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*Original Article*

# Outcomes of upfront primary tumor resection in patients with synchronous *RAS* wild-type metastatic colorectal cancer

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**Abstract:** This multicenter study explored the survival benefits of upfront primary tumor resection (PTR) followed by first-line cetuximab plus chemotherapy in real-world patients with *RAS* wild-type metastatic colorectal cancer (mCRC). Treatment options for mCRC include chemotherapy, targeted therapy, immunotherapy, and surgery. The efficacy of upfront PTR in managing mCRC remains unclear. In this retrospective study, we evaluated the outcomes of upfront PTR in 582 patients with synchronous *RAS* wild-type mCRC who received cetuximab plus chemotherapy as first-line treatment between November 2016 and August 2020. Of these patients, 364 (62.5%) underwent upfront PTR (PTR group) and 218 (37.5%) did not (non-PTR group). Relevant data were collected from 14 medical institutions in Taiwan. No significant differences were discovered between the PTR and non-PTR groups in median overall survival (37.9 vs. 31.7 months; $P = 0.079$) or progression-free survival (13.70 vs. 13.29 months; $P = 0.62$). Compared with patients who did not undergo metastasectomy, those who underwent this surgery exhibited significantly longer median overall survival (29.2 vs. 54.18 months; $P < 0.001$) and progression-free survival (12.8 vs. 15.60 months; $P = 0.013$). Our findings suggest that upfront PTR may not improve oncological outcomes in patients with synchronous *RAS* wild-type mCRC. Cetuximab-based targeted therapy plus chemotherapy appears to be suit-

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able as first-line treatment for these patients. This study indicates that upfront PTR should be considered only for patients exhibiting symptoms such as tumor bleeding, perforation, or obstruction.

**Keywords:** Metastatic colorectal cancer, *RAS* wild-type, upfront primary tumor resection

## Introduction

In 2020, colorectal cancer (CRC) accounted for approximately 1.93 million new cases and 930,000 related deaths [1]. Approximately 20% of all patients with CRC present with metastases at the time of diagnosis [2]. The prognosis of metastatic CRC (mCRC) is influenced by tumor gene profiles, primary tumor location, and response to combinations of systemic therapies [3-6]. Emerging evidence suggests that left-sided CRC is associated with a better prognosis than is right-sided CRC, with notable differences in the genomic and metabolic landscapes between these two subtypes [7, 8]. CRC treatment has evolved considerably, benefiting from advancements in surgical techniques, radiation therapy, and chemotherapy. Chemotherapy remains the cornerstone of CRC treatment, with 5-fluorouracil and its derivatives being used as key drugs for decades. Combination therapies involving chemotherapeutic agents and radiation have been used to achieve high treatment efficacy [9]. Critical genetic mutations influence cancer risks and treatment outcomes. *CHEK2*, a gene that encodes a protein responsible for regulating cell cycle checkpoints and DNA repair, has been associated with an increased risk of breast cancer. Although evidence suggests an association between the pathogenic variants (PVs) of *CHEK2* and the risk of breast cancer, the association with CRC remains to be confirmed. A study involving > 6,000 *CHEK2* PV carriers found that the presence of *CHEK2* PVs (both truncating and missense types) led to a two-fold increase in the risk of breast cancer but did not significantly elevate the risk of CRC [10].

Advanced genetic research has unveiled mutations that influence CRC risks and treatment responses. *BRCA1* and *BRCA2* mutations are associated with increased risks of breast and ovarian cancers but not CRC. *TP53*, a tumor suppressor gene, plays a crucial role in preventing the development of cancer. *TP53* mutations compromise cell cycle control and apoptosis, contributing to genomic instability and cancer progression, even in patients with CRC. Targeted therapies and personalized medicine approaches that focus on specific genetic mutations are becoming integral to CRC treatment because they yield improved outcomes through a tailored regimen [9, 10]. However, treatment of mCRC typically involves resection of both primary and metastatic sites. For asymptomatic patients with synchronous unresectable metastases, initial treatment options include systemic therapy or upfront primary tumor resection (PTR). A study reported that PTR followed by chemotherapy resulted in prolonged overall survival (OS) [11]. However, a randomized clinical trial, JCOG 1007, revealed that upfront PTR followed by chemotherapy offered no survival benefit compared with chemotherapy alone in asymptomatic patients with synchronous unresectable metastases [12]. Systemic chemotherapy plus targeted therapy is essential in the treatment of mCRC. Standard systemic treatment regimens include a combination of 5-fluorouracil, folinic acid, and either oxaliplatin or irinotecan [13, 14]. Several clinical trials have demonstrated that doublet regimens such as FOLFOX (5-fluorouracil, folinic acid, and oxaliplatin) and FOLFIRI (5-fluorouracil, folinic acid, and irinotecan) in combination with antibodies against epidermal growth factor receptor (EGFR) yield improved clinical outcomes in patients with mCRC [15-17]. Thus, anti-EGFR antibodies plus doublet or triplet chemotherapy is the recommended first-line treatment for patients with *RAS* wild-type mCRC [18-22], particularly when cytoreduction is the treatment goal, regardless of the location of the primary tumor [19].

