Comparative survival outcome of synchronous and metachronous brain metastasis from colorectal cancer: A meta-analysis

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Abstract. Synchronous and metachronous brain metastases (BM) are increasingly recognized in patients with colorectal cancer (CRC). This study aimed to assess whether the timing of BM development affects survival outcomes by conducting a systematic review and meta-analysis. A comprehensive search of the Cochrane Library, Embase and MEDLINE databases was performed, covering studies from January 1900 to December 2023. To compare survival outcomes between synchronous and metachronous BM, hazard ratios (HRs) for overall survival (OS) were extracted from the included studies and pooled using a random-effects model. The systematic review included nine retrospective cohort studies comprising 910 patients with BM from CRC. Meta-analysis results showed no significant difference in OS between patients with synchronous and metachronous BM (HR, 0.90; 95% confidence interval, 0.59-1.38; P=0.63). In conclusion, this meta-analysis suggests that the timing of BM development does not impact OS in patients with BM from CRC.

Introduction

Owing to advancements in therapeutic approaches, the overall survival (OS) rates of patients diagnosed with colorectal cancer (CRC) have increased (1). However, as survival rates have improved, a corresponding increase in the incidence of brain metastasis (BM) has been observed in patients with CRC (2,3), with the reported occurrence of BM arising from CRC ranging from 0.1-11% (2). Regarding the timing of BM development, synchronous BM indicates that metastasis occurs around the same time or shortly after a primary cancer. By contrast, metachronous BM refers to cases where a significant interval exists between the diagnosis of a primary tumor and the development of BM (4). The exact time interval for defining synchronous or metachronous BM remains inconclusive in the literature.

The impact of the timing of BM development has been discussed in several studies; however, most of these studies have primarily focused on patients with BM originating from lung cancer or renal cell carcinoma (4-6). Despite the emergence of studies focusing on treatment strategies and prognostic factors for survival outcomes in patients with BM from CRC, uncertainties remain regarding treatment strategies and prognostic factors (7-9), and studies on the impact of synchronous BM and metachronous BM specifically in patients with CRC are limited.

According to the literature, synchronous BM is more likely to be associated with poorly differentiated histology, right-sided CRC and aggressive histopathological features, including higher tumor and lymph node stages (10). Distinguishing between synchronous and metachronous BM may impact the choice of therapeutic interventions, such as considering more aggressive approaches for synchronous BM or prioritizing systemic therapy for metachronous cases (6). Moreover, understanding the timing of BM can facilitate discussions with patients regarding their prognosis, enabling clinicians to tailor communication and support strategies based on the expected disease course. Therefore, the aim of the present study was to assess whether the timing of BM development affects the survival outcomes of patients with BM from CRC by performing a comprehensive review of the published literature and a meta-analysis to quantitatively assess this clinical question.

Materials and methods

Study protocol. A systematic review and meta-analysis was performed according to the guidelines outlined in the Cochrane Handbook for Systematic Reviews and Interventions (11). Reporting of the results of the present study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The present study was registered on the PROSPERO online platform to ensure transparency

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and accessibility of the research protocol (registration no. CRD42023430369; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=430369).

Study selection. A comprehensive search in the Cochrane Library (https://www.cochranelibrary.com), Embase (https://www.embase.com) and MEDLINE (https://www.wolterskluwer.com/zh-tw/solutions/ovid/ovid-medline-901) electronic databases was performed, covering the period from January 1900 to December 2023. The key words were 'colorectal cancer' and 'brain metastasis'. No language restrictions were applied during the search process to ensure inclusivity. A total of two investigators (TCT and KYC) independently performed the searches and identified relevant studies for potential inclusion. Any discrepancies were resolved through consensus between the investigators or by consulting a senior reviewer (YC).

