ASTR

ORIGINAL ARTICLE
pISSN 2288-6575 • eISSN 2288-6796
https://doi.org/10.4174/astr.2018.95.2.64
Annals of Surgical Treatment and Research

Meta-analysis of oncologic effect of primary tumor resection in patients with unresectable stage IV colorectal cancer in the era of modern systemic chemotherapy

Gi Won Ha, Jong Hun Kim, Min Ro Lee

Research Institute of Clinical Medicine of Chonbuk National University-Biomedical Research Institute of Chonbuk National University Hospital, Jeonju, Korea

Purpose: The management of primary tumors in patients with stage IV colorectal cancer remains unclear. This meta-analysis evaluated the survival benefits of primary tumor resection (PTR) in patients with unresectable stage IV colorectal cancer in the era of modern chemotherapy.
Methods: Multiple comprehensive databases were searched for studies comparing survival outcomes in patients with metastatic colorectal cancer who did and did not undergo PTR. Outcome data were pooled, and overall effect size was calculated using random effect models.
Results: Seventeen nonrandomized studies involving 18,863 patients met the inclusion criteria. Meta-analysis showed that PTR significantly improved overall survival (hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.56–0.71; $P < 0.001$) and progression free survival (HR, 0.76; 95% CI, 0.67–0.87; $P < 0.001$). Subgroup analyses and sensitivity analyses, performed by predefined methods, also indicated that PTR improved overall patient survival.
Conclusion: Palliative resection of the primary tumor may have survival benefits in patients with unresectable stage IV colorectal cancer. Randomized controlled trials are needed to determine the optimal treatment for these patients.
[Ann Surg Treat Res 2018;95(2):64-72]

Key Words: Colorectal neoplasms, Palliative care, Colorectal surgery, Prognosis, Survival

INTRODUCTION

Approximately 20%–25% of patients with colorectal cancer present with metastases at the time of diagnosis. Most patients with metastatic colorectal cancer have unresectable disease, but may benefit from chemotherapy or primary tumor resection (PTR) with palliative intent followed by systemic chemotherapy [1]. PTR may improve quality of life and may prevent or ameliorate complications caused by growth of the primary tumor, such as obstruction, perforation or bleeding [2-5]. These complications require emergency surgery, which is associated with high morbidity and mortality rates and less favorable long-term outcomes. Despite the benefits of PTR, it delays the start of systemic chemotherapy, which also provides survival advantages [6,7]. Systemic chemotherapy regimens that contain agents such as irinotecan, oxaliplatin, and targeted agents have improved the prognosis of these patients. Administration of systemic chemotherapy to most patients who lack symptoms related to primary tumors may be sufficient to control the asymptomatic primary lesions, as chemotherapy can shrink tumors and/or control tumor spread [8-11]. Moreover, PTR may lead to postoperative morbidity and mortality, making resection questionable even in patients with asymptomatic tumors.

It is therefore unclear whether PTR with palliative intent

Received October 19, 2017, **Revised** December 27, 2017, **Accepted** January 4, 2018

Corresponding Author: Min Ro Lee
Research Institute of Clinical Medicine, Chonbuk National University Medical School, 567 Baekje-daero, Deokjin-gu, Jeonju 54896, Korea
Tel: +82-63-250-1570, **Fax:** +82-63-271-6197
E-mail: gsminro@jbnu.ac.kr
ORCID code: https://orcid.org/0000-0001-9838-8071

This article was presented at the 16th Asia Pacific Federation of Coloproctology (APFCP 2017) and Eurasian Colorectal Technologies Association (ECTA 2017) (Seoul, Korea, 30 March–1 April 2017).

is safe or provides actual survival benefit. Although three previous meta-analyses reported oncologic outcomes of PTR [2,12,13], 2 of those analyses assessed overall survival (OS) alone, and did not consider the survival outcomes of subgroups. Furthermore, all of these analyses included studies published prior to the introduction of chemotherapeutic regimens that contained irinotecan or oxaliplatin. The current meta-analysis therefore evaluated the survival benefits of PTR in patients with unresectable metastatic colorectal cancer in the era of modern chemotherapy.

METHODS

This meta-analysis followed the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [14]. Multiple comprehensive databases were searched for studies that assessed the oncologic outcomes of PTR in patients with unresectable metastatic colorectal cancer. The study protocol was based on Cochrane Review Methods [15].

Data and literature sources

PubMed (January 1, 1976 to November 23, 2016), Embase (January 1, 1985 to November 23, 2016), and the Cochrane Central Register of Controlled Trials (CENTRAL; January 1, 1987 to November 23, 2016) were searched. There were no restrictions on year or language of publication. The search terms used were "colorectal cancer," "metastatic," "stage IV," "palliative resection," and "survival." After the initial electronic search, articles were manually searched to identify additional studies. All articles were assessed individually before inclusion.