In this study, we analyzed the data of patients from 14 medical institutions in Taiwan. We evaluated the effects of upfront PTR before cetuximab-based targeted therapy plus systemic chemotherapy on the survival outcomes of patients with synchronous *RAS* wild-type mCRC.

## Methods

### *Study design and cohort*

This retrospective, multicenter observational study included patients with histologically confirmed synchronous *RAS* wild-type mCRC; all

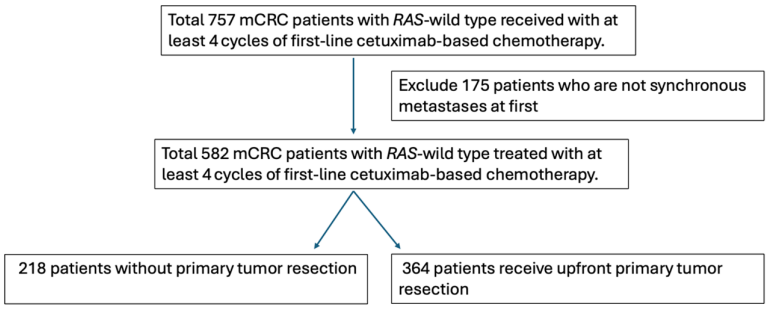


**Figure 1.** Flowchart of nationwide study.

diagnoses were made through imaging studies. The patients received cetuximab-based targeted therapy plus chemotherapy as first-line treatment from November 2016 to August 2020. The inclusion criteria were as follows: being aged ≥ 18 years, having a histologically confirmed diagnosis of *RAS* wild-type mCRC (both *KRAS* and *NRAS*), and receiving at least four cycles of first-line cetuximab plus chemotherapy. Patients who did not meet these criteria or were unwilling to participate in this study were excluded (**Figure 1**).

*Ethical considerations*

This study adhered to the ethical standards outlined in the Declaration of Helsinki. The study protocol and its amendments were approved by the institutional review boards (IRBs) or ethics committees of the 14 participating institutions. The institutions and corresponding IRB approval numbers were as follows: (1) Taipei Veterans General Hospital (approval number: 2017-12-003A), (2) National Taiwan University Hospital (approval number: 202108081RINA), (3) Shuang-Ho Hospital (approval number: N202110007), (4) Chang Gung Memorial Hospital Linkou Branch (approval number: 202101933B0), (5) China Medical University Hospital (approval number: CMUH111-REC3-054), (6) Taichung Veterans General Hospital (approval number: CE21536B), (7) Changhua Christian Hospital (approval number: 211001), (8) National Taiwan University Hospital Yunlin Branch (approval number: 202107123RIPB), (9) Chang Gung Memorial Hospital Chiayi Branch (approval number: 202101933B0), (10) National Cheng Kung University Hospital (approval number: A-ER-110-471), (11) Kaohsiung Medical University (approval number: KMUHIRB-E(I)-20210246), (12) Kaohsiung Chang Gung Memorial Hospital (approval number: 202101933B0), (13) Kaohsiung Veterans General Hospital (approval number: KSVGH21-CT14-06), and (14) E-DA Hospital (approval number: EMRP-110-167).

Given the retrospective nature of this study and the use of anonymized clinical data, the IRB of each participating institution waived the requirement for written informed consent. Initially, we identified 758 patients with mCRC; among them, 583 presented with synchronous metastasis.

