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ORIGINAL RESEARCH

Meta-analysis of outcomes of patients with stage IV colorectal cancer managed with chemotherapy/radiochemotherapy with and without primary tumor resection

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Background: Colorectal cancer is the third leading cause of death worldwide. Currently, novel chemotherapeutic agents are first-line therapy for unresectable stage IV colorectal cancer, while benefits of noncurative primary tumor resection in advanced disease remain debatable.

Objective: This meta-analysis evaluated outcomes of patients with unresectable stage IV colorectal cancer receiving systemic chemotherapy with or without primary tumor resection.

Materials and methods: A database search of PubMed and Cochrane Library databases identified 167 studies that were screened for relevance. After 119 were excluded, 48 were assessed for eligibility and 26 were included for meta-analysis, including 24 retrospective studies, one prospective study, and one randomized, controlled trial. Extracted data included patient demographics (age, sex), clinical data (tumor stage, metastasis), targeted therapy agents, and surgical data (with/without tumor resection). Patients' overall and progression-free survival was compared between groups with/without primary tumor resection.

Results: The 26 studies included 43,903 patients with colorectal cancer, with 29,639 receiving chemotherapy/radiotherapy plus primary tumor resection, and 14,264 managed medically with chemotherapy/chemoradiotherapy alone without primary tumor resection. Patients receiving primary tumor resection plus chemotherapy/radiotherapy had longer overall survival (hazard ratio [HR 0.59], 95% confidence interval [CI] 0.51–0.68; $P<0.001$), with significant differences in overall survival between patients with and without primary tumor resection (HR 0.58, 95% CI 0.49–0.68; $P<0.001$). Longer overall survival was also found among patients receiving primary tumor resection who were treated with bevacizumab/cetuximab targeted therapy agents (HR 0.63, 95% CI 0.46–0.86; $P=0.003$). Patients from three studies who received primary tumor resection had longer progression-free survival (HR 0.73, 95% CI 0.58–0.91; $P=0.005$). Results are limited by retrospective data, inconsistent complications data, and publication bias.

Conclusion: Study results support primary tumor resection in stage IV colorectal cancer, but significant biases in studies suggest that randomized trials are warranted to confirm findings.

Keywords: chemotherapy, colorectal cancer, outcomes, tumor resection

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Introduction

New cases of colorectal cancer (CRC) worldwide totaled 14.1 million in 2012, with 8.2 million deaths, making CRC the third leading cause of death worldwide after lung and liver cancers.[1] In the US, ~134,490 adults will be diagnosed with CRC in 2016

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(95,270 colon, 39,220 rectal), and ~49,190 will die from the disease.[2] Many such CRC-related deaths can be prevented through early detection of precancerous polyps in the colon and rectum, identified during regular screening according to guidelines of the American Cancer Society. However, in 2010, only 59% of US adults aged ≥50 years actually reported undergoing CRC screening.[3] Nevertheless, the death rate per 100,000 individuals per year has been dropping over the last two decades, due to overall increased screening and advances in treatment as well.[4] As a result, >1 million survivors are now living in the US.

The traditional approach to managing incurable stage IV CRC has been surgical resection of the primary tumor or stoma. However, this has changed significantly during the last three decades, favoring a multidisciplinary approach that relies heavily on chemotherapy using novel third-generation targeted therapy agents in combination with second-generation agents.[5,6] This change has led to a dramatic increase in the median overall survival (OS) of CRC patients from 6 months to ~2 years,[7] while surgical resection of the primary tumor in these patients remains controversial.[8–11] A systematic review concluded that resection of the primary tumor in asymptomatic patients with unresectable stage IV CRC who are managed with chemotherapy/radiotherapy was not either associated with prolonged OS or reduced the risk of complications.[12] Ahmed et al asked appropriately if noncurative resection of the primary tumor was advisable in treating stage IV CRC, finding that some of the previous studies did support noncurative resection in advanced CRC.[11] A systematic review indicated that primary tumor resection prognostic factors were found to be significantly associated with OS after multivariate analysis.[13] Tumor-related complication rates remained as high as 29.7% in resected cases compared to 27.6% in the nonresection population.[11] Even with the combined application of primary tumor resection and systemic chemotherapy, only 10%–15% of patients survive for 5 years.[11] Therefore, when resection is being considered, the potential morbidity and effects on quality of life must be determined case by case.

The controversy continues among surgeons in oncology about the relative benefits of resection of primary tumors versus chemotherapy alone, and available data are insufficient to reach consensus. Therefore, this meta-analysis was conducted to evaluate outcomes of patients with unresectable stage IV CRC receiving either systemic chemotherapy alone or combined therapy of primary tumor resection and systemic chemotherapy.

