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# The outcome of primary tumor resection in the unresectable stage IV colorectal cancer patients who received the bevacizumab-containing chemotherapy

Seung-Seop Yeom, MD, Soo Young Lee, MD, PhD, Han Deok Kwak, MD, Chang Hyun Kim, MD, PhD, Young Jin Kim, MD, PhD, Hyeong Rok Kim, MD, PhD*

## Abstract

Primary tumor resection (PTR) for unresectable metastatic colorectal cancer (mCRC) patients has been documented to be associated with postoperative hyper-neovascularization and enhanced growth of metastases, which may be prevented by bevacizumab. This study aimed to investigate the survival outcome of PTR in patients who received palliative bevacizumab-containing chemotherapy (BCT).

From January 2006 to December 2018, medical records of 240 mCRC patients who received palliative BCT at a single tertiary colorectal cancer center were retrospectively reviewed. Patients were classified into three groups: PTR-a (PTR before BCT, n = 60), PTR-b (PTR during BCT, n = 17), and BCT-only group (n = 163). Resectable mCRCs or recurrent diseases were excluded, and the end-point was overall survival (OS) rate.

Three groups had similar age, cell differentiation, location of the primary tumor, and the number of metastatic organs. More than two-thirds of patients who received PTR experienced disease-progressions (PD) during their postoperative chemotherapy-free time (PTR-a vs PTR-b; 66.7% vs 76.5%, $P = .170$), but OS was not inferior to the BCT-only group (PTR-a vs BCT-only; HR 0.477 [95% CI 0.302–0.754], $P = .002$/PTR-b vs BCT-only; HR 0.77 [95% CI 0.406–1.462], $P = .425$). The postoperative chemotherapy-free time was similar between PTR-a and PTR-b (median 32.0 [14–98] days vs 41.0 [18–71] days, $P = .142$), but non-obstructive indications (perforation, bleeding, pain) were the more frequent in the PTR-b than PTR-a. Young age, the number of BCT, and PTR-a were the independent factors for OS.

The efficacy of the PTR for unresectable mCRC has been controversial, but this study demonstrated that PTR should be considered for the unresectable mCRC patients regardless before and during BCT.

**Abbreviations:** BCT = bevacizumab-containing chemotherapy, BV = bevacizumab, mCRC = metastatic colorectal cancer, OS = overall survival, PTR = primary tumor resection.

**Keywords:** bevacizumab, colorectal cancer, primary tumor resection

## 1. Introduction

Colorectal cancer is the second leading cause of cancer death in the USA in 2017.[1] And approximately 20% to 25% of patients with colorectal cancer presented with synchronous metastases, which are unresectable in 75% to 90% of these patients, at the time of diagnosis.[2,3] For these unresectable metastatic colorectal cancer (mCRC) patients, systemic chemotherapy is recommended to increase the survival time.[4] The current approach for treating mCRC includes doublet combinations, as well as the triplet combination combined with a biological agent targeting either the vascular endothelial growth factor in an unselected population or the epidermal growth factor receptor in patients with RAS wild-type tumors.[4]

Bevacizumab (BV) is a recombinant humanized monoclonal antibody against VEGF, and it was approved for treating mCRC by the US Food and Drug Administration in February 2004.[5] BV inhibits tumor growth by suppressing the growth of new blood vessels, reducing interstitial fluid pressure, and enhancing the efficacy of chemotherapeutic agents.[6] The substantial clinical efficacy of BV has been demonstrated in several studies; it prolongs overall and progression-free survival when used in combination with other chemotherapy regimens in the first- or second-line treatment of mCRC.[7–10]

Primary tumor resection (PTR) for unresectable mCRC has been controversial because of the possibility of delayed initiation of systemic chemotherapy. As a result, most of the asymptomatic patients who had unresectable mCRC have been indicated for palliative systemic chemotherapy. By the way, several reports documented postoperative flare-up of neovascularization and enhanced growth of metastatic foci after PTR,[11–13] which might be prevented by BV. Indeed, most of the articles published after approvement of BV, showed a positive association between PTR and survival outcomes.[14–17] As far as we know, few studies have investigated the effects of PTR alone in patients who received bevacizumab-containing chemotherapy (BCT). So we aimed to analyze the survival outcome of the PTR in the patients who received BCT.

