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# The efficacy of bevacizumab in Chinese patients with metastatic colorectal cancer and its effect in different line setting*

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**Abstract** ***Objective:*** We aimed to evaluate the effect of bevacizumab in the palliative treatment of Chinese metastatic colorectal cancer (mCRC) and its efficacy in different lines. ***Methods:*** Patients of mCRC treated with bevacizumab or not at Sun Yat-sen University Cancer Center from 2005 to 2013 were recruited as the study group and control group. The endpoints were objective response rate (ORR), disease control rate (DCR), overall survival (OS) and progression free survival (PFS). The OS and PFS of first-, second- and third-line treatment groups were compared between study group and control group. ***Results:*** The median PFS of the study and the control group were 8.2 months (7.0–9.4 months), 5.7 months (4.7–6.6 months), $P = 0.001$; OS were 26 months (5.4–130.5 months), 18 months (16.6–19.4 months), $P < 0.001$, respectively. The ORR and DCR of first-, second- and third-line were 30.3% (20/66), 20% (6/30), 17.6% (3/17) and 97% (64/66), 86.7% (26/30), 100% (17/17). In the first-line chemotherapy group, the OS of the study group and the control group were 22.9 (5.4–96.7) months and 18 (16.6–19.4) months ($P < 0.001$); PFS were 9.4 (8.4–10.4) months and 5.7 (4.7–6.6) months ($P < 0.001$), respectively. While in the second- and third-line setting, only OS were statistically different, PFS had no significant difference. ***Conclusion:*** The combination of bevacizumab and chemotherapy had a promising short-term and long-term efficacy in Chinese mCRC patients than those without bevacizumab regimens, and the effect could be better reflected in the first-line treatment.

**Key words** bevacizumab; chemotherapy; metastatic colorectal cancer; efficacy

Bevacizumab, the classical anti-angiogenesis drug, had been expected to both prune the immature vessels and normalize tumor vessels by decreasing interstitial fluid pressure and increasing the delivery of drugs and oxygen [1]. It had been approved by the US Food and Drug Administration (FDA) to be used in various cancers such as metastatic colorectal cancer (mCRC) [2–7], advanced non-small cell lung cancer (NSCLC) [8–9], advanced renal cell carcinoma [10–11], metastatic breast cancer [12–13] and so on.

In metastatic colorectal cancer, bevacizumab was widely used in the first-line [2, 6], the second-line [7], and even progression beyond its failure [14]. However, the administration of bevacizumab had always been challenged. Though both of progression-free survival (PFS) and overall survival (OS) were improved significantly in AVF2017, ARTIST, and E3200 trials [2–3, 7], the original short OS of IFL regimen in the former two trials weakened their significances. Moreover, only PFS rather than OS was significantly improved in the NO16966 trial [15], which was also the main reason of FDA withdrawing the license of bevacizumab when combined with pacelitaxel in the first line setting of metastatic breast cancer [16–19].

While few studies focused on effect of bevacizumab in Chinese mCRC patients. Our precious study not only demonstrated the efficacy of bevacizumab, but also found that 4 cycles of bevacizumab was the minimum requirement to benefit patients [20]. Recently, another retrospective study to evaluate its efficacy in Chinese mCRC patients was published. While the mortality and progressive rate of the study, 56.3% and 40.6%, respectively, made the results inconvincible [21]. As a result, the current retrospective study was conducted to evaluate the effect of bevacizumab in the palliative treatment of Chinese mCRC in different lines with case-controlled study.

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## Materials and methods

### Study population

Patients who met the following criterions were selected as study group: (1) Diagnosed as CRC based on pathological specimens of the primary tumor, at the same time with clinical and/or pathological evidences of distant metastasis, at the Sun Yat-sen University Cancer Center from 2005 to 2013 and finished the entire course of first-line chemotherapy in this center; (2) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; (3) Bevacizumab was added to the palliative regimens including oxaliplatin-based, irrinotecan-based regimens and so on; (4) More than 4 cycles of bevacizumab was required, since 4 cycles of bevacizumab was the minimum requirement to benefit patients found in our precious study [20]. Meanwhile, the consecutive mCRC patients in the control group met the same criterions with the study group except for bevacizumab administration. The exclusion criterions of both groups included: (1) No pathological diagnosis; (2) Unclear medical histories; (3) Loss of follow-up.