Materials and methods

Search strategy

The PubMed and the Cochrane Library databases were searched until February 2015 for relevant studies using prespecified eligibility criteria. Only human-subject studies published from 1997 to 2015 were included. The search terms included two combinations: combination 1 (advanced OR stage IV) AND (colorectal cancer) AND (non-resection OR resection) AND (chemotherapy); and combination 2 (colorectal cancer) AND (unresectable OR stage IV) AND chemotherapy; with the search filter: clinical trial, abstract, title-abstract.

Study selection

Titles and abstracts were screened for all studies, and full text was obtained for those meeting the inclusion criteria. Inclusion criteria were: comparative study, majority of patients with stage IV CRC, chemotherapy/radiochemotherapy plus primary tumor resection as one intervention and chemotherapy/radiochemotherapy alone as the other. Chemotherapy included both targeted therapy agents and second-generation agents. Single-arm studies and studies in which nonresection patients did not receive chemotherapy/radiochemotherapy were excluded. Case series, letters, comments, editorials, case reports, proceedings, personal communications, and reviews were also excluded, as well as non-English and non-Chinese studies. Finally, 26 studies were determined eligible for meta-analysis.[14–39]

Primary outcome measures for the studies included were patient outcomes, including OS and free survival (PFS). Two author–reviewers determined the eligibility of all retrieved studies independently, and discrepancies were resolved through consultation with a third reviewer.

Data extraction

Two independent reviewers extracted all data from eligible studies. Extracted data included first author's name, year of publication, study design, interventions, participants and participants' demographics (age, sex), clinical data (tumor stage, metastasis), targeted therapy agents, surgical data (with/without primary resection), and survival (OS and PFS).

Quality assessment

The methodological aspects of nonrandomized studies were assessed using the Newcastle–Ottawa Scale (NOS).[40] This scale comprises eight items categorized into three dimensions: selection, comparability, and exposure. A star system is used for a semiquantitative assessment of study quality, awarding the highest-quality studies a maximum of one

star for each item with the exception of the item related to comparability, which allows assignment of two stars. NOS scores range between zero and nine stars.

Statistical analysis

The primary outcome for this meta-analysis was the hazard ratio (HR) for OS, and the secondary outcome was HR for PFS. Crude or adjusted HRs with 95% confidence interval (CI) were extracted for survival outcomes for each individual study. If available data were presented from the Kaplan–Meier curve, the survival rates at specified times were extracted to reconstruct the HR estimate and its variance, assuming that the rate of patients censored was constant during study follow-up, as described previously.[41] An HR <1 indicated that primary tumor-resection patients were favored. A χ^2-based test of homogeneity was performed, and the inconsistency index (I^2) and Q-statistics were determined. If the I^2-statistic were >50%, a random-effect model was used. Otherwise, fixed-effect models were employed. Pooled effects were calculated, and a two-sided P-value <0.05 was established as statistical significance. Subgroup analysis was also performed to evaluate differences between patients receiving and not receiving targeted therapy agents (bevacizumab/cetuximab). Sensitivity analysis was carried out using the leave-one-out approach. Publication bias was assessed by constructing funnel plots, with the absence of publication bias indicated by data points forming a symmetric funnel-shaped distribution and one-tailed significance level of $P>0.05$ (Egger's test). If publication bias was found, adjusted-effect sizes were calculated using Duval and Tweedie's "trim and fill" procedure.[42] However, a funnel plot is only used if the meta-analysis includes more than ten studies.[43] All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ, USA).

Results

Literature search

Figure 1 summarizes the literature search procedure. A total of 167 studies were identified with the database search and screened for relevance. After 119 were excluded based on the aforementioned criteria, 48 were assessed for eligibility and 26 were finally determined eligible for inclusion in meta-analysis, including 24 retrospective studies, one prospective study, and one randomized controlled trial[14–39] (Figure 1).

Characteristics of included studies

Table 1 summarizes characteristics of the 26 studies included. All included studies were nonrandomized clinical studies, except for Ferrand et al.[37] The 26 studies included a total of 43,903 patients with CRC, among whom 29,639 were treated with chemotherapy/radiotherapy plus primary tumor resection (primary tumor resection group) and 14,264 were first managed medically with chemotherapy/chemoradiotherapy alone (without primary tumor resection group). Patients' ages were fairly similar between studies, ranging from 49 to 73 years. Sex distribution varied between studies, and the proportion of male patients ranged from 33% to 78% (Table 1).

