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Simple Summary: The role of upfront primary tumor resection (PTR) in patients with unresectable synchronous metastatic colorectal cancer without severe symptoms remains controversial. This study aimed to report the clinical outcomes of synchronous unresectable stage IV colorectal cancer patients with or without upfront PTR. A subgroup analysis was performed to determine clinical characteristics associated with better PTR outcomes. In this retrospective study, upfront PTR was marginally associated with overall survival (OS) in multivariate analysis. Subgroup analysis revealed that male sex, good performance, left-sided tumor, low serum carcinoembryonic antigen level, T3 stage, M1a stage, <2 organ metastases, and administration of targeted agents, especially bevacizumab, were related to survival benefits after PTR. Upfront PTR should be considered in selected patients with a favorable prognosis or bevacizumab administration to improve OS in this population.

Abstract: The role of upfront primary tumor resection (PTR) in patients with unresectable metastatic colorectal cancer (CRC) without severe symptoms remains controversial. We retrospectively analyzed the role of PTR in overall survival (OS) in different subgroups. Among 331 patients diagnosed with synchronous metastatic CRC between 2010 and 2020, 223 were analyzed. The PTR group (n = 42) showed better performance ($p = 0.038$); higher frequencies of right-sided origin ($p = 0.014$), T4 stage ($p = 0.005$), M1a stage ($p = 0.015$), and <2 organ metastases ($p = 0.002$); and received fewer targeted agents ($p < 0.001$) than the chemotherapy group (n = 181). The PTR group showed longer OS (20.5 versus 14.0 months, $p = 0.016$), but PTR was marginally related to OS in multivariate analysis ($p = 0.060$). Male sex ($p = 0.022$), good performance status ($p = 0.07$), left-sided tumor ($p = 0.069$), low serum carcinoembryonic antigen level ($p = 0.092$), T3 stage ($p = 0.029$), M1a stage ($p = 0.025$), <2 organ metastases ($p = 0.017$), and administration of targeted agents, especially bevacizumab ($p = 0.024$), were related to survival benefit after PTR. Upfront PTR should be considered when selecting patients with favorable prognoses for bevacizumab administration.

Keywords: colorectal cancer; primary tumor resection; synchronous; metastasis; asymptomatic

1. Introduction

Systemic chemotherapy is the primary treatment for patients with synchronous stage IV colorectal cancer (CRC). Over the past 20 years, advances in systemic treatments, including biologically targeted agents, have led to dramatic improvements in the overall survival (OS) of patients with stage IV CRC, exceeding 30 months [1]. Primary tumor resection (PTR) has been

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performed to manage tumor-related symptoms such as obstruction, perforation, and refractory bleeding in these populations. However, the role of upfront PTR in asymptomatic and mildly symptomatic patients remains controversial. Upfront PTR may prevent primary tumor-related complications during the course of treatment, resulting in emergent surgery and poor oncological outcomes [2,3]. It can improve prognosis by removing the primary tumor source and reducing tumor-derived cytokines or chemokines [4]. However, this delays the administration of systemic treatment, and surgery-related complications are concerning [5,6].

Several retrospective, prospective cohorts, or nationwide registry analyses have shown the survival benefit of the upfront PTR in unresectable metastatic CRC [6]. Yet the heterogeneity of the study population, systemic treatment, and inevitable selection bias prevented definitive conclusions. Furthermore, many variables associated with prognosis or clinical outcomes were missing [14,16]. Recent randomized prospective clinical trials have reported that the upfront PTR group did not show a survival benefit or increased 60-day mortality compared with the chemotherapy-first group [17-19]. However, most studies closed early owing to poor accrual or futility, and a substantial number of participants did not receive any treatment after randomization.

In this study, we aimed to report the clinical outcomes of synchronous unresectable stage IV CRC patients with or without upfront PTR. A subgroup analysis was performed to determine clinical characteristics associated with better PTR outcomes

2. Materials and Methods

2.1. Ethics statements

This study was approved by the Institutional Review Board of St. Vincent Hospital (number: VC23RISI0179).

