (18.4)	0.88	98	11.2 (20.8)	106	6.6 (15.5)	0.21				
Blurred vision	237	6.6 (15.0)	205	5.5 (15.5)	0.46	98	6.5 (16.3)	107	4.7 (14.8)	0.53				
Erection disorders	198	6.6 (18.0)	167	3.2 (14.7)	0.05	77	4.8 (17.7)	90	1.9 (11.6)	0.08				

Overall QLQ-CIPN20 score ^β	15.3 (14.2)	9.5 (11.5)	<0.0001	13.2 (13.4)	6.0 (8.0)	<0.0001
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Percentages may not equal 100% due to rounding.

A lower score represents better functioning.

EXP experimental; *STD* standard-care; *STD+* standard-care with post-operative chemotherapy; *STD-* standard-care without post-operative chemotherapy.

* Number of patients who filled in the concerning question(s)

^β Sum score on all variables except trouble using the pedals and erection disorders.

§ p-value represents the difference in mean scores between the *EXP*, *STD+* and *STD-* groups.

Grey blocks represent clinical differences (which are not statistically significant).

- Differences **between EXP and STD-** in favor of **STD-**: cramps toes or feet (small), weakness in legs (small)
- Differences **between EXP and STD+** in favor of **STD+**: tingling toes or feet (moderate), numbness in toes or feet (small), trouble standing or walking (small)
- Differences **between STD+ and STD-** in favor of **STD-**: tingling fingers or hands (moderate), pain in toes or feet (small), trouble standing or walking (small), cramps toes or feet (small), trouble handling small objects (small)

Table S6

LARS scores in patients without a stoma three years after curative surgery

	EXP (n=102)	STD (n=73)	T-test p-value		STD+ (n=33)	STD- (n=40)	X²† p-value
LARS score			0.02§				0.04
No LARS	22 (21.6)	8 (11.0)			3 (9.1)	5 (12.5)	
Minor LARS	20 (19.6)	10 (13.7)			6 (18.2)	4 (10.0)	
Major LARS	60 (58.8)	55 (75.3)			24 (72.7)	31 (77.5)	

Data is presented as n (%).

EXP experimental; *STD* standard-care; *STD+* standard-care with post-operative chemotherapy; *STD-* standard-care without post-operative chemotherapy; *SD* standard deviation; *LARS* low anterior resection syndrome.

§ Non-parametric test.

† p-value represents the difference between the EXP, STD+ and STD- groups.

Table S7

Toxicity per follow-up moment regarding two subgroups.

	At 6 months							At 12 months												
	Grade 1-2			Grade ≥3				Grade 1-2			Grade ≥3									
	EXP (n=354)		STD (n=352)	EXP (n=354)		STD (n=352)		EXP (n=341)		STD (n=314)	EXP (n=341)		STD (n=314)							
	n	(%)	n	(%)	p-value	n	(%)	n	(%)	p-value	n	(%)	n	(%)	p-value					
Any	165	(47)	161	(46)	0.82	31	(9)	35	(10)	0.59	148	(43)	108	(34)	0.02	25	(7)	19	(6)	0.51
Blood and lymphatic	6	(2)	7	(2)	0.77	0	(0)	1	(<1)	0.32	3	(1)	3	(1)	0.92	0	(0)	0	(0)	1.00
Gastrointestinal, any	61	(17)	71	(20)	0.32	8	(2)	12	(3)	0.36	58	(17)	52	(17)	0.88	6	(2)	6	(2)	0.89
Fatigue	30	(9)	59	(17)	0.001	1	(<1)	1	(<1)	1.00	14	(4)	21	(7)	0.14	0	(0)	0	(0)	1.00
Allergic reaction	0	(0)	1	(<1)	0.32	0	(0)	0	(0)	1.00	0	(0)	0	(0)	1.00	0	(0)	0	(0)	1.00
Weight loss	11	(3)	5	(1)	0.13	0	(0)	0	(0)	1.00	3	(1)	2	(1)	0.72	0	(0)	0	(0)	1.00
Nervous system, any	118	(33)	77	(22)	0.001	5	(1)	0	(0)	0.03	96	(28)	43	(14)	<0.0001	3	(1)	2	(1)	0.72
Respiratory	3	(1)	9	(3)	0.08	0	(0)	0	(0)	1.00	1	(<1)	0	(0)	0.34	1	(<1)	0	(0)	0.34
Renal and urinary	24	(7)	19	(5)	0.44	4	(1)	3	(1)	0.71	13	(4)	16	(5)	0.43	4	(1)	4	(1)	0.91
Skin, any	11	(3)	30	(9)	0.002	0	(0)	2	(1)	0.16	5	(2)	3	(1)	0.55	0	(0)	1	(<1)	0.30
Sexual	27	(8)	25	(7)	0.79	0	(0)	1	(<1)	0.32	27	(8)	27	(9)	0.75	1	(<1)	1	(<1)	0.95
Other	54	(15)	69	(20)	0.13	17	(5)	22	(6)	0.40	36	(11)	31	(10)	0.77	14	(4)	6	(2)	0.10

