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RESEARCH

Impact on survival benefits of asymptomatic primary tumor resection after bevacizumab plus FOLFIRI as first-line therapy for patients with metastatic colorectal cancer with synchronous unresectable metastasis

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Abstract

Background Metastatic colorectal cancer (mCRC) poses a clinical challenge and requires a combination of systemic therapy and conversion surgery. Although first-line chemotherapy and targeted therapy are considered the standard treatments for mCRC, the role of primary tumor resection (PTR) in asymptomatic synchronous mCRC with unresectable metastatic lesion after initial therapy remains relatively underexplored.

Materials A retrospective review was conducted from January 2015 to January 2021, involving 74 patients with synchronous mCRC who received bevacizumab plus FOFIRI as first-line systemic therapy. All 74 patients had unresectable metastatic lesions confirmed through multidisciplinary team discussion. Patient characteristics, PTR data, and radiotherapy (RT) and overall survival (OS) outcomes were analyzed. The patients were categorized into a "PTR" group and a "No PTR" group and then further stratified into "4A," "4B," and "4C" subgroups based on the initial mCRC stage. Additionally, four subgroups—namely "PTR(+)/RT(+)," "PTR(+)/RT(−)," "PTR(−)/RT(+)," and "PTR(−)/RT(−)"—were formed to assess the combined effects of PTR and RT.

Results The median OS for all the patients was 23.8 months (20.5–27.1 months). The "PTR" group exhibited a significantly higher median OS of 25.9 months (21.3–30.5 months) compared with 21.4 months (15.8–27.1 months) in the "No PTR" group ($p = 0.048$). Subgroup analyses revealed a trend of improved survival with PTR in patients with stage IVA and IVB; however, the results were not statistically significant ($p = 0.116$ and 0.493, respectively). A subgroup analysis of PTR and RT combinations revealed no significant difference in median OS rates.

Conclusion For asymptomatic mCRC with synchronous unresectable distant metastasis, PTR following first-line therapy with bevacizumab plus FOLFIRI may provide a potential survival benefit, particularly in stage IVA/IVB patients compared with stage IVC patients. Additionally, RT for primary tumor did not provide an additional OS benefit in mCRC with unresectable metastasis. A prospective randomized trial with a larger sample size is essential to further elucidate the role of PTR in this context.

Keywords Colorectal cancer · Asymptomatic · Unresectable metastasis · Primary tumor resection · First-line bevacizumab plus FOLFIRI

Background

Globally, colorectal cancer (CRC) ranks as the third most commonly diagnosed type of malignant cancer worldwide [1]. The highest annual number of CRC cases was reported in Asia, and the annual incidence rate continues to increase, considerably affecting public health [1]. Although early-stage CRC can be effectively treated with curative surgical resection, managing metastatic CRC (mCRC) poses a considerable clinical challenge that necessitates a combination of systemic therapy and surgery [2–4]. The standard approach to mCRC treatment involves precise first-line systemic therapy tailored on the basis of the *RAS, BRAF* gene type, and microsatellite instability status [5–7]. Surgical

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resection, including primary tumor resection (PTR) and metastasectomy, is often recommended after neoadjuvant systemic therapy and is believed to provide survival benefits for patients with mCRC [7–9]. The combination of PTR and metastasectomy is considered the most favorable scenario following neoadjuvant therapy for curative resection in such patients [8]. However, the role of PTR in the treatment of mCRC with unresectable distant metastasis after first-line therapy remains a topic of controversy.

Several meta-analyses and systemic review articles have explored the effect of PTR on mCRC with unresectable metastasis, with the majority suggesting that PTR contributes to survival benefits [10–12]. However, many of these analyses have included studies where PTR was followed by either intensive or palliative chemotherapy [13–15]. Moreover, systemic therapy typically involves chemotherapy without targeted therapy [13–15]. Notably, survival outcome data for mCRC with synchronous unresectable distant metastasis following neoadjuvant chemotherapy and targeted therapy are lacking. In the present single-institution study, we retrospectively evaluated 74 patients with mCRC with synchronous unresectable distant metastasis who received bevacizumab plus FOLFIRI (folinic acid, 5-fluorouracil, and irinotecan). Real-world data—including those related to the effects of PTR, radiotherapy (RT), and survival outcomes—were analyzed.