2.2. Study design and patients

We retrospectively reviewed the hospital database to identify all patients diagnosed with synchronous stage IV CRC between 2010 and 2020. The inclusion criteria were age 18 years, an initial diagnosis of unresectable stage IV colorectal adenocarcinoma, primary tumors without severe symptoms, and receipt of systemic anti-cancer treatment. Severe primary tumor symptoms were defined as follows: perforation, fistula formation, bleeding causing hemodynamic instability, or obstruction not relieved by a noninvasive procedure.

Among the 331 patients screened, 108 were excluded for the following reasons: 49 patients who received initial metastasectomy for resectable metastases; 32 patients who required emergent primary tumor resection due to severe symptoms; 21 patients who underwent upfront long course chemoradiotherapy; 2 patients had double primary malignancies along with CRC; 4 patients did not receive any systemic chemotherapy. Finally, 223 patients were included in this analysis (Figure 1).

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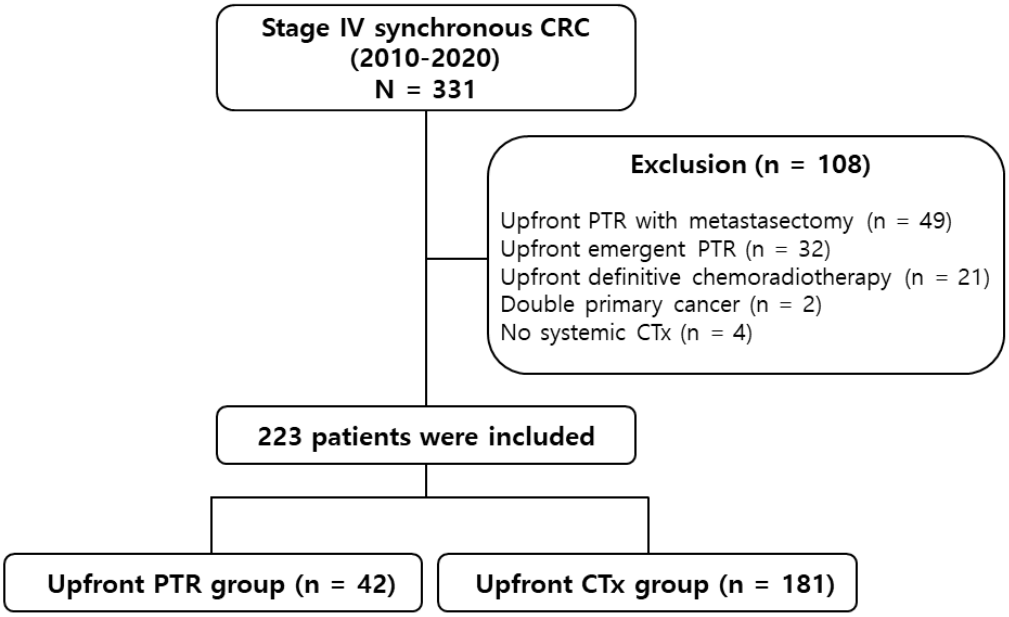

Figure 1. Patient selection flowchart. CRC, colorectal cancer; PTR, primary tumor resection; CTx, chemotherapy.

2.3. Treatment and assessment

PTR was performed in the same manner as surgery for non-metastatic CRC, including an adequate level of lymphadenectomy, and 5-fluorouracil-based cytotoxic chemotherapy was selected as first-line systemic treatment. Bevacizumab has been added since 2014, and cetuximab has been added for the population with wild *RAS* since 2015. Patients were assessed at 6–8-week intervals using computed tomography of the abdomen and chest and serum carcinoembryonic antigen (CEA) levels.

2.4. Statistical analysis

Categorical variables are presented as numbers and percentages and were compared using the chi-square or Fisher exact test. Continuous variables are expressed as median values (range) and were compared using the Student's unpaired t-test or Mann–Whitney U test, as appropriate. A subgroup analysis was performed to determine clinical characteristics associated with better PTR outcomes. OS was measured from the date of the initial treatment (PTR or systemic treatment) until death due to any cause or the last censored date during follow-up. OS was calculated using the Kaplan–Meier method, and differences in survival between the groups were compared using the log-rank test. Significant variables ($p < 0.30$) were included in the multivariate model. A backward elimination process was used to develop the final multivariate model, and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. R version 4.2.2 was used to perform all statistical analyses (The R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/).

