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ORIGINAL ARTICLE

Adjuvant treatment for resected rectal cancer: impact of standard and intensified postoperative chemotherapy on disease-free survival in patients undergoing preoperative chemoradiation—a propensity score-matched analysis of an observational database

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Abstract
Aims Adjuvant chemotherapy for resected rectal cancer is widely used. However, studies on adjuvant treatment following neoadjuvant chemoradiotherapy (CRT) and total mesorectal excision (TME) have yielded conflicting results. Recent studies have focused on adding oxaliplatin to both preoperative and postoperative therapy, making it difficult to assess the impact of adjuvant oxaliplatin alone. This study was aimed at determining the impact of (i) any adjuvant treatment and (ii) oxaliplatin-containing adjuvant treatment on disease-free survival in CRT-pretreated, R0-resected rectal cancer patients.
Method Patients undergoing R0 TME following 5-fluorouracil (5FU)-only-based CRT between January 1, 2008, and December 31, 2010, were selected from a nationwide registry. After propensity score matching (PSM), comparison of disease-free survival (DFS) using Kaplan-Meier analysis and log-rank test was performed in (i) patients receiving no vs. any adjuvant treatment and (ii) patients treated with adjuvant 5FU/capecitabine without vs. with oxaliplatin.
Results Out of 1497 patients, 520 matched pairs were generated for analysis of no vs. any adjuvant treatment. Mean DFS was significantly prolonged with adjuvant treatment (81.8 ± 2.06 vs. 70.1 ± 3.02 months, $p < 0.001$). One hundred forty-eight matched pairs were available for analysis of adjuvant therapy with or without oxaliplatin, showing no improvement in DFS in patients receiving oxaliplatin (76.9 ± 4.12 vs. 79.3 ± 4.44 months, $p = 0.254$). Local recurrence rate was not significantly different between groups in either analysis.
Conclusion In this cohort of rectal cancer patients treated with neoadjuvant CRT and TME surgery under routine conditions, adjuvant chemotherapy significantly improved DFS. No benefit was observed for the addition of oxaliplatin to adjuvant chemotherapy in this setting.

Keywords Rectal cancer · Combined modality treatment · TME surgery · Adjuvant chemotherapy · Propensity score matching

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Introduction

Adjuvant chemotherapy using 5-fluorouracil (5FU) and folinic acid (FA) is the recommended treatment standard for patients undergoing R0 resection for rectal cancer following neoadjuvant chemoradiotherapy (CRT) or short-course radiotherapy (RT) according to European Society of Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines. However, it is acknowledged at least in the ESMO guidelines that the level

of evidence for this recommendation is lower than in colon cancer. In contrast to stage III colon cancer, for which postoperative, adjuvant chemotherapy only has been used since the early 1990s [1, 2], perioperative treatment has always been more complex for rectal cancer, as radiation had to be integrated as an additional component [3]. After preoperative CRT or RT had become standard of care in stage II and III rectal cancer following the landmark German and Dutch rectal cancer trials which demonstrated an improvement in local recurrence rate but not in survival [4–6], the role of postoperative chemotherapy was focused on in four randomized trials, two of which were prematurely closed due to poor accrual [7–10]. Although theoretically, as in colon cancer, adjuvant chemotherapy was expected to improve the distant recurrence rate and survival through the eradication of subclinical micrometastases, no survival benefit could be demonstrated in any of these trials.

Therefore, robust evidence for the use of any adjuvant therapy in pretreated rectal cancer is currently not available. However, recent studies have focused on the intensification of perioperative treatment in rectal cancer through the addition of oxaliplatin to 5FU or capecitabine. Theoretically, a similar benefit from adding oxaliplatin to postoperative 5FU-based therapy as demonstrated in colon cancer in the MOSAIC and NSABP-C07 trials [11–13] would be expected also in rectal cancer. However, with the exception of one study [14], available trials investigated the addition of oxaliplatin to both preoperative and postoperative treatment rather than adjuvant chemotherapy alone [15, 16], making it impossible to draw a conclusion regarding the use of the intensification of adjuvant chemotherapy in pretreated rectal cancer.

In light of all of these results, the role for postoperative chemotherapy in patients undergoing neoadjuvant CRT and surgery for stage II and stage III rectal cancer is currently not well defined. As adjuvant treatment is widely used in daily practice, conducting a randomized trial has proven difficult, and it is unlikely that a sufficiently powered trial of adjuvant treatment vs. observation in pretreated, resected rectal cancer will be completed in the future. In this situation of limited level 1 evidence, large observational registries can contribute valuable information as they usually comprise large numbers of subjects, although the limitations of retrospective analyses must be borne in mind, and appropriate methods must be used to reduce the bias inherent to them. We therefore assessed disease-free survival in patients undergoing total mesorectal excision (TME) for rectal cancer following 5FU-based CRT and either no adjuvant chemotherapy, adjuvant chemotherapy with 5FU or capecitabine only, or adjuvant chemotherapy with 5FU/capecitabine plus oxaliplatin under routine conditions from a large multicentric quality assurance database.