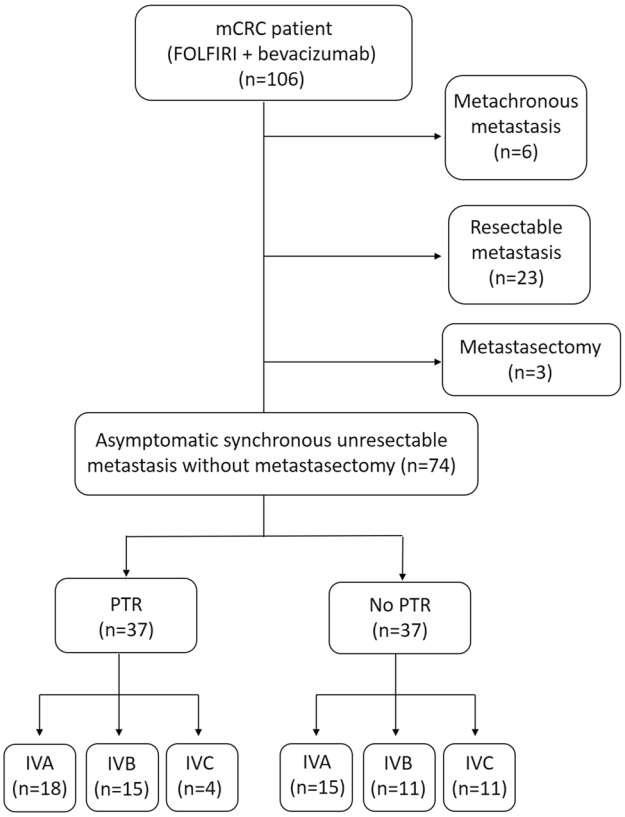


Fig. 1 Flowchart of patient selection and classification

Materials and methods

Patients

Patient selection

From the database of a single medical center, we enrolled 106 patients with mCRC who received bevacizumab plus FOLFIRI as first-line systemic therapy from January 2015 to January 2021. Six of these patients with metachronous mCRC were then excluded. One colorectal surgeon and one radiologist reviewed initial diagnostic computed tomography (CT) images or magnetic resonance images to determine the resectability of the metastatic lesions. Twenty-three patients with mCRC with resectable metastasis were subsequently excluded. Additionally, based on medical records, three patients with mCRC who underwent metastasectomy following systemic therapy were excluded. Thus, the final analysis included 74 patients with mCRC with asymptomatic synchronous unresectable metastasis and no history of metastasectomy. A patient selection flowchart is presented in Fig. 1. The present study protocol was approved by the Institutional Ethics Committee of Kaohsiung Medical University Hospital (KMUHIRB-E(I)-20230267).

Treatment of mCRC

A treatment plan was discussed by a multidisciplinary committee comprising colorectal surgeons, radiologists, gastroenterologists, medical oncologists, radiation oncologists, and pathologists. The first-line therapy principle was established according to the National Comprehensive Cancer Network guidelines and the consensus regarding mCRC treatment in Taiwan [6, 16]. The chemotherapy regimen involved FOLFIRI, and *RAS* and *BRAF* gene mutation statuses were examined [17, 18]. The treatment regimen comprised a 120-min intravenous (IV) infusion of bevacizumab (5 mg/kg) on day 1, followed by a 4-h IV infusion of irinotecan (180 mg/m^2) plus 500 mL of normal saline and leucovorin (200 mg/m^2) plus 5-fluorouracil (2800 mg/m^2) plus 500 mL of normal saline for 42–48 h. This regimen was then repeated once every 2 weeks. Irinotecan dosage adjustments were made based on *UGT1A1* genotyping [7]. RT could be applied to the primary tumor site after multidisciplinary team discussion, as described in our previous studies [19, 20]. Response Evaluation Criteria in Solid Tumors version 1.1, coupled with CT image and magnetic resonance image studies, were used to assess treatment responses [21]. Following first-line therapy, on the basis of the response of the primary tumor and the control of distant metastasis, PTR was

considered after multidisciplinary team discussion. PTR could take the form of either conventional laparotomy or minimally invasive surgery [19]. Colostomy was performed for patients experiencing bowel obstruction, malnutrition, post-intersphincteric resection, or anastomosis leakage [19]. After PTR, the patient received standard systemic therapy to manage metastatic lesions, in accordance with the mCRC treatment consensus in Taiwan [6].

Statistical analysis

On the basis of medical records, patients undergoing PTR after systemic therapy were designated as the "PTR" group. Conversely, those who did not receive PTR throughout the entire course of mCRC treatment were designated as the "No PTR" group. These patients were further classified into the aforementioned "4A," "4B," and "4C" subgroups based on their initially clinically diagnosed mCRC stages (Fig. 1). The patients with mCRC who received RT for primary tumor were classified into the "RT" group, whereas those who did not receive RT were classified into the "No RT" group. Furthermore, the patients with mCRC were subdivided into four groups—namely "PTR(+)/RT(+)," "PTR(+)/RT(−)," "PTR(−)/RT(+)," and "PTR(−)/RT(−)"—depending on whether they received PTR or RT.

Descriptive statistics—including medians, means, and proportions—were employed to characterize patient characteristics and gene alterations. The endpoint of the follow-up period was determined by the patient's date of death, their date of final follow-up, or December 31, 2023. Overall survival (OS) was defined as the time from the date of diagnosis of mCRC to the date of death from any cause, the date of final follow-up, or the study endpoint. Median OS was calculated using the Kaplan–Meier method, and the time-to-event distributions were compared using the log-rank test. A P value of < 0.05 was considered statistically significant. Statistical analysis was conducted using the Statistical Package for the Social Sciences software package (version 20; International Business Machines Corporation Inc., Armonk, NY, USA), as in our previous study [20, 22].

