Supplementary Online Content

Kitz J, Fokas E, Beissbarth T, et al; German Rectal Cancer Study Group. Association of plane of total mesorectal excision with prognosis of rectal cancer: secondary analysis of the CAO/ARO/AIO-04 phase 3 randomized clinical trial *JAMA* Surg. Published online June 6, 2018. doi:10.1001/jamasurg.2018.1607

This supplementary material has been provided by the authors to give readers additional information about their work.

eMETHODS

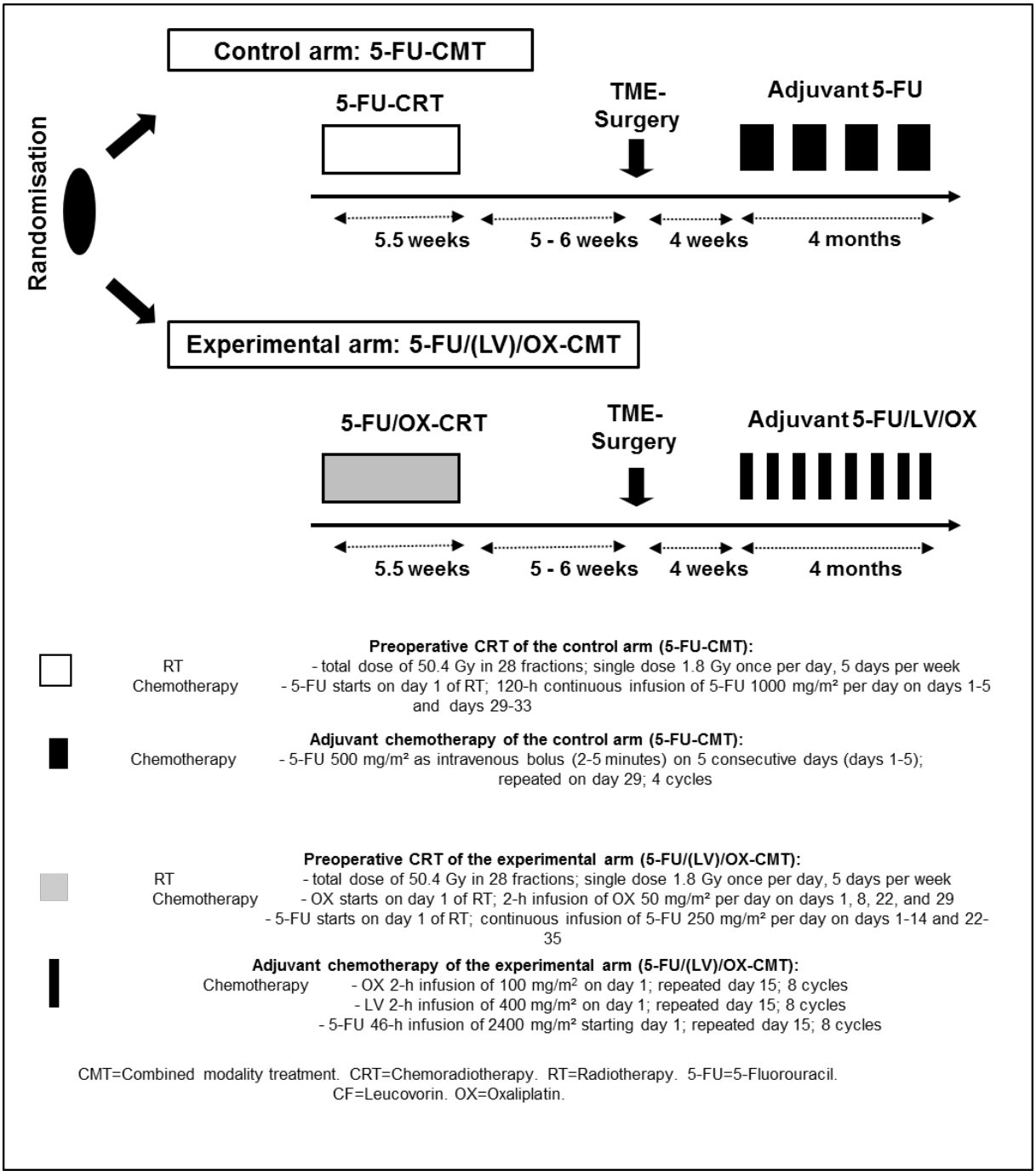
Study design and participants

Patients with rectal adenocarcinoma up to 12 cm above the anal verge with cT3-4 and/or lymph node-positive disease were randomly assigned to receive either standard 5-FU-based CRT (control arm) or oxaliplatin plus 5-FU-based preoperative CRT (investigational arm). Postoperative chemotherapy was administered in both study arms. Surgery was performed 5-6 weeks after completion of CRT using TME, and postoperative chemotherapy was initiated 4 weeks after surgery. Randomization was performed using computer-generated block-randomization codes stratified by center, clinical T category (cT1–4 *vs* cT4), and clinical N category (cN0 *vs* cN1–2) without masking. DFS was the primary endpoint. We hypothesized that addition of oxaliplatin would improve the primary endpoint DFS improve from 75% in the control arm to 82% in the investigational arm at 