## 2. Materials and methods

### 2.1. Study population

Our study cohort comprised 344 consecutive patients with initially unresectable mCRC who underwent palliative 1st-line or 2nd-line BCT at the Chonnam National University Hwasun Hospital from January 2006 to December 2018. Patients who received curative resection followed by conversion chemotherapy, who diagnosed to a recurrent colorectal cancer, who had a resectable mCRC, and who received only the best supportive care were excluded (Table 1).

### 2.2. Data collection

The following parameters were retrospectively collected using medical records: age, sex, tumor differentiation, the location of the primary lesion, the number of BV dose, a line of BV administration, the indication of PTR, postoperative disease-progression status, and mortality. For primary tumor sidedness, right-colon was defined as tumors of the cecum, ascending colon,

and transverse colon and left-colon was defined as tumors of the splenic flexure, descending colon, sigmoid colon, rectosigmoid colon, and rectum. All of the 1st-line chemotherapy regimens were BV plus FOLFOX or FOLFIRI, and distant metastases were recategorized to M stage according to National Comprehensive Cancer Network (NCCN) guidelines, 2018.[4]

### 2.3. Study endpoints and the follow-up

The follow-up period started from the date of surgery or chemotherapy, and it ended when the subjects were expired or decided to receive best supportive care only instead of palliative treatments or lived beyond December 31, 2018. The primary endpoint was the time to death, and the death was confirmed by referencing the Korea National Death Registry. Postoperative chemotherapy-free time and mortality and postoperative disease-progression status were investigated as a second endpoint. The chemotherapy-free time was defined as an interval, from the day of PTR to the postoperative chemotherapy or last follow-up day in patients who did not receive postoperative chemotherapy. The disease-progression status was evaluated by computed tomography scan and analyzed using revised Response evaluation criteria in solid tumors guideline, version 1.1.[18]

### 2.4. Statistical analysis

Fisher exact test and Pearson $\chi^2$ test were used for the analysis of categorical variables. Continuous variables were compared using the Mann–Whitney $U$ test and independent samples $t$ test, and the Kruskal–Wallis test was performed for non-parametric ANOVA. Overall survival (OS) was defined as the interval between the date of mCRC diagnosis and the date of death from all causes; survivors at the date of data cut-off (December 31, 2018) were censored. The Kaplan–Meier method was used to estimate OS; differences in survival were assessed using the generalized Wilcoxon test, and multivariate Cox proportional hazards

**Table 1**

**Patient characteristics.**

| | BCT only (n=163) | Primary tumor resection before BCT (n=60) | Primary tumor resection during BCT (n=17) | P |
|---|---|---|---|---|
| Age (years) | 64.0 (30–85) | 63.5 (29–76) | 59 (45–74) | .191 |
| Male sex (n, %) | 115 (70.6%) | 42 (70.0%) | 10 (58.8%) | .604 |
| Site of primary tumor (n, %) | | | | .377 |
| Right-sided | 42 (25.8%) | 17 (28.3%) | 2 (11.8%) | |
| Left-sided | 121 (74.2%) | 43 (71.7%) | 15 (88.2%) | |
| Differentiation (n, %) | | | | .001 |
| WD/MD | 140 (85.9%) | 40 (66.7%) | 15 (88.2%) | |
| PD/MUC | 18 (11.0%) | 20 (33.3%) | 2 (11.8%) | |
| Unknown | 5 (3.1%) | 0 | 0 | |
| No. of metastatic organ (n, %) | | | | .283 |
| 1 | 82 (50.3%) | 37 (61.7%) | 8 (47.1%) | |
| >1 | 81 (49.7%) | 23 (38.3%) | 9 (52.9%) | |
| M stage (n, %) | | | | .164 |
| M1a | 78 (47.9%) | 27 (45.0%) | 7 (41.2%) | |
| M1b | 52 (31.9%) | 12 (20.0%) | 6 (35.3%) | |
| M1c | 33 (20.2%) | 21 (35.0%) | 4 (23.5%) | |
| No. of bevacizumab cycle (n, median) | 12.0 (2–61) | 16.0 (1–64) | 14.0 (2–54) | .256 |
| Line of bevacizumab | | | | .537 |
| 1st-line | 139 (85.3%) | 50 (83.3%) | 16 (94.1%) | |
| 2nd-line | 24 (14.7%) | 10 (16.7%) | 1 (5.9%) | |