Meta-analysis: overall survival and PFS

Median OS ranged from 4 months to 30.7 months in patients receiving primary tumor resection and 2–23.9 months in patients without primary tumor resection. Four studies, including Kim et al,[36] Cook et al,[35] Ruo et al,[27] and Liu et al,[24] did not provide enough information to estimate HRs for OS; hence, HRs of the 22 evaluable studies were calculated by the method reported in the "Statistical analysis" section. Heterogeneity was observed among the 22 studies; therefore, a random-effect model was used (Q=167.868, I^2=87.49%).

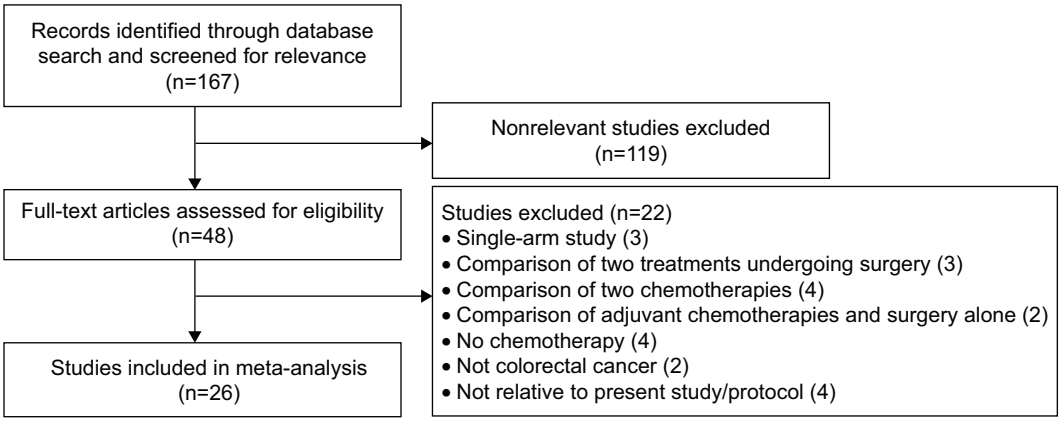


Figure 1 Flow diagram of study selection.

Table 1 Characteristics of included studies

Study	Design	Patients	Group	Age (years)	Male (%)	Tumor stage	Metastasis (%)	Targeted therapy agent	Follow-up (months)	Median OS (months)
Ahmed et al[39]	Retrospective	944	With primary resection	68	55	IV	≥2 sites: 26.2	No	7.1#	10.6
		434	Without primary resection	70	59	IV	≥2 sites: 37.1			3
Matsumoto et al[25]	Retrospective	41	With primary resection	67*	61	IV	1/2/3/4 organs: 53.2/38.3/6.4/2.1	No	21.3	22.6
		47	Without primary resection	62*	70	IV	1/2/3/4 organs: 48.8/34.1/17.1/0			23.9
Tsang et al[31]	Retrospective	8,599	With primary resection	61*	53	IV	NA	No	120	21
		3,117	Without primary resection		60	IV				10
Watanabe et al[33]	Retrospective	46	With primary resection	63	54	IV	Liver/lung/peritoneum/lymph nodes: 73/39/24/30	Bevacizumab/cetuximab/ panitumumab	26	19.9
		112	Without primary resection	60	63	IV	Liver/lung/peritoneum/lymph nodes: 83/31/14/47			19
Boselli et al[38]	Retrospective	17	With primary resection	70	NA	IV	NA	Bevacizumab	7	4
		31	Without primary resection	73	NA	IV				5
Cetin et al[17]	Retrospective	53	With primary resection	55*	55	IV	NA	Bevacizumab	40	23
		46	Without primary resection	52*	59	IV				17
Ferrand et al[37]	RCT	156	With primary resection	64	62	IV	Liver metastases only: 62	No	33#	16.3
		60	Without primary resection	62	73	IV	Liver metastases only: 53			9.5
Kim et al[36]	Retrospective	63	With primary resection	≥75: 13%	67	IV	Liver/lung/liver and lung/peritoneal/pelvic organ/bone/nominated lymph nodes/combined: 48/10/6/27/4/2/3/2	No	NA	14
		62	Without primary resection	≥75: 22%	65	IV	Liver/lung/liver and lung/peritoneal/pelvic organ/bone/nominated lymph nodes/combined: 33/8/7/25/5/5/3/13		NA	8
Karoui et al[21]	Retrospective	85	With primary resection	65	66	IV	Liver only/nodes or peritoneum/lung or others: 60/19/21	No	19.7	30.7
		123	Without primary resection	63	62	IV	Liver only/nodes or peritoneum/lung or others: 62/17/21			21.9
Venderbosch et al[32]	Retrospective	258	With primary resection	63	62	IV	Liver/extrahepatic: 81/9	No	NA	16.7
		141	Without primary resection	60	70	IV	Liver/extrahepatic: 81/19			11.4
Aslam et al[14]	Retrospective	366	With primary resection	70*	54	IV	Liver solitary/lungs only/solitary liver and solitary lung/liver-multiple bilobar/liver-multiple bilobar and lungs/lung only/extramesenteric lymph nodes/multiorgan excluding lungs: 15/15/1/36/4/5/3/10	No	34	NA
		281	Without primary resection	72*	78	IV	Liver solitary/lungs only/solitary liver and solitary lung/liver-multiple unilobar/liver-multiple bilobar/liver-multiple bilobar and lungs/multiorgan excluding lungs: 4/7/5/5/40/15/5			
Chan et al[18]	Retrospective	286	With primary resection	≥70: 40%	57	IV	Liver-dominant/multiple sites: 25/3	No	24	14
		125	Without primary resection	≥70: 40%	58	IV	Liver-dominant/multiple sites: 60/9			6
Seo et al[29]	Retrospective	144	With primary resection	58	65	IV	Liver/lung/peritoneum/distant node/bone/brain: 75.7/31.3/18.8/16/2.8/0.7	Bevacizumab/cetuximab	49	NA