3. Results

3.1. Baseline characteristics

Among the 223 patients, 42 (18.8%) were treated with upfront PTR, and 181 (81.2%) were treated with chemotherapy as the final treatment. The baseline patient characteristics are presented in Table 1. The two treatment groups were well balanced in terms of median age, sex, serum CEA level, tumor differentiation, clinical N stage, and *RAS* status. The median follow-up period was 14.0 months (range, 0.3–92.0 months). Patients who underwent upfront PTR showed a better Eastern Cooperative

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Oncology Group (ECOG) performance status (0/1, $p = 0.038$); higher frequencies of right-sided colon cancer ($p = 0.014$), T4 stage ($p = 0.005$), and M1a stage ($p = 0.015$); and a lower number of organ metastases (0/1, $p = 0.002$).

The upfront chemotherapy group received more irinotecan-based doublets ($p < 0.001$) and targeted agents ($p < 0.001$) than the upfront PTR group as the first line of systemic treatment. The mean times to starting systemic treatment were 50.4 (±5.46) days in the upfront PTR group and 17.3 (±1.40) days in the upfront chemotherapy group ($p < 0.001$). Conversion to R0 resection was performed more frequently in the upfront PTR group than in the upfront chemotherapy group (21.4% vs. 12.2%, $p = 0.004$).

3.2. Variables associated with OS

The median OS was 16.0 months (range, 0.3–92.0 months) in the whole study population. Kaplan–Meier curves showed that the upfront PTR group had a longer OS than the upfront chemotherapy group (20.5 versus [vs.] 14.0 months, $p = 0.016$; Figure 2). In univariate analysis, OS was associated with age, ECOG performance status, primary tumor location, serum CEA level, tumor differentiation, administration of targeted agents, and upfront PTR (Table 2). Multivariate analysis showed that old age (HR, 1.530; 95% CI, 1.118–2.093; $p = 0.008$), poor ECOG performance (HR, 1.445; 95% CI, 1.072–1.948; $p = 0.016$), high CEA level (HR, 1.465; 95% CI, 1.066–2.013; $p = 0.019$), poor differentiation (HR, 2.218; 95% CI, 1.217–4.040; $p = 0.009$), and M1c stage (HR, 1.595; 95% CI, 1.060–2.400; $p = 0.025$) were associated with poorer OS, whereas administration of targeted agent was associated with a longer OS (HR, 0.569; 95% CI, 0.387–0.837; $p = 0.004$). Upfront PTR was marginally associated with OS (HR, 0.679; 95% CI, 0.454–1.017; $p = 0.060$).

3.3. Subgroup analysis favors upfront PTR

Subgroup analyses were performed to identify the clinical subgroups that benefited from upfront PTR (Figure 3). Male sex ($p = 0.022$), good performance status ($p = 0.07$), left-sided tumor ($p = 0.069$), low serum CEA level ($p = 0.092$), T3 stage ($p = 0.029$), M1a stage ($p = 0.025$), and <2 organ metastases ($p = 0.017$) showed a significant trend toward longer OS when upfront PTR was performed. The *RAS* mutational status was not significantly different between the two groups. Upfront PTR was associated with longer OS in patients who received targeted agents ($p = 0.013$), especially in those treated with bevacizumab ($p = 0.024$).

3.4. Primary tumor-related complications

In the upfront chemotherapy group, 46 (25.4%) patients experienced primary tumor-related complications, including obstruction (17.1%), bleeding (2.8%), pain (1.7%), perforation (1.1%), fistula (1.1%), abscess (1.1%), and ischemic changes (0.6%). There was no significant difference between the right- and left-sided tumors. Twenty-six patients received surgical treatment, 15 patients were relieved by non-surgical treatment, and five patients did not recover and died. The median survival time after complications was 83 (1–1,321) days.

Table 1. Baseline characteristics.