EXP experimental; *STD* standard-care.

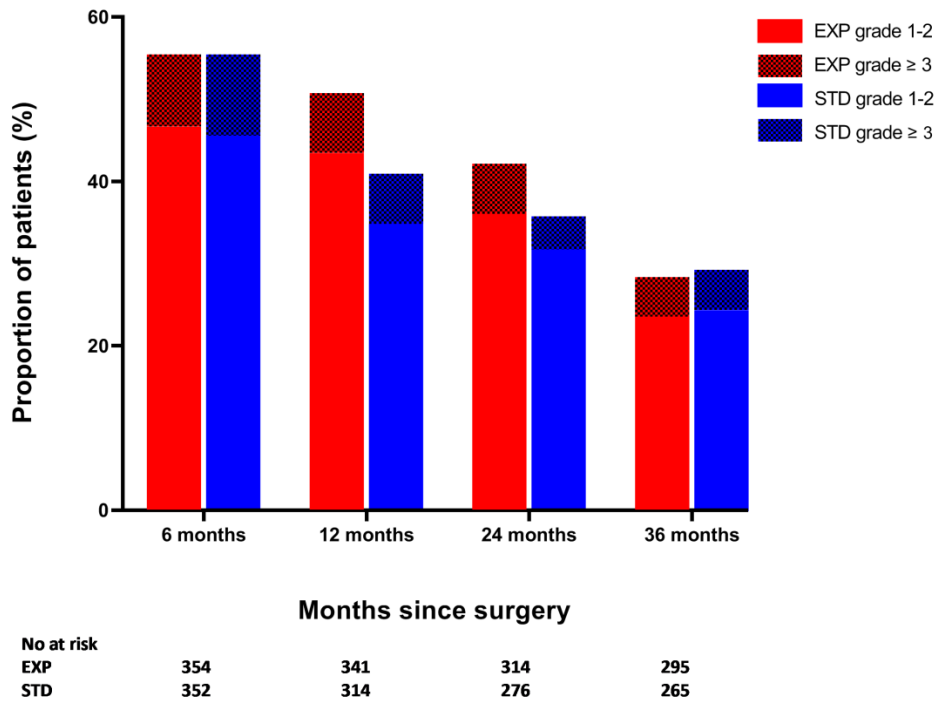
Table S7

Toxicity per follow-up moment regarding two subgroups (continued)