		83	Without primary resection	56	63	IV	Liver/lung/peritoneum/distant node/bone/brain: 80.7/22.9/27.7/16.9/8.4/0			
Bajwa et al[16]	Retrospective	31	With primary resection	NA	NA	IV	NA	No	NA	14
		36	Without primary resection	NA	NA	IV				6
Evans et al[19]	Retrospective	45	With primary resection	72	NA	IV	NA	No	NA	11
		52	Without primary resection	70	NA	IV				7
Galizia et al[20]	Retrospective	42	With primary resection	62	66	IV	NA	Bevacizumab/cetuximab	21	NA
		23	Without primary resection	59	65	IV			16	
Kaufman et al[22]	Retrospective	115	With primary resection	70*	48	IV	NA	No	NA	22
		69	Without primary resection			IV				3
Konyalian et al[23]	Retrospective	62	With primary resection	52*	51	IV	NA	No	NA	NA
		47	Without primary resection	49*		IV				
Benoist et al[15]	Retrospective	32	With primary resection	60	59	IV	NA	No	NA	NA
		27	Without primary resection	61	67	IV				
Cook et al[35]	Retrospective	17,657	With primary resection	67	67	IV	NA	No	NA	Colon: 11 Rectum: 16
		9,097	Without primary resection	70	33	IV				Colon: 2 Rectum: 6
Cummins et al[34]		36	With primary resection	57*	45	Incurable	NA	No	NA	11.5
		15	Without primary resection							4
Michel et al[26]	Retrospective	31	With primary resection	60	55	IV	≥3 liver metastases/≥5 liver metastases/lung: 29/35/16	No	NA	21
		23	Without primary resection	59	70	IV	≥3 liver metastases/≥5 liver metastases/lung: 4/39/13			14
Ruo et al[27]	Retrospective	127	With primary resection	64*	64	IV	Distant sites: 1/2/3: 69/26/6	No	NA	16
		103	Without primary resection	61*	55	IV	Distant sites: 1/2/3: 53/30/17			9
Tebbutt et al[30]	Prospective	280	With primary resection	62*	60	NA	Peritoneal or omental: 20; nonperitoneal or omental: 80	No	30	14
		82	Without primary resection	59*	73		Peritoneal or omental/nonperitoneal or omental: 13/87		19	8.2
Scoggins et al[28]	Retrospective	66	With primary resection	64*	NA	IV	Hepatic nodules/pulmonary nodules/omentum or peritoneum: 85/3/12	No	NA	14.5
		23	Without primary resection	61*	NA	IV	Hepatic nodules/pulmonary nodules/omentum or peritoneum: 87/35/4			16.6
Liu et al[24]	Retrospective	57	With primary resection	66	NA	NA	Liver metastasis: 54	No	NA	11
		5	Without primary resection	72	NA					2

Notes: *Median age, #median follow up month.
Abbreviations: NA, not available; OS, overall survival; RCT, randomized controlled trial.

Overall analysis revealed that patients treated with primary tumor resection in addition to chemotherapy/radiotherapy were associated with longer OS (HR 0.59, 95% CI 0.51–0.68; $P<0.001$) (Figure 2A).

