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Palliative primary tumor resection in minimally symptomatic (asymptomatic) patients with colorectal cancer and synchronous unresectable metastases versus chemotherapy alone (a meta-analysis)

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ABSTRACT *AIM: to evaluate outcomes (overall survival, rate of surgical intervention due to complications of first treatment, 30-day mortality rate) of palliative primary tumor resection (PTR) followed by chemotherapy and chemotherapy/radiotherapy (chemo/RT) alone in patients with asymptomatic or minimally symptomatic colorectal cancer (CRC) and synchronous unresectable metastases.*

MATERIALS AND METHODS: a meta-analysis based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines was conducted on PubMed and Cochrane database. Odds ratio (OR) and 95% confidence interval (95% CI) were used as the treatment effect measure for comparing results. Combined overall effect measures were calculated for a random effect model. All analyses were performed using the Review Manager 5.3 software.

RESULTS: eighteen non-randomized studies, including a total of 2,999 patients (1,737 PTR and 1,262 chemo/RT) were identified. Gender, age, site of primary tumor and distant metastasis of patients were comparable between groups in all analyzed studies. Two-year (38.2% vs. 21.1%; OR 0.42; 95% CI 0.28–0.64; p < 0.0001) and 5-year (12.7% vs. 5.3%; OR 0.45; 95% CI 0.21–0.97; p = 0.04) overall survival rates were significantly higher in the PTR group than in the chemo/RT group. No significant differences in 30-day mortality rate between the two groups (1.7% vs. 1%; OR 1.92; 95% CI 0.79–4.68; p = 0.15). However, the rate of surgical intervention due to complications of first treatment was significantly lower in the PTR group comparing to the chemo/RT group (2.3% vs. 14.53%; OR 0.18; 95% CI 0.08–0.40; p < 0.0001). At the same time, one hundred and fourteen patients (13.8%; OR 0.19; 95% CI 0.09–0.40; p < 0.0001) in the chemo/RT group required surgery for symptoms associated with a primary tumor.

CONCLUSIONS: PTR in patients with asymptomatic or minimally symptomatic CRC and synchronous unresectable metastases significantly improves overall survival, allows to prevent surgical intervention due to complications related to primary tumor and is not associated with increased postoperative mortality rate comparing to systemic chemotherapy/radiotherapy as a treatment of first line. The current data are based on non-randomized comparative studies and data from early terminated randomized controlled trials (RCTs) and further well-designed RCTs are required.

KEYWORDS: *Colorectal cancer; palliative resection; asymptomatic primary tumor; unresectable metastases; chemotherapy; overall survival; meta-analysis*

CONFLICT OF INTEREST: *The authors declare no conflict of interest.*

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INTRODUCTION

Approximately 20% of patients with colorectal cancer (CRC) are diagnosed with stage IV and substantial number of them have unresectable synchronous metastases [1,2]. Currently, palliative primary tumor resection (PTR) for unresectable metastatic CRC is considered as an option

to control tumor related obstruction, perforation or bleeding.PTR is not recommended for patients with minimally symptomatic primary tumor. The standard treatment for these patients according to NCCN [3,4] and ESMO [5,6] guidelines is a systemic chemotherapy and radiotherapy for rectal carcinomas. Comparative studies investigating the benefit of initial palliative PTR for patients with distant metastatic disease demonstrated conflicting results.

Several randomized clinical trials (RCT) comparing PTR followed by chemotherapy and chemo/RT alone were initiated [7–11], but none of them have been completed to date. Numbers of published non-randomized comparative studies reported that PTR can prolong the survival in asymptomatic or minimally symptomatic patients with CRC and synchronous unresectable metastases [12–16], while others found no benefits of PTR [17–27]. One of the major concerns about PTR is the risks of postoperative morbidity and mortality [28], which potentially can delay the initiation of systemic treatment [29], lead to the progression of disease and decrease survival [30–33]. In addition, some authors reported that liver metastases of colorectal origin increased their growth if primary tumor had been removed [34,35].

Most published meta-analyses included data from patients with both symptomatic and asymptomatic primary tumors, and some included studies with heterogeneous population, which may bias the outcomes [36–39].

Thus, the aim of this analysis was to compare outcomes (overall survival, rate of surgical intervention due to complications of first treatment, 30-day mortality rate) in patients with minimally symptomatic (asymptomatic) CRC and synchronous unresectable metastases after palliative PTR followed by chemotherapy or chemo/RT alone.

MATERIALS AND METHOD

Search Strategy

The meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (http://www.prisma-statement.org/) [40]. A literature search was performed through PubMed and Cochrane Database of Systematic reviews, using the following search strategy: (colon OR colorectal OR rectal) AND (cancer OR adenocarcinoma OR neoplasms OR carcinoma) AND ("palliative surgery" OR "primary tumor resection"). No restrictions were applied in terms of language, year or status of publication. Reference lists of selected publications, other systematic reviews or meta-analyses were hand-searched for additional relevant studies. The search period was from September, 1954 to March, 2022.

Inclusion and Exclusion Criteria

In accordance with the population, intervention, comparison, outcomes and study design (PICOS) criteria, the following eligibility criteria were selected for inclusion of the publications in the meta-analysis: (a) population: minimally symptomatic/asymptomatic patients with CRC and synchronous unresectable metastases; (b) intervention: surgical treatment, chemotherapy/radiotherapy; (c) comparison: PTR followed by chemotherapy versus chemo/RT alone; (d) outcomes: overall survival(OS), 30-day mortality rate, rate of surgical intervention due to complications of first treatment compared between two groups; and (e) study design: data from early terminated RCT, prospective/retrospective cohort trials or matched case-control (MCC) trials with sample size greater than 15.

The exclusion criteria were as follows: (a) lack of the sufficient data or outcomes of interest; (b) duplicate publication; (c) patients with primary-tumor symptoms and (d) non-comparative studies, reviews, meta-analyses, letters, case reports or conference abstracts. The search strategy is illustrated by Figure 1.