BCT = bevacizumab-containing chemotherapy, SEMS = self-expandable metallic stent, WD = well-differentiated, MD = moderately differentiated, PD = poorly differentiated, MUC = mucinous, SD = stable disease, PD = progressive disease
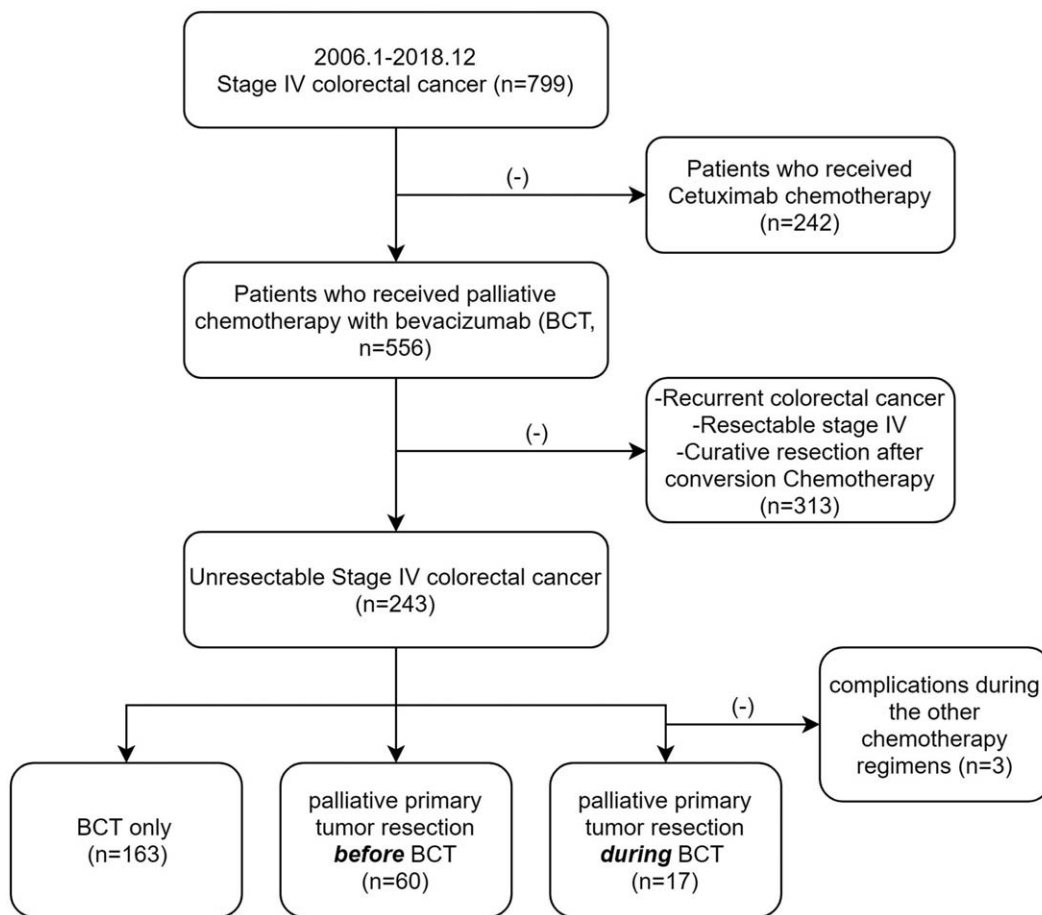
**Figure 1.** Flow chart of patient selection.

regression models were used to evaluate the prognostic impact of PTR on OS by adjusting for several clinical factors. Data are presented as numbers of patients, percentages (%), or hazard ratios (HR) and 95% confidence intervals (CI), as indicated. A $P$-value < .05 was considered statistically significant. All statistical analyses were performed using the using IBM SPSS statistics version 22.0 (SPSS, Inc., Chicago, IL).

## 3. Results

### 3.1. Patient characteristics

Among 240 unresectable mCRC patients who received palliative BCT, 163 included to CT only group, and 60, 17 patients included to PTR-a and PTR -b groups (Fig. 1). Median follow-up duration was BCT-only: 13.0 months, PTR-a: 17.0 months, 19.0 months ($P$=.081, Table 1). Three groups had similar age, sex, the location of the primary tumor, but poorly differentiated (PD) and mucinous adenocarcinomas (MUC) were more included in PTR-a group than the others ($P$=.001, Table 1). Three groups had a similar number of metastases and M stage, and BV was commonly administrated as the 1st-line treatment in three groups (Table 1). Liver, lung, peritoneum, and remote lymph node (LN) were the frequent lesions of metastasis, and about half of the metastases existed in a single organ (Tables 1 and 2).

