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ORIGINAL ARTICLE

Does adjuvant chemotherapy improve the prognosis of patients after resection of pulmonary metastasis from colorectal cancer? A systematic review and meta-analysis

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Abstract

Background It remains controversial whether patients benefit from adjuvant chemotherapy (ACT) after resection of pulmonary metastasis (PM) from colorectal cancer (CRC). This meta-analysis was intended to evaluate the efficacy of ACT in patients after resection of PM from CRC.

Methods We systematically retrieved articles from PMC, PubMed, Cochrane Library, and Embase (up to March 5, 2019). Survival data, including overall survival (OS) and disease-free survival (DFS), were tested by hazard ratios (HRs) and 95% confidence intervals (CIs).

Results We included 18 cohort studies with a total of 3885 patients. The meta-analysis showed that ACT had no significant effect on OS (HR = 0.78; 95% CI = 0.60–1.03; $P = 0.077$) and DFS (HR = 0.91; 95% CI = 0.74–1.11; $P = 0.339$) in patients after resection of PM from CRC. There was no significant difference in OS (HR = 0.79; 95% CI = 0.42–1.50; $P = 0.474$) in patients after resection of PM from CRC treated with bevacizumab (BV). Subgroup analysis showed that ACT did not improve OS (HR = 0.86; 95% CI = 0.57–1.29; $P = 0.461$) in patients who had undergone previous resection of extra PM. ACT did not improve OS in patients who had positive hilar/mediastinal lymph node metastasis (HR = 0.80; 95% CI = 0.57–1.14; $P = 0.22$).

Conclusion In conclusion, ACT does not provide survival benefits for patients after resection of PM from CRC. ACT and targeted agents (BV) are not suggested for these patients.

Keywords Colorectal cancer · Resection of pulmonary metastasis · Adjuvant chemotherapy · Prognosis · Meta-analysis

Introduction

Colorectal cancer (CRC) is the third most common malignant tumor worldwide, and its mortality rate ranks fourth [1]. Postoperative recurrence is the main cause of CRC treatment failure, and 19–28% of patients have metastasis after CRC resection. At present, the lungs are the second most common metastasis site in CRC, which is second only to the liver. Pulmonary metastasis (PM) is found in 10–29% of patients in CRC [2–6]. PM from CRC has the following clinical features. (1) The incidence of PM from colon cancer is 3.5–6%, and the incidence of PM from rectal cancer is 10–18%. Moreover, the incidence of PM from middle and lower rectal cancer is significantly higher than that from upper rectal cancer, which may result from a difference in venous reflux. (2) The incidence of solitary PM in rectal cancer is approximately twice as high as that of colon cancer (12% vs. 6%). (3) The incidence of multiple PMs is higher than that of solitary PM. According to Limmer et al., most patients with PM from CRC have double or multiple metastases, and solitary metastasis is only found in 2–7% of patients. (4) Recurrence of PM after surgery for CRC is correlated with the stage of the primary lesion. Watanabe et al. found that the postoperative incidence of PM was 0.6% in stage I, 2.2% in stage II, 9.8% in stage III, and 24.6% in stage IV [7–9].

The prognosis after PM resection is good, and the 5-year survival rate reaches 30–60% [10, 11]. Postoperative high-risk factors include previous extra PM and preoperative

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carcinoembryonic antigen (CEA) levels ≥ 5 ng/ml, disease-free interval (DFI) ≤ 24 months, multiple PMs, and hilar/mediastinal lymph node metastasis (LNM) [12–15]. Unlike other distant metastases, PM grows slowly and has a better overall prognosis, thus it is not possible to fully adhere to the treatment model for liver metastasis (LM) from CRC. Although the guidelines recommend adjuvant chemotherapy (ACT) for patients with CRC with PM [16–19], whether ACT can be used as a prognostic factor remains controversial. The purpose of this meta-analysis was to evaluate the effect of ACT on the prognosis of patients after resection of PM from CRC.

Materials and methods

Search strategy

We systematically retrieved articles from PMC, PubMed, Cochrane Library, and Embase databases (up to March 5, 2019), restricting the language to English. The search terms included: "colorectal cancer," "colorectal neoplasm," "pulmonary metastasis," "lung metastasis," "pulmonary metastasectomy," "adjuvant chemotherapy," and "postoperative chemotherapy." According to the requirements of different databases, we changed the retrieval strategy and also retrieved the references of the included literature.

Inclusion and exclusion criteria

Studies included in this analysis met the following criteria: (1) CRC and metastatic lesions could be resected based on preoperative assessment; (2) radical resection of CRC and PM was performed, which was confirmed by pathology after surgery; (3) patients with PM from CRC did not receive neoadjuvant chemotherapy; (4) sufficient information was provided in the literature to directly extract or calculate the outcomes; and (5) English full text, excluding conference abstracts, case reports, repeated studies, non-English articles, poor-quality studies, and inability to extract useful data research and review. Two researchers (Chao Zhang and Yuen Tan) extracted relevant data based on independent screening. If there was a disagreement, it was resolved by discussion or a third party.