### Evaluation of efficacy

The short-term effect was evaluated by the independent group based-on criterion of Response Evaluation Criteria in Solid Tumors (RESIST): overall response rate (ORR), disease control rate (DCR); the long-term efficacy was evaluated by illustrating OS and PFS in the three-line treatment as well as comparing OS and PFS between the groups receiving bevacizumab or not.

### Statistical analysis

Patients' OS, PFS, ORR and DCR were the primary statistical endpoints of the study. OS was calculated from diagnosis to death or the date of last follow-up (January 31st, 2014), and PFS was deemed to be the period from the initial treatment of bevacizumab to the progression date by imaging examination according to the RECIST. All the statistical analysis was conducted by SPSS 18.0 software package and the *P* value less than 0.05 was considered with statistically significant.

### Follow-up

The last follow-up was conducted on January 31st, 2014 through telephone interview or medical records review. All the patients in the study and the control group were followed-up closely by then.

## Results

### Patient characteristics and treatment regimens

There were 113 patients entered the study group, all of them accepted bevacizumab (5 mg/kg, every two weeks) in combination with oxaliplatin-based, irinotecan-based and other regimens as a first-, second- and third-line treatment. There were 53 and 56 patients treated with oxaliplatin-based (FOLFOX and XELOX) and irinotecan-based (FOLFIRI) chemotherapy, and the remaining 3 patients were combined with xeloda, xeloda plus CPT-11 and Gemcitabine plus raltitrexed, respectively. The median cycles of bevacizumab were 8.81 (ranged, 4–25). While in the control group, contained 176 patients treated with chemotherapy alone, patients treated with oxaliplatin-based, irinotecan-based, fluorouracil alone (xeloda) chemotherapy were 83% (146/176), 6.3% (11/176) and 2.3% (4/176), respectively. All the patients' characteristics and potential prognostic factors including sex, age, tumor location, pathological type were shown in Table 1.

### OS and PFS were significantly different in the groups of patients receiving bevacizumab or not

In the study group, 99.1% (112/113) and 43.4% (49/113) patients exhibited progressed and died, while all the patients had progressed and died in the control group. The median OS of the study and the control group were 26 months (5.4–130.5 months), 18 months (16.6–19.4 months) ($P < 0.001$) and the median PFS of the study and the control group were 8.2 months (7.0–9.4 months), 5.7 months (4.7–6.6 months) ($P = 0.001$), respectively (Fig. 1, 2).

### The effect of bevacizumab was different in the first-line and second-line, third-line treatment

There were 58.4% (66/113), 26.5% (30/113) and 15.1% (17/113) patients treated with bevacizumab in the first-, the second- and the third-line setting, respectively. In the first-line treatment, the median cycles of bevacizumab was 8.5 (4–25), ORR and DCR were 30.3% (20/66) and 97% (64/66), respectively. Meanwhile, the median cycles of bevacizumab was 6 (4–24) in the second-line setting, ORR and DCR were 20% (6/30) and 86.7 (26/30), respectively. In the third-line treatment, the median cycles of bevacizumab was 6 (4–13), ORR and DCR were 17.6% (3/17) and 100% (17/17), respectively (Table 2).

