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Original Article

Comparative effectiveness of primary tumor resection versus chemotherapy in patients with asymptomatic unresectable metastatic colorectal cancer: a retrospective cohort study using the target trial emulation framework

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Abstract: Patients who undergo primary tumor resection (PTR) reportedly have significantly higher overall survival (OS) than those who do not undergo this procedure. However, this result is only evident in past retrospective studies, and clinical trial results did not show the same trend. Thus, it remains unclear whether primary tumor resection effectively increases survival in patients with metastatic colorectal cancer (mCRC) across different study designs. We compared the OS of patients with asymptomatic unresectable mCRC who underwent PTR with that of those who did not. This retrospective cohort study was designed to be a target trial emulation of a randomized controlled trial (RCT) that would have compared the effectiveness of PTR versus non-PTR in patients with asymptomatic unresectable mCRC from 2009 to 2017. A systematic review and meta-analysis were conducted to compare the efficacy of PTR and non-PTR in patients with mCRC, and corresponding results were compared. This cohort included 1,132 patients for a per-protocol analysis. The PTR group had non-significantly longer survival (adjusted hazard ratio: 0.70, 95% confidence interval: 0.62-1.01) than the non-PTR group in our cohort. A meta-analysis including five RCTs (1,016 patients) and our cohort found that the PTR group did not have a significantly lower mortality rate than the non-PTR group. The results of this cohort study and previous RCTs suggest that PTR is not associated with improved survival compared to systemic chemotherapy combined with targeted therapy among asymptomatic unresectable mCRC patients. Therefore, routine PTR is not recommended in these patients.

Keywords: Colorectal cancer, primary tumor resection, targeted therapy, survival, trial emulation, meta-analysis

Introduction

Colorectal cancer (CRC) is one of the most common types of cancer and a major cause of cancer-related death worldwide [1]. Approximately 20%-25% of patients with colon cancer worldwide have distant metastases during their initial diagnosis. Patients with metastatic colorectal cancer (mCRC) can be categorized into those with unresectable or resectable tumors based on the feasibility of surgical removal at the metastatic site. Additionally, these patients' primary tumors can either be asymptomatic or symptomatic. If a patient has resectable mCRC and undergoes surgical removal of both the primary and metastatic tumors, their survival rate may improve. However, most patients have unresectable mCRC, accounting for approxi-

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mately 75%-90% of cases [2]. For these patients, some studies suggest that not removing the metastatic tumors but performing surgery to remove the primary tumor can still increase survival. However, other research indicates that removing asymptomatic primary tumors could increase the risk of death. This is due to potential delays in chemotherapy and the possibility of surgical complications [3, 4]. Meanwhile, the National Comprehensive Cancer Network guidelines state that patients should only undergo primary tumor resection (PTR) if they are experiencing symptoms or risk factors related to the initial tumor, such as significant bleeding, obstruction, or perforation (https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf). Otherwise, patients with unresectable mCRC should receive intensive systemic chemotherapy along with a targeted drug as first-line therapy.

If patients have an asymptomatic original tumor and unresectable metastatic disease, PTR should be avoided before chemotherapy begins to reduce the risk of tumor-related problems. PTR combined with chemotherapy did not improve survival time compared to chemotherapy alone according to a recent randomized controlled trial (RCT) [3]. In contrast, patients who undergo PTR have been shown in recent studies to have a significantly longer overall survival (OS) than those who do not undergo this procedure. However, all of these analyses were retrospective [5]. Thus, it remains unclear whether PTR effectively increases the survival rates of patients with mCRC across different study designs.

We conducted a nationwide retrospective cohort study to compare PTR with non-PTR in patients with mCRC during this era of effective targeted therapy combined with chemotherapy. We aimed to determine whether PTR improves survival using an approach that emulates a target trial designed as an RCT. Patients with asymptomatic, unresectable mCRC may differ from those with other types of mCRC based on previous research on PTR therapy. Therefore, we also explored patient survival among various mCRC subgroups. Previous meta-analyses of observational studies [5, 6] have reported on the oncologic results of PTR; however, they did not consider subgroup survival results based on the status of patient tumors (such as asymptomatic or symptomatic and resectable or unresectable mCRC). Furthermore, we conducted a systematic review and meta-analysis to assess the survival advantages of PTR for various subgroups of patients with mCRC.

Materials and methods

Study population

This retrospective cohort study was designed to emulate a target trial based on an RCT, comparing the effectiveness of PTR versus non-PTR in asymptomatic unresectable mCRC patients, utilizing data from The National Health Insurance Database (https://nhird.nhri.edu.tw//en/index.htm) [7] and Taiwan Cancer Registry [8] spanning from January 1, 2009, to December 31, 2017, with components including eligibility criteria, treatment strategies, assignment procedures, outcomes, follow-up, causal contrast of interest, and statistical methods (**Table 1**). The aim of replicating a target trial in observational research is to closely mimic the design of an RCT to minimize inherent biases. This strategy seeks to enhance the reliability and efficiency of the research by employing a study design that closely emulates an RCT [3, 9, 10].

The PTR group was defined as patients who undergo chemotherapy combined with targeted therapy after PTR. The non-PTR group was defined as patients receiving chemotherapy combined with targeted therapy as the initial treatment. The index date was defined as the date on which the patient received the first cycle of targeted therapy during the study period (Table S1). We enrolled patients who underwent at least six cycles of targeted therapy, with an interval shorter than 21 days between consecutive cycles (**Figure 1**). We excluded patients if they (1) were younger than 20 years and older than 74 years; (2) had synchronous left- and right-sided tumors; (3) had ever undergone targeted therapy within 1 year before the diagnosis date; (4) had undergone first-line therapy for fewer than six cycles or had a follow-up duration shorter than 3 months; (5) received targeted therapy with intervals longer than 21 days between consecutive cycles; (6) had an interval between PTR and targeted therapy of <8 days and >56 days; (7) in the non-PTR group, chemotherapy was started more than 45 days after diagnosis; in the PTR group, PTR was performed more than 21 days after diagnosis; or (8)

Table 1. Specification and emulation of a target trial evaluating the effect of PTR versus non-PTR on mCRC using real-world data from Taiwan's NHIRD

Component	Target trial	Emulated
Aim	To evaluate the survival benefit of adding upfront PTR to standard chemotherapy for patients with CRC with an asymptomatic primary tumor and synchronous unresectable metastases.	Same
Eligibility	Eligible patients were aged 20-74 years with histologically proven primary colon cancer, rectosigmoid cancer, or upper rectal adenocarcinoma and with between one and three unresectable metastatic diseases confined to the liver, lungs, distant lymph nodes, or peritoneum, evident on computed tomography (CT) or chest X-ray photographs.	Similar to the target trial, we set more criteria to identify unresectable mCRC in the NHIRD as follows: 1. We included patients with metastasectomy (lung and liver) before targeted therapy but excluded those with distant lymph nodes or peritoneum because these are hard to define in NHIRD and the cancer registry. 2. We excluded patients with obstruction and perforation.
Treatment strategies	1. Primary tumor resection plus chemotherapy: between 8 and 56 days postoperatively, chemotherapy with either mFOLFOX6 plus bevacizumab or CapeOX plus bevacizumab was initiated. 2. Chemotherapy with mFOLFOX6 plus bevacizumab or CapeOX plus bevacizumab.	Similar to the target trial, we set more targeted therapies and chemotherapy, such as cetuximab and irinotecan base.
Treatment assignment	Eligible patients are randomly assigned to either treatment group (the same probability of treatment assignment between the two groups).	Using propensity score approaches to generate a study population with a similar probability of treatment assignment between the two groups.
Follow-up	Follow-up begins at treatment assignment and ends at death or loss to follow up, whichever occurs first. Follow-up period: 3 years after accrual completion.	Similar to the target trial (the assignment and initiation of the treatment occur simultaneously in the real-world scenario).
Outcome	OS PFS	OS
Causal contrast	Primary analysis: ITT effect (i.e., the effect of being assigned to PTR+targeted therapy versus targeted therapy alone at baseline, regardless of whether patients continue following the assigned treatment after baseline). Sensitivity analysis: per-protocol effect (i.e., the effect of following the treatment strategies in the study protocol at baseline and after baseline).	The same (using on-treatment analysis, the analog of per-protocol) six cycles. The criteria were based on the fact that biweekly adjuvant chemotherapy for at least six cycles has become the standard therapy for patients with mCRC.
Statistical analysis	Cox proportional hazards model.	Same

Abbreviations: NHIRD, National Health Insurance Research Database; mCRC, metastatic colorectal cancer; PTR, primary tumor resection; CRC, colorectal cancer; mFOLFOX6, modified FOLFOX6; FOLFOX, oxaliplatin, leucovorin, and fluorouracil; CapeOX, oxaliplatin and capecitabine; OS, overall survival; PFS, progression-free survival; ITT, intention-to-treat.

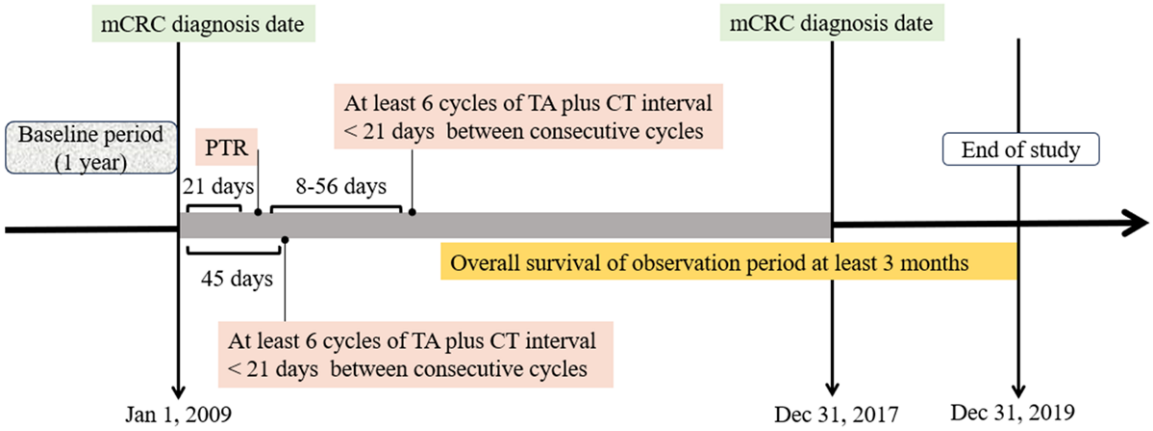


Figure 1. Illustration of the study design and definition of the study period. Abbreviations: mCRC, metastatic colorectal cancer; PTR, primary tumor resection; TA, targeted therapy; CT, chemotherapy.

had undergone metastasectomy. Furthermore, we used a two-step matching algorithm to enhance comparability between the PTR and non-PTR study groups. First, age, sex, diagnosis date, and index date were considered important proxy variables for the underlying patient status. Therefore, they were matched first. Subsequently, greedy propensity score (PS) matching was used to address baseline patient characteristic imbalances between the study groups. The PS was estimated using a logistic regression model, capturing demographic, clinical, and tumor-related variations between the two treatment groups, and subsequently utilized for matching.