Characteristic	Upfront PTR N = 42 (%)	Upfront chemotherapy n = 181 (%)	*p* value
Age (years)			
Median (range)	60 (34–84)	63 (30–82)	0.264
Sex			
Male	31 (73.8)	117 (64.6)	0.259
Female	11 (26.2)	64 (35.4)	
ECOG performance status			
0/1	29 (69.0)	93 (51.4)	0.038
≥2	13 (31.0)	88 (48.6)	

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Primary tumor location			
Right-sided	17 (40.5)	46 (25.4)	0.014
Left-sided	25 (59.5)	135 (74.6)	
CEA (ng/mL)	13.32 (1.0–594)	39.47 (0–86,002)	0.478
Tumor differentiation			
Well	4 (9.5)	20 (11.0)	0.732
Moderate	30 (71.4)	137 (75.7)	
Poor	7 (16.7)	19 (10.5)	
Clinical T stage			
T3	13 (31.0)	100 (55.2)	0.005
T4	29 (69.0)	81 (44.8)	
Clinical N stage			
N0	2 (4.8)	6 (3.3)	0.757
N1	10 (23.8)	52 (28.7)	
N2	30 (71.4)	123 (68.0)	
Clinical M stage			
M1a	21(50.0)	75 (41.4)	0.015
M1b	6 (14.3)	66 (36.5)	
M1c	15 (35.7)	40 (22.1)	
No. of organ metastasis			
0 or 1	30 (71.4)	81 (44.8)	0.002
≥2	12 (28.6)	100 (55.2)	
RAS status			
Wild	16 (38.1)	89 (49.2)	0.707
Mutant	15 (35.7)	72 (39.8)	
NA	11 (26.2)	20 (11.0)	
Time to chemotherapy (days)	50.4 (±5.46)	17.3 (±1.40)	<0.001
1st line chemotherapy			
Fluoropyrimidine alone	5 (11.9)	1 (0.6)	<0.001
Irinotecan doublet	15 (35.7)	108 (59.7)	
Oxaliplatin doublet	22 (52.4)	72 (39.8)	
1st line targeted gent			
Cetuximab	9 (21.4)	78 (43.1)	<0.001
Bevacizumab	13 (31.0)	70 (38.7)	
No	20 (47.6)	34 (18.8)	
Administration of targeted agent	29 (69.0)	153 (84.5)	0.021
No. of lines of systemic treatment	2 (1–7)	2 (1–7)	0.448
Conversion resection (R0)	9 (21.4)	23 (12.7)	0.004

PTR, Primary Tumor Resection; ECOG, Eastern Cooperative Oncology Group; CEA, carcinoembryonic antigen; NA, not available.

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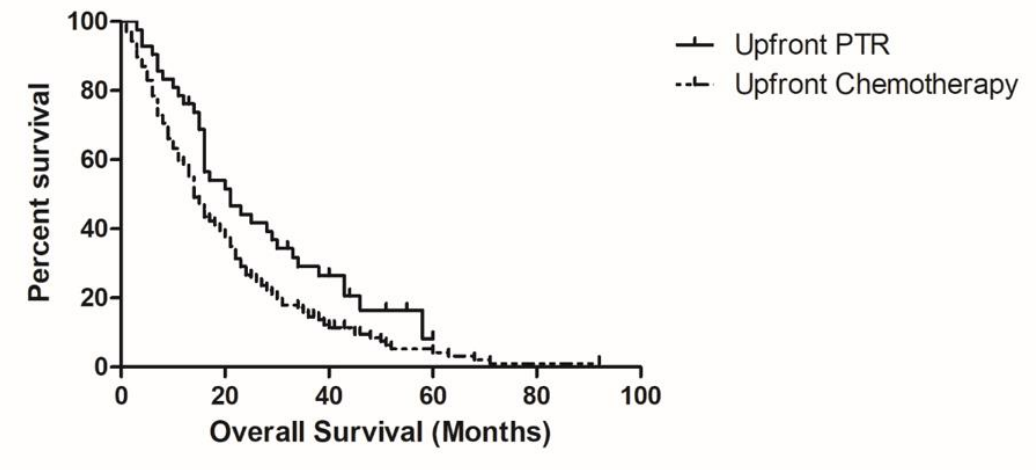

Figure 2. Kaplan–Meier curves of overall survival. PTR, primary tumor resection.

Table 2. Variables associated with overall survival.