### 3.2. Indication and the outcome of palliative surgery (Table 3)

The obstruction was the most common indication in both of PTR-a and PTR-b. However, non-obstructive causes were significantly frequent in PTR-b than in PTR-a ($P$=.005). Among 180 patients who received BCT initially (163 BCT-only + 17 PTR-b), the incidence rate of PTR-b was 9.4% (17 PTR-b/ [163 BCT-only + 17 PTR-b]), and the PTR-b was performed median 4.0 months (1–27) later from the day of first BV administration.

**Table 2**

**Site of the metastases.**

| Organ | n (%) |
|---|---|
| Liver | 182 (74.6) |
| Lung | 68 (27.9) |
| Peritoneum | 59 (24.2) |
| Distant lymph node | 37 (15.2) |
| Bone | 13 (5.3) |
| Ovary | 3 (1.2) |
| Adrenal | 2 (0.8) |
| Spleen | 2 (0.8) |
| Brain | 1 (0.4) |
| Pleura | 1 (0.4) |
| Mediastinum | 1 (0.4) |

**Table 3**

**Indications and the outcome of palliative surgery.**

| | Primary tumor resection before BCT (n = 60) | Primary tumor resection during BCT (n = 17) | P |
|---|---|---|---|
| Reason of palliative surgery, n (%) | | | .005 |
| Obstruction | 52 (86.7%) | 8 (47.1%) | |
| Perforation | 6 (10.0%) | 5 (29.4%) | |
| Bleeding | 1 (1.7%) | 1 (5.9%) | |
| Pain | 1 (1.7%) | 1 (5.9%) | |
| unknown | 0 | 2 (11.8%) | |
| Emergency surgery, n (%) | 24 (40.0%) | 9 (52.9%) | .410 |
| Mortality, n (%) | 0 | 0 | |
| Time from the last BCT (months, median) | – | 4.0 (1–27) | |
| Chemotherapy-free time (days, median) | 32.0 (14–98) | 41.0 (18–71)* | .142 |
| Disease status after surgery, n (%) | | | .170 |
| SD | 18 (30.0%) | 3 (17.6%) | |
| PD | 40 (66.7%) | 13 (76.5%) | |
| Unknown | 2 (3.3%) | 1 (5.9%) | |

BCT = bevacizumab-containing chemotherapy, PD = progressive disease, SD = stable disease.
* Excluded three-patients' data who did not received postoperative chemotherapy.

Emergency surgery was performed in about half of patients commonly in both group (P = .410). Postoperative chemotherapy-free periods (time interval between the date of surgery to the systemic chemotherapy) were similar between two groups (PTR-a; 32 days, PTR-b; 41 days, P = .142), and there were no postoperative mortalities in both groups. In postoperative computed tomography for re-staging, more than two-third of patients in both surgery group, commonly experienced disease-progressions (PTR-a vs PTR-b: 66.7% vs 76.5%, P = .170).

### 3.3. Survival outcome

Median survival time was BCT-only: 23.0 months, PTR-a: 40.0 months, PTR-b: 31.0 months (P = .005, Fig. 2). Compared with BCT-only group, PTR-a and PTR-b associated with longer survival (PTR-a: adjusted HR 0.477, 95% CI 0.302–0.754, P = .002/PTR-b: adjusted HR 0.770, 95% CI 0.406–1.462, P = .425) (Fig. 2). In univariate analysis, left-sided tumor, well/moderately differentiated tumor (WD/MD), M1c, 2nd-line BV were associated with longer survival without statistical significances (Left-sided tumor: HR 0.772, PD/MUC: HR 1.361, M1c: HR 0.694, 2nd-line BV: HR 0.630). In multivariate analysis, young age, PTR-a, and the number of BV use were the independently associated factors for the longer survival (Age: HR 1.024, PTR-a: HR 0.477, No. of BV use: HR 0.980) (Table 4).