In the first-line chemotherapy group, both of OS and PFS were significantly different between study group and control group. The OS of study group and control group was 22.9 (5.4–96.7) months and 18 (16.6–19.4) months ($P < 0.001$), respectively; PFS was 9.4 (8.4–10.4) months and 5.7 (4.7–6.6) months ($P < 0.001$), respectively (Fig. 3, 4). While in the second and third-line setting, only OS was statistically different to the control group, PFS was not. In the second-line chemotherapy group, the OS of bevacizumab group and control group was 33.6 (6.7–130.5) months and 18 (16.6–19.4) months ($P < 0.001$), respectively; PFS was 6.7 (1.9–19.6) months and 5.7 (4.7–6.6)

**Table 1** Patient baseline characteristics in the study and the control group

| Characteristics | Control group ($n$ = 163) | | Study group ($n$ = 113) | | $P$ | | |
|---|---|---|---|---|---|---|---|
| | $n$ | % | $n$ | % | 1* | 2** | 3*** |
| Gender | | | | | | | |
| Male | 104 | 63.8 | 78 | 69 | 0.368 | 0.841 | 0.904 |
| Female | 59 | 36.2 | 35 | 31 | | | |
| Age (years) | | | | | | | |
| Median | 53 | | 53 | | | | |
| Range | 19–83 | | 20–78 | | | | |
| ≤ 60 | 118 | 72.4 | 81 | 71.7 | 0.897 | 0.771 | 0.671 |
| > 60 | 45 | 27.6 | 32 | 28.3 | | | |
| Primary tumor | | | | | | | |
| Colon | 113 | 69.3 | 78 | 69 | 0.482 | 0.980 | 0.293 |
| Rectum | 50 | 30.7 | 35 | 31 | | | |
| Pathological type | | | | | | | |
| Adenocarcinoma | 158 | 96.9 | 109 | 99.1 | 0.233 | | |
| Others | 5 | 3.1 | 1 | 0.9 | | | |

Study group: the group of patients receiving bevacizumab; Control group: the group of patients not receiving bevacizumab. * $P$ value of balance test; ** $P$ value of the elements to PFS (progression free survival); *** $P$ value of the elements to OS (overall survival)

**Table 2** The efficacy of bevacizumab in the study group

| Characteristics | Bevacizumab group | | |
|---|---|---|---|
| | First-line ($n$ = 66) | Second-line ($n$ = 30) | Third-line ($n$ = 17) |
| ORR (%) | 30.3 (20/66) | 20.0 (6/30) | 17.6 (3/17) |
| DCR (%) | 97.0 (64/66) | 86.7 (26/30) | 100.0 (17/17) |
| PFS (months) | 9.5 (1.9–30.1) | 6.7 (1.9–19.6) | 6.0 (1.9–17.3) |
| OS (months) | 22.9 (5.4–96.7) | 33.6 (6.7–130.5) | 35.6 (16.9–85.5) |

**Table 3** Chemotherapy regimen of control and study group

| Chemotherapy regimen | Control group ($n$ = 163) | | Study group | | | | | |
|---|---|---|---|---|---|---|---|---|
| | $n$ | % | First-line ($n$ = 66) | | Second-line ($n$ = 30) | | Third-line ($n$ = 17) | |
| | | | $n$ | % | $n$ | % | $n$ | % |
| Oxaliplatin based | 134 | 82.2 | 33 | 50 | 14 | 46.7 | 6 | 35.3 |
| Irinotecan based | 11 | 6.7 | 31 | 47 | 16 | 53.3 | 10 | 58.8 |
| Fluorouracil alone | 4 | 2.5 | 1 | 1.5 | | | | |
| Other type | 14 | 8.6 | 1 | 1.5 | | | 1 | 5.9 |

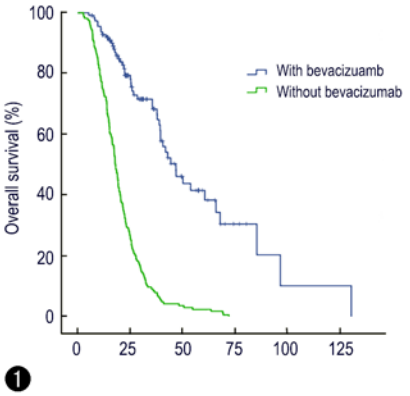
Study group: the group of patients receiving bevacizumab; Oxaliplatin-based: FOLFOX, XELOX; Irinotecan-based: FOLFIRI; Fluorouracil alone: Xeloda. Control group: the group of patients not receiving bevacizumab

months ($P$ = 0.681), , respectively (Fig. 5, 6). Besides, in the third-line setting group, the OS of study group and control group was 35.6 (16.9–85.5) months and 18 (16.6–19.4) months ($P$ < 0.001), respectively; PFS was 6.0 (1.9–17.3) months and 5.7 (4.7–6.6) months ($P$ = 0.982), respectively (Fig. 7, 8).