Patients and methods

Study design

We retrospectively reviewed data from the Quality Assurance in Rectal Cancer Surgery multicenter observational study. Since January 1, 2005, this registry has been prospectively collecting epidemiologic and treatment-related parameters as well as data on the early postoperative course and long-term follow-up of rectal cancer patients from more than 300 hospitals of all levels of care throughout Germany. Whereas the database was kept as a purely surgical registry in the early years, data on neoadjuvant and adjuvant chemotherapy or chemoradiation have been recorded since 2008. Data were collected by the institutions involved in patient care using a standardized questionnaire. Written informed consent was obtained from all patients whose data were collected.

Inclusion/exclusion criteria for retrospective data analysis

All rectal cancer patients documented in the Quality Assurance study database undergoing non-emergency TME surgery following conventionally fractioned neoadjuvant 5FU-based CRT between January 1, 2008, and December 31, 2010, with a documented R0 status at the end of the surgical procedure were included in the present retrospective data analysis. Patients with metastatic disease (UICC stage IV) and patients undergoing emergency surgery, local tumor excision without a formal rectal resection, or incomplete resection (R1 or R2) were excluded. Also, all patients undergoing upfront surgery without neoadjuvant treatment and patients undergoing neoadjuvant short-course RT (without chemotherapy) or CRT involving drugs other than 5FU/folinic acid were excluded.

Data analysis

Two separate analyses were performed. First, to investigate the role of any adjuvant treatment in the predefined patient cohort, two groups were formed (group A, no adjuvant treatment; group B, adjuvant treatment with 5FU or capecitabine with or without oxaliplatin). Since patients were not randomly assigned to either treatment group due to the retrospective nature of the analysis, propensity score matching (PSM) [17, 18] was used to determine the independent impact of adjuvant treatment on disease-free survival (DFS) taking into account age; sex; ASA score; cardiovascular, pulmonary, renal, and hepatic risk factors; tumor distance from the anal verge (<4 cm/4–7.9 cm/8–11.9 cm/12–16 cm); histopathologically determined T stage and lymph node involvement (pT and pN stages); tumor grading; number of examined lymph nodes; presence of anastomotic leakage; case load of the operating surgeon (1–9/10–19/>19 rectal cancer procedures per year);

and histopathologically determined quality of the TME specimen according to the Magnetic Resonance Imaging and Rectal Cancer European Equivalence (MERCURY) grading system (grades 1–3) [19] as possible confounding factors. First, logistic regression using these variables was performed to obtain the propensity score for each patient (defined as the probability to be assigned to group A or B as a result of the individual profile of these covariates). Then, patients in group A and B were matched according to the calculated propensity score using a k nearest neighbors (KNN) algorithm with a threshold of $c \leq 0.01$. After matching, Kaplan-Meier analysis for DFS was performed and DFS was compared between groups A and B using the log-rank test. Additionally, the local recurrence rate between both groups was compared using the same methodology.

To investigate the impact of the addition of oxaliplatin to adjuvant 5FU-based therapy, the subset of patients receiving any adjuvant treatment was then subdivided into group B1 (adjuvant treatment using 5FU/folinic acid or capecitabine without oxaliplatin) and group B2 (adjuvant treatment using 5FU/folinic acid or capecitabine in combination with oxaliplatin) and the analysis was repeated for groups B1 and B2 taking into account the same potential confounders.

As no information was available in the database whether patients assigned to any given chemotherapy had actually completely received it, all patients in the matched cohort were contacted either directly or through their treating family doctors and/or oncologists. Then, DFS was again compared between groups A vs. B and groups B1 vs. B2 using Kaplan-Meier analysis and log-rank test, this time only taking into account patients who had received their chemotherapy with the full number of cycles without dose reductions greater than 25% at any treatment cycle.

Statistical analysis was done using the SPSS Version 21 software package (IBM Corporation, Armonk, NY, USA). DFS values are given as mean +/− standard deviation. A two-sided p value <0.05 was considered significant.

Results

A total of 1497 patients undergoing rectal cancer surgery within the specified timeframe and matching the inclusion/exclusion criteria were identified in the Quality Assurance study database. Of these, 569 did not receive postoperative chemotherapy (group A), whereas 928 were given adjuvant chemotherapy (group B). Among patients who underwent adjuvant treatment, 768 patients received adjuvant 5FU or capecitabine only (group B1) and 160 patients received additional oxaliplatin with their adjuvant chemotherapy (group B2) (Fig. 1). Baseline characteristics of patients in each group are summarized in Tables 1 and 2. Median follow-up was 38 months in groups A and B. When factors influencing DFS in the unmatched cohort