Data extraction and quality assessment

Two researchers extracted the following data from pre-established tables: author, year of publication, country, total number of patients, sex, age, follow-up time, ACT regimen, outcome measures, and Newcastle–Ottawa Scale (NOS) score. The NOS score was used for quality assessment and included three aspects of selection, comparability, and outcome, scoring from 1 to 9 points, with > 6 points considered to be high quality [20].

Statistical analysis

HRs and 95% CIs were used to evaluate the correlation between ACT and prognosis of patients after resection of PM from CRC. If HRs and 95% CIs were reported in the original literature, we extracted the original values directly. Otherwise, according to the methods reported by Parmar et al. [21] and Tierney et al. [22], we obtained the relevant HRs and 95% CIs indirectly from the figures or useful data provided in the literature. In this study, the inter-study heterogeneity was quantified by I^2. $P < 0.10$ and/or $I^2 > 50\%$ showed obvious heterogeneity, and the random-effects model was used for pooled analysis. If the heterogeneity among the studies was not significant, the fixed-effects model was used for the pooled analysis. To explore the source of heterogeneity and increase the reliability of the results, subgroup analysis and meta-regression analysis were performed. To assess the stability of the combined results, a sensitivity analysis was performed. Egger's test [23] and Begg's test [24] were used to identify publication bias. Meta-analysis was carried out using STATA 12.0 software; $P < 0.05$ was considered statistically significant.

Results

Search results and quality assessment

The literature retrieval process is shown in Fig. 1. A total of 3433 articles were retrieved; 975 duplicate articles were removed, and 2412 articles were excluded after reading the title and abstract. The remaining 46 articles were further evaluated by reading the full text, and 28 articles were excluded. This left 18 articles with a total of 3885 patients [9, 25–41]. The basic characteristics of the studies are shown in Table 1. The quality evaluation results of the included cohort studies are shown in Table 2.

Effect of ACT on OS

A total of 16 articles [25–29, 31–41] were included, with 1809 patients undergoing ACT and 1856 patients without ACT. Heterogeneity test showed significant heterogeneity between studies ($I^2 = 74.4\%$, $P < 0.001$). The random-effects model showed that ACT had no significant effect on OS after resection of PM from CRC (HR = 0.78; 95% CI = 0.60–1.03; $P = 0.077$; Fig. 2).