Data Extraction and Quality Assessment

Two authors (I.A. and M.A.) independently reviewed and assessed each study, according to the inclusion and exclusion criteria. In addition, they extracted and summarized the data from the included studies independently. Following information was collected: (a) study characteristics: the first author, country, year of publication, enrollment dates, number of patients, study type; (b) patient baseline characteristics: gender, age, Eastern Cooperative Oncology Group/World

Health Organization Performance Status (ECOG/WHO PS), site of primary tumor, site of distant metastasis, chemotherapeutic regimens; c) study outcomes: overall survival, 30-day mortality rate, rate of surgical intervention due to complication of first treatment. The quality of non-randomized trials was evaluated by using the Newcastle-Ottawa Scale (NOS) criterion [41], which allocates a maximum of 9 points to each study. A score ⩾ 6 indicated good quality [42].

The quality of included studies was determined by examining three factors: patient selection, comparability of the study groups and assessment of outcomes. Risk of bias of non-randomized trials was evaluated using the ROBINS-I [43]. If the mean and standard deviation (S.D.) were not provided, they were calculated using the method described by Wan et al. [44]. Inter-study heterogeneity was assessed by Chi^2 test and I^2 statistics as a measure describing degree of heterogeneity in which $P < 0.05$ was taken to indicate the presence of significant heterogeneity. Odds ratio was used as the treatment effect measure for comparing results. Combined overall effect measures were calculated for a random effect model and were presented with 95% coincidence interval. All p values < 0.05 were considered statistically significant. All analyses were performed using the Review Manager 5.3 software. The registration number in the International Prospective

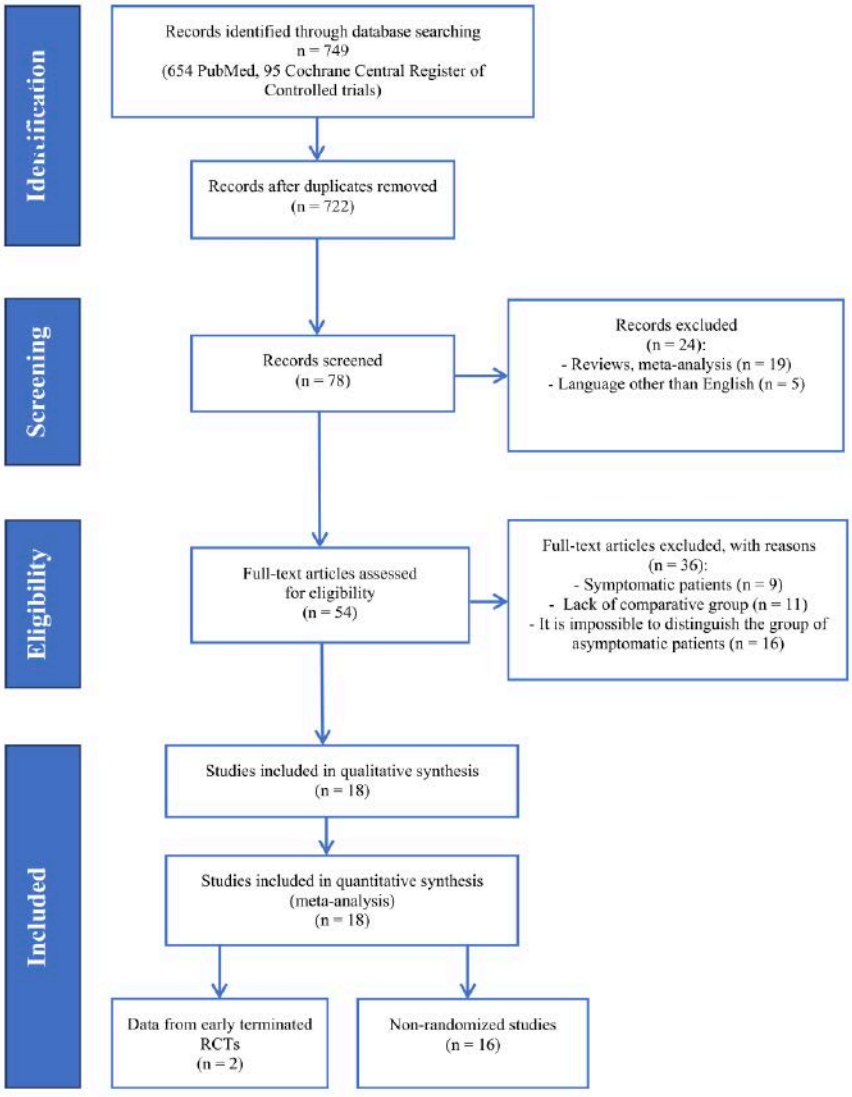

Figure 1. *Block diagram of literature search for a systematic review on PRISMA*

Table 1. The baseline characteristics of the included studies

First author, year of publication	Country	Years of the study	Study type	Patients (n)		NOS
				PTR	Chemo/RT	
Scoggins 1999 [17]	USA	1985–1997	RC, single	66	23	6
Ruo 2003 [12]	USA	1996–1999	RC, single	127	103	6
Michel 2004 [18]	France	1996–1999	RC, single	31	23	6
Benoist 2005 [19]	France	1997–2002	MCC, single	32	27	7
Galizia 2008 [13]	Italy	1995–2005	MCC, single	42	23	6
Seo 2010 [20]	Korea	2001–2008	PC, single	144	83	6
Cetin 2013 [21]	Turkey	2006–2010	RC, multi	53	46	6
Boselli 2013 [22]	Italy	2010–2011	RC, multi	17	31	6
Yun 2014 [23]	Korea	2000–2008	RC with PSM, single	113	113	8
Matsumoto 2014 [24]	Japan	2005–2011	RC, single	41	47	7
Watanabe 2014 [25]	Japan	2002–2009	RC, single	46	112	6
Ahmed 2015 [14]	Canada	1992–2005	RC, multi	521	313	6
Niitsu 2015 [26]	Japan	2007–2013	RC, single	42	15	7
Wang 2016 [15]	China	2011–2013	PC, single	118	73	7
Urvay 2020 [16]	Turkey	2009–2016	RC, multi	139	76	6
Doah 2021 [27]	Korea	2001–2018	RC, single	98	48	7
Park 2020 [45]	Korea	2013–2016	Early terminated RCT, multi	26 (23)*	22 (21)**	8
Kanemitsu 2021 [46]	Japan	2012–2019	Early terminated RCT, multi	81	84	8

*Note: PTR — primary tumor resection; chemotherapy/radiotherapy — chemo/RT; n — number of patients ; PC — prospective cohort study; RC — retrospective cohort study; MCC — Matched Case-Control study; RCT — randomized controlled trial; single — single-centre study; multi — multi-centre study; NOS — Newcastle-Ottawa scale; PSM — propensity score matching; * lost to follow-up n = 3; ** lost to follow-up n = 1*

Register of Systematic Reviews (PROSPERO) was CRD42022325629.