Study selection and data extraction

Article titles and abstracts were screened, and full texts were reviewed independently by 2 reviewers (GWH and MRL), based on the selection criteria. Discrepancies were resolved by discussion between these reviewers.

Included studies assessed the survival outcomes, including OS and progression-free survival (PFS), of patients with metastatic colorectal cancer who did and did not undergo PTR. Studies were excluded if they: (1) assessed patients who had tumor pathology other than adenocarcinoma; (2) assessed patients who were not treated with modern cytotoxic agents, such as irinotecan or oxaliplatin, or were diagnosed with metastatic colorectal cancer before 2000, the beginning of the modern chemotherapy era; (3) assessed patients who underwent simultaneous or subsequent metastasectomy; (4) assessed only specific groups of patients (e.g., elderly or obese patients); (5) had no extractable data and the authors could not be reached to provide additional information; (6) were case series with fewer than 10 patients; and (7) were not published in English.

All eligible studies were reviewed, and all relevant data were extracted independently by 2 reviewers using a predefined data extraction form. The variables recorded were: (1) basic publication information, including name of the first author, year of publication, and number of patients; (2) demographic, clinical, and treatment characteristics of the patients; and (3) patient outcomes (OS and PFS).

Assessment of methodological quality

The methodological quality of the included studies was assessed using the Newcastle-Ottawa quality scale (NOS), which allocates a maximum of 9 points to each study; a score ≥ 6 indicated high quality [16]. The quality of included studies was determined by examining three factors: patient selection, comparability of the study groups and assessment of outcomes.

Statistical analysis

The meta-analysis determined the hazard ratio (HR) with its variance and 95% confidence interval (CI). The presence and extent of heterogeneity were assessed using the Q test and I^2 index, respectively, with a P-value less than 0.1 considered statistically significant [17]. The DerSimonian-Laird random effects model (REM) was used for pooling data in anticipation of cross-study heterogeneity [18]. If sufficient data were available, planned subgroup analyses were performed to evaluate oncologic effects of PTR. Sensitivity analyses were also performed to assess the robustness of the meta-analysis findings [19,20]. Publication bias was assessed by visually inspecting funnel plots of the outcome, and using the Egger weighted linear regression test, in which a P-value less than 0.1 was considered significant [21,22].

All data were analyzed using Review Manager (RevMan 5.3, Cochrane Collaboration, Oxford, UK) and Comprehensive Meta-Analysis ver. 3 (Englewood, NJ, USA).

RESULTS

Description of studies

The predefined searching strategy and manual searching identified 13,577 potentially relevant articles; of these, 2,436 articles were excluded because they were duplicates and 11,070 were excluded because their titles and abstracts did not fulfill the selection criteria. After full text review of the remaining 71 articles, 54 were excluded due to the exclusion criteria of these studies. Therefore, a total of 17 nonrandomized studies were deemed suitable for inclusion (Fig. 1). These studies examined a total of 18,863 patients, 9,575 of whom underwent PTR without metastasectomy. All 17 studies evaluated OS [23-39], whereas only two evaluated PFS [24,35]. Three studies examined patients with colon cancer exclusively [28,32,38],

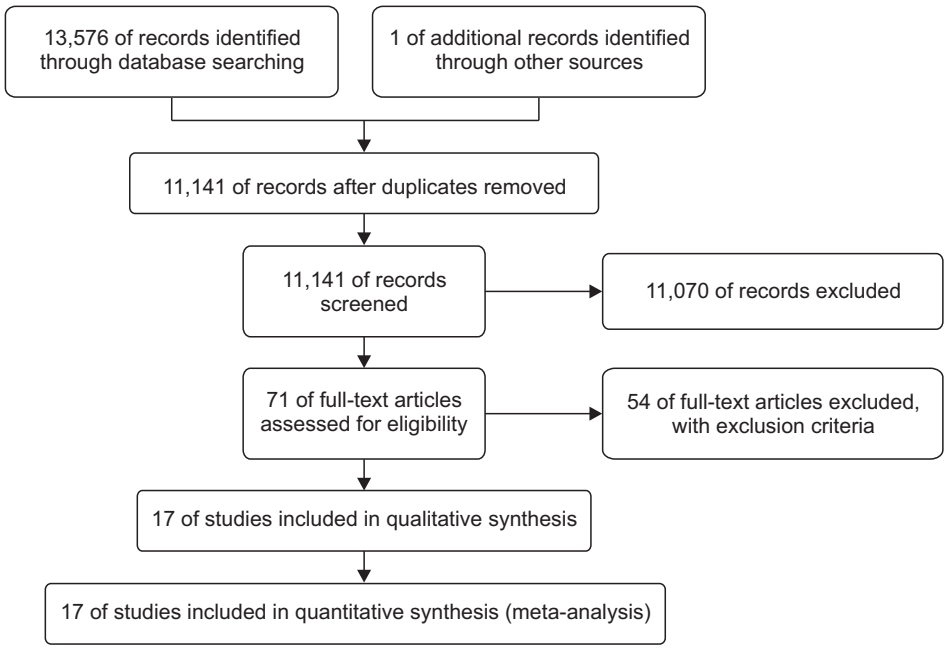

Fig. 1. Flow chart of the literature search according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

