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ORIGINAL ARTICLE

# Outcomes of palliative local treatment in metastatic colorectal cancer patients receiving chemotherapy plus bevacizumab

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## Abstract

**Objective** The aim of this study was to assess the value of palliative local treatment of incurable metastatic lesions in colorectal cancer (CRC) patients receiving chemotherapy plus bevacizumab.

**Methods** Data of 105 patients with histologically confirmed synchronous or metachronous metastatic CRC who received bevacizumab treatment from January 1, 2011 to January 31, 2017 were retrospectively reviewed. Sixteen (15%) patients who were treated with bevacizumab for less than 4 cycles were excluded, and finally, 89 (85%) patients were enrolled. Among them, 33 (37%) patients who received palliative local treatment were categorized into the palliative local treatment group, and the remaining 56 (63%) patients were categorized into the chemotherapy plus bevacizumab group. The primary endpoint was overall survival (OS), which was calculated using Kaplan-Meier survival analyses. Factors possibly influencing survival were evaluated by univariate and multivariate analyses. Adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events, version 4.0. Grades 1–2 and 3–4 AEs of the two groups were compared and analyzed using the Fisher's exact test and $\chi^2$ analysis.

**Results** The median follow-up period was 20.4 months, ranging from 1 to 60 months. The median OS in the palliative local treatment group was 36.3 months (95% CI, 33.5–39.2), and that in the chemotherapy plus bevacizumab group was 20.5 months (95% CI, 17.6–23.4). Both the univariate (HR 0.13, 95% CI, 0.05–0.30, $P < 0.001$) and multivariate (HR 0.16, 95% CI, 0.07–0.39, $P < 0.001$) analyses showed that the addition of palliative local treatment could prolong survival compared with chemotherapy plus bevacizumab alone. There were no significant differences in the rates of common chemotherapy- or bevacizumab-related AEs between the two groups.

**Conclusion** These findings suggest palliative local treatment is an effective and safe method for treating patients with incurable metastatic CRC receiving chemotherapy plus bevacizumab.

**Key words:** metastatic colorectal cancer; palliative local treatment; bevacizumab; chemotherapy; overall survival

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Approximately 50%–60% of patients diagnosed with colorectal cancer (CRC) develop colorectal metastases, and > 65% of these patients have incurable metastatic disease [1–4]. Compared with patients undergoing complete resection of the metastatic and primary lesions, the outcome of those with incurable metastatic lesions is poorer. Fewer than 10% of the patients treated with standard chemotherapy are alive 5 years after treatment [2]. Even in the best case scenario of treatment with combined monoclonal antibodies, such as bevacizumab (a humanized monoclonal antibody that blocks the activity of vascular endothelial growth factor), long-term survival is modest, resulting in only about a 5-month improvement in overall survival (OS) [5–6]. The management of these patients with incurable metastases from metastatic CRC (mCRC) is a therapeutic challenge.

In recent years, a number of palliative local treatment methods have emerged in an attempt to treat incurable mCRC patients, including surgery, radiofrequency ablation, percutaneous microwave coagulation therapy

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(PMCT), transcatheter arterial chemoembolization (TACE), and radiation therapy (RT) [7–11]. Moreover, a recent retrospective study of 1,174 patients reported a survival benefit of palliative local treatment for patients with unresectable mCRC [12]. In this study, Yang *et al* found that the addition of palliative local treatment to chemotherapy was associated with a longer OS than chemotherapy alone (38.73 vs. 19.8 months, $P < 0.01$). The exploration of palliative local treatment reflects the fact that active local disease control plays an important role in the treatment of unresectable mCRC. However, more comprehensive data on the beneficial survival effect of this approach are lacking. No published studies have investigated the combined use of palliative local treatment, targeted drugs (bevacizumab), and chemotherapy in these patients, and the value of palliative local treatment combined with chemotherapy plus bevacizumab for incurable mCRC remains unclear.

The aim of the present study, therefore, was to assess the long-term effect of palliative local treatment of incurable metastatic lesions in mCRC patients receiving chemotherapy plus bevacizumab.

