REVIEW

Addition of Platinum Derivatives to Fluoropyrimidine-Based Neoadjuvant Chemoradiotherapy for Stage II/III Rectal Cancer: Systematic Review and Meta-Analysis

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Abstract

Background: Current guidelines recommend neoadjuvant therapy for patients with stage II or III rectal cancer. The addition of platinum derivatives to fluoropyrimidine-based chemoradiotherapy has been frequently investigated, but their role in this setting remains controversial.

Methods: PubMed, Cochrane Library, and Web of Science were systematically searched for randomized trials comparing chemoradiotherapy with or without platinum agents in stage II or III rectal cancer. Main outcome parameters were overall and disease-free survival, additional outcomes included pathological complete response, isolated local recurrence, distant recurrence, toxicity, and perioperative morbidity. Time-to-event data were pooled as hazard ratios (HRs) by the inverse variance method and binary outcomes as odds ratios (ORs) by the Peto method with their respective 95% confidence interval (CI). All statistical tests were two-sided.

Results: Ten randomized controlled trials with data on 5599 patients were included in the meta-analysis. Platinum derivatives did not statistically significantly improve overall survival (HR = 0.93, 95% CI = 0.82 to 1.05, $P = .23$), disease-free survival (HR = 0.91, 95% CI = 0.83 to 1.01, $P = .07$), or local recurrence (OR = 0.83, 95% CI = 0.66 to 1.05, $P = .12$). However, it led to a statistically significant increase of pathological complete response (OR = 1.31, 95% CI = 1.10 to 1.55, $P = .002$) and a statistically significant reduction of distant recurrence (OR = 0.78, 95% CI = 0.66 to 0.92, $P = .004$). Benefits were accompanied by higher rates of grade 3 or 4 toxicities.

Conclusions: Intensified neoadjuvant chemoradiotherapy with the addition of platinum derivatives cannot be recommended routinely because it did not improve overall or disease-free survival and was associated with increased toxicity. It needs to be elucidated whether the benefits in distant recurrence and pathological complete response may be advantageous for selected high-risk patients.

Rectal cancer accounts for approximately 30%–40% of all colorectal cancers and requires specific treatment strategies because of its anatomical and clinical characteristics (1,2). Oncologic surgery in terms of total mesorectal excision is still the mainstay of curative treatment and has led to increased survival and reduced rates of local recurrence (3,4). In patients with stage II or III (II/III) rectal cancer, neoadjuvant treatment

approaches either as short-course radiotherapy or chemoradiotherapy, usually with fluorouracil-based chemotherapy, are recommended by national and international guidelines (2,5,6). Although neoadjuvant treatment has improved local control in locally advanced stages, it did not lead to improved survival (7,8). Therefore, current approaches concerning neoadjuvant treatment in rectal cancer patients are leading in different

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directions. Whereas some clinicians and researchers pled for a more selective use of neoadjuvant therapy (9,10), others investigated intensified treatment regimens within this setting (11,12). Because a substantial problem after curative surgery of advanced rectal cancer is distant recurrence with rates up to 30% (8,13), the concept of an intensified neoadjuvant therapy seems warranted.

Platinum derivatives such as oxaliplatin are cytotoxic agents leading to DNA cross-links that prohibit DNA replication and subsequently lead to cell apoptosis (14). Furthermore, it has been demonstrated that platinum agents may act as radiosensitizers by various mechanisms (15,16). In the palliative and adjuvant setting of colorectal cancer, oxaliplatin is effective in prolonging progression-free and disease-free survival (17,18). Therefore, integration of platinum agents into neoadjuvant chemoradiotherapy in stage II/III rectal cancer is a promising concept to improve oncologic outcome in these patients (19). Several randomized controlled trials (RCTs) and meta-analyses of these trials have demonstrated favorable short-term outcomes in terms of increased rates of pathological complete response, but this benefit is accompanied by enhanced acute toxicity (20). Therefore, current guidelines do not recommend the routine addition of platinum agents to neoadjuvant chemoradiotherapy (2). Recently, long-term results of some of these trials have been published with contradictory results (21–24).

The current systematic review and meta-analysis aimed to provide the latest high-quality evidence from RCTs on this controversial topic to shed more light on the value of platinum derivatives in the context of neoadjuvant chemoradiotherapy in stage II/III rectal cancer patients.

Methods

Methodological Guidelines and Registration

The current systematic review and meta-analysis evaluates the efficacy and safety of neoadjuvant chemoradiotherapy with a platinum agent vs conventional fluoropyrimidine-based chemoradiotherapy. All stages of the review process were performed in accordance with the recommendations of the Cochrane Collaboration (25), and the report was prepared according to the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) -recommendations (26). This systematic review has been registered prospectively in PROSPERO (CRD42017073064), and the protocol has been published (27).

Systematic Literature Search

A systematic literature search in the electronic databases MEDLINE (via PubMed), Web of Science, and Cochrane Central Register of Controlled Trials was performed up to October 1, 2018 (28). The final PubMed search strategy is provided in the [Supplementary Methods](#) (available online) (27). No language or other restrictions were applied. Similar search strategies were used for the Cochrane Library and Web of Science.

In addition, reference lists of relevant studies and related systematic reviews were screened manually. References citing trials eligible for inclusion were searched using the Science Citation Index via Web of Science. Furthermore, clinical trial registries (www.clinicaltrials.gov, www.clinicaltrialsregister.eu, www.drks.de) were searched for ongoing trials.

Trial Selection

Two authors (FJH and EK) independently screened all identified references for eligibility. Any disagreement was resolved by discussion and consensus. The full selection process is described in the protocol publication (27). The trial selection process is documented by a PRISMA flow diagram giving specific reasons for exclusion of studies at each stage (Figure 1).

We restricted the search to RCTs comparing neoadjuvant chemoradiotherapy with a platinum derivative (eg, oxaliplatin) added to a fluoropyrimidine-based chemotherapy (eg, 5-fluorouracil or capecitabine). Trials evaluating neoadjuvant chemoradiotherapy with any other combined regimen (eg, irinotecan, monoclonal antibodies) or neoadjuvant chemoradiotherapy followed by neoadjuvant chemotherapy before surgery were excluded.

RCTs meeting all the following inclusion criteria were eligible: patients with locally resectable stage II or III rectal cancer (ie, T3/4 tumors or nodal-positive disease) and undergoing neoadjuvant chemoradiotherapy followed by curative-intent surgical resection. Exclusion criteria were nonrandomized studies; animal studies; letters, comments, and editorials; and publications for which the full text was irretrievable. In case of multiple publications on a single clinical trial, all publications were included and the results were used complementarily, but with priority on the longest follow-up.

Outcome Measures

The main outcome parameters were overall survival and disease-free survival. Additional outcome parameters included isolated local recurrence, distant recurrence, pathological complete response, toxicity, postoperative morbidity and mortality, rate of anastomotic leakage, treatment compliance, and quality of life.

Data Extraction

Two authors (FJH and EK) independently extracted data using a predefined electronic data extraction sheet. Trial characteristics and outcomes were extracted for the individual treatment groups as previously described in the protocol publication (3). Any discrepancies concerning the extracted data were discussed and resolved by consensus or by consultation with a third author (PP).

In case of ambiguities concerning the extracted data, corresponding authors of the respective trials were contacted for clarification. If available, data were supplemented by additional, unpublished data (eg, conference proceedings).