This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines. The Institutional Review Board of Kaohsiung Veterans General Hospital approved this study's protocol (KSVGH21-CT2-03). Informed consent was not required for the use of de-identified data.

Study variables and targeted therapy exposure

Demographic variables included the year of diagnosis, year of targeted therapy, age, sex, histological grade, primary tumor location, stage (4A, B, and C), tumor size, lymph node status, radiotherapy, surgical procedures before the index date (Table S2), Charlson comorbidity index score [11, 12] (Table S3), and comedication at 1 year before the index date (Table S4). Additionally, mucinous (codes M-8470 and M-8480-8481) (yes or no) and signet ring cell (code M-8490) (yes or no) histologic types were included in the analyses. Histologic definitions for adenocarcinoma included the following ICD-O codes: M-8140, M-8210-8211, M-8255, M-8260-8261, M-8263, M-8323, M-8470, M-8480-8481, and M-8490. Right-sided colon cancer was defined as a primary tumor located in the cecum, ascending colon, hepatic flexure, or transverse colon, whereas left-sided colon cancer was defined at the splenic flexure, descending colon, sigmoid colon, rectosigmoid junction, or rectum. Based on the American Joint Committee on Cancer CRC staging system, seventh edition, stage 4A indicates distant metastasis to one organ and stage 4B/C to two or more organs. Regarding asymptomatic status, we further analyzed the subgroups as patients with symptomatic unresectable or asymptomatic unresectable mCRC. The primary outcome was OS, which was evaluated from the index date to the end of 2019, as well as death or censorship.

Statistical analysis

Demographic and tumor characteristics were evaluated using descriptive statistics. A standardized mean difference exceeding 0.2 was used to identify differences in baseline covariates between the PTR and non-PTR groups. The OS was calculated using the Kaplan-Meier method and compared with the log-rank test for unadjusted survival differences between the PTR and non-PTR groups. However, the adjusted survival hazard ratios (HRs) for the comparison of the two groups were estimated

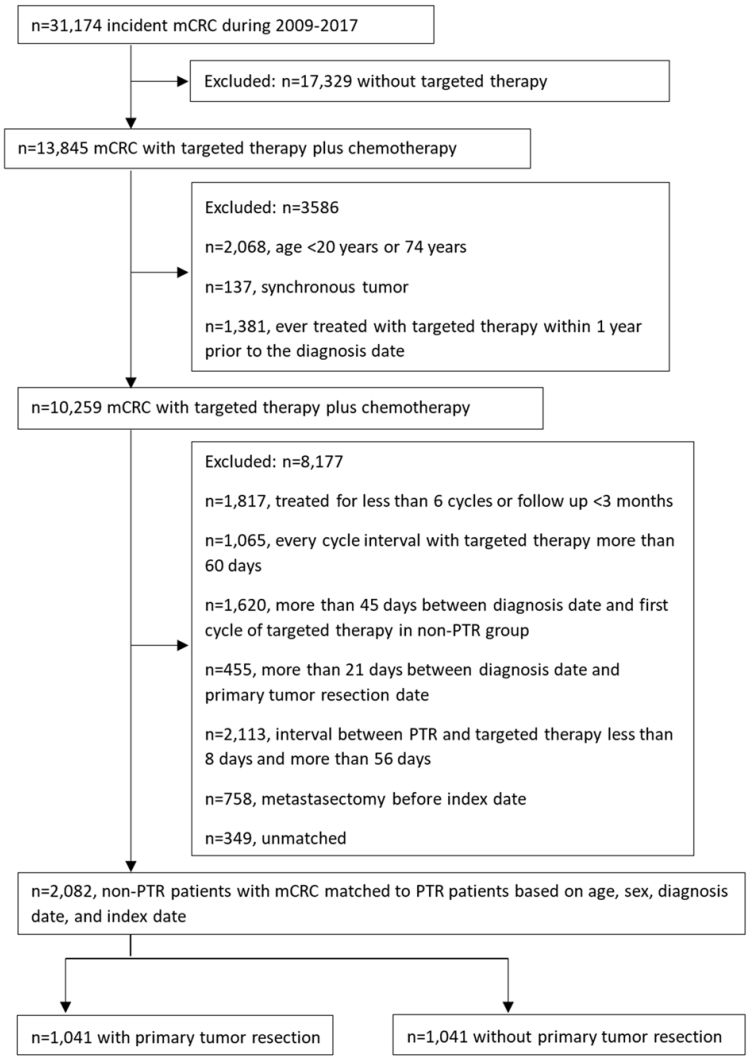


Figure 2. Flow chart of cohort selection of patients with mCRC who received at least six cycles of first-line therapy with cycle intervals shorter than 60 days. Abbreviations: n, number; mCRC, metastatic colorectal cancer; PTR, primary tumor resection.

using multivariate analysis by fitting a Cox proportional hazards model. Because the non-PTR group did not undergo surgery, the variables related to surgery lacked data and could not be used for matching. Therefore, we performed multivariate analysis to adjust for the unmatched variables within the cohort where matching was possible. The results were expressed as HRs and their corresponding 95% confidence intervals (CIs). All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). For all hypotheses tested, analysis items with a two-tailed *P*-value <0.05 were considered statistically significant.

Sensitivity analyses

The following three sensitivity analyses were performed to examine the robustness of our findings. First, patients receiving at least six cycles of first-line therapy with the same regimen with cycle intervals shorter than 21 days may have caused selection bias. Therefore, all patients received at least six cycles of first-line therapy with cycle intervals shorter than 60 days (flow chart of cohort selection is presented in **Figure 2**). Second, we used a logistic regression model to generate a PS for the probability of patients receiving treatment. We generated a Cox proportional hazards model adjusted for the PS and baseline characteristics to compare the survival HR. We identified the comparison group of targeted therapy using one-to-one PS matching and calculated the inverse probability of PTR for weighting. We estimated the OS after PS matching and the stabilized inverse probability of treatment weights (SIPTW) to control for confounding factors and ensure comparativeness. Potential confounders and covariates related to the outcome, such as comorbidities and tumor patterns, were included in the PS model. The SIPTW was used to ensure that samples with the estimated average treatment effect were not lost. When assessing early mortality, we noted a predominant occurrence of deaths within the initial year after the index date. This trend was particularly pronounced in the non-PTR group. Patients who did not survive until the landmark time were less likely to receive aggressive surgical interventions, indicating the presence of survivor treatment bias [13]. Consequently, we conducted a third sensitivity analysis using landmark analysis to overcome the bias. The landmark analysis was focused

Table 2. Keywords used for search strategies

Database	Keywords
PubMed	("metastases" [All Fields] OR "metastatic" [All Fields] OR "stage IV" [All Fields]) AND ("colorectal cancer" [All Fields] OR "colon cancer" [All Fields]) AND "primary" [All Fields] AND (("tumour" [All Fields] OR "tumor" [All Fields] OR "tumours" [All Fields] OR "tumors" [All Fields]) AND ("resect" [All Fields] OR "resectability" [All Fields] OR "resectable" [All Fields] OR "resected" [All Fields] OR "resection" [All Fields])) AND ("mortality"(MeSH Subheading) OR "mortality" [All Fields] OR "survival" [All Fields] OR "survival"(MeSH Terms))
Embase	("metastatic colorectal cancer" OR "metastatic colon cancer") AND "primary tumor resection" AND "survival"
Cochrane library	("metastatic colorectal cancer" OR "metastatic colon cancer") AND "primary tumor resection" AND "survival"

on patients who had survived for a minimum of 1 year following the index date. The rationale behind selecting 1 year as the landmark stems from the consideration that for individuals with a limited likelihood of surviving beyond 12 months, a more conservative approach towards targeted combination chemotherapy might be preferred. Therefore, to ensure that our selection of the landmark did not introduce any additional bias, we conducted sensitivity analyses using pre-determined 6-month landmarks. The subgroup analyses were conducted based on unresectable status, type of targeted therapy, tumor characteristics, stage, tumor size, and KRAS status.

Systematic review and meta-analysis

We conducted a systematic review and meta-analysis to compare the efficacy of PTR and non-PTR for patients with mCRC (PROSPERO's registration number: CRD42023417977; April 28, 2023). This systematic review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses [14] and The Cochrane Collaboration [15]. PubMed, Embase, and the Cochrane Library were searched for eligible articles from the inception of the databases until March 25, 2023. The search keywords were based on the following strategy: "metastatic colorectal cancer" or "metastatic colon cancer" and "primary tumor resection" and "survival" or "mortality". Full details of the search strategies are available in **Table 2**. The reference lists of relevant reports were manually searched to identify any missing relevant research articles or strategies. All RCTs or observational studies were included if they reported (1) patients with mCRC, (2) PTR, and (3) survival or mortality. The exclusion criteria were as follows: (1) patients without mCRC; (2) studies that did not compare PTR to non-PTR or chemotherapy or studies of PTR alone; and (3) studies without retrievable endpoints. Quality assessment of these studies was performed using The Cochrane Collaboration's "Risk of Bias" tool 2.0 for all RCTs [16]. Furthermore, the observational studies included in this meta-analysis were assessed for methodological quality using the Newcastle-Ottawa Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). We conducted the meta-analysis using the DerSimonian and Laird random-effects model. The survival outcome was considered the HR of the OS. If a multivariate analysis was reported, an adjusted HR was used. The overall HR and the 95% CI were calculated using the inverse variance method [17]. Quantitative meta-analyses of the pooled effect estimates were calculated and presented using forest plots. The heterogeneity of the pairwise comparisons was measured using Cochran's Q statistical test and I^2 values. Statistical analyses were performed using Review Manager (RevMan) version 5.3.5 (Cochrane Informatics and Knowledge Management Department) [18].