	At 24 months							At 36 months												
	Grade 1-2			Grade ≥3				Grade 1-2			Grade ≥3									
	EXP (n=314)		STD (n=276)	p-value	EXP (n=314)		STD (n=276)	p-value	EXP (n=295)		STD (n=265)	p-value	EXP (n=295)		STD (n=265)	p-value				
n	(%)	n	(%)		n	(%)	n		(%)	n	(%)		n	(%)	n		(%)			
Any	113	(36)	88	(32)	0.29	19	(6)	11	(4)	0.26	69	(23)	65	(25)	0.75	14	(5)	13	(5)	0.93
Blood and lymphatic	0	(0)	1	(<1)	0.29	0	(0)	0	(0)	1.00	1	(<1)	3	(1)	0.27	0	(0)	0	(0)	1.00
Gastrointestinal, any	52	(17)	48	(17)	0.79	6	(2)	4	(1)	0.67	35	(12)	39	(15)	0.32	3	(1)	5	(2)	0.39
Fatigue	11	(4)	12	(4)	0.60	0	(0)	0	(0)	1.00	8	(3)	10	(4)	0.48	0	(0)	0	(0)	1.00
Allergic reaction	0	(0)	0	(0)	1.00	0	(0)	0	(0)	1.00	0	(0)	0	(0)	1.00	0	(0)	0	(0)	1.00
Weight loss	3	(1)	4	(1)	0.58	0	(0)	0	(0)	1.00	0	(0)	0	(0)	1.00	0	(0)	0	(0)	1.00
Nervous system, any	72	(23)	23	(8)	<0.0001	1	(<1)	0	(0)	0.35	41	(14)	17	(6)	0.004	1	(<1)	0	(0)	0.34
Respiratory	0	(0)	1	(<1)	0.29	0	(0)	0	(0)	1.00	0	(0)	0	(0)	1.00	0	(0)	0	(0)	1.00
Renal and urinary	10	(3)	9	(3)	0.96	4	(1)	2	(1)	0.51	10	(3)	10	(4)	0.81	3	(1)	2	(1)	0.74
Skin, any	5	(2)	1	(<1)	0.14	0	(0)	0	(0)	1.00	1	(<1)	2	(1)	0.50	0	(0)	0	(0)	1.00
Sexual	21	(7)	27	(10)	0.17	0	(0)	0	(0)	1.00	14	(5)	24	(9)	0.043	1	(<1)	0	(0)	0.34
Other	25	(8)	33	(12)	0.10	14	(5)	6	(2)	0.13	20	(7)	16	(6)	0.72	10	(3)	6	(2)	0.43

EXP experimental; *STD* standard-care.

A



B

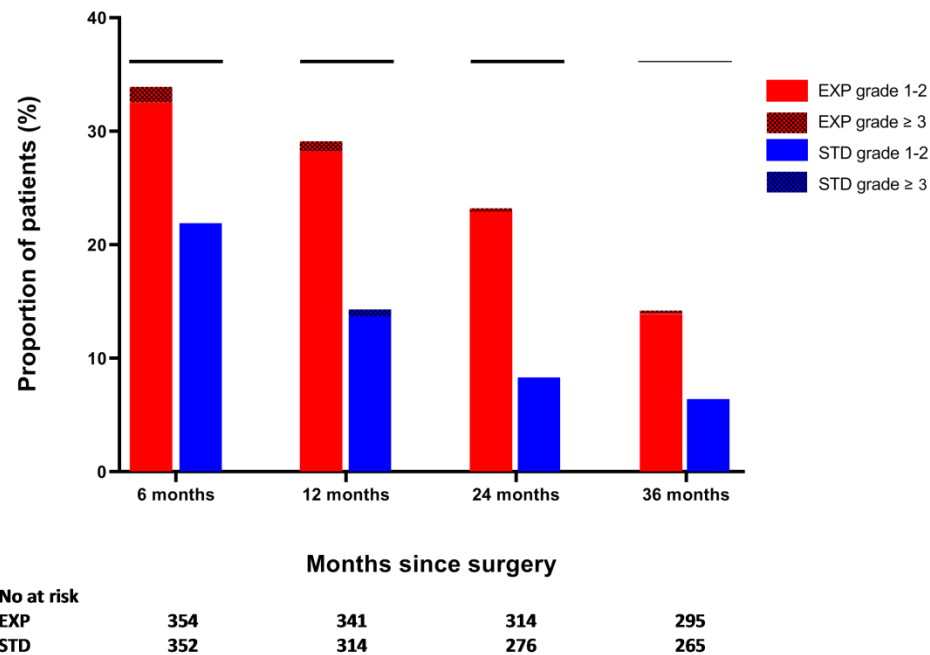


Figure S1

(A) Toxicity per follow-up moment regarding two subgroups, (B) Neurotoxicity per follow-up moment regarding two subgroups.