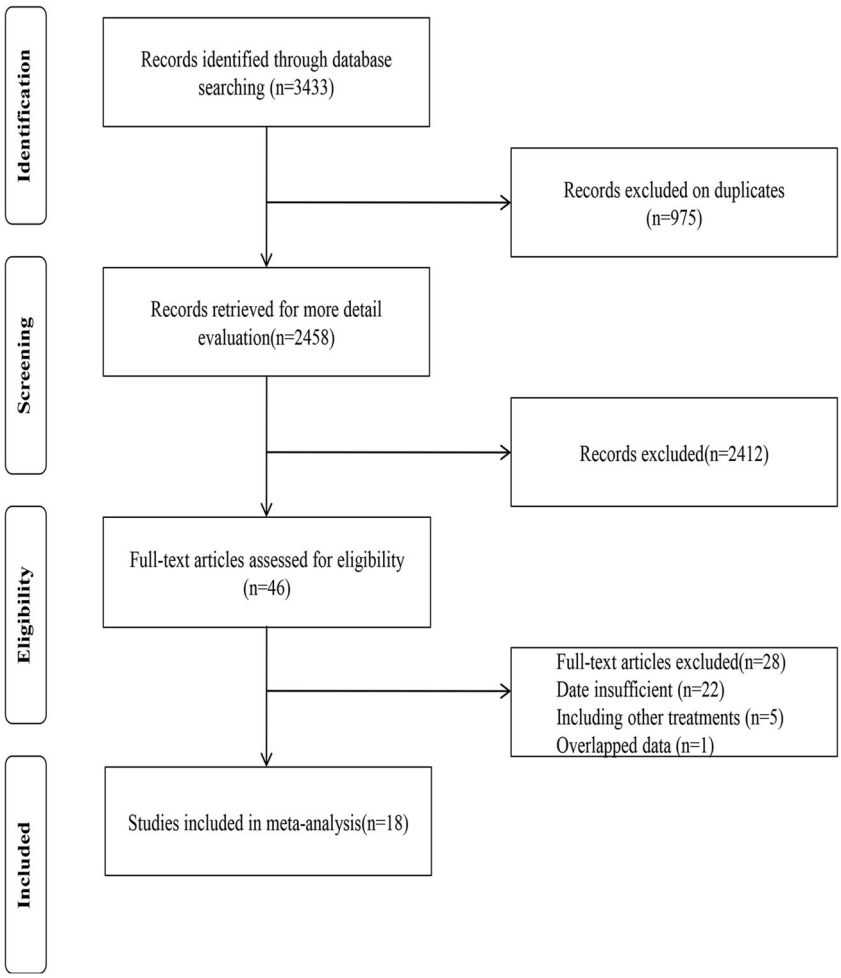

Fig. 1 Flowchart of the selection process of included studies

We performed subgroup and regression analyses according to ethnic background, study quality, sample size, scale of study, previous resection of extra PM, and positive LNM (Table 3). Subgroup analysis according to ethnicity showed that ACT had no significant effect on OS in Asian (HR = 0.71; 95% CI = 0.48–1.05) and western (HR = 0.85; 95% CI = 0.56–1.30) patients after resection of PM from CRC. Heterogeneity was significant in Asian (I^2 = 76.8%, P < 0.001) and western (I^2 = 74.7%, P < 0.001) patients. Subgroup analysis according to study quality showed that ACT had no significant effect on OS in high-quality studies (HR = 0.93; 95% CI = 0.64–1.36), and heterogeneity was significant (I^2 = 80.7%, P < 0.001). ACT improved OS in low-quality studies (HR = 0.65; 95% CI = 0.52–0.82), and heterogeneity was not significant (I^2 = 4.7%, P = 0.396). Subgroup analysis according to sample size showed that ACT had no significant effect on OS in studies with ≥ 200 participants (HR = 0.89; 95% CI = 0.66–1.19) and < 200 participants (HR = 0.65; 95% CI = 0.38–1.13). Heterogeneity was significant in studies with ≥ 200 participants (I^2 = 71.9%, P = 0.002) and < 200 participants (I^2 = 78.4%, P < 0.001). Subgroup analysis according to scale of study showed that ACT had no significant effect on OS in single institution (HR = 0.69; 95% CI = 0.45–1.07) and multicenter (HR = 0.99; 95% CI = 0.75–1.30) studies. Heterogeneity was significant in single institution (I^2 = 78.7%, P < 0.001) and multicenter (I^2 = 52.8%, P = 0.06) studies. Subgroup analysis based on previous resection of extra PM showed that ACT had no significant effect on OS in studies without previous resection of extra PM (HR = 0.75; 95% CI = 0.52–1.08) and those with previous resection of extra PM (HR = 0.86; 95% CI = 0.57–1.29). Heterogeneity was significant in studies without previous resection of extra PM (I^2 = 79.9%, P < 0.001) and those with previous resection of extra PM (I^2 = 51%, P = 0.07). Subgroup analysis based on positive hilar/mediastinal LNM showed that ACT had no significant effect on OS in patients without positive hilar/mediastinal LNM (HR = 0.74; 95% CI = 0.49–1.14) and those with positive hilar/mediastinal LNM (HR = 0.80; 95% CI = 0.57–1.14).

Table 1 Characteristics of included studies

Author	Year	Country	Number (CT/NCT)	Gender (M/F)	Age mean ± SD/median (range)	Follow-up mean ± SD/median (range)	CR	OM	NOS score
Irshad [25]	2001	Canada	49 (16/33)	55 (32/17)	NR	NR	FL	OS	6
Munoz [26]	2007	Spain	55 (26/29)	55 (36/19)	64.5 (41–80)	NR	FL, IR, XELOX	OS	5
Borasio [27]	2011	Italy	137 (16/121)	137 (82/55)	63.8 ± 9.1	41.6 ± 27.6	NR	OS	6
Kaira [28]	2011	Japan	80 (42/38)	80 (53/27)	66 (31–81)	Median, 71	5-FU	OS	6
Kim [29]	2012	Korea	105 (94/11)	105 (64/41)	67.2 ± 10.4	Median, 35.9	FL, IR, XELOX	OS	7
Turan [30]	2014	Turkey	108 (52/56)	108 (58/50)	56 (23–78)	25 (3–107)	5-FU, OX, IR,BV	OS	6
Zampino [31]	2014	Italy	178 (69/109)	NR	61 (19–82)	48 (3.6–172.8)	5-FU, OX, IR	OS	8
Cho [32]	2015	Korea	615 (461/154)	615 (361/254)	58.7 ± 10.4	31 (2–211)	NR	OS	6
Guerrera [33]	2016	Italy	188 (110/78)	188 (109/79)	66 (58–72)	Median, 45	NR	OS	5
Pages [34]	2016	France	354 (122/232)	354 (196/158)	64.1 ± 10.8	42 (1–117)	NR	OS	6
Park [35]	2016	Korea	221 (176/45)	221 (141/80)	62 (30/85)	Median, 34.7	5-FU, FOLFOX, FOLFIRI	DFS,OS	8
Karim [36]	2017	Canada	377 (113/264)	377 (224/153)	64 (17–87)	NR	5-FU, OX, IR	OS	8
Kim [9]	2017	Korea	129 (99/30)	129 (77/52)	56 (33–76)	46.4 (9–111)	5-FU,XEL	DFS	8
Nakajima [37]	2017	Japan	511 (237/274)	NR	NR	NR	FOLFOX, FOLFIRI	OS	7
Park [38]	2017	Korea	91 (63/28)	91 (62/29)	63 (35–83)	46 (11–126)	5-FU, FOLFOX, FOLFIRI	DFS	6
Shiomi [39]	2017	Japan	100 (56/44)	100 (56/44)	64.7 ± 10	Median, 80	OX, IR	OS	6
Menna [40]	2018	Italy	203 (27/176)	203 (115/88)	61.7 ± 14.5	39 (7–154)	BV	OS	7
Imanishi [41]	2019	Japan	384 (192/192)	384 (212/172)	65 (29–85)	54 (0.24–108)	5-FU, OX, IR	OS,DFS	9