Eligibility criteria. The following studies were included in the analysis: i) Prospective, retrospective cohort and case-control studies; ii) studies specifically focusing on patients diagnosed with BM from CRC; and iii) studies reporting survival outcomes for patients with synchronous and metachronous BM. The following studies were excluded from the analysis: Case reports, editorials, letters to the editor, review articles and conference abstracts. The application of these criteria ensured the relevance and appropriateness of the studies included in the analysis.

Data extraction. The data extraction process was performed independently by two investigators (TCT and KYC). The following information was extracted from eligible studies: First author; publication year; inclusion criteria; definition of synchronous brain BM; number of patients; and relevant survival outcomes. This approach ensured the accurate and comprehensive collection of data from the selected studies.

Quality assessment. To assess the risk of bias in the included literature, the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was utilized (12). A total of two investigators (TCT and KYC) independently performed the critical appraisal of the included studies using this tool. When disagreements between the assessors occurred, a third investigator (YC) was consulted to reach a consensus on the item in question.

Statistical analysis. Statistical analyses were performed utilizing the meta package within R software (version R-4.4.2; https://www.r-project.org/). To evaluate the comparative survival outcomes of patients with synchronous and metachronous BM, the hazard ratios (HRs) for OS were acquired based on the survival analysis results from the included studies. These HRs were then pooled with the inverse variance method. The meta-analysis was performed using a random-effects model, and the effect sizes were presented alongside their corresponding 95% confidence intervals (CIs). Heterogeneity among the included studies was assessed using the I^2 statistics proposed by Higgins *et al* (13). I^2 <25% indicated low heterogeneity, I^2=25-50% denoted moderate heterogeneity and I^2 >50% demonstrated high heterogeneity (14).

Results

Study selection. The comprehensive search strategy yielded a total of 6,449 references from the Cochrane library, Embase and MEDLINE electronic databases. After the initial screening of titles and abstracts, 582 duplicate references and 5,806 references deemed irrelevant to the study aims were identified and excluded. Subsequently, the remaining 61 studies underwent a full-text review. A total of nine studies met the inclusion criteria and were included in the final analysis. Fig. 1 presents a visual representation of the study selection process.

Study characteristics. A total of nine retrospective cohort studies (15-23), published between 2002 and 2023, were included in the analysis. These studies collectively involved 910 patients diagnosed with BM from CRC. The definition of synchronous BM varied among the nine studies: In five studies, synchronous BM was defined as occurring within the first (16), second (22), third (20), sixth (19) or twelfth (17) month after the diagnosis of primary CRC; however, the remaining four studies (15,18,21,23) did not provide a specific or explicit definition of synchronous BM. The basic characteristics of the included studies are presented in Table I.

Quality assessment of the included studies. A quality assessment of the included studies using the ROBINS-I tool demonstrated that 4 studies were classified as having a serious risk of bias, whilst the remaining 5 studies were deemed to have a moderate risk of bias. Fig. 2 presents a graphical representation of the risk-of-bias assessment.

Comparative survival outcome. A total of three studies (15,20,21) were excluded from the meta-analysis due to the absence of HR data. The meta-analysis of six studies that compared the survival outcomes of patients with synchronous BM and metachronous BM revealed no statistically significant difference in OS between the two groups (HR, 0.90; 95% CI, 0.59-1.38; Fig. 3). Notably, no statistical heterogeneity was observed among these studies (I^2=0%).

Discussion

The present study performed a comprehensive review of the existing literature and a meta-analysis to assess the relationship between BM timing and survival outcomes in patients with CRC. The results demonstrated no significant difference in OS between patients with synchronous or metachronous BM. This finding suggests that the timing of BM diagnosis may not be a substantial factor in OS outcome for patients with CRC, highlighting the importance of individualized treatment strategies that consider other patient-specific factors.