Results

Cohort characteristics

Between January 1, 2009, and December 31, 2017, we identified 1,132 patients with unresectable mCRC who met the inclusion criteria (**Figure 3**), all of whom underwent PTR combined with targeted therapy plus chemotherapy or targeted therapy plus chemotherapy alone and were enrolled in this study. The patients' characteristics are summarized in **Table 3**.

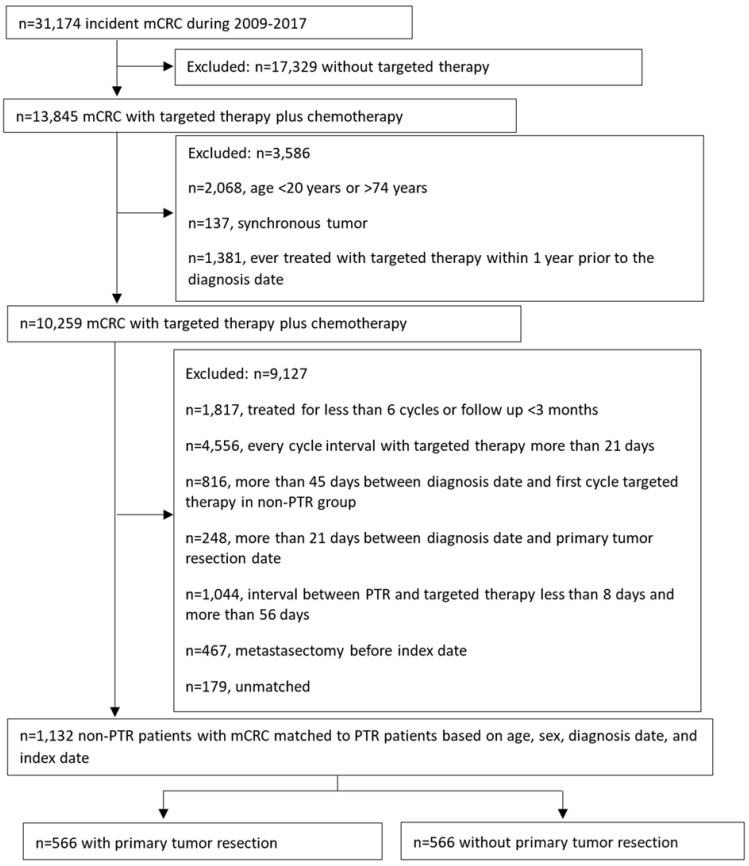


Figure 3. Flow chart of cohort selection. Abbreviations: n, number; mCRC, metastatic colorectal cancer; PTR, primary tumor resection.

OS of this cohort study

Overall, 1,003 (88.6%) patients died during the follow-up period, with 472/566 (83.4%) and 531/566 (93.8%) in the PTR and non-PTR groups, respectively. The median OS was significantly better in the PTR group (21.19 months; 95% CI, 19.9-22.48) than in the non-PTR group (16.69 months; 95% CI, 15.64-17.46), with an adjusted HR of 0.79 (95% CI, 0.62-1.01) among patients with unresectable mCRC (**Figures 4** and S1).

Sensitivity analyses

All patients received at least six cycles of first-line targeted therapy combined with chemotherapy and cycle intervals with targeted therapy shorter than 60 days (**Figure 2** and **Table 3**). The adjusted HRs of the OS associated with the PTR and non-PTR groups was 0.95 (95% CI, 0.80-1.14). Generally, the OS after PS matching and SIPTW between the two groups yielded HRs of 0.77 (95% CI, 0.58-1.01) and 0.81 (95% CI, 0.65-1.00) among patients with unresectable mCRC, respectively. The patients' characteristics after PS matching and SIPTW are summarized in **Table 4**. In the 6-month and 1-year landmark analyses, we observed no survival benefit associated with PTR (**Figure 4**). No significant difference was observed in subgroup analyses for OS outcome (**Figure 4** and Table S7).

Systematic review and meta-analysis

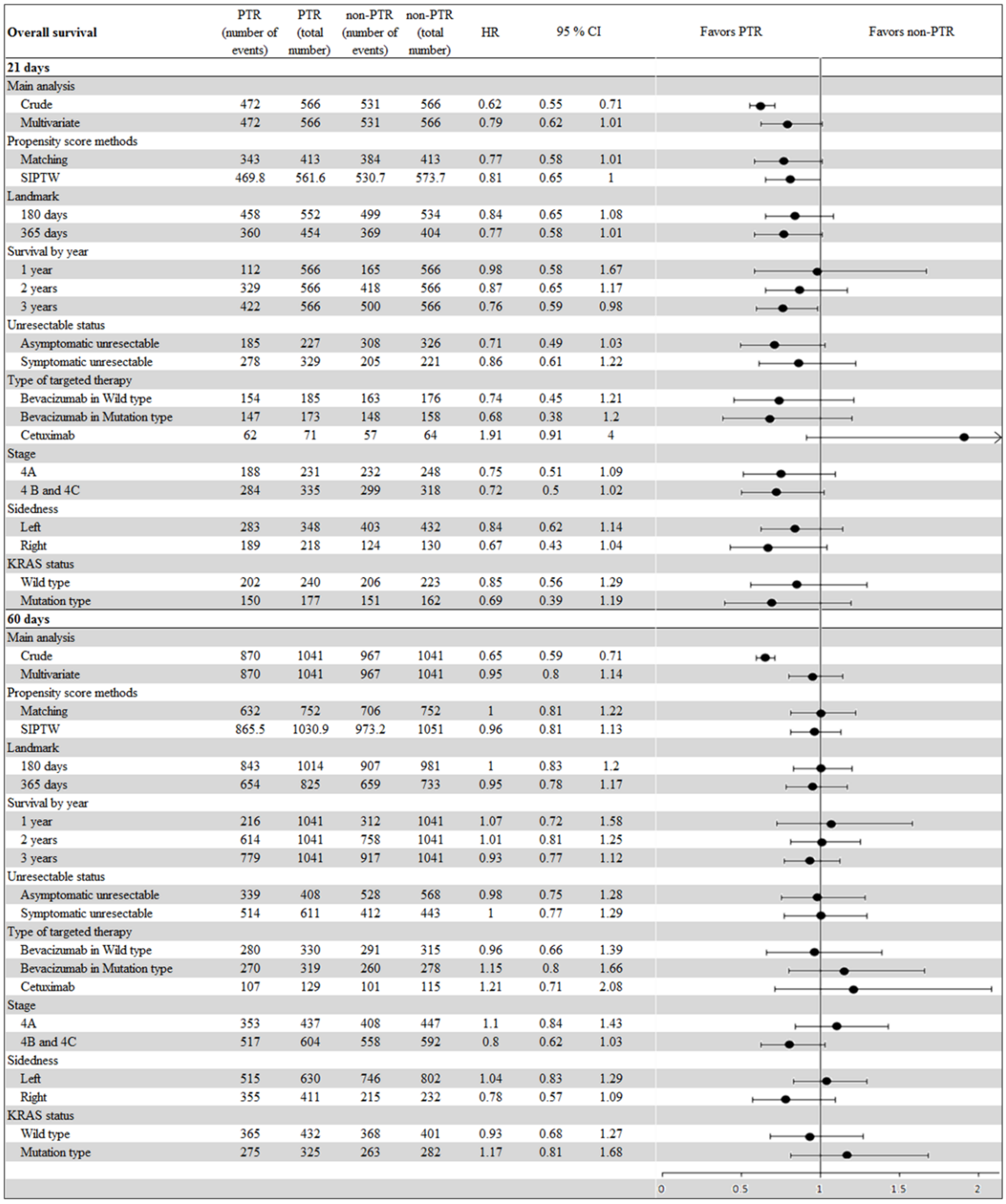
Through the search strategy for electronic databases, 2,188 studies were identified. Six RCTs and 57 observational studies were included in the meta-analysis (**Figure 5**), and all of these reported outcomes related to OS. The characteristics and measured effects of the 63 studies are summarized in Table S5, and the risk of bias assessments and Newcastle-Ottawa Scale are shown in **Figure 6** and Table S6, respectively. **Table 5** presents the meta-analysis results using data. The pooled estimated HR of the RCTs was 1.12 (95% CI, 0.97-1.29), showing a non-significant difference in OS between the PTR and non-PTR groups. In contrast, the pooled estimated HR was 0.60 (95% CI, 0.53-0.67) for the retrospective studies. Based on all studies, a significant increase was observed in OS with an HR of 0.63 (95% CI, 0.56-0.71). The subgroup analysis revealed that for patients with asymptomatic unresectable mCRC, OS showed a non-significant benefit between the PTR and non-PTR groups in the high-quality studies. However, in patients with symptomatic unresectable mCRC, OS was significantly better in the PTR group than in the non-PTR group in the high-quality studies. In patients with resectable mCRC, OS was significantly better in the PTR group than in the non-PTR group. Subgroup analyses across historical periods revealed that PTR used to have a major impact on OS but that this benefit

Table 3. Baseline characteristics of patients with unresectable mCRC who underwent primary tumor resection or not within 21 days of targeted therapy gap and 60 days of targeted therapy gap