RESULTS

Study Characteristics

A total of 749 articles were identified at the initial literature search. After full text review of the remaining54 articles, 36 were excluded as they did not match the inclusion and exclusion criteria of this meta-analysis. Among these excluded studies, some were excluded due to the lack of comparative group, the others because they included data from patients with both symptomatic and asymptomatic primary tumors or it was not possible to distinguish the group of asymptomatic patients. Finally, 18 studies [12–27,45,46] were included in the meta-analysis (Fig. 1), with a total of 2,999 patients, of whom 1,737 were treated with PTR followed by chemotherapy (the PTR group) and 1,262 patients were first managed with chemo/RT alone (the chemo/RT group). There were 2matched case-control studies [13,19], 2 prospective cohort studies [15,20], 12 retrospective cohort study [12,14,16–18,21–27], and 2 studies with data from early terminated RCTs [45,46]. The baseline characteristics of the included studies are shown in Table 1. Heterogeneity of the studies ranged from 0% to 66%. The quality assessments of all NRCTs were evaluated using NOS and the results ranged from 6 to 8 stars, which corresponded to good quality. Risk of bias in the included studies was evaluated by using the ROBINS-I scale. All the included studies had an overall risk of bias: «low» — 3 studies, «moderate» — 12 studies, «severe» — 3 studies, «critical» — 0 studies.

Patients' Characteristics

The baseline characteristics of patients are reported in Table 2,3 and the information about available outcomes is demonstrated in Table 4,5. The rate of surgical intervention due to complications of first treatment was reported in 14 studies (Table 4). Gender, age, site of primary tumor and distant metastasis, ECOG/WHO PS of patients in the PTR and the chemo/RT groups were comparable in those studies. There were 571/952 (60%)

Table 2. *The baseline characteristics of patients*

First author	Age (Mean ± SD/median)		Gender (M/F)		ECOG/WHO PS 0-1/ ⩾ 2		Site of primary tumor C/(R or RS)		*Site of distant metastasis* (liver ± other location/ extra hepatic disease	
	PTR	Chemo/RT	PTR	Chemo/RT	PTR	Chemo/RT	PTR	Chemo/RT	PTR	Chemo/RT
Scoggins [17]	64 ± 13	64,75 ± 12,25	NA	NA	NA	NA	52/14	12/11	56/10	20/3
Ruo [12]	64 ± 10,83	61 ± 10,5	81/46	57/46	NA	NA	90/37	66/37	97/30	53/50
Michel [18]	59.8*	58.9*	17/14	16/7	25/6	21/2	28/3	15/8	31/0	23/0
Benoist [19]	60 ± 13	61 ± 12	19/13	18/9	NA	NA	23/9	23/4	32/0	27/0
Galizia [13]	62 ± 13	59 ± 14	28/14	15/8	31/11	17/6	35/7	18/5	42/0	23/0
Seo [20]	58*	56*	94/50	52/31	133/11	70/13	71/73	56/27	109/35	67/16
Cetin [21]	55 ± 11,25	52 ± 12,75	29/24	27/19	NA	NA	39/14	26/20	53/0	46/0
Boselli [22]	70 ± 7,5	73 ± 6,75	NA	NA	14/3	23/8	11/6	13/18	17/0	31/0
Yun [23]	59 ± 10,67	60 ± 8,67	73/40	68/45	NA	NA	70/43	79/34	96/17	100/13
Matsumoto [24]	66 ± 9,98	62,3 ± 8,39	25/16	33/14	38/3	44/3	29/12	36/11	NA	NA
Watanabe [25]	63 ± 10	60 ± 8,83	25/21	71/41	NA	NA	39/7	88/24	34/12	93/19
Ahmed [14]	69 ± 11,83	71 ± 9,5	297/224	186/127	419/102	200/113	365/156	196/117	400/121	243/70
Niitsu [26]	61.5 ± 4,13	59,8 ± 5,25	8/34	7/8	42/0	15/0	31/11	4/11	NA	NA
Wang [15]	57 ± 9,17	58 ± 8,5	65/53	43/30	103/15	61/12	73/45	42/31	NA	NA
Urvay [16]	59 ± 10,5	62 ± 9,83	85/54	51/25	101/38	44/32	NA	NA	NA	NA
Doah [27]	68 ± 14,29	67,8 ± 9,92	49/49	29/19	NA	NA	68/30	27/21	72/26	31/17
Park [45]	62.3 ± 11,8	58.8 ± 12,1	21/5	12/10	25/1	20/2	17/9	18/4	NA	NA
Kanemitsu [46]	64,3 ± 7,54	65 ± 9,04	45/36	45/39	81/0	84/0	75/6	78/6	60/21	60/24