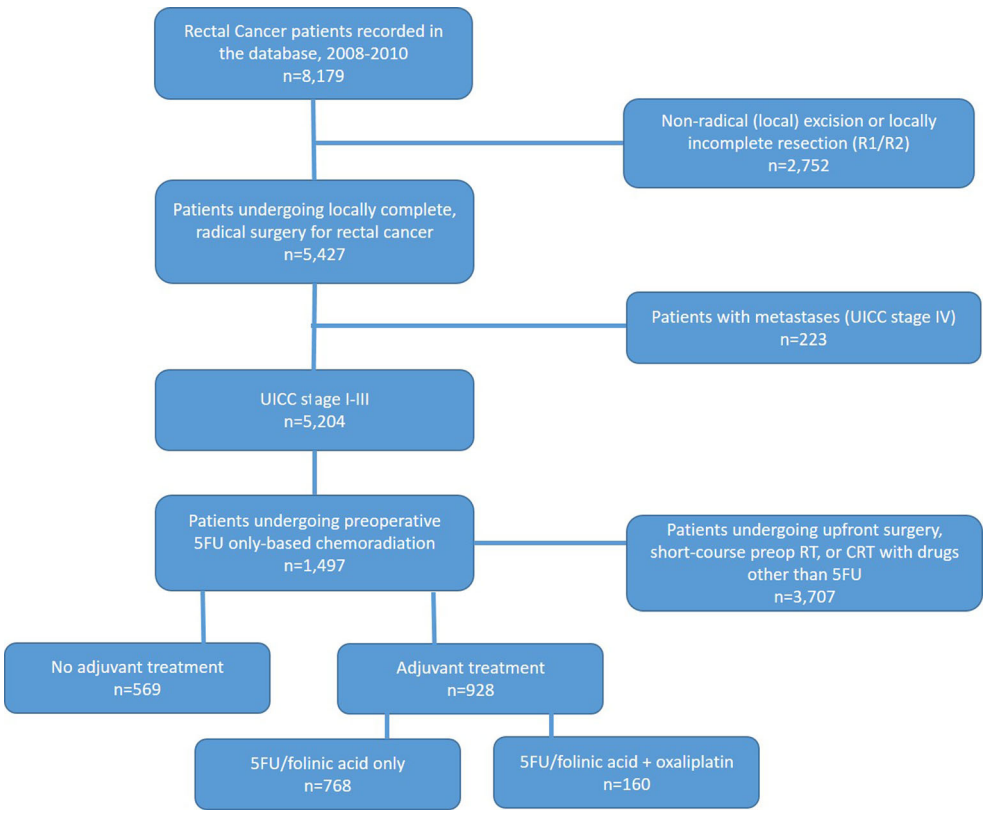


Fig. 1 Study flowchart describing patient selection from the database for analysis

Table 1 Baseline characteristics for groups A and B

		Group A—no adjuvant treatment (n = 569)		Group B—adjuvant treatment (n = 928)		p
		n or median	Per cent of total	n or median	Per cent of total	
Age		68.5 (23.0–89.0) years		67.0 (26.0–88.0) years		0.02
Sex	Male	385	67.7	621	67.0	0.788
	Female	184	32.3	306	33.0	
ASA	I	29	5.2	90	9.7	<0.001
	II	306	54.4	541	58.5	
	III	219	38.9	288	31.1	
	IV	9	1.6	6	0.6	
Cardiovascular risk factors	No	193	34.8	394	43.0	0.002
	Yes	361	65.2	523	57.0	
Pulmonary risk factors	No	492	88.8	842	91.8	0.054
	Yes	62	11.2	75	8.2	
Renal risk factors	No	526	94.9	884	96.4	0.175
	Yes	28	5.1	33	3.6	
Hepatic risk factors	No	545	98.4	897	97.8	0.457
	Yes	9	1.6	20	2.2	
ypT stage	ypT0	34	6.0	64	6.9	0.383
	ypT1	43	7.6	70	7.5	
	ypT2	206	36.3	293	31.6	
	ypT3	268	47.2	465	50.1	
	ypT4	17	3.0	36	3.9	
ypN stage	ypN0	435	76.4	608	65.5	<0.001
	ypN1	97	17.0	213	23.0	
	ypN2	37	6.5	107	11.5	
Mean number of involved lymph nodes		0.92		1.11		<0.001
anastomotic leak	No	512	90.0	860	92.7	0.068
	Yes	57	10.0	68	7.3	
Tumor distance from anal verge	<4 cm	125	22.0	163	17.6	0.138
	4–7.9 cm	234	41.1	417	44.9	
	8–11.9 cm	188	33.0	303	32.7	
	12–16 cm	22	3.9	45	4.8	
Tumor grade	G1	26	4.6	33	3.6	0.518
	G2	457	80.7	765	82.7	
	G3	83	14.7	127	13.7	
Number of examined lymph nodes		14 (1–61)		14 (1–66)		0.36
Number of involved lymph nodes		0 (0–60)		0 (0–24)		<0.001
Case load of the operating surgeon (rectal cancer procedures per year)	1–9	75	13.5	137	14.9	0.007
	10–19	221	39.7	428	46.6	
	>19	260	46.8	354	38.5	
TME grade (MERCURY)	grade 1	416	83.0	746	86.2	0.267
	grade 2	71	14.2	101	11.7	
	grade 3	14	2.8	18	2.1	

were calculated using Cox regression analysis, age, cardiovascular and renal comorbidity, ypT stage, ypN stage, tumor distance from the anal verge, number of lymph nodes examined, and TME MERCURY grade, and administration of adjuvant chemotherapy were all found to be significantly associated with DFS (Table 3).