Results

Patient characteristics

Of the 74 patients with mCRC analyzed in this study, the liver was the most common metastatic site (68.9%), followed by the lung (31.1%) and then the peritoneum (21.6%). Among the 74 patients, 37 were classified into each of the "PTR" and "No PTR" groups. The median time interval between the initiation of FOLFIRI plus bevacizumab treatment and PTR was 8.1 months (3.9–15.8 months). No significant difference in age, sex, or body mass index was noted between the two groups. All the enrolled patients with mCRC exhibited adequate general condition for first-line systemic therapy, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. No significant difference in ECOG performance status was identified between the two groups ($P = 0.288$). In the "PTR" group, 18 (48.6%), 15 (40.6%), and 4 (10.8%) patients were classified as stage IVA, stage IVB, and stage IVC, respectively. In the "No PTR" group, 15 (40.6%), 11 (29.7%), and 11 (29.7%) patients were classified as stage IVA, stage IVB, and stage IVC, respectively. No significant difference in the distribution of mCRC stages was noted between the groups ($P = 0.193$).

All the enrolled mCRC cases were adenocarcinomas, with the majority being well or moderately differentiated types ("PTR" group: 91.9%; "No PTR" group: 97.3%; $P = 0.919$). Five (13.5%) and 11 patients (29.7%) in the "PTR" and "No PTR" groups, respectively, had carcinoembryonic antigen levels exceeding 5 ng/dL at the initial diagnosis ($P = 0.295$). In the "PTR" group, 24 patients (64.9%) received RT on the primary tumor, whereas in the "No PTR" group, 12 patients (32.4%) received RT on the primary tumor ($P = 0.587$). All the enrolled patients received elective PTR because of the asymptomatic nature of the primary tumor.

In the "PTR" group, 19 patients (51.3%) showed a partial response after first-line therapy with FOLFIRI plus bevacizumab, while in the "No PTR" group, 21 patients (56.8%) experienced progressive disease after first-line therapy. Although it was not statistically significant ($P = 0.085$), a trend toward a better response to treatment was noticed in the "PTR" group. The median number of lines of systemic therapy for both the "PTR" and "No PTR" groups was two, corresponding to second-line treatment. ($P = 0.143$). The characteristics of the enrolled patients are summarized in Table 1.

Gene alterations

In the "PTR" group, 12 patients (32.4%) exhibited wild-type *KRAS*, and 15 patients (40.5%) had *KRAS* mutation. In the "No PTR" group, 20 patients (56.8%) exhibited wild-type *KRAS*, and 13 patients (43.2%) exhibited *KRAS* mutation ($P = 0.713$). In the "PTR" group, 12 patients (32.4%) exhibited wild-type *NRAS*, and one patient (2.7%) had *NRAS* mutation. In the "No PTR" group, 18 patients (48.6%) had wild-type *NRAS*, and no patients exhibited *NRAS* mutation ($P = 0.615$). Regarding *BRAF* status, 27 patients (73.0%) were diagnosed as having wild-type *BRAF* in the "PTR" group. In the "No PTR" group, 31 patients (83.8%) exhibited wild-type *BRAF* ($P = 0.475$). Regarding *UGT1A1* presentation, in the "PTR" group, 19 patients (51.4%) had the TA6/TA6 type, and six patients (16.2%) had the TA6/TA7 type.

Table 1 Patients Characteristics of PTR and No PTR groups ($n=74$)

Location of metastasis ($n=74$)[a]			
Liver	51 (68.9%)		
Lung	23 (31.1%)		
Peritoneum	16 (21.6%)		
Para-aortic lymph node	12 (16.2%)		
Adrenal gland	6 (8.1%)		
Bone	4 (5.4%)		
Ovary	3 (4.1%)		
Characteristic	PTR (n = 37)	No PTR (n = 37)	*P* value
Age (years, median) (range)	59 (36–82)	56 (26–79)	0.188
Gender			
Male	23 (62.2%)	21 (56.8%)	0.733
Female	14 (37.8%)	16 (43.2%)	
BMI kg/m^2 (mean) (range)[b]	23.5 (16.7–31.0)	25.0(16.0–34.4)	0.074
ECOG[c]			
0	20 (54.1%)	10 (27.0%)	0.288
1	17 (45.9%)	27 (73.0%)	
Clinical stage			
IVA	18 (48.6%)	15 (40.6%)	0.193
IVB	15 (40.6%)	11 (29.7%)	
IVC	4 (10.8%)	11 (29.7%)	
Histology (adenocarcinoma)			
Well or moderately differentiated	34 (91.9%)	36 (97.3%)	0.919
Poorly differentiated	3 (8.1%)	1 (2.7%)	
Sidedness			
Left colon	30 (81.1%)	30 (81.1%)	1.000
Right colon	7 (18.9%)	7 (18.9%)	
Pretreatment CEA[d]			
≦5 ng/dL	32 (86.5%)	26 (70.3%)	0.295
> 5 ng/dL	5 (13.5%)	11 (29.7%)	
Radiotherapy on primary tumor			
Yes	24 (64.9%)	12 (32.4%)	0.587
No	13 (35.1%)	25 (67.6%)	
Nature of PTR			
Elective	37 (100%)	37 (100%)	1.000
Emergency	0 (0%)	0 (0%)	
Response after 1st line therapy			
Partial response	19 (51.3%)	7 (18.9%)	0.085
Stable disease	16 (43.2%)	9 (24.3%)	
Progressive disease	2 (5.4%)	21 (56.8%)	
Lines of systemic therapy			
1st	10	11	0.143
2nd	9	10	
3rd	13	7	
4th	5	6	
5th	0	3	
Median lines of systemic therapy	2	2	

[a] Because of multiple organ metastasis, the sum of the percentage exceeds 100%

[b] BMI: body mass index

[c] ECOG: Eastern Cooperative Oncology Group performance status

[d] CEA: carcinoembryonic antigen

In the "No PTR" group, 27 patients (73.0%) had the TA6/TA6 type, and three patients (8.1%) had the TA6/TA7 type. No statistical significance in terms of *UGT1A1* presentation was observed between the two groups ($P=0.929$). Further details of gene alterations are presented in Table 2.