A random-effect model was used for analysis of the subgroup of studies (n=17) that recruited patients receiving second-generation agents without targeted therapy agents (bevacizumab/cetuximab) (Q=122.248, I^2=86.91%). Results showed significant differences in OS between patients with and without primary tumor resection (HR 0.58, 95% CI 0.49–0.68; $P<0.001$). In addition, a random-effect model was also used for analysis of the subgroup of studies (n=5) that also recruited patients receiving targeted therapy agents (bevacizumab/cetuximab) (Q=39.433, I^2=89.86%). Results indicated that among patients receiving primary tumor resection, longer OS was also found among those receiving bevacizumab/cetuximab targeted therapy agents (HR 0.63, 95% CI 0.46–0.86; P=0.003).

Only three studies[17,32,37] provided enough information to estimate HRs for PFS. Heterogeneity was observed among the three studies, and thus a random-effect model was used (Q=5.124, I^2=60.97%). Overall analysis revealed that patients who received primary tumor resection were associated with longer PFS (HR 0.73, 95% CI 0.58–0.91; P=0.005) (Figure 2B).

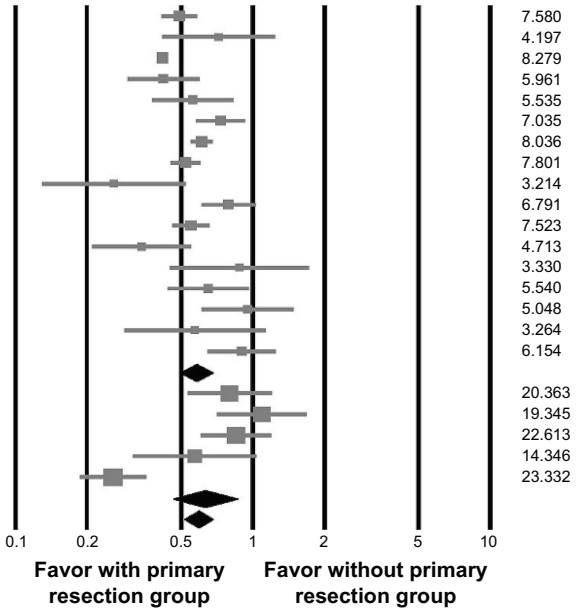
Sensitivity analysis

Sensitivity analyses were performed using the leave-one-out approach, in which meta-analysis of OS and PFS was

A

OS

Study	Hazard ratio	Lower limit	Upper limit	Z-value	P-value	Relative weight
Ahmed et al[39]	0.49	0.41	0.58	–8.06	0.000	7.580
Matsumoto et al[25]	0.72	0.42	1.24	–1.18	0.238	4.197
Tsang et al[31]	0.42	0.40	0.44	–37.60	0.000	8.279
Ferrand et al[37]	0.42	0.30	0.59	–4.91	0.000	5.961
Karoui et al[21]	0.56	0.38	0.83	–2.91	0.004	5.535
Venderbosch et al[32]	0.73	0.58	0.92	–2.61	0.009	7.035
Aslam et al[14]	0.61	0.55	0.68	–9.13	0.000	8.036
Chan et al[18]	0.52	0.45	0.60	–8.91	0.000	7.801
Bajwa et al[16]	0.26	0.13	0.52	–3.81	0.000	3.214
Evans et al[19]	0.79	0.61	1.03	–1.76	0.078	6.791
Kaufman et al[22]	0.55	0.46	0.66	–6.49	0.000	7.523
Konyalian et al[23]	0.34	0.21	0.55	–4.39	0.000	4.713
Benoist et al[15]	0.88	0.45	1.73	–0.37	0.710	3.330
Cummins et al[34]	0.65	0.44	0.96	–2.16	0.030	5.540
Michel et al[26]	0.95	0.61	1.48	–0.23	0.821	5.048
Tebbutt et al[30]	0.57	0.29	1.13	–1.61	0.107	3.264
Scoggins et al[28]	0.90	0.65	1.25	–0.63	0.528	6.154
Subgroup I	**0.58**	**0.49**	**0.68**	**–6.77**	**0.000**	
Watanabe et al[33]	0.80	0.53	1.20	–1.08	0.279	20.363
Boselli et al[38]	1.09	0.71	1.68	0.39	0.697	19.345
Cetin et al[17]	0.85	0.60	1.20	–0.93	0.352	22.613
Seo et al[29]	0.57	0.31	1.04	–1.84	0.066	14.346
Galizia et al[20]	0.26	0.19	0.36	–8.22	0.000	23.332
Subgroup II	**0.63**	**0.46**	**0.86**	**–2.94**	**0.003**	
Pooled effect	**0.59**	**0.51**	**0.68**	**–7.37**	**0.000**	