Critical Appraisal

Risk of bias of included RCTs was analyzed by means of the Cochrane Collaboration's tool for assessing risk of bias in RCTs (29). Each of the following domains were evaluated at trial level: random sequence generation and allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective outcome reporting (reporting bias); and other bias (eg, baseline imbalances, early termination of the trial, industry or funding bias, missing sample size calculation or other deficiencies of the statistical analysis). Each potential source of bias was graded as "high," "low," or "unclear" risk with a justification for the judgment presented in the Results section.

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flowchart. RTCs = randomized controlled trials.

The quality of the body of evidence and the strength of recommendations at outcome level were assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach (30). The GRADE system considers the following factors: study quality and risk of bias, indirectness of evidence, unexplained heterogeneity and inconsistency of results between studies, imprecision of results, and publication bias.

Statistical Analysis

Hazard ratios (HRs) together with their respective 95% confidence intervals (CIs) were assessed as effect measures for time-to-event data. If a study reports adjusted and unadjusted hazard ratios, the adjusted hazard ratio was used for the primary analysis. If hazard ratios were not reported but adequate information (eg, Kaplan-Meier plots) was available, the estimation methods described by Parmar and Tierney were applied to

estimate hazard ratios and respective 95% confidence intervals (31,32). For dichotomous outcomes, odds ratios (ORs) together with their respective 95% confidence intervals were considered as effect measures.

Hazard ratios were pooled in meta-analyses by the generic inverse variance method and odds ratios by the Peto method. *P* values for the overall effects were calculated based on a two-sided *Z*-test for independent samples for effect measures on the log scale. A *P* value less than .05 was considered as statistically significant. Taking the assumable heterogeneity of included trials into account, the random-effects model was used to calculate overall effect estimates. However, results of fixed-effects models were also calculated and potential differences discussed. *I*² statistics were calculated to investigate statistical heterogeneity between individual trial results. In case of substantial, statistical heterogeneity (*I*² > 75%), no meta-analysis was performed for the respective outcome. The *I*² statistic follows a χ^2 distribution so that *P* values are based on a χ^2 test of no differences in intervention effects among studies.

To verify the results of the primary analysis for the survival endpoints, sensitivity analyses with unadjusted hazard ratios where available were conducted.

The following subgroup analyses were performed for the main outcome measures to elucidate potential heterogeneity: adjuvant vs no adjuvant treatment with another subdivision of adjuvant therapy into trials that added oxaliplatin to the interventional arm in the adjuvant setting; 5-fluorouracil (5-FU) vs capecitabine. A funnel plot displaying treatment effect against standard error was created to assess potential publication bias for the outcome pathological complete response, because this outcome was reported in all included trials.

For the main outcome parameters overall and disease-free survival, a power calculation according to Jackson and Turner was performed retrospectively (33) to quantify the probability of a statistically significant meta-analysis result anticipating the obtained overall hazard ratio in this systematic review. Meta-analytic results were graphically displayed by Forest plots. R version 3.4.4 (34) and the R meta package version 4.9-1 (developed by Guido Schwarzer) were used for all statistical analyses.

Differences Between Protocol and Review

The subgroup analysis of adjuvant vs no adjuvant treatment was amended by an additional subdivision into trials that performed adjuvant therapy with a fluoropyrimidine in the control group and added oxaliplatin in the interventional group.

The initially planned subgroup analysis of stage II vs stage III rectal cancer could not be performed because the trials did not provide sufficiently detailed information on this aspect. Additionally, the final search strategy differed slightly from the search strategy that is available in the published protocol (Supplementary Methods, available online).

Results

Systematic Literature Search and Trial Selection

The systematic literature search yielded 4620 results. After stepwise literature screening, a total of 10 RCTs that were reported in 13 publications and three conference proceedings were finally included in the current systematic review and meta-analysis (Figure 1) (11,12,21,22,35–44).

Full manuscripts were available for nine trials, whereas the results of the PETACC-6 trial were available as a detailed presentation from the American Society of Clinical Oncology 2018 conference (23). Furthermore, the data from the publications of the STAR-01 and FOWARC trials were amended by additional information on long-term outcomes from sufficiently detailed conference proceedings, respectively (24,44). Additionally, the authors of four trials (23,35,36,41) were contacted to clarify some ambiguities in the published reports or to provide additional information.

The present meta-analysis contains data on a total of 5599 patients, of whom 2813 (50.2%) were treated with conventional fluoropyrimidine-based neoadjuvant chemoradiotherapy and 2786 (49.8%) were treated with the addition of a platinum agent to fluoropyrimidine-based neoadjuvant chemoradiotherapy. Seven of these trials reported survival endpoints with a follow-up period ranging from 36 to 120 months (Table 1). In nine of the trials, the applied platinum derivative was oxaliplatin with a weekly dose ranging from 50 to 85 mg/m² (21–23,35,36,38,39,41,42), whereas cisplatin (100 mg/m² on day 1 and

29) was used in one pilot trial (40). 5-FU was applied during neoadjuvant chemoradiotherapy in four trials (22,35,40,42), four trials used capecitabine (11,21,23,38), one trial applied 5-FU in the control and capecitabine and oxaliplatin in the interventional arm (39), and one trial was four-armed: 5-FU vs 5-FU and oxaliplatin vs capecitabine vs capecitabine and oxaliplatin (41). The latter trial was handled like a two-arm trial: 5-FU or capecitabine vs 5-FU and oxaliplatin or capecitabine and oxaliplatin. The FOWARC trial was conducted in a three-arm design including one arm of neoadjuvant chemotherapy without radiation. For the purpose of the current analysis, only data from the two arms comprising neoadjuvant chemoradiotherapy (5-FU vs mFOLFOX) were extracted (42). CAO/ARO/AIO-04 used different 5-FU application modes in the control and the interventional arm of the trial: 5-FU was applied by continuous venous infusion on days 1–5 and 29–33 at a dose of 1000 mg/m² per day in the control arm vs a prolonged venous infusion on days 1–14 and 22–35 at a dose of 225 mg/m² per day in the interventional arm (22).

Planned full radiation dose was 50.4 Gray (Gy) in nine trials with only minor differences in application mode, whereas one trial applied different radiation regimens in the capecitabine (45 Gy) and capecitabine/oxaliplatin (50 Gy) arms (37). There was no information on adjuvant treatment in two trials (38,41), one multicenter trial left the decision of adjuvant treatment to the discretion of the respective institution (128/293 [43.7%] in capecitabine arm vs 125/291 [43.0%] in capecitabine/oxaliplatin arm) (11), and adjuvant therapy was routinely applied in the remaining seven trials (21–23,35,39,40,42). Of these, one trial applied 5-FU-based adjuvant therapy in both arms (11,35), and three trials applied a modified FOLFOX regimen in both arms (21,39,40). In two trials, 5-FU was administered in the control group, whereas (m)FOLFOX was given in the experimental group (22,42), and in the PETACC-6 trial, capecitabine was applied in the control arm, whereas capecitabine/oxaliplatin was given in the experimental arm (23). Further characteristics of chemotherapy and radiation are provided in Table 2.

Surgery was performed within 6–8 weeks after the end of radiation in six trials (11,35,39–42), whereas the other trials reported the period between radiation and surgery with a minimum of 4 weeks up to a maximum of 10 weeks (21–23,38). Surgical details were reported very variably among the trials and are displayed in Table 3.

Critical Appraisal

An adequate method of random sequence generation was described in all trials. Six trials also reported a viable approach for allocation concealment (11,22,23,35,41,42), but four RCTs did not describe allocation concealment in their reports, representing an unclear risk (21,38–40).