one examined patients with rectal cancer exclusively [25], and 13 examined patients with colorectal cancer [23,24,26,27,29-31,33-37,39]; in 3 of the latter studies, data on patients with colon cancer could be separated from data on patients with rectal cancer [34,37,39]. Thirteen studies evaluated patients who received targeted chemotherapy [23,24,26-35,39]. In eight studies, all patients who did not undergo PTR received systemic chemotherapy [23,24,28,30,32,33,35,36]. Four studies evaluated oncologic outcomes using large databases [34,36-38]. Seven studies assessed HR for OS using propensity score analysis [27,29,31,32,36-38].

Evaluation of methodological quality showed that 14 studies scored high (≥6) on the NOS [24- 28,30-36,38,39]. Tables 1 and 2 summarize the characteristics of all 17 included studies.

Outcome measures

Analysis of oncologic outcomes after PTR indicated that all 17 studies, involving 18,863 patients, reported data on OS. Pooled analysis showed that PTR increased OS rate (HR, 0.63; 95% CI, 0.56–0.71; I^2 = 83%) (Fig. 2). Two studies, involving 1,038 patients, reported PFS after PTR, with PTR found to increase rate (HR, 0.76; 95% CI, 0.67–0.87, I^2 = 0%) (Fig. 3).

The effects of PTR on OS were also determined in patient subgroups, depending on chemotherapy regimens and tumor location. These subgroups included (1) patients who received targeted chemotherapy, (2) all patients in the non-PTR group underwent chemotherapy, and (3) patients with colon or rectal cancer alone. OS was increased in groups of patients who received chemotherapy that included a targeted agent (bevacizumab, cetuximab, or panitumumab) (HR, 0.65; 95% CI, 0.58–0.73; I^2 = 37%); patients in the non-PTR group who received chemotherapy (HR, 0.63; 95% CI, 0.57–0.70; I^2 = 19%) and patients with colon cancer alone who underwent PTR (HR, 0.63; 95% CI, 0.48–0.85; I^2 = 90%). Because only one study reported OS in patients with rectal cancer alone, subgroup analysis was not performed.

Sensitivity analyses, performed using predefined methods, indicated the robustness of all OS results of this meta-analysis. Reanalysis of the data using an alternative statistical effects model (HR, 0.54; 95% CI, 0.52–0.56; I^2 = 83%), analysis of high-quality studies (NOS ≥ 6) (HR, 0.62; 95% CI, 0.54–0.70; I^2 = 81%), analysis of studies reported by surgeons (HR, 0.62; 95% CI, 0.51–0.75; I^2 = 89%), analysis of studies reported by medical oncologist (HR, 0.64; 95% CI, 0.57–0.72; I^2 = 36%), and analysis of studies using large databases (HR, 0.64; 95% CI, 0.50–0.83; I^2 = 96%) all showed that PTR was associated with increased OS. Finally, analysis of studies using HRs for OS from propensity score analysis showed that PTR was associated with increased OS (HR, 0.64; 95% CI, 0.52–0.80; I^2 = 88%). Table 3 summarizes the results of these subgroup and sensitivity analyses.

Publication bias

Publication bias was analyzed using the Egger weighted linear regression test, which assesses the asymmetry of funnel plots. The funnel plot for OS (P = 0.01) was found to be asymmetric, indicating publication bias (Fig. 4).

DISCUSSION

To our knowledge, this is the first meta-analysis to assess the oncologic effect of PTR for patients diagnosed with unresectable stage IV colorectal cancer in the era of modern chemotherapy.