3-years (hazard ratio of 0.81). The sample size required in this trial was 1200 patients using a power of 80% and a type I error of 5%. Secondary endpoints included the plane (quality) of TME surgery, pathological complete response, resection status, the proportion of patients having R0 resection, the number of patients having sphincter-sparing surgery, overall survival, local and distant recurrence, acute and late toxicity.
Safety and compliance analyses included patients as treated, efficacy endpoints were examined using the intention-to-treat principle. The trial registration number was number NCT00349076 (ClinicalTrials.gov).

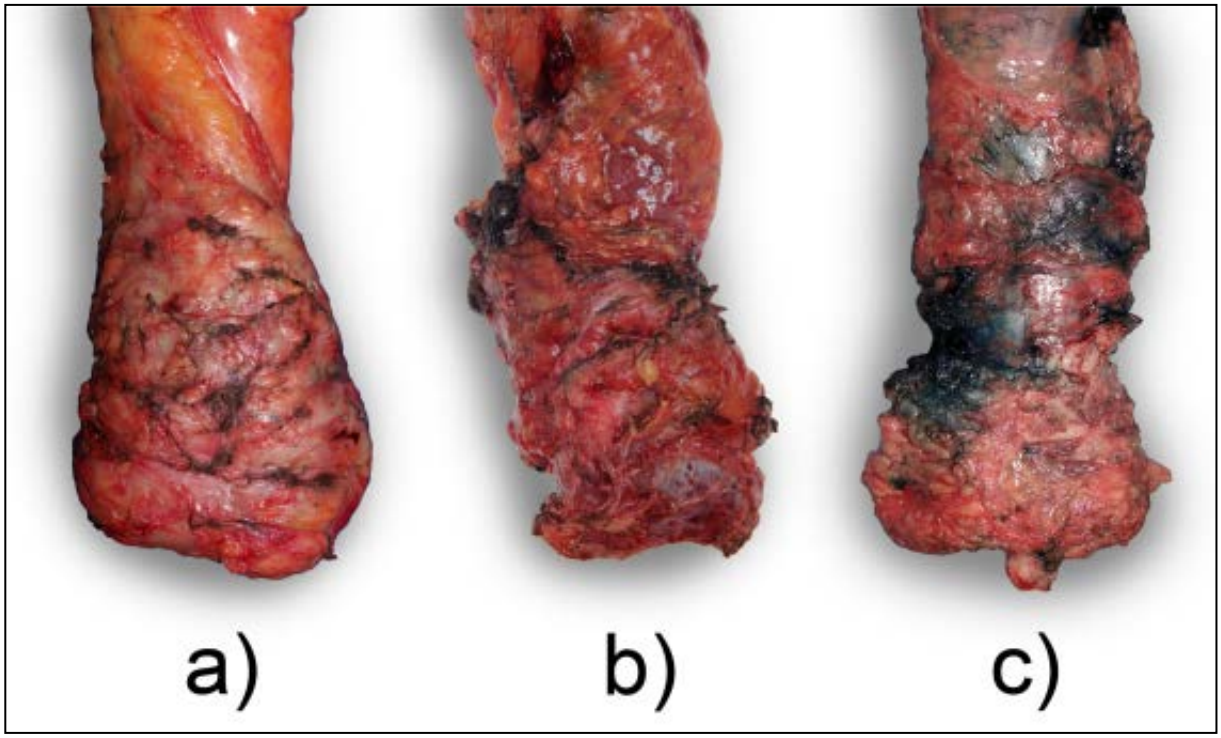
Follow-up

Follow-up examinations were performed at 3-month intervals during the first 2 years after surgical operation, and then annually up to 5 years. Follow-up included patient history, physical examination, ultrasound of the abdomen, and serum carcinoembryonic antigen. Computed tomography of the abdomen and pelvis was repeated 3 months after treatment completion. Colonoscopy was conducted at 6 months if previously omitted, otherwise at 1 year and 5 years. Chest radiography was performed on an annual basis up to a total of 5 years post-treatment. Histological confirmation was advocated in case of suspicious clinical and radiological findings indicating locoregional and/or distant recurrence.