Concerning blinding, one RCT was described as double-blind but no placebo control was implemented and the treatment schedules differed substantially (39). Thus, it can be assumed that blinding was not effectively achieved, and the risk of bias for this domain still had to be judged as unclear. One trial described that assessment of pathological complete response was assessed by two pathologists who were blinded to group allocation, but no further measures of blinding were applied within this trial (42). All other trials did not describe any methods of blinding (11,21–23,35,38,40,41). Although complete blinding is not ethically reasonable within a trial assessing highly toxic drugs such as platinum agents, measures of blinding

Table 1. Trial characteristics

Study/Reference(s)	Primary endpoint*	Study period	Country	No. of trial centers	Survival follow-up period, months	Sample size of ITT analysis		Age, y		Sex, No.			
						FP CRT	Platin CRT	FP CRT	Platin CRT	FP CRT		Platin CRT	
										Male	Female	Male	Female
NSABP R-04: O'Connell et al., 2014 (43) and Allegra et al., 2015 (41)	3-year local-regional control	July 2004–August 2010 (74 months)	United States	Multicenter	60	641	643	≤59: 371 patients ≥60: 285† patients	≤59: 404 patients ≥60: 255† patients	442†	214†	447†	212†
STAR-01: Aschele et al., 2011 (35) and 2016 (44)	Overall survival	November 2003–August 2008 (58 months)	Italy	41	120	379	368	63 (20–75)†	62 (33–75)†	259	120	245	123
FOWARC: Deng et al., 2016 (42) and 2018 (24)	3-year disease-free survival	June 2010–February 2015 (57 months)	China	15	36	158	162	54 ± 11.9§	52.2 ± 11.8§	103†	62†	114†	51†
ACCORD 12/0405 PRODIGE 2: Gerard et al., 2010 (37), 2012 (11), and Azria et al., 2017 (36)	Pathological complete response	November 2005–July 2008 (33 months)	France	56	60	293	291	63 (34–80)†	61 (25–80)†	191	102	196	95
Haddad et al., 2017 (38)	Tumor down-staging	October 2012–January 2014 (16 months)	Iran	1	NA	28	25	63 ± 11§	51 ± 16§	20†	11†	23†	9†
Jiao et al., 2015 (21)	3-year overall survival	July 2007–July 2010 (37 months)	China	1	36	102	101	55.9 ± 2.3§	55.8 ± 2.4§	68†	35†	59†	44†
Kayal et al., 2014 (40)	NA	January 2011–March 2013 (27 months)	India	1	NA	24	25	20–30: 2 patients 31–40: 7 patients 41–50: 9 patients 51–60: 4 patients >60: 2 patients	20–30: 2 patients 31–40: 8 patients 41–50: 8 patients 51–60: 7 patients >60: 0 patients	18	6	18	7

(continued)

Table 1. (continued)

Study/Reference(s)	Primary endpoint*	Study period	Country	No. of trial centers	Survival follow-up period, months	Sample size of ITT analysis		Age, y		Sex, No.			
						FP CRT	Platin CRT	FP CRT	Platin CRT	Male	Female	Male	Female
CAO/ARO/AIO-04: Rödel et al., 2012 (12) and 2015 (22)	3-year disease-free survival	July 2006–February 2010 (44 months)	Germany	88	36	623	613	62 ± 10§	62 ± 10§	440	183	434	179
Saha et al., 2015(39)	NA	April 2011–March 2013 (24 months)	India	1	NA	21	21	20 to ≤30: 2 patients 30 to ≤40: 6 patients 40 to ≤50: 7 patients 50 to ≤60: 8 patients 60 to ≤70: 3 patients 60 to ≤70: 2 patients	20 to ≤30: 2 patients 30 to ≤40: 2 patients 40 to ≤50: 6 patients 50 to ≤60: 6 patients 60 to ≤70: 6 patients 60 to ≤70: 0 patients	17	4	16	5
PETACC-6: Schmoll et al., 2018 (23)	3-year disease-free survival	November 2008–September 2011 (35 months)	Germany (international trial)	n.i.	60	544	537	0–60: 255 patients 60–70: 180 patients 70–100: 70–100:					
112 patients†	0–60: 238 patients 60–70: 189 patients 70–100: 120 patients‡	394†	153†	380†	167†								

*Detailed definitions of primary endpoints can be found in the [Supplementary Material](#) (available online). FP CRT = fluoropyrimidine-based chemoradiotherapy; ITT = intention to treat; NA = not applicable; n.i. = no information; platin CRT = chemoradiotherapy with addition of a platinum agent.

†Numbers differ from ITT sample size because baseline data are provided for all included patients.

‡Median (range).

§Mean ± SD.

Table 2. Details of chemoradiotherapy (CRT)

Study/ Reference(s)	Oncologic performance scale, No.		Details of neoadjuvant radiation		Details of neoadjuvant CHT		Details of adjuvant CHT	
	FP CRT	Platin CRT	FP CRT	Platin CRT	FP CRT	Platin CRT	FP CRT	Platin CRT
NSABP R-04: O'Connell et al., 2014 (43) and Allegra et al., 2015 (41)	ECOG 0-1	ECOG 0-1	1.8 Gy/25 daily fractions/5 wk + boost of 5.4 Gy/3 fractions (boost of 10.8 Gy/3 fractions for T4 or fixed distal tumors) 50.4 Gy (55.8 Gy)	1.8 Gy/25 daily fractions/5 wk + boost of 5.4 Gy/3 fractions (boost of 10.8 Gy/3 fractions for T4 or fixed distal tumors) 50.4 Gy (55.8 Gy)	5-FU (225mg/m ² per d × 5 days CVI) N = 328* CAPE (825mg/m ² bid × 5 days) N = 325*	5-FU (225 mg/m ² per d × 5 days CVI) + OX (50mg/m ² once per week) N = 327* CAPOX (CAPE 825 mg/m ² bid × 5 days + OX 50 mg/m ² once per week) N = 328*	n.i.	n.i.
STAR-01: Aschele et al., 2011 (35) and 2016 (44)	WHO 0 = 330 1 = 48 2 = 1	WHO 0 = 324 1 = 44 2 = 0	1.8 Gy/28 daily fractions 50.4 Gy	1.8 Gy/28 daily fractions 50.4 Gy	5-FU (225 mg/m ² per d × 5 days CVI)	5-FU (225 mg/m ² per d × 5 days CVI) + OXA (60 mg/m ² per wk)	Fluorouracil-based adjuvant chemotherapy	Fluorouracil-based adjuvant chemotherapy
FOWARC: Deng et al., 2016 (42) and 2018 (24)	ECOG 0-1	ECOG 0-1	1.8-2 Gy/23 to 28 daily fractions 46-50.4 Gy	1.8-2 Gy/23 to 28 daily fractions 46-50.4 Gy	de Gramont schedule (leucovorin 400 mg/m ² + 5-FU 400 mg/m ² per bolus + 2.4 g/m ² over 48 h CVI every 2 wk) × 5 cycles	mFOLFOX6 (OX 85 mg/m ² + leucovorin 400 mg/m ² + 5-FU 400 mg/m ² per bolus + 2.4 g/m ² over 48 h CVI every 2 wk) × 7 cycles	de Gramont schedule (leucovorin 400 mg/m ² + 5-FU 400 mg/m ² per bolus + 2.4 g/m ² over 48 h CVI every 2 wk) × 7 cycles	mFOLFOX6 (OX 85 mg/m ² + leucovorin 400 mg/m ² + 5-FU 400 mg/m ² per bolus + 2.4 g/m ² over 48 h CVI every 2 wk) × 7 cycles
ACCORD 12/0405 PRODIGE 2: Gerard et al., 2010 (37), 2012 (11), and Azria et al., 2017 (36)	ECOG 0 = 229 1 = 43 2 = 1 Missing = 20	ECOG 0 = 229 1 = 51 2 = 1 Missing = 10	1.8 Gy/25 daily fractions 45 Gy	2 Gy/25 daily fractions 50 Gy	CAPE (800mg/m ² bid × 5 days)	CAPE (800 mg/m ² bid × 5 d + OX 50 mg/m ² once per week)	“Adjuvant treatment left to the discretion of each institution” –128/293; most frequent regimen leucovorin + 5-FU over 48 h	“Adjuvant treatment left to the discretion of each institution” –125/291; most frequent regimen leucovorin + 5-FU over 48 h
Haddad et al., 2017 (38)	WHO 0 = 25 I-II = 6*	WHO 0 = 24 I-II = 8*	1.8 Gy/23-25 daily fractions + boost of 5.4 Gy/3 fractions 50-50.4 Gy	1.8 Gy/23-25 daily fractions + boost of 5.4 Gy/3 fractions 50-50.4 Gy	CAPE (825 mg/m ² bid × 5 days)	CAPE (825 mg/m ² bid × 5 d + OX 60 mg/m ² once per wk) × 5-6 cycles	n.i.	n.i.