Table 1. Summary of the included studies

Study	Design	Study period	PTR (n)	Non-PTR (n)	Symptomatic resections (%)	Primary site (rectum, %)		Outcome measures	NOS scale
						PTR	Non-PTR		
Ahmed [39] 2016	RCS, Single	2006–2010	232	248	55	28	41	OS	6
Alwadi [38] 2016	RCS, Large database	2003–2005	5,332	3,010	0	0	0	OS	6
Gulack [37] 2016	RCS, Large database	2003–2006	231	1,215	NR	8.2	46.7	OS	5
't Lam-Boer [36] 2016	RCS, Large database	2008–2011	1,484	3,177	NR	13	32	OS	7
Wang [35] 2016	PCS, Single	2011–2013	118	73	0	38	42.5	OS, PFS	8
Wong [34] 2016	RCS, Large database	2009–2015	216	394	NR	3	36	OS	8
Kodaz [33] 2015	RCS, Single	2007–2013	34	44	NR	NR	NR	OS	7
de Mestier [32] 2014	RCS, Single	2004–2008	69	27	NR	0	0	OS	8
Gresham [31] 2014	RCS, Multi	2006–2008	378	139	NR	18.3	39.6	OS	6
Miyamoto [30] 2014	RCS, Single	2005–2011	68	63	NR	42	30	OS	7
Yoon [29] 2014	PCS, Single	2000–2007	195	66	43	34.9	63.6	OS	5
Boselli [28] 2013	RCS, Single	2010–2011	17	31	0	0	0	OS	7
Park [27] 2013	RCS, Single	2000–2009	527	320	27	NR	NR	OS	7
Kim [26] 2012	RCS, Single	2000–2009	63	83	93	35.2	44.8	OS	6
Verberne [25] 2012	RCS, Single	2002–2006	26	62	7	100		OS	7
Verderbosch [24] 2011 (1)	RCS, Multi	2003–2004	258	141	NR	22	34	OS, PFS	6
Verderbosch [24] 2011 (2)	RCS, Multi	2005–2006	289	159	NR	18	27	OS, PFS	6
Tanoue [23] 2010	RCS, Single	2005–2009	38	36	NR	42	53	OS	5

PTR, primary tumor resection; RCS, retrospective cohort study; PC1S, prospective cohort study; Single, single center study; Multi, multicenter study; OS, overall survival; PFS, progression free survival; NOS, Newcastle-Ottawa quality scale; NR, not reported.

Table 2. Clinical characteristics of included studies

Study	Metastatic spread	Chemotherapy regimens	CTx received (%)		Radiation therapy (%)		Median survival (mo)	
			PTR	Non-PTR	PTR	Non-PTR	PTR	Non-PTR
Ahmed [39] 2016	Liver, lung, peritoneum, bone, brain	FOLFOX/FOLFIRI ± bevacizumab, cetuximab, panitumumab	64	50	14	18	27	14
Alwadi [38] 2016	NR	NR	61.7	46.2	0	0	20.3	10
Gulack [37] 2016	NR	NR	46.2	66	6.1	47.9	9.2	7.6
't Lam-Boer [36] 2016	Liver, lung, peritoneum	NR	54	100	NR	NR	20.7	11.9
Wang [35] 2016	NR	FOLFOX/XELOX/FOLFIRI + bevacizumab	100		0	11	22.5	17.8
Wong [34] 2016	Liver, other distant	Oxaliplatin/Irinotecan ± bevacizumab, cetuximab	78	74	NR	NR	21	17
Kodaz [33] 2015	Liver, lung, other distant	FOLFOX/FOLFIRI ± bevacizumab, cetuximab	97	100	NR	NR	25	16
de Mestier [32] 2014	Liver, lung, other distant	FOLFOX/FOLFIRI ± bevacizumab	100		0	0	23.1	22.1
Gresham [31] 2014	Liver, extrahepatic	FOLFOX/FOLFIRI ± bevacizumab, capecitabine, 5FU	68	50.4	NR	NR	17.9	7.9
Miyamoto [30] 2014	Liver, lung, other distant	FOLFOX/FOLFIRI ± bevacizumab, cetuximab	100	100	NR	NR	30.4	24.1
Yoon [29] 2014	Liver	FOLFOX/FOLFIRI/XELOX/XELIRI/FL/capecitabine ± bevacizumab, cetuximab	85.1	71.2	NR	NR	21	10
Boselli [28] 2013	Liver	FOLFOX ± bevacizumab	64.7	100	0	0	4	5
Park [27] 2013	Liver, lung, peritoneum, other distant	Oxaliplatin/Irinotecan/capecitabine ± bevacizumab, cetuximab	91	86.9	NR	NR	21.4	14.1
Kim [26] 2012	Liver, lung, peritoneum, other distant	FOLFOX/FOLFIRI ± bevacizumab	58.1	74	4.8	25	14	8
Verberne [25] 2012	Liver, lung, other distant	NR	58	34	0	19	10	
Verderbosch [24] 2011 (1)	Liver, extrahepatic	Capecitabine/irinotecan/oxaliplatin	100		0	0	16.7	11.4
Verderbosch [24] 2011 (2)	Liver, extrahepatic	Capecitabine/oxaliplatin/bevacizumab ± cetuximab	100		NR	NR	20.7	13.4
Tanoue [23] 2010	Liver, lung, peritoneum	FOLFOX/FOLFIRI ± bevacizumab, cetuximab	100		NR	NR	30.6	20.8

CTx, chemotherapy; PTR, primary tumor resection; NR, not reported.