n represents the number of evaluable patients (excluding missing).

Toxicity was scored with a range of 3 months at 6, 12, 24, and 36 months.

The horizontal lines represent statistically significant differences in any toxicity grade between the groups; non-bold line $p=0.002$ and bold line $p<0.0001$.

EXP experimental; STD standard-care.

Table S8

Late toxicity regarding three subgroups

	At 6 months													
	Grade 1-2					Grade ≥ 3								
	EXP (n=354)		STD+ (n=174)		STD- (n=178)		EXP (n=354)		STD+ (n=174)		STD- (n=178)	p-value		
n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)		p-value	
Any	165	(47)	101	(58)	60	(34)	< 0.0001	31	(9)	15	(9)	20	(11)	0.61
Blood and lymphatic	0	(0)	1	(1)	0	(0)	0.22	0	(0)	1	(1)	0	(0)	0.22
Gastrointestinal, any	61	(17)	37	(21)	34	(19)	0.53	8	(2)	4	(2)	8	(5)	0.30
Fatigue	30	(9)	44	(25)	15	(8)	< 0.0001	1	(<1)	1	(1)	0	(0)	0.60
Allergic reaction	0	(0)	1	(1)	0	(0)	0.22	0	(0)	0	(0)	0	(0)	1.00
Weight loss	11	(3)	1	(1)	4	(2)	0.19	0	(0)	0	(0)	0	(0)	1.00
Nervous system, any	118	(33)	74	(43)	3	(2)	< 0.0001	5	(1)	0	(0)	0	(0)	0.08
Respiratory	3	(1)	8	(5)	1	(5)	0.003	0	(0)	0	(0)	0	(0)	1.00
Renal and urinary	24	(7)	3	(2)	16	(9)	0.01	4	(1)	0	(0)	3	(2)	0.26
Skin, any	11	(3)	26	(15)	4	(2)	< 0.0001	0	(0)	2	(1)	0	(0)	0.05
Sexual	27	(8)	8	(5)	17	(10)	0.20	0	(0)	1	(1)	0	(0)	0.22
Other	54	(15)	39	(22)	30	(17)	0.12	17	(5)	9	(6)	13	(7)	0.48

EXP experimental; STD standard-care; STD+ standard-care with post-operative chemotherapy; STD- standard-care without post-operative chemotherapy.

Table S8

Late toxicity regarding three subgroups (continued)

	At 12 months													
	Grade 1-2					Grade ≥ 3								
	EXP (n=341)		STD+ (n=156)		STD- (n=158)	p-value	EXP (n=341)		STD+ (n=156)		STD- (n=158)	p-value		
n	(%)	n	(%)	n	(%)		n	(%)	n	(%)				
Any	148	(43)	64	(41)	44	(28)	0.004	25	(7)	7	(5)	12	(8)	0.44
Blood and lymphatic	0	(0)	0	(0)	1	(1)	0.21	0	(0)	0	(0)	0	(0)	1.00
Gastrointestinal, any	58	(17)	26	(17)	26	(17)	0.99	6	(2)	1	(1)	5	(3)	0.25
Fatigue	14	(4)	14	(9)	7	(4)	0.07	0	(0)	0	(0)	0	(0)	1.00
Allergic reaction	0	(0)	0	(0)	0	(0)	1.00	0	(0)	0	(0)	0	(0)	1.00
Weight loss	3	(1)	2	(1)	0	(0)	0.40	0	(0)	0	(0)	0	(0)	1.00
Nervous system, any	96	(28)	41	(26)	2	(1)	<0.0001	3	(1)	1	(1)	1	(1)	0.94
Respiratory	1	(<1)	0	(0)	0	(0)	0.63	1	(<1)	0	(0)	0	(0)	0.63
Renal and urinary	13	(4)	7	(5)	9	(6)	0.64	4	(1)	1	(1)	3	(2)	0.59
Skin, any	5	(2)	2	(1)	1	(1)	0.73	0	(0)	1	(1)	0	(0)	0.20
Sexual	27	(8)	13	(8)	14	(9)	0.94	1	(<1)	1	(1)	0	(0)	0.59
Other	36	(11)	12	(8)	19	(12)	0.43	14	(4)	2	(1)	4	(3)	0.22