Previous studies evaluating this relationship in different cancer types yielded mixed results. Flannery *et al* (24) reported that patients with non-small-cell lung cancer and solitary metachronous BM had greater rates of survival compared with those with synchronous BM. Similarly, Ruste *et al* (4) reported lower survival rates in patients with clear cell renal cell carcinoma with synchronous BM compared with those with metachronous BM. However, a more recent study by Potthoff *et al* (5), reported no significant impact of BM timing

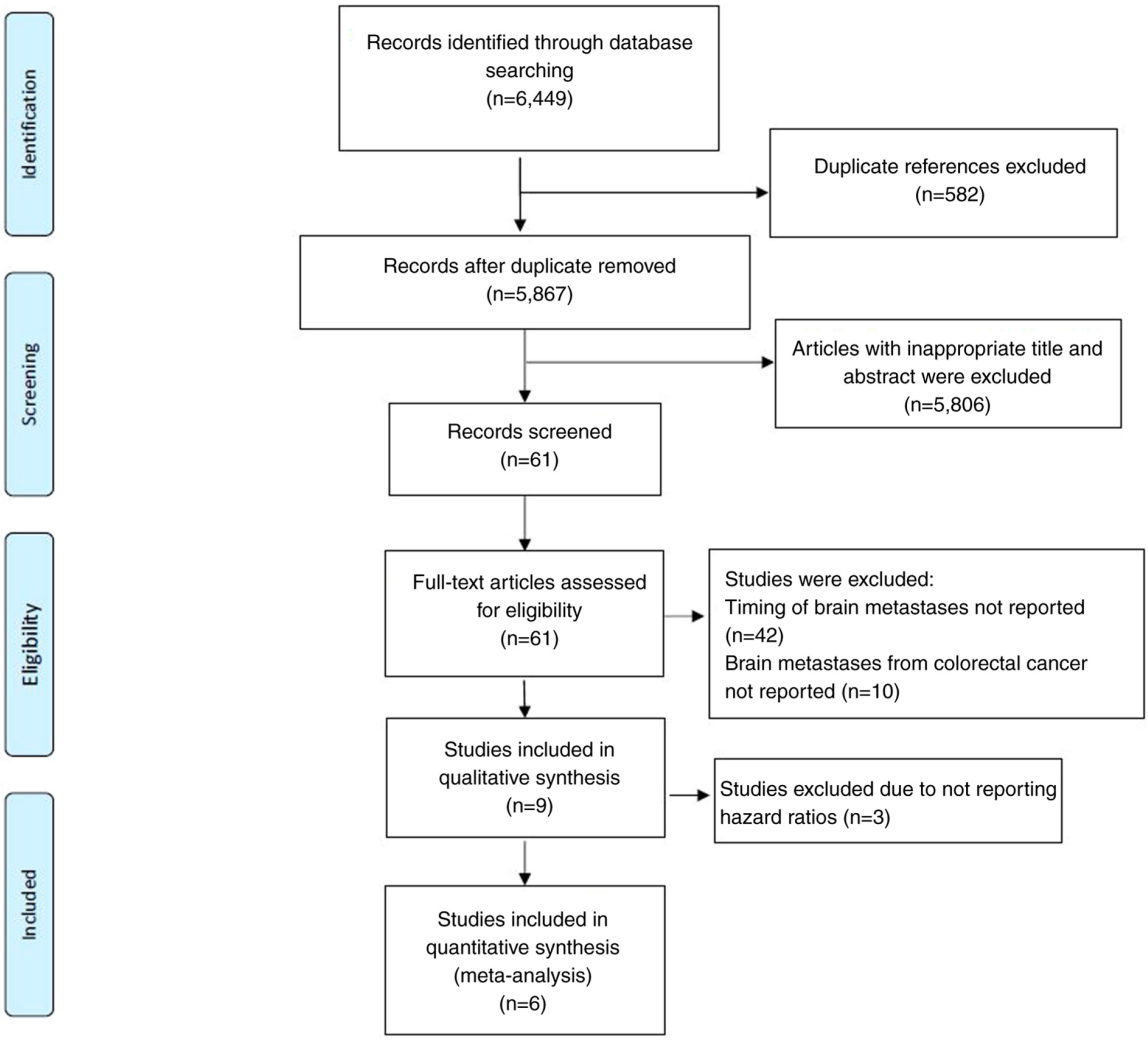

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of the selection of eligible studies.