CT, chemotherapy; *NCT*, nonchemotherapy; *CR*, chemotherapy regimens; *OM*, outcome measures; *5-FU*, fluorouracil; *IR*, irinotecan; *LV*, leucovorin; *OX*, oxaliplatin; *BV*, bevacizumab; *FL*, fluorouracil plus leucovorin; *XEL*, capecitabine; *FOLFOX*, FL plus OX; *XELOX*, XEL plus OX; *FOLFIRI*, 5-FU plus LV plus IR; *NOS*, Newcastle–Ottawa Scale; *NR*: not reported; *OS*, overall survival; *DFS*, disease-free survival

Table 2 Results of quality assessment using the Newcastle–Ottawa Scale for cohort studies

Author	Selection				Comparability		Outcome			Total score
	REC	SNEC	AE	DO	SC	AF	AO	FU	AFU	
Irshad [25]	1	1	1	1	1	0	1	0	0	6
Munoz [26]	1	1	1	1	0	0	1	0	0	5
Borasio [27]	1	1	1	1	0	0	1	0	1	6
Kaira [28]	1	1	1	1	0	0	1	0	1	6
Kim [29]	1	1	1	1	0	0	1	1	1	7
Turan [30]	1	1	1	1	0	0	1	1	0	6
Zampino [31]	1	1	1	1	0	1	1	1	1	8
Cho [32]	1	1	1	1	0	0	1	1	0	6
Guerrera [33]	1	1	1	1	0	0	1	0	0	5
Pages [34]	1	1	1	1	0	0	1	1	0	6
Park [35]	1	1	1	1	1	0	1	1	1	8
Karim [36]	1	1	1	1	1	0	1	1	1	8
Kim [9]	1	1	1	1	1	0	1	1	1	8
Nakajima [37]	1	1	1	1	0	0	1	1	1	7
Park [38]	1	1	1	1	0	0	1	0	1	6
Shiomi [39]	1	1	1	1	0	0	1	1	0	6
Menna [40]	1	1	1	1	0	0	1	1	1	7
Imanishi [41]	1	1	1	1	1	1	1	1	1	9

REC, representativeness of the exposed cohort; *SNEC*, selection of the nonexposed cohort; *AE*, ascertainment of exposure; *DO*, demonstration that outcome of interest was not present at start of study; *SC*, study controls for age; *AF*, study controls for any additional factors (chemoradiotherapy and other control factors); *AO*, assessment of outcome; *FU*, follow-up long enough for outcomes to occur; *AFU*, adequacy of follow-up of cohorts; "1" means that the study is satisfied the item and "0" means the opposite situation

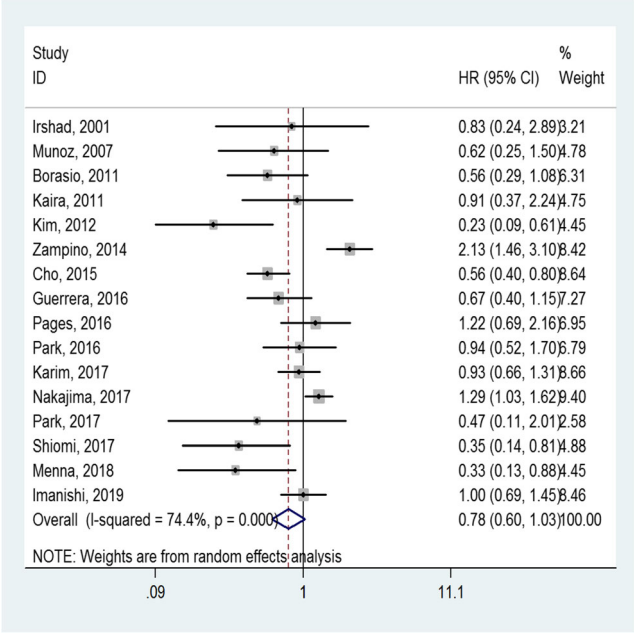

Fig. 2 Forest plot for the association between adjuvant chemotherapy and OS in patients after resection of pulmonary metastasis from colorectal cancer

Heterogeneity was not significant in patients without positive hilar/mediastinal LNM ($I^2 = 42.3\%$, $P = 0.123$) and heterogeneity was significant in patients with positive hilar/mediastinal LNM ($I^2 = 81.5\%$, $P < 0.001$). Meta-regression analysis showed that these factors were not the source of heterogeneity (all $P > 0.05$).