eFigure 1. Treatment schedule of the CAO/ARO/AIO-04 randomized phase 3 trial.



eFigure 2. Total mesorectal excision (TME) quality in surgical specimens. Examples of ***(a)*** mesorectal plane (TME quality: "good") with complete and smooth surface and without coning; ***(b)*** intramesorectal plane (TME quality "moderate") with moderately irregular surface; ***(c)*** muscularis propria plane (TME quality "poor") with severely irregular surface.



eTable 1. Association of the pathologist-based quality of TME with pretreatment patient and tumor factors in operated patients receiving preoperative 5-FU based chemoradiotherapy with or without oxaliplatin

	Total N (%)	Mesorectal N (%)	Intramesorectal N (%)	muscularis propria N (%)	P-value
	1152 (100%)	930 (80.7%)	169 (14.7%)	53 (4.6%)	
Study Arm (randomized)					
5-FU	588 (51.0%)	475 (80.8%)	84 (14.3%)	29 (4.9%)	0.820
5-FU + Oxaliplatin	564 (49.0%)	455 (80.7%)	85 (15.1%)	24 (4.3%)	
Age - Mean (SD)	62.2 (±10.0)	61.9 (±10.0)	63.6 (±9.5)	62.3 (±10.5)	
<= median 63.5 years	578 (50.2%)	475 (82.2%)	78 (13.5%)	25 (4.3%)	0.450
> median 63.5 years	574 (49.8%)	455 (79.3%)	91 (15.9%)	28 (4.9%)	
Gender					
male	820 (71.2%)	673 (82.1%)	115 (14.0%)	32 (3.9%)	0.110
female	332 (28.8%)	257 (77.4%)	54 (16.3%)	21 (6.3%)	
ECOG-PS					
Grade 0	901 (78.2%)	738 (81.9%)	125 (13.9%)	38 (4.2%)	0.120
Grade 1+2	239 (20.7%)	182 (76.2%)	42 (17.6%)	15 (6.3%)	
Missing	12 (1.0%)	10 (83.3%)	2 (16.7%)	0 (0.0%)	
BMI - Mean (SD)	27.0 (±4.4)	27.0 (±4.4)	26.9 (±4.6)	26.4 (±4.5)	
(14-25)	390 (33.9%)	308 (79.0%)	60 (15.4%)	22 (5.6%)	0.630
(25-30)	508 (44.1%)	419 (82.5%)	70 (13.8%)	19 (3.7%)	
(30-49)	250 (21.7%)	200 (80.0%)	38 (15.2%)	12 (4.8%)	
Missing	4 (0.3%)	3 (75.0%)	1 (25.0%)	0 (0.0%)	
clinical T					
cT2	47 (4.1%)	37 (78.7%)	10 (21.3%)	0 (0.0%)	**<0.001**
cT3	1022 (88.7%)	837 (81.9%)	144 (14.1%)	41 (4.0%)	
cT4	78 (6.8%)	54 (69.2%)	13 (16.7%)	11 (14.1%)	
Missing	5 (0.4%)	2 (40.0%)	2 (40.0%)	1 (20.0%)	
clinical N					
cN0	288 (25.0%)	247 (85.8%)	30 (10.4%)	11 (3.8%)	**0.041**
cN1-2	837 (72.7%)	662 (79.1%)	135 (16.1%)	40 (4.8%)	
Missing	27 (2.3%)	21 (77.8%)	4 (14.8%)	2 (7.4%)	
Distance from anal verge					
0-5	376 (32.6%)	273 (72.6%)	75 (19.9%)	28 (7.4%)	**< 0.001**
5-10	564 (49.0%)	480 (85.1%)	65 (11.5%)	19 (3.4%)	
>10	107 (9.3%)	92 (86.0%)	12 (11.2%)	3 (2.8%)	
Missing	105 (9.1%)	85 (81.0%)	17 (16.2%)	3 (2.9%)	

Grading					
G1	62 (5.4%)	49 (79.0%)	12 (19.4%)	1 (1.6%)	0.530
G2	926 (80.4%)	752 (81.2%)	129 (13.9%)	45 (4.9%)	
G3	92 (8.0%)	72 (78.3%)	16 (17.4%)	4 (4.3%)	
Missing	72 (6.2%)	57 (79.2%)	12 (16.7%)	3 (4.2%)	