### 4. Discussion

This study demonstrated the conflicting results of the PTR in patients who received BCT: regardless of the order between PTR and chemotherapy, PTR needed more than one month of postoperative chemotherapy-free time, and more than two-thirds of patients experienced disease-progressions during their postoperative chemotherapy-free time T. However, interestingly, the OS was not inferior to that of the BCT-only patients. Rather, the PTR-a showed statistically significantly longer survival month, and the PTR-b had also similar survival month to the BCT-only group. This retrospective study also demonstrated that about 10% of BCT-only patients had a risk of PTR during the BCT. Previous articles reported the increased survival outcome of the

PTR in the unresectable mCRC patients.[14–17,19–24] However, we had three patients (17.6%) who did not continue systemic chemotherapy. The reasons were due to the persistent BV complication (53 yr/M) and the loss of willing for further chemotherapy (74 yr/F, 66 yr/M). Taking into account the probability of treatment discontinuance after PTR, it looks like that PTR-a can be regarded as a more proper option than the PTR-b. But PTR-a also has a risk of complications.

PTR-a has been studied to avoid discontinuation of palliative systemic chemotherapy due to a tumor-related complication during the chemotherapy, but the PTR-a has also been controversial because it also causes delayed or discontinuation of chemotherapy due to complications[25–27] or results in a disturbance of homeostasis, which may lead to immunosuppression and faster growth of metastases.[28] An important concern of the opposites to the PTR was that PTR stimulates peritumoral neovascularization and, thus, accelerated growth of the metastatic lesion. Indeed, it was reported that suppressed production of endogenous anti-angiogenesis inhibitors (angiostatin and endostatin), and a flare-up in vessel neoformation.[29] Our study also demonstrated that the majority of the patients who underwent PTR experienced disease-progressions (PTR-a: 66.7%, PTR-b: 76.5%), but they survived longer than the BCT-only patients. PTR may be associated with the accelerated disease-progressions, but decreased tumor burden and concentrated chemotherapy to metastatic lesions by PTR looks increased survival time than non-PTR patients.

Another possible factor for the increased survival months of the PTR may be the BV administration. BV is a monoclonal antibody that targets vascular endothelial growth factor which suppresses neovascularization nearby cancer, and the effectiveness for 1st-line, 2nd-line, and maintenance therapy in combination with or without other chemotherapy regimens have been well-established by previous studies.[7–10,30,31] BV may have a synergistic effect when it used for patients who underwent PTR, to control accelerated neovascularization of metastases. Indeed, a lot of previous studies which were published before approvement of the BV concluded that PTR before chemotherapy had no survival benefit than patients who did not undergo PTR,[21–23] but recent papers and meta-analyses are recommending PTR before palliative chemotherapy.[14–17] Recently, a population-based cohort study in 2017,
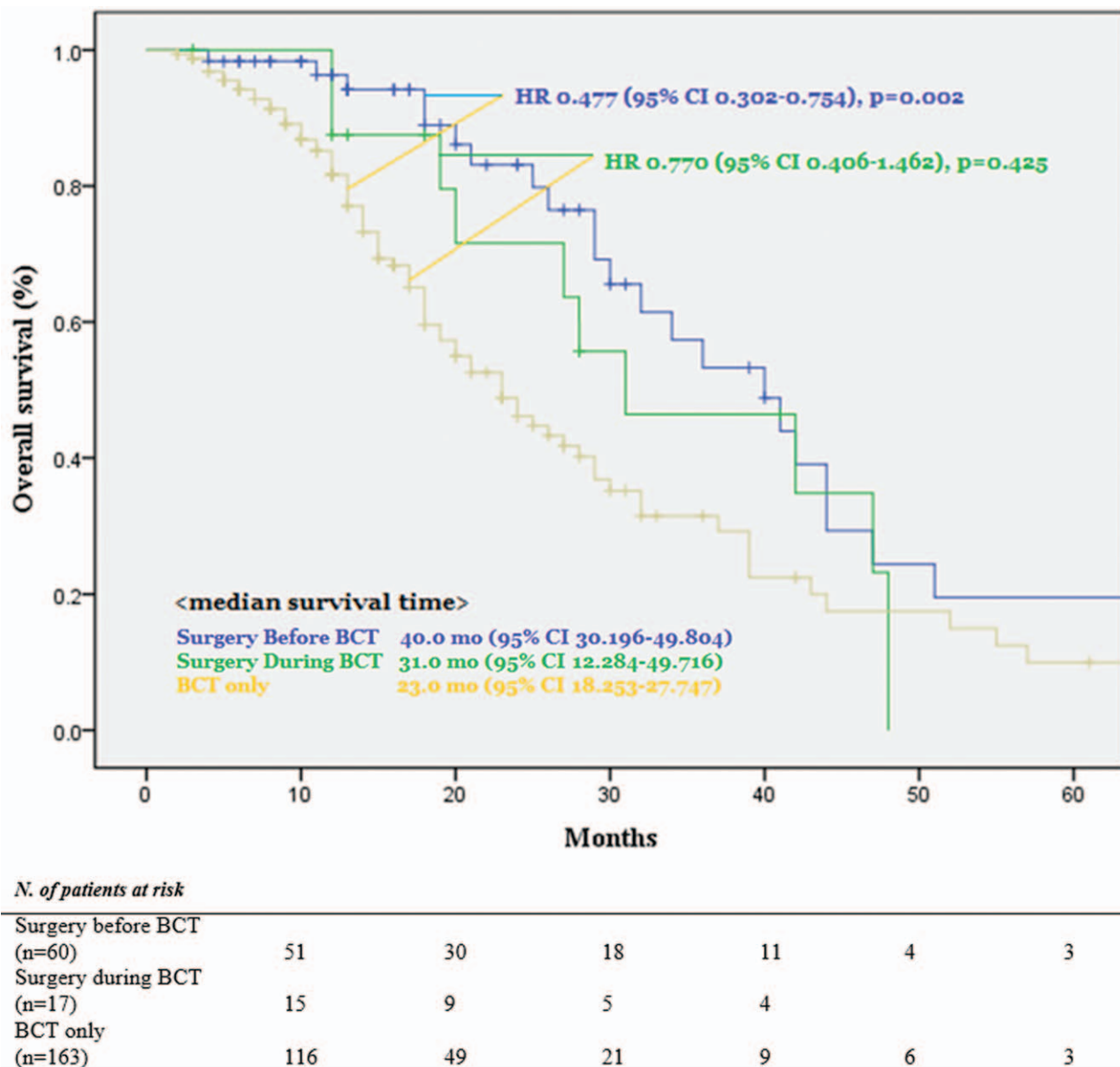
**Figure 2.** Overall survival.