*Data collection*

Data on the following clinicopathological characteristics were collected: patients' age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, primary tumor location, tumor stage, metastasis count and location, carcinoembryonic antigen level, and intervention type (PTR or metastasectomy). However, specific surgical details such as operation time, procedure type, and blood loss volume were not documented.

*Study outcomes*

The primary outcomes were OS and progression-free survival (PFS). The secondary outcomes were the occurrence of adverse events (AEs) and the proportion of patients undergoing R0 resection. AEs were assessed on the basis of the Common Terminology Criteria for Adverse Events (version 5.0) [23] and were classified as hematologic AEs or nonhematologic AEs.

*Statistical analysis*

Statistical analyses were performed using SPSS (version 20; IBM Corporation, Armonk, NY, USA). OS was defined as the interval from the date of mCRC diagnosis to that of death from any cause, final follow-up, or the study conclusion. PFS was defined as the interval from the date of first-line treatment initiation to that of tumor progression or death from any cause. Median PFS and median OS were calculated using the Kaplan-Meier method. Time-to-

**Table 1.** Demographics and baseline characteristics of 582 *RAS* wild-type synchronous mCRC

| | Non-PTR (N = 218) | PTR (N = 364) | *P* value |
|---|---|---|---|
| Age (mean) | 60.5 (34-90) | 61.8 (24-92) | 0.235 |
| Sex | | | 0.123 |
| Male | 156 (71.6%) | 238 (65.4%) | |
| Female | 62 (28.4%) | 126 (34.6%) | |
| Location of primary tumor | | | 0.16 |
| Left-sided | 203 (93.1%) | 318 (87.4%) | |
| Right-sided | 14 (6.4%) | 43 (11.8%) | |
| Both | 1 (0.5%) | 2 (0.5%) | |
| Unknown | 0 (0.0%) | 1 (0.3%) | |
| Clinical tumor stage | | | 0.56 |
| T1/T2 | 18 (8.3%) | 34 (9.4%) | |
| T3/T4 | 200 (91.7%) | 330 (90.6%) | |
| Clinal nodal stage | | | 0.32 |
| N0/N1 | 92 (42.2%) | 162 (44.5%) | |
| N2/N3 | 126 (57.8%) | 202 (55.5%) | |
| Metastases sites | | | 0.1 |
| Liver | 161 | 228 | |
| Lung | 59 | 77 | |
| Distant lymph nodes | 25 | 56 | |
| Peritoneum | 35 | 80 | |
| Others | 47 | 64 | |
| CEA level (ng/ml) (mean) | 732.95 | 585.52 | 0.615 |
| Metastasectomy | | | 0.001 |
| No | 199 (91.3%) | 226 (62.1%) | |
| Yes | 19 (8.7%) | 138 (37.9%) | |

event distributions were compared using a log-rank test. Significance was set at $P < 0.05$.

## Results

### *Clinicodemographic characteristics of the patients*

**Table 1** presents the clinicodemographic characteristics of the study cohort. The cohort comprised 582 patients who received first-line cetuximab plus chemotherapy. Among them, 364 patients (62.5%) underwent PTR (PTR group), whereas 218 (37.5%) did not (non-PTR group). The mean ages of the PTR and non-PTR groups were 61.8 and 60.5 years, respectively.

No significant between-group difference was observed in age, sex, primary tumor location, clinical tumor stage, or the number of distant metastatic organs (all $P > 0.05$). However, significant differences were observed in the distribution of patients undergoing metastasectomy; this proportion was higher in the PTR group than in the non-PTR group ($P = 0.001$).

### *Results of survival analysis*

The PTR and non-PTR groups did not differ significantly in terms of median PFS (13.70 vs. 13.29 months; $P = 0.62$; **Figure 2A**) or median OS (37.9 vs. 31.7 months; $P = 0.079$; **Figure 3A**). In the PTR group, the median OS was 38.01 months for patients who underwent R0 resection and 26.35 months for those who underwent R1+R2 resection ($P = 0.022$; **Figure 3B**; **Table 2**).