## Materials and methods

### Patient selection

This was a retrospective study conducted at the Department of Oncology, Tongji Hospital, Huazhong University of Science and Technology. Here, we reviewed data of consecutive patients with histologically confirmed synchronous or metachronous mCRC treated with bevacizumab from January 1, 2011 to January 31, 2017. For all these patients, key eligibility criteria included: (1) treatment with bevacizumab for at least 4 cycles; (2) World Health Organization Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; (3) adequate organ function according to the following laboratory values: absolute neutrophil count, > 1,500/μL; hemoglobin level, > 9.0 g/dL; platelet count, > 75,000/μL; bilirubin level, < 2.0 mg/dL; transaminase level, < 3 times the normal upper limit (5 times for patients with liver metastasis); and serum creatinine level, < 150 μmol/L; and (4) a life expectancy of > 3 months. Eligible patients were divided into two groups based on whether they received palliative local treatment. Palliative local treatment included surgery, PMCT, TACE and RT. Patients who underwent nontherapeutic exploratory laparotomy or emergency surgery for obstruction, hemorrhage and perforation, or biliary drainage were excluded from the palliative local treatment group. The remaining patients were categories into the chemotherapy plus bevacizumab group. The characteristics of the patients in both the groups are summarized in Table 1. The Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology approved this retrospective study.

### Systemic treatment regimen

Patients who had received standard palliative chemotherapy combined with bevacizumab were enrolled. The first- and second-line regimens included oxaliplatin- or irinotecan-containing chemotherapy. The third- and later-line therapies had no mandatory requirement. Bevacizumab was given at 5 mg/kg per 2 weeks or 7.5 mg/kg per 3 weeks respectively. One cycle was defined as 14 days or 21 days.

The dosage, delivery, and schedule of the main therapeutic regimens were administered according to the National Comprehensive Cancer Network guidelines (version 2, 2016). Bevacizumab was continued after first-line bevacizumab progression unless the patients refused treatment for cost, side effects or other reasons, in which case chemotherapy agents were changed from the first-line chemotherapy agents.

### Principles of palliative local treatment

To evaluate whether cases with incurable metastases are suitable for palliative local treatment, careful discussion and supervision must be carried out by a multidisciplinary team (MDT) in our center. Before the administration of palliative local treatment, adequate assessment and communication should be undertaken among medical oncologists, radiologists, surgeons, and patients so that a suitable treatment strategy that optimizes related issues such as which lesions to treat and the timing of intervention can be developed. In general, the principles of palliative local treatment for cases with incurable metastatic lesions in our center are as follows: (1) to relieve symptoms, such as pain, hemorrhage, dysuresia, and bowel movement disorders, caused by intrapelvic tumors; (2) to prevent metastatic disease-related injury such as obstructive jaundice, pathological fractures of the bone and spinal cord paralysis; or (3) to control isolated new lesions or lesions that continue to enlarge when most of the remaining lesions are well-controlled (caused by tumor heterogeneity) during or after chemotherapy. In this study, patients were allowed to receive one or more types or multiple administrations of palliative local treatments. Written informed consent was required before palliative local treatment was administered.

### Data information and statistical analysis

The clinicopathological parameters which we evaluated included age, sex, ECOG performance status, primary location (left or right side), grade of tumor differentiation, number of metastatic lesions, previous adjuvant chemotherapy (yes or no), KRAS status, pretreatment serum carcinoembryonic antigen (CEA)

levels (ng/mL), and survival period (months). The patient follow-up period ranged from 1 to 60 months, and the survival period was calculated from the date on which mCRC diagnosis was confirmed until the latest follow-up date. The detailed information of palliative local treatment among the 89 patients are summarized in Fig. 1, included the proportion and types of palliative local treatment administered. Adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events, version 4.0. Patient data and all patient follow-up information were collected into our electronic medical records database, including the latest follow-up or date of demise.

The primary endpoint was OS. Independent sample *t*-tests were used for statistical analysis of continuous variables, and the Fisher's exact test and $\chi^2$ analysis were used, as appropriate, for categorical data. All factors possibly influencing survival were evaluated using univariate and subsequently, multivariate analyses. Survival curves were generated according to the Kaplan-Meier method, and the differences in patient survival periods were determined by employing the log-rank test. A $P$ value < 0.05 was accepted as statistically significant. The Cox regression model and the Cox proportional hazards model were used for the analyses taking into account all variables simultaneously. All data were analyzed by the Statistical Package for the Social Sciences, version 19.0 (SPSS Inc., Chicago, IL, USA).