The results of logistic regression analysis to identify factors associated with the probability of a given patient to

Table 2 Baseline characteristics for groups B1 and B2

		Group B1—adjuvant treatment with 5FU/capecitabine only (n = 768)		Group B2—adjuvant treatment with 5FU/capecitabine + oxaliplatin (n = 160)		p
		n or median	Per cent of total	n or median	Per cent of total	
Age		67.0 (26.0–85.0) years		65.0 (29.0–88.0) years		0.017
Sex	Male	515	67.1	106	66.3	0.827
	Female	252	32.9	54	33.8	
ASA	I	71	9.3	19	11.9	0.035
	II	464	60.6	77	48.4	
	III	227	26.6	61	38.4	
	IV	4	0.5	2	1.3	
Cardiovascular risk factors	No	329	43.1	65	42.2	0.835
	Yes	434	56.9	89	57.8	
Pulmonary risk factors	No	705	92.4	137	89.0	0.156
	Yes	58	7.6	17	11.0	
Renal risk factors	No	738	96.7	146	94.8	0.244
	Yes	25	3.3	8	5.2	
Hepatic risk factors	No	749	98.2	148	96.1	0.110
	Yes	14	1.8	6	3.9	
ypT stage	ypT0	52	6.8	12	7.5	0.966
	ypT1	58	7.6	12	7.5	
	ypT2	246	32.0	47	29.4	
	ypT3	383	49.9	82	51.2	
	ypT4	29	3.8	7	4.4	
ypN stage	ypN0	522	68.0	86	53.8	<0.001
	ypN1	170	22.1	43	26.9	
	ypN2	76	9.9	31	19.4	
Anastomotic leak	No	711	92.6	149	93.1	0.809
	Yes	57	7.4	11	6.9	
Tumor distance from anal verge	<4 cm	131	17.1	32	20.0	0.706
	4–7.9 cm	344	44.8	73	45.6	
	8–11.9 cm	254	33.1	49	30.6	
	12–16 cm	39	5.1	6	3.8	
Tumor grade	G1	28	3.7	5	3.1	0.718
	G2	635	83.0	130	81.3	
	G3	102	13.3	25	15.6	
Number of examined lymph nodes		14 (1–66)		14 (6–38)		0.162
case load of the operating surgeon	1–9	124	16.3	119	8.2	<0.001
(rectal cancer procedures per year)	10–19	363	47.8	13	40.9	
	>19	273	35.9	65	50.9	
TME grade (MERCURY)	grade 1	620	86.4	81	85.7	0.837
	grade 2	84	11.7	126	11.6	
	grade 3	14	1.9	17	2.7	

receive adjuvant chemotherapy which were to be used to calculate the propensity score are displayed in Table 4. Propensity score matching yielded 520 patients in group A and 520 patients in group B for a total matched cohort of 1040 patients assessable for the impact of any adjuvant chemotherapy (5FU/capecitabine +/− oxaliplatin) vs. no adjuvant chemotherapy. The distribution of baseline characteristics in both groups (A and B) of the matched cohort was verified using Pearson's correlation and Student's t test. No significant differences between matched groups A and B

Table 3 Results of Cox regression analysis to identify factors influencing DFS for comparison of groups A (no adjuvant treatment) vs. B (any adjuvant treatment) before propensity score matching

		Regression coefficient	*p*	Odds ratio	95% confidence interval	
					Lower limit	Upper limit
Age		0.021	0.013	1021	1004	1037
Comorbidity	Cardiovascular	0.475	0.004	1608	1160	2231
	Pulmonary	0.359	0.143	1431	0,886	2312
	Renal	0.681	0.018	1975	1125	3466
ypT stage			0.000			
ypT1 vs. ypT0		0.441	0.474	1555	0.464	5208
ypT2 vs. ypT0		0.745	0.153	2107	0.758	5858
ypT3 vs. ypT0		1343	0.009	3831	1394	10,533
ypT4 vs. ypT0		1657	0.005	5243	1644	16,720
ypN stage			0.000			
ypN1 vs.ypN0		0.775	0.000	2171	1552	3038
ypN2 vs. ypN0		1026	0.000	2790	1799	4327
Distance from anal verge			0.011			
4–7.9 cm vs. <4 cm		1280	0.004	3595	1497	8634
8–11.9 cm vs. <4 cm		0.853	0.049	2346	1004	5482
12–16 cm vs. <4 cm		0.778	0.075	2177	0.925	5125
Number of lymph nodes examined		−0.027	0.046	0,973	0.948	0.999
TME grade (MERCURY)			0.011			
Grade 1 vs. grade 0		0.569	0.003	1767	1206	2588
Grade 2 vs. grade 2		−0.228	0.659	0.796	0.289	2189
No adjuvant treatment vs. adjuvant treatment		0.509	0.001	1664	1219	2271

were found. When the Cox regression was repeated in the matched cohort, only age, renal and pulmonary comorbidity, ypT stage, ypN stage, TME MERCURY grade, and administration of adjuvant chemotherapy showed significant association with DFS (Table 5).