Effect of ACT on DFS

A total of four articles on ACT [9, 35, 38, 41] were included, with 508 patients undergoing ACT and 295 patients without ACT. Heterogeneity was not significant ($I^2 = 30.7\%$, $P = 0.228$). The fixed-effects model showed that ACT had no significant effect on DFS in patients after resection of PM from CRC (HR = 0.91; 95% CI = 0.74–1.11; $P = 0.339$; Fig. 3).

Effect of BV on OS

A total of two articles on BV [30, 40] were included, with 82 patients undergoing adjuvant BV and 229 patients without adjuvant BV. Heterogeneity was not significant

Table 3 Subgroup and meta-regression analyses

Subgroup	No. of studies	Pooled HR (95% CI)		Meta-regression	Heterogeneity	
		Fixed	Random	*P* value	I^2 (%)	*P* value
Location						
Asia	8	0.92 (0.79–1.07)	0.71 (0.48–1.05)	0.505	76.8	0.0
Western	8	1.02 (0.85–1.24)	0.85 (0.56–1.30)		74.7	0.0
NOS score						
High-quality	7	1.15 (1.00–1.33)	0.93 (0.64–1.36)	0.215	80.7	0.0
Low-quality	9	0.65 (0.53–0.80)	0.65 (0.52–0.82)		4.7	0.396
Sample size						
≥ 200	7	0.98 (0.85–1.12)	0.89 (0.66–1.19)	0.427	71.9	0.002
< 200	9	0.92 (0.73–1.16)	0.65 (0.38–1.13)		78.4	0.0
Scale of study						
Single institution	10	0.81 (0.67–0.97)	0.69 (0.45–1.07)	0.87	78.7	0.0
Multicenter	6	1.09 (0.93–1.28)	0.99 (0.75–1.30)		52.8	0.06
Resection of extra pulmonary metastases						
No	10	0.88 (0.75–1.02)	0.75 (0.52–1.08)	0.795	79.9	0.0
Yes	6	1.11 (0.91–1.35)	0.86 (0.57–1.29)		51	0.07
Positive lymph nodes						
No	6	0.84 (0.64–1.10)	0.74 (0.49–1.14)	0.706	42.3	0.123
Yes	10	0.99 (0.87–1.13)	0.80 (0.57–1.14)		81.5	0.0

HR, hazard ratio; *CI*, confidence interval

(I^2 = 0.0%, *P* = 0.953). The fixed-effects model showed that adjuvant BV had no significant effect on OS in patients after resection of PM from CRC (HR = 0.79; 95% CI = 0.42–1.50; *P* = 0.474; Fig. 4).

Sensitivity analysis

We conducted a sensitivity analysis of prognosis (OS) in patients receiving ACT after resection of PM from CRC.