Abbreviations: 5FU, 5-fluorouracil; CRT, chemoradiotherapy; Ox, oxaliplatin; TME, total mesorectal excision; PS, performance status; Significant p-values are marked in bold.

eTable 2. Correlation of pathologist-based with surgeon-based TME quality

		Pathologist-based TME quality				
		Mesorectal	Intermesorectal	Muscularis propria	Unknown/missing	N
Surgeon-based TME quality	Mesorectal	827 (86.4%)	83 (8.7%)	12 (1.3%)	35 (3.7%)	957
	Intermesorectal	27 (22.3%)	68 (56.2%)	22 (18.2%)	4 (3.3%)	121
	Muscularis Propria	2 (10%)	3 (15.0%)	15 (75.0%)	0 (0%)	20
	Unknown/missing	74 (65.6%)	15 (13.3%)	4 (3.5%)	20 (17.7%)	113
	N	930	169	53	59	

eTable 3. Impact of pre-treatment clinical and pathologic factors on 3-year outcomes after preoperative 5-FU chemoradiotherapy +/- Oxaliplatin and surgery

	N	3-year DFS % (95% CI)	P-Value	3-year cumulative incidence of distant metastases % (95% CI)	P-Value	3-year cumulative incidence of local recurrences after local R0/R1 resection % (95% CI)	P-Value	3-year OS % (95% CI)	P-Value
Study Arm									
5-FU-CRT	623	71.2 [67.6-74.9]	**0.032**	23.1 [19.6-26.5]	**0.041**	4.9 [3.1-6.7]	**0.011**	88.0 [85.4-90.7]	0.763
5-FU/Ox-CRT	613	75.9 [72.5-79.6]		19.2 [15.8-22.5]		3.2 [1.7-4.7]		88.7 [86.1-91.4]	
Age (median)									
Age ≤63.6	623	74.4 [70.9-78.1]	0.958	19.0 [15.6-22.2]	0.139	3.6 [2.0-5.2]	0.585	86.1 [83.3-89.0]	**0.014**
Age>63.6	613	72.6 [69.1-76.3]		23.3 [19.8-26.7]		4.5 [2.8-6.2]		90.5 [88.1-93.0]	
Gender									
male	874	73.0 [70.0-76.1]	0.358	21.8 [18.9-24.6]	0.319	4.6 [3.1-6.1]	0.224	88.6 [86.5-90.9]	0.649
female	362	74.9 [70.3-79.7]		19.7 [15.2-23.9]		2.8 [1.0-4.6]		87.5 [84.0-91.3]	
ECOG-PS									
Grade 0	958	76.8 [74.1-79.6]	**<0.001**	19.0 [16.4-21.6]	**<0.001**	3.4 [2.1-4.6]	**0.013**	90.8 [88.9-92.7]	**<0.001**
Grade 1+2	264	62.4 [56.5-68.8]		29.1 [22.9-34.8]		7.2 [3.6-10.7]		79.3 [74.3-84.8]	
BMI									
≤25	425	73.5 [69.3-77.9]	0.877	22.1 [17.8-26.1]	0.694	4.6 [2.4-6.7]	0.651	89.6 [86.6-92.7]	0.612
25-30	538	74.0 [70.3-77.9]		20.8 [17.1-24.3]		3.8 [2.0-5.5]		89.1 [86.4-91.9]	
>30	269	73.3 [68.0-79.0]		20.4 [15.1-25.4]		3.9 [1.4-6.4]		85.1 [80.8-89.8]	
cT-category									