Heterogeneity test

Subgroup I: No target therapy agent (bevacizumab/cetuximab) used
Q=122.248, df=16, $P<0.001$, I^2=86.91%

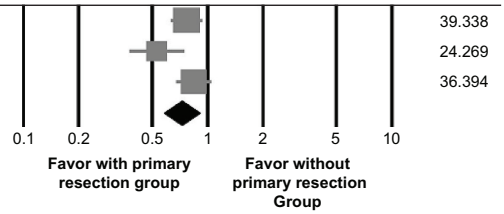
Subgroup II: target therapy agent (bevacizumab/cetuximab) used
Q=39.433, df=4, $P<0.001$, I^2<89.86%

Overall
Q=167.868, df=21, $P<0.001$, I^2=87.49%

B

PFS

Study	Hazard ratio	Lower limit	Upper limit	Z-value	P-value	Relative weight
Cetin et al[17]	0.77	0.64	0.93	–2.67	0.008	39.338
Ferrand et al[37]	0.53	0.38	0.74	–3.66	0.000	24.269
Venderbosch et al[32]	0.84	0.68	1.04	–1.57	0.116	36.394
Pooled effect	0.73	0.58	0.91	–2.81	0.005	



Heterogeneity test: Q=5.124, df=2, P=0.077, I^2=60.97%

Figure 2 Meta-analysis of treatment effect in (**A**) OS rate and (**B**) PFS rate between patients with and without primary tumor resection.
Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Table 2 Sensitivity analysis

Study	Hazard ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Overall survival					
Ahmed et al[39]	0.6	0.51	0.69	−6.73	<0.001
Matsumoto et al[25]	0.58	0.51	0.67	−7.35	<0.001
Tsang et al[31]	0.6	0.53	0.69	−7.49	<0.001
Watanabe et al[33]	0.58	0.5	0.67	−7.47	<0.001
Boselli et al[38]	0.57	0.5	0.66	−7.81	<0.001
Cetin et al[17]	0.58	0.5	0.67	−7.59	<0.001
Ferrand et al[37]	0.6	0.52	0.69	−6.91	<0.001
Karoui et al[21]	0.59	0.51	0.68	−7.13	<0.001
Venderbosch et al[32]	0.58	0.50	0.67	−7.44	<0.001
Aslam et al[14]	0.59	0.51	0.68	−6.89	<0.001
Chan et al[18]	0.59	0.51	0.69	−6.68	<0.001
Seo et al[29]	0.59	0.51	0.68	−7.22	<0.001
Bajwa et al[16]	0.6	0.52	0.69	−7.02	<0.001
Evans et al[19]	0.58	0.5	0.67	−7.56	<0.001
Galizia et al[20]	0.61	0.53	0.71	−6.79	<0.001
Kaufman et al[22]	0.59	0.51	0.69	−6.89	<0.001
Konyalian et al[23]	0.6	0.52	0.69	−6.94	<0.001
Benoist et al[15]	0.58	0.51	0.67	−7.46	<0.001
Cummins et al[34]	0.59	0.51	0.68	−7.26	<0.001
Michel et al[26]	0.58	0.5	0.66	−7.63	<0.001
Tebbutt et al[30]	0.59	0.51	0.68	−7.24	<0.001
Scoggins et al[28]	0.58	0.5	0.66	−7.7	<0.001
Progression-free survival					
Cetin et al[17]	0.68	0.43	1.07	−1.68	0.093
Ferrand et al[37]	0.8	0.69	0.92	−3.04	0.002
Venderbosch et al[32]	0.66	0.46	0.94	−2.28	0.023

performed with each study removed in turn (Table 2). The direction and magnitude of combined estimates of OS did not vary markedly after removing the studies, indicating good reliability of the meta-analysis and that data were not overly influenced by any study. However, for PFS, sensitivity analysis indicated that pooled estimates might have been affected by one study.[17] After that study had been removed, no significant differences were found in PFS between patients with primary tumor resection and those without primary tumor resection (Table 2).

Publication bias

Results via Egger's test indicated possible publication bias for findings regarding OS (t=3.024, one-tailed, P=0.003), as summarized in Figure 3. After simulation by the trim-and-fill method to look for missing studies based on the random-effect model, the imputed point estimate was changed to 0.48 (95% CI 0.42–0.55). However, for PFS, the power of the test for publication bias was too low to distinguish chance from real asymmetry, due to the small number of studies (Figure 3).

Quality assessment

Table 3 summarizes study quality. In general, the studies included had moderate to high quality. However, the one included RCT[37] could not be properly evaluated for quality using the NOS (Table 3).