Primary tumor resection	Patients with unresectable mCRC within 21 days of targeted therapy gap			Patients with unresectable mCRC within 60 days of targeted therapy gap		
	Non-PTR (N=566), n (%); mean/SD	PTR (N=566), n (%); mean/SD	SMD	Non-PTR (N=1041), n (%); mean/SD	PTR (N=1041), n (%); mean/SD	SMD
Death	531 (93.8)	472 (83.4)	0.33	967 (92.89)	870 (83.57)	0.29
Sex			0.03			0.02
Male	322 (56.9)	314 (55.5)		548 (52.6)	556 (53.4)	
Age, years	56 (10.5)	55.8 (10.8)	0.02	56.2 (10.6)	56 (11)	0.02
<50	154 (27.2)	158 (27.9)		280 (26.9)	281 (27)	
50-59	181 (32)	174 (30.7)		332 (31.9)	321 (30.8)	
60-69	171 (30.2)	176 (31.1)		303 (29.1)	322 (30.9)	
≥70	60 (10.6)	58 (10.2)		126 (12.1)	117 (11.2)	
Year of targeted therapy			0.1			0.15
2011	37 (6.5)	32 (5.7)		77 (7.4)	80 (7.7)	
2012	88 (15.5)	86 (15.2)		143 (13.7)	151 (14.5)	
2013	95 (16.8)	96 (17)		172 (16.5)	165 (15.9)	
2014	84 (14.8)	89 (15.7)		182 (17.5)	179 (17.2)	
2015	82 (14.5)	82 (14.5)		128 (12.3)	131 (12.6)	
2016	83 (14.7)	85 (15)		155 (14.9)	156 (15)	
2017	85 (15)	84 (14.8)		161 (15.5)	153 (14.7)	
2018	12 (2.1)	12 (2.1)		23 (2.2)	26 (2.5)	
Radiotherapy	77 (13.6)	24 (4.2)	0.33	166 (15.9)	49 (4.7)	0.38
Charlson comorbidity index	2.6 (1)	2.5 (0.8)	0.15	2.6 (0.9)	2.5 (0.9)	0.09
Tumor sidedness			0.37			0.4
Right	130 (23)	218 (38.5)		232 (22.29)	411 (39.48)	
Left	432 (76.3)	348 (61.5)		802 (77.04)	630 (60.52)	
Tumor differentiation grade			1.03			1.1
Well-differentiated	28 (5)	12 (2.1)		47 (4.51)	19 (1.83)	
Moderately differentiated	284 (50.2)	405 (71.6)		524 (50.34)	758 (72.81)	
Poorly differentiated	58 (10.3)	128 (22.6)		95 (9.13)	223 (21.42)	
Undifferentiated or anaplastic	3 (0.5)	16 (2.8)		5 (0.48)	29 (2.79)	
Histologic type			0.33			0.33
Adenocarcinoma	544 (96.1)	490 (86.6)		996 (95.68)	904 (86.84)	
Mucinous	15 (2.7)	60 (10.6)		31 (2.98)	113 (10.85)	
Signet ring cell carcinoma	7 (1.2)	16 (2.8)		14 (1.34)	24 (2.31)	
Tumor size			0.93			0.87
<4 cm	92 (16.3)	147 (26)		184 (17.68)	262 (25.17)	
4-5 cm	59 (10.4)	130 (23)		116 (11.14)	230 (22.09)	
>5 cm	187 (33)	255 (45.1)		337 (32.37)	493 (47.36)	
Stage			0.06			0.14
4A	248 (43.8)	231 (40.8)		447 (42.94)	437 (41.98)	
4B+4C	318 (56.2)	335 (59.2)		592 (56.87)	604 (58.02)	
CEA			0.38			0.38
Positive	465 (82.2)	374 (66.1)		858 (82.42)	686 (65.9)	
KRAS status			0.11			0.13
Mutation	162 (28.6)	177 (31.3)		282 (27.09)	325 (31.22)	
Wild type	223 (39.4)	240 (42.4)		401 (38.52)	432 (41.5)	
Bowel obstruction	217 (38.3)	315 (55.7)	0.39	432 (41.5)	584 (56.1)	0.3
Bowel perforation	9 (1.6)	32 (5.7)	0.25	27 (2.59)	68 (6.53)	0.19
Positive lymph node number (mean ± SD)	5.7 (6.7)	7.1 (7.2)	0.2	4.9 (6.3)	7.3 (7.7)	0.35

TA type			0.04		0.04
Bevacizumab	502 (88.7)	495 (87.5)		926 (88.95)	912 (87.61)
Cetuximab	64 (11.3)	71 (12.5)		115 (11.05)	129 (12.39)

Abbreviations: mCRC, metastatic colorectal cancer; PTR, primary tumor resection; N, total number; n, number; SD, standard deviation; SMD, standardized mean difference; CEA, carcinoembryonic antigen; TA type, targeted therapy type.



Overall survival	PTR (number of events)	PTR (total number)	non-PTR (number of events)	non-PTR (total number)	HR	95 % CI	
21 days							
Main analysis							
Crude	472	566	531	566	0.62	0.55	0.71
Multivariate	472	566	531	566	0.79	0.62	1.01
Propensity score methods							
Matching	343	413	384	413	0.77	0.58	1.01
SIPTW	469.8	561.6	530.7	573.7	0.81	0.65	1
Landmark							
180 days	458	552	499	534	0.84	0.65	1.08
365 days	360	454	369	404	0.77	0.58	1.01
Survival by year							
1 year	112	566	165	566	0.98	0.58	1.67
2 years	329	566	418	566	0.87	0.65	1.17
3 years	422	566	500	566	0.76	0.59	0.98
Unresectable status							
Asymptomatic unresectable	185	227	308	326	0.71	0.49	1.03
Symptomatic unresectable	278	329	205	221	0.86	0.61	1.22
Type of targeted therapy							
Bevacizumab in Wild type	154	185	163	176	0.74	0.45	1.21
Bevacizumab in Mutation type	147	173	148	158	0.68	0.38	1.2
Cetuximab	62	71	57	64	1.91	0.91	4
Stage							
4A	188	231	232	248	0.75	0.51	1.09
4 B and 4C	284	335	299	318	0.72	0.5	1.02
Sidedness							
Left	283	348	403	432	0.84	0.62	1.14
Right	189	218	124	130	0.67	0.43	1.04
KRAS status							
Wild type	202	240	206	223	0.85	0.56	1.29
Mutation type	150	177	151	162	0.69	0.39	1.19
60 days							
Main analysis							
Crude	870	1041	967	1041	0.65	0.59	0.71
Multivariate	870	1041	967	1041	0.95	0.8	1.14
Propensity score methods							
Matching	632	752	706	752	1	0.81	1.22
SIPTW	865.5	1030.9	973.2	1051	0.96	0.81	1.13
Landmark							
180 days	843	1014	907	981	1	0.83	1.2
365 days	654	825	659	733	0.95	0.78	1.17
Survival by year							
1 year	216	1041	312	1041	1.07	0.72	1.58
2 years	614	1041	758	1041	1.01	0.81	1.25
3 years	779	1041	917	1041	0.93	0.77	1.12
Unresectable status							
Asymptomatic unresectable	339	408	528	568	0.98	0.75	1.28
Symptomatic unresectable	514	611	412	443	1	0.77	1.29
Type of targeted therapy							
Bevacizumab in Wild type	280	330	291	315	0.96	0.66	1.39
Bevacizumab in Mutation type	270	319	260	278	1.15	0.8	1.66
Cetuximab	107	129	101	115	1.21	0.71	2.08
Stage							
4A	353	437	408	447	1.1	0.84	1.43
4B and 4C	517	604	558	592	0.8	0.62	1.03
Sidedness							
Left	515	630	746	802	1.04	0.83	1.29
Right	355	411	215	232	0.78	0.57	1.09
KRAS status							
Wild type	365	432	368	401	0.93	0.68	1.27
Mutation type	275	325	263	282	1.17	0.81	1.68

Figure 4. Subgroup analyses of overall survival for intervals shorter than 21 days or more than 60 days between consecutive cycles. Abbreviations: PTR, primary tumor resection; HR, hazard ratio; CI, confidence interval; SIPTW, stabilized inverse probability of treatment weights.

Table 4. Baseline characteristics of patients with unresectable mCRC who underwent primary tumor resection or not within 21 days of targeted therapy gap adjusted using PSM and SIPTW

Primary tumor resection	Patients with unresectable mCRC within 21 days of targeted therapy gap, PSM			Patients with unresectable mCRC within 21 days of targeted therapy gap, SIPTW		
	Non-PTR (N= 413), n (%); mean/SD	PTR (N=413), n (%); mean/SD	SMD	Non-PTR (N=573.7), n (%); mean/SD	PTR (N=561.6), n (%); mean/SD	SMD
Death	384 (92.98)	343 (83.05)	0.31	530.66 (92.49)	469.84 (83.66)	0.28
Sex			0.06			0.02
Male	213 (51.6)	225 (54.5)		324 (56.5)	312 (55.6)	
Age, years	56 (10.7)	56.1 (10.5)	0.01	55.7 (10.7)	55.9 (10.6)	0.02
<50	114 (27.6)	108 (26.2)		162.8 (28.4)	153 (27.2)	
50-59	131 (31.7)	136 (32.9)		183.7 (32)	178.9 (31.9)	
60-69	125 (30.3)	124 (30)		171.8 (29.9)	172.6 (30.7)	
≥70	43 (10.4)	45 (10.9)		55.4 (9.7)	57.2 (10.2)	
Year of systemic therapy			0.14			0.11
2011	27 (6.5)	25 (6.1)		35.6 (6.2)	31.7 (5.7)	
2012	58 (14)	66 (16)		93.2 (16.2)	95.8 (17.1)	
2013	78 (18.9)	69 (16.7)		94.6 (16.5)	89 (15.8)	
2014	55 (13.3)	61 (14.8)		79.6 (13.9)	87.9 (15.7)	
2015	57 (13.8)	56 (13.6)		83.4 (14.5)	79.8 (14.2)	
2016	58 (14)	66 (16)		80.8 (14.1)	85.2 (15.2)	
2017	68 (16.5)	59 (14.3)		93.3 (16.3)	78.8 (14)	
2018	12 (2.9)	11 (2.7)		13.2 (2.3)	13.4 (2.4)	
Radiotherapy	18 (4.4)	24 (5.8)	0.07	50.5 (8.8)	49.4 (8.8)	0
Charlson comorbidity index	2.5 (0.9)	2.5 (0.9)	0.01	2.5 (0.9)	2.5 (0.9)	0
Tumor sidedness			0.01			0.02
Right	118 (28.57)	116 (28.09)		182.6 (31.83)	175.66 (31.28)	
Left	295 (71.43)	297 (71.91)		389.13 (67.82)	385.91 (68.72)	
Missing	0 (0)	0 (0)		2 (0.35)	0 (0)	
Tumor differentiation grade			1.02			1.02
Well-differentiated	17 (4.12)	7 (1.69)		26.12 (4.55)	11.24 (2)	
Moderately differentiated	203 (49.15)	307 (74.33)		284.09 (49.52)	412.37 (73.43)	
Poorly differentiated	47 (11.38)	85 (20.58)		73.51 (12.81)	133.15 (23.71)	
Undifferentiated or anaplastic	3 (0.73)	10 (2.42)				
Missing	143 (34.62)	4 (0.97)		190 (33.12)	4.81 (0.86)	
Histologic type			0.1			0.04
Adenocarcinoma	394 (95.4)	392 (94.92)		517.41 (90.19)	512.84 (91.32)	
Mucinous	14 (3.39)	13 (3.15)		42.95 (7.49)	37.06 (6.6)	
Signet ring cell carcinoma	5 (1.21)	8 (1.94)		13.36 (2.33)	11.68 (2.08)	
Tumor size			0.83			0.81
<4 cm	72 (17.43)	113 (27.36)		92.66 (16.15)	150.95 (26.88)	
4-5 cm	46 (11.14)	100 (24.21)		60.5 (10.55)	131.61 (23.44)	
>5 cm	142 (34.38)	174 (42.13)		207.14 (36.11)	240.34 (42.8)	
Missing	153 (37.05)	26 (6.3)		213.42 (37.2)	38.67 (6.89)	
Stage			0.14			0
4A	178 (43.1)	175 (42.37)		241.55 (42.1)	236.46 (42.11)	
4B+4C	235 (56.9)	238 (57.62)		332.17 (57.9)	325.11 (57.89)	
CEA			0.09			0.03
Positive	326 (78.93)	318 (77)		412.29 (71.86)	411.22 (73.23)	
KRAS status			0.04			0
Mutation	127 (30.75)	132 (31.96)		167.35 (29.17)	163.21 (29.06)	
Wild type	172 (41.65)	167 (40.44)		237.76 (41.44)	227.99 (40.6)	
Missing	114 (27.6)	114 (27.6)		168.61 (29.39)	170.38 (30.34)	