Significant differences were observed in median OS between patients undergoing metastasectomy and those not undergoing metastasectomy ($P < 0.001$; **Figure 4A**). The median OS was 54.93 months for patients undergoing R0 resection, 35.78 months for those undergoing R1+R2 resection, and 29.21 months for those not undergoing metastasectomy ($P <$

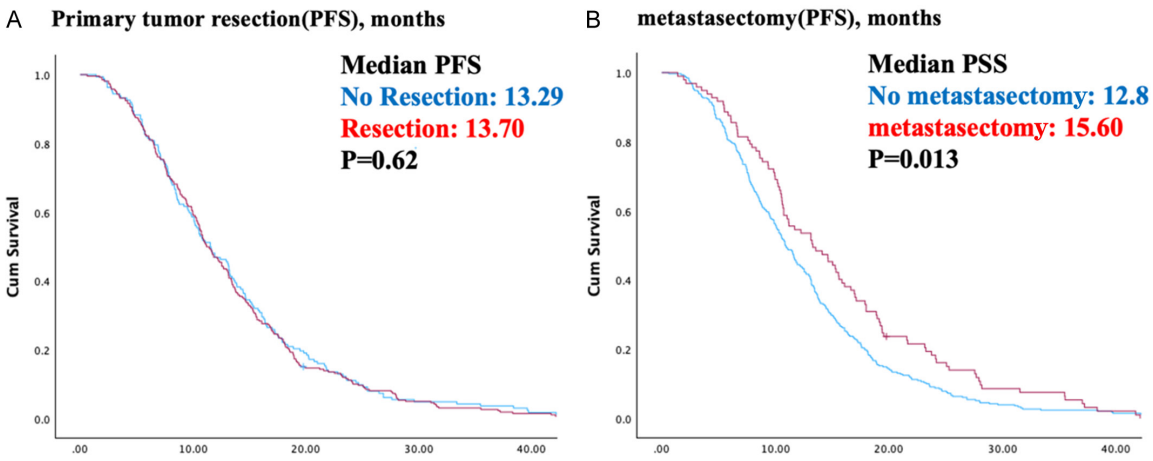


**Figure 2.** A. Progression free survival of PTR. B. Progression free survival of metastasectomy.

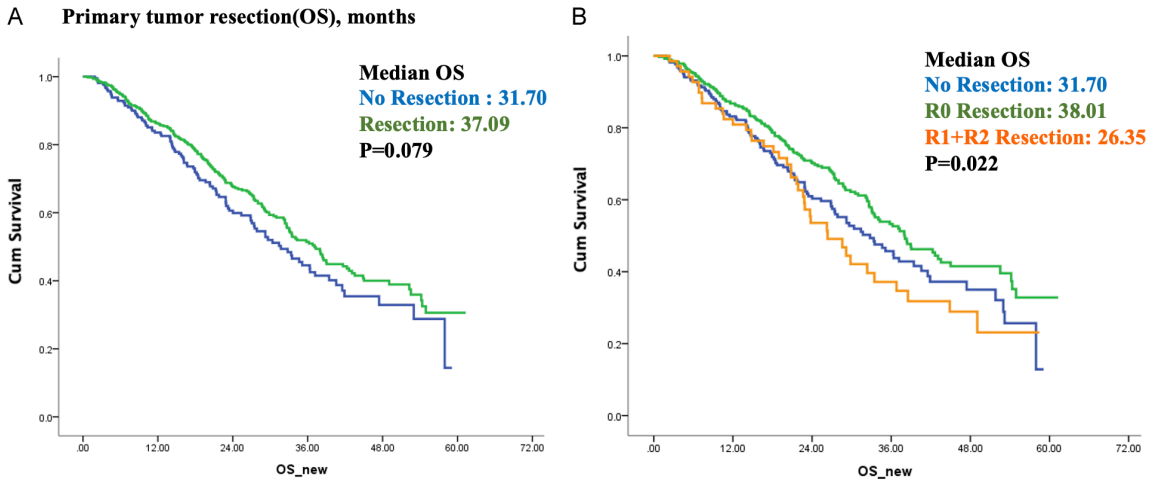


**Figure 3.** A. Overall survival of PTR. B. Overall survival between no resection, R0 resection or R1+2 resection.

**Table 2.** Median overall survival in R0 resection, R1+R2 resection and no resection

| | Overall survival time (months) | *P* value |
|---|---|---|
| Primary tumor resection | | 0.002 |
| R0 resection | 38.01 | |
| R1+R2 resection | 26.35 | |
| No resection | 31.70 | |
| Metastasectomy | | < 0.001 |
| R0 resection | 54.93 | |
| R1+R2 resection | 35.78 | |
| No resection | 29.21 | |

0.001; **Figure 4B**; **Table 2**). Additionally, median PFS differed significantly between patients undergoing metastasectomy and those not undergoing metastasectomy (15.60 and 12.80 months; *P* = 0.013; **Figure 2B**).