Survival and treatment outcome

Primary tumor resection

Overall, the median OS period for all the enrolled patients was 23.8 months (20.5–27.1 months). The estimated 3-year OS rate was 23.0%, and the estimated 5-year OS rate was 5.7% (Fig. 2A). In the group analysis of survival outcomes, the "PTR" group exhibited a median OS period of 25.9 months (21.3–30.5 months), with estimated 3-year and 5-year OS rates of 32.4% and 8.9%, respectively. By contrast, in the "No PTR" group, the median OS period was 21.4 months (15.8–27.1 months), with estimated 3-year and 5-year OS rates of 13.5% and 2.7%, respectively. The OS outcome in the "PTR" group was significantly superior to that in the "No PTR" group ($P=0.048$; Fig. 2B).

In the subgroup analysis, we compared the survival outcomes across multiple mCRC stages. For stage IVA, the "PTR-4A" group demonstrated a median OS period of 28.8 months (13.9–43.7 months). The estimated 3-year OS rate was 33.3%, and the estimated 5-year OS rate was 11.1%. By contrast, in the "No PTR-4A" group, the median OS period was 21.0 months (14.4–27.6 months), with an estimated 3-year OS rate of 13.3% and an estimated 5-year OS rate of 6.7%. Although the "PTR-4A" group exhibited a trend of a longer OS period than did the "No PTR-4A" group, the difference was not statistically significant ($P=0.116$; Fig. 2C).

In the stage IVB analysis, the "PTR-4B" group demonstrated a median OS period of 24.3 months (18.7–29.9 months), with an estimated 3-year OS rate of 40.0% and an estimated 5-year OS rate of 8.0%. In the "No PTR-4B" group, the estimated median OS period was 25.1 months (15.6–34.6 months), with an estimated 3-year OS rate of 18.2% and an estimated 5-year OS rate of 0.0%. Although the "No PTR-4B" group exhibited a slightly longer OS period than did the "PTR-4B" group, the "PTR-4B" group revealed superior 3-year and 5-year OS rates. No significant difference was noted between the OS outcomes of these two subgroups ($P=0.493$; Fig. 2D).

In the stage IVC analysis, the "PTR-4C" group demonstrated a median OS period of 22.9 months (16.4–29.4 months), with an estimated 2-year OS rate of 50.0% and an estimated 3-year OS rate of 0.0%. In the "No PTR-4C" group, the estimated median OS period was 16.6 months (10.1–23.0 months), with an estimated 2-year OS rate of 27.3% and an estimated 3-year OS rate of 9.1%. No significant difference in OS outcomes was observed between the stage IVC subgroups ($P=0.760$; Fig. 2E).

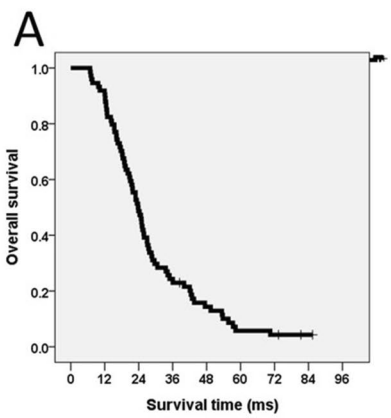
Table 2 Gene alteration status (patients, $N=74$)

Gene alteration	PTR ($n=37$)	No PTR ($n=37$)	*P* value
KRAS mutation			
Wild type	12 (32.4%)	20 (56.8%)	0.713
Mutation	15 (40.5%)	13 (43.2%)	
N/A	10 (27.0%)	4 (10.8%)	
NRAS mutation			
Wild type	12 (32.4%)	18 (48.6%)	0.615
Mutation	1 (2.7%)	0 (0.0%)	
N/A	24 (64.9%)	19 (51.4%)	
BRAF mutation			
Wild type	27 (73.0%)	31 (83.8%)	0.475
Mutation	0 (0.0%)	0 (0.0%)	
N/A	10 (27.0%)	6 (16.2%)	
UGT1A1			
TA6/TA6	19 (51.4%)	27 (73.0%)	0.929
TA6/TA7	6 (16.2%)	3 (8.1%)	
TA7/TA7	0 (0.0%)	0 (0.0%)	
N/A	12 (32.4%)	7 (18.9%)	

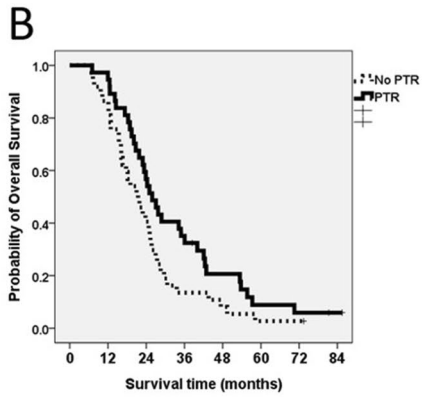
Radiotherapy

In the "RT" group, the estimated median OS period was 22.9 months (18.6–27.2 months), with an estimated 3-year OS rate of 19.4% and an estimated 5-year OS rate of 6.5%. Conversely, in the "No RT" group, the estimated median OS survival period was 24.8 months (21.1–28.5 months), with an estimated 3-year OS rate of 26.3% and an estimated 5-year OS rate of 5.3%. No significant difference was noted between the OS outcomes of the two groups ($P=0.650$; Fig. 3A).