Bowel obstruction	160 (38.74)	228 (55.21)	0.33	214.94 (37.46)	308.83 (54.99)	0.37
Bowel perforation	6 (1.45)	24 (5.81)	0.3	7.46 (1.3)	30.8 (5.48)	0.26
Positive lymph node number (mean ± SD)	6.2 (7.2)	7 (7.3)	0.12	5.4 (7)	7.2 (7.8)	0.23
TA type			0.02			0.01
Bevacizumab	358 (86.68)	361 (87.41)		506.33 (88.25)	493.38 (87.86)	
Cetuximab	55 (13.32)	52 (12.59)		67.4 (11.75)	68.2 (12.14)	

Abbreviations: mCRC, metastatic colorectal cancer; PTR, primary tumor resection; PSM, propensity score matching; SIPTW, stabilized inverse probability of treatment weights; N, total number; n, number; SD, standard deviation; SMD, standardized mean difference; CEA, carcinoembryonic antigen; TA type, targeted therapy type.

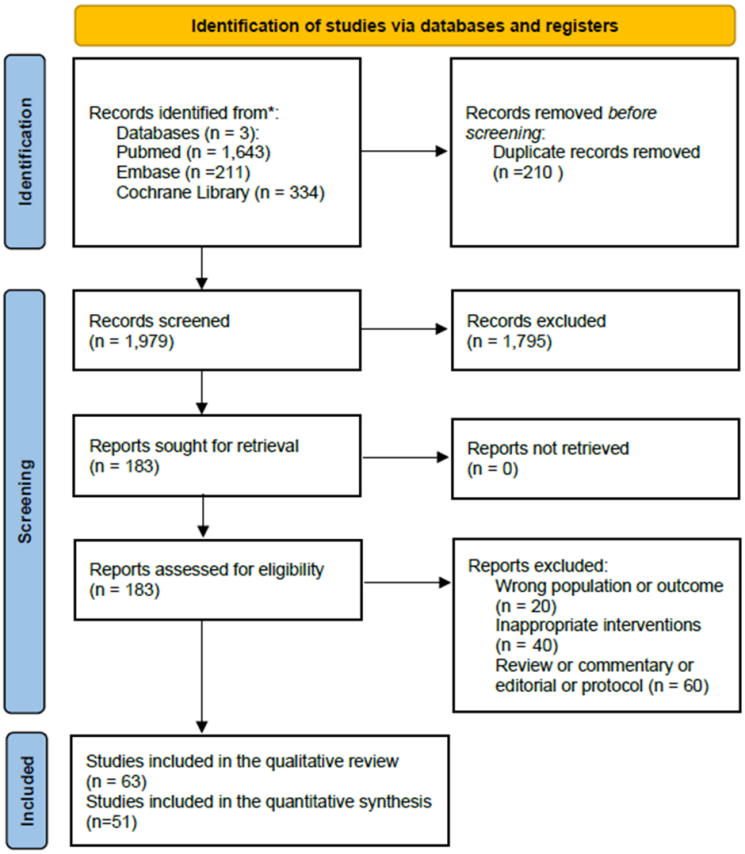


Figure 5. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines flowchart summarizing study identification and selection. Abbreviation: n, number.

has diminished due to improvements in medical technology and treatment options.

Discussion

Our systematic literature review indicated that globally, more than 50% of patients with mCRC undergo routine PTR. This practice is likely rooted in historical treatment recommendations that suggested better survival outcomes with PTR. Most studies in our systematic literature review were retrospective, and the results demonstrated that PTR had a better OS outcome than non-PTR. However, our results revealed a substantial analytical bias in assessing the impact of PTR on survival outcomes compared to non-PTR. Nevertheless, our review of RCTs demonstrated that the survival benefits of PTR are not superior to those of non-PTR, specifically among patients with asymptomatic unresectable mCRC. Subgroup analyses of our systematic literature review were conducted for the subpopulations of asymptomatic unresectable, symptomatic unresectable, and resectable mCRC. In all subgroup analyses, the survival efficacy of PTR was better than that of non-PTR. However, when subgroup analyses of asymptomatic unresectable mCRC were performed based on the quality of the studies, high-quality research revealed no significant difference in survival outcomes between the PTR and non-PTR groups. In these retrospective studies, a pronounced selection bias was evident in the choice between PTR and non-PTR. This bias primarily stemmed from the non-randomized nature of treatment selection between the intervention and non-intervention groups, along with a lack of well-characterized indications for assignment. Consequently, the selected analytical methods greatly influenced the study outcomes. Patients with a higher burden of comorbidities that could contribute to all-cause mortality were less likely to opt for PTR. Moreover, patients with lower performance status

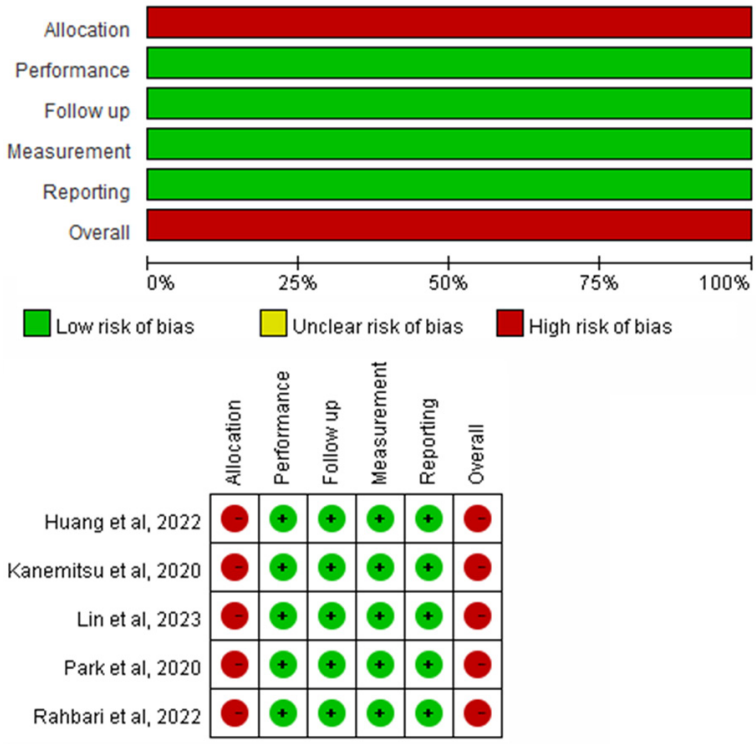


Figure 6. Risk of bias assessment of quality of included RCTs. Abbreviation: RCT, randomized controlled trial.

and a weaker will to survive tended to select non-invasive systemic chemotherapy over aggressive PTR treatment. The probability of receiving aggressive PTR treatment was lower for patients with a higher tumor load and a greater risk of cancer-related mortality. Using PS analysis can alleviate the influence of selection bias by factoring in the conditional treatment probability based on all pertinent known variables feasible for incorporation within the propensity model. Nonetheless, similar to conventional risk adjustment techniques, PS analyses are vulnerable to the constraints imposed by unmeasured factors that play a role in shaping treatment selection bias.

The application of the target trial framework is imperative for assessing the causal impact of interventions based on observational data. Precisely formulating the protocol of the target trial before its emulation using observational data serves to avert numerous prevailing design challenges, contributing to robust research methodologies in the medical journal literature [9]. In high-mortality diseases, an additional significant bias impacting the determination of survival outcomes is intrinsic to the duration of survival and its consequential effect on the probability of patients being allocated to a specific treatment regimen. This phenomenon is commonly referred to as survivor bias [13]. For patients with an unfavorable survival prognosis potentially facing imminent demise shortly after diagnosis, the possibility of undergoing surgical resection might have been unattainable. Consequently, this circumstance reinforces an inherent disparity in survival outcomes, underscoring the relatively diminished prognosis for the nonsurgical cohort. A pragmatic solution to address this challenge is through the utilization of the landmark method [19]. Previous studies have been hindered by insufficient adjustments for both treatment selection and survivor bias, highlighting the need to employ more comprehensive methodologies in our study to address and mitigate both biases. Following this approach, we could no longer substantiate a survival advantage associated with PTR.