*Note: PTR — primary tumor resection; chemotherapy/radiotherapy — chemo/RT; SD — standard deviation; ECOG/WHO PS — Eastern Cooperative Oncology Group/ World Health Organization Performance Status; M — male; F — female; C — colon; R — rectum; RS — rectosigmoid colon; NA — not available; * — median*

males in the PTR group and 486/804 (60%) in the chemo/RT group ($p = 0.89$; test for heterogeneity: df = 12 (P = 0.50), $I^2 = 0\%$) in 13 studies, data were not available in 1 study. In 12 studies the mean difference of age between the two groups was 0.90 (95% CI: -0.30 to 2.10; $p = 0.14$; test for heterogeneity: df = 11 (P = 0.23), $I^2 = 22\%$; $n = 1564$). There were 309/1,018 (30%) patients with rectal or rectosigmoid colon tumors in the PTR group and 243/827 (29%) in the chemo/RT group in 14 studies ($p = 0.46$; test for heterogeneity: df = 13 (P = 0.005), $I^2 = 57\%$). In 11 studies patients with metastatic liver disease were prevalent in both groups: 682/833 (82%) and 543/685 (79%) in the PTR and the chemo/RT groups, respectively ($p = 0.71$; test for heterogeneity: df = 6 (P = 0.007), $I^2 = 66\%$), data were not available in 3 studies. In 7 studies with available ECOG/WHO PS scores, most patients in both groups had scores from 0 to 1: 436/483 (90%) patients in the PTR group and 317/355 (89%) in the chemo/RT group(P = 0.22; test for heterogeneity: df = 5 (P = 0.53), $I^2 = 0\%$). Thirty-day mortality rate was assessed in 16 studies (Table 4). Gender, age, site of primary tumor and distant metastasis, ECOG/WHO PS was similar between the two groups in these studies. There were 579/994 (58%) males in the PTR group and 493/819 (60%) in the chemo/RT group in 14 studies ($p = 0.6$; test for heterogeneity: df = 13 (P = 0.29), $I^2 = 15\%$), but data were not available in 2 studies. In 14 studies the mean difference of age between the two groups was 0.77 (95% CI: -0.36 to 1.91;

Table 3. *The baseline characteristics of patients. Chemotherapy regimens*

First author	PTR	Chemo/RT
Scoggins [17]	NA	5-FU-based CT ± RT
Ruo [12]	NA	5-FU ± leucovorin ± RT
Michel [18]	Oxaliplatin/irinotecan	Oxaliplatin/irinotecan ± RT
Benoist [19]	5-FU ± leucovorin ± irinotecan	5-FU ± leucovorin ± irinotecan
Galizia [13]	5-FU ± oxaliplatin/irinotecan	5-FU ± oxaliplatin/irinotecan
Seo [20]	5-FU ± oxaliplatin/ irinotecan	5-FU ± oxaliplatin/ irinotecan
Cetin [21]	IFL + bevacizumab/XELOX + bevacizumab/ FOLFIRI + bevacizumab	XELOX + bevacizumab/FOLFIRI + bevacizumab
Boselli [22]	FOLFOX ± bevacizumab	FOLFOX ± bevacizumab
Yun [23]	Oxaliplatin-based CT ± targeted agents/ irinotecan-based CT ± targeted agents/ 5-fluorouracil-based CT ± targeted agents	Oxaliplatin-based CT ± targeted agents/ irinotecan-based CT ± targeted agents/ 5-fluorouracil-based CT ± targeted agents
Matsumoto [24]	FOLFOX/FOLFIRI/oxaliplatin + S-1 (SOX)/ CPT-11 + UFT/LV/simplifiedLV5FU2/UFT/LV	FOLFOX ± bevacizumab/FOLFOX ± cetuximab/ FOLFIRI ± bevacizumab/irinotecan + S-1 (IRIS)/ oxaliplatin + S-1 + bevacizumab ± RT
Watanabe [25]	5-FU/ IFL/ FOLFOX/FOLFIRI + SOL/FOLFOX + sunitinib regimen + bevacizumab/FOLFIRI + bevacizumab	5-FU/ IFL/ FOLFOX/FOLFIRI + SOL/ FOLFOX + sunitinib regimen + bevacizumab/ FOLFIRI + bevacizumab
Ahmed [14]	5-FU + leucovorin/oxaliplatin-based CT ± bevacizumab/irinotecan-based CT ± bevacizumab	5-FU + leucovorin/oxaliplatin-based CT ± bevacizumab/irinotecan-based CT ± bevacizumab ± RT
Niitsu [26]	mFOLFOX6 ± bevacizumab or cetuximab or panitumumab/XELOX ± bevacizumab or cetuximab or panitumumab/FOLFIRI	mFOLFOX6 ± bevacizumab or cetuximab or panitumumab/XELOX ± bevacizumab or cetuximab or panitumumab/FOLFIRI
Wang [15]	FOLFOX/XELOX/FOLFIRI + bevacizumab	FOLFOX/XELOX/FOLFIRI + bevacizumab ± RT
Urvay [16]	(FOLFIRI or FOLFOX or XELOX) ± (bevacizumab or cetuximab or panitumumab)	(FOLFIRI or FOLFOX or XELOX) ± (bevacizumab or cetuximab or panitumumab)
Doah [27]	Fluorouracil/capecitabine/(fluorouracil ocapecitabine) + (irinotecan or oxaliplatin) ± (bevacizumab or cetuximab)	Fluorouracil/capecitabine/(fluorouracil or capecitabine) + (irinotecan or oxaliplatin) ± (bevacizumab or cetuximab)
Park [45]	(FOLFIRI or FOLFOX) ± (cetuximab or bevacizumab)	(FOLFIRI or FOLFOX) ± (cetuximab or bevacizumab)
Kanemitsu [46]	mFOLFOX6 + bevacizumab/CapeOX + bevacizumab/ irinotecan/TAS-102/ EGFR antibodies/ S-1	mFOLFOX6 + bevacizumab/CapeOX + bevacizumab/ irinotecan/TAS-102/ EGFR antibodies/ S-1

Note: PTR — primary tumor resection; chemotherapy/radiotherapy — chemo/RT; NA — not available; FOLFIRI = 5-FU + leucovorin + irinotecan; FOLFOX = 5-FU + leucovorin + oxaliplatin; S-1 = tegafur + gimeracil + oteracilpotassium; CapeOX = capecitabine + oxaliplatin