(continued)

Table 2. (continued)

Study/Reference(s)	Oncologic performance scale, No.		Details of neoadjuvant radiation		Details of neoadjuvant CHT				Details of adjuvant CHT	
	FP CRT	Platin CRT	FP CRT	Platin CRT	CAPE	FP CRT	CAPOX	Platin CRT	FP CRT	Platin CRT
Jiao et al., 2015 (21)	ECOG 0 = 82 1 = 16 2 = 5*	ECOG 0 = 83 1 = 15 2 = 5*	2 Gy/25 daily fractions 50.4 Gy	2 Gy/25 daily fractions 50.4 Gy	CAPE (800 mg/m ² bid. × d 1-14 and d 22-25)	FP CRT (800 mg/m ² bid. × d 1-14 and d 22-25)	CAPOX (CAPE 800 mg/m ² bid × d 1-14 and d 22-25 + OX 60 mg/m ² d 1, 8, 22, and 29)	Platin CRT	mFOLFOX6 (OX 85 mg/m ² + leucovorin 400 mg/m ² + 5-FU 400 mg/m ² bolus + 2.4 g/m ² over 46-48 h CVI every 2 wk) × 6-8 cycles	mFOLFOX6 (OX 85 mg/m ² + leucovorin 400 mg/m ² + 5-FU 400 mg/m ² bolus + 2.4 g/m ² over 46-48 h CVI every 2 wk) × 6-8 cycles
Kayal et al., 2014 (40)	ECOG 0 = 2 I = 16 II = 6	ECOG 0 = 2 I = 17 II = 6	1.8 Gy/28 daily fractions 50.4 Gy	1.8 Gy/28 daily fractions 50.4 Gy	5-FU (leucovorin 20 mg/m ² + 5-FU 350 mg/m ² × d 1-5 CVI and d 29-33)	5-FU (350 mg/m ² CVI × d 1-5 and d 29-33) + CIS (100 mg/m ² × d 1 and 29)	5-FU (250 mg/m ² per day CVI × d 1-14 and d 22-35) + OX 50 mg/m ² × d 1, 8, 22, and 29)	Platin CRT	mFOLFOX6 (4 months)	mFOLFOX6 (4 months)
CAO/ARO/AIO-04: Rödel et al., 2012 (12) and 2015 (22)	ECOG 0 = 475 I-II = 141 Missing = 7	ECOG 0 = 483 I-II = 123 Missing = 7	1.8 Gy/28 daily fractions 50.4 Gy	1.8 Gy/28 daily fractions 50.4 Gy	5-FU (1000 mg/m ² per day CVI over 5 d × d 1-5 and d 29-33)	5-FU (1000 mg/m ² per day CVI × d 1-14 and d 22-35) + OX 50 mg/m ² × d 1, 8, 22, and 29)	5-FU (500 mg/m ² bolus × d 1-5 and d 29) × 4 cycles	Platin CRT	5-FU/LV/OX (OX 100 mg/m ² × d 1 and 15 + leucovorin 400 mg/m ² × d 1 and 15 + 5-FU 2.4 g/m ² over 46 h CVI d 1-2 and d 15-16)	5-FU/LV/OX (OX 100 mg/m ² × d 1 and 15 + leucovorin 400 mg/m ² × d 1 and 15 + 5-FU 2.4 g/m ² over 46 h CVI d 1-2 and d 15-16)
Saha et al., 2015 (39)	ECOG 0 = 4 1 = 16 2 = 1	ECOG 0 = 3 1 = 16 2 = 2	1.8 Gy/28 daily fractions 50.4 Gy	1.8 Gy/28 daily fractions 50.4 Gy	5-FU (leucovorin 20 mg/m ² + 5-FU 350 mg/m ² × d 1-5 CVI and d 29-33)	5-FU (leucovorin 20 mg/m ² + 5-FU 350 mg/m ² × d 1-5 CVI and d 29-33)	CAPOX (CAPE 1000 mg/m ² bid × d 1-14 and d 25-38 + OX 85 mg/m ² × d 1 and 29)	Platin CRT	m-FOLFOX6 (4 months)	m-FOLFOX6 (4 months)
PETACC-6: Schmoll et al., 2018 (23)	WHO 0 = 420 1-2 = 127*	WHO 0 = 432 1-2 = 115*	1.8 Gy/25 daily fractions + optional boost of 5.4 Gy/3 fractions (d 36-38) 45 Gy/50.4 Gy	1.8 Gy/25 daily fractions + optional boost of 5.4 Gy/3 fractions (d 36-38) 45 Gy/50.4 Gy	CAPE (825 mg/m ² bid × d 1-33 w/o weekends)	CAPE (825 mg/m ² bid × d 1-33 w/o weekends)	CAPOX (CAPE 825 mg/m ² bid × d 1-33 w/o weekends + OX 50 mg/m ² × d 1, 8, 15, 22, and 29)	Platin CRT	CAPE (1000 mg/m ² bid × d 1-15 every 3 wk for 6 cycles)	CAPOX (CAPE 1000 mg/m ² bid × d 1-15 + OX 130 mg/m ² × d 1 every 3 wk for 6 cycles)

*Numbers differ from ITT sample size because baseline data are provided for all included patients. 5-FU = 5-fluorouracil; bid = twice per day; CAPE = capecitabine; CHT = chemotherapy; CIS = cisplatin; CVI = continuous venous infusion; ECOG = Eastern Cooperative Oncology Group; FP CRT = fluoropyrimidine-based chemoradiotherapy; Gy = Gray; ITT = intention to treat; LV = leucovorin; n.i. = no information; OX = oxaliplatin; platin CRT = chemoradiotherapy with addition of a platinum agent; WHO = World Health Organization.