## Results

### Patients

Between January 1, 2011 and January 31, 2017, data of 105 consecutive mCRC patients who received bevacizumab treatment were retrospectively reviewed; 16 (15%) patients who were treated with bevacizumab for less than 4 cycles were excluded. Finally, 89 (85%) patients were enrolled. Among them, 33 (37%) received

**Table 1** Characteristics of patients

| Categorical Variable | Total ($n$ = 89) | | CT-B +local treatment ($n$ = 33) | | CT-B ($n$ = 56) | | $P$ |
|---|---|---|---|---|---|---|---|
| | $n$ | % | $n$ | % | $n$ | % | |
| Ages (years) | | | | | | | 0.724 |
| < 60 | 60 | 67.4 | 23 | 69.7 | 37 | 66.1 | |
| ≥ 60 | 29 | 33.6 | 10 | 30.3 | 19 | 33.9 | |
| Sex | | | | | | | 0.606 |
| Male | 49 | 55.1 | 17 | 51.5 | 32 | 57.1 | |
| Female | 40 | 44.9 | 16 | 48.5 | 24 | 42.9 | |
| ECOG PS | | | | | | | 0.936 |
| 0–1 | 67 | 75.3 | 25 | 75.8 | 42 | 75.0 | |
| 2 | 22 | 24.7 | 8 | 24.2 | 14 | 25.0 | |
| Site of primary tumour | | | | | | | 0.444 |
| Left side | 66 | 74.2 | 26 | 78.8 | 40 | 71.4 | |
| Right side | 23 | 25.8 | 7 | 21.2 | 16 | 28.6 | |
| Tumor differentiation (grade) | | | | | | | 0.142 |
| Well/Moderate | 50 | 56.2 | 23 | 69.7 | 27 | 48.2 | |
| Poor | 20 | 22.5 | 5 | 15.2 | 15 | 26.8 | |
| Unknown | 19 | 21.3 | 5 | 15.2 | 14 | 25.0 | |
| Number of metastatic lesions | | | | | | | 0.128 |
| < 5 | 29 | 32.6 | 14 | 42.4 | 15 | 26.8 | |
| ≥ 5 | 60 | 67.4 | 19 | 57.6 | 41 | 73.2 | |
| Previous adjuvant chemotherapy | | | | | | | 0.106 |
| Yes | 31 | 34.8 | 15 | 45.5 | 16 | 28.6 | |
| No | 58 | 65.2 | 18 | 54.5 | 40 | 71.4 | |
| KRAS status | | | | | | | 0.270 |
| Wild type | 11 | 12.4 | 6 | 18.2 | 5 | 8.9 | |
| Mutation type | 29 | 32.6 | 8 | 24.2 | 21 | 37.5 | |
| Unknown | 49 | 55.1 | 19 | 57.6 | 30 | 53.6 | |
| Pre-treatment CEA (ng/mL) | | | | | | | 0.152 |
| Normal (< 5 ng/mL) | 32 | 36.0 | 15 | 45.5 | 17 | 30.4 | |
| Abnormal (≥ 5 ng/mL) | 57 | 64.0 | 18 | 54.5 | 39 | 69.6 | |

CT-B: chemotherapy plus bevacuzimab; ECOG PS: Eastern Cooperative Oncology Group performance status; CEA: carcinoembryonic antigen

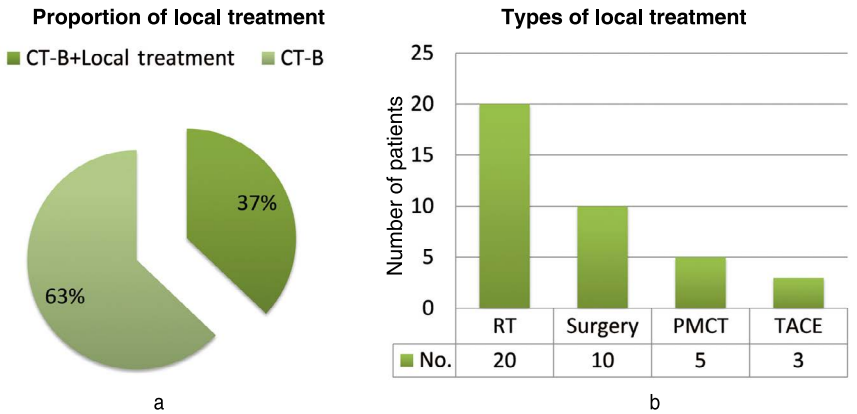


**Fig. 1** Palliative local treatment in colorectal cancer patients with incurable metastatic lesions. (a) Pie chart of the proportion of palliative local treatment in colorectal cancer patients receiving combined treatment of chemotherapy and bevacizumab; (b) Histogram of the types of palliative local treatment in colorectal cancer patients with incurable metastatic lesions. RT: radiation therapy; PMCT: percutaneous microwave coagulation therapy; TACE: transcatheter arterial chemoembolization