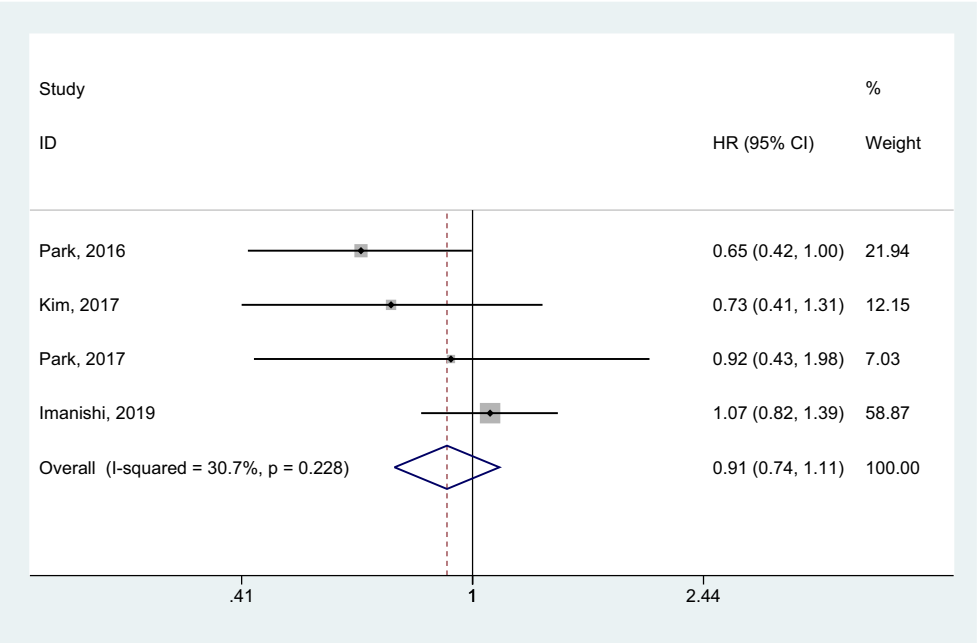

Fig. 3 Forest plot for the association between adjuvant chemotherapy and DFS

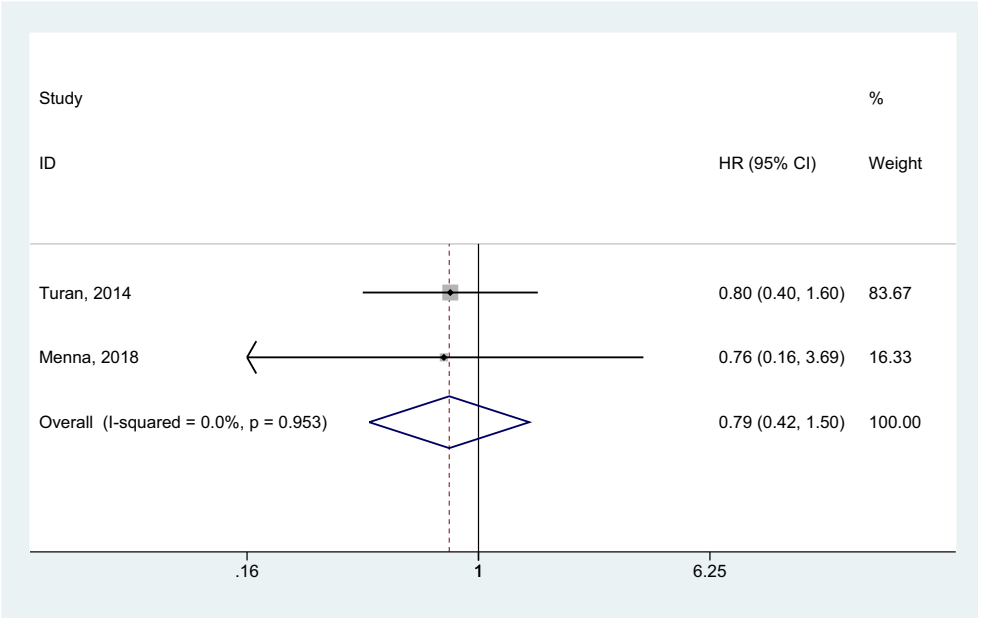

Fig. 4 Forest plot for the association between bevacizumab and OS

Included studies were deleted item by item to evaluate the effect of a single study on the pooled analysis. The pooled analysis was not substantially changed and was robust (Fig. 5).

Publication bias

The Egger's and Begg's test showed that there was no obvious publication bias in the studies of the effect of ACT on OS in patients after resection of PM from CRC (*P* value for Egger: 0.024; Fig. 6a; *P* value for Begg: 0.115; Fig. 6b).

Discussion

Compared with LM from CRC, suggestions for comprehensive treatment of PM from CRC are scarce, which is related to the disease characteristics of CRC. LM from CRC is found in > 80% of patients with advanced CRC. LM often becomes a

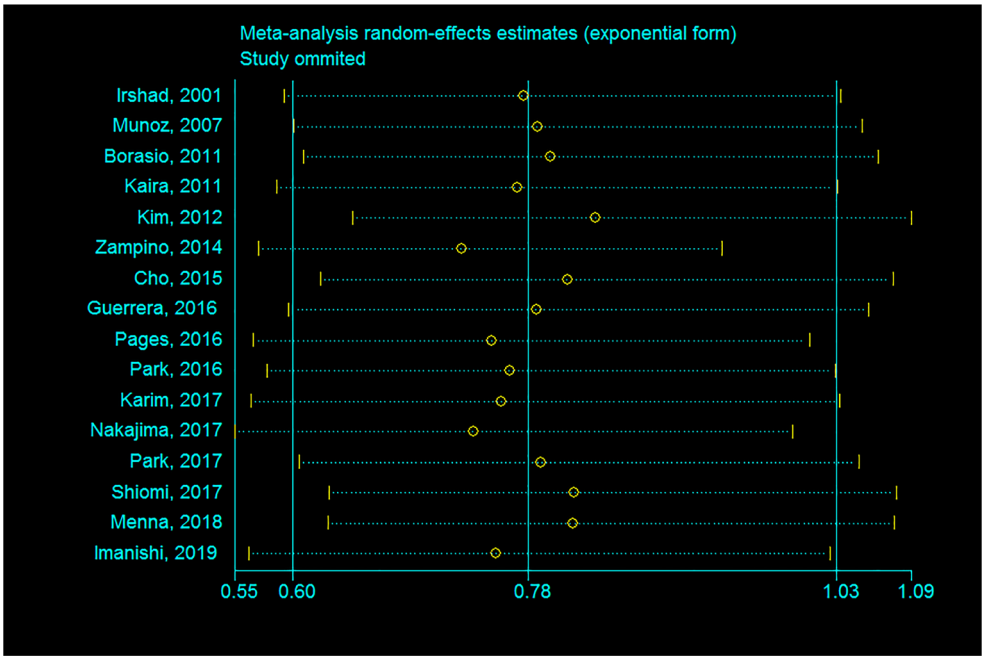

Fig. 5 Sensitivity analysis of prognosis (OS) in patients receiving adjuvant chemotherapy after resection of pulmonary metastasis from colorectal cancer