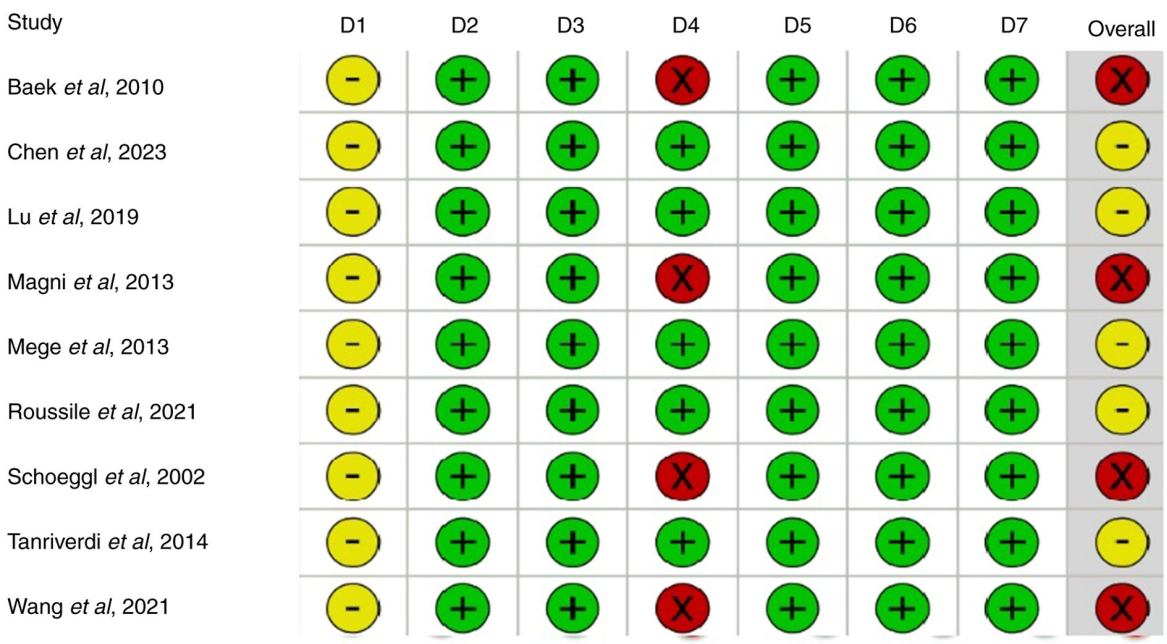

Figure 2. Summary of risk of bias assessment using ROBINS-I tool. Green indicates low risk of bias, yellow indicates moderate risk of bias and red indicates serious risk of bias. D1, bias due to confounding factors; D2, bias in selection of participants into the study; D3, bias in classification of interventions; D4, bias due to deviations from intended interventions; D5, bias due to missing data; D6, bias in measurement of outcomes; D7, bias in selection of the reported result.

Table I. Basic characteristics of the included studies.