Annals of Surgical Treatment and Research 2018;95(2):64-72

ASTR

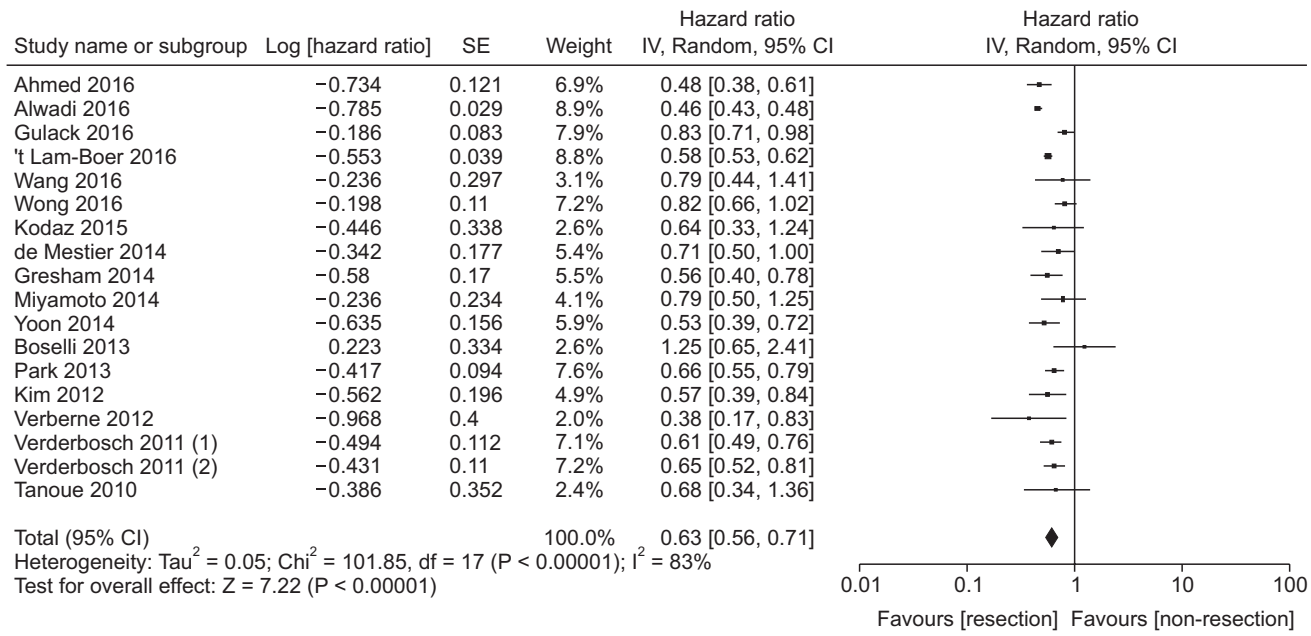

Fig. 2. Forest plot and meta-analysis of the effects of primary tumor resection on overall survival. SE, standard error; CI, confidence interval; df, degree of freedom.

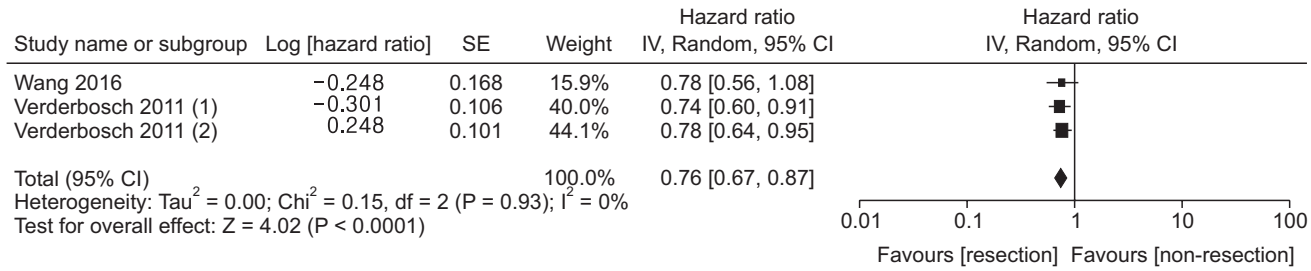

Fig. 3. Forest plot and meta-analysis of the effects of primary tumor resection on progression-free survival. SE, standard error; CI, confidence interval; df, degree of freedom.