The patients' treatment details in each sub-group were showed in Table 3 (the difference of oxaliplatin-based and irinotecan-based chemotherapy in each sub-group had no significant difference, $P$ = 0.591).

## Discussion

The status of bevacizuamb to the patients of Caucasian and Chinese mCRC was firstly settled by AVF2017 [2] and ARTIST [3], respectively. Both of studies showed that OS and PFS were notably prolonged in the bevacizumab group at first-line treatment. And both clinical trails showed obvious short median OS in the control group (15.6 and 13.4 months in AVF2017 and ARTIST trials, respectively). Thus, the strength of efficacy was weakened, however, the results indicated that bevacizumab were similar effective in Chinese mCRC as in Caucasian mCRC patients. Recently, an one-armed study demonstrated the efficacy of bevacizumab by evaluate the OS, PFS, ORR and DCR in Chinese mCRC patients. However, the small patient sample may contribute the higher mortality and progressive rate (56.3% and 40.6%, respectively) [21]. Our precious study recruited 200 patients initially diagnosed as mCRC from 2004 to 2010, also designed as case-controlled study. We found that patients received more than 4 cycles of bevacizumab showed a significantly prolonged

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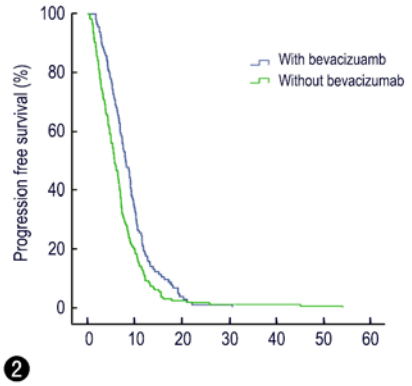


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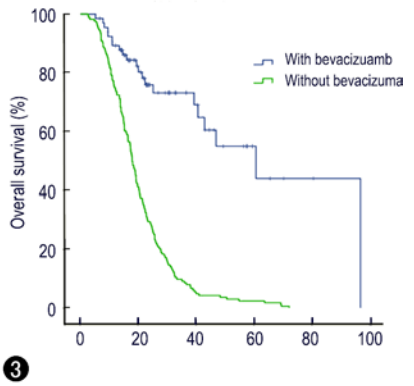


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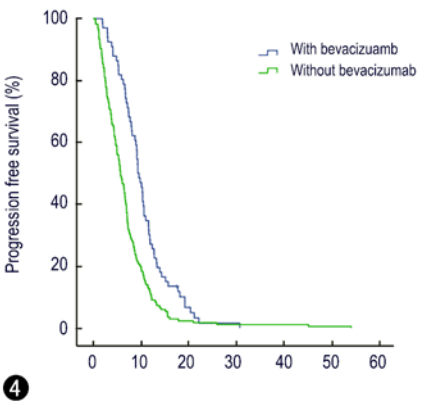
**Fig. 1** The OS of patients with or without bevacizumab
**Fig. 2** The PFS of patients with or without bevacizumab
**Fig. 3** The OS of patients with bevacizumab in the first-line treatment and without bevacizumab

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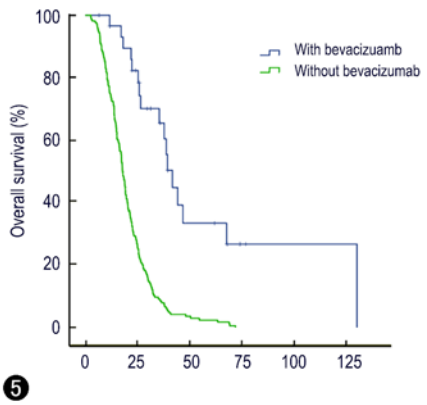