Our study simulated the enrollment criteria of an RCT, where patients diagnosed with mCRC within 21 days were required to undergo PTR, and those in the PTR group were further mandated to receive at least six cycles of targeted combination chemotherapy within 8-56 days postoperatively. Additionally, for the non-PTR group, patients diagnosed within 45 days (primarily due to the pre-approval process for targeted therapies in Taiwan, which entails waiting time) were mandated to undergo at least six cycles of targeted combination chemotherapy, with the treatment cycle intervals for both groups required to be <21 days. Moreover, age, sex, diagnosis date, and index date were matched between the two groups to ensure that the PTR and non-PTR groups were comparable and characterized by good exchangeability. Both cohorts also excluded patients who underwent lung or liver resection during the entire study period, as metastasectomy can affect prognosis. We conducted various sensi-

Table 5. Subgroup analyses of overall mortality

Group variable	Subgroup	Number of studies	HR (95% CI)	Heterogeneity
Whole population		51	0.63 (0.56-0.71)	98%
Study design	RCT	5	1.12 (0.97-1.29)	0%
	Non-RCT	46	0.6 (0.53-0.67)	98%
Historical periods	Before 2000	5	0.46 (0.4-0.53)	0%
	2000-2010	29	0.60 (0.51-0.71)	99%
	After 2010	17	0.72 (0.62-0.85)	88%
Asymptomatic unresectable mCRC population		17	0.82 (0.71-0.94)	88%
Study quality	High	13	0.92 (0.80-1.05)	34%
	Low	4	0.6 (0.46-0.77)	52%
Symptomatic unresectable mCRC population		19	0.61 (0.52-0.72)	96%
Study quality	High	7	0.88 (0.8-0.96)	46%
	Low	12	0.53 (0.47-0.61)	82%
Resectable mCRC population		17	0.55 (0.47-0.64)	95%

Abbreviations: HR, hazard ratio; CI, confidence interval; mCRC, metastatic colorectal cancer; RCT, randomized controlled trial.

tivity analyses, including landmark analysis, to address survival bias, and the results indicated no significant difference between the PTR and non-PTR groups. There is an intriguing phenomenon where, in another sensitivity analysis, extending the treatment cycle interval to <60 days revealed that PTR may increase the risk of death. However, no significant difference was observed. This result suggests that for patients who experience a delay in initiating targeted combination chemotherapy due to undergoing PTR, subsequent delays in receiving the cycles of targeted therapy may impact their physical condition, thereby triggering rapid tumor progression. This situation leads to an increased risk of death in the PTR group. This indirectly indicates that in cases of asymptomatic unresectable mCRC, prioritizing PTR not only lacks benefits for survival outcomes but might also increase the risk of death. Therefore, selecting targeted combination chemotherapy as the initial treatment should be considered.

The strength of our study lies in its distinctiveness from previous research. We incorporated a substantial patient cohort and emulated an RCT research design, thereby enhancing the study's representativeness and statistical power. This approach effectively mitigated random errors and facilitated more definitive conclusions. This study had some limitations. First, similar to other observational studies using administrative databases, assessing the treatment intent posed challenges. For instance, it remains uncertain whether patients receiving chemotherapy are driven by a strong will to survive and intend to undergo tumor resection in the future or if their choice is purely for supportive care purposes. In the regression model, we accounted for tumor characteristics and fundamental attributes (such as age, sex, diagnosis date, and the date of initiation of targeted therapy) for matching between the two groups to minimize potential confounding effects to the greatest extent possible. Simultaneously, the non-PTR group with weaker survival determination might experience higher early mortality rates; however, this potential confounder's impact was mitigated using landmark analysis, as deaths related to supportive treatment are frequently associated with earlier mortality.

Additionally, our results contradict the viewpoint proposed by previous large registry studies but are consistent with the findings of some small-scale RCTs.

In conclusion, this study demonstrates that in routine practice with non-selective patients who have colon cancer with unresectable metastases, PTR does not confer a survival advantage; however, it may delay the initiation of systemic therapy. These results also highlight that the previously observed treatment-related benefits might have been overestimated due to biases not accounted for by standard analytical methods. Recently, there has been a remarkable improvement in the survival rates of this

patient population. Therefore, the potential for performing PTR following initial systemic chemotherapy should be continuously assessed.

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Disclosure of conflict of interest

None.

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Table S1. List of Anatomical Therapeutic Chemicals (ATC) codes of drugs approved in Taiwan for the treatment of metastatic colorectal cancer

Drugs	ATC codes
Fluorouracil	ATC L01BC02
Capecitabine	ATC L01BC06
Tegafur/Gimeracil/Oteracil	ATC L01BC53
Oxaliplatin	ATC L01XA03
Irinotecan	ATC L01XX19
Panitumumab	ATC L01XC08
Cetuximab	ATC L01XC06
Bevacizumab	ATC L01XC07

Table S2. List of surgical procedure codes in the National Health Insurance Research Database (NHIRD) for treating metastatic colorectal cancer

Surgical procedure	Surgical procedure codes
Primary tumor resection	"73011B", "73012B", "73013B", "73014B", "73015B", "73017B", "73045B", "73046B", "73047B", "73048B", "74205B", "74206B", "74222B", "74223B", "74213B", "74214B", "74216B", "74217B", "N26022", "N26023", and "N26027"
Metastatic liver resection	"75002B", "75003B", "75004B", "75005B", "75015B", "75016B", "75017B", "75018B", "N26019", "N26018", "37042C", "37043C", and "37044C"
Metastatic lung resection	"67023B", "67042B", "67050B", "67051B", "67053B", and "N26010"

Table S3. Comorbidity 1 year before the index date

Comorbidities	ICD-9 codes	ICD-10 codes
Diabetes mellitus	250	E100, E101, E106, E108-E111, E116, E118-E121, E126, E128-E131, E136, E138-E141, E146, E148, and E149
Diabetes with end organ damage	2504-2506	E107, E117, E127, E137, E147, E102-E105, E112-E115, E122-E125, E132-E135, and E142-E145
Peripheral vascular disease	441, 4439, 7854, and V434	I70, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, and Z959
Heart failure	428	I099, I110, I130, I132, I255, I420, I43, I50, and P290
Cerebrovascular disease	430-438	I60-I69, G45, G46, and H34
Dementia	290	F00, F03, G30, F051, and G311
Chronic pulmonary disease	490-496, 500-505, and 5064	J40-J47, J60-J67, I278, I279, J684, J701, and J703
Connective tissue disease	7100, 7101, 7104, 7140-7142, 725, and 71481	
Myocardial infarction	410 and 412	I21, I22, and I252
Ulcer disease	5310, 5317, 5320, 5327, 5330, 5337, 5340, and 5347	K25 and K28
Mild liver disease	5712, 5714, 5715, and 5716	K700-K703, K709, K713, K714, K715, K717, K760, K762, K763, K764, K768, K769, Z944, B18, K73, K74, and 5716
Hemiplegia	342 and 3441	G81, G82, G041, G114, G801, G802, G830-G834, and G839
Moderate or severe renal disease	582, 585, 586, and 588	N18, N19, I120, I131, N250, Z940, Z992, 5830-5837, N032-N037, N052-N057, and Z490-Z492
Any malignant neoplasm	140-172, 174-195, and 200-208	C00-C26, C60-C76, C30-C34, C37-C41, C43, C45, C58, C60, C81-C85, C88, and C90-C97
Moderate or severe liver disease	5722-5728 and 4560-4562	I850, I859, I864, I982, K704, K711, K21, K729, K765, K766, and K767
Metastatic solid tumor	196-199	C77-C80
AIDS	042-044	B20, B21, B22, and B24
Intra-abdominal infection	567	

Abbreviations: ICD, International Classification of Diseases; AIDS, acquired immunodeficiency syndrome.

Table S4. We also defined information about medication to treat these specific comorbidities from the NHIRD using the World Health Organization's ATC classification system

Co-medications	ATC codes
Beta blockers	C07
Calcium channel blockers	C08
Diuretics	C03
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers	C09
Anti-diabetes mellitus agent	A10
Antiplatelets	B01AC
Anti-hemorrhage agent	B02
Antidyslipidemia agent	C10A
Antifungal agent	J02A
Antibacterial agent	J01
Non-selective nonsteroidal anti-inflammatory drugs	M01AB, M01AE, and M01AC
Selective nonsteroidal anti-inflammatory drugs	M01AH
Cardiac glucosides	C01A
Antiarrhythmics agents	C01B

Patients were considered to be taking these medications if there was at least one prescription 1 year before the index date.
Abbreviations: NHIRD, National Health Insurance Research Database; ATC, Anatomical Therapeutic Chemicals.