reported that PTR was not associated with improved survival compared with systemic chemotherapy, but they used old data of the National Cancer Data Base of the USA between 2003 and 2005.[20]

A recent meta-analysis of seventy-seven studies demonstrated a low rate of mortality (4.5%) and the major adverse events (10.2%) after the PTR-a,[17] and a high-incidence of anastomotic leakage of 26.6% was reported postoperatively from a large-single center's retrospective study.[32] However, the studies reported that the complications from BV seem not associated with survival outcome. In actually, while BV has been largely hypothesized to increase perioperative complications in resected colorectal cancer patients. But this association has not achieved statistical significance in presently available trials and complica-tion-associated survival differences also. This retrospective study also showed statistically significant longer survival months of the

PTR-a than the BCT-only, and no one experienced surgical-site complications as like anastomotic dehiscence during BCT following PTR in this study.

Interestingly, PTR during BCT (PTR-b) was not related to the prolonged postoperative chemotherapy-free time compared to PTR-a. And PTR-b also did not compromise the survival outcome than that of the BCT-only patients. By the way, the survival curve of the PTR-b was closer to the survival curve of PTR-a, than of BCT-only, although the $P$-value was not significant between PTR-b and BCT-only. Many series have reported BV-related complications like perforation, bleeding, and fistula, which could be associated with tumor shrinkage,[33–37] and several studies have reported that good responders to the chemotherapy had a high-survival rate.[38,39] In the present study, patients with those complications also significantly more included in the PTR-b, and this can be a bias to interpret the

**Table 4**

Univariate and multivariate analysis for associated factors to overall survival.