palliative local treatment and were categorized into the palliative local treatment group, and the remaining 56 (63%) were categorized into the chemotherapy plus bevacizumab group (Fig. 2). The baseline characteristics were generally balanced between the two groups. There was no significant difference in relation to age, sex, ECOG performance status, primary location (left or right side), grade of tumor differentiation, number of metastatic lesions, previous adjuvant chemotherapy (yes or no), KRAS status, and pretreatment serum CEA levels (ng/mL) in the patients receiving palliative local treatment compared with those receiving chemotherapy plus bevacizumab. Additional details of the characteristics of all patients are summarized in Table 1.

The detailed information of palliative local treatment received by the 89 patients was well-summarized, as presented in Fig. 1. More than a third (37%) of the patients received palliative local treatment, and > 15% of them were treated with two different types of palliative local treatment. Of those administered palliative local treatment, 20 received RT for incurable metastatic lesions, 10 received surgery, 5 received PMCT, and 3 received TACE. The organs of local treatment were varied, and included the liver, lung, bone, ovary, lymph nodes of the retroperitoneal space and pelvic cavity, and metastatic nodules (Fig. 1).

## Survival

The median follow-up period was 20.4 months, ranging from 1 to 60 months. Among the patients in the palliative local treatment group, 17 (52%) had died by the last follow-up and 16 (48%) were alive. In the chemotherapy plus bevacizumab treatment group, 29 (52%) patients had died by the last follow-up and 27 (48%) were alive. In the survival analysis of the 89 mCRC patients, the addition of palliative local treatment to chemotherapy and bevacizumab was associated with a significant increase in OS compared with chemotherapy plus bevacizumab alone (HR 0.13, $P < 0.001$, Fig. 3). The median OS with palliative local treatment and chemotherapy plus bevacizumab were 36.3 months (95% CI, 33.4–39.2) and 20.5 months (95% CI, 17.6–23.4), respectively.

Eight patient-, tumor-, and therapy-related characteristics that could potentially influence survival were identified in our study (Table 2). As more than half of the patients' KRAS status were unknown, we did not include it in further analyses. We found that two factors, including the number of metastatic lesions (HR 2.37, $P = 0.016$), and previous adjuvant chemotherapy (yes vs no, HR 2.32, $P = 0.014$) were significantly associated with outcome in a univariate analysis. A multivariate analysis adjusted for all 8 factors also indicated that the number of metastatic lesions (HR 2.55, $P = 0.015$), and previous adjuvant chemotherapy (yes vs no, HR 2.21, $P = 0.041$) were significantly associated with OS. Univariate analysis of the palliative local treatment for OS showed that the addition of palliative local treatment was associated with an increased OS (HR 0.13, 95% CI, 0.05–0.30, $P < 0.001$). This effect was virtually unchanged after adjustment for the number of metastatic lesions and previous adjuvant chemotherapy by multivariate analysis (HR 0.16, 95% CI, 0.07–0.39, $P < 0.001$), suggesting that the association between OS and palliative local treatment is independent of these factors (Tables 2 and 3). Furthermore, we performed multivariate analyses with adjustment for all the 8 factors listed in Table 2 and obtained similar results for OS (HR 0.16, 95% CI, 0.06–0.41, $P < 0.001$).

## Safety

All patients in both groups experienced at least one AE. Among them, grade 1–2 and 3–4 AEs were compared between the two groups (Table 4). In both groups, the most frequently occurring AE was leukopenia, affecting 94% of the total patients in the palliative local treatment group and 92% of the total patients in the chemotherapy plus bevacizumab treatment group. Grade 3–4 AEs were not common in both groups. The most frequently occurring grade 3–4 AE was neutropenia, affecting 24% of the total