Mean DFS in group B (adjuvant treatment) was significantly prolonged in comparison to group A (no adjuvant treatment) (group B, 81.8 ± 2.06 months; group A, 70.1 ± 3.02 months, $p < 0.001$). Kaplan-Meier curves for DFS for matched patients in groups A and B are displayed in Fig. 2. No difference in the local recurrence rate between groups A and B was found ($p = 0.706$; data not shown). Mean overall survival (OS) was 87.7 months in group B and 76.9 months in group A ($p < 0.001$).

Table 4 Results of logistic regression to identify factors to calculate propensity score for no vs. any adjuvant treatment (groups A vs. B)

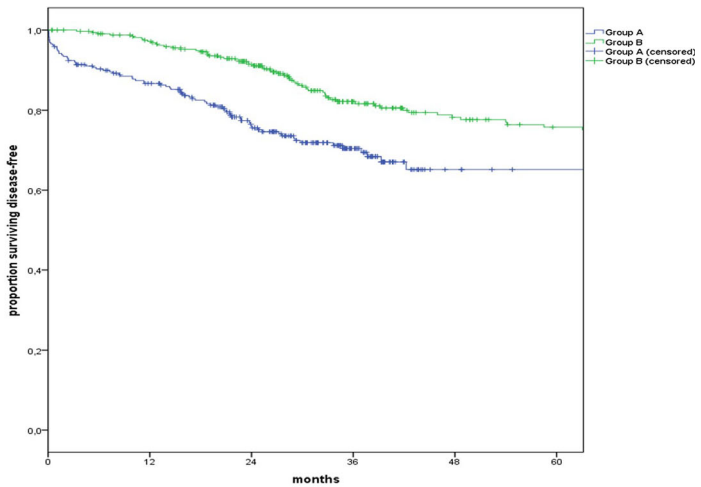
	Regression coefficient	*p*	Odds ratio	95% confidence interval	
				Lower limit	Upper limit
Age	−0.018	0.006	0.982	0.970	0.995
ASA stage		0.037			
ASA 1 vs. ASA 4	1633	0.009	5120	1493	17.563
ASA 2 vs. ASA 4	1205	0.040	3337	1058	10.523
ASA 3 vs. ASA 4	1079	0.067	2943	0.929	9326
ypN stage		0.000			
ypN1 vs. ypN0	0.430	0.004	1537	1144	2065
ypN2 vs. ypN0	0.929	0.000	2533	1590	4034
number of procedures per surgeon per year		0.006			
>9 vs. ≤9	0.368	0.041	1445	1016	2056
>19 vs. ≤9	0.382	0.003	1466	1142	1881

Table 5 Results of Cox regression analysis to identify factors influencing DFS for comparison of groups A (no adjuvant treatment) vs. B (any adjuvant treatment) after propensity score matching

	Regression coefficient	*p*	Odds ratio	95% confidence interval	
				Lower limit	Upper limit
Age	0.021	0.048	1022	1000	1043
Comorbidity	0.652	0.003	1919	1257	2929
Pulmonary	0.555	0.039	1741	1028	2951
Renal	0.796	0.010	2218	1206	4078
pT stage		0.001			
pT1 vs. pT0	0.942	0.253	2566	0.509	12,926
pT2 vs. pT0	1266	0.082	3547	0.850	14,795
pT3 vs. pT0	1752	0.016	5767	1394	23,865
pT4 vs. pT0	2465	0.002	11,761	2383	58,054
pN stage		0.000			
pN1 vs. pN0	0.717	0.001	2049	1325	3168
pN2 vs. pN0	0.946	0.001	2575	1453	4562
Number of lymph nodes examined	−0.029	0.075	0,971	0.940	1003
TME grade (MERCURY)		0.006			
Grade 1 vs. grade 0	0.759	0.002	2137	1333	3424
Grade 2 vs. grade 2	−0.082	0.891	0,922	0.286	2974
No adjuvant treatment vs. adjuvant treatment	0.616	0.001	1851	1292	2653

After contacting all patients or their treating physicians for follow-up information, adequate information regarding treatment completeness was obtained from 316 of the 520 patients in group B (60.8%). Of these, 280 (88.6%) had received their adjuvant chemotherapy without treatment interruptions or discontinuations and without dose reductions >25% at any cycle, whereas in 36 patients (11.4%), dose reductions and/or treatment interruptions or discontinuations were recorded. When only the 280 patients from group B who had received their full adjuvant chemotherapy were included in the analysis, DFS was 88.7 ± 2.25 months, which was again significantly longer than DFS in the 520 patients without adjuvant chemotherapy ($p < 0.001$).

The results of the Cox regression analysis to identify factors influencing DFS among the 928 patients who received adjuvant chemotherapy are displayed in Table 6, showing ASA group, renal comorbidity, ypT stage, ypN stage, and tumor distance from the anal verge as significant factors.