$p = 0.18$; test for heterogeneity: df = 13 (P = 0.18), $I^2 = 25\%$; $n = 1{,}669$). There were 326/1,077 (30%) patients with rectal or rectosigmoid colon tumors in the PTR group and 272/873 (31%) in the chemo/RT group in 16 studies ($p = 0.16$; test for heterogeneity: df = 15 (P = 0.0005), $I^2 = 62\%$). The information about extent of metastatic disease was available in 12 studies: patients with metastatic liver disease were 699/850 (82%) and 574/716 (80%) in the PTR and the chemo/RT groups, respectively ($p = 0.71$; test for heterogeneity: df = 6 (P = 0.007), $I^2 = 66\%$). In 9 studies with available ECOG/WHO PS scores, most patients in both groups had scores from 0 to 1: 492/542 (91%) in the PTR

Table 4. *Outcomes: rate of surgical intervention due to complication of first treatment, 30-day mortality*

First author	Patients (n)		Surgical intervention due to complication of first treatment (%)		30-day mortality (%)	
	PTR	Chemo/RT	PTR	Chemo/RT	PTR	Chemo/RT
Scoggins [17]	66	23	3	8,7	4,6	0
Ruo [12]	127	103	4,7	29	1,6	0
Michel [18]	31	23	0	21,7	0	0
Benoist [19]	32	27	0	14,8	0	0
Galizia [13]	42	23	0	17,4	0	0
Seo [20]	144	83	2,8	4,8	0	0
Cetin [21]	53	46	5,7	4,4	0	0
Boselli [22]	17	31	NA	NA	29,4	19,3
Yun [23]	113	113	0,9	0	0,9	2,7
Matsumoto [24]	41	47	0	38,3	0	0
Watanabe [25]	46	112	0	16	0	0
Ahmed [14]	521	313	NA	NA	4,8	NA
Niitsu [26]	42	15	NA	20	0	0
Wang [15]	118	73	5,1	6,6	2,5	0
Urvay[16]	139	76	NA	NA	NA	9,2
Doah [27]	98	48	0	27,1	0	0
Park [45]	26	22	0	18,2	3,8	0
Kanemitsu [46]	81	84	1,2	13	4	0

Note: PTR — primary tumor resection; chemotherapy/radiotherapy — chemo/RT; NA — not available; n — number of patients

group and 355/401 (89%) in the chemo/RT group (P = 0.17; test for heterogeneity: df = 6 (P = 0.65), I^2 = 0%).

Two-year overall survival was assessed in 7 studies (Table 5). The groups were comparable in terms of sex, age, site of primary tumor and distant metastasis. There were 299/484 (62%) males in the PTR group and 196/324 (60%) in the chemo/RT group (p = 0.75; test for heterogeneity: df = 5 (P = 0.25), I^2 = 24%) in 6 studies, data were not available in 1 study. In 7 studies the mean difference of age between the two groups was 0.13 (95% CI: -2.05 to 2.31; p = 0.91; test for heterogeneity: df = 6 (P = 0.07), I^2 = 49%; n = 897). There were 121/411 (29%) patients with rectal or rectosigmoid tumors in the PTR group and 92/271 (34%) in the chemo/RT group (p = 0.48; test for heterogeneity: df = 5 (P = 0.12), I^2 = 43%) in 6 studies, data were not available in one study. In 4 studies patients with metastatic liver disease were prevalent in both groups: 227/267 (85%) and 123/176 (70%) in the PTR and the chemo/RT groups, respectively (p = 0.3; test for heterogeneity: df = 1 (P = 0.09), I^2 = 65%), data were not available in 3 studies. There were significant differences between the two groups in the comorbidity in 4 studies with available ECOG/WHO PS scores: 260/325 (80%) patients in the PTR group and 142/194 (73%) in the chemo/RT grouphad scores from 0 to 1 (p = 0.03; test for heterogeneity: df = 3 (P = 0.72), I^2 = 0%). Though in most studies fluorouracil-based chemotherapy regimens combined with targeted agents was used, the protocols of systemic treatment varied in great degree (Table 3). Because in most studies median follow-up was reported without range, it was impossible to calculate the mean and standard deviation using the method described by Wan and colleagues [44].

Table 5. Outcomes: overall survival (OS), median survival

First author	Patients (n)		Follow-up mean ± SD/ median (months)	OS (%)		Median survival (months)		P value
	PTR	Chemo/RT		PTR	Chemo/RT	PTR	Chemo/RT	
Scoggins [17]	66	23	NA	17 (2-year)	18 (2-year)	14,5	16,6	0,59
Ruo [12]	127	103	NA	25 (2-year)	6 (2-year)	16	9	0,001
Michel [18]	31	23	NA	NA	NA	21	14	0,718
Benoist [19]	32	27	24*	44 (2-year)	41 (2-year)	23	22	0,753
Galizia [13]	42	23	16*	38 (2-year)	17 (2-year)	15,2	12,3	0,03
Seo [20]	144	83	49*	NA	NA	22	14	NS
Cetin [21]	53	46	NA	NA	NA	23	17	0,322
Boselli [22]	17	31	7*	17,6 (1-year)	19,4 (1-year)	4	5	NS
Yun [23]	113	113	16 ± 26,5	4,9 (5-year)	3,5 (5-year)	17,2	14,4	0,16
Matsumoto [24]	41	47	21,3*	NA	NA	23,9	22,6	NS
Watanabe [25]	46	112	26*	NA	NA	19,9	19	NS
Ahmed [14]	521	313	NA	NA	NA	19,7	8,4	< 0,0001
Niitsu [26]	42	15	19,2/13,4**	NA	NA	23,9	13,4	0,093
Wang [15]	118	73	20*	NA	NA	22,5	17.8	< 0,01
Urvay [16]	139	76	24,6 ± 17,4	57 (2-year) 19 (5-year)	30 (2-year) 8 (5-year)	29,6	14,2	< 0,001
Doah [27]	98	48	18*	NA	NA	18	15	0,15
Park [45]	23	21	15*	69,5 (2-year)	44,8 (2-year)	NA	NA	0,058
Kanemitsu [46]	81	84	22,1*	32,9 (3-year)	33 (3-year)	25,9	26,4	0,72

*Note: PTR — primary tumor resection; chemotherapy/radiotherapy — chemo/RT; NA — not available; n — number of patients; OS — overall survival; NS — no significant differences (P > 0,05); SD — standard deviation; * — median; ** — 19,2 months in the PTR group and 13,4 in Chemo/RT group (median)*

The median follow-up of the studies ranged from 15 to 24.6 months.