This meta-analysis found that PTR was associated with increased OS in patients with unresectable metastatic colorectal cancer. This result is similar to that of previous meta-analyses [2,12,13]. However, these previous analyses included studies that evaluated patients diagnosed with colorectal cancer before the introduction of modern chemotherapy regimens which led to a major transition in the treatment of metastatic colorectal cancer [40]. Irinotecan was introduced in 1996, and it was reported that irinotecan provided survival benefits in patients with metastatic colorectal cancer in 2000 [41]. Therefore, we chose a time period of diagnosis beginning in 2000. The number of new chemotherapeutic agents has increased significantly over the past decade, with these new agents playing an important role in the treatment of metastatic colorectal cancer. Therefore, the present meta-analysis included studies that assessed patients treated with modern cytotoxic agents, such as irinotecan or oxaliplatin, or assessed patients diagnosed with metastatic colorectal cancer after 2000.

The present study provides a more detailed assessment of oncologic outcomes, using subgroup and sensitivity analyses, than previous studies. We found that PTR was associated with increased PFS. PTR was also found to be associated with increased OS from the analysis of studies including patients who received target agents, and from the analysis of studies in which all patients in non-PTR group received chemotherapy. Despite selection bias, these results suggest that PTR may be an independent prognostic factor for OS, similar to a study that reported that PTR itself was an independent predictor of response to bevacizumab [42]. PTR may reduce the concentrations of tumor-derived protumorigenic chemotactic cytokines that regulate cancer metastasis [43,44]. Primary tumors may have unique attributes that support tumor progression. Primary tumors frequently exhibit higher genetic variability than metastases and, therefore, may have greater

Table 3. Subgroup and sensitivity analyses of overall survival

Variable	No. of studies	No. of cases	HR	95% CI	P-value	Heterogeneity			
						Cochrane Q	df (Q)	I^2 (%)	P-value
All studies	17	18,863	0.63	0.56–0.71	<0.001	101.85	17	83	<0.001
Subgroup analyses									
Colon cancer alone	6	9,751	0.63	0.48–0.85	0.002	49.16	5	90	<0.001
Target agent	13	3,927	0.65	0.58–0.73	<0.001	18.93	12	37	0.090
All chemotherapy in non-PTR group	8	6,126	0.63	0.57–0.70	<0.001	9.85	8	19	0.280
Sensitivity analyses									
Fixed effect model	17	18,863	0.54	0.52–0.56	<0.001	101.85	17	83	<0.001
High-quality studies	14	17,082	0.62	0.54–0.70	<0.001	73.29	14	81	<0.001
Surgeons	9	15,197	0.62	0.51–0.75	<0.001	70.42	8	89	<0.001
Medical oncologist	9	3,666	0.64	0.57–0.72	<0.001	12.50	8	36	0.130
Large database analysis	4	15,059	0.64	0.50–0.83	<0.001	75.96	3	96	<0.001
HR using propensity score analysis	7	20,703	0.64	0.52–0.80	<0.001	51.54	6	88	<0.001

HR, hazard ratio; CI, confidence interval; df (Q), degree of freedom.

Fig. 4. Funnel plots of included studies in the analysis for the effects of primary tumor resection on overall survival. SE, standard error.

capacity to generate new metastatic clones resistant to ongoing treatments [40,45,46]. Additionally, we tried to separately analyze patients with colon cancer and rectal cancer, because the natural history, complications and therapeutic options differ in these 2 groups. We found that PTR was associated with increased OS in patients with colon cancer. However, it was impossible to analyze patients with rectal cancer, because only one of the 17 included studies separately analyzed patients with rectal cancer.

This meta-analysis had several limitations. There was potential heterogeneity among the included studies, despite our use of definite exclusion criteria and our performance of subgroup and sensitivity analyses. Because all included studies were nonrandomized, selection bias was likely. Patient performance status, presence of symptoms, tumor burden, and various surgical techniques may have influenced the oncologic outcomes of PTR. Moreover, most studies included in this analysis did not specify reasons or criteria for nonresection. The included studies were retrospective in design, suggesting a possible bias in decision-making for individual patients, which may have influenced oncologic outcomes. Although the factors that may have influenced the selection of patients for surgery remain unclear, patients who were younger in age and had fewer comorbidities and metastases were more likely to undergo PTR, whereas patients who were older, sicker and had many metastatic foci were less likely to undergo surgery. Finally, Publication bias was found in the analysis of OS. However, using the Trim-and-Fill method, under both of the fixed effects model and the REM for the outcomes, our results were not affected by this bias.

In conclusion, surgical resection of the primary tumor without metastasectomy may have survival benefits in patients with unresectable stage IV colorectal cancer. Continued advances in modern chemotherapy and appropriate local

treatments including PTR would improve survival outcomes. Randomized controlled trials are needed to determine the optimal treatment for these patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

The authors thank the reviewers for their extremely thorough and helpful reviews and suggestions.