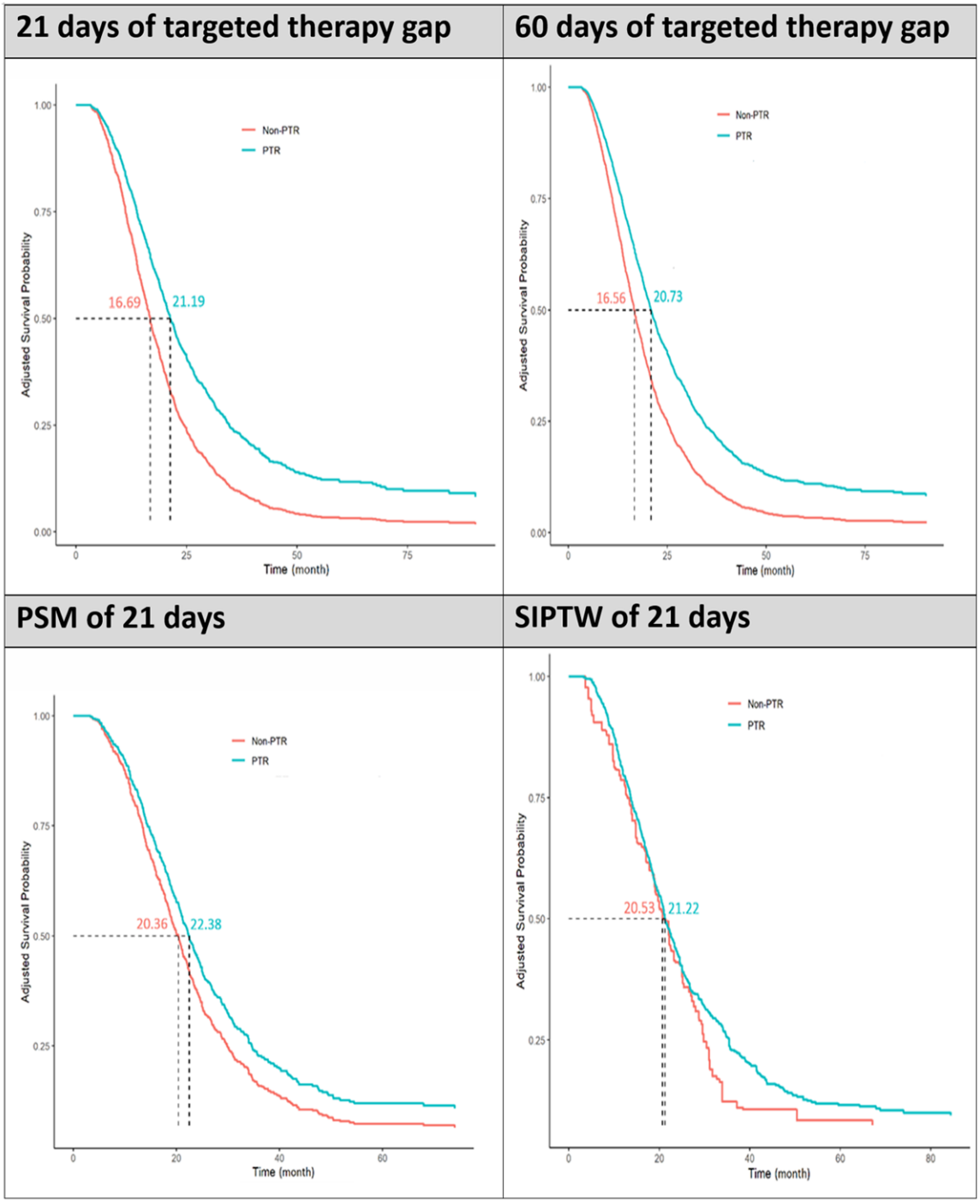

Figure S1. Kaplan-Meier plots of patients with unresectable mCRC who underwent primary tumor resection or not within 21 days of targeted therapy gap, 60 days of targeted therapy gap, and with adjustment using PSM and SIPTW. Abbreviations: mCRC, metastatic colorectal cancer; PTR, primary tumor resection; PSM, propensity score matching; SIPTW, stabilized inverse probability of treatment weight.

Table S5. Characteristics and summary results of the included studies assessing efficacy in patients with metastatic colorectal cancer

Study	Country	Study design	Study peri-od	Unresect-able status	Asympto-matic status	Pa-tient num-ber	Interven-tion	Compari-son	Median survival (months, 95% CI)	OS, HR (95% CI)
Michel et al. [1]	French	RCS	1996-1999	Yes	No	54 I: 31 C: 23	PTR	Non-PTR	I: 21 C: 14	N/A
Costi et al. [2]	Italy	RCS	1994-2003	No	No, 65% asymptomatic	130 I: 83 C: 47	PTR	Non-PTR	I: 9 (5.5-13.5) C: 4 (2.2-5.8)	
Konyalian et al. [3]	USA	RCS	1991-2002	No	No	109 I: 62 C: 47	PTR	Non-PTR or chemo-therapy	N/A	Adjusted: 0.34 (0.21-0.55)
Bajwa et al. [4]	UK	RCS	1999-2005	Yes	Yes	67	PTR	Non-PTR	N/A	N/A
Cellini et al. [5]	USA	RCS	2002-2008	Yes	No	31 I: 22 C: 9	PTR	Non-PTR	I: 32 C: 37	N/A
Chan et al. [6]	UK	RCS (Provincial Cancer Registry)	2000-2002	No	No	411 I: 286 C: 125	PTR	Non-PTR	I: 14 C: 6	Crude: 0.58 (0.36-0.82)
Mik et al. [7]	Poland	RCS	1996-2000	No	No	134 I: 52 C: 82	PTR	Non-PTR	N/A	Adjusted: 0.58 (0.36-0.82)
Oliveira et al. [8]	Portugal (poster)	RCS	1997-2006	No	No	216	PTR	Non-PTR	N/A	Adjusted: 0.61 (0.42-0.88)
Tanoue et al. [9]	Japan	RCS	2005-2009	Yes	No	74 I: 38 C: 36	CT+PTR	CT	I: 30.6 C: 20.8	N/A
Karoui et al. [10]	France	RCS	1998-2007	Yes	No	208 I: 85 C: 123	CT+PTR	CT	I: 30.7 (22.2-39.3) C: 21.9 (16.1-27.7)	Adjusted: 0.56 (0.38-0.83)
Boselli et al. [11]	Italy	RCS	2010-2011	Yes	Yes	48 I: 17 C: 31	PTR+CT	CT	I: 4 C: 5	N/A
Cetin et al. [12]	Turkey	RCS	2006-2010	Yes	No	99 I: 53 C: 46	PTR+CT+BV	CT+BV	I: 23 C: 17	
Rahbari et al. [13]	Germany	Multicenter RCT (SYNCHRONOUS Trial)	2011-2013	Yes	Yes	393 I: 187 C: 206	Upfront PTR+CT	CT	I: 16.7 (13.2-19.2) C: 18.6 (16.2-22.3)	0.95 (0.74-1.22)
Ferrand et al. [14]	France	RCS	1997-2001	Yes	No	216 I: 156 C: 60	PTR+CT	Non-PTR or CT		0.42 (0.3-0.6)
Ahn et al. [15]	Korea	RCS	2001-2009	No	No	64 I: 28 C: 36	PTR+CT	CT	I: 12.43 (9.38-15.49) C: 3.58 (2.34-4.81)	Adjusted: 0.14 (0.43-0.05)
de Mestier et al. [16]	France	RCS	2004-2008	Yes	No	96 I: 69 C: 27	PTR	Non-PTR	I: 23.1 (14.6-27.8) C: 22.1 (12.3-23.7)	Adjusted: 0.71 (0.50-1.00)

Duraker et al. [17]	Turkey	Prospective cohort study	1993-2004	Yes	Yes	164 I: 110 C: 54	PTR	Non-PTR	I: 11 C: 5.5	Adjusted: 0.48 (0.32-0.72)
Gresham et al. [18]	Canada	RCS	2006-2008	No	No	517 I: 378 C: 139	PTR+CT	CT	I: 21.2 C: 13.4	Adjusted: 0.56 (0.4-0.78)
Ishihara et al. [19]	Japan	Multicenter RCS	1997-2007	Yes	No	1982 I: 1782 C: 200	PTR	Non-PTR	I: 16.9 C: 6.2	Adjusted: 0.41 (0.33-0.53)
Kim et al. [20]	Korea	RCS	2006-2010	Yes	Yes	324 I: 72 C: 252	PTR+CT	CT	I: 17.2 (14.9-19.5) C: 13.6 (10.6-14.2)	N/A
Matsumoto et al. [21]	Japan	RCS	2005-2011	Yes	Yes	88 I: 41 C: 47	PTR+CT	CT	I: 23.9 C: 22.6	Adjusted: 0.72 (0.42-1.25)
Miyamoto et al. [22]	Japan	RCS	2005-2011	Yes	No	131 I: 68 C: 63	PTR+CT	CT	I: 30.4 C: 24.1	N/A
Tsang et al. [23]	California	RCS (California Cancer Registry)	1996-2007	No	No	11,716 I: 8,599 C: 3,117	PTR	CT	I: 21 (20-21) C: 10 (10-11)	Adjusted: 0.42 (0.39-0.44)
Watanabe et al. [24]	Japan	RCS	2002-2009	Yes	Yes	158 I: 46 C: 112	PTR+CT	CT	I: 19.9 C: 19	Crude: 0.81 (0.53-1.19)
Yoon et al. [25]	Korea	Prospective cohort study	2000-2007	Yes	No	261 I: 195 C: 66	PTR+CT	CT	I: 21 C: 10	Adjusted: 0.53 (0.39-0.73)
Yun et al. [26]	Korea	RCS	2000-2008	Yes	Yes	416 I: 218 C: 198	PTR+CT	CT	I: 17.2 C: 14.4	Adjusted: 0.81 (0.65-1.02)
Ahmed et al. [27]	Canada	RCS	1992-2005	No	Yes	834 I: 521 C: 313	PTR	Non-PTR or CT	N/A	Adjusted: 0.47 (0.39-0.57)
Kodaz et al. [28]	Turkey	RCS	2007-2013	Yes	No	78 I: 34 C: 44	PTR+CT	CT	I: 25 (19.65-30.34) C: 16 (12.83-19.61)	N/A
Niitsu et al. [29]	Japan	RCS	2007-2013	Yes	Yes	57 I: 42 C: 15	PTR+CT	CT	I: 23.9 C: 13.4	Adjusted: 0.77 (0.36-1.67)
Slesser et al. [30]	UK	RCS	2005-2010	No	No	116 I: 49 C: 67	PTR+CT	CT	I: 2.70 years (2.01-3.31) C: 2.53 years (1.97-3.10)	Adjusted: 1.1 (0.48-2.52)
Xu et al. [31]	USA	RCS (SEER)	1988-2010	No	No	PTR	Non-PTR	44,514 I: 27,931 C: 16,583		Adjusted: 0.45 (0.44-0.46)
Ahmed et al. [32]	Canada	RCS	2006-2010	No	No	PTR	Non-PTR	569 I: 313 C: 256		Adjusted: 0.44 (0.35-0.56)