Table 3. Surgical details

Study/Reference(s)	UICC stage (No. of patients)		T stage (No. of patients)		N stage (No. of patients)		Height of tumor, cm (No. of patients)		Period between radiation and surgery, wk		Details of surgical procedure (No. of patients)	
	FP CRT	Platin CRT	FP CRT	Platin CRT	FP CRT	Platin CRT	FP CRT	Platin CRT	FP CRT	Platin CRT	FP CRT	Platin CRT
	FP CRT	Platin CRT	FP CRT	Platin CRT	FP CRT	Platin CRT	FP CRT	Platin CRT	FP CRT	Platin CRT	FP CRT	Platin CRT
NSABP R-04: O'Connell et al., 2014 (43), and Allegra CJ et al., 2015 (41)	Clinical II (406) III (250)	Clinical II (406) III (253)	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.	6–8	6–8	Sphincter-preserving surgery (388 of 636)	Sphincter-preserving surgery (372 of 644)
STAR-01: Aschele et al., 2011 (35) and 2016 (44)	Clinical II (134) III (242) m.d. (3)	Clinical II (122) III (246)	Clinical T1–2 (7) T3 (307) T4 (65)	Clinical T1–2 (17) T3 (300) T4 (50) m.d. (1)	Clinical N0 (134) N+ (242) m.d. (3)	Clinical N0 (122) N+ (246) m.d. (9)	<4 = 89 4–8 (202) >8 (81) m.d. (7)	<4 = 70 4–8 (213) >8 (76) m.d. (9)	6–8	6–8	LAR/TME (n = 282) APR (n = 72) Other (n = 8)	LAR/TME (n = 276) APR (n = 64) Other (n = 11)
FOWARC: Deng et al., 2016 (42) and 2018 (24)	Clinical II (37) III (128)	Clinical II (30) III (135)	Clinical T2 (8) T3 (100) T4 (57)	Clinical T2 (3) T3 (106) T4 (56) T4 (47)	Clinical N0 (37) N1 (84) N2 (44)	Clinical N0 (30) N1 (88) N2 (47)	<5 (90) 5–10 (70) >10 (5)	<5 (83) 5–10 (75) >10 (7)	Approx. 7	Approx. 7	Sphincter-preserving TME surgery (119 of 141)	Sphincter-preserving TME surgery (130 of 149)
ACCORD 12/0405 PRODIGE 2: Gerard et al., 2010 (37), 2012 (11), and Azria et al., 2017 (36)	Clinical II (85) III (205) m.d. (3)	Clinical II (78) III (211) m.d. (2)	Clinical T2 (23) T3 (255) T4 (15)	Clinical T2 (21) T3 (254) T4 (16)	Clinical N0 (85) N+ (205) m.d. (3)	Clinical N0 (78) N+ (211) m.d. (2)	<6 (204) >6 (89)	<6 (184) >6 (107)	6	6	LAR/TME (n = 195) APR (n = 67) Other (n = 25)	LAR/TME (n = 205) APR (n = 61) Other (n = 21)
Haddad et al., 2017 (38)	Clinical II (4) III (27)	Clinical II (3) III (29)	Clinical T1–2 (4) T3 (26) T4 (1)	Clinical T1–2 (1) T3 (28) T4 (3)	Clinical N0 (4) N1 (14) N2 (13)	Clinical N0 (3) N1 (10) N2 (19)	6.4 (3.3)	6.0 (2.6)	Mean approx. 10	Mean approx. 10	n.i.	n.i.
Jiao et al. 2015 (21)	Clinical II (23) III (80)	Clinical II (22) III (81)	Clinical T1–2 (3) T3 (61) T4 (39)	Clinical T1–2 (2) T3 (66) T4 (35)	Clinical N0 (23) N1 (56) N2 (24)	Clinical N0 (22) N1 (54) N2 (27)	<4 (25) 4–8 (57) >8 (21)	<4 (24) 44–88 (58) >8 (21)	6–10	6–10	LAR/TME (n = 80) APR (n = 22) Other (n = 1)	LAR/TME (n = 87) APR (n = 15) Other (n = 1)
Kayal et al., 2014 (40)	n.i.	n.i.	Clinical T3 (7) T4 (17)	Clinical T3 (8) T4 (17)	n.i.	n.i.	n.i.	n.i.	6–8	6–8	n.i.	n.i.
CAO/ARO/AIO-04: Rödel et al., 2012 (12) and 2015 (22)	Clinical II (159) III (451) m.d. (13)	Clinical II (146) III (452) m.d. (15)	Clinical T2 (32) T3 (537) T4 (50) m.d. (4)	Clinical T2 (22) T3 (549) T4 (41) m.d. (1)	Clinical N0 (159) N+ (451) m.d. (13)	Clinical N0 (146) N+ (452) m.d. (15)	<5 (216) 5–10 (336) >10 (64) m.d. (7)	<5 (249) 5–10 (302) >10 (55) m.d. (7)	5–6	5–6	LAR/TME (n = 416) APR (n = 152) Other (n = 47)	LAR/TME (n = 398) APR (n = 151) Other (n = 47)

(continued)

Table 3. (continued)

Study/Reference(s)	UICC stage (No. of patients)		T stage (No. of patients)		N stage (No. of patients)		Height of tumor, cm (No. of patients)		Period between radiation and surgery, wk		Details of surgical procedure (No. of patients)	
	FP CRT	Platin CRT	FP CRT	Platin CRT	FP CRT	Platin CRT	FP CRT	Platin CRT	FP CRT	Platin CRT	FP CRT	Platin CRT
Saha et al., 2015 (39)	n.i.	n.i.	Clinical T3 (6) T4 (15)	Clinical T3 (6) T4 (15)	n.i.	n.i.	n.i.	n.i.	6-8	6-8	LAR/TME (16) APR (4) m.d. (0)	LAR/TME (17) APR (3) Other (1) n.i.
PETACC-6: Schmoll et al., 2018 (23)	Clinical II (118) III (393) m.d. (36)	Clinical II (120) III (389) m.d. (38)	Clinical T2 (36) T3 (466) T4 (42) m.d. (3)	Clinical T2 (33) T3 (469) T4 (43) m.d. (2)	Clinical N0 (118) N+ (393) m.d. (36)	Clinical N0 (120) N+ (389) m.d. (38)	≤5 (236) 5-10 (266) >10 (45)	≤5 (237) 5-10 (270) >10 (40)	4-8	4-8	n.i.	n.i.

*Mean ± SD. APR = abdominoperineal resection; FP CRT = fluoropyrimidine-based chemoradiotherapy; LAR = low anterior resection; m.d. = missing data; n.i. = no information; platin CRT = chemoradiotherapy with addition of a platinum agent; TME = total mesorectal excision; UICC = Union for International Cancer Control.

nevertheless could have been implemented, for instance, concerning outcome assessment of specific outcomes (eg, pathologists or personnel assessing quality of life). The main outcome parameters of this meta-analysis (overall survival and disease-free survival) can be considered as hard outcome measures, which are most probably not influenced by blinding, but other outcomes such as pathological complete response or toxicity might have been influenced. Thus, the risk for performance and detection bias had to be judged as unclear in all trials.

Eight trials provided a detailed CONSORT flowchart or sufficient information on dropouts and losses to follow-up in their report (11,21-23,35,38-40,42). One trial provided a flowchart but the numbers in the further analyses of the publications differed; however, these ambiguities could be resolved after contacting the corresponding author (41).

A detailed trial protocol was available for only one trial (22), but three further trials provided sufficient information on pre-specified endpoints and analysis in the respective trial registry or on a publicly accessible web page (23,41,42). One trial was registered but did not provide sufficiently detailed information in the registry (11), whereas the remainder was not registered nor was a protocol available, leading to a judgment of unclear risk concerning reporting bias (21,35,38-40).

Concerning other sources of bias, three trials were judged at high risk because they were prone to small sample bias, and potential industry bias in one case, or did not present any funding information in the other two cases (38-40). Furthermore, these two trials did not report a sample size calculation (39,40). Five trials were judged as unclear risk of other bias because of potential industry bias or a potential conflict of interest (11,21,23,35,42). CAO/ARO/AIO-04 was judged to be at unclear risk of other bias because of the differing 5-FU application modes in the two arms of the trial (23). The remaining trial was free of other sources of bias (22,41,42). An overview of the risk of bias assessment is provided in [Supplementary Figure 1](#) (available online).