Five-year overall survival was assessed in 2 studies (Table 5). Gender, age, follow-up of patients in the PTR and the chemo/RT groups were similar in those studies. There were 158/252 (63%) males in the PTR group and 119/189 (63%) in the chemo/RT group (P = 0.93; test for heterogeneity: df = 1 (P = 0.27), I^2 = 18%). The mean difference of age between the two groups in those studies was — 1.92 (95% CI: -3.87 to 0.03; P = 0.05; test for heterogeneity: df = 1 (P = 0.30), I^2 = 8%; *n* = 441). The mean difference of follow-up between the two groups was 0.00 (95% CI: -3.98 to 3.98; P = 1.00; test for heterogeneity: df = 1 (P = 1.00), I^2 = 0%; *n* = 441). Only 1 study reported the data site of primary tumor and distant metastasis of patients: 43/113 (38%) patients were with rectal tumor in the PTR group and 34/113 (30%) in the chemo/RT group (P = 0.52), 96/113 (85%) patients in the PTR group and 100/113 (88%) in the chemo/RT group had metastatic liver disease (P = 0.43). Only 1 study had the data comorbidity available, most of the patients had ECOG PS 0-1: 101/139 (73%) patients in the PTR group and 44/76 (58%) in the chemo/RT group (P = 0.12).

Outcomes: rate of surgical intervention due to complications of first treatment and 30-day mortality rate

There were 14 studies [12,13,15,17–21,23–25,27,45,46] that evaluated the rate of surgical intervention due to complications of first treatment (1,018 patients in the PTR group and 827 patients in the chemo/RT group) and 16 studies [12,13,15,17–27,45,46] that reported 30-day mortality rate (1,077 patients in the PTR group and 873 patients in the chemo/RT group) (Table 4).

There were significant differences between the two groups in the rate of surgical intervention due to complications of first treatment (2.3% vs.14.53%; OR 0.18; 95%CI 0.08 — 0.40; P < 0.0001; test for heterogeneity: df = 13 (P = 0.02), I^2 = 50%; *n* = 1,845) (Fig. 2A). One hundred and fourteen patients (13.8%; OR 0.19; 95%CI 0.09 — 0.40; P < 0.0001) in the chemo/RT group underwent surgery for symptoms related to the primary tumor (Fig. 2B). There were no significant differences between the two groups in the 30-day mortality rate (1.7% vs. 1%; OR 1.92; 95% CI 0.79–4.68; P = 0.15; test for heterogeneity: df = 6 (P = 0.71), I^2 = 0%; *n* = 1,950) (Fig. 2C).

Outcomes: 2-year and 5-yearoverall survival

Two-year overall survival was reported in 7 studies [12,13,15–17,19,45], including 547 patients in the PTR group and 346 patients in the chemo/RT group (Table 5). There were significant differences between the two groups in 2-year OS (38.2%vs. 21.1%; OR 0.42; 95% CI 0.28 — 0.64; P < 0.0001; test for heterogeneity: df = 6 (P = 0.20), I^2 = 29%; *n* = 893) (Fig. 3A). Five-year overall survival was assessed in 2 studies [16,23], including 252 patients in the PTR group and 189 patients in the chemo/RT group (Table 5). There were significant differences between the two groups in 5-year OS (12.7% vs. 5.3%; OR 0.45; 95%CI 0.21 — 0.97; P = 0.04; test for heterogeneity: df = 1 (P = 0.49), I^2 = 0%; *n* = 441) (Fig. 3B).