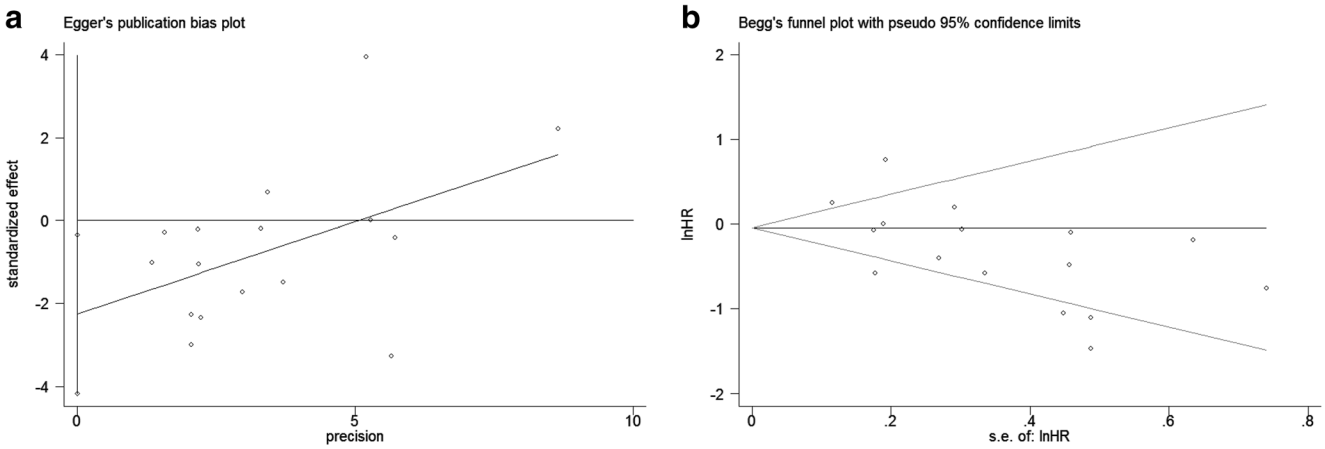

Fig. 6 Publication bias plot of prognosis (OS) in patients receiving adjuvant chemotherapy after resection of pulmonary metastasis from colorectal cancer

determinant of prognosis, and approximately 50% of CRC patients die from LM. However, the median survival time of patients with PM from CRC who have not been treated is only 5–7 months. Although the prognosis of patients is improved by surgery, it is still not ideal. Thus, current research is focused on how to improve the prognosis of patients treated with surgery [42, 43]. Although the European Society for Medical Oncology (ESMO) recommends referencing LM and ACT for patients after resection of PM, the biology of LM and PM differs [44]. Therefore, the purpose of our study was to explore whether patients could benefit from ACT after resection of PM.

This meta-analysis included 18 articles with a total of 3885 patients. Our study showed that ACT had no significant effect on OS in patients after resection of PM from CRC. Two recent combined studies showed that ACT did not improve OS in patients after resection of LM from CRC [45, 46], which is consistent with our findings. Some researchers believe that ACT can improve the prognosis of patients after resection of PM from CRC [29, 32, 39, 40]. The possible reasons for our negative outcomes are as follows. (1) The progress of PM is slow, and this inert biological behavior may weaken the survival benefit of ACT. (2) The proportion of patients with high-risk factors is high in studies with improving prognosis. Shiomi et al. [39] reported that the proportion of patients with DFI < 36 months was 78%. However, only a small proportion of patients have high-risk factors in studies that do not improve prognosis. For example, Park et al. [35] suggested that the proportion of patients with CEA levels ≥ 5 ng/ml was only 20.9% and that simple metastasis resection can achieve good prognosis, which may lead to the effect of ACT being less obvious. (3) There were differences in ACT regimen. Most of the included studies that did not benefit from ACT were based on 5-fluorouracil (5-FU) monotherapy. For example, Imanishi et al. [41] showed that 71% of patients received 5-FU alone in surgery plus ACT group. Mitry et al. [47] showed that 5-FU did not improve the prognosis of patients after resection of metastasis from CRC, and this study was consistent with our results. The standard chemotherapy regimen for advanced colon cancer is fluorouracil + leucovorin + oxaliplatin (FOLFOX) or oxaliplatin + capecitabine (XELOX), which is more effective than 5-FU [48, 49]. It is unclear whether the ACT regimen in our study, including oxaliplatin-based will lead to favorable results, but this was not evident from the study by Nakajima et al. at least [37] (HR = 1.29; 95% CI = 1.03–1.62). However, it is unknown whether more aggressive ACT regimens will be tolerated by patients after resection of PM from CRC, and whether they will bring survival benefits. We also look forward to more oxaliplatin-based combination chemotherapy research to provide more guidance. Our subgroup analysis showed that ACT had no significant effect on OS in some of the patients with high-risk factors, such as previous resection of extra PM (HR = 0.86; 95% CI = 0.57–1.29; $P = 0.461$) and positive hilar/mediastinal LNM (HR = 0.76; 95% CI = 0.57–1.12; $P = 0.165$). This may have been related to the low proportion of patients with these high-risk factors. For example, Munoz et al. [26] showed that only 18.2% of patients had extra PM, and Borasio et al. [27] showed that only 5.1% of patients had hilar/mediastinal LNM. Our subgroup analysis also demonstrated that ACT improved OS in low-quality studies (HR = 0.65; 95% CI = 0.52–0.82; $P < 0.01$), which may have been related to the insufficient correction of important confounding factors.