REFERENCES

1. Cook AD, Single R, McCahill LE. Surgical resection of primary tumors in patients who present with stage IV colorectal cancer: an analysis of surveillance, epidemiology, and end results data, 1988 to 2000. Ann Surg Oncol 2005;12:637-45.
2. Stillwell AP, Buettner PG, Ho YH. Meta-analysis of survival of patients with stage IV colorectal cancer managed with surgical resection versus chemotherapy alone. World J Surg 2010;34:797-807.
3. Ruo L, Gougoutas C, Paty PB, Guillem JG, Cohen AM, Wong WD. Elective bowel resection for incurable stage IV colorectal cancer: prognostic variables for asymptomatic patients. J Am Coll Surg 2003;196:722-8.
4. Cummins ER, Vick KD, Poole GV. Incurable colorectal carcinoma: the role of surgical palliation. Am Surg 2004;70:433-7.
5. Benoist S, Pautrat K, Mitry E, Rougier P, Penna C, Nordlinger B. Treatment strategy for patients with colorectal cancer and synchronous irresectable liver metastases. Br J Surg 2005;92:1155-60.
6. Fakih MG. Metastatic colorectal cancer: current state and future directions. J Clin Oncol 2015;33:1809-24.
7. Gustavsson B, Carlsson G, Machover D, Petrelli N, Roth A, Schmoll HJ, et al. A review of the evolution of systemic chemotherapy in the management of colorectal cancer. Clin Colorectal Cancer 2015;14:1-10.
8. Scoggins CR, Meszoely IM, Blanke CD, Beauchamp RD, Leach SD. Nonoperative management of primary colorectal cancer in patients with stage IV disease. Ann Surg Oncol 1999;6:651-7.
9. Crane CH, Janjan NA, Abbruzzese JL, Curley S, Vauthey J, Sawaf HB, et al. Effective pelvic symptom control using initial chemoradiation without colostomy in metastatic rectal cancer. Int J Radiat Oncol Biol Phys 2001;49:107-16.
10. Tebbutt NC, Norman AR, Cunningham D, Hill ME, Tait D, Oates J, et al. Intestinal complications after chemotherapy for patients with unresected primary colorectal cancer and synchronous metastases. Gut 2003;52:568-73.
11. Poultsides GA, Servais EL, Saltz LB, Patil S, Kemeny NE, Guillem JG, et al. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. J Clin Oncol 2009;27:3379-84.
12. Clancy C, Burke JP, Barry M, Kalady MF, Calvin Coffey J. A meta-analysis to determine the effect of primary tumor resection for stage IV colorectal cancer with unresectable metastases on patient survival. Ann Surg Oncol 2014;21:3900-8.
13. Lee KC, Ou YC, Hu WH, Liu CC, Chen HH. Meta-analysis of outcomes of patients with stage IV colorectal cancer managed with chemotherapy/radiochemotherapy with and without primary tumor resection. Onco Targets Ther 2016;9:7059-69.
14. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264-9,
15. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. Oxford (UK): The Cochrane Collaboration; 2011.
16. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Ottawa (ON): Ottawa Hospital Research Institute; c2018 [cited 2017 Jun 27]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
19. Thabane L, Akhtar-Danesh N. Guidelines for reporting descriptive statistics in health research. Nurse Res 2008;15:72-81.
20. Patsopoulos NA, Evangelou E, Ioannidis JP. Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. Int J Epidemiol 2008;37:1148-57.
21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
22. Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR. Empirical assessment of effect of publication bias on meta-analyses. BMJ 2000;320:1574-7.
23. Tanoue Y, Tanaka N, Nomura Y. Primary site resection is superior for incurable metastatic colorectal cancer. World J Gastroenterol 2010;16:3561-6.