The risk for publication bias was assessed by visual inspection of a funnel plot regarding the outcome pathological complete response because this parameter was reported in all trials ([Supplementary Figure 2](#), available online). The funnel plot showed a slight asymmetry in the lower left corner, indicating a lack of small trials with results in favor of the control group. Because of the low number of included trials, no formal test of funnel plot asymmetry was performed according to the recommendations of the Cochrane Handbook (25).

Main Outcomes

In the primary analysis, no statistically significant difference was observed for overall survival (HR = 0.93, 95% CI = 0.82 to 1.05, $P = .23$; $I^2 = 0\%$) (21-23,35,36,41,42) ([Figure 2A](#)). The result for overall survival was corroborated by all sensitivity and subgroup analyses. Interestingly, the effect even shifted slightly toward the fluoropyrimidine chemoradiotherapy in the subgroup of capecitabine compared with the 5-FU subgroup ([Supplementary Figure 3](#), available online).

Similarly, disease-free survival was not statistically significantly improved by the addition of a platinum agent in the primary meta-analysis (HR = 0.91, 95% CI = 0.83 to 1.01, $P = .07$; $I^2 = 0\%$; [Figure 2B](#)). In the sensitivity analysis including the unadjusted hazard ratio of ACCORD 12/0405 PRODIGE 2, the result just reached the statistical significance level in favor of the platinum group (HR = 0.89, 95% CI = 0.81 to 0.99, $P = .02$; $I^2 = 0\%$).

Figure 2. Forest plots for survival endpoints. Analyses for (A) overall survival (OS) and (B) disease-free survival (DFS) are shown. Hazard ratios (HRs) were pooled in meta-analyses by the generic inverse variance method, and P values for the overall effects were calculated based on a two-sided Z-test for independent samples for effect measures on the log scale. 5-FU = 5-fluorouracil; CI = confidence interval; CRT = chemoradiotherapy.

Figure 3. Forest plot for pathological complete response. Odds ratios (ORs) were pooled in meta-analyses by the Peto method, and P values for the overall effects were calculated based on a two-sided Z-test for independent samples for effect measures on the log scale. 5-FU = 5-fluorouracil; CI = confidence interval; CRT = chemoradiotherapy.

The statistically significant result for disease-free survival could also be observed in the 5-FU subgroup, whereas no difference between the treatment groups could be found in the capecitabine subgroup (Supplementary Figure 4, available online).

For both survival outcome parameters, no differences regarding the subgroup analysis of adjuvant vs no adjuvant treatment could be observed irrespective of whether oxaliplatin was added to adjuvant treatment in the interventional arm. The probability to detect a statistically significant difference between the treatment groups in this meta-analysis based on the observed data was 22.8% for overall survival and 44.2% for disease-free survival based on the retrospective power analysis (33).

Secondary Outcomes

The pathological complete response rate was reported by all trials and demonstrated a statistically significant benefit for

neoadjuvant chemoradiotherapy with a platinum agent (OR = 1.31, 95% CI = 1.10 to 1.55, $P = .002$; $I^2 = 22.0\%$; Figure 3) with 503 of 2752 (18.3%) patients in the platinum group and 411 of 2769 (14.8%) in the conventional chemoradiotherapy group (21–23,35,36,38–42). Concerning isolated local recurrence, a statistically nonsignificant difference resulted in the meta-analysis of six trials, with 144 of 2344 (6.1%) patients in the platinum group and 169 of 2342 (7.2%) in the fluoropyrimidine-based group suffering from an isolated local recurrence (OR = 0.83, 95% CI = 0.66 to 1.05, $P = .12$; $I^2 = 0\%$; Figure 4A) (11,21–24,41).

On the other hand, fewer patients sustained a distant recurrence after neoadjuvant chemoradiotherapy with the addition of a platinum derivative (OR = 0.78, 95% CI = 0.66 to 0.92, $P = .004$; $I^2 = 0\%$; Figure 4B) (11,21–23). In absolute numbers, a distant recurrence occurred in 311 of 1560 (19.9%) patients after platinum-amplified neoadjuvant chemoradiotherapy and 381 of 1571 (24.3%) after conventional chemoradiotherapy.

A**Study**

ACCORD 12/0405 PRODIGE 2: Gerard, J.-P. et al. 2010 & 2012 & Azria, D. et al. 2017
 CAO/ARO/AIO-04: Rödel, C. et al. 2012 & 2015
 Jiao, D. et al. 2015
 NSABP R-04: O'Connell, M. J. et al. 2014 & Allegra, C. J. et al. 2015
 FOWARC: Deng, Y. et al. 2016 & 2018
 PETACC-6: Schmoll, H.J. et al. 2018

Fixed effect model**Random effects model**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.61$

Test for overall effect (random effects): $z = -1.54$ ($p = 0.12$)

B**Study**

ACCORD 12/0405 PRODIGE 2: Gerard, J.-P. et al. 2010 & 2012 & Azria, D. et al. 2017
 Jiao, D. et al. 2015
 CAO/ARO/AIO-04: Rödel, C. et al. 2012 & 2015
 PETACC-6: Schmoll, H.J. et al. 2018

Fixed effect model**Random effects model**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.54$

Test for overall effect (random effects): $z = -2.91$ ($p = 0.004$)

Figure 4. Forest plots for recurrence endpoints. Analyses for (A) local recurrence and (B) distant recurrence are shown. Odds ratios (ORs) were pooled in meta-analyses by the Peto method, and P values for the overall effects were calculated based on a two-sided Z-test for independent samples for effect measures on the log scale. 5-FU = 5-fluorouracil; CI = confidence interval; CRT = chemoradiotherapy.

The meta-analysis of overall grade 3 or 4 toxicity demonstrated a marked statistical heterogeneity with an I^2 value of 87.0%. Thus, according to the prespecified methods in the protocol and the recommendations of the Cochrane Collaboration, no meta-analysis for this outcome is presented. Regarding specific dimensions of toxicities no less than grade 3, the addition of a platinum agent resulted in a statistically significant increase of diarrhea (seven trials: OR = 2.59, 95% CI = 1.88 to 3.58, $P < .001$; $I^2 = 55.4\%$) (12,21,35,37,38,42,43); nausea (five trials: OR = 2.71, 95% CI = 1.61 to 4.55, $P < .001$; $I^2 = 0\%$) (12,21,35,42,43); neurosensory toxicity (six trials: OR = 4.14, 95% CI = 2.45 to 6.98, $P < .001$; $I^2 = 0\%$) (12,21,35,37,38,43); and fatigue (five trials: OR = 3.43, 95% CI = 2.25 to 5.22, $P < .001$; $I^2 = 0\%$) (12,21,35,37,43) (Supplementary Figure 5, available online). Radiation dermatitis (six trials: OR = 1.24, 95% CI = 0.71 to 2.15, $P = .45$; $I^2 = 48.1\%$) (12,35,37,38,42,43) and hematological toxicity (four trials: OR = 1.04, 95% CI = 0.70 to 1.54, $P = .84$; $I^2 = 0\%$) did not differ statistically significantly between the two groups (Supplementary Figure 5, available online). Specific hematological toxicity (anemia, neutropenia, etc) was inconsistently reported among trials and could not be pooled. Neither postoperative 60-day mortality (five trials: OR = 0.74, 95% CI = 0.34 to 1.63, $P = .45$; $I^2 = 0\%$) (12,35,37,42,43), postoperative morbidity (six trials: OR = 1.10, 95% CI = 0.98 to 1.23, $P = .12$; $I^2 = 0\%$) (12,23,35,37,42,43), nor anastomotic leakage (five trials: OR = 1.21, 95% CI = 0.94 to 1.55, $P = .14$; $I^2 = 0\%$) (12,35,37,42,43) demonstrated a statistically significant difference (Supplementary Figure 6, available online).