First author/s, year	Inclusion criteria	SBM definition	Age at initial diagnosis	Sex	Number of BM	Extracranial metastases		Primary tumor location	Histopathology or grade	Sample size, n		MST, months		HR for OS (SBM vs. MBM)	(Refs.)
						Negative/ positive	Location			SBM	MBM	SBM	MBM		
Baek *et al*, 2011	Patients with symptomatic CRC BM receiving WBRT, RS or surgery	NA	Median: 54 years; range: 19-77 years	Male: 63 (53%) and female: 55 (47%)	1: 58 (50%); 2-3: 31 (26%); and >3: 28 (24%); missing: 1 (0.9%)	6/112	Lung: 89 (75%); intra-19 (16%); abdominal LN: 42 (36%); intra-thoracic/ neck LN: 31 (26%); bone: 43 (36%); and peritoneum: 21 (18%)	Ascending colon: differentiated: Transverse colon: 6 (5%); descending colon: 5 (4%); sigmoid colon: 17 (14%); and rectum: 72 (61%)	Well or moderately 89 (75%); poorly differentiated, mucinous or signet ring cell carcinoma: 15 (13%); and unknown: 14 (12%)	57	61	3.4 (2.5-4.30)	4.6 (3.3-5.9)	NA	(15)
Chen *et al*, 2023	Patients with CRC BM under treatment (local, systemic or combination therapy)	An interval of <1 month between the diagnosis of CRC and the development of BM	<65 years: 33 (51%) and ≥65 years: 32 (49%)	Male: 32 (49.2%) and female: 33 (50.8%)	<4: 43 (78.5%) and ≥4: 22 (21.5%)	16 (24.7%)/ 49 (75.3%)	-Right colon: 10 (15.4%) and left colon: 55 (84.6%)	Adeno-carcinoma: 62 (95.4%); mucinous adenocarcinoma: 1 (1.5%); and carcinoma: 2 (3.1%)		15	50	NA	NA	0.831 (0.438-1.575)	(16)
Lu *et al*, 2019	Patients with CRC BM receiving single treatment including neurosurgery, WBRT or RS, chemotherapy, or multi-disciplinary treatment including neurosurgery plus chemo-therapy or radiotherapy plus chemotherapy	BM within 12 months of diagnosis of the primary CRC	≤60 years: 50 (62.5%) and >60 years: 30 (37.5%)	Male: 52 (65%) and female: 28 (35%)	1: 44 (55%) and ≥2: 36 (45%)	13 (16.25%)/-	Lung metastasis: 56 (70%) and other organ and rectum: metastases: 11 (13.75%)	Right colon: 9 (11.25%); left colon: 21 (26.25%); 50 (62.5%)	NA	6	74	22 (0.5-43.5)	6 (4.5-7.5)	2.16 (0.71-6.63)	(17)
Magni *et al*, 2014	Patients with CRC BM	NA	Median: 58; range:	Male: 25 (61%)	1: 22 (53.7%);	2 (5%)/ 39 (95%)	- Colon: 17 (41.5%)	G1-G2: 20 (48.8%); G3: 7		7	34 (2.3-u)	21.4 (3.2-	4.2 (0.144-	0.52	(18)

Table I. Continued.