Patients at risk							
	A	520	421	295	140	41	34
	B	520	482	396	262	210	188

Fig. 2 Disease-free survival in groups A (no adjuvant treatment) and B (adjuvant treatment)

Table 6 Results of Cox regression analysis to identify factors influencing DFS for comparison of groups B1 (adjuvant treatment without oxaliplatin) vs. B2 (adjuvant treatment with oxaliplatin) before propensity score matching

	Regression coefficient	*p*	Odds ratio	95% confidence interval	
				Lower limit	Upper limit
Age	0.019	0.055	1019	1000	1039
ASA group		0.002			
SA 2 vs. ASA 1	−0.162	0.595	0.850	0.468	1546
ASA 3 vs. ASA 1	0.020	0.952	1020	0.531	1960
ASA 4 vs. ASA 1	3821	0.000	45,640	5402	385,601
Renal comorbidity	1068	0.011	2909	1278	6622
ypT stage		0.003			
ypT1 vs. ypT0	0.903	0.274	2466	0.490	12,415
ypT2 vs. ypT0	0.934	0.203	2545	0.603	10,734
ypT3 vs. ypT0	1652	0.023	5216	1256	21,652
ypT4 vs. ypT0	1778	0.026	5916	1237	28,287
ypN stage		0.000			
ypN1 vs. ypN0	0.770	0.000	2160	1432	3258
ypN2 vs. ypN0	1203	0.000	3330	2020	5491
Distance from anal verge		0.005			
4–7.9 vs. <4 cm	1280	0.010	3595	1353	9558
8–11.9 vs. <4 cm	0.825	0.083	2281	0.898	5794
12–16 vs. <4 cm	0.418	0.389	1520	0.586	3938

Results of the logistic regression to calculate factors to be included into propensity calculation are shown in Table 7.

Propensity score matching yielded a total matched cohort of 296 patients (148 receiving 5FU or capecitabine only (group B1) and 148 patients receiving additional oxaliplatin (group B2)). Again, baseline characteristics were well balanced between groups B1 and B2 after matching. Median follow-up was 48.7 months for groups B1 and B2. When the Cox regression was repeated in the matched cohort, only cardiovascular comorbidity and ypN stage showed significant association with DFS (Table 8).

No significant DFS difference between groups B1 and B2 was found (group B1, 79.3 ± 4.44 months; group B2, 76.9 ± 4.12 months, $p = 0.456$). DFS curves for matched patients in groups B1 and B2 are displayed in Fig. 3. Again, local recurrences occurred with similar frequency in groups B1 and B2 ($p = 0.499$; data not shown). Mean OS was 85.3 months in group B1 and 82.5 months in group B2 ($p = 0.382$).

After contacting all patients or their treating physicians for follow-up information, adequate information regarding treatment completeness was obtained from 76 of the 148 patients (51.4%) in group B1 and from 80 of the 148 patients (54.1%) in group B2. Of the patients for whom adequate information was obtained, 62 of 76 (81.6%) in group B1 and 76 of 80 (95.0%) in group B2 had received their adjuvant chemotherapy without treatment interruptions or discontinuations and without dose reductions >25% at any cycle, whereas in 14 patients (18.4%) and 4 patients (5.0%) in groups B1 and B2,

Table 7 Results of logistic regression to identify factors to calculate propensity score for adjuvant treatment without vs. with oxaliplatin (groups B1 vs. B2)

	Regression coefficient	*p*	Odds ratio	95% confidence interval	
				Lower limit	Upper limit
Age	−0.019	0.034	0.981	0.963	0.999
ypN stage		0.003			
ypN1 vs. ypN0	0.454	0.041	1575	1018	2438
ypN2 vs. ypN0	0.865	0.002	2375	1390	4058
Number of lymph nodes examined	−0.041	0.010	0.960	0.930	0.990
Number of procedures per surgeon per year		0.002			
>9 vs. ≤9	0.563	0.106	1757	0.887	3478
>19 vs. ≤9	1052	0.002	2863	1452	5645

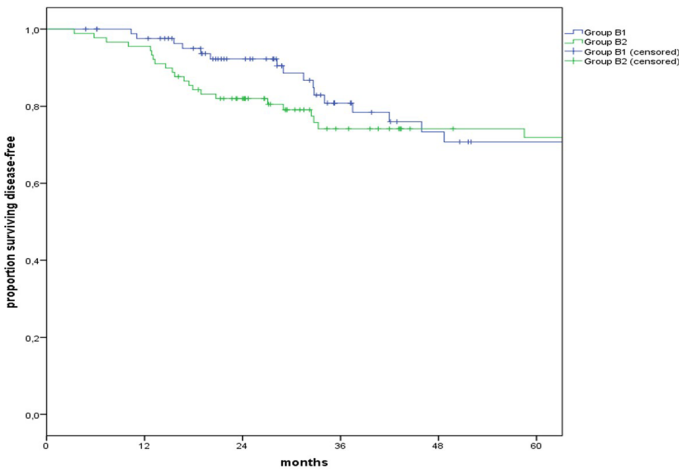
Table 8 Results of Cox regression analysis to identify factors influencing DFS for comparison of groups B1 (adjuvant treatment without oxaliplatin) vs. B2 (adjuvant treatment with oxaliplatin) after propensity score matching