	Univariate	Multivariate	
	p-value	HR (95% CI)	*p*-value
Age (≥ 60)	0.001	1.530 (1.118–2.093)	0.008
Male	0.160	1.239 (0.904–1.699)	0.183
ECOG ≥ 2	0.001	1.445 (1.072–1.948)	0.016
Right-side colon cancer	0.038	1.342 (0.962–1.874)	0.084
CEA ≥ 30 (ng/mL)	0.012	1.465 (1.066–2.013)	0.019
Tumor differentiation	0.031	2.218 (1.217–4.040)	0.009
Clinical T4 stage	0.782		
Clinical N1/2 stage	0.399		
Clinical M1c stage	0.148	1.595 (1.060–2.400)	0.025
No. of organ metastasis (≥2)	0.120		
RAS mutation	0.718		
Administration of targeted agent	0.003	0.569 (0.387–0.837)	0.004
Upfront PTR	0.019	0.679 (0.454–1.017)	0.060

HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; CEA, carcinoembryonic antigen; PTR, Primary Tumor Resection.

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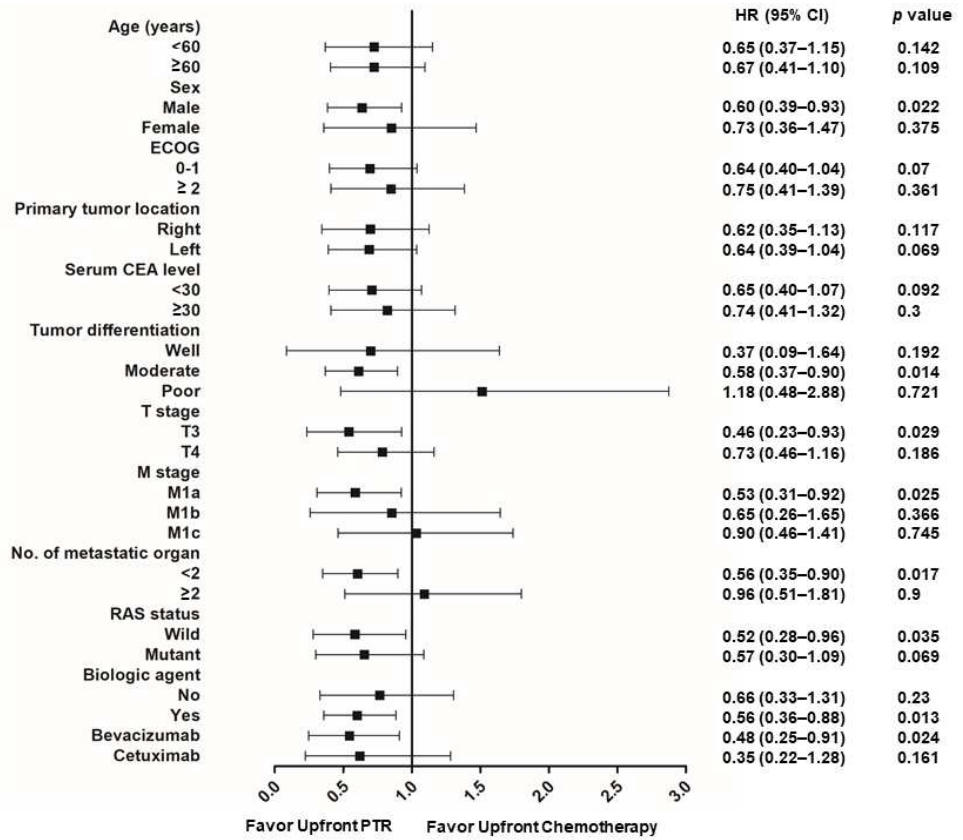

Figure 3. Forest plot of overall survival. PTR, primary tumor resection; ECOG, Eastern Coopera-tive Oncology Group; CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio.