First author/s, year	Inclusion criteria	SBM definition	Age at initial diagnosis	Sex	Number of BM	Extracranial metastases		Primary tumor location	Histopathology or grade	Sample size, n		MST, months		HR for OS (SBM vs. MBM)	(Refs.)
						Negative/ positive	Location			SBM	MBM	SBM	MBM		
	undergoing surgical resection, WBRT, SRT and systemic chemotherapy with or without biological agents		23-75; ≤65 years: 29 (70.7%) and >65 years: 12 (29.3%)	and female: 12 (39%)	≥2: 17 (41.5%); and unknown: 2 (4.9%)			and rectum: 24 (58.5%)	(17.1%); and unknown: 14 (34.1%); KRAS mutated: 17 (41.5%); KRAS wild type: 11 (26.8%);and KRAS not reported 13 (31.7%)				5.1)	1.89)	
Mege *et al*, 2013	Patients with CRC BM undergoing surgical resection with or without postoperative WBRT or RS	BM diagnosed within 6 months after the diagnosis of CRC	<65 years: 15 (54%) and >65 years: 13 (46%)	Male: 13 (46%) and female: 15 (54%)	1: 23 (82%) and 2: 5 (18%)	NA	-	Colon: 15 (54%) and rectum: 13 (46%)	NA	12	16	Median OS:12		0.5 (0.1-2.6)	(19)
Roussile *et al*, 2021	Patients with CRC BM undergoing surgical resection or RS with or without postoperative WBRT	BM diagnosed within 3 months after the diagnosis of CRC	<65 years: 160 (44.7%) and ≥65 years: 198 (55.3%)	Male: 205 (57.3%) and female: 153 (42.7%)	1: 198 (56.9%); ≥2: 151 (43.1%); and missing: 96 (27.6%)	49 (13.9%)/ 303 (86.1%)	-	Ascending colon: 71 (20.3%); descending colon: 130 (37.3%); and rectum: 148 (42.4%)	Well or moderately differentiated: 224 (89.2%); poorly differentiated: 27 (10.8%); and missing: 107 (42.8%)	58	300	9.7	4.8	NA	(20)
Schoeggl *et al*, 2002	Patients with CRC BM receiving RS with or without WBRT	NA	Median: Radiosurgery, 69 years and radiosurgery with WBRT, 63 years	Male: 23 (65.7%) and female: 12 (34.3%)	1: 24 (68.6%) and ≥2: 11 (31.4%)	22 (63%)/ 13 (37%)	-	NA	NA	NA	NA	4.5	5.9	NA	(21)
Tanriverdi *et al*, 2014	Patients with CRC BM undergoing surgical resection, WBRT, RS or supportive care	BM diagnosed within 2 months after the diagnosis of CRC	≤65 years: 54 (41%) and >65 years: 79 (59%)	Male: 70 (53%) and female: 63 (47%)	1: 15 (11%); 2-3: 41 (31%); and >3: 77 (58%)	15 (11%)/ 118 (89%)	-	Rectum: 74 (56%); recto-sigmoid and sigmoid colon: 23 (17%); transverse colon: 12 (9%); and	Grade 2: 21 (16%); grade 3: 93 (70%); and unknown: 19 (14%)	19	114	26.4 (20.0-32.9)	25.0 (21.5-28.4)	1.14 (0.31-4.13)	(22)

Table I. Continued.

First author/s, year	Inclusion criteria	SBM definition	Age at initial diagnosis	Sex	Number of BM	Extracranial metastases		Primary tumor location	Histopathology or grade	Sample size, n		MST, months		HR for OS (SBM vs. MBM)	(Refs.)
						Negative/ positive	Location			SBM	MBM	SBM	MBM		
								ascending colon and cecum: 24 (18%)							
Wang *et al*, 2021	Patients with CRC BM with or without surgical resection for BM	NA	Median, 63 years; range: 37-72 years	Male: 41 (63.1%) and female: 24 (36.9%)	1: 37 (56.9%) and ≥2: 28 (43.1%)	20 (30.8%)/ 45 (59.2%)	-	Colon cancer: 24 (36.9%) and rectal cancer: 41 (63.1%)	CEA negative: 25 (38.5%); CEA positive: 35 (53.8%); and unknown: 5 (7.7%)	4	61	NA	NA	0.802 (0.231-2.783)	(23)

BM, brain metastasis; CRC, colorectal cancer; HR, hazard ratio; MBM, metachronous brain metastasis; MST, median survival time; NA, not applicable; OS, overall survival; RS, radiosurgery; SBM, synchronous brain metastasis; SRT, stereotactic radiotherapy; WBRT, whole brain radiotherapy; u, undefined time; CEA, carcinoembryonic antigen.

Figure 3. Forest plot for the overall survival of patients with synchronous vs. metachronous brain metastasis from colorectal cancer. HR, hazard ratio; SE, standard error; CI, confidence interval; IV, inverse variance; df, degrees of freedom.

on survival in a broader patient population with BM from several primary cancers. Notably, the inclusion of different primary cancer types in their study led to substantial variations in the characteristics of the included patients. The present study focused on BM from CRC, and the results demonstrated that the synchronous or metachronous nature of BM did not significantly affect the survival outcome.