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P | HR | 95% CI | P |
| Age | 1.025 | 1.007–1.044 | .008 | 1.024 | 1.006–1.043 | .008 |
| Male gender | 0.963 | 0.645–1.438 | .853 | | | |
| Site of primary tumor | | | | | | |
|   Right-sided | 1 | | | | | |
|   Left-sided | 0.772 | 0.496–1.202 | .252 | | | |
| Differentiation | | | | | | |
|   WD/MD | 1 | | | | | |
|   PD/MUC | 1.361 | 0.845–2.193 | .205 | | | |
| M stage | | | | | | |
|   M1a | 1 | | | | | |
|   M1b | 1.234 | 0.814–1.871 | .322 | | | |
|   M1c | 0.694 | 0.416–1.158 | .162 | | | |
| Treatment | | | | | | |
|   BCT only | 1 | | | 1 | | |
|   PTR before BCT | 0.481 | 0.305–0.759 | .002 | 0.477 | 0.302–0.754 | .002 |
|   PTR during BCT | 0.722 | 0.382–1.368 | .318 | 0.770 | 0.406–1.462 | .425 |
| No. of bevacizumab cycle | 0.981 | 0.966–0.996 | .015 | 0.980 | 0.965–0.996 | .015 |
| Line of bevacizumab | | | | | | |
|   1st-line | 1 | | | | | |
|   2nd-line | 0.630 | 0.364–1.092 | .100 | | | |

BCT = bevacizumab-containing chemotherapy, MD = moderately differentiated, MUC = mucinous, PD = poorly differentiated, PTR = primary tumor resection, WD = well-differentiated.

favorable survival outcome of the PTR-b. Thus, the favorable outcome of PTR-b in this study seems not to be used as a basis for supporting BCT-only. Further researches will be necessary which are including evaluation of the relationship between the complications during postoperative BCT, and the effect to survival outcome after PTR in the patients who received BCT. PTR-a seems to be considered for the unresectable mCRC patients until the reliable negative pieces of evidence are accumulated.

This study has several limitations. First, this study is a small retrospective study, suggesting a possible bias in decision-making for individual patients, which may have influenced oncologic outcomes although the factors that may have affected the selection of patients for surgery to remain unclear. Second, there is a possibility that PTR during BCT, was indicated for 'more favorable' patients and consequently showed better prognosis. On the other hand, patients with poor physical status could be included in BCT-only group. And the outcome of the patient group who received PTR before BV administration could be exaggerated, because patients' data who did not receive BV administration after PTR were excluded, who might have severe morbidity or poor performance status. Although, severe complication rate after PTR-a is expected to be rare. Third, the molecular features of tumors as like MSI, RAS/BRAF mutation status, and several clinicopathological factors were not included in the analyses of this retrospective study. However, the effects of the variables are also not clear, and our variables as like young age, male, left-sidedness of the primary tumor, well differentiation, M1c, 2nd-line BV administration showed similar associations and hazard-ratios to OS compared to recent large-scale trials.[14,17,40–42]

The efficacy of PTR for unresectable mCRC is controversial. However, PTR in the patients who received BCT was associated with longer survival than that of the BCT-only patients, and PTR during BCT was also not associated with a significant delay of postoperative chemotherapy. PTR seems to be a good palliative treatment option for the unresectable mCRC patients to increase survival outcome, regardless of before and during the BCT. In our knowledge, this is the first study, which focused on the outcome of PTR in the patients who received BCT, and further studies should be performed to determine the optimal treatment approach for the unresectable mCRC patients.

## Author contributions

**Conceptualization:** Seung-Seop Yeom, Young Jin Kim, Hyeong Rok Kim.

**Data curation:** Seung-Seop Yeom, Soo Young Lee, Young Jin Kim, Hyeong Rok Kim.

**Formal analysis:** Seung-Seop Yeom, Chang Hyun Kim, Hyeong Rok Kim.

**Funding acquisition:** Seung-Seop Yeom, Hyeong Rok Kim.

**Investigation:** Seung-Seop Yeom, Hyeong Rok Kim.

**Methodology:** Seung-Seop Yeom, Young Jin Kim, Hyeong Rok Kim.

**Project administration:** Seung-Seop Yeom, Hyeong Rok Kim.

**Resources:** Seung-Seop Yeom.

**Software:** Seung-Seop Yeom.

**Supervision:** Seung-Seop Yeom, Young Jin Kim, Hyeong Rok Kim.

**Validation:** Seung-Seop Yeom, Han Deok Kwak.

**Visualization:** Seung-Seop Yeom.

**Writing – original draft:** Seung-Seop Yeom.

**Writing – review & editing:** Seung-Seop Yeom.

Seung-Seop Yeom orcid: 0000-0003-3651-222X.

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