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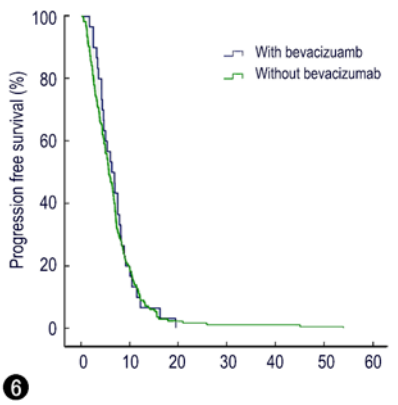


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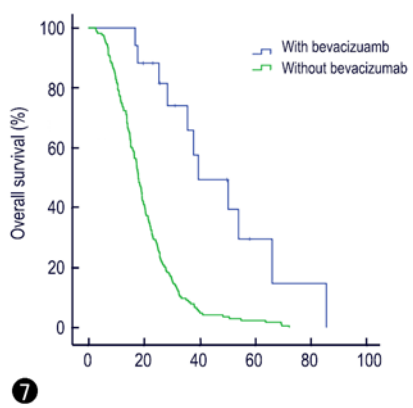
**Fig. 4** The PFS of patients with bevacizumab in the first-line treatment and without bevacizumab
**Fig. 5** The OS of patients with bevacizumab in the second-line treatment and without bevacizumab
**Fig. 6** The PFS of patients with bevacizumab in the second-line treatment and without bevacizumab

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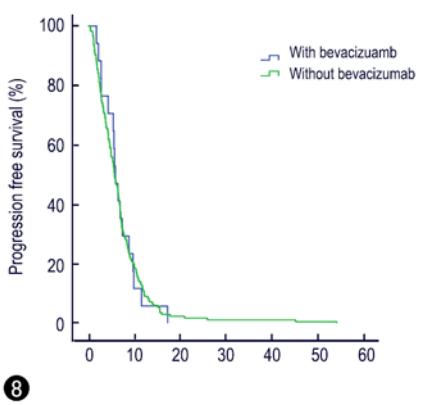


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**Fig. 7** The OS of patients with bevacizumab in the third-line treatment and without bevacizumab
**Fig. 8** The PFS of patients with bevacizumab in the third-line treatment and without bevacizumab

overall survival than patients in the control group [20]. The patients receiving bevacizumab more than 3 times showed an increased risk compared to the patients in control group of developing new metastatic lesions in the liver (17/23 vs. 25/55, respectively, $P = 0.022$) and other organs (14/23 vs. 19/55, respectively, $P = 0.032$). Our findings in accordance with most clinical trails that bevacizumab was effective when combined with chemotherapy in the first-line setting.

Later, bevacizumab was demonstrated to be beneficial in combination with different chemotherapy regimens, in the second-line treatment and the progression beyond its

failure in the studies of NO16966 [15], BICC-C [4], ML18147 [22] and so on. To our best knowledge, our study is the first one to compare the effect of bevacizumab among different lines treatment when combined with chemotherapy. Firstly, it was shown that not only ORR and DCR but also OS and PFS were promising after addition of bevacizumab in three different-line treatment of the current study. Furthermore, the addition of bevacizumab was definitely contributed to the strengthening of effect, and may be better reflected in the first-line treatment (22.9, 18 months and 9.4, 5.7 months in OS and PFS, respectively, $P < 0.001$, $P < 0.001$). While in the second and the third-line setting, only OS rather than PFS could be distinguished in the groups with or without bevacizumab. The real reason was unknown, however, it maybe relate to the following possibility: the small patient sample in the second and third line setting; the antiangiogenic mircro-environment could change after the former treatments; the tumor was refractory after several lines chemotherapy. All those challenges will be uncovered after enlarging of patients' sample and prospective study.

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