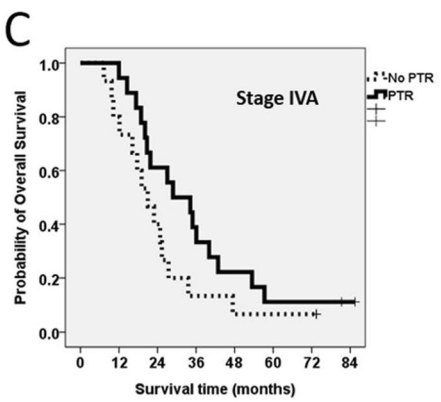
In the subgroup analysis, the median OS period for the "PTR(+)/RT(+)" group was 23.3 months (20.3–26.4 months), with an estimated 3-year OS rate of 25.0% and an estimated 5-year OS rate of 10.0%. In the "PTR(+)/RT(−)" group, the estimated median OS period was 36.1 months (19.4–52.7 months), with an estimated 3-year OS rate of 46.2% and an estimated 5-year OS rate of 7.7%. The median OS period for the "PTR(−)/RT(+)" was 15.4 months (1.7–29.1 months), with estimated 3-year and 5-year OS rates of 8.3% and 0.0%, respectively. In the "PTR(−)/RT(−)" group, the estimated median OS period was 21.9 months (15.6–28.2 months), with estimated 3-year and 5-year OS rates of 16.0% and 4.0%, respectively. Overall, no significant differences were observed among the OS outcomes of these four subgroups ($P=0.174$; Fig. 3B).



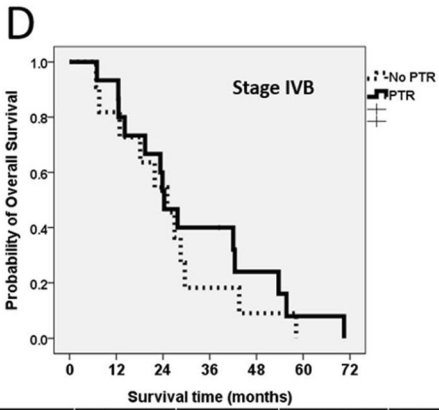
Median survival period (months)	3-year survival rate (%)	5-year survival rate (%)
23.8 (20.5-27.1)	23.0%	5.7%



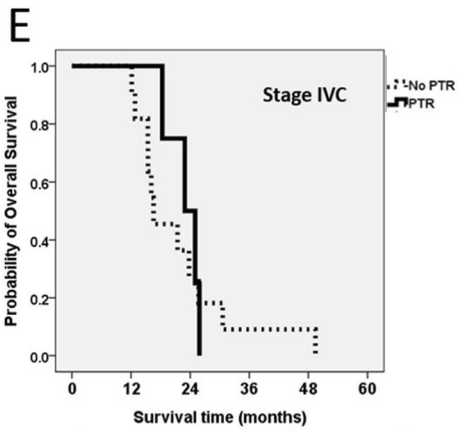
	Median survival period (months)	3-year survival rate (%)	5-year survival rate (%)	P value
PTR	25.9(21.3-30.5)	32.4%	8.9%	0.048
No PTR	21.4(15.8-27.1)	13.5%	2.7%	



	Median survival period (months)	3-year survival rate (%)	5-year survival rate (%)	P value
PTR	28.8(13.9-43.7)	33.3%	11.1%	0.116
No PTR	21.0(14.4-27.6)	13.3%	6.7%	

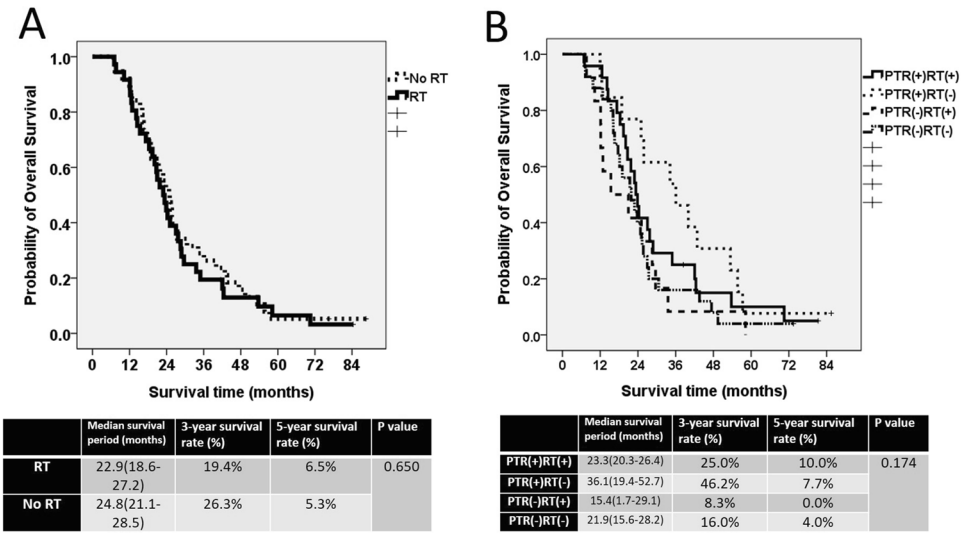


	Median survival period (months)	3-year survival rate (%)	5-year survival rate (%)	P value
PTR	24.3(18.7-29.9)	40.0%	8.0%	0.493
No PTR	25.1(15.6-34.6)	18.2%	0.0%	