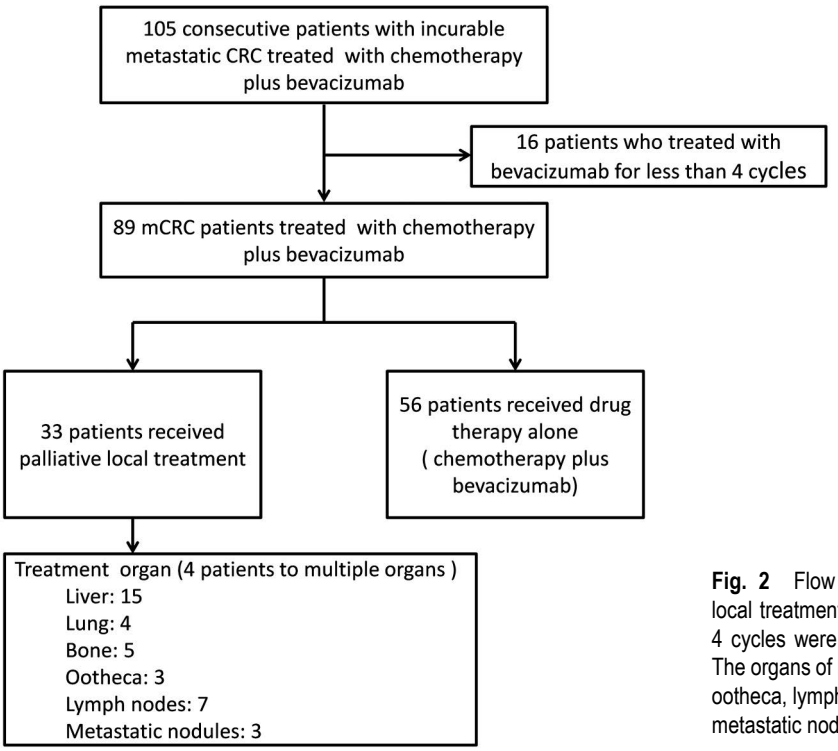


**Fig. 2** Flow chart of patient inclusion and overview of palliative local treatment. 16 patients treated with bevacizumab for less than 4 cycles were excluded; a total of 89 patients were thus enrolled. The organs of local treatment were varied, including liver, lung, bone, ootheca, lymph nodes of retroperitoneal space and pelvic cavity, and metastatic nodules

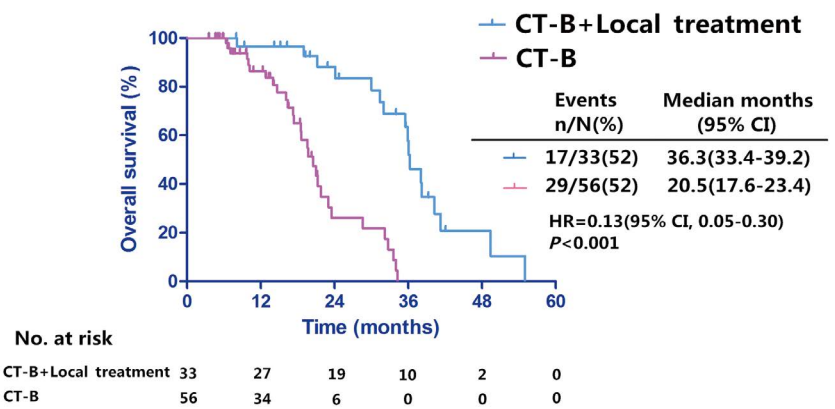


**Fig. 3** Kaplan-Meier overall survival curves for patients who had received palliative local treatment combined with chemotherapy plus bevacuzimab or who had only received chemotherapy plus bevacuzimab. CT-B: chemotherapy plus bevacuzimab; HR: hazard ratio; CI: confidence interval

patients in the palliative local treatment group and 23% of the total patients in the chemotherapy plus bevacizumab group. There were no significant differences in the rates of common chemotherapy-related AEs between the two groups. It was worth noting that the bevacizumab-related AEs were also recorded and patients in the palliative local treatment group had similar rates of bevacizumab-related AEs as compared to those in the chemotherapy plus bevacizumab group. For example, the incident rates of grade 1 or 2 hypertension, proteinuria, and bleeding were 24%, 15%, and 42%, respectively, for the palliative local treatment group, and 21%, 18%, and 45%, respectively, for the chemotherapy plus bevacizumab group. The addition of palliative local treatment did not increase the rate of bevacizumab-induced AEs.