He et al. [33]	China	RCS	2005-2012	No	No	PTR	Non-PTR	387 I: 254 C: 133	I: 20.8 C: 14.8	Adjusted: 0.64 (0.45-0.89)
Samalavicius et al. [34]	Lithuania	RCS	2008-2012	Yes	Yes	CT+PTR	CT	183 I: 120 C: 63		Adjusted: 0.57 (0.37-0.86)
Shida et al. [35]	Japan	RCS	1997-2013	Yes	No 76% asymptomatic	PTR	Non-PTR	770 I: 429 C: 341	I: 20.2 C: 13.1	Adjusted: 0.6 (0.5-0.71)
't Lam-Boer et al. [36]	Nether-lands	RCS (Netherlands Cancer Registry)	2008-2011	No	No	PTR	CT	6,213 I: 2,746 C: 3,467	I: 17.2 (16.3-18.1) C: 11.5 (11.0-12.0)	Adjusted: 0.58 (0.47-0.72)
Wang et al. [37]	China	RCS	2011-2013	Yes	No	PTR+CT+BV	CT+BV	191 I: 118 C: 73	I: 22.5 C: 17.8	
Wong et al. [38]	Australia	RCS (TRACC)	2009-2015	No	No	CT+PTR	Non-PTR or CT	610 I: 216 C: 394	I: 21 C: 17	Adjusted: 0.82 (0.62-1.09)
Alawadi et al. [39]	USA (Houston)	RCS (NCDB)	2003-2005	Yes	No	PTR+CT	CT	12,154 I: 8,641 C: 6,513		Adjusted: 0.46 (0.43-0.48)
Mehta et al. [40]	USA	RCS (SEER)	2000-2011	No	No	PTR	CT	6,368 I: 4,152 C: 2,216		Adjusted: 0.79 (0.74-0.86)
Cao et al. [41]	China	RCS	2005-2015	Yes	No	PTR	Non-PTR	133 I: 103 C: 30	I: 26.17 C: 15.9	
Korkmaz et al. [42]	Turkey	Multicenter RCS	2006-2015	Yes	No	PTR+CT+BV	CT+BV	341 I: 210 C: 131	I: 27.4 (23.1-31.7) C: 18.3 (14.3-22.4)	Adjusted: 0.52 (0.29-0.93)
Lau et al. [43]	Singapore	RCS	2004-2014	Yes	No	PTR+CT	CT	255 I: 145 C: 110	I: 22.7 (19.5-25.9) C: 12.1 (10.0-14.3)	Adjusted: 0.43 (0.34-0.55)
Maroney et al. [44]	USA	RCS	2004-2012	Yes	No	PTR+CT	CT	65,543 I: 36,048 C: 29,495	I: 22 C: 13	Adjusted: 0.90 (0.88-0.93)
Shida et al. [45]	Tokyo	RCS	2006-2013	Yes	No 65% asymptomatic	PTR+CT	CT	208 I: 108 C: 100	I: 32.9 C: 23.5	Adjusted: 0.70 (0.49-1.00)
Chen et al. [46]	China	RCS (SEER)	2010-2016	Yes	No	PTR	Non-PTR	21,405 I: 9,049 C: 12,356	I: 22 C: 12	Adjusted: 0.53 (0.50-0.56)
Ergun et al. [47]	Turkey	RCS	2007-2017	Yes	Yes	PTR+CT	CT	147 I: 56 C: 91	I: 21.8 C: 17	Adjusted: 0.65 (0.41-1.02)
Huang et al. [48]	USA	RCS (SEER)	2004-2013	Yes	No	PTR+CT	CT	48,126 I: 26,606 C: 21,520	N/A	Adjusted: 0.67 (0.63-0.75)

Kim et al. [49]	Korea	RCS	2000-2018	Yes	No	PTR+CT	CT	600 I: 315 C: 285	N/A	Adjusted: 0.41 (0.22-0.76)
Park et al. [50]	Korea	Multicenter RCT	2013-2016	Yes	Yes	PTR+CT	CT	52 I: 27 C: 25	N/A	1.31 (0.9-1.9)
Urvay et al. [51]	Turkey	RCS	2009-2016	Yes	No	PTR+CT	CT	215 I: 139 C: 76	I: 29.5 C: 14.2	N/A
Doah et al. [52]	Korea	RCS	2001-2018	Yes	Yes	PTR+CT	Non-PTR or CT	146 I: 98 C: 48	I: 18 C: 15	Adjusted: 0.61 (0.4-0.94)
Kanemitsu et al. [53]	Japan	RCT (JCOG1007)	2012-2019	Yes	Yes	PTR+CT	CT	165 I: 81 C: 84	N/A	1.11 (0.78-1.58)
Kawamura et al. [54]	Japan	Multicenter RCS	2008-2015	Yes	No	PTR+CT	CT	616 I: 414 C: 202	N/A	Adjusted: 0.51 (0.42-0.64)
Benavides et al. [55]	Spain	Multicenter RCS		Yes	Yes	PTR+CT	CT	1,334 I: 642 C: 692	I: 25.0 (23.3-26.7) C: 20.3 (18.6-22.4)	Adjusted: 0.75 (0.63, 0.89)
Van der Kruijssen et al. [56]	Nether-lands	RCS		No	No	PTR+CT	CT	199 I: 139 C: 60	N/A	Adjusted: 0.59 (0.42-0.82)
Cheng et al. [57]	USA	RCS (SEER)	2010-2016	No	No	PTR	Non-PTR	581 I: 171 C: 410	N/A	Adjusted: 0.65 (0.53-0.81)
Ho et al. [58]	Hong Kong	Multicenter RCS	2015-2020	No	No	PTR+CT	Non-PTR or CT	162 I: 68 C: 94	I: 28 (16-47) C: 12 (6-31)	Adjusted: 0.49 (0.30-0.79)
Huang et al. [59]	China	RCT	2015-2020	Yes	Yes	CT+PTR	CT	86 I: 42 C: 44	N/A	0.95 (0.55-1.62)
Sertesen et al. [60]	Turkey	RCS	2009-2020	Yes	Yes	CT+PTR	CT	111 I: 64 C: 47	I: 39.0 (33.8-44.1) C: 27.9 (16.8-39.0)	Adjusted: 0.43 (0.27-0.69)
Lin et al. [61]	China	Multicenter RCT	2012-2018	Yes	Yes	PTR+CT	CT	320 I: 160 C: 160	I: 27.2 C: 29.4	1.3 (0.99-1.72)
Vatandoust et al. [62]	Australia	RCS (SAMCRC)	2006-2014	Yes	No	PTR	CT	1,584 I: 1,010 C: 574	I: 16.9 (15.4-18.8) C: 11.8 (10.3-13)	Adjusted: 0.71 (0.63-0.81)
Von Einem et al. [63]	Germany	RCS (FIRE 3)		No	No	PTR	CT	436 I: 339 C: 97	N/A	Crude: 1.17 (0.88-1.55)

Abbreviations: CI, confidence interval; OS, overall survival; HR, hazard ratio; PTR, primary tumor resection; BV, bevacizumab; C, comparison; CT, chemotherapy; I, intervention; RCS, retrospective cohort study; RCT, randomized controlled trial; N/A, not applicable; TRACC, Treatment of Recurrent and Advanced Colorectal Cancer registry; NCDB, National Cancer Data Base; SEER, Surveillance, Epidemiology, and End Results; JCOG, Japan Clinical Oncology Group; SAMCRC, South Australian metastatic colorectal cancer.

Table S6. Newcastle-Ottawa Scale for assessing the quality of included observational studies

Study	Newcastle-Ottawa Scale Score (Total)	Newcastle-Ottawa Scale		
		Selection	Comparability	Exposure/Outcome
Michel et al. [1]	5	★★		★★★
Costi et al. [2]	5	★★		★★★
Konyalian et al. [3]	5	★★		★★★
Bajwa et al. [4]	6	★★	★	★★★
Cellini et al. [5]	5	★★		★★★
Chan et al. [6]	7	★★★★		★★★
Mik et al. [7]	6	★★	★	★★★
Oliveira et al. [8]	6	★★★	★	★★
Tanoue et al. [9]	5	★★		★★★
Karoui et al. [10]	7	★★★★		★★★
Boselli et al. [11]	5	★★		★★★
Cetin et al. [12]	5	★★		★★★
Ahn et al. [15]	5	★★		★★★
de Mestier et al. [16]	8	★★★★	★	★★★
Duraker et al. [17]	6	★★	★	★★★
Gresham et al. [18]	7	★★★★		★★★
Ishihara et al. [19]	5	★★		★★★
Kim et al. [20]	7	★★★★		★★★
Matsumoto et al. [21]	8	★★★★	★	★★★
Miyamoto et al. [22]	5	★★		★★★
Tsang et al. [23]	7	★★★★		★★★
Watanabe et al. [24]	7	★★★★		★★★
Yoon et al. [25]	6	★★★		★★★
Yun et al. [26]	8	★★★★	★	★★★
Ahmed et al. [27]	7	★★★★		★★★
Kodaz et al. [28]	6	★★	★	★★★
Niitsu et al. [29]	8	★★★★	★	★★★
Slesser et al. [30]	8	★★★★	★	★★★
Xu et al. [31]	6	★★★		★★★
Ahmed et al. [32]	5	★★		★★★
He et al. [33]	7	★★★★		★★★
Samalavicius et al. [34]	6	★★★		★★★
Shida et al. [35]	6	★★★		★★★
‘t Lam-Boer et al. [36]	7	★★★★		★★★
Wang et al. [37]	7	★★★	★	★★★
Wong et al. [38]	8	★★★★	★	★★★
Alawadi et al. [39]	8	★★★★	★	★★★
Mehta et al. [40]	7	★★★★		★★★
Cao et al. [41]	6	★★★		★★★
Korkmaz et al. [42]	5	★★		★★★
Lau et al. [43]	6	★★	★	★★★
Maroney et al. [44]	8	★★★★	★	★★★
Shida et al. [45]	8	★★★★	★	★★★
Chen et al. [46]	6	★★★		★★★
Ergun et al. [47]	8	★★★★	★	★★★

Huang et al. [48]	6	★★★		★★★
Kim et al. [49]	6	★★	★	★★★
Urvay et al. [51]	6	★★★		★★★
Doah et al. [52]	8	★★★★	★	★★★
Kawamura et al. [54]	5	★★		★★★
Benavides et al. [55]	5	★★		★★★
van der Kruijssen et al. [56]	5	★★		★★★
Cheng et al. [57]	6	★★	★	★★★
Ho et al. [58]	6	★★	★	★★★
Sertesen et al. [60]	6	★★	★	★★★
Vatandoust et al. [62]	6	★★	★	★★★
Von Einem et al. [63]	6	★★	★	★★★
Ferrand et al. [14]	5	★★		★★★
Our study	9	★★★★	★★	★★★

Table S7. Subgroup analyses of overall survival according to therapy regimen

Overall survival	HR	95% CI L	95% CI U
Patients with unresectable mCRC within 21 days of targeted therapy gap			
Type of therapy			
Irinotecan base	0.77	0.60	1
Patients with unresectable mCRC within 60 days of targeted therapy gap			
Type of therapy			
Irinotecan base	0.94	0.78	1.14
Patients with unresectable mCRC within 21 days of targeted therapy gap			
Type of therapy			
Bevacizumab + irinotecan in wild type	0.86	0.51	1.47
Bevacizumab + irinotecan in mutation type	0.67	0.36	1.24
Cetuximab + irinotecan	1.89	0.82	4.34
Patients with unresectable mCRC within 60 days of targeted therapy gap			
Type of therapy			
Bevacizumab + irinotecan in wild type	0.98	0.67	1.45
Bevacizumab + irinotecan in mutation type	1.19	0.81	1.75
Cetuximab + irinotecan	1.13	0.65	1.98

Abbreviations: HR, hazard ratio; CI, confidence interval; L, lower; U, upper.

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