Discussion

This meta-analysis was conducted to update the evidence regarding benefits of noncurative primary tumor resection for treating stage IV CRC in patients being treated with chemotherapy/radiochemotherapy. Outcome data of patients receiving chemotherapy with and without primary tumor resection were compared with data of patients receiving chemotherapy alone. Overall analysis of 26 studies, including ~44,000 CRC patients, revealed that patients treated with primary tumor resection and chemotherapy were associated with longer OS than patients treated with chemotherapy alone. That is, ~30,000 patients who received primary tumor resection combined with chemotherapy with targeted therapy or second-generation therapy had longer OS and PFS than ~15,000 patients receiving targeted therapy or

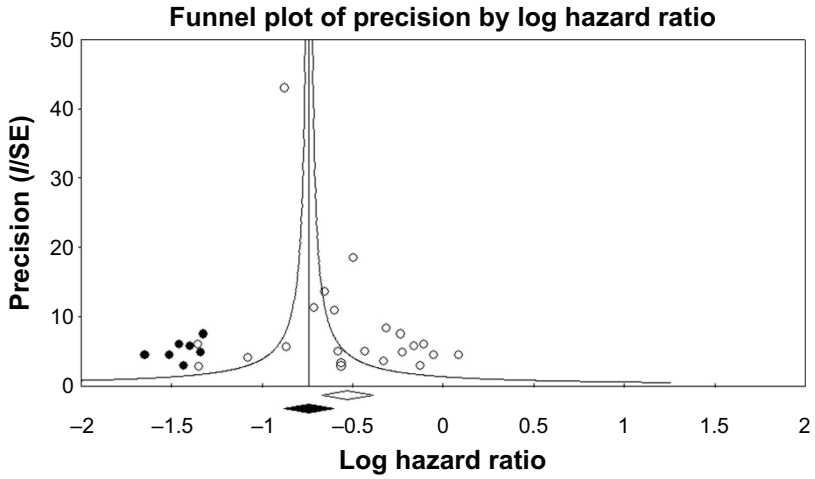


Figure 3 Funnel plots for overall survival showing the distribution of published study outcomes (open circles) and simulated outcomes (black circles) estimated by "trim and fill" procedure.
Note: Imputed data (black circles) are simulated data to compensate for an asymmetric funnel plot.
Abbreviation: SE, standard error.

second-generation chemotherapy agents without resection. Sensitivity analysis, however, showed that OS data were more reliable than data for PFS, results of which were found only in three of the 26 included studies. Results also showed that among patients receiving primary tumor resection, longer OS was found among those receiving bevacizumab/cetuximab targeted therapy agents.

Table 3 Quality assessment

Study	Selection[a]	Comparability[b]	Outcome[c]
Ahmed et al[39]	****	**	***
Matsumoto et al[25]	****	**	**
Tsang et al[31]	****	**	***
Watanabe et al[33]	****	**	***
Boselli et al[38]	****	**	**
Cetin et al[17]	****	**	***
Kim et al[36]	****	**	***
Karoui et al[21]	****	**	**
Venderbosch et al[32]	****	*	***
Aslam et al[14]	****	**	**
Chan et al[18]	****	**	***
Seo et al[29]	****	**	***
Bajwa et al[16]	****	**	**
Evans et al[19]	****		***
Galizia et al[20]	****	**	**
Kaufman et al[22]	****		***
Konyalian et al[23]	****	**	***
Benoist et al[15]	****	**	***
Cook et al[35]	****	**	***
Cummins et al[34]	****		**
Michel et al[26]	****	*	**
Ruo et al[27]	****	*	***
Tebbutt et al[30]	****	**	**
Scoggins et al[28]	****	**	***
Liu et al[24]	****		**

Notes: [a]Maximum of ****: representativeness of the exposed cohort; selection of the non-exposed cohort; ascertainment of exposure; and demonstration that outcome of interest was not present at start of study. [b]Maximum of **: comparability of cohorts on the basis of the design or analysis. *Represents only one of the 2 items being fulfilled. [c]Maximum of ***: assessment of outcome; was followed up long enough for outcome to occur; and adequacy of follow-up of cohorts.

Results of previous systematic reviews and meta-analyses conducted between 2011 and 2014 were somewhat mixed, being both consistent and inconsistent with results of the present study.[10–12,44,45] In 2011, Verhoef et al[10] found that results of 24 included studies were unclear regarding survival outcomes among asymptomatic CRC patients, but median OS seemed to be improved in resected patients in the majority of studies. This understated result was more defined in the meta-analysis conducted by Ahmed et al,[11] who performed prespecified subgroup analyses assessing the survival of patients with minimally symptomatic primary tumors and patients receiving second- and third-generation anticancer therapy. Those authors found that the retrospective data favored primary tumor resection in patients with advanced CRC, but they noted the low quality of the evidence at that time, suggesting that better-quality cohort studies and well-designed randomized trials were necessary to assess all outcomes adequately, especially survival outcomes.