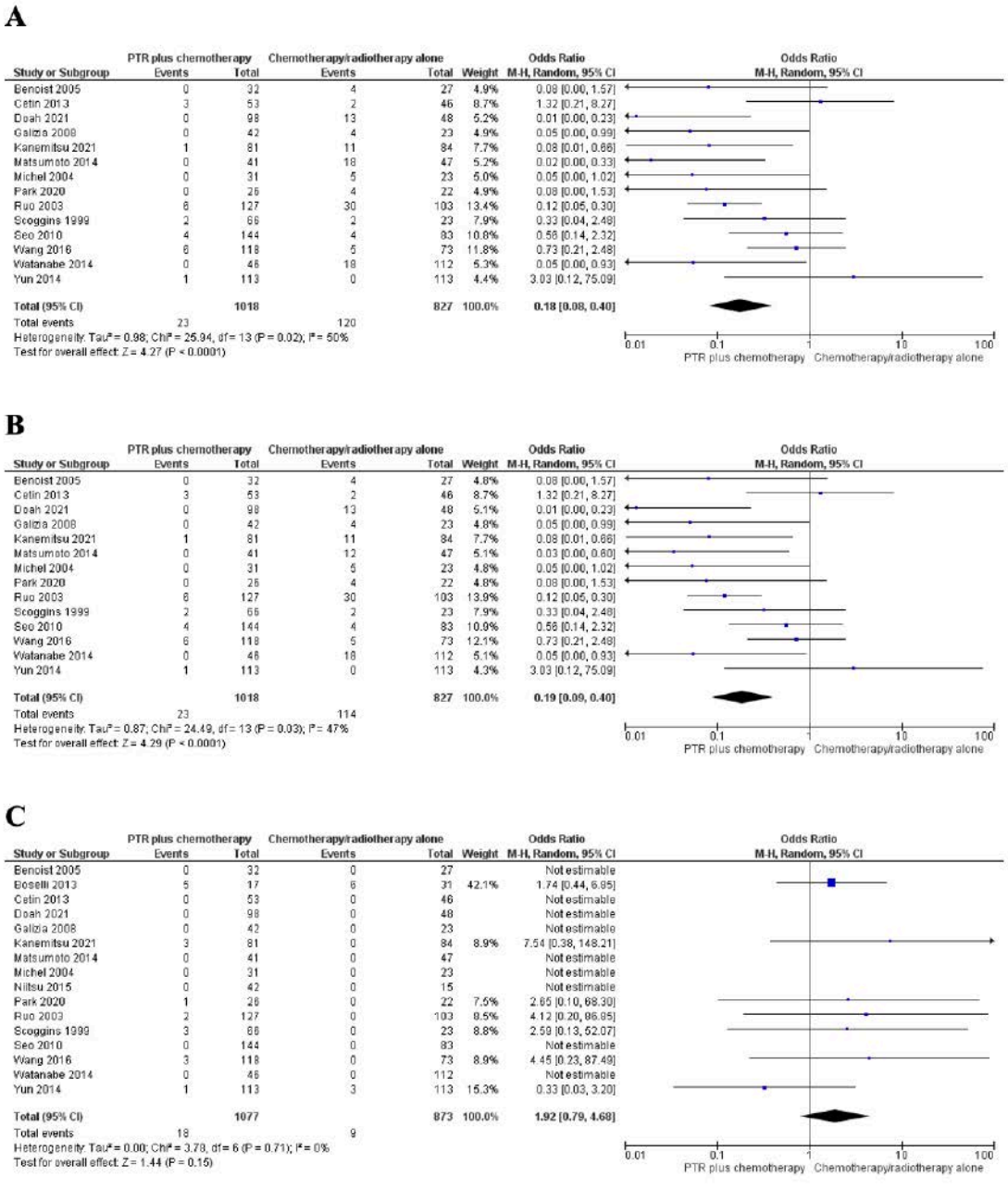

Figure 2. *Forest plots of odds ratios of: rate of surgical intervention due to complications of first treatment (A), rate of surgical intervention due to complications of first treatment, included only patients underwent surgery for symptoms linked to the primary tumor in the chemo/RT group (B) and 30-day mortality rate (C)*

Table 6. *Randomized controlled trials (RCTs)*

RCT name	Country	RCT №	Primary outcome	Simple size	Study start year/ estimated study completion year	Status
SYNCHRONOUS [7]	Germany	ISRCTN30964555	3 years OS	800 → 392	2011-2019	Ongoing/no longer recruiting
CAIRO4 [8]	Netherlands	NCT01606098	5 years OS	360	2012-2020	Recruiting
CCRe-IV [9]	Spain	NCT02015923	2 years OS	336	2013-2018	Ongoing/ no longer recruiting
CLIMAT [10]	France	NCT02363049	2 years OS	278	2014-2018	Recruiting
PTR Trial [47]	Korea	NCT01978249	2 years OS	480	2013-2016	Early terminated*
China multicenter [11]	China	NCT02149784	3 years OS	480	2015-2019	Recruiting
JCOG1007 [48]	Japan	UMIN000008147	3 years OS	770 → 280	2012-2020	Early terminated*

*Note: * — trial was early terminated because of the difficulties of participant enrolment.*

DISCUSSION

The necessity of palliative PTR for asymptomatic or minimally symptomatic patients with CRC and synchronous unresectable metastases is controversial. Currently, only results of non-randomized studies are available on this issue. Several RCTs were initiated comparing PTR followed by chemotherapy with chemo/RT alone in patients with unresectable disseminated metastatic CRC, but not completed yet (Table 6).

Two RCTs [47,48] were terminated early because of the complicated enrolment of patients. Kanemitsu et al. [46] published an interim analysis of early terminated RCT for165 enrolled patients (81 in the PTR and 84 in the chemo/RT groups) and reported that PTR had no benefits in terms of survival, but resulted in higher postoperative mortality rate. Three-year OS was 32.9% in the PTR group and 33% in the chemo/RT group. Median OS was 25.9 months in the PTR group and 26.4 months in the chemo/RT group. Three patients (4%) died due to complications within 30 days after surgery in the PTR group. However, the patients in the chemo/RT group had a higher rate of complications requiring operation after first treatment compared with palliative primary tumor resection (13%vs.1.2%). The study was terminated early by a decision of the Data and Safety Monitoring Committee, and thus the planned statistical power of70% in the

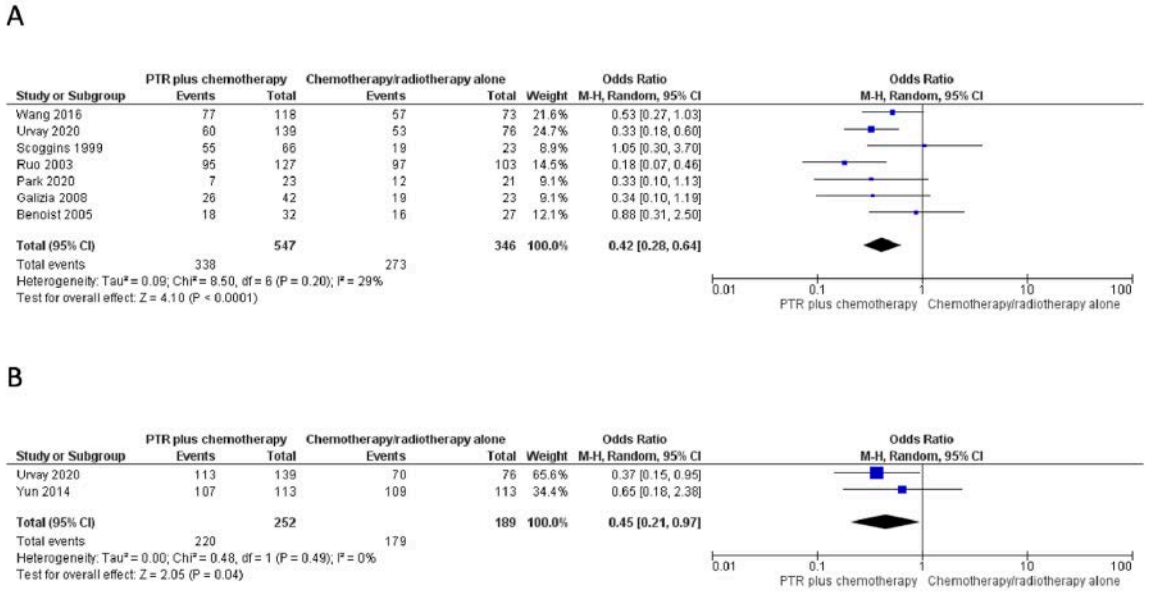

Figure 3. *Forest plots of odd ratios of 2-year overall survival (A) and 5-year overall survival (B)*

planned sample size of 280 patients was not achieved.