	Median survival period (months)	2-year survival rate (%)	3-year survival rate (%)	P value
PTR	22.9(16.4-29.4)	50.0%	0.0%	0.760
No PTR	16.6(10.1-23.0)	27.3%	9.1%	

Fig. 2 **A** Overall survival curve. **B** Overall survival curve for "PTR" and "No PTR." (**C**) Overall survival curve for "PTR-4A" and "No PTR-4A." (**D**) Overall survival curve for "PTR-4B" and "No PTR-4B." (**D**) Overall survival curve for "PTR-4C" and "No PTR-4C."



	Median survival period (months)	3-year survival rate (%)	5-year survival rate (%)	P value
RT	22.9(18.6-27.2)	19.4%	6.5%	0.650
No RT	24.8(21.1-28.5)	26.3%	5.3%	

	Median survival period (months)	3-year survival rate (%)	5-year survival rate (%)	P value
PTR(+)RT(+)	23.3(20.3-26.4)	25.0%	10.0%	0.174
PTR(+)RT(-)	36.1(19.4-52.7)	46.2%	7.7%	
PTR(-)RT(+)	15.4(1.7-29.1)	8.3%	0.0%	
PTR(-)RT(-)	21.9(15.6-28.2)	16.0%	4.0%	

Fig. 3 **A** Overall survival curve for "RT" and "No RT." (**B**) Overall survival curve for "PTR(+)/RT(+)," "PTR(+)/RT(−)," "PTR(−)/RT(+)," and "PTR(−)/RT(−)."

Discussion

Many studies have investigated the therapeutic impact of PTR on asymptomatic synchronous mCRC with unresectable distant metastasis. Furthermore, many studies have indicated that PTR may offer some survival benefits. However, most PTRs discussed in previous studies refer to procedures conducted before chemotherapy [23, 24]. Accordingly, some randomized controlled trials (RCTs) have been initiated subsequently. The CAIRO4 Phase 3 trial reported that PTR followed by systemic therapy resulted in higher 60-day mortality than systemic therapy alone, and there was no survival benefit [25, 26]. The SYNCHRONOUS trial, comprising 393 patients, reported that PTR prior to chemotherapy did not extend the OS period for synchronous unresectable mCRC [27–29]. The ongoing GRECCAR 8 trial, which aimed to include 290 patients, has yet to yield available results [30].

The JCOG1007 RCT investigated the role of PTR in asymptomatic synchronous unresectable CRC metastasis [31]. The findings of that study revealed that PTR conducted prior to systemic chemotherapy provided no survival benefit [31]. Consequently, the primary treatment approach for asymptomatic mCRC with synchronous unresectable metastasis shifted toward systemic therapy [5, 6]. Although the application of standard targeted therapy plus chemotherapy yielded response rates of 55% to 60% for mCRC [32], this success raises a clinical question: In a scenario where an asymptomatic synchronous mCRC patient receives standard systemic therapy and exhibits tumor shrinkage in both the primary tumor and metastasis but where the distant metastatic lesion remains unresectable, should PTR be performed?

PTR is imperative in cases of symptomatic primary tumors to address complications such as bleeding and bowel obstruction [33]. However, for patients with asymptomatic mCRC who have undergone systemic therapy, the decision to undergo PTR involves weighing the potential advantages and disadvantages of such resection. The potential advantages of PTR as described as follows: 1) Prevention of imminent tumor-related complications such as bowel obstruction, tumor bleeding, and bowel perforation; 2) removal of RT- or chemotherapy-resistant tumor cells; and 3) reduction of the tumor burden [14, 15]. Conversely, the potential major disadvantages of PTR lie in the interruption of systemic therapy. During PTR, chemotherapy is usually delayed for approximately 2 weeks before and after the surgery to avoid immune compromise [20, 34], and the administration of anti-vascular endothelial growth factor monoclonal antibodies, such as bevacizumab, is often postponed for at least 28 days before and after colorectal surgery [35, 36]. Additionally, PTR may contribute to the progression of distant metastatic lesion growth due to the release of wound-healing factors and the removal of a source of angiostatin from the primary tumor [37, 38].

The present study focused on the role of PTR after neoadjuvant systemic therapy and aimed to address the question outlined above, namely whether PTR should be performed for patients with mCRC with synchronous unresectable distant metastasis after neoadjuvant systemic therapy. The standard first-line targeted therapy comprises an anti-epidermal growth factor receptor agent (cetuximab or panitumumab) and an anti-vascular endothelial growth factor agent (bevacizumab) [39]. Although the anti-epidermal growth factor receptor agent is effective, it can be administered only to patients with wild-type *RAS* [40]. To ensure homogeneity and avoid potential confounding factors in OS outcomes, this study enrolled patients with mCRC who received a single systemic regimen—namely FOLFIRI chemotherapy plus bevacizumab targeted therapy—regardless of whether

wild-type *RAS* or *RAS* mutation was present. The comparisons of basic patient characteristics revealed no statistical significance in each variable between the "PTR" and "No PTR" groups. Consequently, the composition of patients with mCRC in both groups was similar; this feature enhances the credibility of the study results.