EXP experimental; STD standard-care; STD+ standard-care with post-operative chemotherapy; STD- standard-care without post-operative chemotherapy.

Table S8

Late toxicity regarding three subgroups (continued)

	At 24 months													
	Grade 1-2					Grade ≥ 3								
	EXP (n=314)		STD+ (n=131)		STD- (n=145)		EXP (n=314)		STD+ (n=131)		STD- (n=145)			
n	(%)	n	(%)	n	(%)	p-value	n	(%)	n	(%)	n	(%)	p-value	
Any	113	(36)	46	(35)	42	(29)	0.32	19	(6)	6	(5)	5	(3)	0.48
Blood and lymphatic	0	(0)	0	(0)	1	(1)	0.22	0	(0)	0	(0)	0	(0)	1.00
Gastrointestinal, any	52	(17)	27	(21)	21	(15)	0.39	6	(2)	2	(2)	2	(1)	0.91
Fatigue	11	(4)	5	(4)	7	(5)	0.79	0	(0)	0	(0)	0	(0)	1.00
Allergic reaction	0	(0)	0	(0)	0	(0)	1.00	0	(0)	0	(0)	0	(0)	1.00
Weight loss	3	(1)	2	(2)	2	(1)	0.85	0	(0)	0	(0)	0	(0)	1.00
Nervous system, any	72	(23)	21	(16)	2	(1)	<0.0001	1	(<1)	0	(0)	0	(0)	0.64
Respiratory	0	(0)	1	(1)	0	(0)	0.17	0	(0)	0	(0)	0	(0)	1.00
Renal and urinary	10	(3)	4	(3)	5	(3)	0.98	4	(1)	1	(1)	1	(1)	0.80
Skin, any	5	(2)	0	(0)	1	(1)	0.28	0	(0)	0	(0)	0	(0)	1.00
Sexual	21	(7)	13	(10)	14	(10)	0.39	0	(0)	0	(1)	0	(0)	1.00
Other	25	(8)	15	(12)	18	(12)	0.26	14	(5)	2	(2)	4	(3)	0.26

EXP experimental; STD standard-care; STD+ standard-care with post-operative chemotherapy; STD- standard-care without post-operative chemotherapy.

Table S8

Late toxicity regarding three subgroups (continued)