Currently, the primary local treatment options for BM from CRC consist of surgical resection, radiotherapy or a combination of both (8). Surgical resection is considered feasible and appropriate for specific cases of BM from CRC. This approach is often employed for solitary or limited BMs and can help in reducing tumor burden and alleviating symptoms (25). Radiosurgical modalities, such as Gamma Knife or CyberKnife, are specialized techniques that deliver highly focused radiation to the BM while minimizing the impact on surrounding healthy tissues. These modalities are commonly used for small and well-defined metastatic lesions that may not be amenable to surgical resection (26). Whole brain radiotherapy is employed when multiple metastases are present throughout the brain, and can be used as adjuvant therapy following surgical resection to target remaining or potential microscopic metastases (27). We hypothesize that the status of BM as synchronous or metachronous can potentially impact subsequent treatment approaches, which in turn may affect OS. Thus, the need for further research in this area is crucial.

Although the results of the present study demonstrated that the synchronous or metachronous nature of BM did not significantly impact the survival outcome, these findings should be interpreted with caution. Despite no significant statistical heterogeneity demonstrated in the meta-analysis results, differences were observed among the included studies. For instance, in the study by Mege *et al* (19), the mean OS after BM was 12 months, which is similar to that reported in the study by Potthoff *et al* (5), which was not included in this research as it included several types of BM rather than just BM from CRC. In the study by Potthoff *et al*, the mean survival

was also around 12-13 months. However, Roussile *et al* (20), reported a worse survival rate, with the OS for the synchronous and metachronous groups demonstrated to be 9.7 and 4.8 months, respectively. These differences may be attributed to the complex nature of the patients with cancer themselves and variations in treatment modalities and patient selection. Furthermore, the present study was unable to ascertain whether the treatments received by the synchronous and metachronous groups differed within each study.

The present meta-analysis has several limitations that should be acknowledged. Firstly, all the studies included in the analysis were retrospective in nature. As patients with cancer belong to a complex population, multiple potential factors can introduce bias and limitations in data collection, which may have impacted the accuracy and reliability of the findings. For example, our previous study (8) reported that surgery for CRC BM had improved survival outcomes compared with radiotherapy. However, the analysis in the present study focused on BM timing. The lack of detailed treatment information in the present analysis may impact the accuracy of the results. Secondly, despite the fact that a comprehensive search was performed, the number of studies that ultimately met the inclusion criteria and reported synchronous and metachronous BM was relatively small. Furthermore, certain studies included in the analysis did not provide comparative results between the two groups, but rather reported noncomparative measures, such as median survival times. Therefore, direct comparative data for the analysis were limited. Thirdly, owing to insufficient information in the included studies, the present study was unable to determine whether the distributions of treatments differed between the synchronous and metachronous BM groups within each study. Fourthly, the definition of synchronous and metachronous BM varied across the included studies and certain studies did not explicitly define or specify the timing criteria for synchronous BM. Lastly, the impact of primary tumor location on outcomes is also worth exploring, such as comparisons between the rectum and colon or between the right-sided and left-sided colon. However, the studies included in the present analysis did not assess both the timing of BM and the primary tumor location simultaneously. Therefore, a subgroup analysis based on the included studies could not be performed and is an aspect that requires further research in the future. Nevertheless, despite these limitations, the present study is the first meta-analysis to assess this clinical question that comprises large patient samples from multicenter data with low heterogeneity, to our best knowledge. Further research, including large, randomized prospective cohort studies with standardized definitions of synchronous BM and treatment protocols, is warranted.

In conclusion, the findings of the present meta-analysis indicate that there is no difference in OS between patients with synchronous and metachronous BM arising from CRC. Given the limitations of the present study, further research with prospective designs and larger sample sizes is needed to obtain more robust and conclusive evidence.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

TCT contributed to the conceptualization, formal analysis and writing original draft. JS and KYC contributed to statistical analysis consultation, validation and review and editing the manuscript. HML contributed to analysis and interpretation of data, supervision and review and editing of the manuscript. YC contributed to conceptualization, formal analysis, writing original draft, and review and editing the manuscript. TCT and YC confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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