Another RCT was terminated early because of the lack of patient enrolment and cessation of funding. Park et al. [45] published an interim analysis with a sample size of 44 patients (23in the PTR group and 21 in the chemo/RT group), whichwasapproximately10-fold smaller than the planned sample size of 480 patients. The researchers found that PTR followed by chemotherapy had only benefit for 2-year cancer-specific survival over chemotherapy alone (72.3%vs. 47.1%; P = 0.049). Although 2-year OS was higher by 25% in the PTR group (69.5% vs. 44.8%), the difference did not reach statistical significance (P = 0.058), which indicates that the study was obviously underpowered. The complications requiring operation after first treatment were found only in the chemo/RT group and the rate was 18.2%, though palliative PTR was associated with a postoperative mortality rate of 3.8%.

Most previous meta-analyses evaluating the role of PTR for patients with CRC and synchronous unresectable metastases included data from patients with both symptomatic and asymptomatic primary tumors [36–39]. The first meta-analysis including only asymptomatic patients was published by Cirocchiet al. in 2012 [49]. The authors included only seven non-randomized trials with 1,086 patients and reported that PTR in asymptomatic patients with unresectable advanced CRC did not improve OS comparing to chemo/RT alone and did not prevent surgical interventions due to complications related to primary tumor. Nevertheless, the authors did not find an association of high postoperative mortality with PTR. Our outcomes are not corresponding to this meta-analysis except the data on postoperative mortality. It can be explained by several new studies published on this issue since 2012 which may change the outcomes. In addition, the authors reported survival outcomes in only 4 studies with 443 patients. Hendren et al. [29] reported that postoperative complications in patients with CRC who underwent surgical resection of the primary tumor were independently associated with a delay in adjuvant chemotherapy, which, in turn, may lead to the progression of the disease and decrease survival. However, Cochrane systematic review, published by Claassen et al. [50] and based on 3 RCTs (351 participants), showed that immediate treatment with chemotherapy did not provide a clear survival benefit compared to delayed chemotherapy for asymptomatic incurable metastatic colorectal cancer (HR = 1.17; 95% CI 0.93–1.46). To date, several cohort studies analyzing the data from national registries have also been published. Some published comparative studies showed survival benefit of PTR over chemotherapy alone [51,52,53], while other studies found no advantages [54]. We did not include these papers into our meta-analysis because it was impossible to distinguish the group of asymptomatic patients in these population-based studies.

In this meta-analysis heterogeneity of the studies ranged from 0% to 66%. There was no significant heterogeneity between the included studies in gender, age, ECOG/WHO PS in analysis rate of surgical intervention due to complications of first treatment and 30-day mortality rate. Nonetheless, there was significant heterogeneity between the studies in term of primary tumor location (colon and rectal/rectosigmoid) and site distant metastasis (hepatic and extrahepatic) in analysis rate of surgical intervention due to complications of first treatment: df = 13 (P = 0.005), I^2 = 57%; df = 6 (P = 0.007), I^2 = 66%, respectively. Significant heterogeneity also was seen in site of primary tumor location (colon and rectal/rectosigmoid) and distant metastasis (hepatic and extrahepatic tumor burden) in analysis of 30-day mortality rate: df = 15 (P = 0.0005), I^2 = 62%; df = 6 (P = 0.007), I^2 = 66%, respectively. There was no significant heterogeneity between the included studies in gender, age, comorbidity, site of primary tumor and distant metastasis in analysis of 2-year OS. In contrast, significant heterogeneity among the studies in terms of gender, age, follow-up was detected in the analysis of 5-year OS. It was impossible to assess the heterogeneity between the included studies in comorbidity, site of primary tumor and distant metastasis because data were available in only 1 of 2 studies. The results of the presented meta-analysis demonstrate that asymptomatic or minimally symptomatic patients with stage IV CRC have benefits from palliative primary tumor resection followed by chemotherapy over chemotherapy and/or radiotherapy alone, such as improvement of the overall survival rate: for 2-year OSOR 0.42,

95%CI 0.28 — 0.64(P < 0.0001) and for5-year OS OR 0.45; 95%CI 0.21– 0.97 (P = 0.04). Also, PTR has advantage as prophylaxis of primary tumor related complications: OR 0.19; 95%CI 0.09– 0.40 (P < 0.0001).

There are some limitations in this meta-analysis. Most included patients had good performance status (ECOG PS 0-1), and therefore were good candidates for both aggressive chemotherapy and surgical palliation. In all included studies patients with metastatic liver metastatic disease were prevalent; however, an extent of metastases, their number and size varied in a great degree, which influenced oncologic outcomes. The chemotherapy protocols between the included studies were heterogeneous among patients, though most patients received fluorouracil-based combination chemotherapy regimens with monoclonal antibodies. The current analysis was also limited by unavailable data in some studies. We did not contact the authors to achieve additional data which were not published, although it would potentially improve the quality of the meta-analysis. But the main drawback was the lack of RCTs. SYNCHRONOUS (ISRCTN30964555), CAIRO4 (NCT01606098), CCRe-IV (NCT02015923), CLIMAT (NCT02363049) and China multicenter (NCT02149784) are still in progress, and acquisition of data allows to elucidate the role of PTR in treatment of disseminated CRC.

CONCLUSION

The results of this meta-analysis have demonstrated that PTR in patients with asymptomatic or minimally symptomatic CRC and synchronous unrespectable metastases significantly improves overall survival, allows to prevent surgical intervention due to complications related to primary tumor and is not associated with increased postoperative mortality rate comparing to systemic chemotherapy and/or radiotherapy as a treatment of first line. The current data are based on non-randomized comparative studies and data from early terminated RCTs and further well-designed RCTs are required.

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