Cirocchi et al[12] highlighted the clinical issue of chemotherapy with and without primary tumor resection as one of determining how best to palliate patients with advanced, unresectable CRC. These authors included only seven non-randomized trials with 1,086 patients, finding that primary tumor resection in asymptomatic patients with unresectable advanced CRC who were being managed with systemic chemotherapy agents did not improve OS. This may have been due to the small sample; the study was sufficiently vigorous otherwise. While chemotherapy with novel targeted agents was shown to prolong survival, a previous meta-analysis[13]

also reported improved survival and lower incidence of emergency surgery in patients treated with primary tumor resection. Clearly, managing the tumor itself is a critical aspect of palliation, and there is still no consensus on the benefits of resection in this population. Another meta-analysis by Anwar et al[44] asked the important question all investigators have asked: "Is there a survival benefit?" After analyzing 21 studies in which the majority demonstrated survival benefits of palliative primary tumor resection, they found that the combination of selection bias, incomplete follow-up, and lack of standardized reporting of complications limited the interpretation of data. However, multivariate analysis in that study did show that tumor burden and performance status were major independent prognostic variables among the patient population and suggested that primary tumor resection should be based on these factors, rather than presence or absence of symptoms. Finally, the investigators could only conclude that there "may be" a survival benefit for primary tumor resection in stage IV CRC.

A meta-analysis by Clancy et al,[45] which was conducted to determine the effects on survival of primary tumor resection in patients with stage IV unresectable, metastatic CRC, found, as we did, that primary tumor resection confers a survival advantage in advanced CRC with unresectable metastases, but significant selection bias was found in the included studies. Some of the same studies were included in the meta-analysis as in our study and those authors also suggested that only randomized controlled trials will validate these findings.

In addition, another recent meta-analysis conducted in 2015 focused on the survival benefits of chemotherapy alone, showing that oxaliplatin and capecitabine or infusional/bolus 5-fluorouracil-based chemotherapy plus bevacizumab (XELOC + B and FOLFOX + B) are active,[46] approved first-line combination therapies for advanced CRC with improved OS (23.7 months) and PFS (10.3 months) when bevacizumab is part of the combination. However, the included retrospective studies were not homogeneous for site, extent of disease, performance status, comorbidities, or *KRAS* status (mutant or wild type). Although the present study did not focus on systemic chemotherapy, results did show that longer OS was found among resected patients receiving bevacizumab/cetuximab targeted therapy agents.

In general, among recent meta-analyses seeking answers to the question of resection benefits in advanced CRC, many patients who were in the primary tumor-resection population of studies included were those with a more favorable performance status and better overall prognosis in terms of fewer metastatic sites. Another issue may be that data on systemic chemotherapy are inconsistent between the included studies, or as Verhoef et al[10] noted: "few if any data on the use of systemic therapy are presented." Limitations in patient selection and systemic therapy data may indeed skew results and may be important factors influencing results for OS and PFS. While the present study was intended to update the evidence on the benefits of primary tumor resection in advanced CRC, it agrees with other investigators that prospective studies with adequate data on the chemotherapy agents used are needed to determine the value of resection.

Limitations

This meta-analysis has certain limitations, especially that most included studies were retrospective. In addition, complication/safety data were not reported by all included studies and thus were not assessed, which does not give a full picture of the benefits of primary tumor resection plus chemotherapy/radiotherapy for treating advanced CRC patients. The chemotherapy protocols between included studies were heterogeneous among patients in the nonresection group: some were treated with stent/bypass alone, and the studies did not report the subgroup data of chemotherapy. Possible publication bias may be inevitable during the time of decision making. Primary tumor resection may have a high proportion of patients who are unfit for chemotherapy or chemoradiotherapy, especially for data from retrospective studies. However, this might not be necessarily true for some included studies that treated patients with initial resection of primary tumor before chemotherapy and used chemotherapy as an adjuvant therapy.

Conclusion

Results of this systematic review and meta-analysis clearly show that patients with advanced CRC who receive primary tumor resection plus chemotherapy/radiotherapy have longer OS than those not receiving primary tumor resection. However, although results of this study support primary tumor resection in combination with chemotherapy/radiochemotherapy for treating stage IV CRC, possible publication bias was noted for findings regarding OS. Therefore, randomized trials are warranted to confirm findings of the present study.

Disclosure

The authors report no conflicts of interest in this work.

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