	Regression coefficient	*p*	Odds ratio	95% confidence interval	
				Lower limit	Upper limit
Cardiovascular comorbidity	0.672	0.047	1959	1010	3800
Renal comorbidity	1505	0.053	4506	0.981	20,710
ypN stage		0.001			
ypN1 vs. ypN0	1186	0.001	3274	1583	6771
ypN2 vs. ypN0	1545	0.002	4686	1772	12,393
Distance from anal verge		0.058			
4–7.9 vs. <4 cm	1360	0.082	3895	0.841	18,032
8–11.9 vs. <4 cm	1050	0.169	2856	0.641	12,726
12–16 vs. <4 cm	0.161	0.842	1174	0.241	5715

respectively, dose reductions and/or treatment interruptions or discontinuations were recorded. When only the 76 patients from group B1 and the 80 patients from group B2 who had received their full adjuvant chemotherapy were included in the analysis, DFS was 86.2 ± 4.83 vs. 84.4 ± 5.49 months for groups B2 vs. B1, with no significant difference between groups ($p = 0.790$).

Discussion

The rationale for the current treatment standard of administering adjuvant chemotherapy with or without oxaliplatin to patients with UICC stage II and stage III rectal cancer mainly stems from extrapolation from colon cancer studies [1, 2] and from studies in rectal cancer patients treated before the introduction of neoadjuvant treatment [20–22]. In the era of neoadjuvant RT or CRT for rectal cancer, the use of adjuvant chemotherapy has been examined in four randomized trials, all of them failing to show a significant DFS or OS benefit but none of them able to change the current guideline standard. However, the four studies were not fully comparable in their methodology, limiting the validity of the evidence generated by them. Two of the studies were closed prematurely due to poor accrual [7, 8] and two [9, 10] used the same reduced-dose chemotherapy schedule that was part of preoperative CRT also as adjuvant treatment, potentially limiting its systemic efficacy. Finally, patients were included into two of the studies based on their clinical tumor stage prior to treatment (cTcN stage) [9, 10] whereas randomization was performed based on postoperative findings (ypTypN stage) in the other two [7, 8]. As a result of these non-constant methodologies, meta-analyses of these studies have also yielded varying results. In one meta-analysis of individual patient data [23], no benefit from the use of adjuvant chemotherapy with respect to DFS, OS, or distant recurrence rate was found; however, in a subgroup analysis, patients with rectal cancer located 10–15 cm from the anal verge had improved DFS and fewer distant recurrences if they received adjuvant treatment. A second meta-analysis found significantly improved DFS with the use of adjuvant



Patients at risk							
	B1	148	139	104	63	49	42
	B2	148	141	108	72	57	53

Fig. 3 Disease-free survival in groups B1 (adjuvant treatment with 5FU/capecitabine only) and B2 (adjuvant treatment with 5FU/capecitabine + oxaliplatin)

chemotherapy in studies randomizing patients according to their postoperative tumor stage, whereas no benefit from adjuvant treatment was recorded from studies enrolling patients based on their clinical tumor stage before start of treatment [24]. Although the role for adjuvant chemotherapy in rectal cancer patients treated with neoadjuvant RT or CRT is therefore not clear, studies have mainly focused on the intensification of perioperative treatment through the addition of oxaliplatin in recent years. Two of the recently presented studies (CAO/ARO/AIO-04 and PETACC-6) [15, 16] have investigated the addition of oxaliplatin to both preoperative and postoperative treatment, making it difficult to draw a conclusion regarding the effect of postoperative oxaliplatin (when the drug is intended to eradicate residual micrometastatic disease rather than serve as a radiosensitizer) alone. Only the Korean phase II ADORE study [14] specifically addressed the issue of adding oxaliplatin to the adjuvant chemotherapy regimen in patients who had undergone preoperative 5FU-based CRT plus TME surgery and still had ypN+ or ypT3-4ypN0 disease. This study found a significantly improved DFS for the intensified regimen, a subgroup analysis indicating that the effect was limited to patients with lymph node-positive disease.

In this complicated field of available evidence and established standard practice, we believe that despite their retrospective nature, the results presented here can add valuable information to the debate. Similar to other retrospective studies [25, 26], our results indicate a substantial DFS benefit from adjuvant chemotherapy in patients undergoing neoadjuvant CRT and TME surgery for rectal cancer. This DFS benefit must be mainly attributed to a decrease in distant recurrences as the local recurrence rate was not different between the groups. Retrospective studies on the effect of adjuvant chemotherapy are frequently criticized for their proneness for selection bias (patients in good condition after surgery preferably being selected for adjuvant treatment, making it impossible to differentiate the effects of treatment and patient fitness on survival); however, this issue was addressed in our study by using propensity score matching taking into account all factors that may have influenced the clinician's decision to recommend adjuvant treatment and for which data were available in our database. Even though it is a general problem of propensity score matching that only factors that are known to influence the target variable and for which data are available can be included in the calculation of the propensity score, and there may have been factors influencing the decision to administer adjuvant chemotherapy that we were not aware of or had no data for, baseline characteristics were well balanced after matching, creating a "pseudo-randomized" cohort for further analysis. Moreover, one of the strengths of our Quality Assurance registry is that it reflects the situation under routine clinical care conditions which may be different from the environment of a thoughtfully planned, closely supervised clinical study. Although the surgical quality was generally good with approximately 85% of the TME specimens being graded as MERCURY grade I by the pathologist and more than three quarters of patients having at least 12 lymph nodes examined, no quality assessment was performed regarding neoadjuvant CRT and no central pathology review was available. One might argue that this limits the validity of our data; however, as most rectal cancer patients in Germany are treated in community or district hospitals rather than academic cancer centers, these data may possibly provide a more accurate image of real-life patient care than a prospective study would yield.