## Discussion

Despite advances in chemotherapy, most patients with incurable mCRC succumb to the disease within 20 months of diagnosis [13]. In an effort to improve survival, new therapeutic approaches, such as targeted therapy and palliative local treatment, have gained much support in the last decade. Targeted therapies, such as bevacizumab, have been proven to be effective in combination with chemotherapy or as single agents for the treatment

**Table 2** Univariate analysis and multivariate analysis of prognostic factors for overall survival using the Cox proportional hazards model, evaluated in all patients ($n$ = 89)

| Factors | Number of patients | Median OS (95% CI) (months) | Univariate analysis | | | multivariate analysis | | |
|---|---|---|---|---|---|---|---|---|
| | | | HR | 95% CI | *P* | HR | 95% CI | *P* |
| Ages (years) | | | | | | | | |
| < 60 | 60 | 30.0 (20.02–39.98) | 1.000 | | | 1.000 | | |
| ≥ 60 | 29 | 23.5 (11.16–35.84) | 0.702 | 0.373–1.322 | 0.273 | 0.805 | 0.406–1.596 | 0.535 |
| Sex | | | | | | | | |
| Male | 49 | 28.6 (18.05–39.15) | 1.000 | | | 1.000 | | |
| Female | 40 | 33.6 (17.49–49.71) | 0.699 | 0.380–1.284 | 0.248 | 0.864 | 0.457–1.632 | 0.652 |
| ECOG PS | | | | | | | | |
| 0–1 | 67 | 31.4 (20.18–42.62) | 1.000 | | | 1.000 | | |
| 2 | 22 | 23.0 (18.34–27.67) | 1.415 | 0.683–2.928 | 0.350 | 0.978 | 0.418–2.289 | 0.959 |
| Site of primary tumour | | | | | | | | |
| Left side | 66 | 30.0 (19.00–41.00) | 1.000 | | | 1.000 | | |
| Right side | 23 | 23.0 (6.44–39.56) | 1.132 | 0.555–2.307 | 0.733 | 0.681 | 0.297–1.560 | 0.363 |
| Tumor differentiation (grade) | | | | | | | | |
| Well/Moderate | 50 | 31.4 (24.87–37.93) | 1.000 | | | 1.000 | | |
| Poor | 20 | 19.0 (18.13–19.87) | 1.825 | 0.896–3.718 | 0.097 | 1.536 | 0.676–3.485 | 0.305 |
| Unknown | 19 | 23.5 (18.78–28.22) | 0.917 | 0.318–2.641 | 0.873 | 0.759 | 0.237–2.424 | 0.641 |
| Number of metastatic lesions | | | | | | | | |
| < 5 | 29 | 35.5 (32.84–38.16) | 1.000 | | | 1.000 | | |
| ≥ 5 | 60 | 23.0 (20.01–25.99) | 2.365 | 1.172–4.771 | 0.016 | 2.549 | 1.197–5.426 | 0.015 |
| Previous adjuvant chemotherapy | | | | | | | | |
| Yes | 31 | 35.5 (32.67–38.33) | 1.000 | | | 1.000 | | |
| No | 58 | 23.5 (12.66–34.34) | 2.322 | 1.189–4.535 | 0.014 | 2.213 | 1.033–4.740 | 0.041 |
| Pre-treatment CEA (ng/mL) | | | | | | | | |
| Normal (< 5 ng/mL) | 32 | 31.4 (20.19–42.61) | 1.000 | | | 1.000 | | |
| Abnormal (≥ 5 ng/mL) | 57 | 24.1 (12.26–35.94) | 0.970 | 0.529–1.779 | 0.922 | 1.087 | 0.545–2.166 | 0.813 |

Multivariate analyses were adjusted for all factors listed in Table. OS: overall survival; NR: not reported; CEA: carcinoembryonic antigen; HR: hazard ratio; CI: confidence interval

**Table 3** Associations between palliative local treatment and overall survival based on univariate analysis and multivariate analysis

| Palliative local treatment | Number of patients | Median OS (95% CI) (months) | univariate analysis | | | multivariate analysis | | |
|---|---|---|---|---|---|---|---|---|
| | | | HR | 95% CI | *P* | HR | 95% CI | *P* |
| No (CT-B) | 33 | 20.5 (17.63–23.37) | 1.000 | | | 1.000 | | |
| Yes (CT-B + Local treatment) | 56 | 36.3 (33.45–39.15) | 0.127 | 0.054–0.302 | < 0.001 | 0.161 | 0.066–0.394 | < 0.001 |

Multivariate analyses in this table were adjusted for number of metastatic lesions and previous adjuvant chemotherapy. Similar results were obtained when multivariate analyses were adjusted for all the factors listed in Table 2 (data not shown). OS: overall survival; CT-B: chemotherapy plus bevacuzimab; HR: hazard ratio; CI: confidence interval

of mCRC, and they have been widely used in clinical practice [5, 14–16]. Recent studies have also confirmed that adding palliative local treatment improves the long-term outcome of incurable mCRC patients [11–12, 17]. Palliative local treatment has thus become another new treatment option for incurable mCRC.