The information about treatment compliance in the individual trials was too heterogeneous to be pooled in a meta-analysis. Six trials reported the rate of patients completing full-dose radiotherapy, of which three trials showed a statistically significant reduced proportion of full-dose radiotherapy in the chemoradiotherapy group with the addition of a platinum agent (11,23,35) and three trials did not show statistically significant differences (21,22,38). The rate of participants receiving full-dose radiotherapy allocated to the control group ranged from 87.1% to 100% compared with an 83.8% to 94.9% rate of participants allocated to the group with platinum-enhanced chemoradiotherapy. Two studies reported a proportion of

patients completing at least 80% or 90% of full-dose radiotherapy and did not show statistically significant differences between the two groups (24,41). Finally, two studies did not report any radiotherapy compliance data (39,40). Two trials reported discontinuation of chemotherapy, which was statistically significantly higher in the group undergoing chemoradiotherapy with the addition of a platinum agent (35,41). Furthermore, in the PETACC-6 trial, the proportion of patients receiving more than 90% of full-dose concurrent chemotherapy was statistically significantly lower in the platinum agent chemoradiotherapy group (23). In contrast, more patients in the chemoradiotherapy group with the addition of a platinum derivative had full-dose chemotherapy in the CAO/ARO/AIO-04 and FOWARC trials (12,42). Measures of chemotherapy compliance did not statistically significantly differ in one trial (21). Three studies did not report any useful chemotherapy compliance data (38–40). None of the trials reported quality of life data, thus it could not be considered in the meta-analysis.

Applying the GRADE approach, the quality of the evidence was high for the main outcome parameters overall and disease-free survival, as well as for pathological complete response. Regarding local and distant recurrence, the quality of the evidence was judged as moderate because of the reduced sample size and some inconsistency in reporting of these outcomes among the primary RCTs. Finally, the quality of evidence for the toxicity outcomes was judged as moderate because of some imprecision or heterogeneity (Table 4).

Discussion

This is the most comprehensive meta-analysis including recently published or overtly presented long-term oncological outcomes of RCTs evaluating the addition of platinum derivatives to neoadjuvant chemoradiotherapy in stage II/III rectal cancer patients. The aggregated data demonstrate no difference in overall or disease-free survival for patients receiving neoadjuvant chemoradiotherapy with a platinum agent. The low post hoc calculated power suggests that the observed difference was

Table 4. Summary of findings: addition of a platinum agent to neoadjuvant fluoropyrimidine-based chemoradiotherapy for stage II/III rectal cancer*

Outcomes	Relative effect		No. of participants (trials)	Quality of the evidence GRADE†	Comments
	HR (95% CI)	OR (95% CI)			
Overall survival (3–6 years)	0.93 (0.82 to 1.05)	—	5766 (7 trials)	⊕⊕⊕⊕ High	—
Disease-free survival (3–6 years)	0.91 (0.83 to 1.01)	—	5766 (7 trials)	⊕⊕⊕⊕ High	—
Local recurrence (3–5 years)	—	0.83 (0.66 to 1.05)	4686 (6 trials)	⊕⊕⊕⊖ Moderate	Limited sample size; some inconsistency in reporting among trials
Distant recurrence (3–5 years)	—	0.78 (0.66 to 0.92)	3131 (4 trials)	⊕⊕⊕⊖ Moderate	Limited sample size; some inconsistency in reporting among trials
Pathological complete response	—	1.31 (1.10 to 1.55)	5521 (10 trials)	⊕⊕⊕⊕ High	—
Toxicity outcome parameters	—	—	Max. 4696 (7 trials)	⊕⊕⊕⊖ Moderate	Some imprecision; some heterogeneity

*Patients or population: patients with stage II/III rectal cancer. Settings: neoadjuvant chemoradiotherapy with subsequent surgery. Intervention: chemoradiotherapy with a fluoropyrimidine and addition of a platinum derivative (eg, oxaliplatin). Comparison: chemoradiotherapy with a fluoropyrimidine. CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; HR = hazard ratio; OR = odds ratio. An em dash (—) indicates no information was available.

†GRADE Working Group grades of evidence are as follows: High quality = further research is very unlikely to change our confidence in the estimate of effect. Moderate quality = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality = we are very uncertain about the estimate.

unlikely to reveal statistical significance. This is mostly because the magnitude of the observed effect is rather small. However, rates of pathological complete response and distant recurrence were improved, but no statistically significant difference in the rate of isolated local recurrence was observed. The benefits in distant recurrence and pathological complete response are achieved at the cost of more-frequent grade 3/4 toxicities. Unfortunately, none of the trials provided quality-of-life data, which would be another crucial factor in the decision process for or against an intensified therapy with the addition of platinum agents. Taken all together, the current findings oppose a widespread or routine use of this strategy, because of the increased toxicity and lack of improvement in survival.

In comparison to previous systematic reviews on this topic (20,45–48), the current work includes additional studies and long-term data from PETACC-6 (5-year survival) (23), FOWARC (3-year survival) (24), and ACCORD 12/0405 PRODIGE 2 (5-year survival) (36), which have not been considered in previous meta-analyses. Furthermore, some of the previous meta-analysis presented methodological flaws, for instance, time-to-event data were analyzed as dichotomous outcomes (45–47) instead of the generally recommended method by log hazard ratios and its standard error (25). Second, some previous meta-analyses included trials that used oxaliplatin in the adjuvant setting only after conventional neoadjuvant chemoradiotherapy and surgery (46). Third, critical appraisal was omitted completely (45), performed with inappropriate methodology (48), or reported insufficiently in previous systematic reviews (46,47). Within the current analysis, the quality of included studies was rigorously evaluated according to the Cochrane

Collaboration's risk of bias tool (29), and subsequently, the quality of the whole body of evidence and resulting recommendations were assessed in accordance with the GRADE methodology (30). In summary, in contrast to previous meta-analysis, the current systematic review and meta-analysis was conducted with high-quality standards strictly adhering to the recommendations of the Cochrane Collaboration concerning conduct of the meta-analysis (25) and to PRISMA regarding the report (26).

Thus, setting the results into perspective against previous meta-analyses, the current results provide an enhanced power and validity because of the increased sample size and longer follow-up. The Cochrane review from 2015 could not perform a meta-analysis concerning survival because only one trial reported survival data at that time without a statistically significant difference in overall and disease-free survival (21). De Felice et al. (45) and Yang et al. (47) did not find any differences in overall or disease-free survival in their respective meta-analysis of four RCTs, which is in line with the results of our meta-analysis. On the other hand, the meta-analyses of Fu et al. (46) and Zheng et al. (48) demonstrated a statistically significant benefit in disease-free survival after 3 years, but not for overall survival. One of them included only a few number of RCTs (48), and the other included one trial that assessed the addition of a platinum agent in the adjuvant setting only (46) as possible explanation for these different findings. In contrast to the current analysis and two of the other meta-analyses (45,47), Zheng et al. found a statistically significant lower rate of local recurrence after neoadjuvant chemoradiotherapy with the addition of a platinum derivative (48). This is probably because they analyzed not only isolated local recurrences but also cases with simultaneous

distant recurrence. Both previous meta-analyses that assessed rates of distant recurrence are in line with the current work demonstrating a statistically significant improvement for the platin-amplified chemoradiotherapy (45,47). Finally, all previous meta-analyses corroborate the findings of increased pathological complete response as well as increased toxicity for the experimental group (20,45–48).