As oxaliplatin is not standard of care as part of adjuvant treatment for rectal cancer in Germany, the matched patient cohort for the analysis of adjuvant therapy with or without oxaliplatin was relatively small. The addition of oxaliplatin to postoperative chemotherapy was not associated with a difference in DFS or OS in our study, thus not supporting the use of this drug in this setting. This is in contrast to the results from the phase 2 ADORE study [14], in which a significant benefit from an oxaliplatin-containing regimen compared to 5FU/folinic acid in terms of DFS was demonstrated. As no other trials are available that specifically investigated the use of postoperative oxaliplatin in addition to 5FU/folinic acid in pretreated rectal cancer, controversy regarding this issue is likely to persist. In the ADORE study, a subgroup analysis indicated that the beneficial effect of treatment intensification was limited to patients with lymph node-positive disease; however, given the small cohort size in our study that could be analyzed for the DFS impact of chemotherapy with vs. without oxaliplatin, we were not able to further subdivide this cohort to perform subgroup analyses and thus could not investigate a possible association of lymph node positivity with a treatment benefit from oxaliplatin.

Our study has several limitations. In addition to the lack of quality control for neoadjuvant CRT and histopathological assessment as well as the possibility that factors that were not included in the propensity score analysis may have impacted on the decision for or against adjuvant chemotherapy with or without oxaliplatin in a given patient, perhaps the most important one is that no reliable information was available in the database as to the completeness of the adjuvant chemotherapy protocols performed. To address this issue, we attempted to obtain this information by contacting all patients or their treating physicians at the time of data analysis. This was successful in 60.8% of the patients included into the analysis of no vs. any adjuvant treatment (group B) and in 51.4 and 54.1% of the patients in groups B1 and B2, respectively, that were analyzed for the DFS impact of adjuvant chemotherapy with vs. without oxaliplatin. Of the patients for whom this information was obtained, more than 80% in each group had received their prescribed chemotherapy fully and without major dose reductions. Moreover, the results of the DFS analysis were not different from the entire

matched cohort when only patients who had received their full postoperative chemotherapy were included. Although a more complete follow-up would certainly be desirable, we believe that these figures justify the conclusion that our results obtained in the full matched cohort are valid. In relation to the randomized trials available, adherence to the prescribed adjuvant chemotherapy protocol was rather good in our study population. Only between 43% [10] and 74% [7] of patients completed the study protocol in the trials on adjuvant treatment vs. no adjuvant treatment, while only 68 and 53% of patients received the full scheduled dose of adjuvant therapy in the capecitabine-only and capecitabine + oxaliplatin arms of the PETACC-6 trial, respectively. As the patient's ability to tolerate chemotherapy shortly [27] after major surgery will continue to be a major obstacle to the conduct of adjuvant chemotherapy trials, it is unlikely that a definitive answer to the question if and according to which protocol rectal cancer patients should receive adjuvant chemotherapy following preoperative CRT and TME surgery will be obtained from future studies. Given the better tolerance for chemotherapy in the preoperative compared to the postoperative setting as well as the considerable capacity of chemotherapy alone to downstage rectal cancer even without concurrent radiation [28], currently recruiting studies are focusing on the optimization of the treatment sequence, namely, the administration of all chemotherapy prior to surgery [29], and on a more selective use of radiation for patients who achieve insufficient downstaging of their cancers following chemotherapy alone [30].

Conclusion

In the field of conflicting evidence, and in the absence of reliable data from randomized trials, our results lend support to the position that patients undergoing neoadjuvant 5FU-based CRT and TME surgery should receive adjuvant chemotherapy. Regarding the use of adjuvant oxaliplatin in addition to a fluoropyrimidine, our analysis does not demonstrate any benefit from this treatment approach, although this must be interpreted with caution due to the limited cohort size, which does not permit to perform valid subgroup analyses.

Author contributions BG conceptualized and designed the study, was involved in data collection and analysis, and wrote the manuscript. HP was involved in designing the study, data collection, interpretation, and analysis and helped to write the manuscript. FB and FP were involved in data collection, interpretation, and analysis. RO did the statistical analysis and was involved in data processing for presentation. KR, IG, HL, and CBr were involved in data collection and interpretation, as well as data extraction and processing from the Quality Assurance database. CBe helped to integrate the reviewer's comments into the revised version and was involved in collecting additional data for manuscript revision as well as the processing of these data for presentation. All authors approved the final manuscript.

Compliance with ethical standards

Conflict of interest All authors declare that no financial and personal relationships with other people or organizations that could inappropriately influence (bias) their existing work. This includes, but is not limited to, employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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