In the present study, the median OS period for the "PTR" group was 25.9 months, which was significantly longer than 21.4 months observed in the "No PTR" group ($P=0.048$). However, the "No PTR" group had more stage IVC patients (29.7%) than the "PTR" group (10.8%). To mitigate the potential prognostic impact of different cancer stages on OS, we conducted subgroup analyses according to clinical stages. The median OS period in the "PTR-4A" subgroup was longer than that in the "No PTR-4A" subgroup (28.8 and 21.0 months, respectively), and the OS curves exhibited clear separation. However, the OS difference was less evident between the "PTR-4B" and "No PTR-4B" subgroups (24.3 and 25.1 months, respectively); the "PTR-4B" group exhibited a higher survival rate, but the OS curve exhibited many crossover points. Regarding stage IVC, the OS curve for the "PTR-4C" group appeared chaotic because of the limited number of patients. These results indicate that PTR may play a relatively pivotal role in mCRC cases with single-organ involvement. For multiorgan or peritoneal carcinomatosis mCRC, systemic therapy remains the primary treatment approach [9].

A possible reason behind the observed survival benefit in patients who underwent PTR may be an advantage such as the removal of chemotherapy-resistant tumor cells or the reduction of tumor burden, as mentioned in the preceding paragraph. However, selection bias may have influenced these results given the retrospective study design and the nonrandomized grouping method [41]. For example, we failed to clarify detailed "T" and "N" stages for each patient; consequently, advanced primary tumor (ex: T4N2M1a) and localized primary tumor (ex: T2N0M1a) may have been categorized as the same stage (stage IVA). Many studies have reported that T4 tumors exhibit inferior survival prognoses compared with T1, T2, and T3 tumors in patients with mCRC [13, 42, 43]. Furthermore, T4 primary tumors pose a greater challenge for curative surgical resection [44], potentially leading to a higher likelihood of their being classified into the "No PTR" group.

Moreover, the treatment response varied between the two groups. Approximately half of the patients in the "PTR" group exhibited a partial response, whereas in the "No PTR" group, twenty-one patients (56.8%) showed signs of progressive disease (Table 1). Although the difference did not reach statistical significance ($P=0.085$), patients in the "PTR" group demonstrated a trend of more favorable outcome. This finding aligns with our clinical practice, whereas PTR and metastasectomy are less commonly performed in mCRC patients with poor response [34]. However, despite undergoing PTR, patients in the "PTR" group still had unresectable metastatic lesions. The presence of such unresectable metastases was identified as a major determinate of poor prognosis [45]. Since neither the "PTR" nor "No PTR" groups were able to undergo metastasectomy, we hypothesize that PTR may offer an additional survival benefit beyond the differences in treatment response.

Lau et al. conducted a single-institution retrospective review to investigate the role of PTR in mCRC treatment. Their results revealed that treatment with PTR plus chemotherapy led to a significantly longer OS period compared with chemotherapy alone [14]. By contrast, JCOG1007, an RCT, reported that treatment with PTR plus chemotherapy yielded an OS period of 25.9 months, which was similar to that obtained with chemotherapy alone (26.7 months) [31]. Despite their similar study designs in terms of patient grouping, these two studies yielded divergent results. Both studies focused on the role of PTR before systemic therapy for mCRC, which differs from the aim of the present study. However, this instance serves as an illustrative example of how selection bias can affect study outcomes and underscores the importance of RCTs in accurately interpreting clinical dilemmas. Compared with our treatment experience, the median OS period for patients with mCRC who received cetuximab or bevacizumab plus FOLFIRI as first-line therapy was 30 or longer months [17, 46]. For patients with mCRC with peritoneal carcinomatosis who received the same first-line therapy, the median OS period was 24.6 months [9]. In the present study, all the enrolled patients had unresectable metastasis, and the median OS period in the "PTR" group was 25.9 months. This similarity in survival outcomes suggests that our enrolled patients did not belong to a specific outlier group.

In the OS analysis, regarding PTR and RT, the "No RT" group exhibited a longer median OS period than the "RT" group (22.9 months vs. 24.8 months, $P=0.650$). Moreover, the estimated 3-year OS rates in the "No RT" group were superior to those in the "RT" group. In our four-subgroup OS analysis based on PTR and RT, among the patients with mCRC who underwent PTR, those who did not receive RT had a longer OS period than those who received RT (23.3 months vs. 36.1 months, $P=0.271$, Supplementary Fig. 1A). Similarly, for patients with mCRC who did not undergo PTR, those who did not receive RT on the primary tumor had a longer OS period than those who received RT on the primary tumor (15.4 months vs. 21.9 months, $P=0.737$, Supplementary Fig. 1B). These results indicate the advanced T/N stage of the primary tumor. In our clinical practice, RT is typically administered to treat advanced CRC with local invasion or lymphadenopathy [19, 20]. Thus, RT indirectly reflects a more advanced T/N stage of the primary tumor, contributing to a shorter OS period [13, 42, 43].