**Table 3** presents the AEs associated with cetuximab-based targeted therapy plus chemotherapy; AEs were categorized into hematologic and nonhematologic AEs. Anemia was the most common AE, followed by neutropenia. The most frequent AEs were grade 1/2 AEs in both groups; grade 3/4 AEs were observed in < 10% of all patients in the study groups. No significant between-group difference was observed in any hematologic or nonhematologic AE except neutropenia. For neutropenia, grade 1/2 AEs were more common in the PTR group than in the non-PTR group, whereas grade 3/4 AEs were more common in the non-PTR group than in the PTR group (*P* = 0.006; **Table 3**).

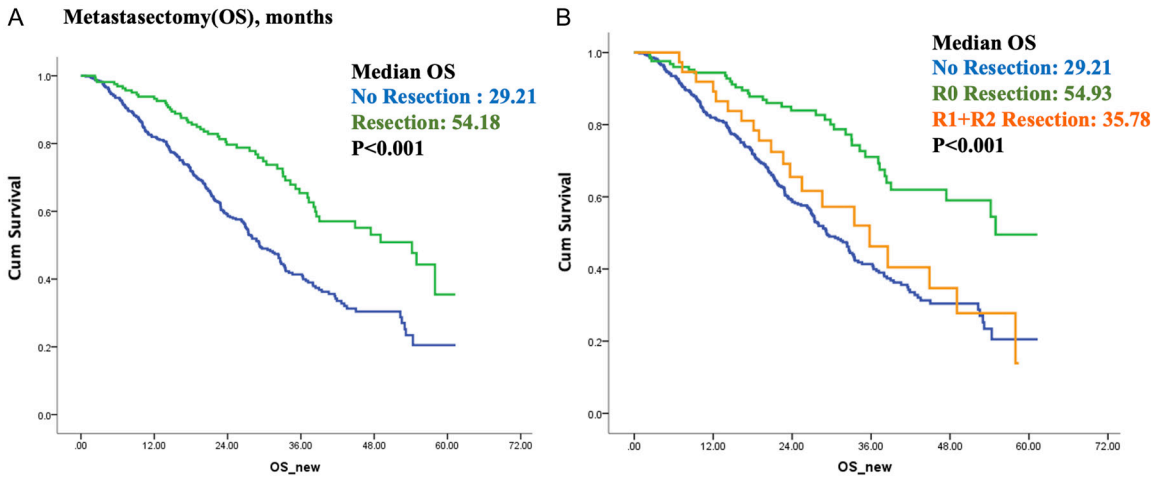


**Figure 4.** A. Overall survival of metastasectomy. B. Overall survival between no resection, R0 resection or R1+2 resection.

## Discussion

The efficacy of upfront PTR in managing synchronous mCRC remains under debate. Its primary benefits relate to symptom relief, particularly for cancer-related problems such as obstruction, bleeding, or perforation. In asymptomatic patients, the potential benefits of PTR must be weighed against the risks of surgery-associated morbidity and mortality. Moreover, surgery often requires considerable recovery time, during which postoperative complications may occur, potentially delaying systemic therapy and worsening disease prognosis.

Although some studies have suggested that upfront PTR can extend OS [24-27], most of these studies were retrospective in nature. However, the randomized clinical trial JCOG 1007 demonstrated that upfront PTR followed by chemotherapy resulted in no survival benefits over chemotherapy alone in patients with asymptomatic primary tumors and synchronous unresectable metastases [12]. Another randomized clinical trial, CAIRO4 [28], revealed higher risks of 60-day mortality in patients with mCRC who underwent PTR followed by systemic therapy than in those who received systemic therapy alone. The CAIRO4 study compared the efficacy of upfront PTR combined with systemic therapy to that of systemic therapy alone in treating synchronous unresectable mCRC in patients without severe primary tumor symptoms. This phase III randomized trial enrolled 206 patients who received either PTR followed by chemotherapy and bevacizumab or chemotherapy and bevacizumab alone. The results revealed no significant OS benefit of PTR; the median OS was 20.1 months in the PTR group and 18.3 months in the non-PTR group. Furthermore, PFS was similar in the groups. Notably, the rates of early mortality and delayed systemic therapy were relatively high in the PTR group, and these rates may have influenced the clinical outcomes. In summary, the CAIRO4 study found no benefits of routine upfront PTR for asymptomatic patients with mCRC; this procedure did not improve survival outcomes and instead delayed essential systemic therapy [29].