24. Venderbosch S, de Wilt JH, Teerenstra S, Loosveld OJ, van Bochove A, Sinnige HA, et al. Prognostic value of resection of primary tumor in patients with stage IV colorectal cancer: retrospective analysis of two randomized studies and a review of the literature. Ann Surg Oncol 2011;18:3252-60.
25. Verberne CJ, de Bock GH, Pijl ME, Baas PC, Siesling S, Wiggers T. Palliative resection of the primary tumour in stage IV rectal cancer. Colorectal Dis 2012;14:314-9.
26. Kim SK, Lee CH, Lee MR, Kim JH. Multivariate analysis of the survival rate for treatment modalities in incurable stage IV colorectal cancer. J Korean Soc Coloproctol 2012;28:35-41.
27. Park JH, Kim TY, Lee KH, Han SW, Oh DY, Im SA, et al. The beneficial effect of palliative resection in metastatic colorectal cancer. Br J Cancer 2013;108:1425-31.
28. Boselli C, Renzi C, Gemini A, Castellani E, Trastulli S, Desiderio J, et al. Surgery in asymptomatic patients with colorectal cancer and unresectable liver metastases: the authors' experience. Onco Targets Ther 2013;6:267-72.
29. Yoon YS, Kim CW, Lim SB, Yu CS, Kim SY, Kim TW, et al. Palliative surgery in patients with unresectable colorectal liver metastases: a propensity score matching analysis. J Surg Oncol 2014;109:239-44.
30. Miyamoto Y, Watanabe M, Sakamoto Y, Shigaki H, Murata A, Sugihara H, et al. Evaluation of the necessity of primary tumor resection for synchronous metastatic colorectal cancer. Surg Today 2014;44:2287-92.
31. Gresham G, Renouf DJ, Chan M, Kennecke HF, Lim HJ, Brown C, et al. Association between palliative resection of the primary tumor and overall survival in a population-based cohort of metastatic colorectal cancer patients. Ann Surg Oncol 2014;21:3917-23.
32. de Mestier L, Neuzillet C, Pozet A, Desot E, Deguelte-Lardiere S, Volet J, et al. Is primary tumor resection associated with a longer survival in colon cancer and unresectable synchronous metastases? A 4-year multicentre experience. Eur J Surg Oncol 2014;40:685-91.
33. Kodaz H, Erdogan B, Hacibekiroglu I, Turkmen E, Tozkir H, Albayrak D, et al. Primary tumor resection offers higher survival advantage in KRAS mutant metastatic colorectal cancer patients. Hepatogastroenterology 2015;62:876-9.
34. Wong SF, Wong HL, Field KM, Kosmider S, Tie J, Wong R, et al. Primary tumor resection and overall survival in patients with metastatic colorectal cancer treated with palliative intent. Clin Colorectal Cancer 2016;15:e125-32.
35. Wang Z, Liang L, Yu Y, Wang Y, Zhuang R, Chen Y, et al. Primary tumour resection could improve the survival of unresectable metastatic colorectal cancer patients receiving bevacizumab-containing chemotherapy. Cell Physiol Biochem 2016;39:1239-46.
36. 't Lam-Boer J, Van der Geest LG, Verhoef C, Elferink ME, Koopman M, de Wilt JH. Palliative resection of the primary tumor is associated with improved overall survival in incurable stage IV colorectal cancer: a nationwide population-based propensity-score adjusted study in the Netherlands. Int J Cancer 2016;139:2082-94.
37. Gulack BC, Nussbaum DP, Keenan JE, Ganapathi AM, Sun Z, Worni M, et al. Surgical resection of the primary tumor in stage IV colorectal cancer without metastasectomy is associated with improved overall survival compared with chemotherapy/radiation therapy alone. Dis Colon Rectum 2016;59:299-305.
38. Alawadi Z, Phatak UR, Hu CY, Bailey CE, You YN, Kao LS, et al. Comparative effectiveness of primary tumor resection in patients with stage IV colon cancer. Cancer 2017;123:1124-33.
39. Ahmed S, Leis A, Chandra-Kanthan S, Fields A, Reeder B, Iqbal N, et al. Surgical management of the primary tumor in stage IV colorectal cancer: a confirmatory retrospective cohort study. J Cancer 2016;7:837-45.
40. Tsang WY, Ziogas A, Lin BS, Seery TE, Karnes W, Stamos MJ, et al. Role of primary tumor resection among chemotherapy-treated patients with synchronous stage IV colorectal cancer: a survival analysis. J Gastrointest Surg 2014;18:592-8.
41. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med 2000;343:905-14.
42. Ghiringhelli F, Bichard D, Limat S, Lorgis V, Vincent J, Borg C, et al. Bevacizumab efficacy in metastatic colorectal cancer is dependent on primary tumor resection. Ann Surg Oncol 2014;21:1632-40.
43. Cambien B, Richard-Fiardo P, Karimdjee BF, Martini V, Ferrua B, Pitard B, et al. CCL5 neutralization restricts cancer growth and potentiates the targeting of PDGFRβ in colorectal carcinoma. PLoS One 2011;6:e28842.
44. Chen HJ, Edwards R, Tucci S, Bu P, Milsom J, Lee S, et al. Chemokine 25-induced signaling suppresses colon cancer invasion and metastasis. J Clin Invest 2012;122:3184-96.
45. Marusyk A, Polyak K. Tumor heterogeneity: causes and consequences. Biochim Biophys Acta 2010;1805:105-17.
46. Goranova TE, Ohue M, Shimoharu Y, Kato K. Dynamics of cancer cell subpopulations in primary and metastatic colorectal tumors. Clin Exp Metastasis 2011;28:427-35.