These promising results prompted us to carry out the current study. To prove whether a more active treatment strategy could further improve the survival of incurable mCRC patients, we designed this retrospective study to identify the effectiveness of additional palliative local treatment in incurable mCRC patients who had received chemotherapy plus bevacizumab. As a result, we found that the addition of palliative local treatment to the standard treatment of chemotherapy plus bevacizumab could significantly improve survival for mCRC patients compared with those who had only received the standard treatment of chemotherapy plus bevacizumab. It should

**Table 4** Adverse events relevant to treatment

| Adverse events | CT-B +Local Treatment (*n* = 33) | | CT-B (*n* = 56) | | *P* |
|---|---|---|---|---|---|
| | Grade 1–2 *n* (%) | Grade 3–4 *n* (%) | Grade 1-2 *n* (%) | Grade 3–4 *n* (%) | |
| Leukopenia | 25 (76) | 6 (18) | 40 (71) | 12 (21) | 0.906 |
| Neutropenia | 22 (67) | 8 (24) | 38 (68) | 13 (23) | 0.993 |
| Anemia | 19 (58) | 2 (6) | 31 (55) | 1 (2) | 0.507 |
| Thrombocytopenia | 14 (42) | 1 (3) | 25 (45) | 1 (2) | 0.918 |
| Nausea | 25 (76) | 5 (15) | 43 (77) | 7 (13) | 0.921 |
| Vomiting | 11 (33) | 2 (6) | 15 (27) | 3 (5) | 0.782 |
| Diarrhoea | 9 (27) | 3 (9) | 17 (30) | 4 (7) | 0.918 |
| Fatigue | 18 (55) | 2 (6) | 34 (61) | 3 (5) | 0.850 |
| Thrombosis | 0 (0) | 0 (0) | 0 (0) | 1 (2) | 0.440 |
| Hypertension | 8 (24) | 3 (9) | 12 (21) | 7 (13) | 0.865 |
| Proteinuria | 5 (15) | 2 (6) | 10 (18) | 3 (5) | 0.942 |
| Bleeding | 14 (42) | 1 (3) | 25 (45) | 2 (4) | 0.965 |
| Any infection | 12 (36) | 2 (6) | 19 (34) | 1 (2) | 0.519 |
| Liver toxicity | 8 (24) | 1 (3) | 18 (32) | 1 (2) | 0.697 |

Data are number (%) or p value. CT-B: chemotherapy plus bevacuzimab

be noted that the survival (median OS of 36.3 months) of the patients who had received combined treatment of chemotherapy, bevacizumab and palliative local treatment in our cancer center is one of the longest, as compared to historical published results of chemotherapy combined with bevacizumab [5, 18–20]. Of particular note, the patients included in our study all had highly advanced mCRC. Approximate 60% had more than 5 metastatic lesions. Moreover, the addition of palliative local treatment did not appear to exacerbate drug-induced grade 3 AEs, such as bleeding. In fact, we do not think the two new treatment options (targeted treatment and palliative local treatment) were independent of each other in improving survival of incurable mCRC patients. The addition of bevacizumab could significantly increase the tumor response rate, thus creating more opportunities for mCRC patients to accept more types and repeats of local treatment, further improving the survival of these patients. A combination of chemotherapy, targeted treatment and local treatment is important and effective in comprehensive treatment strategies and may be synergistic.

Our study had some limitations. First, this was a retrospective analysis of our experience. Second, the sample size of the study was small. Finally, there was a selection bias in patients receiving palliative local treatment, although we tried our best to reduce the bias by making treatment decisions using an MDT model. Further studies will be needed to address these issues.

In summary, the present study demonstrated that a survival benefit could be achieved with palliative local treatment of incurable metastatic lesions in mCRC patients who received chemotherapy and bevacizumab. However, considering the retrospective nature and small sample size of study, well-designed prospective clinical trials will be needed to validate these results.

## Conflicts of interest

The authors indicated no potential conflicts of interest.

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