Furthermore, the multicenter randomized clinical trials SYNCHRONOUS and CCRe-IV concluded that upfront PTR followed by systemic chemotherapy did not extend OS in patients with colon cancer and synchronous unresectable metastases [30]. A meta-analysis of eight studies (three randomized controlled trials and five case-matched studies; 1,221 patients) investigated the survival benefits of PTR for asymptomatic patients with mCRC and unresectable metastases. The results indicated no significant difference in OS between PTR followed by chemotherapy and chemotherapy alone. However, cancer-specific survival was slightly better in the PTR group than in the non-PTR group. The meta-analysis concluded that although PTR enhanced cancer-specific survival, measured from initial treatment to CRC-related death [31], it did not significantly affect

**Table 3.** Hematological and nonhematologic adverse events associated with cetuximab and chemotherapy

| | Non-PTR with Chemotherapy and Cetuximab (n = 218) | Upfront PTR with Chemotherapy and Cetuximab (n = 364) | *P* value |
|---|---|---|---|
| Hematologic | | | |
| Anemia | | | 0.534 |
| Grade 1/2 | 112 (51.4%) | 131 (36%) | |
| Grade 3/4 | 5 (2.3%) | 7 (1.9%) | |
| Neutropenia | | | 0.006 |
| Grade 1/2 | 57 (26.2%) | 99 (27.2%) | |
| Grade 3/4 | 21 (9.6%) | 13 (3.6%) | |
| Febrile neutropenia | | | 0.273 |
| Grade 1/2 | 2 (0.9%) | 2 (0.6%) | |
| Grade 3/4 | 3 (1.4%) | 1 (0.3%) | |
| Thrombocytopenia | | | 0.515 |
| Grade 1/2 | 15 (6.9%) | 18 (4.9%) | |
| Grade 3/4 | 2 (0.9%) | 1 (0.3%) | |
| Nonhematologic | | | |
| Diarrhea | | | 0.867 |
| Grade 1/2 | 65 (29.8%) | 76 (20.9%) | |
| Grade 3/4 | 3 (1.4%) | 4 (1.1%) | |
| Nausea | | | 0.492 |
| Grade 1/2 | 88 (40.4%) | 122 (33.5%) | |
| Grade 3/4 | 1 (0.5%) | 3 (0.8%) | |
| Vomiting | | | 0.168 |
| Grade 1/2 | 70 (32.1%) | 85 (23.3%) | |
| Grade 3/4 | 1 (0.5%) | 5 (1.4%) | |
| ALT increased | | | 0.230 |
| Grade 1/2 | 24 (11%) | 35 (9.6%) | |
| Grade 3/4 | 1 (0.5%) | 1 (0.3%) | |
| AST increased | | | 0.230 |
| Grade 1-2 | 24 (11%) | 35 (9.6%) | |
| Grade 3-4 | 1 (0.5%) | 1 (0.3%) | |
| Bilirubin increased | | | 0.716 |
| Grade 1-2 | 7 (3.3%) | 12 (3.3%) | |
| Grade 3-4 | 1 (0.5%) | 1 (0.3%) | |
| Creatine increased | | | 0.111 |
| Grade 1-2 | 13 (5.9%) | 19 (5.2%) | |
| Grade 3-4 | 0 (0%) | 4 (1.1%) | |

OS. A systematic review and meta-analysis of 10 studies (48,696 patients) compared upfront PTR with upfront systemic therapy in terms of their efficacy in treating mCRC. The findings revealed significantly better OS in the PTR group than in the systemic therapy group. However, this OS benefit was observed primarily in retrospective cohort studies that involved propensity score matching or inverse probability treatment weighting. By contrast, randomized controlled trials (RCTs) reported no significant OS benefits of upfront PTR. Notably, in RCTs, the 60-day mortality rate was higher in the PTR group than in the systemic therapy group; this finding indicates that upfront PTR is associated with a risk of surgical complications. The reviewers concluded that the efficacy of upfront PTR in managing asymptomatic mCRC remains unclear. PTR may be beneficial for a carefully selected cohort of patients, but it

carries risks that must be explored in large-scale RCTs [32].