Looking at the individual trial level, only the CAO/ARO/AIO-04 trial achieved a statistically significant result in favor of the oxaliplatin group regarding any survival endpoint—in this particular case, disease-free survival (23). This finding must be seen with caution and might be explained at least in part by the fact that different application schedules of 5-FU were used in the control and interventional arm of the trial. Additionally, the adjuvant treatment in this study also differed between the control (5-FU) and the interventional arm (5-FU + OXA). Thus, the findings of CAO/ARO/AIO-04 cannot be solely attributed to the addition of platinum agents in the neoadjuvant setting and should be considered only in the light of the complete treatment schedules, which were used within this trial (22).

Taking a closer look at the subgroup analyses, it seems noteworthy that the subgroup analysis of 5-FU vs capecitabine suggests a pronounced positive effect of the combination therapy in trials that used 5-FU as a fluoropyrimidine backbone. In contrast to the findings of this subgroup analysis, NSABP R-04, the only trial that assessed both 5-FU vs capecitabine with or without oxaliplatin in a four-arm design, demonstrated similar effects for 5-year overall and disease-free survival for 5-FU vs capecitabine (41). On the other hand, a meta-analysis on 5-FU vs capecitabine (without oxaliplatin) during neoadjuvant chemoradiotherapy for locally advanced rectal cancer even demonstrated superiority of capecitabine compared to 5-FU (49). These contradictory results could also be explained in part by the differing treatment schedules of the CAO/ARO/AIO-04 trial, which led to the statistically significant result for the 5-FU subgroup in the subgroup analysis of disease-free survival (22) and the negative results of PETACC-6, which shift the result of the capecitabine subgroup to a lesser effect (24). In any case, the findings of the subgroup analyses have to be considered as exploratory and do not permit firm conclusions but should be considered in the planning phase of future trials on this topic.

The subgroup analysis on adjuvant treatment, which was subdivided into three groups—no adjuvant therapy, same adjuvant therapy in both groups, and fluoropyrimidine in control group vs fluoropyrimidine plus oxaliplatin in interventional group—showed no statistically significant differences in the effect for overall and disease-free survival. This finding underlines current best evidence, which demonstrates that there is no additional benefit of adjuvant therapy for rectal cancer after neoadjuvant chemoradiotherapy followed by curative surgery (50).

In colon cancer, subgroup analyses of trials assessing the addition of oxaliplatin to adjuvant chemotherapy showed beneficial survival effects only in patients with stage III disease (51,52). Therefore, a subgroup analysis was planned for stage II vs stage III disease during the design phase of this meta-analysis. However, unfortunately none of the trials included in the current analysis provided sufficiently detailed information in their reports to perform this subgroup analysis. Nevertheless, this subgroup analysis would have been of particular importance because of the frequent problem of clinical overstaging in rectal cancer, which may result in unnecessary, ineffective, and even harmful overtreatment (53).

Considering the secondary outcome measures—the clinical impact of the benefit in the pathological complete response

rate—is rather limited, because it has been shown that pathological complete response is not a reliable surrogate parameter in predicting survival (54). Furthermore, the benefit in distant recurrence has to be interpreted with caution because it is based on a limited number of only four trials and thus a limited sample size. This is highlighted by the fact that the reduced rate of distant recurrence did not translate into better disease-free survival in the meta-analysis of seven trials. Nevertheless, it needs to be elucidated whether the benefit in distant recurrence can be corroborated in specific subgroups of patients, in particular those at high risk for distant recurrence. Based on preoperative magnetic resonance imaging, several risk factors for synchronous or metachronous metastases have been identified, such as extramural vascular invasion (55,56) or involvement of the circumferential resection margin (57), which could be used to stratify treatment decisions. Regarding extramural vascular invasion, a recent meta-analysis demonstrated an almost fourfold increased risk of developing metastases in patients with preoperative extramural vascular invasion compared with patients without (58). The included trials of the current meta-analysis did not use such factors to stratify treatment. Thus, it will be an important task in the pursuit of a tailored approach for locally advanced rectal cancer to investigate whether specific high-risk subgroups might benefit from an intensified neoadjuvant CRT and whether low-risk patients might be successfully managed even without neoadjuvant CRT (59).

In addition to imaging findings, some biomarkers predicting platinum sensitivity or resistance in colorectal cancer patients have been identified by former studies (60,61), but yet there is no reliable biomarker that would allow for individualized treatment decisions regarding the addition of platinum agents in this patient cohort. It will be the task of future research to test the value of such biomarkers in selecting patients for an individual intensified treatment regimen.

There are some limitations that have to be borne in mind in the interpretation of the current results. Because individual patient data were not available for all the included trials, the present meta-analysis is based on pooled data from the primary trial reports. Therefore, a further analysis of patient-level factors that might affect the efficacy or toxicities of the interventions was not possible. Because the current analysis was a pragmatic evaluation of the addition of platinum derivatives to neoadjuvant chemoradiotherapy, there remains some clinical heterogeneity. For instance, treatment schedules of the included trials varied moderately despite the low statistical heterogeneity of the meta-analyses. Some of these heterogeneities are addressed by the performed subgroup analyses. However, we refrained from splitting the groups into more detail because this would have divided the analysis into smaller pieces, which would have reduced power. Another potential source of heterogeneity is the variation of primary endpoints in the individual trials and variations in endpoint definitions, particularly of the endpoint disease-free survival (Supplementary Table S1, available online). The (known) heterogeneities are clearly addressed in this systematic review and, thus, have to be considered in the interpretation of the results. Furthermore, some included data were available only in abstract form or by direct contact with the corresponding authors of the individual trials. However, especially considering the included long-term results of FOWARC and PETACC-6, the data were extracted from publicly available presentations from the American Society of Clinical Oncology 2018 annual meeting, which provided well-detailed information (23,24).

Despite these limitations, the current systematic review and meta-analysis provides the most comprehensive and

up-to-date information on the frequently discussed value of platinum agents in neoadjuvant chemoradiotherapy for rectal cancer. The strict methodology and evaluation of the resulting quality of the body of evidence allows strong conclusions. This permits thorough information on potential benefits and risks of this approach within the shared decision-making process for clinicians and patients alike.

In conclusion, the current meta-analysis provides good quality evidence that a general addition of a platinum derivative to neoadjuvant fluoropyrimidine-based chemoradiotherapy does not improve overall and disease-free survival but does result in statistically significantly improved rates of distant recurrence and pathological complete response. On the other hand, these benefits are accompanied by an increased toxicity. These findings suggest that this intensified treatment strategy cannot be recommended routinely because of the lack of improvement in survival and increased toxicity. These findings may have relevant impact on future clinical practice and guidelines.

On the other hand, it needs to be elucidated by future research whether this strategy provides benefits for selected patients who may be at high risk of developing distant metastases considering its lower rate of distant recurrence and increased rate of pathological complete response. Furthermore, it may represent a viable treatment option in the armamentarium of radiation and medical oncologists for patients with a distinct indication, oligometastatic and locally advanced disease, or ambition for aggressive therapy despite the above-mentioned increased toxicities. In the context of other novel multimodal treatment concepts and results from translational studies, this may enable a more tailored approach to rectal cancer in the future.

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