	N	3-year DFS % (95% CI)	P-Value	3-year cumulative incidence of distant metastases % (95% CI)	P-Value	3-year cumulative incidence of local recurrences after local R0/R1 resection % (95% CI)	P-Value	3-year OS % (95% CI)	P-Value
cT2	54	77.7 [66.8-90.4]	**< 0.001**	12.9 [2.6-22.2]	**< 0.001**	2.1 [0.0-6.2]	0.179	87.7 [78.9-97.5]	**0.009**
cT3	1086	74.8 [72.2-77.6]		20.4 [17.8-22.9]		3.8 [2.6-5.0]		89.1 [87.2-91.1]	
cT4	91	56.7 [47.2-68.2]		34.8 [23.6-44.4]		8.8 [2.3-14.9]		80.3 [72.3-89.2]	
cN-category									
cN0	305	74.4 [69.5-79.7]	0.654	19.6 [14.7-24.2]	0.779	3.0 [0.9-5.0]	0.919	88.5 [84.8-92.4]	0.654
cN1-2	903	73.4 [70.5-76.4]		21.7 [18.8-24.4]		4.4 [3.0-5.8]		88.2 [86.0-90.4]	
Grading									
G1	64	68.2 [56.9-81.7]	**< 0.001**	21.8 [9.9-32.2]	**0.001**	3.7 [0.0-8.7]	0.108	93.1 [86.7-99.9]	**< 0.001**
G2	998	75.7 [73.0-78.5]		19.4 [16.8-22.0]		3.6 [2.4-4.8]		89.9 [88.0-91.9]	
G3	100	56.8 [47.6-67.8]		35.9 [25.1-45.1]		9.7 [3.1-15.8]		71.7 [62.8-81.8]	
Distance from anus									
0-5 cm	402	70.1 [65.5874.8]	0.056	25.3 [20.7-29.6]	**0.043**	3.9 [1.89-6.0]	0.874	89.1 [86.0-92.4]	0.946
5-10 cm	608	75.2 [71.71-78.8]		19.2 [15.9-22.5]		4.1 [2.43-5.8]		87.9 [85.3-90.7]	
>10 cm	114	73.7 [65.71-82.6]		18.8 [10.7-26.2]		4.3 [0.06-8.3]		88.6 [82.7-94.9]	

Abbreviations: DFS, disease-free survival; OS, overall survival; 5-FU, 5-fluorouracil; CRT, chemoradiotherapy; Ox, oxaliplatin; TME, total mesorectal excision; ECOG-PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index;

Significant p-values are marked in bold

eTable 4. Multivariate analysis of different covariables on 3-year outcomes after preoperative 5-FU chemoradiotherapy +/- oxaliplatin and surgery

	DFS		Cumulative incidence of distant metastases		Cumulative incidence of local recurrences after local R0/R1 resection		OS	
	HR [95% CI]	**p-value**	**HR [95% CI]**	**p-value**	**HR [95% CI]**	**p-value**	**HR [95% CI]**	**p-value**
Pathologist-based TME								
mesorectal vs intramesorectal	1.13 [0.83-1.53]	0.439	1.13 [0.80-1.60]	0.484	1.35 [0.62-2.97]	0.449	1.30 [0.87-1.94]	0.206
mesorectal vs muscularis propria	1.41 [0.90-2.20]	0.135	1.40 [0.85-2.33]	0.188	2.62 [1.11-6.18]	**0.028**	1.26 [0.68-2.32]	0.457
ypN-category								
ypN+ vs ypN0	2.09 [1.65-2.66]	**<0.001**	2.54 [1.94-3.33]	**<0.001**	2.22 [1.18-4.16]	**0.013**	1.89 [1.35-2.62]	**<0.001**
ypT-category								
ypT3 vs ypT0-2	1.73 [1.32-2.27]	**<0.001**	1.96 [1.43-2.68]	**<0.001**	1.27 [0.60-2.67]	0.530	1.74 [1.19-2.54]	**0.004**
ypT4 vs ypT0-2	2.54 [1.47-4.37]	**<0.001**	2.35 [1.24-4.48]	**0.009**	2.89 [0.93-9.02]	0.067	3.51 [1.79-6.90]	**<0.001**
Treatment arm								
5-FU/Ox-CRT vs 5-FU CRT	0.79 [0.62-0.99]	**0.039**	0.79 [0.61-1.03]	0.079	0.45 [0.24-0.86]	**0.015**	0.88 [0.64-1.21]	0.444
Circumferential resection margin (CRM)								
>1mm vs ≤1 mm	1.58 [1.08-2.31]	**0.017**	1.29 [0.83-1.99]	0.256	3.60 [1.66-7.79]	**0.001**	1.55 [0.94-2.56]	0.083
>1mm vs pCR	0.41 [0.23-0.73]	**0.002**	0.36 [0.17-0.77]	**0.008**	0.24 [0.03-1.87]	0.172	0.43 [0.19-0.97]	**0.041**

Abbreviations: DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; 5-FU, 5-fluorouracil; Ox, oxaliplatin; TME, total mesorectal excision; CRT, chemoradiotherapy; pCR, pathologic complete response;

*Patients with R2-resection were also included in the multivariate analysis for cumulative incidence of distant metastases and overall survival