Our multicenter study revealed no positive effect of upfront PTR on oncological outcomes in patients with synchronous *RAS* wild-type mCRC. Most of our patients had left-sided cancer, and all were treated with cetuximab. The anti-EGFR antibody cetuximab was approved by the US Food and Drug Administration in 2004. The CRYSTAL study demonstrated that compared with FOLFIRI alone, cetuximab plus FOLFIRI reduced the risk of disease progression in patients with *RAS* wild-type mCRC [16]. Our findings suggest that upfront PTR does not provide survival benefits over systemic chemotherapy plus targeted therapy in patients with synchronous *RAS* wild-type mCRC.

First-line cetuximab-based targeted therapy plus chemotherapy can effectively increase the likelihood of metastasectomy, thereby reducing the tumor burden and improving survival outcomes. In our study, OS was significantly better in patients who underwent metastasectomy than in those who did not (54 vs. 29 months; $P < 0.001$). This improvement may be attributable to the facts that metastases amenable to surgical removal are typically less disseminated and that patients eligible for metastasectomy often have better ECOG performance status than ineligible patients do. The resectability of metastatic sites in mCRC is a crucial factor that determines overall prognosis. Common metastatic sites include the liver, lungs, peritoneum, bones, and brain, with the liver being a common site of metastases. Surgical resection of liver metastases can improve prognosis. The median survival duration for patients with unresectable liver metastases is generally 13-18 months [30]. Therefore, cytoreductive strategies are crucial in the treatment of mCRC; these strategies offer advantages such as reduced tumor burden and enhanced response to systemic therapy. Guidelines from the European Society for Medical Oncology and the American Society of Clinical Oncology recommend cytoreductive strategies as a treatment goal; such strategies can contribute to long-term survival outcomes in patients with colorectal metastases to the liver, lung, peritoneum, or lymph nodes [30, 32-36]. Clinical trials have demonstrated that early tumor shrinkage during mCRC treatment with first-line cetuximab plus chemotherapy can improve prognosis and survival outcomes [37-39]. Furthermore, patients with *RAS* wild-type mCRC who achieve tumor shrinkage are highly likely to undergo metastasectomy, which is associated with improved survival [40, 41]. We observed improved survival outcomes in patients who underwent R0 resection. However, even when R0 resection could not be achieved, patients who underwent R1 or R2 resection still had better survival than did those who did not undergo metastasectomy. Similar findings were reported by a single-center retrospective study, which concluded that palliative resection in patients with mCRC led to longer OS than did no resection, particularly in younger patients with better ECOG status; however, this benefit was not observed in patients carrying tumors with poorly differentiated histology [42].

In our multicenter cohort study, hematologic and nonhematologic AEs did not differ significantly between the two groups. The most common AEs were grade 1/2 AEs, whereas grade 3/4 AEs occurred in small percentages of patients in both groups. Our study has several limitations. First, this was a retrospective study with a relatively small sample size. Smaller sample sizes can lead to lower statistical power, making it difficult to detect significant between-group differences. Second, the timing of metastasectomy was dependent on the patients' general health and willingness, which might have biased the outcomes. Third, the details of the surgical procedures, including those for PTR and metastasectomy, were not well-recorded, and the associated complications were not described. Fourth, this was a multicenter study; thus, data heterogeneity and selection biases could not be ruled out. Nonetheless, Unverzagt et al. indicated that treatment effects reported by single-center studies are often larger than those reported by multicenter studies, suggesting biases in single-center studies [43]. Finally, we did not evaluate the patients' quality of life in this study.

## Conclusion

Although our multicenter retrospective study confirmed the clinical benefit of cetuximab-based targeted therapy plus chemotherapy as a first-line treatment in patients with synchronous *RAS* wild-type mCRC, upfront PTR did not prolong OS or PFS. In summary, upfront PTR should be avoided in patients with asymptomatic primary tumors and synchronous mCRC.

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## Disclosure of conflict of interest

None.

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