Our pooled analysis showed that ACT had no significant effect on DFS in patients after resection of PM from CRC. Only Park et al. [35] considered that ACT improves DFS in patients after resection of PM from CRC. They also determined that ACT improves the prognosis of low-risk patients in particular, which is consistent with our previous

explanation and related to the short survival expectation of high-risk patients after surgery.

The emergence of molecular targeted agents has extended the OS of patients with metastatic CRC (mCRC) from 6 to 12 months to nearly 30 months [50]. However, BV, as a commonly used anti-vascular endothelial growth factor (VEGF)/VEGF receptor-targeted agent, improves progression-free survival in patients with mCRC treated with FOLFOX, XELOX, capecitabine, 5-FU + leucovorin + irinotecan (FOLFIRI), or 5-FU + leucovorin + oxaliplatin + irinotecan (FOLFOXIRI). Therefore, the National Comprehensive Cancer Network recommends a combination of BV and oxaliplatin-based chemotherapy as first-line treatment for mCRC; however, most studies were in patients with nonresectable metastatic lesions [51–53]. Our study showed that adjuvant BV had no significant effect on OS (HR = 0.79; 95% CI = 0.42–1.50; P = 0.474), which may be related to the low number of studies that included BV monotherapy. More effective combinations of ACT in the future need to be validated.

Patients do not benefit from ACT after resection of PM from CRC; therefore, it is unknown whether these patients would benefit from perioperative chemotherapy, even though perioperative chemotherapy for LM from CRC has made remarkable achievements [54]. Hawkes et al. [55] confirmed that perioperative ACT reduced the size of metastases in 62% of patients with PM from CRC, the disease control rate reached 92%, and the toxicity of ACT did not increase, but there was no significant improvement in OS. Pages et al. [34] found that neoadjuvant chemotherapy did not improve the prognosis of patients (HR = 2.43; 95% CI = 0.82–7.18; P = 0.1). Establishment of a scoring system based on prognostic factors and screening of patients with poor prognosis for perioperative ACT seem to be reasonable suggestions, and more research is needed to verify the effect of perioperative chemotherapy on prognosis.

We found high heterogeneity in the analysis of the efficacy of ACT in patients after resection of PM from CRC. Subgroup and regression analyses showed that location, NOS score, sample size, scale of study, resection of extra PM, and positive hilar/mediastinal LNM were not sources of heterogeneity. We concluded that heterogeneity may have arisen from the differences in the basic characteristics of the study populations.

Our study had some limitations. The toxicity of ACT was not studied in the included articles, and the research was incomplete. The basic characteristics of patients (such as lung resection margins) and ACT regimens in each study were different or not reported, resulting in high heterogeneity of our results. Our study was restricted to English language articles, and thus other suitable studies may have been excluded, leading to bias. Furthermore, the included studies were all cohort studies and not randomized controlled trials, which may have led to lower quality in the methodology. Moreover, because each of the included studies included multiple ACT regimens (such as 5-FU, irinotecan, and/or oxaliplatin), we were unable to perform a subgroup analysis of different ACT regimens, which might lead to several more efficient ACT regimens (such as oxaliplatin-based) not being further studied. This is the focus of our follow-up research. Despite these limitations, our meta-analysis is believed to be the first study of the efficacy of ACT in patients after resection of PM from CRC and may be important for guiding the treatment of such patients after surgery.

Conclusions

Our study demonstrated that ACT did not improve OS and DFS in patients after resection of PM from CRC, nor did adjuvant BV improve OS after resection of PM from CRC. In the future, larger studies and better-designed clinical research are needed to resolve the controversy and to investigate oxaliplatin-based ACT for PM from CRC.

Authors' contributions HMX designed the research. CZ took part in designing the study, extracted the data, analyzed the date, and drafted the manuscript. YET collected the data and analyzed the date. All the authors approved the final version.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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