Conversely, a comparison of the OS outcomes based on RT revealed a trend toward a longer OS period for patients with mCRC who received RT and underwent PTR compared with those who underwent RT without PTR (23.3 months vs. 15.4 months, $P=0.226$, Supplementary Fig. 2A). Similarly, for patients with mCRC who did not receive RT, a longer OS period was observed for those who underwent PTR than for those who did not (36.1 months vs. 21.9 months, $P=0.049$, Supplementary Fig. 2B). These results suggest that under similar primary tumor T/N stage conditions, PTR may provide a survival benefit to patients with mCRC with unresectable metastasis after first-line systemic therapy.

Because the tumor burden of metastatic lesions is a crucial factor influencing poor prognosis [47, 48], a reduction in tumor burden due to PTR is unlikely to be the primary reason for the observed differences in OS outcomes. Although selection bias may contribute to a portion of the survival benefit, it is insufficient to account for all the differences in the present results given the analysis of OS periods based on PTR and RT, as described previously. Because systemic therapy is the gold standard for the treatment of mCRC [6], the OS outcome in mCRC is expected to have the strongest relationship with this type of therapy. One plausible explanation for the observed differences could be chemotherapy-induced psychological distress. In the context of mCRC treatment, psychological distress often accompanies chemotherapy and serves as a hidden detrimental factor affecting quality of life and the treatment course [49, 50]. Some studies have introduced psychological support and care to alleviate anxiety and depression in patients with mCRC [51, 52]. On the basis of our clinical observations, patients with mCRC may experience psychological exhaustion after a prolonged course of systemic therapy. The perception of an endless need for treatment can lead to a sense of despair, potentially causing patients to contemplate discontinuing their treatment. PTR may act as a treatment milestone and strengthen patients' confidence in the treatment plan. Such a psychological boost could motivate patients to persevere through subsequent long-term treatment, thereby indirectly contributing to the prolonged OS period. However, in this retrospective study, we were unable to collect psychological assessment data to validate this hypothesis. The treatment lines in "PTR" and "No PTR" groups did not reveal statistical difference to support our hypothesis.

Several studies have explored the therapeutic efficacy of metastasis-directed RT and have reported promising outcomes [53, 54]. However, the effect of RT on primary tumor in mCRC treatment has not been studied extensively. In the present study, we analyzed the survival outcomes associated with RT intervention in patients with mCRC. The findings of our study indicated that RT applied to the primary tumor did not confer additional benefits to OS in patients with mCRC. This result aligns with our previous treatment results observed in cases of locally advanced rectal cancer with synchronous metastasis [19]. Compared with systemic therapy alone, the combination of RT and systemic therapy led to prolonged local recurrence-free survival and progression-free survival but no significant difference in OS [19]. The present data reveals that similar survival outcomes can be observed in the treatment of metastatic colon cancer as well as in that of rectal cancer.

This study was a retrospective analysis conducted at a single center; such a study design is associated with limitations, such as a small patient sample. Therefore, the sample size may not have been sufficient for robust subgroup analyses. General patient condition was assessed solely on the basis of performance status, and essential laboratory data—such as those related to liver function, renal function, and underlying disease—were not included. Some details regarding primary tumor, such as T/N stage, were not available, and although RT was used as an indirect measure for evaluating primary tumor T/N stage, it cannot precisely reflect the primary tumor condition. The treatment response was uneven between the two groups. A trend toward better treatment response was observed in the "PTR" group. The absence of an assessment of the patients' psychological status, along with a lack of a questionnaire to evaluate the scale of psychological exhaustion, weakens the hypothesis related to psychological stress. Furthermore, data on treatment response following first-line therapy and PTR were unavailable. Additionally, selection bias due to the aforementioned limitations and the retrospective nature of this study could not be ruled out.

Conclusion

The present study provides real-world insights into the treatment impact of PTR on patients with mCRC undergoing first-line therapy. In cases of mCRC with synchronous unresectable metastasis, PTR may offer a potential survival benefit following neoadjuvant chemotherapy and targeted therapy. This therapeutic effect of PTR is especially pronounced in stages IVA and IVB. Furthermore, our findings indicate that RT on the primary tumor does not provide additional benefits to OS in the context of mCRC with unresectable metastasis. To establish a clearer understanding of the genuine effects of PTR following systematic therapy, larger-scale prospective, randomized trials are needed, especially in patients with control of their disease (stable disease, partial response or complete response) following first-line treatment.

Abbreviations BMI: Body mass index; CEA: Carcinoembryonic antigen; CRC: Colorectal cancer.; mCRC: Metastatic colorectal cancer.; CT: Computed tomography.; ECOG: Eastern Cooperative Oncology Group.; FOLFIRI: Folinic acid, 5-fluorouracil, and irinotecan.;

IV: Intravenous.; OS: Overall survival.; PTR: Primary tumor resection.; RCT: Randomized controlled trial.; RT: Radiotherapy

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Declarations

Ethics approval and consent to participate The present study protocol was approved by the Institutional Ethics Committee of Kaohsiung Medical University Hospital (KMUHIRB-E(I)-20230267). Consent to participate is not applicable due to retrospective study design.

Consent for publication On behalf of all co-authors, the corresponding author has obtained the consent for publication.

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