4. Discussion

In this study, less than 20% of patients received upfront PTR among synchronous metastatic CRC patients with no or few primary tumor symptoms. This indicates that PTR was performed in highly selected patients, and most patients received chemotherapy as the initial treatment. The PTR group showed a longer OS in univariate analysis, but this was not statistically significant after adjusting for other variables. PTR seemed to be beneficial in some subgroups: male patients and patients with a good performance status, a left-sided tumor, a low CEA level, a T3 or M1a stage, and <2 organ metastases. Primary tumor-related complications occurred in 25.4% of patients in the upfront chemotherapy group, but most were relieved by surgery or intervention.

Upfront PTR for patients with initial stage IV CRC without severe primary tumor symptoms was performed at various frequencies according to the surgeon's discretion or multidisciplinary team policy. The overall frequency of PTR has decreased recently [20-22], but many clinicians continue to perform upfront PTR before chemotherapy to prevent primary tumor-related complications during the course of treatment and/or to improve OS.

The primary tumor-related complication rate in patients with CRC receiving chemotherapy varies between 11% and 35%, and approximately half of the patients require surgical intervention [5,16,23-28]. Here, a quarter of patients in the upfront chemotherapy group experienced primary tumor-related complications. Most complications were relieved by surgery or intervention; however, a few patients did not recover because the complications occurred near the end of life. Obstruction was the most common complication, which is consistent with other studies' findings [5,28]. Emergent colectomy is associated with higher morbidity and mortality rates than elective surgery [2,3]. In this study, colectomy was performed in only 14 patients, whereas the other patients were treated with bypass, stent insertion, and radiation. To avoid emergency surgery, patients should be carefully monitored for potential bowel obstruction during chemotherapy.

In the era of modern chemotherapy and targeted agents, OS, tumor response, and disease control rates have increased. The frequency of primary tumor-related complications since 2000 has continued to vary; therefore, it is not clear how they have changed since modern systemic treatments have been

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introduced [6,23-27,29]. Furthermore, there are concerns about the use of bevacizumab when the primary tumor is not resected because bevacizumab can cause bleeding, a fistula, or bowel perforation. The effect of bevacizumab administration on the PTR benefit is still controversial [7,23,25,29]. Some studies have reported that upfront PTR is associated with longer OS in bevacizumab-treated patients with CRC [23,30]. In this study, a higher rate of primary tumor-related complications was observed in the subgroups treated with targeted agents; however, the difference was not statistically significant (22.7% vs. 12.2%, $p = 0.136$, data not shown), which could be due to the longer OS in this population. The frequency did not differ according to the type of targeted agent used (23.5% for bevacizumab and 20.0% for cetuximab). Yet, surgical treatments were performed more frequently in the bevacizumab-treated subgroup than in the non-bevacizumab treatment subgroup (13.7% vs. 7.9%), which could partially explain why upfront PTR was favored in the bevacizumab subgroup in the subgroup analysis.

The survival benefit of upfront PTR in patients with synchronous metastatic CRC has only been demonstrated in retrospectively analyzed studies. Selection bias was inevitable in cases in which upfront PTR was performed: good performance status, liver-only metastasis, few organ metastases, non-rectal origin, or low serum CEA level [10,15,31-38], which could have misleading results. Additionally, the study population was heterogeneous in terms of the presence of symptoms, timing of PTR (before or during chemotherapy), and/or application or type of systemic treatment [7-13,15,32,39]. To adjust for these imbalances and heterogeneity, some studies have applied statistical methods, such as multivariate analysis or propensity matching [22,39,40]. Several studies, including ours, have shown that PTR is not associated with improved OS after adjusting for confounding factors [6,22,39,41]. Moreover, prognostic variables and therapeutic strategies have evolved over the decades, and insufficient data collection in many studies makes the role of upfront PTR debatable [14,16].

The role of the PTR in OS remains controversial in the era of biologic-targeted agents [23,39,42]. A few prospective randomized trials comparing upfront PTR with bevacizumab plus chemotherapy have been conducted to answer this question and concluded that upfront PTR was futile in terms of 60-day mortality or OS. However, most were closed early due to poor accrual or the assumed futility of the upfront PTR, which limited the statistical power supporting the conclusions [17,18]. iPACS was the first randomized controlled trial to suggest the utility of upfront PTR for asymptomatic, synchronous, unresectable metastatic CRC. However, it enrolled patients with ≤3 metastatic diseases and more than half were T3 or N0/1, which could question true unresectability [17]. Rahbari et al. also reported that upfront PTR did not prolong OS; however, more patients in the PTR group did not receive any systemic treatment after PTR, similar to that in the iPACS study [19]. This advantage of PTR for asymptomatic patients with CRC is difficult to validate in randomized clinical trials because many factors are involved in the decision-making process of PTR, including patient or clinician preference and various clinical situations that cannot be easily controlled in clinical trials.