	At 36 months													
	Grade 1-2					Grade ≥ 3								
	EXP (n=295)		STD+ (n=123)		STD- (n=142)		EXP (n=295)		STD+ (n=123)		STD- (n=142)			
n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	p-value		
Any	69	(23)	31	(25)	34	(24)	0.93	14	(5)	4	(3)	9	(6)	0.50
Blood and lymphatic	1	(<1)	1	(1)	2	(1)	0.46	0	(0)	0	(0)	0	(0)	1.00
Gastrointestinal, any	35	(12)	20	(16)	19	(13)	0.48	3	(1)	1	(1)	4	(3)	0.27
Fatigue	8	(3)	5	(4)	5	(4)	0.76	0	(0)	0	(0)	0	(0)	1.00
Allergic reaction	0	(0)	0	(0)	0	(0)	1.00	0	(0)	0	(0)	0	(0)	1.00
Weight loss	0	(0)	0	(0)	0	(0)	1.00	0	(0)	0	(0)	0	(0)	1.00
Nervous system, any	41	(14)	13	(11)	4	(3)	0.002	1	(<1)	0	(0)	0	(0)	0.64
Respiratory	0	(0)	0	(0)	0	(0)	1.00	0	(0)	0	(0)	0	(0)	1.00
Renal and urinary	10	(3)	3	(2)	7	(5)	0.54	3	(1)	1	(1)	1	(1)	0.94
Skin, any	1	(<1)	0	(0)	2	(1)	0.23	0	(0)	0	(0)	0	(0)	1.00
Sexual	14	(5)	14	(11)	10	(7)	0.05	1	(<1)	0	(0)	0	(0)	0.64
Other	20	(7)	7	(6)	9	(6)	0.92	10	(3)	0	(0)	6	(4)	0.09

EXP experimental; STD standard-care; STD+ standard-care with post-operative chemotherapy; STD- standard-care without post-operative chemotherapy.

Information on the EORTC QLQ-C30 questionnaire

The EORTC QLQ-C30 (1) is a validated questionnaire to measure health-related QoL in cancer patients. The questionnaire consists of five different functional scales (global health, physical, role, cognitive, emotional, and social functioning), three symptom scales (fatigue, pain, and nausea/vomiting) and six single items (dyspnea, appetite loss, sleep disturbance, constipation, diarrhea and financial impact).

Reference

1. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European organization for research and treatment of cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85(5):365–76.

Information on the EORTC QLQ-CR29 questionnaire

The EORTC QLQ-CR29 (2), is divided into four function scales (urine frequency, blood and mucus in stool, stool frequency and body image) and 19 single items (urine incontinence, dysuria, abdominal pain, buttock pain, bloating, dry mouth, hair loss, taste, anxiety, weight, flatulence, fecal incontinence, sore skin, embarrassment, stoma care problems, sexual interest (men), sexual interest (women), impotence and dyspareunia). In addition, a higher score on the sexual items corresponds to a higher degree of health-related quality of life.

Reference

2. van der Hout A, Neijenhuijs KI, Jansen F, van Uden-Kraan CF, Aaronson NK, Groenvold M, et al. Measuring health-related quality of life in colorectal cancer patients: systematic review of measurement properties of the EORTC QLQ-CR29. *Support Care Cancer*. 2019;27(7):2395–412.

Information on the EORTC QLQ-CIPN20 questionnaire

The EORTC QLQ-CIPN20 (3) assesses symptoms and function limitations related to chemotherapy-induced peripheral neuropathy during the past week. This questionnaire is divided into three scales: sensory scale (tingling, numbness, pain, instability when walking or standing, distinguishing temperature, and hearing), motor scale (cramps, writing, manipulation small objects and, weakness) and autonomic scale (vision, dizziness after changing position and, erection disorder).

Reference

3. Postma TJ, Aaronson NK, Heimans JJ, Muller MJ, Hildebrand JG, Delattre JY, et al. The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: The QLQ-CIPN20. *Eur J Cancer*. 2005.

Information on the LARS score

Bowel dysfunction was scored among patients without a stoma by the validated LARS score consisting of five questions about incontinence for flatus and liquid stool, frequency, clustering, and urgency and results were scored in 0-42 points (4, 5). A score of 0-20 points represents no LARS, 21-29 points minor LARS, and 30-42 points major LARS. Patients with missing items in the LARS score were excluded.

Reference

4. Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: Development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. *Ann Surg.* 2012;255(5):922–8.
5. Juul T, Ahlberg M, Biondo S, Emmertsen KJ, Espin E, Jimenez LM, et al. International validation of the low anterior resection syndrome score. *Ann Surg.* 2014;259(4):728–34.