Subgroup analyses could provide clues as to which patients could benefit from PTR. First, PTR could be associated with improved OS when performed in patients with a good performance status who can receive systemic treatment after PTR. The administration of polychemotherapy is a key determinant of OS [7]. In particular, patients receiving targeted agents showed a significantly favorable prognosis after PTR compared with the subgroup receiving chemotherapy alone. This indicates that patients with good performance who can tolerate and are willing to receive active systemic treatment could consider upfront PTR to improve their OS. The PTR group showed a considerable delay in chemotherapy administration; therefore, PTR should be avoided in patients whose conditions can rapidly deteriorate.

The extent of metastasis is also an important factor. Our study showed that patients with less extensive organ metastasis had favorable outcomes after PTR, which is consistent with other studies' results [34,43,44]. The serum CEA level reflects the extent of the tumor burden, and the subgroup with a low CEA level was also associated with PTR benefit [35]. The benefits of PTR on OS differed according to the primary tumor site. In our study, upfront PTR was performed more often in right-sided CRC for diagnostic purposes. However, patients with right-sided CRC did not show a clear benefit from upfront PTR, whereas patients with left-sided CRC showed a trend toward favoring PTR. Several studies have reported similar results in that right-sided colon cancer is related to a reduced OS benefit after PTR compared to left-sided tumors [18,45,46]. Right-sided colon cancer is associated with poorly differentiated histology, advanced stage at diagnosis, *BRAF* mutations, or

consensus molecular subtype 1, which is related to a poor prognosis. Therefore, PTR should be performed with caution in patients with right-sided CRC.

Only a few studies have reported controversial results regarding the presence of tumor *RAS* mutations [30,47], which were not related to the PTR benefit in this study. Age did not affect the benefit of PTR [21,48], whereas the female sex showed more upfront PTR benefits than the male sex, including in this study [7]. Most subgroups showing an OS benefit after PTR are associated with a favorable prognosis. Therefore, PTR should be considered in patients with stage IV CRC with favorable prognostic factors.

This study had some limitations. First, this study was conducted in a single center, and the sample size was too small, especially in the PTR group, to draw statistically significant results. Second, some data were inaccurate or missing due to the retrospective design of the study. Our study enrolled patients between 2000 and 2010; standard chemotherapy was changed, and some patients did not have molecular results associated with clinical outcomes. Finally, all patients received systemic therapy, which does not reflect the fact that some did not receive further treatment with or without PTR. Nonetheless, we attempted to collect variables associated with clinical outcomes in patients with stage IV CRC and showed the clinical role of PTR on OS according to these variables.

5. Conclusions

Upfront PTR in patients with asymptomatic or symptomatic stage IV CRC should be considered when selecting patients with a favorable prognosis. Caution is warranted in patients with unfavorable characteristics, including a poor performance status, a right-sided tumor, a high CEA level, or extensive metastasis. Systemic chemotherapy, including biological agents, is the main treatment, and upfront PTR may be beneficial, especially for bevacizumab-treated patients with CRC. However, further validation in a larger patient population is required.

Author Contributions: H.J.A. and B.K. conceived of this work; J.E.S., H.J.A., B.Y.S., H.K., H.S.P., H.C., H.K., B.K., R.N.Y., and J.M. performed the data acquisition, analysis, and interpretation; J.E.S. drafted the manuscript; and H.J.A., B.K., S.H.K., J.L., H.C.L., J.J., K.L., and J.M.L substantially revised the manuscript. All authors reviewed the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of St. Vincent Hospital (protocol code VC23RISI0179 and date of approval Aug/03/2023).

Informed Consent Statement: Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

Data Availability Statement: The data are available upon request from the corresponding author.

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Conflicts of Interest: The authors declare no conflicts of interest.

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